Title

Association of traumatic brain injury with dementia and memory decline in older adults in the United States

Journal

Alzheimer's & Dementia, 16(6)

ISSN

1552-5260

Authors

Grasset, Leslie
Glymour, M Maria
Yaffe, Kristine
et al.

Publication Date

2020-06-01

DOI

10.1002/alz.12080

Peer reviewed

Published in final edited form as:

Alzheimers Dement. 2020 June ; 16(6): 853–861. doi:10.1002/alz.12080.

Association of Traumatic Brain Injury With Dementia and Memory Decline in Older Adults in the United States

Leslie Grasset[1], **M. Maria Glymour**[2], **Kristine Yaffe**[3], **Samuel L Swift**[4], **Kan Z. Gianattasio**[5], **Melinda C. Power**[5], **Adina Zeki Al Hazzouri**[6]

[1]Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, Team VINTAGE, UMR 1219, F-33000 Bordeaux, France; Inserm, CIC1401-EC, F-33000 Bordeaux, France

[2]Department of Epidemiology and Biostatistics, University of California San Francisco

[3]Department of Neurology, Epidemiology and Biostatistics, University of California San Francisco

[4]Division of Epidemiology, Department of Public Health Sciences, University of Miami

[5]Department of Epidemiology and Biostatistics, Milken Institute School of Public Heath, George Washington University

[6]Department of Epidemiology, Mailman School of Public Health, Columbia University

Abstract

INTRODUCTION: To examine associations of history of TBI with LOC with dementia incidence and memory decline.

METHODS: We studied 2,718 participants from the 1992 enrollment cohort of the HRS aged 65 years or older in 2000. History of TBI with LOC was self-reported in 1992. Dementia was assessed using four algorithms established in HRS. Participants were followed from 2000–2014 with repeated measures of dementia and memory performance. Cox models and linear mixed-effects models were used.

RESULTS: In 1992, 11·9% of the participants reported a history of TBI with LOC. In fully-adjusted models for all four algorithms, participants with a history of TBI with LOC had no statistically significant difference in dementia incidence nor in memory decline, compared to participants without TBI history.

DISCUSSION: Our study did not find evidence of a long-term association between history of TBI with LOC (of unknown frequency and severity) and dementia incidence or memory decline.

Keywords

Traumatic brain injury; dementia; cognitive decline; longitudinal

Corresponding author: Leslie Grasset, PhD, INSERM U1219, University of Bordeaux, 146 rue Léo Saignat 33077 Bordeaux cedex, Phone: +33 5 57 57 13 93, leslie.grasset@u-bordeaux.fr.

Declaration of interest

The authors report no conflict of interest.

1. Background

Traumatic brain injuries (TBI) are frequent, especially in military soldiers and contact-sport players.[1] TBIs are associated with large economic costs, as more than 10 million individuals worldwide have sustained a brain trauma at some point in their lifetime severe enough to result in either mortality or hospitalization.[2] The true prevalence of TBI is likely to be higher than currently estimated, since milder TBIs are often underreported.[2, 3] In the US, approximately 2.3 million TBIs occurred in 2016, with a death rate of 17.0/100,000.[4, 5] Since most TBIs are non-fatal, survivors often experience many unfavorable outcomes such as psychiatric conditions and physical disability.[6, 7] Yet, many of the consequences of surviving a TBI remain poorly understood and relatively unexplored.

Recently, there has been growing interest in investigating the relationship between TBI and dementia. Dementia is highly prevalent at older ages[8], and similar to TBI, dementia also leads to increased disability, mortality and health care costs.[9] While immediate cognitive impairment is a well-known adverse outcome of TBI, the long-term consequences at older age are less consistent. On one hand, there is existing evidence to support an association between moderate to severe TBI and increased dementia risk [10–17] or Alzheimer's Disease (AD) risk.[10, 18–22] On the other hand, some other recent studies showed no difference in dementia incidence,[23–28] AD dementia,[23, 24, 29] or AD biomarkers or neuropathological measures [23, 28, 30] between individuals with and without a history of moderate to severe TBI. In particular, the lack of relationship in studies of moderate/severe TBI and AD neuropathology may suggest that the etiological associations are less so understood. In addition, the long-term effect of mild TBI is also debated and has been less investigated. Some studies specifically assessing mild TBI did not report an association with dementia or AD,[10, 31] and when an association is found,[32] the effect is often weaker than for moderate to severe TBI.[13, 14, 16, 20, 33] Similarly, studies of the relationship between TBI and cognitive decline have also been mixed.[28, 34–39]

The inconsistent findings on the association between TBI history and dementia may reflect differences in study populations, the type of samples used (autopsy-based, population-based, or clinical cohort), insufficient sample size, short follow-up time, or the presence of reverse causation when TBI could have occurred at older age. Moreover, self-reported TBI, which is often used in epidemiologic studies, is likely to be milder TBI than the one diagnosed clinically, further contributing to those inconsistencies. Finally, previously published studies were often not nationally representative and results may not be generalizable to the general population. Using large and national data from the Health and Retirement Study (HRS), the objective of the present study is to examine the long-term relationship between history of TBI with loss of consciousness (LOC) and dementia risk, assessed with four established algorithms for dementia diagnosis, and memory decline over a 14-year period.

2. Methods

2.1. Study population

The Health and Retirement Study (HRS) is a nationally representative population-based cohort of Americans aged 50 years and older and their spouses of any age. The HRS used

area level probability sampling of US households with supplemental oversampling of Black individuals, Hispanic individuals, and Florida residents. The initial interview took place in 1992 and HRS participants were re-interviewed every 2 years until 2016 on a range of sociodemographic, health and cognitive measures. Detailed information about the sampling procedures, study design, instruments, and data access are available online (http://hrsonline.isr.umich.edu). All HRS participants gave verbal informed consent for their participation in the study; HRS data collection was approved by the Health Sciences and Behavioral Sciences institutional review board at the University of Michigan.

Our study sample included participants who were eligible in HRS 1992 core interview (N=9,794), the time when TBI exposure was ascertained. All of the 9,794 participants had a TBI assessment in 1992 (i.e. no missing values in our predictor of interest). Of those, we then limited the sample to 2,718 participants who were ages 65+ in HRS 2000 core interview, being our baseline for dementia and memory score follow-up (eFigure 1). All participants were from the original HRS cohort and no participants from later enrollment cohorts were included in this analysis. Participants were followed until death, dropout or the 2014 study exam.

2.2. Assessment of Dementia and memory score: outcomes of interest

Dementia incidence and change in memory score are the primary outcomes, and both were ascertained every two years between 2000 and 2014. We began our follow-up in year 2000 to maintain consistency across the dementia algorithms since some proxy information, which is used to create the algorithms, was first collected in year 2000.

Dementia: We compared four commonly used algorithms for dementia diagnosis that were developed in the HRS sample, and we applied the published coefficients as parameterized in Gianattasio et al.[40] Details of these algorithms are described elsewhere.[41–44] Briefly:

1. Langa-Kabeto-Weir (LKW) algorithm, a cut point summary score from 0 to 27, includes cognition and IADL data, as well as proxy information. Dementia was defined with a cutoff of 6 or less (7–11 being Cognitive Impairment No Dementia (CIND))[41, 44];
2. Herzog & Wallace (HW) algorithm, a cut point summary score from 0 to 35, includes cognition data and proxy information. Dementia was defined with a cutoff of 8 or less[42];
3. Wu algorithm, a logistic regression-based dementia probability score, includes demographics and cognition data, as well as proxy information. Dementia was defined at a threshold of 0.5 or higher[43]; and
4. Crimmins algorithm, a multinomial logistic regression-based dementia probability score, including demographics, cognition, and ADL and IADL data, as well as proxy information. Dementia was defined at a threshold of 0.5 or higher.[44]

Overall performances across algorithms have been assessed against the Aging, Demographics, and Memory Study (ADAMS) clinical dementia diagnosis as gold standard.

In analyses weighted to represent the age-eligible US population, it has been found that the HW algorithm maximized specificity, the Crimmins algorithm maximized sensitivity, and the Wu algorithm maximized accuracy. The most sensitive algorithms tended to be the least specific, yet they presented fair overall accuracy compared to clinical diagnosis, ranging from 87% to 94%. Details on the algorithms and their validity have been published elsewhere.[40]

Memory score: The memory score was assessed according to the methods of Wu and colleagues.[43] It is a quantitative summary metrics that combines, into a single scale, results from cognitive tests (word immediate and delayed recall), including those completed by a proxy respondent (IQCODE and proxy memory score) for severely impaired HRS participants. The composite memory score was developed using core HRS questionnaire items calibrated against the Aging, Demographics, and Memory Study (ADAMS) sample, a subset of HRS participants who underwent detailed in-person neuropsychological batteries. Using the models derived from the ADAMS cohort, memory score was estimated for all HRS participants based on the HRS core component measures. In our sample, the score ranges from −1.74 to 2.11, with lower memory score indicating worse cognition. Further details have been published elsewhere.[43]

2.3. Traumatic brain injury with loss of consciousness (TBI with LOC): predictor of interest

TBI was assessed during the 1992 exam by the question: “Have you ever been unconscious due to a head injury?”. The exposure was thus defined as history of TBI with loss of consciousness (LOC). Every participant in the initial HRS sample answered the TBI question, with no missing data in our analysis sample.

2.4. Covariates

HRS participants reported sociodemographic information such as age, gender, race, veteran status, and education (coded as less than high school or GED, high school, some college, or master’s or professional degree). In year 2000 (our study baseline), information on marital status, ever smoking, self-report of physician-diagnosed medical comorbidities (hypertension, diabetes, lung disease, arthritis, cancer, heart disease, and stroke), and depressive symptoms were collected. Depression was measured via the eight-item Center for Epidemiologic Studies Depression Scale (CES-D), which asks respondents to report whether they experienced eight specific depressive symptoms over the past week. Based on prior studies, depression was defined as a score of 3 or higher.[45]

2.5. Statistical analysis

We compared participant’s characteristics at baseline according to history of TBI with LOC using *t* tests with person-level weights to generate P values for continuous variables. Median and interquartile range, or mean and standard deviation, are reported according to degree of normality. For categorical variables, $\chi 2$ statistics with person-level weights were used.

Participants with missing value for dementia algorithm scores in year 2000, as well as participants with prevalent dementia in year 2000, according to any of the four algorithms

defined above, were excluded from the analyses. Participants contributed observed time at risk beginning in 2000. Incidence rates of dementia (per 1,000 person-years) by history of TBI with LOC were calculated by dividing the number of dementia cases in each TBI category by the number of person-years at risk contributed by participants within that category. Incidence rate differences were computed as well.

For survival analyses of the relationship between TBI with LOC and dementia incidence across the 14-year period, participant's age was considered as the time scale, and as such an entry point (age in 2000) and an ending point (age at dementia diagnosis or censoring) were modeled to address left truncation. Participants who remained free of dementia were censored at the age of their latest follow-up before drop out where their dementia status was known or by 2014 (end of follow up). We modeled dementia diagnosis from each of the four algorithms as a separate outcome. After verifying that the proportional hazards assumption was met, we assessed a series of two Cox proportional hazards models to examine the association between history of TBI with LOC and the risk of dementia. Model 1 was adjusted for gender, race and education, and model 2 was additionally adjusted for veteran status, marital status, smoking status, medical comorbidities, and depressive symptoms, all assessed in year 2000. Person-level probability weights at time of participants' enrollment (year 1992) were applied to account for complex survey design.

We assessed memory score performance across the 14-year period using longitudinal linear mixed-effects models, adjusted for the same covariates as with the dementia outcome. Time was defined as the number of years since baseline (2000). A quadratic term for time was tested and retained in the model as it improved model fit. Interactions between time and covariates (gender, race, education, veteran status, marital status, smoking status, medical comorbidities, and depressive symptoms) were tested and retained in the models when significant or improving model fit – these interactions test whether the cognitive slope varied according to these covariates. We specified participant level random intercepts and slopes with an unstructured covariance. The effect estimate of TBI quantifies the difference in the baseline cognitive scores for persons with or without TBI with LOC history, whereas the interaction of TBI with time (i.e. slope) quantifies the effect of TBI with LOC on the change in cognitive score over the 14-year period. The goodness of fit of each model was assessed using residual plots. Person-level weights at time of participants' enrollment (1992) were applied to account for complex survey design.

In addition to the main analyses, to increase statistical power and minimize potential outcome misclassification, we repeated the analysis of TBI and dementia risk, however using the continuous scores and probabilities – instead of the original dichotomous dementia diagnosis – in linear mixed models, thus exploring their evolution over the 14-year period. Furthermore, as exploratory analyses, we have examined possible interactions between TBI status and each of sex, race, education and veteran status. All analyses were conducted using SAS version 9.4.

3. Results

Of the 2,718 eligible HRS participants, 318 (11.9% of the weighted sample) reported a history of TBI (Table 1). Participants with history of TBI with LOC were more likely to be men, veterans and have ever smoked. They also reported more heart disease, stroke, and arthritis compared to participants without a history of TBI. The mean duration of follow-up time was around 13 years. Follow up times did not significantly differ between individuals with or without history of TBI with LOC.

The number of incident dementia cases which occurred between 2000 and 2014 ranged from 240 to 434 across the four algorithms (Table 2). Overall, incidence rates ranged from 8.7/1000 person-year for the HW algorithm to 16.8/1000 person-years for the LKW algorithm. There were no significant differences in incidence rates of dementia between individuals with or without history of TBI with LOC across the algorithms.

Risks of dementia according to history of TBI with LOC are presented in Table 3 according to the different algorithms. For all four algorithms, participants with a history of TBI had no statistically significant difference in dementia incidence compared to participants without history of TBI with LOC, in minimally adjusted models (LKW HR=0.92 (0.66–1.29); HW HR=1.02 (0.67–1.54); Wu HR=1.12 (0.79–1.60); and Crimmins HR=0.92 (0.65–1.30)). Results remained similar in fully-adjusted models. Stratified analyses presenting interactions between TBI status and each of sex, race, education, and veteran status are presented in eTable 1. Most interactions were not significant between men and women, yet with point estimates being in the protective direction for women. For race, interactions were not consistently significant across all dementia algorithms. Effect estimates were mostly protective among whites, though non-significant. Among Blacks and Hispanics, effect estimates were mostly in the harmful direction (i.e. greater risk) and were non-significant, except for the HW algorithm. For education, while associations were mostly null, point estimates tended to be protective among those with high level of education and in the harmful direction among those with low level of education, except for the Crimmins algorithm. Finally for veteran status, point estimates seemed to be inconsistent across algorithms, and though non-significant, point estimates tended to be in the harmful direction among veterans.

The associations between history of TBI with LOC and the memory score decline are presented in Table 4. Memory score significantly declined over the 14-year follow-up period (β for linear time trend= −0.02, 95% CI (−0.02, −0.01), and β for quadratic time term= −0.002, 95% CI (−0.002, −0.002)). There was no significant relation between history of TBI with LOC and memory score or memory decline. In particular, participants with history of TBI with LOC had similar baseline memory function (β= −0.008, 95% CI (−0.05, 0.03)), as well as similar memory decline over time compared to participants without TBI with LOC history (β= −0.001, 95% CI (−0.007, 0.005)), in minimally adjusted models. These results remained similar in fully-adjusted models.

When examining dementia scores and probabilities from the four algorithms as continuous, we found no association between history of TBI with LOC on baseline performances nor on

changes over time across all four algorithms (eTable 2), which was consistent with the results from the Cox proportional hazard models in Table 3.

4. Discussion

In a nationally representative prospective cohort of older adults free of dementia at baseline, we did not find evidence for any long-term associations between history of TBI with LOC (of unknown frequency and severity) and risk of dementia over 14 years of follow-up. These results were consistent across four established dementia algorithms. Similarly, decline in memory performance did not differ between participants with or without history of TBI with LOC.

Our findings did not confirm the harmful effect of TBI on dementia risk found in several other studies.[10–14, 16, 20, 32, 46] For example, two recent large population-based studies from Denmark and Sweden have reported an increased risk of dementia in individuals with a TBI diagnosis, even among persons with an injury more than 10 years prior to dementia diagnosis.[13, 14] Moreover, associations between dementia and mild TBI were weaker than the ones with moderate/severe TBI, yet they were still significant. Their risk estimate for the relationship between TBI and dementia (for example for the Danish study, global HR=1.24 (1.21–1.27)) fell within the 95% confidence intervals of our risk estimates, for most algorithms, which may suggest a lack of statistical power to detect similar significant associations in our HRS sample. Further, these studies used national registries and medical records for ascertainment of TBI exposure and dementia diagnosis which may also have limitations. Dementia is often under diagnosed in the elderly population. Yet, patients diagnosed with a TBI may be more likely to have medical follow-up and thus be diagnosed with dementia at older ages, which could bias results. In addition, exposures and adjustment factors may also be under diagnosed or not reported in registries or medical records, especially for milder TBI or other psychiatric disorders. In studies with short follow-up,[11, 16, 19, 20] reverse causation cannot be excluded, since patients with dementia may be at higher risk for fall and TBI. In addition, other studies showing an association between TBI and dementia have focused only on US military veterans.[15, 17, 33] In these studies, unmeasured confounding, for example by psychiatric comorbidities frequent among veterans such as post-traumatic stress disorder (PTSD), depression, or presence of multiple traumas, which are also risk factors for dementia, cannot be excluded. In our stratified analysis by veteran status, interactions were mostly non-significant, yet with a trend toward more risk for veteran, even though estimates were inconsistent across algorithms. Unlike most previous studies which included White participants, our cohort is racially/ethnically diverse and oversampled Blacks and Hispanics. Yet, stratified analyses still showed no associations among Whites as well as among Blacks and Hispanics. Similarly, in our stratified analyses by education, interactions were mostly non-significant, even though there was a trend for lower risk of dementia among those with high school education or more, suggesting a role for cognitive reserve.

However, our findings showing no association between TBI history with LOC and dementia are consistent with the results of several other recent studies looking at dementia,AD, or AD biomarkers or neuropathology.[23–26, 28, 30] In particular, a recent report highlighted two

well conducted studies showing no association with AD.[47] The first study, analyzing data from three population-based studies, found no associations between TBI with more or less than an hour of LOC and dementia or Alzheimer's disease (AD).[23] In addition, among participants who underwent autopsy, no associations were found between TBI with LOC (regardless of the LOC duration) and neuropathologic markers (for example neuritic plaques or neurofibrillary tangles). The second study, among veterans identified through Veterans Administration records, showed no effect of TBI on cognition or amyloid positivity, though the sample size was small.[30] Another recent study among participants from the National Alzheimer's Coordinating Center (NACC) who consented to brain donation and neuropathological examination did not evidence an association between reported TBI history and Alzheimer's disease neuropathology, global Clinical Dementia Rating score, or cognitive test performance.[28] In addition, our results on memory decline are in line with a recent study using a HRS subsample of 984 participants, showing more subjective memory impairment but no differences by TBI status regarding measures of objective cognitive function.[35] Our findings are also consistent with a recent study among participants from the NACC database aged 50 years and older suggesting that TBI with LOC history is not associated with rates of cognitive change.[34] It may be possible that TBI mainly impact global dementia or vascular dementia risk rather than Alzheimer's disease risk. Yet, our study builds upon this prior literature by being the first to use a well-characterized, representative population-based sample with a study design that minimizes possible reverse causation through a long follow-up period, and by using four different established algorithms for dementia definition to examine the association between TBI and dementia.

A major limitation of the present study is the self-report nature of the TBI exposure assessment. While self-reported TBIs are often used in epidemiologic studies, they are likely to be milder than the ones clinically diagnosed, which might explain the lack of association found in our results. In fact, the prevalence of TBI history in our study is similar to that reported in other previously published population-based studies with self-reported TBI assessment,[23, 24, 26] and higher than the prevalence reported by studies based on national registries or medical claims. This is further consistent with self-reported TBI being, on average, milder than the one clinically diagnosed (e.g. from medical records or inpatient visits). Furthermore, while our measure of TBI includes loss of consciousness (LOC), the duration of the LOC and the severity of the TBI are unknown. Definitions for milder TBI assessment are also diverse in how severity is ascertained, further contributing to the inconsistencies in the literature.[13, 14, 16, 32, 33] The frequency of TBI was also not known, and thus individuals with TBI who are classified as exposed may have sustained a single mild TBI, which may then explain the lack of associations. Further, misclassification bias may have occurred, either because TBI exposure assessment relied on participants' recall, or because participants without TBI with LOC who are classified as being 'unexposed' may have actually sustained single or repetitive mild TBIs but without LOC, or subconcussive impact. Finally, due to the lag between history of TBI with LOC assessment in 1992 and cognition and dementia outcome ascertainment beginning 2000, it is possible to have missed on new TBIs with LOC occurring between 1992 and 2000 and which may have contributed to the lack of associations in our study. In conclusion, dementia risk is clearly a function of TBI severity and frequency, and the absence of those measures reflects a lack of

refinement in the definition and assessment of TBI which contribute to the inconsistent findings across the literature. While this is a major limitation in our study and the field broadly, future studies should attempt to address this gap using tools such as misclassification bias analyses. Another limitation of this work is that, as detailed in the methods section, the assessment of dementia relied on algorithms rather than on a clinical diagnosis. While the four algorithms have varying predictive values, they have all shown a fair accuracy compared to clinical diagnosis.[40] Our analysis is strengthened by the use of all four algorithms, and our results were consistent across these algorithms. Moreover, in a sensitivity analysis modeling dementia scores and probabilities as continuous variables, no trend toward worse baseline scores or decline in the TBI group was evidenced, showing little impact of misclassification for dementia cases. However, we cannot exclude that a potential differential misclassification may be biasing results toward the null. In addition, the absence of clinical diagnosis or biomarkers or neuropathological measures does not allow us to investigate any etiologic associations. Information on other neurologic diseases such as Parkinson's disease would have also been of interest. Finally, even though we adjusted our analyses for major risk factors for dementia and cognitive decline, residual confounding may remain due to unmeasured confounders. For example, we were not able to take into account the role of family history or APOE status.

Despite these limitations, this study has important strengths. Our work relies on a prospective, nationally-representative population-based cohort study with a long follow-up and sufficient sample size, providing an adequate setting to detect the long-term association between history of TBI with LOC and risk of dementia or memory decline. Additionally, four different definitions and well-established algorithms of dementia have been compared to strengthen our conclusions, and results were overall consistent across those definitions. Finally, due to the 8-year lag between TBI assessment and beginning of incidence follow-up, TBI exposure was ascertained at a time when participants were free of dementia, thus limiting the possibility of reverse causation. This long and well powered study confirms other recent studies in the US reporting no association and provide representative results from the general US population of the long term effect of TBI with LOC on dementia risk.

In conclusion, contrary to some studies, this work does not provide evidence of a long-term association between TBI with LOC and dementia risk or memory decline. Further studies in the general population with a more rigorous assessment of TBI exposure would be needed to explore the lifelong association between TBI, across the severity spectrum, and dementia, its different etiologies, and cognitive decline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

M.M.G and A.Z were supported by RF1AG055486 from the National Institute of Aging; K.Z.G. and M.C.P were supported by R03 AG055485 from the National Institute of Aging.

The funders had no role in study design, in data collection, analysis, and interpretation, or in writing of report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

References

[1]. Daneshvar DH, Nowinski CJ, McKee AC, Cantu RC. The epidemiology of sport-related concussion. Clin Sports Med. 2011;30:1–17, vii. [PubMed: 21074078]

[2]. Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G, Kobusingye OC. The impact of traumatic brain injuries: a global perspective. NeuroRehabilitation. 2007;22:341–53. [PubMed: 18162698]

[3]. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. J Head Trauma Rehabil. 2006;21:375–8. [PubMed: 16983222]

[4]. Taylor CA, Bell JM, Breudung MJ, Xu L. Traumatic Brain Injury–Related Emergency Department Visits, Hospitalizations, and Deaths — United States, 2007 and 2013. MMWR Surveill Summ. 2017;66:1–16.

[5]. Injury GBDTB, Spinal Cord Injury C. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18:56–87. [PubMed: 30497965]

[6]. Selassie AW, Zaloshnja E, Langlois JA, Miller T, Jones P, Steiner C. Incidence of long-term disability following traumatic brain injury hospitalization, United States, 2003. J Head Trauma Rehabil. 2008;23:123–31. [PubMed: 18362766]

[7]. Bombardier CH, Fann JR, Temkin NR, Esselman PC, Barber J, Dikmen SS. Rates of major depressive disorder and clinical outcomes following traumatic brain injury. JAMA. 2010;303:1938–45. [PubMed: 20483970]

[8]. Collaborators GBDD. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18:88–106. [PubMed: 30497964]

[9]. Prince MJ. World Alzheimer report 2015: the global impact of dementia. published online Aug 252015.

[10]. Plassman BL, Havlik RJ, Steffens DC, Helms MJ, Newman TN, Drosdick D, et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology. 2000;55:1158–66. [PubMed: 11071494]

[11]. 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;83:1080–5. [PubMed: 22842203]

[12]. Nordstrom P, Michaelsson K, Gustafson Y, Nordstrom A. Traumatic brain injury and young onset dementia: a nationwide cohort study. Ann Neurol. 2014;75:374–81. [PubMed: 24812697]

[13]. Nordstrom A, Nordstrom P. Traumatic brain injury and the risk of dementia diagnosis: A nationwide cohort study. PLoS Med. 2018;15:e1002496. [PubMed: 29381704]

[14]. Fann JR, Ribe AR, Pedersen HS, Fenger-Gron M, Christensen J, Benros ME, et al. Long-term risk of dementia among people with traumatic brain injury in Denmark: a population-based observational cohort study. Lancet Psychiatry. 2018;5:424–31. [PubMed: 29653873]

[15]. Barnes DE, Kaup A, Kirby KA, Byers AL, Diaz-Arrastia R, Yaffe K. Traumatic brain injury and risk of dementia in older veterans. Neurology. 2014;83:312–9. [PubMed: 24966406]

[16]. 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;71:1490–7. [PubMed: 25347255]

[17]. Yaffe K, Lwi SJ, Hoang TD, Xia F, Barnes DE, Maguen S, et al. Military-related risk factors in female veterans and risk of dementia. Neurology. 2019;92:e205–e11. [PubMed: 30541865]

[18]. Fleminger S, Oliver DL, Lovestone S, Rabe-Hesketh S, Giora A. Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. J Neurol Neurosurg Psychiatry. 2003;74:857–62. [PubMed: 12810767]

[19]. LoBue C, Wadsworth H, Wilmoth K, Clem M, Hart J Jr., Womack KB, et al. Traumatic brain injury history is associated with earlier age of onset of Alzheimer disease. Clin Neuropsychol. 2017;31:85–98. [PubMed: 27855547]

[20]. Guo Z, Cupples LA, Kurz A, Auerbach SH, Volicer L, Chui H, et al. Head injury and the risk of AD in the MIRAGE study. Neurology. 2000;54:1316–23. [PubMed: 10746604]

[21]. Schaffert J, LoBue C, White CL, Chiang HS, Didehbani N, Lacritz L, et al. Traumatic brain injury history is associated with an earlier age of dementia onset in autopsy-confirmed Alzheimer's disease. Neuropsychology. 2018;32:410–6. [PubMed: 29389151]

[22]. Perry DC, Sturm VE, Peterson MJ, Pieper CF, Bullock T, Boeve BF, et al. Association of traumatic brain injury with subsequent neurological and psychiatric disease: a meta-analysis. J Neurosurg. 2016;124:511–26. [PubMed: 26315003]

[23]. 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;73:1062–9. [PubMed: 27400367]

[24]. 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;84:177–82. [PubMed: 23172868]

[25]. Breteler MM, de Groot RR, van Romunde LK, Hofman A. Risk of dementia in patients with Parkinson's disease, epilepsy, and severe head trauma: a register-based follow-up study. Am J Epidemiol. 1995;142:1300–5. [PubMed: 7503050]

[26]. Mehta KM, Ott A, Kalmijn S, Slooter AJ, van Duijn CM, Hofman A, et al. Head trauma and risk of dementia and Alzheimer's disease: The Rotterdam Study. Neurology. 1999;53:1959–62. [PubMed: 10599765]

[27]. LoBue C, Cullum CM, Didehbani N, Yeatman K, Jones B, Kraut MA, et al. Neurodegenerative Dementias After Traumatic Brain Injury. J Neuropsychiatry Clin Neurosci. 2018;30:7–13. [PubMed: 29061090]

[28]. Sugarman MA, McKee AC, Stein TD, Tripodis Y, Besser LM, Martin B, et al. Failure to detect an association between self-reported traumatic brain injury and Alzheimer's disease neuropathology and dementia. Alzheimers Dement. 2019;15:686–98. [PubMed: 30852157]

[29]. Julien J, Joubert S, Ferland MC, Frenette LC, Boudreau-Duhaime MM, Malo-Veronneau L, et al. Association of traumatic brain injury and Alzheimer disease onset: A systematic review. Ann Phys Rehabil Med. 2017;60:347–56. [PubMed: 28506441]

[30]. Weiner MW, Harvey D, Hayes J, Landau SM, Aisen PS, Petersen RC, 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;3:177–88. [PubMed: 28758146]

[31]. Godbolt AK, Cancelliere C, Hincapie CA, Marras C, Boyle E, Kristman VL, 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:S245–56. [PubMed: 24581910]

[32]. Lee YK, Hou SW, Lee CC, Hsu CY, Huang YS, Su YC. Increased risk of dementia in patients with mild traumatic brain injury: a nationwide cohort study. PLoS One. 2013;8:e62422. [PubMed: 23658727]

[33]. Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K. Association of Mild Traumatic Brain Injury With and Without Loss of Consciousness With Dementia in US Military Veterans. JAMA Neurol. 2018;75:1055–61. [PubMed: 29801145]

[34]. Tripodis Y, Alosco ML, Zirogiannis N, Gavett BE, Chaisson C, Martin B, et al. The Effect of Traumatic Brain Injury History with Loss of Consciousness on Rate of Cognitive Decline Among Older Adults with Normal Cognition and Alzheimer's Disease Dementia. J Alzheimers Dis. 2017;59:251–63. [PubMed: 28655133]

[35]. 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:e1002246. [PubMed: 28267747]

[36]. Ruttan L, Martin K, Liu A, Colella B, Green RE. Long-term cognitive outcome in moderate to severe traumatic brain injury: a meta-analysis examining timed and untimed tests at 1 and 4.5 or more years after injury. Arch Phys Med Rehabil. 2008;89:S69–76. [PubMed: 19081444]

[37]. Millis SR, Rosenthal M, Novack TA, Sherer M, Nick TG, Kreutzer JS, et al. Long-term neuropsychological outcome after traumatic brain injury. J Head Trauma Rehabil. 2001;16:343–55. [PubMed: 11461657]

[38]. Dikmen SS, Machamer JE, Powell JM, Temkin NR. Outcome 3 to 5 years after moderate to severe traumatic brain injury. Arch Phys Med Rehabil. 2003;84:1449–57. [PubMed: 14586911]

[39]. Himanen L, Portin R, Isoniemi H, Helenius H, Kurki T, Tenovuo O. Longitudinal cognitive changes in traumatic brain injury: a 30-year follow-up study. Neurology. 2006;66:187–92. [PubMed: 16434651]

[40]. Gianattasio KZ, Wu Q, Glymour MM, Power MC. Comparison of Methods for Algorithmic Classification of Dementia Status in the Health and Retirement Study. Epidemiology. 2019;30:291–302. [PubMed: 30461528]

[41]. Alzheimer's A 2010 Alzheimer's disease facts and figures. Alzheimers Dement. 2010;6:158–94. [PubMed: 20298981]

[42]. Herzog AR, Wallace RB. Measures of cognitive functioning in the AHEAD Study. J Gerontol B Psychol Sci Soc Sci. 1997;52 Spec No:37–48.

[43]. Wu Q, Tchetgen Tchetgen EJ, Osypuk TL, White K, Mujahid M, Maria Glymour M. Combining direct and proxy assessments to reduce attrition bias in a longitudinal study. Alzheimer Dis Assoc Disord. 2013;27:207–12. [PubMed: 22992720]

[44]. Crimmins EM, Kim JK, Langa KM, Weir DR. Assessment of cognition using surveys and neuropsychological assessment: the Health and Retirement Study and the Aging, Demographics, and Memory Study. J Gerontol B Psychol Sci Soc Sci. 2011;66 Suppl 1:i162–71. [PubMed: 21743047]

[45]. Turvey CL, Wallace RB, Herzog R. A revised CES-D measure of depressive symptoms and a DSM-based measure of major depressive episodes in the elderly. Int Psychogeriatr. 1999;11:139–48. [PubMed: 11475428]

[46]. Gardner RC, Yaffe K. Traumatic brain injury may increase risk of young onset dementia. Ann Neurol. 2014;75:339–41. [PubMed: 24550062]

[47]. Weiner MW, Crane PK, Montine TJ, Bennett DA, Veitch DP. Traumatic brain injury may not increase the risk of Alzheimer disease. Neurology. 2017;89:1923–5. [PubMed: 28978654]

Table 1:

Baseline characteristics of study participants according to TBI status, HRS, 2000–2014

	Total sample	No TBI (n=2400)	TBI (n=318)	P value
Women	1487 (54.7)	1375 (57.3)	112 (34.8)	<.0001
Age, mean (SD)	66.7 (1.3)	66.7 (1.3)	66.8 (1.4)	0.27
Non white	521 (12.5)	489 (13.2)	32 (7.5)	0.003
Education				0.02
Less than high school or GED	891 (29.3)	793 (29.4)	98 (28.2)	
High school	882 (33.7)	793 (34.5)	89 (28.0)	
College	474 (18.2)	405 (17.5)	69 (23.5)	
Master's or professional degree	471 (18.8)	409 (18.7)	62 (20.3)	
Non Partnered	843 (28.6)	749 (28.6)	94 (28.8)	0.93
Veterans	807 (30.6)	676 (28.9)	131 (43.7)	<.0001
Hypertension	1342 (47.2)	1185 (47.0)	157 (48.9)	0.38
Diabetes	463 (15.6)	423 (15.9)	40 (13.0)	0.27
Cancer	319 (12.4)	283 (12.6)	36 (11.2)	0.74
Heart disease	554 (20.1)	473 (19.4)	81 (25.3)	0.02
Stroke	191 (6.5)	153 (5.7)	38 (12.3)	<.0001
Lung disease	229 (8.0)	191 (7.6)	38 (10.8)	0.13
Arthritis	1544 (56.2)	1343 (55.2)	201 (63.6)	0.01
CESD				0.22
<3	2150 (80.1)	1907 (80.6)	243 (76.5)	
>=3	354 (12.6)	308 (12.3)	46 (14.8)	
Missing	214 (7.3)	185 (7.1)	29 (8.7)	
Ever smoke	1682 (62.1)	1455 (61.0)	227 (70.1)	0.001
No. of follow-up interviews, median (IQR)	7 (5–8)	7 (5–8)	7 (4–8)	0.16
Follow-up time, median (IQR)	13 (8–14)	13 (8–14)	13 (7–14)	0.32
Baseline memory score, mean (SD)	1.05 (0.4)	1.09 (0.4)	1.05 (0.4)	0.09

TBI: Traumatic Brain Injury; GED: general educational development; CESD: Center for Epidemiologic Studies Depression Scale; IQR: interquartile range.

Data are presented as raw numbers with weighted percentage for categorical variables, and weighted t test for continuous variables.

Table 2:

Incidence of dementia, as classified by the four algorithms, by history of TBI status, HRS 2000–2014

	N	Number of dementia cases	Person-years at risk	IR (95% CI)	IRD (95% CI)
LKW					
Overall	2414	434	25905	16.8 (15.2 ; 18.3)	-
Without TBI	2128	391	22929	17.1 (15.4 ; 18.7)	Ref
TBI	286	43	2976	14.5 (10.1 ; 18.8)	−2.6 (−7.2 ; 2.0)
HW					
Overall	2477	240	27549	8.7 (7.6 ; 9.8)	-
Without TBI	2181	211	24410	8.6 (7.5 ; 9.8)	Ref
TBI	296	29	3140	9.2 (5.9 ; 12.6)	0.6 (−3.0 ; 4.2)
Wu					
Overall	2470	351	27037	13.0 (11.6 ; 14.3)	-
Without TBI	2174	310	23946	12.9 (11.5 ; 14.4)	Ref
TBI	296	41	3091	13.3 (9.2 ; 17.3)	0.3 (−4.0 ; 4.6)
Crimmins					
Overall	2367	403	25853	15.6 (14.1 ; 17.1)	-
Without TBI	2092	364	22932	15.9 (14.2 ; 17.5)	Ref
TBI	275	39	2921	13.4 (9.2 ; 17.5)	−2.5 (−7.0 ; 2.0)

TBI: Traumatic Brain Injury; LKW: Langa-Kabeto-Weir; HW: Herzog & Wallace.

Table 3:

Association* between history of TBI and risk of dementia according to the four algorithms, HRS, 2000–2014

	LKW (n=2414)		HW (n=2477)		Wu (n=2470)		Crimmins (n=2367)	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Model 1								
TBI history vs. not	0.92 (0.66 ; 1.29)	0.64	1.02 (0.67 ; 1.54)	0.94	1.12 (0.79 ; 1.60)	0.52	0.92 (0.65 ; 1.30)	0.64
Model 2								
TBI history vs. not	0.90 (0.65 ; 1.26)	0.54	1.02 (0.67 ; 1.55)	0.94	1.16 (0.81 – 1.65)	0.42	0.89 (0.63 ; 1.25)	0.49

TBI: Traumatic Brain Injury; LKW: Langa-Kabeto-Weir ; HW: Herzog & Wallace.

Model 1 adjusted for gender, race and education. Model 2 was additionally adjusted for veteran status, marital status, depressive symptoms, ever have hypertension, diabetes, cancer, heart disease, stroke, lung disease, arthritis, and ever smoking.

*Using Cox Proportional Hazards models

Alzheimers Dement. Author manuscript; available in PMC 2021 March 17.

Table 4:

Association* between history of TBI and memory score trajectory, 2000–2014

	Model 1		Model 2	
	β (95% CI)	P value	β (95% CI)	P value
Memory score				
TBI history	−0.008 (−0.05, 0.03)	0.68	−0.0003 (−0.03, 0.03)	0.95
Time	−0.02 (−0.02, −0.01)	<.0001	−0.01 (−0.02, −0.007)	<.0001
Quadratic time	−0.002 (−0.002, −0.002)	<.0001	−0.002 (−0.002,−0.002)	<.0001
TBI history *time	−0.001 (−0.007, 0.005)	0.71	−0.002 (−0.008, 0.004)	0.56

TBI: Traumatic Brain Injury

Model 1 adjusted for age, gender, race and education. Model 2 was additionally adjusted for veteran status, marital status, depressive symptoms, ever have hypertension, diabetes, cancer, heart disease, stroke, lung disease, arthritis, and ever smoking.

*Using Linear Mixed Models.

Alzheimers Dement. Author manuscript; available in PMC 2021 March 17.