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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 (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 OR=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

Traumatic Brain Injury; Dementia; Alzheimer's Disease; Twin Studies

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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 which 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 is often collected decades after exposure and thus is 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, which 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.

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.

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 from 1917–1927. As part of the study, surviving and consenting individuals were administered a cognitive status measure every 3–4 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

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complete twin pairs (6420 individuals) where 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, 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 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.

Head injury: Information about TBI was collected by trained interviewers during telephone interviews at either Wave 3 (1996–1998) or Wave 4 (2000–2001) for all nondemented 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 a) history of occurrence of TBI severe enough to require medical attention or cause loss of consciousness (LOC), b) presence and duration of LOC, c) number of TBIs and d) 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 4 groups: never smoked, smoked in the past but quit, current smoker, and missing. Alcohol overuse was defined as 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 3 groups: Alcohol overuse present, alcohol overuse absent or missing.

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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 DSM-III- R 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 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 one 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

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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 vs 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 all 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 cotwin-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 cotwin-control analyses is provided by the lack of a significant difference in the association between TBI and dementia in MZ and DZ pairs. The cotwin-control analysis combined both 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 ANOVAs 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 onsamplefreq power, employing 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 cotwin control group in Table 2. TBIs were more common among those who later developed

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dementia (38.5%) compared to those who did not have dementia (24.1%) (p<0.001). 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<0.001). For those with both TBI and dementia, participants incurred their first TBIs an average of 39.02 (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 (HR=2.00; 95% CI=0.97–4.12; p=0.06) compared to those with AD (HR=1.23; 95% CI=0.76–2.00; p=0.39) (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=0.05) (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=0.07). However, the interaction for zygosity and TBI only approached significance for AD (p=0.08), 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 signifcantly 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=0.52) 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 Odds ratio (OR) = 1.56; 95% CI=1.03–2.40; p=0.04; Figure 1). 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=0.61).

When the cotwin 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=0.07) and for AD (McNemar OR=1.60; 95% CI=0.68–3.94; p=0.33), but decreased for non-AD dementia (OR=2.17; 95% CI=0.77–6.95; p=0.17), albeit none of the results reached statistical significance.

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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 cotwin-control sample. However, since 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. Due to the limited number of twins with APOE genotype, we were not able to examine if 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 confirmation 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, Aβ42, 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 life-time history of TBI with the less severe TBI's 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

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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 out the impact of each on the association between TBI and dementia. It is also noted that although cotwin control analyses have more statistical power than non-twin samples of comparable size, the power for some of analyses was limited as evidenced by the relatively wide confidence intervals 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 life span 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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Research in Context

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.

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.

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.

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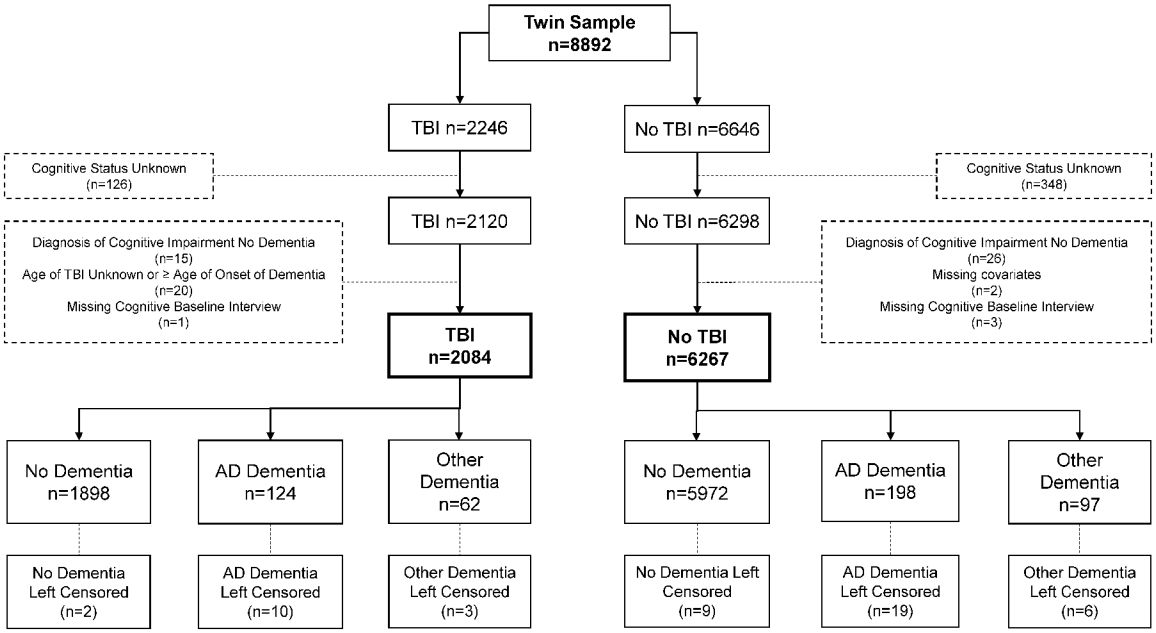

Figure 1.
Flowchart of study population.

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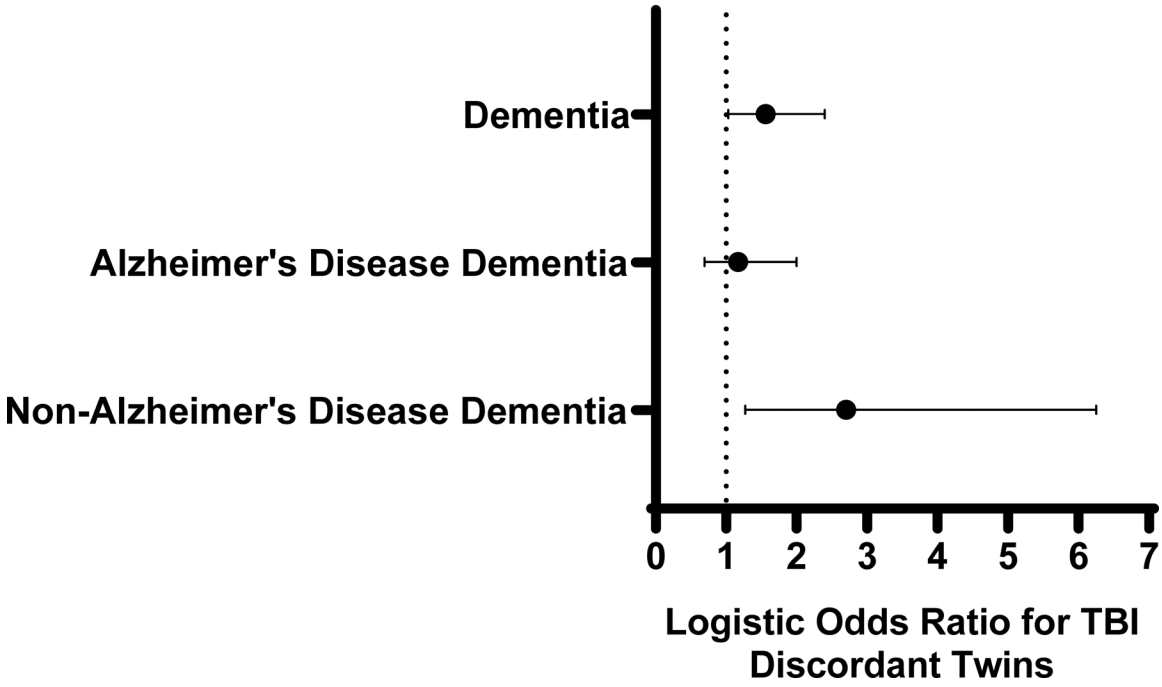

Figure 2.
Logistic odds ratios for TBI and all-cause dementia, Alzheimer's disease dementia, and non-Alzheimer's disease dementia in twin pairs discordant for both TBI and dementia. Bars represent 95% confidence intervals.

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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* n= 322 (3.86%)	Non-Alzheimer's Disease Dementia† n=159 (1.90%)	p-value No Dementia vs 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)	<0.001
MZ Twins‡	66.8 (3.0)					
DZ Twins	66.9 (3.0)					
Age of onset or censoring age§ Mean (SD)	75.2 (4.1)	75.3 (3.9)	73.9 (5.8)	73.9 (6.0)	73. 9 (5.5)	<0.001
MZ Twins	75.5 (4.0)					
DZ Twins	75.1 (4.1)					
TBI = Yes N (%)	2084 (23.0)	1898 (24.1)	186 (38.7)	124 (38.5)	62 (39.0)	<0.001
MZ Twins¶	994 (25.8)					
DZ Twins	985 (24.6)					
TBI with LOC# = Yes						
N (%)	1455 (17.8)	1314 (17.0)	141 (29.3)	94 (31.0)	47 (30.7)	<0.001
Age of first TBI						
N**	2041	1857	184	122	62	
Mean (SD)	32.6 (23.1)	32.4 (23.1)	35.0 (22.4)	34.0 (22.4)	36.9 (22.3)	0.142
Number of TBI						
N (%)	1648	1518	130			
One	(19.9)	(81.5)	(75.1)	87 (75.0)	43 (75.4)	<0.001
More than one	388 (4.7)	345 (18.5)	43 (24.8)	29 (25.0)	14 (24.5)	
Education						
Mean years (SD)	13.2 (3.2)	13.2 (3.2)	13.1 (3.3)	13.1 (3.2)	13.0 (3.5)	0.207

TBI= traumatic brain injury; LOC= loss of consciousness.

*63 of those with an Alzheimer's disease diagnosis had a neuropathologically confirmed diagnosis.

†Among the non-AD dementias, 64 had vascular dementia, 58 had dementia of unknown etiology, 36 had fronto-temporal dementia, Lewy body dementia, or a range of other types of dementia. Twenty four of those with non-Alzheimer's disease diagnosis had a neuropathologically confirmed diagnosis. Among the the entire group of non-Alzheimer's disease dementias, 64 had vascular dementia, 58 had dementia of unknown etiology, 11 had fronto-temporal dementia, 11 Parkinson's disease dementia, 8 had Lewy body dementia, and the remaining 7 had a range of other types of dementia.

‡MZs = monozygotic. DZs = dizygotics. 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=0.07).

§Age of onset for those with dementia. For those without dementia, censoring age was age at death, one year after last contact by study, or age lost to follow-up. MZs and DZs differed significantly on this variable (p<0.05).

¶MZs and DZs did not differ on the proportion with a history of TBI (p=0.23).

#Information on LOC was unknown for 145 with no dementia and 25 with dementia.

**Information for age of first TBI was unknown for 43 men.

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Table 2.

Sample characteristics for cotwin control sample

	Demented First N=100	Not Demented or Demented Last N=100	P-Value
Age of Onset or censoring age *			
Mean (SD)	71.01 (6.78)	77.85 (5.09)	<.001
Number with TBI			
N (%)	55 (55)	42 (42)	0.07
Age of first TBI			
Mean (SD)	36.47 (21.08)	40.0 (23.64)	0.44
Number with LOC			
n (%) †	37 (37)	31 (31)	0.13
Education			
Mean years (SD)	13.34 (3.33)	12.77 (3.58)	0.25

TBI= traumatic brain injury; LOC= loss of consciousness

*Age of onset for those with dementia. For those without dementia, censoring age was age at death, one year after last contact by study, or age lost to follow-up.

†LOC was unknown for 11 of those with Dementia First and 5 who were Not Demented or Demented Last

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Table 3.

Hazard ratios for TBI and risk of dementia in full sample

	All Dementia Hazard Ratio (95% CI), p-value	Alzheimer's Disease Hazard Ratio (95% CI), p-value	Non-Alzheimer's Disease Dementia Hazard Ratio (95% CI), p-value
TBI = yes*	1.44 (0.97–2.14), p=0.07	1.23 (0.76–2.00), p=0.39	2.00 (0.97–4.12), p=0.06
Monozygotic Twins† n=1618 pairs	TBI 1.71 (1.00–2.94), p=0.05	TBI 1.85 (0.94–3.63), p=0.08	TBI 1.50 (0.61–3.67), p=0.37
Dizygotic Twins n=1592 pairs	TBI 1.15 (0.63–2.09), p=0.21	TBI 0.77 (0.37–1.57), p=0.47	TBI 3.33 (0.92–12.11), p=0.07
Age of TBI < 25 years old	TBI 1.31 (0.81–2.12), p=0.28 TBI < 25 years old 1.23 (0.68–2.22), p=0.49	TBI 1.20 (0.68–2.12), p=0.54 TBI < 25 years old 1.07 (0.52–2.01), p=0.86	TBI 1.60 (0.65–3.95), p=0.31 TBI < 25 years old 1.53 (0.53–4.36), p=0.43
Time since TBI (per 10 years)	TBI 1.40 (0.73–2.68), p=0.31 Time since TBI 1.07 (0.88–1.15), p=0.92	TBI 1.40 (0.65–3.02), p=0.39 Time since TBI 0.97 (0.82–1.14), p=0.68	TBI 1.52 (0.45–5.15), p=0.50 Time since TBI 1.07 (0.85–1.34), p=0.59
TBI with LOC	TBI 2.31 (0.98–5.46), p=0.06 TBI with LOC 0.55 (0.23–1.32), p=0.18	TBI 2.48 (0.76–8.10), p=0.13 TBI with LOC 0.40 (0.12–1.32), p=0.13	TBI 2.20 (0.62–7.85), p=0.22 TBI with LOC 1.00 (0.25–3.95), p=1.00
Number of TBIs	TBI 1.39 (0.91–2.14), p=0.14 >1 TBI 1.07 (0.77–1.49), p=0.68	TBI 1.18 (0.70–1.97), p=0.54 >1 TBI 1.12 (0.74–1.69), p=0.61	TBI 2.03 (0.92–4.50), p=0.08 >1 TBI 0.98 (0.57–1.67), p=0.93

TBI= traumatic brain injury; LOC= loss of consciousness; CI = confidence interval. Some variables do not equal the total number of TBIs due to missing data.

*Analysis excluded 49 individuals who had an event prior to their baseline interview date or their twin's baseline interview date. N=8302

†The number of monozygotic twins and dizygotic twins includes in which both members of the twin pair.

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Table 4.

Covariate models and sensitivity analyses for hazard ratios for TBI and risk of dementia

	All Dementia Hazard Ratio (95% CI), p-value	Alzheimer's Disease Hazard Ratio (95% CI), p-value	Non-Alzheimer's Disease Dementia Hazard Ratio (95% CI), p-value
TBI	1.50 (0.98–2.27) p=0.06	TBI 1.39 (0.83–2.31) p=0.21	TBI 2.13 (0.97–4.68) p=0.06
Years of education	1.01 (0.92–1.10), p=0.92	0.92 (0.80–1.06), p=0.24	1.077 (0.92–1.26), p=0.36
Alcohol overuse past or present (reference = No)	Overall p= 0.75	Overall p=0.99	Overall p=0.14
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=0.25	Overall p=0.48	Overall p=0.22
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 *	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=0.03	1.22 (0.79–1.88) p=0.38	2.23 (1.16–4.29) p=0.02

* The HR for Missing for Smoking applies to both smoking and alcohol overuse because individuals missing smoking were also missing alcohol overuse.