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Brain Injury and Later-Life Cognitive Impairment and Neuropathology: The Honolulu-Asia Aging Study

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Abstract

Background: Findings are inconsistent regarding the role of traumatic head injury in the subsequent development of neurologic outcomes.

Objective: Examine the relationship between head injury and later cognitive impairment.

Methods: A sample of 3,123 Japanese-American men was assessed for history of head injury and evaluated for cognitive impairment using the Cognitive Abilities Screening Instrument (CASI). For a subsample of 676 respondents, neuropathologic results from those with and without head injury were compared.

Results: Although the crude model showed an association between history of head injury and later severe cognitive impairment, the relationship lost significance in the adjusted model (OR = 1.320, CI: 0.90–1.93), regardless of time between injury and impairment. Similar to cognitive impairment, hippocampal sclerosis was observed significantly more in the brains of respondents with a history of head injury in the crude model, but the relationship weakened in the adjusted model (OR = 1.462, CI: 0.68–3.12). After adjustment, decedents with a head injury demonstrated marginally higher brain weight (OR = 1.003, CI: 1.00–1.01).

Conclusion: We did not find a relationship between head injury and subsequent cognitive decline in this cohort. The neuropathology results also displayed no strong association between history of head injury and specific brain lesions and characteristics. These results support other findings in prospective cohorts. However, they could be influenced by the demographic make-up of the sample (male Japanese-Americans) or by the observation that the majority reported only a single head injury.

Keywords

Alzheimer's disease; brain lesions; cognitive dysfunction; dementia; Honolulu-Asia Aging Study; neuropathology; traumatic brain injury

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INTRODUCTION

There is a long-standing question of whether traumatic brain injury (TBI) affects later-life cognitive function. In the early 1900 s, a condition called *dementia pugilistica* was used to describe progressive neurodegeneration in boxers resulting in a 'punch drunk' state [1]. More recently, a condition observed among athletes with repeat head injuries has been termed chronic traumatic encephalopathy (CTE) and has been shown to be associated with a variety of neurologic outcomes [2, 3]. Although the recognition of CTE has renewed interest in the association between head injury and neurologic outcomes, researchers have been addressing this question for decades, with mixed results. Even the findings from several meta-analyses have not been entirely consistent, as Table 1 summarizes.

The pathological mechanism by which a TBI may increase the risk for cognitive decline has not been established. Evidence suggests TBIs increase the accumulation of multiple abnormal proteins commonly associated with neurodegeneration, include tau, amyloid-β, α-synuclein, and tar DNA binding protein-43 [4, 5]. TBIs may also cause substantial metabolic disturbances resulting in excitotoxicity, neuroinflammation, and oxidative stress [5, 6]. Some researchers suggest TBIs can trigger cerebrovascular pathology, predisposing individuals to neurodegenerative diseases [7, 8]. Others suggest the neuropathologic changes resulting from TBI may represent a distinct disease process rather than the initiation of development of a specific condition, such as Alzheimer's disease (AD) [9-14].

With the current study, we examined the relationship between traumatic head injury and subsequent cognitive function in the Honolulu-Asia Aging Study (HAAS), a population-based prospective cohort of Japanese-American men living in Hawaii stemming from the Honolulu Heart Program (HHP) [15]. Additionally, brain autopsies conducted on a subset of the sample allowed for the comparison of neuropathologic changes in individuals with a history of head trauma. In the HAAS, head injury data were self-reported and cognitive impairment was measured using the Cognitive Abilities Screening Instrument (CASI) [16]. The pathology data were obtained from a thorough assessment of brain tissue by clinical neuropathologists. Given the combination of cognitive and neuropathologic outcomes in a well-defined cohort, our results add uniquely to an expanding collection of research to understand the possible effects of head injury on subsequent neurologic outcomes.

METHODS

Study population

At the fourth exam (1991–1993), a subset of the cohort with no dementia was identified. Those who agreed to participate were placed in the HAAS, which was designed to study cognitive function and diseases of aging [17]. This group of 3,734 men, representing almost 80% of the surviving HHP cohort, was examined approximately every two to three years through 2012. The average length of follow-up was 10.6 years. In addition to self-reported information on general health status, respondents were assessed for cognitive function with the CASI at each follow-up exam. Excluding respondents with missing data for head injury, the final sample for the TBI analysis was 3,123 participants. A subset of respondents agreed to a brain autopsy upon death, allowing for neuropathology assessment of 676 participants.

Definition of cognitive impairment

The CASI is a comprehensive screening instrument specifically designed for the cross-cultural assessment of cognitive impairment and dementia [16]. It combines measures of attention, concentration, orientation, memory, language, visual construction, abstraction, and judgement to create a composite score ranging from 1 to 100. It includes items identical or similar to ones used in three validated cognitive assessments: the Hasegawa Dementia Screening Scale (HDSS), the Mini-Mental State Examination (MMSE), and the Modified Mini-Mental State (3MS). As such, estimated scores for the HDSS, MMSE, and 3MS can be calculated from the CASI. They are only estimates because some items had to be modified to allow for larger cross-cultural reach.

For this analysis, a CASI score of less than 60 was used to indicate severe cognitive impairment, while a score from 60 to 74 was considered to reflect mild to moderate impairment, and a score of 74 or greater indicated negligible or no cognitive impairment. The HAAS sample was restricted to respondents whose baseline (HHP exam 4) CASI score was 60 or greater. During subsequent exams, if a respondent's CASI score fell below 74 they underwent additional evaluation including a neurological exam, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Neuropsychological Assessment Battery, the Behavior Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), and Clinical Dementia Rating (CDR). More than 90% of the included participants had died before the final examination cycle. The last recorded CASI score available for each respondent was used to determine the presence (n = 515) or absence (n = 2,608) of severe cognitive impairment. For the majority of respondents, once their CASI score fell below 60, it did not rebound. Of the 538 respondents who ever had a CASI score less than 60,217 (40.3%) had additional CASI scores recorded after dipping below this threshold. Of these, 183 (84.3%) stayed below 60, while 34 (15.7%) had at least one subsequent CASI score at or above 60.

Definition of traumatic brain injury

Head injury data were obtained by self-report at baseline (HHP exam 4) of any head injuries 'severe enough to have lost consciousness.' Additionally, respondents were asked about 'serious head injuries with more than a momentary loss of consciousness' at exams 8 through 12 (2002–2012). Respondents who reported a head injury at exam 4 or exams 8–12 were coded as having a history of TBI (n = 216). Only 6% of these respondents had more than one TBI and none had more than 3. As such, we included these respondents with those reporting a single injury. Those who had no head injury at exam 4 and reported no follow-up injuries were coded as negative for TBI (n = 2,907). The respondents were asked about when the injury occurred. This information was used in addition to the date of the respondent's last CASI test to estimate the age of the injury at final CASI assessment.

Neuropathologic assessment

Details on the neuropathologic assessment have been published previously [15]. Briefly, brain tissue was examined for the presence of AD lesions using Braak staging [18] and Lewy bodies using the McKeith score [19]. Microvascular lesions and lacunar infarcts were counted from multiple areas of the brain and the presence of unilateral or bilateral hippocampal sclerosis was noted. Counts of neuritic and diffuse plaques were performed and

the presence of evidence of trauma or subdural hematoma was observed. Brain weight was obtained prior to dissection. A combined index was calculated using the measures for AD lesions, Lewy bodies, microvascular lesions, hippocampal sclerosis, and brain weight. The index had a range from 0 (no pathology) to 5 (moderate to severe presence of all five characteristics).

Covariates

Covariates were calculated using a range of demographic and health data obtained at baseline (HHP exam 4). Health status measures included presence or absence of diabetes, hypertension, hearing impairment, and a history of depression. Stroke history was monitored until the final CASI. Lifestyle measures included smoking and drinking status (ever versus never) at baseline as well as educational attainment in years. Additional risk factors included apolipoprotein ε4 allele positivity (*APOE* ε4) and family history of AD. Military status was also examined, using a sample limited to respondents born in 1910 or later as the majority of military service in this cohort was during World War II. Age at death, follow-up time, and CASI score at baseline were also used.

Statistical analyses

Pearson's chi-square and *t* tests (Pooled or Satterthwaite) were used to examine bivariate differences between respondents with and without a history of TBI. Multivariate logistic regression was used to compare respondents with and without severe cognitive impairment at their final CASI test. To account for variable follow-up times, the number of days between baseline and final CASI was controlled for in the analysis. Cox Proportional Hazard regression models using follow-up time were also run, but the main results did not change. As such, the results reported here are from logistic regression models for ease of interpretation. Multivariate regression analyses were also adjusted for age at baseline, CASI score at baseline, educational attainment, *APOE* ε4 status, and history of stroke. For the neuropathology analyses, multivariate logistic regression models controlled for age at death, final CASI score, and time between final CASI and death. An alpha value of 0.05 was used for all analyses. All analyses were conducted using SAS 9.4 statistical package (Cary, NC).

RESULTS

Table 2 shows the results of the comparison of respondents with and without a history of TBI. The two groups showed significant differences between their final CASI score ($p = 0.0110$), CASI score at baseline ($p < 0.0001$), and follow-up time ($p < 0.0001$). Multivariate logistic analyses showed that, after controlling for CASI score at baseline and follow-up time, respondents with a history of TBI were no more likely to have a final CASI score below 60 than those without a TBI (OR = 1.422, CI: 0.99–2.05; data not shown).

Table 3 displays the differences between respondents with and without severe cognitive impairment (CASI score <60) at the final CASI assessment. Crude estimates and those controlling for CASI score at baseline, follow-up time, age at baseline, education, *APOE* ε4 status, and history of stroke are shown. Although a history of hearing problems at baseline was marginally associated with cognitive impairment (OR = 1.277, CI: 1.02–1.60, $p =$

0.0306), it was not included in the adjusted model because the relationship lost significance when controlling for the other covariates. In the crude model, having a history of TBI increased the risk for severe cognitive impairment by more than 50% (OR = 1.537, CI: 1.10–2.15, $p = 0.0115$). However, the relationship did not retain significance after adjusting for relevant covariates (OR = 1.320, CI: 0.90–1.93, $p = 0.1534$). No association was observed when limiting the sample to old injuries (5+ years before the final CASI) or new injuries (<5 years from the final CASI; data not shown). The same results were obtained when respondents who were lost to follow-up during the study were excluded (data not shown).

Looking at the subsample of respondents with a history of TBI, those with severe cognitive impairment at the final assessment were significantly older at the time of their first injury (71.7 years versus 60.5 years; Table 3). Although the magnitude of effect was not large, it remained marginally significant after controlling for covariates (OR = 1.017, CI: 1.00–1.04).

Table 4 displays the neuropathology results for those with and without a history of TBI. Crude estimates and those controlling for age at death, final CASI score, and time between final CASI and death are shown. In the crude model, respondents with a history of TBI were almost 130% more likely to show hippocampal sclerosis (OR = 2.298, CI: 1.17–4.50, $p = 0.0152$). However, the relationship weakened after controlling for covariates (OR = 1.462, CI: 0.68–3.12, $p = 0.3266$). Conversely, brain weight showed no difference in the crude model, but displayed marginal significance in the adjusted model (OR = 1.003, CI: 1.00–1.01, $p = 0.0174$). In this sample, respondents with a history of TBI had slightly heavier brains at death than those without. Results excluding respondents who were lost to follow-up were the same (data not shown).

DISCUSSION

The results from this study suggest no significant association between history of TBI and development of severe cognitive impairment or neuropathologic changes. Although a small, but statistically significant association with TBI was observed in the crude model, this relationship did not hold once the model was adjusted for relevant covariates. The results did not change when examining old or new injuries (5+ years and <5 years from final CASI, respectively) or when respondents lost to follow-up were excluded. Among respondents who reported a TBI, those with severe cognitive impairment were older at the time of injury than those who did not develop impairment. This calls into question the possibility of reverse causality. That is, people in the early stages of cognitive impairment may be more likely to fall and incur a brain injury. Previous studies have shown that a diagnosis of dementia increases the chances of one or more falls [20]. However, there was a greater number of recent injuries (<5 years before final CASI) among those without severe cognitive impairment than those with, suggesting reverse causation is not playing a role.

The current findings support the results of several studies looking at TBI and cognitive impairment using large, prospective cohorts. Crane et al. [11] found no association between TBI with loss of consciousness (LOC) and incident dementia in three large cohorts: Adult Changes in Thought (ACT), Religious Orders Study (ROS), and Memory and Aging Project (MAP). Dams-O'Connor et al. [12] also found no relationship between TBI with LOC and

dementia or AD in the ACT cohort. No association was found in the Rotterdam Study [21] or in the Canadian Study of Health and Ageing (CSHA) [22]. Within the National Alzheimer's Coordinated Center (NACC) Uniform Data Set, there are conflicting results about the importance of TBI in subsequent cognitive decline or dementia [14, 23-25]. However, several studies using the NACC consistently found a relationship between earlier onset of cognitive decline and history of TBI [23, 26, 27].

Some studies have examined age at head injury as a factor for subsequent cognitive impairment. Gardner et al. [28] found the association between TBI and risk of dementia was stronger among older adults. In our sample, among respondents with a history of TBI, those with severe cognitive impairment at their final CASI assessment were significantly older at the time of their first injury. This may reflect increased vulnerability to TBI with age as a consequence of age-related decline in resilience or increase in frailty. Alternatively, it could be a result of older respondents in the early stages of dementia being more likely to fall.

Our neuropathology results partially align with the findings from three large prospective cohorts in which an increase in Lewy bodies and microinfarcts was observed among individuals with a history of TBI, but no difference was seen in neuritic plaques or neurofibrillary tangles [11]. Other studies have also shown no difference in AD pathology between people with and without a history of TBI [27, 29], while some have found an increase in amyloid beta precursor protein or amyloid plaques [13, 30]. Although neuronal loss from the hippocampus has been demonstrated as a result of TBI [31, 32], other studies have found no difference in hippocampal volume [10]. We observed more hippocampal sclerosis in respondents with a history of TBI, but the relationship was lost after adjusting for covariates. The pathology of TBI is complex and dependent on a number of variables, including age at injury, severity of injury, and time to death. Variations in these and other variables may explain the inconsistent neuropathological results observed across studies.

Although our study results suggest no association between TBI and cognitive impairment or neuropathology, it is possible the absence of correlation is an artifact of the demographic make-up of the cohort (Japanese-American men). However, Kondo et al. [33] found an association among their cohort of elderly Japanese. Alternatively, the results may be influenced by the fact the majority of our respondents reported only a single head injury. Although evidence exists that even a single injury can increase the risk of dementia and cause neurodegenerative pathology [34], the risk may be negligible until multiple injuries have occurred.

One issue in this body of research that is often cited as part of the explanation for the inconsistent results is the lack of a standardized definition for TBI and the use of varied criteria for diagnosis of neurodegenerative disease [12, 35]. Beyond the lack of standardized definition, injury data are obtained from different data sources across the studies. Self-reported head injury data may suffer from recall bias, but may also capture more mild events. Hospital data are generally accurate, but exclude those who did not seek medical treatment as a result of their injury. Additionally, there is no agreed upon scale for injury severity, though many researchers used length of time spent unconscious as a metric. There is evidence to suggest that increased frequency or severity of the injury may increase the risk

of dementia [36]. Only 6% of our cohort reported more than one head injury and severity in terms of time of LOC was only collected at baseline. At subsequent exams, respondents were asked if they had a head injury with more than momentary loss of consciousness. As such, we were not able to make comparisons based on the severity or frequency of injury.

It is interesting to note our results demonstrate no association between a history of TBI and service in the military. There is much concern about the effects of combat on the future health of service members and several studies have found an increased risk for neurodegenerative diseases among veterans with a history of TBI [36-42]. The cohort for this study may be slightly different in regard to their military experience. The vast majority of the veterans in the group served during World War II and may have been exposed to qualitatively different injury risks than those serving in more recent combat.

As with other research of similar design, there are limitations to be considered when interpreting the results of this study. Any information collected via self-report is subject to recall bias that may affect the accuracy of the results. The longitudinal study design allowed for the collection of injury data prior to onset of cognitive impairment, which should reduce this bias. However, we still relied on the respondent's memory, the accuracy of which may vary depending on cognitive function. To measure cognitive impairment, we used the CASI screening instrument, which has been validated as an effective tool for measuring cognitive impairment and progression of dementing disorders across cultures [16]. However, it has limitations in its use as a proxy for determining the presence of dementia. Ideally, multiple metrics should be used in this determination.

As a result of data collection methodology, the study was also limited in what could be examined. In the sample, only 6% of respondents reported multiple head injuries, and data on injury-related amnesia LOC were only collected at baseline. As such, we were unable to test for differences by injury frequency or severity. Given the composition of the cohort, we were also unable to examine the relationship by gender or race. The sample definition also brings generalizability of the results into question, given the cohort consists only of men with Japanese ancestry. However, previous studies using the HAAS data have shown similar findings as other cohorts, including the Nun Study, the ROS, and the MAP [17, 43, 44].

The current study has many strengths, including the longitudinal study design, large cohort size, and high participation rates. Data were collected prospectively, reducing bias, and there was a long follow-up period for monitoring cognitive function, up to 21 years. With exams every two to three years, the HAAS obtained considerable data on the changing health and behavior of the cohort as it aged. The availability of autopsy data for a subset of the sample allowed for neuropathologic assessment, another strength of the study.

Conclusion

In this prospective cohort, there was no association between a history of TBI and subsequent severe cognitive impairment. This is in accordance with studies looking at other prospective cohorts [11, 12, 21, 22]. Additionally, we found no strong neuropathologic differences with a history of TBI. However, the results However could be influenced by the demographic

make-up of the sample or by the observation that the majority of respondents reported only a single head injury.

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Table 1

Summary of results from five meta-analyses examining brain injury and neurologic outcomes

Meta-analysis	# of studies*	Pooled results	
Mortimer et al. [45]	8	RR for head trauma and AD	**1.82 (1.26–2.67)**
	8	• Among men	**2.67 (1.64–4.41)**
	7	• Among women	0.85 (0.43–1.70)
	5	• TBI ≤10 years before dementia onset	**5.33 (1.55–18.3)**
	5	• TBI >10 years before dementia onset	**1.63 (1.04–2.57)**
	5	• Age of AD onset <70 years	**1.95 (1.12–3.48)**
	5	• Age of AD onset 70+ years	**1.81 (1.03–3.25)**
Launer et al. [46]	4	RR for head trauma and dementia	1.14 (0.74–1.56)
	4	RR for head trauma and AD	1.02 (0.68–1.51)
	4	• Among men	1.66 (0.94–2.95)
Fleminger et al. [47]	15	OR for head injury and AD	**1.58 (1.21–2.06)**
	8	• Among men	**2.29 (1.47–3.58)**
	7	• Among women	0.91 (0.56–1.47)
	7	• Studies conducted after 1991	1.35 (0.94–1.94)
Perry et al. [48]	7	OR for TBI and dementia	1.36 (0.84–2.19)
	19	OR for TBI and AD	**1.40 (1.02–1.90)**
	15	OR for TBI and PD	**1.45 (1.18–1.78)**
	2	OR for TBI and MCI	**2.69 (1.51–4.77)**
Li et al. [49]	11	RR for head injury and dementia	**1.63 (1.34–1.99)**
	5	• Among men	**1.81 (1.38–2.38)**
	1	• Among women	1.30 (0.60–2.81)
	28	RR for head injury and AD	**1.51 (1.26–1.80)**
	11	• Among men	**1.70 (1.35–2.13)**
	5	• Among women	1.17 (0.89–1.53)
	2	RR for head injury with LOC and dementia	0.92 (0.67–1.27)
	8	RR for head injury with LOC and AD	1.49 (0.91–2.43)

AD, Alzheimer's disease; LOC, loss of consciousness; MCI, mild cognitive impairment; OR, odds ratios; PD, Parkinson's disease; RR, relative risk; TBI, traumatic brain injury. NOTE: Bolding identifies significant results.

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* Length of follow-up ranged from 0 to 43 years across all studies.

Table 2

Comparison of characteristics among respondents with and without a history of head injury

Parameter	TBI+ (*n* = 216) % (#), Mean (SD)	TBI−(*n* = 2907)	*p**	OR (95% CI)‡
Final CASI score <60	**22.7% (49)**	**16.0% (466)**	**0.0110**	**1.537 (1.10–2.15)**
CASI score at baseline	**88.1 (6.9)**	**86.0 (8.2)**	**<0.0001**	**1.038 (1.02–1.06)**
Follow-up time (y)	**10.6 (6.3)**	**8.0 (6.0)**	**<0.0001**	**01.073 (1.05–1.10)**
Age at baseline (y)	77.2 (4.1)	77.7 (4.3)	0.0779	0.970 (0.94–1.00)
Education (y)	11.1 (3.4)	10.7 (3.1)	0.0862	1.042 (1.00–1.09)
*APOE ε*4 positive	23.0% (49)	18.3% (523)	0.0903	1.333 (0.96–1.86)
Parent(s) with AD	8.7% (17)	6.3% (165)	0.1935	1.411 (0.84–2.38)
Relative with AD	9.1% (19)	7.8% (219)	0.5193	1.175 (0.72–1.92)
Ever had depression	2.3% (5)	1.0% (28)	0.0604	2.442 (0.93–6.39)
Ever had hearing problem	25.8% (55)	20.9% (606)	0.0929	1.304 (0.96–1.81)
Ever had a stroke	18.5% (40)	17.5% (507)	0.6944	1.074 (0.75–1.53)
Hypertension at baseline	18.5% (40)	18.0% (524)	0.8594	1.033 (0.72–1.48)
Diabetes at baseline	15.0% (32)	17.4% (501)	0.3590	0.834 (0.57–1.23)
Ever smoked at baseline	59.8% (128)	62.8% (1824)	0.3854	0.882 (0.66–1.17)
Ever drank at baseline	62.7% (133)	58.8% (1704)	0.2654	1.178 (0.88–1.57)
Served in military§	31.1% (61)	30.0% (736)	0.7343	1.056 (0.77–1.45)

AD, Alzheimer's disease; APOE e4, apolipoprotein allele e4; CASI, Cognitive Abilities Screening Instrument; SD, standard deviation; TBI, traumatic brain injury. NOTE: Dichotomous measures are shown as percentage and sample size while continuous measures are displayed as mean and standard deviation (SD). Bolding identifies significant results.

* *p* value for Pearson chi-square or Satterthwaite *t* value.

‡ Odds ratio (OR) and 95% confidence interval (95% CI) for parameter.

§ Limited to respondents born in 1910 or after.

Table 3

Comparison of characteristics among respondents with and without severe cognitive impairment (final CASI <60) at their final CASI assessment

Parameter	SCI+(*n* = 515) % (#), Mean (SD)	SCI−(*n* = 2608) % (#), Mean (SD)	*p**	Unadjusted OR (95% CI)‡	Adjusted† OR (95% CI)‡
History of TBI	**9.5% (49)**	**6.4% (167)**	**0.0115**	**1.537 (1.10–2.15)**	1.320 (0.90–1.93)
CASI score at baseline	**82.1 (8.7)**	**86.9 (7.7)**	**<0.0001**	**0.935 (0.93–0.95)**	**0.908 (0.89–0.92)**
Follow-up time (y)	**11.7 (5.0)**	**7.5 (6.0)**	**<0.0001**	**1.126 (1.11–1.15)**	**1.217 (1.19–1.25)**
Age at baseline (y)	**78.5 (4.5)**	**77.6 (4.2)**	**<0.0001**	**1.049 (1.03–1.07)**	**1.105 (1.08–1.14)**
Education (y)	**9.9 (3.1)**	**10.9 (3.1)**	**<0.0001**	**0.902 (0.87–0.93)**	0.964 (0.93–1.00)
***APOE ε*4 positive**	**25.3% (129)**	**17.3% (443)**	**<0.0001**	**1.616 (1.29–2.02)**	**1.778 (1.38–2.30)**
Ever had a stroke	**26.6% (137)**	**15.8% (410)**	**<0.0001**	**1.939 (1.55–2.42)**	**2.008 (1.56–2.59)**
Ever had hearing problem	**24.9% (127)**	**20.6% (534)**	**0.0306**	**1.277 (1.02–1.60)**	1.198 (0.93–1.54)
Parent(s) with AD	7.1% (31)	6.4% (151)	0.5931	1.115 (075–1.67)	1.091 (0.69–1.73)
Relative with AD	8.4% (42)	7.8% (196)	0.6336	1.088 (0.77–1.54)	1.001 (0.67–1.49)
Ever had depression	1.4% (7)	1.0% (26)	0.4545	1.377 (0.59–3.19)	1.749 (0.62–4.97)
Hypertension at baseline	18.1% (93)	18.1% (471)	0.9934	0.999 (0.78–1.23)	0.895 (0.68–1.18)
Diabetes at baseline	16.3% (83)	17.4% (450)	0.5284	0.921 (0.71–1.19)	1.237 (0.93–1.65)
Ever smoked at baseline	59.0% (302)	63.3% (1650)	0.0656	0.834 (0.69–1.01)	1.052 (0.84–1.31)
Ever drank at baseline	56.1% (286)	59.7% (1551)	0.1283	0.862 (0.71–1.04)	0.958 (0.77–1.19)
Served in military§	26.7% (111)	30.7% (686)	0.1025	0.822 (0.65–1.04)	1.047 (0.79–1.39)
Among those with a TBI¶	(*n* = 48)	(*n* = 162)			
Age at first TBI (y)	**71.7 (20.1)**	**60.5 (17.0)**	**.0002**	**1.033 (1.02–1.05)**	**1.017 (1.00–1.04)**

AD, Alzheimer's disease; *APOE ε*4, apolipoprotein allele e4; CASI, Cognitive Abilities Screening Instrument; CI, confidence interval; OR, odds ratio; SCI, severe cognitive impairment; SD, standard deviation; TBI, traumatic brain injury. NOTE: Dichotomous measures are shown as percentage and sample size while continuous measures are displayed as mean and standard deviation (SD). Bolding identifies significant results.

* *p* value for Pearson chi-square or Satterthwaite *t* value.

† Adjusted for CASI score at baseline, age at baseline, follow-up time, education, *APOE ε*4 status, and history of stroke.

‡ Odds ratio (OR) and 95% confidence interval (95% CI) for parameter.

§ Limited to those born in 1910 or after.

[¶] Unable to calculate age at TBI for six respondents due to missing data.

Table 4

Neuropathologic characteristics among respondents with and without a history of head injury

Parameter	TBI+(*n* = 51) % (#), Mean (SD)	TBI−(*n* = 625) % (#), Mean (SD)	*p**	Unadjusted OR (95% CI)‡	Adjusted† OR (95% CI)‡
AD lesions	45.1% (23)	40.6% (254)	0.5336	1.200 (0.68–2.13)	1.103 (0.60–2.04)
Lewy bodies	9.8% (5)	12.7% (79)	0.5524	0.750 (0.29–1.94)	0.704 (0.24–2.07)
Microvascular lesions	39.2% (20)	31.9% (199)	0.2827	1.378 (0.77–2.48)	1.395 (0.76–2.57)
Hippocampal sclerosis	**25.5% (13)**	**13.0% (81)**	**0.0129**	**2.298 (1.17–4.50)**	1.462 (0.68–3.12)
Brain weight (grams)	**1224 (100)**	**1213 (123)**	0.5287	1.001 (0.10–1.00)	**1.003 (1.00–1.01)**
Neuritic plaques	68.6% (35)	61.9% (387)	0.3416	1.345 (0.73–2.48)	0.954 (0.50–1.82)
Diffuse plaques	64.7% (33)	62.4% (390)	0.7435	1.105 (0.60–2.00)	0.835 (0.45–1.56)
Trauma§	19.6% (10)	11.7% (73)	0.0972	1.844 (0.89–3.84)	1.923 (0.90–4.11)
Subdural hematoma§	25.5% (13)	15.7% (98)	0.0690	1.840 (0.95–3.58)	1.831 (0.92–3.65)
Combined index	1.05 (0.94)	1.03 (0.83)	0.7566	1.055 (0.75–1.47)	0.765 (0.49–1.19)
Total # of microinfarcts	2.53 (4.0)	2.42 (4.3)	0.8558	1.006 (0.95–1.07)	1.006 (0.94–1.08)
Total # of lacunar infarcts	2.12 (3.9)	1.75 (3.0)	0.5220	1.034 (0.95–1.12)	1.033 (0.95–1.12)
Total # of infarcts	4.65 (5.7)	4.17 (6.0)	0.5863	1.012 (0.97–1.06)	1.013 (0.97–1.06)

AD, Alzheimer's disease; CI, confidence interval; OR, odds ratio; SD, standard deviation; TBI, traumatic brain injury. NOTE: Dichotomous measures are shown as percentage and sample size while continuous measures are displayed as mean and standard deviation (SD). Bolding identifies significant results.

* *p* value for Pearson chi-square or Satterthwaite *t* value.

† Adjusted for age at death, final CASI score, and time between final CASI score and death.

‡ Odds ratio (OR) and 95% confidence interval (95%CI) for parameter estimate.

§ Remote or acute.