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History of Traumatic Brain Injury Interferes with Accurate Diagnosis of Alzheimer's Dementia: A Nation-Wide Case-Control Study

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Abstract

Background: Traumatic brain injury (TBI) and Alzheimer's disease (AD) bear a complex relationship, potentially increasing risk of one another reciprocally. However, recent evidence suggests post-TBI dementia exists as a distinct neurodegenerative syndrome, confounding AD diagnostic accuracy in clinical settings. This investigation sought to evaluate TBI's impact on the accuracy of clinician-diagnosed AD using gold standard neuropathological criteria.

Methods: In this preliminary analysis, data was acquired from the National Alzheimer's Coordinating Center (NACC), which aggregates clinical and neuropathologic information from Alzheimer's Disease Centers across the United States. Modified National Institute on Aging-Reagan criteria were applied to confirm AD by neuropathology.

Results: Among participants with clinician-diagnosed AD, TBI history was associated with misdiagnosis (false positives) (OR = 1.351 (95% CI: 1.091 – 1.674), $p = 0.006$). Among participants without clinician-diagnosed AD, TBI history was not associated with false negatives.

Discussion: TBI moderates AD diagnostic accuracy. Possible AD misdiagnosis can mislead patients, influence treatment decisions, and confound research study designs. Further work examining the influence of TBI on dementia diagnosis is warranted.

Keywords

Traumatic brain injury; Alzheimer's disease; Dementia; Chronic traumatic encephalopathy; Diagnostic accuracy; Neuropathology; Neurodegeneration; Acquired brain injury; Neurology

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INTRODUCTION

There has been growing interest in studying the dynamic relationship between traumatic brain injury (TBI) and Alzheimer's dementia (AD). This mounting attention is congruent with the current epidemiological data for both conditions: both TBI and AD are associated with rapidly growing clinical and economic burden. Global incidence of TBI increased by 3.6% and prevalence by 8.4% between 1990 and 2016.¹ Six million Americans in 2017 had AD or mild cognitive impairment (MCI) due to AD with projections estimating 15 million Americans to be affected by 2060.² Considering economic resources, TBI is associated with a lifetime societal cost of approximately \$76.5 billion.³ In 2014, AD-related expenditures were \$214 billion with AD healthcare expenses consuming as much as 66–75% of family household income for affected people.⁴

The relationship between TBI and dementia has been explored for decades, with case studies dating back to the early 20th century detailing patients who developed dementia within a few years following TBI with loss of consciousness.^{5,6} While a clear causal mechanism for progression from TBI to a delayed dementia syndrome has not yet been established, patients with self-reported TBI show an earlier onset of cognitive decline related to AD, independent of ApoE4 status and gender.^{7,8} An analysis of 2,100 patients with AD neuropathological changes found that those with TBI who suffered loss of consciousness were diagnosed with dementia three years earlier than those without TBI.⁹ A meta-analysis of 32 studies with over two million individuals found that TBI increased the risk of AD by 51%, though TBI without loss of consciousness was not associated with dementia.¹⁰ Taken together, these studies provide compelling evidence that sustaining a TBI may prompt or moderate the trajectory of cognitive decline processes in some individuals.

TBI and the dementias also share pathophysiology on a cellular level. Animal models of TBI display the neuropathology of neurodegenerative diseases including alpha synuclein aggregation (Parkinson's disease), amyloid plaque aggregation (AD), tau protein aggregation (AD and other tauopathies), and neuronal damage to the hippocampus.^{11,12} In addition, chronic traumatic encephalopathy (CTE), a progressive neurodegenerative syndrome associated with repetitive mild TBI, often presents with tau protein aggregation, which acts as a catalyst for neurodegenerative processes and has also been observed in AD.¹³ Additionally, TBI can induce neurovascular injuries which promote "A β production and perivascular accumulation, arterial stiffness, tau hyperphosphorylation and tau/A β -induced blood brain barrier damage".¹⁴ In sum, this TBI-related neuropathological changes are similar to those seen in AD.

Previous authors have cautioned that declines in functional and cognitive domains post-TBI (which may bear notable latency periods prior to onset/clinical detection) bear high risk of being misdiagnosed as AD in the absence of an appropriate, formalized diagnostic label.⁵ Much of the current literature regarding diagnostic accuracy of testing and screening modalities focuses on detection of either TBI or AD in isolation of each other.^{15–17} Studies taking a more integrative approach, that is, evaluating the role of TBI on rates of dementia misdiagnosis, are scarce if not absent from the literature. This topic is challenging to study, as the risk for diagnosis of dementia increases in patients having a TBI history compared to

those without (and vice versa). The current study aims to bridge these gaps by evaluating history of TBI as a potential moderator of AD diagnostic accuracy.

The primary objective of this preliminary study was to evaluate the impact of TBI on accuracy of clinically diagnosed AD. To achieve this, the present investigation bore the following specific objectives: To evaluate (1) Impact of TBI on distributions of false positives, true positives, false negatives and true negatives and to calculate test validity and related metrics (positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity) for both those with history of TBI and those without; (2) Associations between TBI and diagnostic accuracy (confirmed by presence or absence of AD-specific neuropathological findings) among participants with clinician-diagnosed AD (false positives vs. true positives); and (3) Associations between TBI and diagnostic accuracy (confirmed by presence or absence of AD-specific neuropathological findings) among participants without clinician-diagnosed AD (false negatives vs. true negatives).

We hypothesized that history of TBI would be associated with AD misdiagnosis via an increase in false positives but not false negatives. Specifically, we hypothesized: (1) History of TBI would be associated with declining test validity, particularly regarding specificity and PPV; (2) History of TBI would be associated with AD misdiagnosis such that those with clinician-diagnosed AD, without AD-specific neuropathological findings on autopsy, would exhibit elevated rates of TBI; and (3) History of TBI would not be associated with AD misdiagnosis among those without clinician-diagnosed AD (i.e. no differences in TBI between false negative and true negative groups).

METHODS

Participants

We utilized data from the National Alzheimer's Coordinating Center (NACC), which aggregates information from AD Centers (ADCs) across the United States. This study specifically utilized the clinical NACC-Uniform Data Set (NACC-UDS) and the NACC-Neuropathology (NACC-NP) dataset. The NACC-UDS collects data on participants enrolled at ADCs since 2005 and includes participants with a range of cognitive statuses, including normal cognition, MCI, and dementia. Post-mortem NACC-NP data were collected from the program's inception until June 2019.

Subjects join ADCs based on institution-specific protocols, and may enroll due to clinician referral, self-referral, community outreach efforts, and on a volunteer basis for participants with normal cognition. ADCs that collect neuropathology data require participants to agree to autopsy before being accepted for the NACC-UDS data series. Written informed consent was obtained for all participants. The dataset also provides information for demographic variables including age at death, sex, race, and education. Subjects for whom TBI was not assessed, or complete AD clinical and neuropathological data were not collected, were excluded. A CONSORT figure detailing application of inclusion/exclusion criteria and subject grouping for analyses is presented (Figure 1).

Traumatic Brain Injury and Clinician-Diagnosed AD Variables

The NACC-UDS variable NACCTBI (Form A5: Subject Health History) is derived from participant or informant self-report of TBI history. Any number, type, or severity of reported TBI is coded as a “yes”, and absence of TBI as a “no”. Participants whose TBI history was unknown or not available were excluded from this study. In the NACC-UDS, Form D1: Clinician Diagnosis, the variable NACCALZD was used to identify clinical determination of AD. A single clinician or a consensus group review medical history, neurological exam findings, and neuropsychological test results for subjects with cognitive impairment and reach a clinical diagnosis of MCI, AD, or some other dementia.

Gold Standard AD Neuropathology Variables

Despite AD being diagnosed clinically, neuropathological diagnosis at autopsy is considered the definitive gold standard. Various pathological criteria for establishing AD exist, which consider different factors such as the presence of extracellular beta-amyloid protein and neurofibrillary tangles composed of tau proteins.^{18,19} We utilized Section 6 of the NACC-NP dataset which provides a standardized protocol of post-autopsy neuropathological information for patients in the NACC-UDS. We used two AD-specific variables based on the National Institute of Aging (NIA)-Reagan criteria for diagnosis of AD based on consensus postmortem recommendations: Braak stage for neurofibrillary degeneration and density of neocortical neuritic plaque CERAD score.²⁰ The modified NIA-Reagan criteria uses combinations of Braak staging and CERAD score to classify confidence of AD diagnosis into four categories: high confidence, two medium confidence categories, and low confidence. High confidence consists of frequent neuritic plaques and Braak stages of V or VI. One medium confidence category includes moderate or frequent neuritic plaques and Braak stages of V or VI. The other medium confidence category consists of frequent neuritic plaques and Braak stages of III-VI. The low confidence category is made by moderate or frequent neuritic plaques and Braak stages of III-VI. This method has been previously established to be consistent between institutions and was used in a similar study.²¹ We used these modified NIA-Reagan criteria to create a definitive AD gold standard for subjects in this dataset.

Statistical Analysis

Descriptive statistics were used to compare demographic variables between those with and without a history of TBI. Welch’s t-tests were used to evaluate differences within continuous variables and Pearson’s chi-square tests within proportions. We then created a dichotomous AD neuropathological variable which grouped the medium and high confidence categories to represent the presence of AD, and the low confidence category to represent the lack of AD neuropathology. This case-control study evaluated specific objectives using the following statistical tests and approach:

Objective (1): Chi-square test of independence was performed on all participants to measure differences in distributions of false positives, true positives, false negatives and true negatives dependent on history of TBI. PPV, NPV, sensitivity, and specificity were calculated for those with history of TBI and those without.

Objective (2): Only participants with clinician-diagnosed AD were included for analysis. Cases were identified as participants without gold standard AD-specific neuropathology findings (false positives); controls were identified as participants with gold standard AD-specific neuropathology findings (true positives). Chi-square test of independence was performed to assess interaction between TBI and neuropathology-confirmed diagnostic accuracy among participants with clinician-diagnosed AD. Binomial logistic regressions were performed to ascertain odds ratios of exposure (TBI) between groups, adjusted for age at death, sex, and race.

Objective (3): Only participants without clinician-diagnosed AD were included for analysis. Cases were identified as participants with gold standard AD-specific neuropathology findings (false negatives); controls were identified as participants without gold standard AD-specific neuropathology findings (true negatives). Chi-square test of independence was performed to assess interaction between TBI and neuropathology-confirmed diagnostic accuracy among participants without clinician-diagnosed AD. Binomial logistic regressions were performed to ascertain odds ratios of exposure (TBI) between groups, adjusted for age at death, sex, and race.

The significance threshold for all statistical tests was set at $p < 0.05$. Yates' continuity correction was applied to all chi-square testing described above. Statistical testing was conducted using R Version 3.6.0.

RESULTS

Participant Characteristics

Relevant demographic characteristics of all participants (Objective 1) are presented in Table 1. Age at death and sex were associated with history of TBI ($p = 0.016$ and $p < 0.001$, respectively). Participants without TBI history had a mean age of 80.8 years at time of death and were 47.7% female, while participants with history of TBI had a mean age of 79.7 years at death and were 32.6% female (Table 1). Neither racial composition nor years of education were significantly different. For Objective 2 (just participants with clinician-diagnosed AD), those with AD-specific neuropathological findings differed from those without in age at death (80.5 years vs. 86.3 years, $p < 0.001$) and sex (48.2% female vs. 43.5% female, $p = 0.014$). They did not differ significantly in racial composition or years of education (Supplemental Table 1). For Objective 3 (just participants without clinician-diagnosed AD), those with AD-specific neuropathological findings differed from those without in age at death only (79.1 years vs. 77.9 years, $p = 0.025$). They did not differ significantly in sex, race, or years of education (Supplemental Table 2).

TBI and AD Diagnosis Test Validity: Objective (1)

The relationship between TBI and clinician AD diagnosis test validity was evaluated among all participants. Chi-square testing showed the distributions of true positives, false positives, true negatives, and false negatives to differ significantly among those with history of TBI and those without, $\chi^2(3, N = 5,687) = 8.3085$, $p = 0.040$ (Table 2). Regarding clinician AD diagnosis, the following metrics were calculated among those with history of TBI as

compared to those without: Positive predictive value (0.664 vs. 0.723, respectively); Negative predictive value (0.760 vs. 0.783, respectively); Sensitivity (0.821 vs. 0.842, respectively); Specificity (0.577 vs. 0.639, respectively).

TBI and AD Diagnostic Accuracy: Objective (2)

The relationship between TBI and AD diagnostic accuracy (confirmed by presence or absence of gold standard AD-specific neuropathological findings) was evaluated among participants with clinician-diagnosed AD. Chi-square testing demonstrated significant interaction between diagnostic accuracy and TBI history, $\chi^2(1, N = 3,506) = 6.9371, p = 0.008$. Binomial logistic regression showed significantly increased TBI within the false positive group as compared to the true positive group, both in a univariate model and one adjusting for age at death, sex, and race (unadjusted OR = 1.323 (95% CI: 1.078 – 1.623), $p = 0.007$; adj. OR = 1.351 (95% CI: 1.091 – 1.674), $p = 0.006$). These findings are presented in Table 3.

TBI and AD Diagnostic Accuracy: Objective (3)

The relationship between TBI and AD diagnostic accuracy (confirmed by presence or absence of gold standard AD-specific neuropathological findings) was evaluated among participants without clinician-diagnosed AD. Chi-square testing showed that, among those without an AD diagnosis, TBI was not associated with diagnostic accuracy (false negatives as compared to true negatives), $\chi^2(1, N = 2,181) = 0.6652, p = 0.415$. Similarly, binomial regression analysis showed TBI was not associated with any differences in false as opposed to true negatives in either the unadjusted model ($p = 0.373$), or a model adjusted for age at death, sex, and race ($p = 0.420$). Regression results are displayed in Table 4.

DISCUSSION

To our knowledge, this is the first study to present evidence that a patient history of TBI contributes to reduced accuracy of clinically diagnosed AD through an increased risk of false positives. Regarding the primary objective of this investigation, TBI history had a significant impact on distributions of true positives, false positives, true negatives, and false negatives as demonstrated by chi-square testing. As such, clinician diagnoses of AD among participants with a history of TBI displayed poorer metrics of test validity, particularly PPV and specificity (which vary with the proportion of false positives), as hypothesized. Furthermore, the present results indicate that detrimental impacts of TBI on diagnostic accuracy are mediated through an increase in false positive rates but not false negative rates. Specifically, participants with a misdiagnosis of AD (false positive) were 35.1% more likely to belong to the TBI group as compared to those with a correct AD diagnosis (true positives), highlighting a potentially causal role for TBI and its complications in facilitating diagnostic inaccuracy.

A subset of individuals with history of TBI (especially repetitive TBI) are increasingly thought to be at risk for a neurodegenerative condition with substantial, and often progressive, impacts on many domains of memory, cognition, and functioning.^{22,23} This neuropsychiatric dysfunction may present as a constellation of symptoms with the potential

to closely mimic timelines and phenomenology of AD, however, a growing body of literature suggests that post-TBI degenerative changes may represent a distinct clinical syndrome.^{5,24} Compellingly, dementias associated with TBI tend to exhibit earlier age of onset as compared to AD.^{25,26} Regardless of pathology or relationship to TBI, early onset dementia is frequently misdiagnosed, potentially compounding diagnostic challenges associated with TBI.^{25,26} Additionally, one study examining a large proportion of patients with diagnosed AD found that TBI was associated with a threefold greater risk of disinhibition, highlighting the possibility of distinct, behavioral symptomatology.²⁷ Notably, TBI is also understood to affect the course of AD, with TBI-associated pathology hastening decline towards clinically significant AD.²⁸ While further work is required to confirm and fully characterize this phenomenon, caution should be exercised when evaluating etiologies of dementing illness in patients and study participants with history of TBI.

It should be noted that a large body of evidence has highlighted close associations between TBI and AD, with a two-fold increase in AD following TBI.^{10,29} As such, increased diagnoses of AD in the context of dementia may be expected even in the absence of diagnostic inaccuracy. In addition to AD, TBI may be accounting for similarly increased rates of other dementias here as has been noted elsewhere,³⁰ confounding increased risk of AD pathology secondary to TBI. Compounding this, TBI may also be contributing to the unique neurodegenerative syndrome discussed above, presenting another confounding factor and obscuring increases in AD pathology secondary to TBI.

This provides crucial context to the finding that TBI is associated with AD misdiagnosis via elevated false positives but not false negatives. However, although TBI contributes to reduced diagnostic accuracy, it is important to note that correct AD diagnosis represents a substantial challenge for clinicians even without this additional complication. Grappling with similarities in clinical presentation, misdiagnosis rate of AD relative to other dementias is above 20%.¹⁵ Given the significantly elevated rates of TBI among participants who have received misdiagnoses of AD, our findings highlight the importance of further research into a distinct post-TBI dementia syndrome.

Although there are few studies on misdiagnosis of TBI in dementia patients, significant insight can be gained from the misdiagnosis of disorders of mental health in patients with TBI. For instance, regarding PTSD, patients with severe TBI were unable to follow screening tool directions and erroneously endorsed PTSD symptoms with resultant overdiagnosis of PTSD.³¹ As, in the context of dementia and TBI, cognitive difficulties could give rise to similar mistakes, extra precautions are warranted should clinicians utilize self-report measures. Further studies are also needed to better understand the pathology behind these cases of TBI-related dementia that have been misdiagnosed as AD. Before CTE was understood to be a pathologically and clinically distinct syndrome, it was often misdiagnosed as AD. It was only after autopsy studies of the brain that CTE was understood to have pathologic characteristics that were similar to but distinct from AD.³² There is a paucity of research on whether dementia related to a history of incidental TBI is a clinically or pathologically distinct syndrome from other dementias, similar to how CTE is a distinct syndrome. The methodologies of most studies on the topic rely on clinician diagnosis, which based on the results of our study may be inadequate to make the clinical distinction between

AD and TBI-related dementia. For example, one study found that the Clinical Dementia Rating global score has an acceptable interrater reliability for diagnosing dementia in patients with TBI, however, memory, judgment and problem solving, and community affairs domains had less reliability.³³

Additionally, cognitive reserve may impact the relationship between clinical phenotypes and neuropathological findings. Relevantly, in AD, higher levels of amyloid- β ³⁴ and tau³⁵ pathology have been demonstrated to correlate with increased years of formal education in patients with AD with identical symptomatology. Likewise, cognitive reserve may protect against memory decrements associated with the neuropathology of TBI and incident TBI may lead to a decrease in remaining cognitive reserve.³⁶ As such, cognitive reserve may be an important consideration when evaluating the influence of TBI on both clinician diagnosis and neuropathological findings.

It is possible that misdiagnoses may be due to difficulty differentiating the etiology of clinical symptoms like memory, personality, judgement, comport, among others in AD and related conditions. It is also possible that less AD neuropathology needs to develop in TBI patients for clinicians to pick up on the same constellation of symptoms. Regardless of the cause, the incongruence between clinician-assigned AD diagnoses and AD neuropathological findings has global implications. Regarding actual misdiagnosis, even subtle rates of misdiagnoses have a significant impact on clinical trial enrollment as even a 20% misdiagnosis rate, when coupled with a 50% study response rate, would double the subjects necessary to maintain the same statistical power.²¹ From a research standpoint, recruiting individuals for clinical trials who may not truly have AD can compromise the validity of findings. Additionally, the clinical consequences which may accompany post-TBI dementia are not well established, highlighting the possibility that patients may be given inaccurate assessments of prognosis if misdiagnosed with AD. Our results also implicate a clear need for improved clinical measures with greater predictive power and higher specificity towards identifying the associated cause of delayed dementia symptoms in patients with TBI history. The clinician's task of selecting a dementia diagnosis while evaluating nonspecific neuropsychiatric symptoms is difficult and may yield significant subjective error.

Limitations

While the large sample size and depth of neuropathological data available represent substantial strengths of this investigation, certain limitations should be noted when interpreting the present findings and generalizing to other contexts. As discussed previously, this sample is enriched with respect to participants with cognitive impairment and dementing illness and, as such, data related to true and false negatives in particular may vary substantially in comparison to the general population. Furthermore, history of TBI was elicited by self-report in the present sample without the use of an externally-validated TBI screening tool. Thus, it is probable that rates of TBI are underreported here given memory deficits which often accompany TBI and neurodegenerative conditions broadly. Finally, impact of TBI on neuropsychiatric symptoms and subsequent risk of misdiagnosis likely varies with severity of injury. Data on injury severity was not collected and therefore this

important factor could not be adjusted for. Further investigation is required to fully elucidate the impact of TBI on the accuracy of clinically-diagnosed AD.

CONCLUSION

This study provides evidence that TBI is associated with worse clinician diagnostic accuracy of AD as a result of increased false positives but not false negatives. The large sample size of the NACC database utilized here represents an important strength of this study, providing ample power for statistical modeling and allowing for analysis of clinical outcomes and neuropathology with implications for research and clinical practice. Clinical misdiagnoses can have implications on therapeutic approaches, physician interactions with patients, patient expectations of morbidity and mortality, and numerous psychosocial factors that extend beyond the clinic. Researchers and clinicians ought to take TBI diagnostic errors into account when designing projects and analyzing studies. Future research is needed to study patterns of neuropathology in patients misdiagnosed with AD. Additionally, further work is also needed to better characterize TBI neuropathology and how it may interact with, or mimic, AD neuropathology. Ultimately, it is important to link our understanding of neuropathology with our improving clinical discernment of disease processes to bolster diagnostic precision and the therapeutic efficacy of treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

CONSORT figure outlining application of inclusion/exclusion criteria and formation of samples/case-control groups regarding analyses pertinent to Objectives (1), (2), & (3).

Table 1.

Participant characteristics of subjects included for analyses regarding Objective (1), stratified by TBI history.

Characteristic *	No History of TBI (n = 4,910)	History of TBI (n = 777)	Statistic ^	p-Value
Age at Death	80.8 (SD = 11.5)	79.7 (SD = 11.8)	$T = -2.420$ $df = 1024.5$	0.0157
Sex				
Male	2566 (52.3%)	524 (67.4%)	$X^2 = 61.676$ $df = 1$	<0.0001
Female	2344 (47.7%)	253 (32.6%)		
Race				
White	4612 (93.9%)	746 (96.0%)	$X^2 = 9.625$ $df = 6$	0.1414
Black	200 (4.1%)	19 (2.4%)		
Other	98 (2.0%)	12 (1.5%)		
Education				
Years of Education	15.3 (SD = 3.2)	15.5 (SD = 3.1)		
No High School Degree	278 (5.7%)	40 (5.2%)	$T = -1.709$ $df = 1028.4$	0.0877
High School	1800 (37.1%)	269 (35.1%)		
Bachelors	1367 (28.2%)	212 (27.6%)		
Masters	873 (18.0%)	159 (20.7%)		
Doctorate	532 (11.0%)	87 (11.3%)		

* No. (%) unless listed otherwise, age at death is presented as mean in years;

^ Chi-square test reported for proportions and Welch two-sample t-test reported for continuous variables. Bolded p-values denote statistical significance ($p < 0.05$).

Table 2.

Proportions of participants with and without AD-specific findings on neuropathology segregated by history of TBI. Proportions of participants with given diagnostic statuses are presented for both TBI and non-TBI groups.

	History of TBI	No History of TBI
Clinician Diagnosed AD		
AD-Specific Neuropathology Present (True Positive)	322 (41.4%)	2185 (44.5%)
AD-Specific Neuropathology Absent (False Positive)	163 (21.0%)	836 (17.0%)
AD Not Diagnosed (Other Dementia/No Dementia Diagnosed)		
AD-Specific Neuropathology Present (False Negative)	70 (9.0%)	409 (8.3%)
AD-Specific Neuropathology Absent (True Negative)	222 (28.6%)	1480 (30.1%)
Statistic	$X^2 = 8.3085$ $df = 3$	$p = 0.0401$

Table 3.

Binomial logistic regression modeling examining associations between TBI and gold standard, AD-specific neuropathology among participants with clinician-diagnosed AD.

Unadjusted Model	OR (95% CI)	<i>p</i> -Value
TBI	1.323 (1.078 – 1.623)	0.0073
Adjusted Multivariate Model		
TBI	1.351 (1.091 – 1.674)	0.0059
Age at Death	1.065 (1.056 – 1.074)	<0.0001
Sex	0.690 (0.590 – 0.807)	<0.0001
Race	1.006 (0.995 – 1.018)	0.2927

Results of unadjusted, univariate model and multivariate model adjusted for age at death, sex, and race are presented. Bolded *p*-values denote statistical significance ($p < 0.05$).

Table 4.

Binomial logistic regression modeling examining associations between TBI and gold standard, AD-specific neuropathology among participants without clinician-diagnosed AD.

Unadjusted Model	OR (95% CI)	<i>p</i> -Value
TBI	0.876 (0.656 – 1.171)	0.3730
Adjusted Multivariate Model		
TBI	0.887 (0.662 – 1.188)	0.4202
Age at Death	0.991 (0.982 – 0.999)	0.0289
Sex	1.181 (0.957 – 1.456)	0.1209
Race	1.007 (0.991 – 1.023)	0.4121

Results of unadjusted, univariate model and multivariate model adjusted for age at death, sex, and race are presented. Bolded *p*-values denote statistical significance ($p < 0.05$).