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Failure to Detect an Association Between Self-Reported Traumatic Brain Injury and Alzheimer's Disease Neuropathology and Dementia

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Abstract

INTRODUCTION: Recent research with neuropathologic or biomarker evidence of Alzheimer's disease (AD) casts doubt on traumatic brain injury (TBI) as a risk factor for AD. We leveraged the National Alzheimer's Coordinating Center (NACC) to examine the association between self-reported TBI with loss of consciousness (LOC) and AD neuropathologic changes, and with baseline and longitudinal clinical status.

METHODS: The sample included 4761 autopsy participants (453 with remote TBI with LOC; 2822 with AD neuropathologic changes) from NACC.

RESULTS: Self-reported TBI did not predict AD neuropathologic changes ($p>0.10$). Reported TBI was not associated with baseline or change in dementia severity or cognitive function in participants with or without autopsy-confirmed AD.

DISCUSSION: Self-reported TBI with LOC may not be an independent risk factor for clinical or pathological AD. Research that evaluates number and severity of TBIs is needed to clarify the neuropathological links between TBI and dementia documented in other large clinical databases.

Keywords

Alzheimer's disease; Traumatic brain injury; Cognitive decline; Neurodegenerative disease; NACC; concussion

1. BACKGROUND

A history of traumatic brain injury (TBI) has long been viewed as a risk factor for later life dementia disorders, including Alzheimer' disease (AD) dementia[1]. Several studies[2–5] have demonstrated that individuals with a history of TBI, particularly moderate to severe TBI, are at increased risk for dementia due to AD[6]. Population-based studies indeed found that a history of a single TBI (including mild TBI) increased risk of receiving a diagnosis of dementia and this risk was exacerbated for severe TBI and those with a history of repeated TBIs[2,4]. Among U.S. veterans, a history of TBI of any severity more than doubled the risk of dementia[5]. A limitation of these clinical studies and other observational studies on the association between TBI and AD dementia is the lack of evidence of underlying AD neuropathologic changes via *in vivo* biomarkers or neuropathological examination. This is important, as 20–30% of individuals clinically diagnosed with AD will not have AD neuropathologic changes at autopsy and about 40% of individuals with cognitive impairment

not attributed to AD will have AD neuropathologic changes[7]. The use of clinical diagnoses without neuropathological confirmation or biomarker evidence limits causal and mechanistic inferences that can be made regarding TBI and AD or other causes of dementia.

Two small autopsy studies from 2001 that were descriptive in nature showed a potential relationship between “residual closed TBI lesions” and AD neuropathologic changes[8,9]. However, recent research actually casts doubt that TBI may be specifically related to AD pathology. In a pooled dataset of 7130 participants from the Religious Orders Study, the Memory and Aging Project, and the Adult Changes in Thought cohorts[10], TBI history with loss of consciousness (LOC) was not associated with a clinical diagnosis of AD dementia or with AD neuropathologic changes at autopsy. In the pooled analyses, TBI with LOC <1 hour predicted increased risk for frontal or temporal cortical Lewy bodies and TBI with LOC ≥1 hour predicted cerebral microinfarcts. History of TBI with LOC ≥1 hour was associated with incidence of clinical Parkinson’s disease in the ACT cohort. Similarly, in a sample of U.S. veterans, TBI of any severity was also associated with a greater incidence of Parkinson’s disease[11].

Weiner et al.[12] found that within a group of Vietnam-era veterans, a remote history of TBI with LOC >5 minutes and/or alteration of consciousness >24 hours was not associated with increased amyloid positivity using amyloid (florbetapir) positron emission tomography (PET) imaging compared to a control group. TBI history did not predict traditional magnetic resonance imaging (MRI) markers of AD (e.g., hippocampal volume) in this cohort. In a population-based sample, a self-reported history of TBI predicted increased amyloid positivity using Pittsburgh compound B (PiB)-PET imaging among those diagnosed with mild cognitive impairment (MCI), but not among those with normal cognition[13]. In that study, TBI history was not associated with fluorodeoxyglucose-PET or hippocampal volume.

One resource that may be valuable to clarify the equivocal reports on TBI and AD is the National Alzheimer’s Coordinating Center (NACC) Uniform Data Set (UDS) and Neuropathology Data Set (NDS). These large databases compile information from Alzheimer’s Disease Centers (ADCs) across the U.S. and provide the opportunity to examine longitudinal clinical data from individuals with neuropathological confirmation of AD and other pathologies. Two recent NACC-UDS studies showed that self-reported TBI with LOC failed to predict cognitive decline in participants diagnosed with normal cognition or individuals with probable AD dementia[14] and, similarly, self-reported TBI with LOC did not predict conversion from MCI to AD dementia or changes in dementia severity over time; TBI was associated with younger age of MCI diagnosis[15]. These studies did not include neuropathological confirmation of AD. A recent study[16] among autopsy-confirmed cases of AD from the NACC-NDS found that individuals who reported a remote history of TBI had onset of clinical symptoms and dementia approximately 3 years earlier than non-TBI participants. That study did not examine TBI as an independent risk factor for AD neuropathologic changes or other neuropathology.

The objective of this study was to leverage the NACC-UDS and NDS to clarify the equivocal reports on the relationship between self-reported TBI and AD. We utilized the

NACCUDS and NDS data from 4761 individuals to test the following: 1) the association between self-reported history of TBI with LOC and odds for having AD neuropathologic changes and other neurodegenerative and non-neurodegenerative disease neuropathological diagnoses, and 2) the relationship between self-reported history of TBI with LOC and rate of cognitive decline and odds for dementia in participants with and without autopsy-confirmed AD. Importantly, the number of TBIs participants experienced was not known and thus we only examined a history of at least one TBI with LOC.

2. METHODS

2.1 Participants and Design

The sample included 4761 deceased participants from the NACC-UDS and NACC-NDS who completed UDS visits between 2005 and 2017. The NACC was established in 1999 by the National Institute on Aging (NIA) to promote AD research and provides a publicly available database of clinical and neuropathological data gathered from ADCs across the U.S. Each ADC contributes standardized cognitive, behavioral, and functional participant data from annual evaluations to form the NACC-UDS[17–19]. Within this sample, participants completed between 1 and 11 annual study visits (mean = 3.47, SD = 2.38) and data came from 34 separate ADCs. A subset of NACC-UDS participants consented to brain donation and neuropathological examination; these participants form the NACC-NDS[17,20,21]. The NACC database was approved by the University of Washington Institutional Review Board. Informed consent was obtained at the ADC where data collection occurred. A formal data request was submitted to NACC for this study. Only participants who had data available from both the UDS and NDS were included.

2.2 Traumatic Brain Injury History

Self-reported TBI history, and other health history variables, are collected through a clinician-led interview conducted with the participant and informant (Form A5 of the NACC UDS). The specific instructions for Form A5 are as follows, “Below, record the presence or absence of a history of these conditions at this visit, as determined by the clinician’s best judgment following the medical history interview with the subject and co-participant.” In the UDS (versions 1 and 2), self-reported TBI history is coded using two variables: TRAUMBRF and TRAUMEXT. These variables refer to a self-reported history of at least one TBI with LOC <5 minutes or ≥5 minutes, respectively; thus, all reported TBIs were associated with LOC. Number of TBIs is not known.

For this study, TRAUMBRF and TRAUMEXT were combined into a single grouping variable, known as the “TBI+” group. Each reported injury was coded as “recent/active” or “remote/inactive,” referring to whether the injury had occurred within the year prior to the study visit. Individuals were classified in the TBI group if they met the following criteria: 1) they reported a remote/inactive history of TBI at their initial visit, and 2) they did not report a new recent/active TBI at any subsequent study visit. All individuals in the TBI+ group sustained their injury at least one year prior to their baseline visit. Individuals who had a recent/active TBI at any study visit were excluded from analyses to reduce the possibility of

reverse causality. Individuals without a reported TBI at all study visits were included in the non-TBI group, herein referred to as the “TBI-” group.

2.3 Neuropathology

Neuropathological data were recorded using a standardized Neuropathology Form and Coding Guidebook[17,22,23]. The NACC-NDS has been revised several times since 2002, with the most recent revision in 2014 (version 10). There are differences in the data elements and data coding between versions 1–9 and version 10. When possible, the NACC recoded and/or created derived variables to harmonize data across versions 1–9 and 10. The NACC-NDS derived (i.e., versions 1–10, unless otherwise specified) variables examined included NACCNEUR (CERAD neuritic plaque score), NACCBRAA (Braak staging), NACCAMY (cerebral amyloid angiopathy [CAA]), and NACCLEWY (Lewy body pathology). Regarding frontotemporal lobar degeneration (FTLD) tau pathology, NPFTDTAU is used in version 10 to code for any FTLD-tau pathology, whereas the pathologies were coded separately in versions 1–9. Thus, NPFTDTAU was combined with the following variables from versions 1–9 to code for the presence of FTLD-tau pathology: NPFRONT (frontotemporal dementia and parkinsonism with tau-positive or argyrophilic inclusions), NACCPICK (Pick’s disease), NACCCBD (corticobasal degeneration), NACCPROG (progressive supranuclear palsy), and NPTAU (other tauopathies). FTLD with TAR DNA-binding protein (TDP)-43 pathology was coded in version 10 as NPFTDTDP. Cerebrovascular disease variables included: NACCARTE (arteriolosclerosis), NACCAVAS (atherosclerosis of the circle of Willis), NACCINF (infarcts and lacunes), NACCMICR (microinfarcts), and NPSCL (medial temporal sclerosis, later recoded as NPHIPSCL for hippocampal sclerosis in version 10; the two variables were combined).

The NACC Neuropathology Coding Guidebook instructs neuropathologists from each ADC that a number of stains are acceptable (with preferred methods recommended) for beta-amyloid (immunohistochemistry [preferred], thioflavin-S, silver histochemical stains) and tau (Gallyas stains originally employed, but tau immunostains and other silver stains are acceptable). Despite the independent staining protocols and evaluations, excellent agreement for ratings of AD neuropathologic change across a subset of the NACC ADCs has been reported[24]. The NACCNEUR and NACCBRAA variables were combined to compute a binary variable for autopsy-confirmed AD neuropathologic changes. NACCNEUR refers to the density of neocortical plaques rated on a scale from 0 (no plaques) to 3 (frequent plaques). Neuritic plaques are defined by the NACC Neuropathology Coding Guidebook as “plaques with argyrophilic, thioflavin-S-positive or tau-positive dystrophic neurites with or without dense amyloid cores.” NACCBRAA is the Braak staging of neurofibrillary degeneration rated on a scale from 0 (no degeneration) to VI (widespread degeneration that has spread to the neocortex). For an individual to be classified as having AD neuropathologic changes (i.e., AD+), they had to have evidence of at least moderate pathology for both plaques and tangles[16,20,21]. That is, they had to have a CERAD staging score of 2 or 3 and a Braak score of 3 or higher. Participants who met only one of these criteria were excluded from primary analyses examining AD+; however, a sensitivity analysis was performed with these participants included. These individuals were not excluded from analyses that did not include AD neuropathologic changes in the model.

The presence of Lewy bodies was examined and, if present, coded by the location of their predominant aggregation, either in the brainstem, limbic system, neocortex, or unspecified. Classification of Lewy body pathology is modified from McKeith et al.[25] and alpha-synuclein immunohistochemistry is encouraged. We examined the overall presence of Lewy bodies, as well as Lewy body pathology in the neocortex. Analyses examining neocortical Lewy body pathology excluded individuals with predominant Lewy body aggregation in other regions. FTLD tau pathology was evaluated using a dichotomous variable that coded for the presence of any of the FTLD tauopathies (i.e., NPFRONT, NACCPICK, NACCCBD, NACCPROG, NPTAU, and NPFTDTAU). Evaluations of all FTLD subtypes adhere to published guidelines. FTLD-TDP-43 was also coded as a dichotomous variable and was only available for participants evaluated using version 10 of the NDS. This included any TDP-43-immunoreactive inclusions, including neuronal cytoplasmic inclusion, neuronal intra nuclear inclusion, dystrophic neurite, and glial cystoplasmic inclusion (distinct from MSA).

Atherosclerosis, arteriolosclerosis, and CAA were rated on a scale from 0 (not present) to 3 (severe). These three variables were dichotomized into moderate/severe (score of 2 or 3) versus none/mild (score of 0 or 1). Using special stains for amyloid (e.g., Congo red, thioflavin-S or beta-amyloid immunostaining) and adapted guidelines[26,27], the presence and severity of global CAA was determined. Overall severity was rated as opposed to individual vessels. Version 10 of the NACC Neuropathology Diagnosis Codebook describes CAA as follows: Mild CAA (score of 1) is defined as scattered positivity in parenchymal and/or leptomeningeal vessels, possibly in only one brain area; moderate CAA (score of 2) refers to intense positivity in many parenchymal and/or leptomeningeal vessels; and severe CAA (score of 3) involves widespread (more than one brain area) of intensive positivity in parenchymal and leptomeningeal vessels. Atherosclerosis was defined as intimal and medial fibrofatty atheromatous plaques in the large arteries of the circle of Willis. Arteriolosclerosis was defined as concentric hyaline thickening of the media arterioles. Infarcts and lacunes, microinfarcts, and hippocampal sclerosis were all included in the analyses using dichotomous ratings (0 = absent, 1=present). The variable for infarcts and lacunes combined data (across Neuropathology Form versions 1 thru 10) on large cerebral artery infarcts, lacunes, and gross infarcts.

2.4 Clinical status

The global rating from the Clinical Dementia Rating (CDR) scale assessed dementia severity at each UDS visit[28,29]. The CDR stages dementia severity through the assessment of memory, orientation, judgment/problem solving, community affairs, home and hobbies, and personal care. Each domain is rated on a scale from 0 (no impairment) to 3 (severe impairment) and an algorithm is used to calculate a global severity rating designated as: 0 (no dementia), 0.5 (questionable dementia/MCI), 1.0 (mild dementia), 2.0 (moderate dementia), and 3.0 (severe dementia). All participants received a formal clinical diagnosis (i.e., normal cognition; cognitively impaired not MCI; MCI; dementia) either through a multidisciplinary consensus conference or a single clinician’s judgment. Established criteria were used for MCI[30] and dementia[31] diagnoses.

All participants completed a standardized battery of neuropsychological tests[17,19]. We examined four neuropsychological tests that are routinely administered as part of dementia evaluations, are (or have been) core NACC-UDS tests, and are sensitive to AD[19]. These included the Mini-Mental State Examination (MMSE), 30-item short form Boston Naming Test (BNT), Wechsler Adult Intelligence Scale-Revised Digit Symbol Coding (WAIS-R DSC), and Logical Memory IIA (LM-IIA) as measures of global cognition, confrontation naming, processing speed and working memory, and episodic memory, respectively. Raw scores were used.

2.5 Statistical Analyses

All statistical analyses were conducted in R version 3.1.1[32]. Logistic regression models (both binomial and ordinal) were conducted using the “rms” package. Binary logistic regression examined the associations between self-reported TBI history with AD neuropathologic changes, Lewy bodies, FTLD, atherosclerosis, arteriolosclerosis, CAA, microinfarcts, infarcts and lacunes, and hippocampal sclerosis. For the clinical analyses, global CDR rating and performance on the neuropsychological tests served as outcomes. The relationship between self-reported TBI history with baseline CDR and neuropsychological test performance, as well as longitudinal changes in CDR and neuropsychological test performance were examined. Ordinal logistic regression models were used to predict CDR rating and multiple linear regression models were used for the four neuropsychological tests. The analyses were conducted across the entire sample and repeated within AD+ individuals to determine if self-reported TBI specifically influences the clinical presentation of AD. The longitudinal analyses only included individuals with >1 study visit and predicted CDR or neuropsychological test performance at the final study visit while including the baseline score as a covariate. Coefficients are interpreted as predicting the residual variance not accounted by the baseline score, i.e., changes between the baseline and final study visits.

For all models, *APOE ε4* carrier status (0=non-carriers, 1=carriers), age, race (0=white, 1=other), sex (1=male, 2=female), and years of education were included as covariates. For neuropathological analyses, age at death was used as the covariate. Age at baseline was used as the covariate for clinical outcomes. For the longitudinal analyses examining changes in clinical status over time, the number of years between the baseline and final study visits was included as an additional covariate to account for differences in the length of follow-up between participants.

3. RESULTS

3.1 Participants

Demographics and clinical characteristics are shown in Table 1. Refer to Table 2 for neuropathological characteristics (by self-reported TBI and clinical diagnostic groupings). A flow chart demonstrating participant selection is shown in Figure 1. Overall, 4761 participants were included in analyses, with 453 individuals in the TBI+ group and 4308 in the TBI- group (note that for analyses that examined AD neuropathologic changes, the sample included 342 and 3,477 individuals in the TBI+ and TBI- groups, respectively,

following exclusion of individuals who did meet criteria for having AD neuropathologic changes). Of the 453 TBI+ individuals, 338 reported a TBI with brief LOC, 133 reported a TBI with extended LOC, and 18 reported a history of both. Compared to the TBI- group, the TBI+ group was two years younger, on average, at baseline and more likely to be male. Clinical diagnostic status was similar between the TBI+ and TBI- groups at baseline, with the majority being diagnosed with dementia at baseline. About three-fourths of participants had at least one follow-up visit, with a mean follow-up interval of 3.8 years. The two groups did not differ with regard to the frequency of neuropathological diagnoses with the exception of atherosclerosis, which was slightly more common in the TBI- group, and FTLD TDP-43 pathology, which was more common in the TBI+ group.

3.2 Neuropathological findings

Binary logistic regression models examined the relationship between self-reported TBI history and AD neuropathologic changes, as well as Lewy body, FTLD, and cerebrovascular disease at autopsy (Table 3). After accounting for demographics and APOE ε4 carrier status, self-reported TBI history was not significantly related to AD neuropathologic changes, atherosclerosis, microinfarcts, macroinfarcts, CAA, hippocampal sclerosis, FTLD tau pathology, or Lewy bodies in any location or within the neocortex (neocortical analysis not shown in the Table; OR=0.88, 95% CI: 0.64–1.23; p=0.465). However, the self-reported TBI + group had increased odds for having moderate-to-severe arteriolosclerosis (OR=1.27, 95% CI: 1.00–1.61; p=0.0498) that was driven by individuals with brief LOC (OR=1.38, 95% CI: 1.06–1.80; p=0.018). There was not a significant relationship between TBI with extended LOC and arteriolosclerosis (OR=1.11, 95% CI: 0.71–1.72; p=0.655). The TBI+ group also had increased odds for having FTLD TDP-43 pathology (OR=1.98, 95% CI: 1.08–3.61; p=0.027).

An additional sensitivity analysis (not shown in Table 3) was conducted to determine the relationship between self-reported TBI and AD neuropathologic changes after including individuals who were initially excluded from these analyses (Figure 1) due to meeting only one of the Braak and CERAD staging criteria. In an ordinal logistic regression model with these individuals ordered between AD- and AD+ groups (i.e., low-, mid-, and severe-AD neuropathologic changes), self-reported TBI history did not predict AD neuropathologic changes (OR = 0.92, 95% CI: 0.75–1.14; p = 0.460). Further, self-reported TBI history was not related to CERAD neuritic plaques (OR = 0.91, 95% CI: 0.72–1.14; p = 0.394) or Braak neurofibrillary tau degeneration (OR = 1.12, 95% CI: 0.87–1.45; p = 0.388). The null effect of self-reported TBI history on AD neuropathologic changes was present for both men (OR = 0.90, 95% CI: 0.64–1.27; p = 0.554) and women (OR = 1.65, 95% CI: 0.89–3.07; p = 0.111). The relationship between self-reported TBI and AD neuropathologic changes was not significant for individuals with brief LOC (OR = 1.09, 95% CI: 0.77–1.54; p = 0.634) or for individuals with extended LOC (OR = 1.14, 95% CI: 0.65–1.97; p = 0.652).

3.3 Association between self-reported TBI history and CDR rating

Table 4 displays the results of ordinal logistic regression models examining self-reported TBI history and baseline dementia status (as determined by global CDR rating). The outcome index was trichotomized to determine the ability of self-reported TBI history to

distinguish between people with no impairment (CDR = 0.0), questionable impairment (CDR=0.5), and definite impairment (CDR≥1.0). Self-reported TBI history was not a significant predictor of global CDR rating in the entire sample or in the AD+ individuals. Self-reported TBI history was not associated with baseline diagnostic status in the entire sample or the AD+ participants (p's>0.37; data not shown).

An additional set of analyses examined the relationship between self-reported TBI history and changes in CDR (Table 5). Given that the majority of participants were diagnosed with dementia at baseline, the analyses were repeated within individuals with a CDR at 1.0 at baseline to evaluate whether self-reported TBI history was associated with the clinical progression of dementia. Self-reported TBI history was not a significant predictor of CDR at the final study visit across the entire sample and in the AD+ participants.

3.4 Association between self-reported TBI history and neuropsychological test performance

Self-reported TBI history was not significantly associated with performance on any of the four neuropsychological measures at baseline, both across the entire sample and in the AD+ participants (Table 6). For the longitudinal analyses, self-reported TBI history was not significantly related to changes on any of the tests over time among the entire sample or in the AD+ participants.

3.5 Power analyses

Given that the majority of the results reported were non-significant, it is important to address whether the analyses were adequately powered to detect significant effects (i.e., the Type II Error rate or β value). Power analyses were conducted using the "pwr" package for R. The baseline sample sizes of 342 individuals with a self-reported TBI history and 3477 without a self-reported TBI (sample sizes are after exclusion of individuals who did not meet the defined criteria for having AD neuropathologic changes, Figure 1) had 80% power to detect an effect size of 0.16 (traditionally considered a very small effect), which is comparable to an odds ratio of 1.33, using the conversion formula developed by Chinn[33]. For the sub-analyses within AD+ participants (250 TBI+ and 2572 TBI-), the analyses had 80% power to detect a small effect size of 0.19, corresponding to an odds ratio of 1.40.

4. DISCUSSION

The current study examined the relationship between self-reported TBI history with LOC and neuropathologically-confirmed AD in 4761 autopsy participants from the NACC-UDS and NDS. We failed to identify a statistically significant association between a remote self-reported history of a TBI with LOC and AD neuropathologic changes, after controlling for *APOE ε4* carrier status, age, race, sex, and years of education. Self-reported history of TBI with LOC was not related to the presence of Lewy bodies, FTLD-tau, CAA, hippocampal sclerosis, microinfarcts, or macroinfarcts. Self-reported history of TBI with LOC did not emerge as a statistically significant predictor of baseline or change (over a mean 3.8-year follow-up interval) in dementia severity or cognitive test performance in participants with or

without autopsy-confirmed AD. Findings from this autopsy sample cast doubt on self-reported history of TBI with LOC as an independent risk factor for AD.

The lack of association between clinical and pathological AD in this study and others[10,12] conflicts with recent studies that have linked TBI history with AD dementia in population-based cohorts[2,4] and U.S. military veterans[5]. These studies were without neuropathologic examination or *in vivo* biomarker assessments and relied on clinical diagnoses of AD dementia often obtained by ICD billing codes. Consequently, the etiology of dementia in those samples is unclear and diagnostic misclassification is possible[7]. Different types of TBI exposure may trigger distinct neurodegenerative diseases and related cognitive and neuropsychiatric decline. For example, there has been an accumulation of *in vivo* and *ex vivo* evidence that suggests exposure to repetitive symptomatic concussions and/or asymptomatic subconcussions incurred during contact and collision sport participation, military service, and other sources[34,35], may be associated with cognitive and neuropsychiatric disorders[36–49], especially from chronic traumatic encephalopathy (CTE)[35,46,50–54]. A population-based study of individuals in Sweden who were 50 years of age or older found the relationship between TBI and dementia was weakest for a single mild TBI and strongest for multiple TBIs (and more severe TBI)[2]. A similar pattern for repeated TBIs was observed in a Danish population-based cohort[4]. Number of TBIs was not examined for this study. Assessment of repeated TBIs was only recently added to the NACC UDS version 3.0 and it will be important to examine its relationship with clinical and neuropathological outcomes once sufficient data is collected.

Neuropathological evidence also links a history of TBI with LOC with increased risk for Lewy body accumulation[10]. We did not find a relationship between TBI and Lewy body accumulation. In the ACT cohort, only those with a history of TBI with LOC for ≥1 hour were at increased risk for Lewy bodies[10], suggesting that more severe head trauma may be needed to precipitate this pathology (which may be the case for AD[8,9]); although, TBI with LOC for <1 hour was associated with frontal and temporal cortex Lewy bodies in the ROS and MAP cohorts[10]. Again, that study did not include history of exposure to repetitive head impacts (RHI) and recent research links contact and collision sport participation with increased odds for Lewy body pathology[55]. There remains a need to differentiate how different types of TBI histories and exposures influence the clinical and neuropathological presentation of the different types of neurodegenerative disorders.

Although self-reported TBI may not be an independent risk factor for the pathological development of AD, the population-based studies provide compelling evidence that individuals with a history of TBI are more likely to receive a clinical diagnosis of dementia. There are several explanations for this phenomenon: (1) TBI may reduce an individual's resiliency to the pathophysiological changes associated with aging, AD, or other neurodegenerative disease pathology; (2) TBI may be related to pathological processes (e.g., neuroinflammation, polygenic risk[56]) that could lead to neurodegeneration; (3) individuals with TBI, particularly military veterans, might have more medical (e.g., diabetes, hypertension) and psychiatric (e.g., depression, posttraumatic stress disorder) co-morbidities that could influence vulnerability to dementia; and (4) individuals with a TBI might be more likely to seek medical care for cognitive decline due to heightened concerns from patients

and providers. Despite these explanations, we did not find a relationship between TBI and a clinical diagnosis of dementia. This may be because a majority of the participants with a TBI history had cognitive impairment or dementia at baseline. The use of formal diagnostic procedures (e.g., consensus conferences) to diagnose dementia may be more reliable than review of billing codes that is often done for the population studies. Previous research from the NACC Data Set also failed to find a relationship between TBI history with LOC and rate of cognitive decline[14,15]. Data from NACC are representative of a clinic-based population enriched for AD and the findings may not generalize to other settings.

Interesting findings from the current study were that self-reported history of TBI with LOC was associated with arteriolosclerosis and FTLD TDP-43 pathology. These findings could represent a Type I error given the number of analyses performed. Further, TBI with brief LOC predicted arteriolosclerosis and extended LOC did not. Additionally, the TDP-43 variable was only available for participants who were evaluated using NDS form 10 and the finding is based off 18 individuals with reported TBI history and FTLD TDP-43 pathology. That said, there is extant literature that links TBI with various alterations in the cerebrovascular system[57]. TDP-43 proteinopathy has been observed in individuals with CTE[58] and increased cortical non-phosphorylated TDP-43 was found at autopsy in individuals with a single TBI[59]. Replication of these findings will be important for further interpretation, as well as understanding the specific type of FTLD-TDP with which TBI might be associated. Similarly, although the current study focused on AD and other neurodegenerative disorders, future research should examine other consequences of TBI that can occur across the clinical continuum, including various molecular changes (e.g., oxidative stress, mitochondrial abnormalities).

Despite the many strengths of the NACC data sets, TBI history data are self-reported and was somewhat crude for UDS versions 1 and 2. The current sample had a mean age in the mid-70s and many of the participants were demented at baseline. Recall bias due to passage of time and/or cognitive impairment may have resulted in TBI exposure misclassification. To determine the extent to which TBI exposure misclassification from cognitive impairment may have influenced our findings, the analyses examining self-reported history of TBI and AD neuropathologic changes were repeated after excluding individuals with dementia at their final study visit. A null effect persisted (OR = 1.67, 95% CI: 0.86–3.24, p = 0.128). As shown in Table 2, there were comparable rates of AD neuropathologic changes for those with and without a reported history of TBI across the clinical continuum. Although self-report is feasible, ecologically valid, and standard among the broader literature on TBI and AD, it can introduce certain biases, particularly in a cognitively impaired population, that could contribute to the inconsistent results observed across studies. There was also lack of data on the timing, severity, and number of TBIs, with a majority of TBIs in the TBI+ group being of mild severity. Age of TBI would be important to examine, as resilience to the later-life clinical consequences of TBI may depend on when the injury occurred. Notably, in order to limit bias from reverse causality, only individuals with a remote history of TBI at their baseline UDS visit were included and individuals who had a recent/active TBI at any study visit were excluded. Given that many of the TBI+ (and TBI-) participants were demented at the baseline UDS visit, it is unknown how long participants were demented prior to baseline.

Data collection and recording for the NACC-NDS have evolved since its inception in 2002 and there are discrepancies across NDS versions, but these have largely been resolved through derived variables. Extant evidence supports the comparability of neuropathological data across the ADCs[24]. However, neuropathological diagnostic misclassification due to variations across the ADCs in the neuropathology work-up (e.g., staining protocols) is a possible limitation. For example, results from the BrainNet Europe Consortium show that ratings of AD neuropathological lesions can be influenced by factors such as staining methodology, diagnostic protocols (i.e., CERAD, Braak, NIA-Reagan), scales used (e.g., quantitative versus dichotomized), and lesion severity [60–63]. Lack of inclusion of CTE is an additional limitation. Evaluation of CTE was added to version 10 of the NDS and there are too few cases to date to have included CTE. Harmonized and optimal protocols sensitive to CTE p-tau pathology need to be added to NACC. There were more males in the TBI+ group and this group may have had more participants with a history of RHI from contact sport participation and thereby underlying CTE pathology could have been present in this group. Because CTE is associated with recurrent head trauma, a relationship between TBI with LOC and CTE may not have been present. Among 66 participants who had a history of contact sport participation (determined through medical record review) from the Mayo Clinic Jacksonville brain bank, 21 had the neuropathological diagnostic ‘CTE lesion’[51]. CTE was not found in 198 individuals without a history of contact sport participation, including 33 who had a history of head trauma unrelated to contact sport participation. Neuropathological evaluation of CTE in NACC will facilitate research on the neuropathological consequences of head trauma.

Finally, based on traditional hypothesis testing, it cannot be definitively concluded that no effect exists (i.e., confirm the null hypothesis). Significant differences could exist between groups that were not detected due to an insufficient sample size and/or natural variability that occurs across samples. The power analyses indicated sufficient power to detect modest effect sizes, corresponding to odds ratios of ~1.3–1.4. This effect size range is smaller than the effects found in a recent epidemiological study (e.g., OR=1.81)[2].

CONCLUSIONS

The present study adds to the recent research that has included autopsy or *in vivo* biomarker evidence of underlying AD neuropathologic changes and fails to show a statistically significant association between a reported remote history of TBI with LOC with clinical or pathological AD. Moving forward, it is critical to resolve the different conclusions between the epidemiological and the biomarker and neuropathology studies, and further research examining specific causal and mechanistic factors linking TBI history to clinical dementia is indicated.

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Abbreviations:

ADNC	Alzheimer's disease neuropathologic changes
LOC	loss of consciousness
NACC	National Alzheimer's Coordinating Center
NDS	Neuropathology Data Set
TBI	traumatic brain injury
UDS	Uniform Data Set

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HIGHLIGHTS

- Remote history of self-reported TBI with loss of consciousness (LOC) was not related to Alzheimer's disease (AD) neuropathologic changes
- Self-reported TBI with LOC was largely unrelated to other neurodegenerative diseases
- Self-reported TBI with LOC did not predict baseline or change in dementia severity or cognitive function in participants with AD neuropathologic changes

RESEARCH IN CONTEXT

Systematic review: We reviewed the literature using PubMed, Google Scholar, and references from research articles. Traumatic brain injury (TBI) has long been viewed as a risk factor for Alzheimer's disease (AD). Recent research with autopsy or *in vivo* biomarker evidence of underlying AD neuropathologic changes suggests that this may not be the case. These studies are cited.

Interpretation: Reported remote history of TBI with loss of consciousness was not associated with AD neuropathologic changes in 4761 autopsy participants from the National Alzheimer's Coordinating Center Uniform and Neuropathology Data Sets (OR=1.10, 95% CI: 0.82–1.40), after accounting for demographics and APOE ε4. Among individuals who had autopsy-confirmed AD, reported TBI did not predict baseline or longitudinal change in clinical status.

Future directions: Self-reported TBI may not be an independent risk factor for clinical or pathological AD. Future research is needed to clarify the neuropathological links between TBI and dementia documented in multiple large clinical databases.

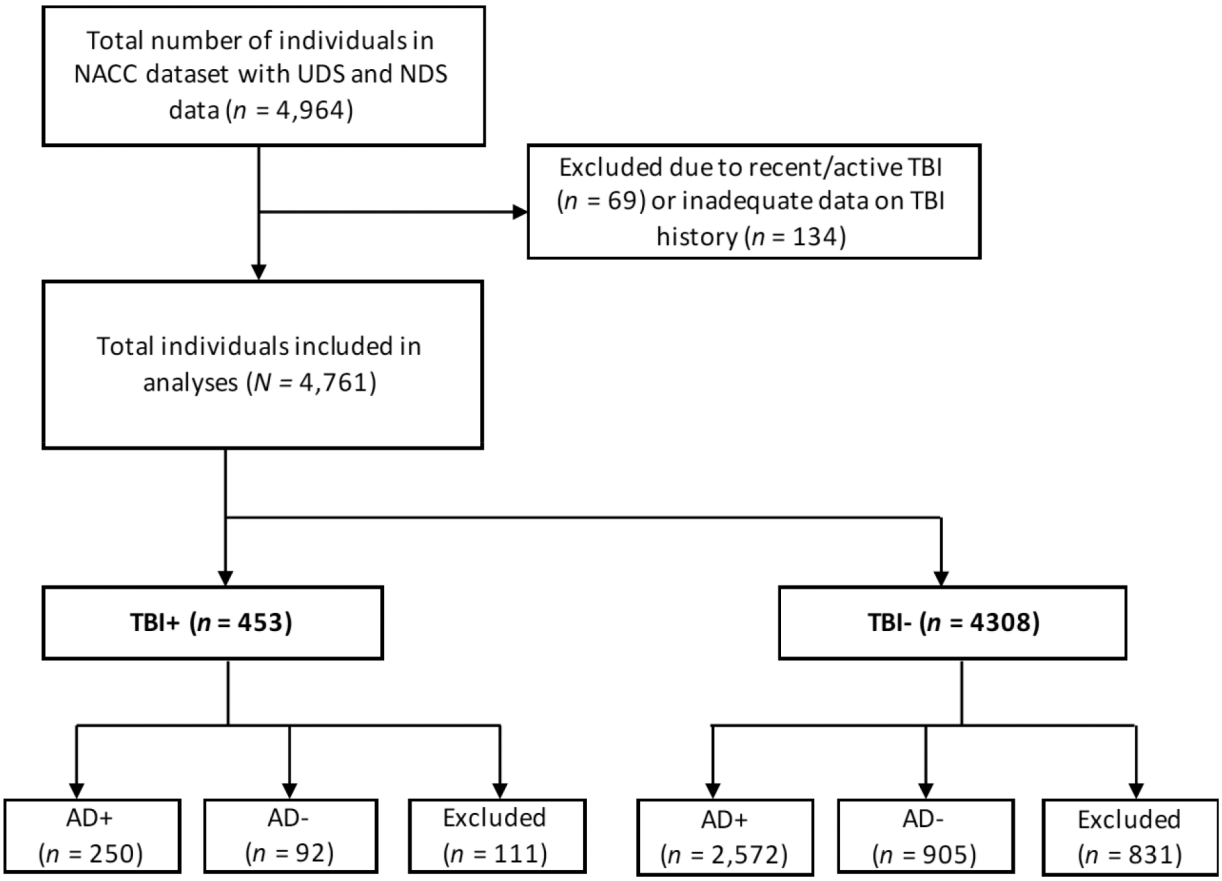

Figure 1.

Participant flow chart. ADNP = Alzheimer's disease neuropathology. AD+ and AD- refers to the presence or absence of autopsy-confirmed Alzheimer's disease neuropathologic changes. AD+ was defined by a CERAD score of 2 or 3 and a Braak score of 3 or higher. Individuals were excluded from analyses examining AD neuropathologic changes if they did not meet both criteria for inclusion; sensitivity analyses showed that reported TBI history still did not predict AD neuropathologic changes when these individuals were not excluded. Note that for analyses that examined AD neuropathologic changes, the sample included 342 and 3477 individuals in the TBI+ and TBI- groups, respectively, following exclusion of individuals who did meet criteria for having AD neuropathologic changes. These individuals were not excluded for analyses that did not include the binary AD neuropathologic changes variable in the model.

Table 1.

Demographics and clinical characteristics of the sample. AD = Alzheimer's disease. APOE = Apolipoprotein E. FTLD = Frontotemporal lobar degeneration. Individuals were classified in the TBI+ group if they met the following criteria: 1) they reported a remote/inactive history of TBI at their initial (baseline) visit, and 2) they did not report a new recent/active TBI at any subsequent study visit. Individuals who had a recent/active TBI at any study visit were excluded from analyses to reduce the possibility of reverse causality. For between-groups comparisons, independent samples t-tests were used for continuous variables and chi-square tests of independence were used for nominal and ordinal variables. Percent values account for missing data and individuals excluded for each variable.

	TBI+ Group	TBI- Group	*p*
Baseline *n*	453	4308	--
Age (baseline)	74.0 (11.9)	75.9 (11.2)	< 0.001
Sex (% male)	324 (71.5%)	2258 (52.4)	$\chi^2 = 60.30$, $p < 0.001$
Race (% White)	440 (97.1%)	4037 (93.7%)	$\chi^2 = 8.55$, $p = 0.003$
Years of Education	15.4 (3.2)	15.2 (0.2)	0.200
APOE ε4 carrier status	175 (43.3%)	1675 (44.3%)	$\chi^2 = 0.14$, $p = 0.708$
Diagnosis at baseline			
Normal	64 (14.1%)	765 (17.8%)	$\chi^2 = 4.68$, $p = 0.197$
Impaired, Non-MCI	8 (1.8%)	83 (1.9%)	
MCI	61 (13.5%)	616 (14.3%)	
Dementia	320 (70.6%)	2844 (66.0%)	
n with at least one follow-up	335 (74.0%)	3218 (74.7%)	$\chi^2 = 0.12$, $p = 0.728$
Follow-up length (Years)	3.6 (2.2)	3.8 (2.3)	0.139
Age at final visit	77.7 (12.3)	80.3 (10.9)	< 0.001
Diagnosis at final visit			
Normal	23 (6.9%)	394 (12.2%)	$\chi^2 = 15.61$, $p = 0.001$
Impaired, Non-MCI	8 (2.4%)	44 (1.4%)	
MCI	41 (12.2%)	262 (8.1%)	
Dementia	263 (78.5%)	2518 (78.2%)	
Age at death	79.0 (12.2)	81.6 (10.8)	<0.001
AD Neuropathologic Changes (%)	250 (73.1%)	2572 (74.0%)	$\chi^2 = 0.12$, $p = 0.726$
Atherosclerosis	152 (34.3%)	1679 (39.5%)	$\chi^2 = 4.49$, $p = 0.034$
Arteriolosclerosis	174 (46.2%)	1601 (41.8%)	$\chi^2 = 2.62$, $p = 0.105$
Microinfarcts	102 (22.6%)	833 (19.4%)	$\chi^2 = 2.62$, $p = 0.106$
Infarcts/Lacunes	91 (20.2%)	853 (19.9%)	$\chi^2 = 0.02$, $p = 0.886$
Cerebral Amyloid Angiopathy	128 (29.0%)	1274 (30.4%)	$\chi^2 = 0.40$, $p = 0.529$
Hippocampal Sclerosis	51 (11.5%)	477 (11.5%)	$\chi^2 < 0.01$, $p = 0.990$
Lewy Bodies (any location)	150 (33.3%)	1389 (32.5%)	$\chi^2 = 0.14$, $p = 0.712$
Lewy Bodies (neocortex only)	53 (15.0%)	542 (15.8%)	$\chi^2 = 0.15$, $p = 0.699$

	TBI+ Group	TBI- Group	*p*
FTLD tau pathology	60 (14.1%)	480 (15.4%)	$\chi^2 = 0.51$, $p = 0.477$
FTLD TDP-43 pathology	18 (14.9%)	92 (8.1%)	$\chi^2 = 6.69$, $p = 0.010$

Table 2.

Rates of neuropathology by reported TBI history and cognitive diagnosis at the final study visit prior to death. * $p < 0.05$ for differences between groups, based on chi-square tests of independence.

	NC		MCI		Dementia	
	TBI+	**TBI-**	**TBI+**	**TBI-**	**TBI+**	**TBI-**
AD Neuropathologic Changes (%)	10 (50.0%)	100 (32.9%)	13 (50.0%)	137 (60.1%)	219 (77.1%)	2318 (79.7%)
Atherosclerosis	12 (41.4%)	210 (43.5%)	21 (42.0%)	150 (44.2%)	113* (32.5%)	1291* (38.2%)
Arteriolosclerosis	13* (54.2%)	117* (28.4%)	21 (47.7%)	137 (44.5%)	132 (45.1%)	1330 (43.5%)
Microinfarcts	9 (30%)	118 (24.5%)	12 (23.5%)	91 (26.5%)	74 (20.8%)	617 (18.1%)
Infarcts/Lacunes	6 (20%)	103 (21.4%)	15 (29.4%)	100 (29.2%)	65 (18.4%)	634 (18.6%)
Cerebral Amyloid Angiopathy	4 (13.8%)	66 (14.0%)	8 (16.0%)	60 (18.0%)	112 (32.3%)	1140 (34.2%)
Hippocampal Sclerosis	0 (0.0%)	9 (2.0%)	5 (10.0%)	22 (6.8%)	43 (12.4%)	455 (13.7%)
Lewy Bodies (any location)	4 (13.3%)	72 (15.0%)	11 (21.6%)	80 (23.4%)	134 (37.9%)	1225 (36.0%)
Lewy Bodies (neocortex only)	1 (3.7%)	9 (2.1%)	5 (11.1%)	24 (8.3%)	47 (17.6%)	507 (18.9%)
FTLD tau pathology	2 (6.9%)	46 (11.1%)	6 (12.0%)	47 (14.9%)	50 (15.1%)	500 (15.9%)
FTLD TDP-43 pathology	0 (0.0%)	3 (2.5%)	0 (0.0%)	2 (2.1%)	18* (18.6%)	86* (9.5%)

Table 3.

Binary logistic regression models examining the relationships between reported TBI history and neuropathology at autopsy. Odds ratio decimals rounded to the nearest hundredth and are based on a one unit increase in the predictor variable. AD = Alzheimer's disease. CAA = Cerebral amyloid angiopathy. APOE = Apolipoprotein E. FTLD = Frontotemporal lobar degeneration.

	AD Neuropathologic Changes				**Moderate-severe atherosclerosis**			
	OR	95% CI	Wald Z	*p*	OR	95% CI	Wald Z	*p*
APOE ε4 carrier	6.27	5.15–7.64	18.24	< 0.001	1.00	0.87–1.14	−0.07	0.945
Age at death	1.03	1.03–1.04	9.13	< 0.001	1.07	1.06–1.08	19.23	< 0.001
Sex	1.12	0.93–1.33	1.21	0.227	0.94	0.82–1.08	−0.87	0.383
Race	1.11	0.74–1.65	0.50	0.616	1.51	1.11–2.04	2.64	0.008
Education	1.00	0.97–1.03	−0.06	0.954	0.99	0.97–1.01	−0.02	0.411
TBI History	1.10	0.82–1.49	0.65	0.518	0.88	0.69–1.11	−1.11	0.267
	Moderate-severe arteriolosclerosis				**Microinfarcts**			
	OR	95% CI	Wald Z	*p*	OR	95% CI	Wald Z	*p*
APOE ε4 carrier	1.25	1.09–1.43	3.23	0.001	1.10	0.94–1.29	1.20	0.232
Age at death	1.03	1.02–1.04	9.74	< 0.001	1.05	1.04–1.06	12.44	< 0.001
Sex	1.17	1.01–1.34	2.16	0.031	0.92	0.78–1.09	−0.95	0.341
Race	0.97	0.72–1.31	−0.20	0.844	1.46	1.04–2.05	2.21	0.027
Education	0.98	0.96–1.00	−1.84	0.065	0.98	0.96–1.01	−1.47	0.141
TBI History	**1.27**	**1.00–1.61**	**1.96**	**0.0498**	1.23	0.94–1.60	1.53	0.127
	Infarcts/Lacunes				**Moderate-severe CAA**			
	OR	95% CI	Wald Z	*p*	OR	95% CI	Wald Z	*p*
APOE ε4 carrier	1.01	0.86–1.19	0.17	0.865	3.19	2.77–3.67	16.11	< 0.001
Age at death	1.06	1.05–1.07	13.04	< 0.001	1.00	1.00–1.01	2.47	0.013
Sex	0.98	0.83–1.16	−0.21	0.832	0.82	0.71–0.95	−2.62	0.009
Race	1.72	1.24–2.39	3.23	0.001	1.19	0.86–1.65	1.06	0.288
Education	0.98	0.96–1.01	−1.25	0.213	0.97	0.95–1.00	−2.27	0.023
TBI History	1.00	0.76–1.32	0.02	0.983	0.96	0.76–1.22	−0.33	0.744
		Hippocampal Sclerosis			**Lewy Body Pathology (any region)**			
	OR	95% CI	Wald Z	*p*	OR	95% CI	Wald Z	*p*
APOE ε4 carrier	1.12	0.92–1.37	1.14	.256	1.75	1.53–2.00	8.26	< 0.001
Age at death	1.03	1.02–1.04	5.76	< .001	0.99	0.99–1.00	−2.59	0.010
Sex	0.97	0.79–1.20	−0.25	.806	0.71	0.61–0.81	−4.91	< 0.001
Race	1.23	0.80–1.91	0.94	.348	1.14	0.84–1.55	0.86	0.392
Education	1.02	0.99–1.06	1.47	.142	1.00	0.98–1.02	0.06	0.955
TBI History	1.02	0.73–1.43	0.14	.892	1.00	0.80–1.25	−0.01	0.993
	FTLD-tau pathology				**FTLD TDP-43 pathology**			
	OR	95% CI	Wald Z	*p*	OR	95% CI	Wald Z	*p*
APOE ε4 carrier	0.44	0.37–0.54	−8.30	< 0.001	0.58	0.37–0.92	−2.30	0.021

Age at death	0.98	0.98–0.99	−4.44	< 0.001	0.94	0.92–0.95	−6.72	< 0.001
Sex	0.98	0.82–1.18	−0.20	0.839	1.06	0.66–1.68	0.23	0.815
Race	0.66	0.41–1.07	−1.68	0.093	0.47	0.11–2.04	−1.01	0.314
Education	1.00	0.97–1.03	0.00	1.000	1.09	1.00–1.18	2.06	0.039
TBI History	0.86	0.63–1.18	−0.94	0.350	**1.98**	**1.08–3.61**	**2.21**	**0.027**

Table 4.

Ordinal logistic regression models examining the relationships between reported TBI history and global Clinical Dementia Rating (CDR) score at baseline. Odds ratio decimals rounded to the nearest hundredth and are based on a one unit increase in the predictor variable. AD+ = autopsy-confirmed Alzheimer's disease neuropathologic changes. APOE = Apolipoprotein E.

	Discriminating between CDR of 0, 0.5, and ≥ 1							
	Entire Sample				***AD+ Individuals***			
	OR	**95% CI**	**Wald Z**	***p***	**OR**	**95% CI**	**Wald Z**	***p***
APOE ε4 carrier	2.13	1.88–2.40	12.10	<0.001	1.63	1.38–1.91	5.88	<0.001
Age at baseline	0.96	0.95–0.97	−14.21	<0.001	0.97	0.96–0.98	−6.82	<0.001
Sex	0.76	0.67–0.86	−4.28	<0.001	0.81	0.68–0.96	−2.45	0.014
Race	1.45	1.08–1.95	2.47	0.013	1.93	1.29–2.89	3.20	0.001
Education	0.93	0.91–0.95	−7.49	<0.001	0.92	0.89–0.94	−6.29	<0.001
TBI History	1.02	0.83–1.26	0.22	0.823	0.90	0.68–1.20	−0.71	0.480

Table 5.

Ordinal logistic regression models examining the relationships between reported TBI history and global Clinical Dementia Rating (CDR) score at the final study visit. Odds ratio decimals rounded to the nearest hundredth and are based on a one unit increase in the predictor variable. AD+ = autopsy-confirmed Alzheimer's disease neuropathologic changes. APOE = Apolipoprotein E.

	Predicting final CDR across all individuals							
	Entire Sample				*AD+ Individuals*			
	OR	95% CI	Wald Z	*p*	OR	95% CI	Wald Z	*p*
APOE ε4 carrier	1.50	1.30–1.73	5.60	< 0.001	1.14	0.95–1.37	1.43	0.153
Age at baseline	0.96	0.95–0.97	−12.17	< 0.001	0.96	0.95–0.97	−9.32	< 0.001
Time since baseline	1.19	1.15–1.23	10.73	< 0.001	1.30	1.25–1.36	11.82	< 0.001
Baseline CDR	13.89	11.82–16.32	31.97	< 0.001	9.09	7.57–10.93	23.51	< 0.001
Sex	1.03	0.89–1.19	0.42	0.673	1.01	0.83–1.22	0.10	0.924
Race	0.97	0.70	−0.21	0.830	1.04	0.69–1.57	0.21	0.834
Education	1.01	0.98–1.03	0.62	0.535	1.01	0.98–1.04	0.62	0.534
TBI History	0.91	0.73–1.14	−0.80	0.424	0.76	0.56–1.04	−1.71	0.087
	Predicting final CDR in individuals with CDR = 1 at baseline							
	Entire Sample				*AD+ Individuals*			
	OR	95% CI	Wald Z	*p*	OR	95% CI	Wald Z	*p*
APOE ε4 carrier	0.92	0.70–1.19	−0.66	0.510	0.80	0.58–1.09	−1.37	0.170
Age at baseline	0.97	0.96–0.98	−4.89	< 0.001	0.98	0.96–0.99	−2.94	0.003
Time since baseline	1.41	1.31–1.51	9.15	< 0.001	1.51	1.39–1.65	9.17	< 0.001
Sex	1.25	0.95–1.65	1.61	0.108	1.02	0.74–1.41	0.12	0.904
Race	1.09	0.62–1.93	0.30	0.764	0.97	0.50–1.88	−0.09	0.931
Education	1.00	0.96–1.04	−0.04	0.971	1.00	0.94–1.05	−0.18	0.856
TBI History	1.08	0.72–1.62	0.36	0.721	1.18	0.70–1.99	0.63	0.526

Table 6.

Multiple linear regression models demonstrating the relationships between reported TBI history and total raw score on four neuropsychological tests, both at baseline and at the final study visit. *APOE ε4* carrier status, age at baseline, sex, race, and education were included as covariates in all models (not shown in table). Scores at baseline and time since baseline (in years) were also included as covariates in the longitudinal models; TBI history predicted residual changes in scores between baseline and the final visit. AD+ = autopsy-confirmed Alzheimer's disease neuropathologic changes, MMSE = Mini Mental State Exam, BNT = Boston Naming Test (30-item odd-numbered short form), WAIS-R DSC = Wechsler Adult Intelligence Scale-Revised Digit Symbol Coding, LM-IIA = Logical Memory IIA.

	MMSE at Baseline							
	Entire Sample				*AD+ Individuals*			
	B	SE	*t*	*p*	B	SE	*t*	*p*
TBI History	0.15	0.42	0.35	0.726	0.61	0.57	1.06	0.290
	MMSE at final study visit							
	Entire Sample				*AD+ Individuals*			
	B	SE	*t*	*p*	B	SE	*t*	*p*
Time since baseline	−0.09	0.08	−1.17	0.241	−0.28	0.11	−2.60	0.009
TBI History	−0.19	0.50	−0.39	0.699	0.11	0.71	0.15	0.881
	BNT at Baseline							
	Entire Sample				*AD+ Individuals*			
	B	SE	*t*	*p*	B	SE	*t*	*p*
TBI History	0.22	0.43	0.51	0.609	0.53	0.58	0.91	0.365
	BNT at final study visit							
	Entire Sample				*AD+ Individuals*			
	B	SE	*t*	*p*	B	SE	*t*	*p*
Time since baseline	−0.22	0.07	−3.32	0.001	−0.29	0.10	−2.92	0.004
TBI History	−0.01	0.45	−0.03	0.973	0.69	0.69	0.99	0.321
	WAIS-R DSC at Baseline							
	Entire Sample				*AD+ Individuals*			
	B	SE	*t*	*p*	B	SE	*t*	*p*
TBI History	−1.66	0.90	−1.84	0.065	−1.50	1.22	−1.23	0.219
	WAIS-R DSC at final study visit							

	Entire Sample				*AD+ Individuals*			
	B	SE	*t*	*p*	B	SE	*t*	*p*
Time since baseline	−0.42	0.14	−2.91	0.004	−0.51	0.22	−2.30	0.021
TBI History	−1.16	0.98	−0.16	0.874	−0.19	1.66	−0.11	0.911
LM-IIA at Baseline								
	Entire Sample				*AD+ Individuals*			
	B	SE	*t*	*p*	B	SE	*t*	*p*
TBI History	0.09	0.31	0.31	0.759	0.10	0.31	0.31	0.759
LM-IIA at final study visit								
	Entire Sample				*AD+ Individuals*			
	B	SE	*t*	*p*	B	SE	*t*	*p*
Time since baseline	0.01	0.05	0.30	0.767	−0.07	0.06	−1.27	0.205
TBI History	−0.34	0.31	−1.11	0.267	0.34	0.39	0.87	0.384