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Association of Traumatic Brain Injury with Late Life Neuropathological Outcomes in a Community-Based Cohort

Laura E. Gibbons[a], **Melinda C. Power**[b], **Rod L. Walker**[c], **Raj G. Kumar**[d], **Alia Murphy**[b], **Caitlin S. Latimer**[e], **Amber L. Nolan**[e], **Erica J. Melief**[e], **Allison Beller**[e], **Marika Bogdani**[e], **C. Dirk Keene**[e], **Eric B. Larson**[a], **Paul K. Crane**[a], **Kristen Dams-O'Connor**[d,*]

[a]General Internal Medicine, School of Medicine, University of Washington, Seattle, WA, USA

[b]George Washington University Milken Institute School of Public Health, Washington, DC, USA

[c]Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA

[d]Department of Rehabilitation and Human Performance, Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[e]Department of Laboratory Medicine and Pathology, School of Medicine, University of Washington, Seattle, WA, USA

Abstract

Background: Prior studies into the association of head trauma with neuropathology have been limited by incomplete lifetime neurotrauma exposure characterization.

Objective: To investigate the neuropathological sequelae of traumatic brain injury (TBI) in an autopsy sample using three sources of TBI ascertainment, weighting findings to reflect associations in the larger, community-based cohort.

Methods: Self-reported head trauma with loss of consciousness (LOC) exposure was collected in biennial clinic visits from 780 older adults from the Adult Changes in Thought study who later died and donated their brain for research. Self-report data were supplemented with medical record abstraction, and, for 244 people, structured interviews on lifetime head trauma. Neuropathology outcomes included Braak stage, CERAD neuritic plaque density, Lewy body distribution, vascular pathology, hippocampal sclerosis, and cerebral/cortical atrophy. Exposures were TBI with or without LOC. Modified Poisson regressions adjusting for age, sex, education, and *APOE ε*4 genotype were weighted back to the full cohort of 5,546 participants.

Results: TBI with LOC was associated with the presence of cerebral cortical atrophy (Relative Risk 1.22, 95% CI 1.02, 1.42). None of the other outcomes was associated with TBI with or without LOC.

*Correspondence to: Kristen Dams-O'Connor, PhD, Icahn School of Medicine at Mount Sinai, Department of Rehabilitation and Human Performance, Department of Neurology, Brain Injury Research Center, One Gustave Levy Place, Box 1163, New York, NY 10029, USA. Tel.: +1 212 241 2221; kristen.dams-o'connor@mountsinai.org.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

SUPPLEMENTARY MATERIAL

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Conclusion: TBI with LOC was associated with increased risk of cerebral cortical atrophy. Despite our enhanced TBI ascertainment, we found no association with the Alzheimer's disease-related neuropathologic outcomes among people who survived to at least age 65 without dementia. This suggests the pathophysiological processes underlying post-traumatic neurodegeneration are distinct from the hallmark pathologies of Alzheimer's disease.

Keywords

Alzheimer's disease; atrophy; dementia; neuropathology; traumatic brain injury

INTRODUCTION

Although traumatic brain injury (TBI) is widely recognized as a risk factor for dementia [1, 2], results from studies investigating the association of TBI with subsequent development of Alzheimer's disease (AD) and related dementias (ADRDs) have been mixed [3–5]. Differences in study design, sample selection, analytic strategy, TBI exposure assessment, and dementia diagnosis methods make it difficult to directly compare study findings. Most of the recent studies investigating AD risk following TBI have used data from the National Alzheimer's Coordinating Center (NACC) database; these findings suggest earlier onset of AD among those with TBI [6–8] though rate of disease progression after diagnosis may not differ from uninjured controls [9, 10]. While recruitment methods differ across NACC sites, many draw from memory clinics and, by virtue of being housed in academic medical centers, tend not to represent the wider community [11, 12]. Several other recent studies of all-cause dementia risk following TBI have relied on administrative health claims data from national health registries [13–15] and Veteran's Health Administration records [16, 17]; these studies all reported that TBI is associated with increased risk for dementia. However, these studies also acknowledge that reliance on International Classification of Diseases (ICD) codes for ascertainment of TBI and dementia may result in focus on moderate to severe TBI and misclassification of dementia status, as well as the potential for reverse causation to impact findings. To the contrary, one recent study in a population-representative cohort, the Health and Retirement Study, found no associations between TBI with loss of consciousness (TBI with LOC) and dementia incidence or memory decline [18]. This is similar to our own previous findings, which did not find an association between TBI and incident dementia in the Adult Changes in Thought (ACT) or Religious Orders Study-Memory and Aging Project (ROS-MAP) cohorts [19].

While some studies have identified associations between severe TBI exposure and AD neuropathology [20, 21], relatively few studies have investigated associations of TBI with postmortem AD/ADRD neuropathology in prospective dementia cohorts. In 2016, we reported an association of TBI with LOC with microinfarcts and Lewy body pathology in the ACT study and the ROS-MAP, but found no association of TBI with LOC with AD neuropathology [19]. We more recently expanded this analysis on a subset of ACT participants and reported absence of TBI with LOC-related differences in quantitative measures of pTau or amyloid-β (Aβ) [22]. A study using autopsy data from the NACC reported an association of TBI with LOC under 5 minutes (but not longer duration LOC) with arteriolosclerosis, but there was no association of TBI with LOC with other standard

neuropath outcomes including AD neuropathology [23]. Another recent study of TBI and AD/ADRD neuropathology in a community-dwelling sample included Japanese-American men and found no association between lifetime TBI with LOC and AD or any other standard AD/ADRD neuropathologic outcomes [24]. In all of these studies [7, 19, 23, 24], TBI exposure data were limited to a single self-report question about injuries resulting in LOC and did not use structured screening tools to characterize lifetime exposure to repetitive head trauma and TBI across the severity spectrum.

There has been particular interest in long-term outcomes of head trauma exposure in the context of contact sports and military service. Repetitive head impacts (RHI) as sustained by American football players has been associated with chronic traumatic encephalopathy (CTE) [25] neuropathology, which often co-exists with other neurodegenerative pathologies [26], particularly in advanced age [22]. The neuropathology of RHI has not been extensively investigated in population-based samples, but the potential negative implications of RHI in community-based brain banks are beginning to be appreciated [26]. To date, although neurodegenerative neuropathology has been documented in case series of military service members exposed to RHI and TBI [27–31], CTE neuropathology was uncommon in military service members who did not have additional exposure to contact sports [32]. Small cohort studies have not found strong evidence that military service itself confers risk for CTE or other neurodegenerative proteinopathy [33, 34].

Prior studies into the neuropathologic sequelae of head trauma, including earlier studies in ACT, have been limited by incomplete lifetime head trauma exposure characterization. ACT and other population based samples rely on single-item queries to define lifetime TBI [19], and consequent case misclassification could impact findings. Other studies rely exclusively on medical records for a discrete period of time, brief screen of isolated TBI history, or estimates of sport and/or military service participation without information about more severe TBI [13, 15, 35]. In the current study, we used expanded ascertainment data from medical records and structured interviews on lifetime head trauma exposure to conduct a comprehensive investigation into the neuropathological associations of head trauma in a large autopsy sample. By using selection weights to account for selection into the autopsy sample, our findings attempt to reflect the associations in the larger, community-based cohort.

METHODS

The ACT study started in 1994 and as of the September 2018 data freeze had enrolled 5,546 randomly selected community-dwelling, Seattle-area Kaiser Permanente Washington (formerly Group Health) members without dementia, aged 65 and above. Consenting participants receive *APOE* genotyping at recruitment. All participants are followed every 2 years with detailed clinical and cognitive assessments until death, development of dementia, or drop-out [36, 37]. Participants are invited to participate in brain donation upon death. Detailed study design and data collection procedures have been published [38]. The ACT study was approved by the Kaiser Permanente and University of Washington Institutional Review Boards.

TBI and RHI exposure

We used three complementary data sources to characterize TBI exposure in this sample. First, we used self-report to a single item question. Through February 2016, the ACT study administered a single "legacy TBI with LOC" item that ascertained whether participants had previously experienced "an injury so severe that you lost consciousness". If that item was endorsed, subsequent items addressed type of injury including head injury and LOC duration with response options including under 9 minutes, 10–59 minutes, and over one hour. We therefore additionally investigated TBI with LOC greater than one hour, which is a conservative operationalization of "moderate-severe" TBI traditionally defined as LOC greater than 30 minutes [39, 40].

Second, we used the Brain Injury Screening Questionnaire (BISQ), a structured interview on lifetime head trauma exposure [41] that was collected during ACT study visits from 2014 to 2018. The BISQ collects data retrospectively on TBI through the date of data collection. The BISQ uses contextual recall cues to query whether the participant sustained a blow to the head in any of 20 contexts (e.g., in a motorcycle crash, on a playground) across the lifespan. For each reported blow to the head, subsequent items characterize duration of altered mental status and duration of unconsciousness if applicable. Note that of the three TBI ascertainment sources, only the BISQ queries TBI that did not result in LOC. The BISQ also includes brief modules that query sources of RHI exposure including contact sports and military service. All self-report exposure data were collected when participants were known not to have dementia. The BISQ was also administered after dementia diagnosis and/or postmortem in a structured interview to informants/proxies of individuals in the ACT autopsy cohort.

Third, data on year and duration of TBI with LOC were extracted from medical records of ACT participants across their entire history of enrollment in Kaiser Permanente Washington, based on all paper charts and every clinical encounter documented in electronic medical record (Supplementary Methods 1).

ACT does not collect routine study data after a dementia diagnosis, leading to possible differential classification as to who sustained a TBI with LOC after diagnosis. In addition, the ACT legacy TBI query item was not collected after February 2016, though BISQ and chart review data were available for some participants. For these reasons we used baseline exposure (i.e., history of TBI with LOC as reported at study entry) as our primary exposure. We classified someone as having a TBI with LOC if it was reported in any of the 3 TBI data sources (at study entry), whether or not it had been captured in any of the other two.

We formed the following indices of TBI exposure: 1) Any TBI with LOC before ACT study baseline, our primary exposure, 2) TBI with LOC before baseline, categorized as an hour or less, and more than an hour, 3) TBI with or without LOC before baseline (among those with the BISQ). We made additional versions of each of these based on TBI exposure information collected after study entry rather than just at baseline.

To characterize potential exposure to RHI, we used data from two additional modules of the BISQ which query nature and duration of exposure to military service and contact sports respectively (see Supplementary Methods 2).

Neuropathology

Neuropathology protocols have been published previously [19, 42–44]. Brain donation for research is optional for ACT participants, of whom 29% have provided written consent through processes approved by the Kaiser and UW IRBs. Brain procurement, processing, preservation, and neuropathological analysis are performed in a manner that meets or exceeds established consensus (NIA-AA) guidelines for the assessment of AD neuropathologic change [45, 46] and have been described recently [22]. Briefly, for donors with <8h postmortem interval (PMI), a rapid autopsy is performed in which one hemisphere is dissected fresh and samples rapid frozen, while in all donors the hemibrain (rapid) or whole brain (non-rapid) is fixed for at least two weeks in 10% neutral-buffered formalin, coronally sectioned, and examined neuropathologically. Key components of the gross neuropathological exam include assessment of cerebral cortical and hippocampal atrophy, the presence (and maximum diameter) of the lateral ventricles at the level of the temporal pole, identification of any mass, cavitary, hemorrhagic, or other types of lesions, and other components of a standard thorough neuropathological exam. The tissues are well-documented photographically and then sampled according to NIA-AA guidelines. Samples are then processed, paraffin-embedded, sectioned, and stained histochemically and/or immunohistochemically for microscopic examination for Aβ plaque distribution as measured by Thal phase [47], neurofibrillary tangle distribution as measured by Braak stage [48], and cortical neuritic plaque density according to Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Additional assessments are performed for the presence and severity of cerebral amyloid angiopathy (CAA), hippocampal sclerosis, LATE (limbic-predominant age-related TDP-43 encephalopathy) stage and presence and distribution of Lewy body disease. CAA was assessed by analysis of an Aβ immunostain (6 E10, Biolegend, 803003) performed on the striate cortex section and severity was defined as follows: mild, involving leptomeninges only; moderate, involving vessels in the cortex; and severe, involving a majority of vessels in the cortex. Hippocampal sclerosis was assessed on hematoxylin and eosin and Luxol fast blue (H&E/LFB) stain and defined as substantial pyramidal cell loss and gliosis in CA1 and subiculum [46]. LATE staging was performed according to 2019 consensus-based recommendations with evaluation of TDP-43 immunohistochemistry (ID3, Biolegend, 829901) on amygdala, hippocampus, and middle frontal cortex sections [49]. Lewy body disease was evaluated by H&E/LFB in the brainstem sections, and by immunohistochemistry (LB509 for alpha synuclein, Invitrogen, 180215) in the amygdala, anterior cingulate cortex, and middle frontal cortex staining [45, 46] per NIA-AA guidelines [46]. H&E/LFB was also used to detect the presence of macroscopic infarcts and presence and location of cerebral microinfarcts across 12 sections (bilateral middle frontal gyrus, superior and middle temporal gyri, inferior parietal lobule, occipital/calcarine cortex, basal ganglia at the level of the anterior commissure, and thalamus at the level of the subthalamic nucleus). Microinfarcts were categorized as deep (basal ganglia or thalamus) versus cortical [46]. We dichotomized most neuropathologic measures as high versus low/none based on associations with dementia [43]. High measures included

Braak stage V or VI, moderate or frequent CERAD scores, Thal phase 3–5, any amyloid angiopathy, any microinfarcts, any macroscopic infarcts, any Lewy bodies, any hippocampal sclerosis, or any cerebral cortical atrophy, as measured by the presence of any dilatation in the lateral ventricles at the level of the temporal tip. Cerebral cortical atrophy was also considered as a measured outcome. Estimation of expected brain weight was calculated as 200+ the posterior fossa contents (brainstem, cerebellum) weight/0.15, according to published protocols [50]. We then calculated the total fixed brain weight/expected brain weight ratio.

Statistical methods

For each of the TBI exposures, we used modified Poisson regression models that employ robust standard errors [51] to compute adjusted rate ratios (RR) and 95% confidence intervals, adjusting for autopsy age, sex, years of education, the presence of any *APOE ε*4 alleles, and ACT enrollment cohort (1994–1996 versus subsequent). For all analyses based on baseline TBI status, we also adjusted for any post-baseline TBI events (yes/no/unknown). We incorporated weights in the regression models to account for selection into the autopsy sample from the broader ACT cohort, including people who were alive or had died but did not have an autopsy. These weights were estimated from a logistic regression model (see Supplementary Methods 3), and we used a bootstrapping procedure that accounted for the error in estimating the weights [52]. We could not do this for the sport and military exposures due to the small number of people assessed for RHI exposures.

We conducted a sensitivity analysis examining the impact of potentially missing TBI after dementia diagnosis on the effect of lifetime TBI with LOC. We matched each dementia case who had TBI data ($n = 331$) with a control based on baseline age and age at death. If the control had their first TBI after the dementia-onset age of the case, we recoded that person to no TBI. We compared the results in this reclassified dataset to the results in this sample before the reclassification.

RESULTS

TBI exposure

As of the data freeze, 815 of the 5,546 participants had died and donated their brains for research. Of these, we had baseline TBI data on 811, 780 of whom had *APOE* genotype data and form our analytic sample. Table 1 compares select covariates between our analytic sample and the broader ACT cohort. Table 2 presents detailed exposure and outcome information for our analytic sample. Based on the ACT legacy questions, 121 people (16%) had TBI with LOC before baseline (Table 3). BISQ data had been collected on 244 of the people in our sample. Of these 78 were self-report and 166 were proxy reports. Most of the proxies were adult children (81%) and spouses (12%), the rest being other relatives or friends. The proxy reports were post-mortem and potentially identified TBI after dementia diagnosis. Proxies had known the deceased for a median of 62 years (range 19–85). Based on the BISQ, 29 people (12%) had TBI with LOC in the years before ACT study baseline (Table 3). Chart review data were successfully obtained from 735 people in our sample. This review spanned a median of 47 years (interquartile range 35–57, range 6–99). TBI with

LOC was identified in 35 (4%) in the years before ACT study baseline. Across these three sources, 154 people were identified as having TBI with LOC before baseline. The majority were identified using the legacy item (121; 79%), and the remaining cases were based on the BISQ ($n = 6$), chart review ($n = 25$), or both ($n = 2$).

In our primary analyses, TBI with LOC before baseline was associated with increased risk of any cerebral cortical atrophy (RR: 1.22, 95% CI: 1.02, 1.42) (Table 4). The risk estimate was smaller in the analysis that did not weight back to the full cohort (RR 1.14 (1.03, 1.27)). The risk estimate was slightly lower for TBI with LOC when predicting the extent of atrophy as a continuous measure in centimeters (RR 1.20 (0.98, 1.45) per centimeter). Baseline TBI with LOC was not associated with any of the other neuropathological outcomes (Table 4).

To examine the contributions of our refined TBI ascertainment data, we calculated the risk for any cerebral cortical atrophy associated with each TBI exposure data source. Using just the ACT legacy TBI item, the RR was 1.13 (0.92, 1.36), and after adding in the BISQ it was 1.17 (0.95, 1.38), compared with 1.22 (1.02, 1.42) in the primary analysis, which included all 3 sources (all estimates weighted back to the full cohort). Omitting the 6 TBI with LOC identified only by proxy report gave results nearly identical to the results that included all sources (weighted-back RR 1.21 (1.01, 1.41)). Similarly, all null findings remained null when TBI identified via proxy report were excluded.

Duration of LOC was known for 145 of those with TBI with LOC at baseline. Duration was over an hour in only 19 people at baseline, restricting our analyses to the more common neuropathology findings. In the analyses weighting back to the full cohort, TBI of either duration was not associated with any of the 8 neuropathologic outcomes (Table 5). Before weighting back to the full cohort, it appeared TBI with LOC over an hour was associated with deep (RR 1.79 (1.09, 2.95)) and any (RR 1.44 (1.03, 2.02)) microinfarcts.

The BISQ identified individuals who sustained TBI with and *without* LOC. In analyses including TBI without LOC per the BISQ, no outcomes were statistically significant after weighting back to the cohort (Table 6). In the unweighted cohort, Braak score of V or VI and the presence of any cerebral atrophy were significant (Braak RR 1.54 (1.06, 2.23); atrophy RR 1.19 (1.01, 1.39)).

In other secondary analyses, we used lifetime TBI with LOC as the exposure, including post-baseline TBI. Again, cerebral cortical atrophy was the only outcome associated with lifetime TBI with LOC among the 725 with complete exposure data (weighted-back RRs 1.17 (1.00, 1.34) for any atrophy and 1.23 (1.04, 1.45) for centimeters of atrophy; participants with incomplete data post baseline were excluded; Supplementary Table 1). Unlike the baseline analyses, an LOC of an hour or less was associated with an increase in cerebral cortical atrophy (RR 1.22 (1.01, 1.45); Supplementary Table 2). There was also an increased point estimate for LOC of over one hour, but it did not approach statistical significance. None of the other outcomes were associated with duration of LOC. Cerebral cortical atrophy (centimeters) was the only outcome associated with TBI *with* or *without* LOC in the 244 with lifetime data (RR 1.36 (1.01, 1.74); Supplementary Table 3).

Sensitivity analyses to examine the potential impact of lack of follow-up after dementia diagnosis suggested that differential misclassification was not a problem as the relative risks were quite similar (Supplementary Table 4).

RHI exposure

Of the 244 BISQ surveys included in this report, 216 included questions about military service and 212 included questions about lifetime history of organized sports [53]. Only 23 (11%) reported any participation in contact sports. There was no association between any participation or years of participation in contact sports and any of the outcomes (Supplementary Table 5). In the 93 men with BISQ military data, 64 (69%) reported military service and 15 (16%) experienced combat. There was no association between military service or combat experience with neuropathological endpoints (Supplementary Tables 6 and 7). BISQ military service data were available on 123 women, but only 5 served, so their exposures were not analyzed.

DISCUSSION

Among people who survived to at least age 65 without dementia, TBI with LOC was associated with increased risk of cerebral cortical atrophy, but not with any of the neuropathological findings specifically related to AD. The effect of TBI on cortical atrophy was significant when restricting to TBI with LOC; including TBI without LOC attenuated the risk.

Recent studies reporting mostly null findings for TBI and AD-related neuropathology [19, 23, 24] motivated the current study, given that these findings contradict decades of prior research supporting an association of TBI with AD risk. Prior studies investigating neuropathological AD [19, 23, 24] relied on single-item self-report measures of TBI with LOC, which may have resulted in under-reporting of lifetime exposure [54] and they did not measure injuries that do not result in LOC or exposure to RHI. When individuals with mild TBI and/or RHI are classified into the unexposed group, overall TBI/RHI findings may be biased toward the null. The current study incorporates multiple sources of TBI exposure information, including a legacy single-item ascertainment measure, a structured lifetime TBI exposure tool (BISQ) [41], proxy report of lifetime TBI exposure (proxy BISQ), and medical records review. While potential differential misclassification remains, our results suggest that imprecise exposure ascertainment does not fully explain previously reported null findings [19, 23, 24].

We further sought to investigate whether selection bias may have impacted prior null findings [19, 24], as selection bias is known to impact generalizability of findings from autopsy cohorts [52]. We are not aware of any other autopsy studies of post-traumatic neurodegeneration which have been able to examine potential selection bias. In the current study, we found significant associations between baseline TBI with LOC over an hour and microvascular lesions that disappeared after adjusting for autopsy selection. This was not only because of wider confidence intervals due to incorporating errors in estimating the weights; the risk estimates were lower. Conversely, the risk estimate for baseline TBI with LOC and cerebral cortical atrophy increased slightly with weighting. Our current

methods [52], which adjust for factors that impact selection into brain autopsy, lend greater confidence that the null associations reported here are generalizable to the population of interest and are not unique to this selected autopsy cohort.

The current finding of an association between TBI with LOC and cerebral cortical atrophy merits careful consideration, since the diffuse cerebral cortical atrophy likely includes some contribution of parenchymal loss in cerebral cortex proper (gray matter) as well as subcortical white matter. Axonal degeneration is a known pathophysiological mechanism of clinical impairment and decline following TBI. Rotational and other kinetic forces on the brain within the skull results in diffuse damage to the cytoskeletal network of neurofilaments and microtubules that support axonal integrity [55]. Traumatic axonal injury is characterized by degradation to the myelin sheath that permits transport of proteins; the disruption of axonal transport can cause swelling and consequent apoptosis [56]. Axonal degradation and progressive microstructural change over time many years post-injury have been reported in *in vivo* neuroimaging studies [57–59], suggesting that progressive selective atrophy may be a central contributor to neurodegeneration after moderate-severe TBI. With respect to the cerebral cortex and other gray matter structures, degeneration and loss of cortical parenchyma can occur in response to many factors, including neurodegenerative disease, primary (local) vascular or traumatic brain injury, and retrograde degeneration secondary to axonal injury.

In our analyses, we do not see an association between TBI and common neurodegenerative neuropathologies (AD, Lewy body dementia, etc.) nor other obvious neuropathological changes that lend evidence to a primarily cortical lesion. Growing evidence suggests that generalized and/or regional brain atrophy, which has in some cases been shown to be inversely related to [60] AD/ADRD-related neuropathologic change, may be an independent contributor to clinical dementia [61] and cognitive decline [62] above and beyond standard ADRD neuropathology. Future studies that incorporate neuroimaging and quantitative image analysis approaches combined with gray and white matter specific stains may shed light on the principal etiology of this finding.

In the subsample who provided data on contact sport participation and military service, we found no increased risk for neuropathological indices of dementia or neurodegenerative disease. This finding aligns with a prior neuropathology-focused study of ACT participants, less than 1% of those examined had diagnostic neuropathologic features of CTE [22]. However, we only had RHI exposure information from the BISQ, leaving us underpowered for this analysis. Furthermore, two-thirds of the reports were by proxies, increasing the chance of misclassification; even self-reported BISQ data may be subject to differential misclassification if those who are able to recall remote and clinically inconsequential events are overall higher-functioning. Future research in larger samples, with detailed lifetime head trauma exposure data using structured self- and proxy-report tools, is needed to better understand how RHI relates to subsequent neurodegenerative disease risk in unselected samples.

This study is generalizable to individuals who survive to at least age 65 (average age at entry was 77) without dementia and who are willing to consent into a longitudinal research

study. By virtue of this, anyone with early onset dementia following TBI [63] or reduced life expectancy following TBI [64, 65], would not be included in this study. Like other recent studies that investigated TBI-dementia associations in older adult cohorts, this study may under-estimate the true risk for cognitive and functional decline and clinical dementia following TBI that is well documented in prospective TBI cohort studies given focus on those who recover sufficiently to be dementia-free at sample enrollment. That said, these findings further support the notion that people who sustained a remote TBI but live late into older adulthood without becoming demented are at no greater risk for AD/ADRD than their uninjured peers.

This study leveraged neuropathological data collected over three decades and focused on dementia-associated neurodegenerative disease outcomes; this study was not designed to specifically assess for TBI-related neuropathologies nor were subjects recruited based on TBI-exposure status. We view this as a significant strength of the study, providing the opportunity to assess a cohort unbiased by selection for TBI exposure, or a requirement of seeking healthcare for TBI. However, prospective, population-based studies that include in their design clinical and neuropathological assessments that include relevant TBI-related outcomes are needed to supplement information we can glean from existing brain aging and neurodegeneration cohorts. For example, thorough assessment for CTE-neuropathologic change is still not routinely performed in most brain biorepositories, and we lack tools to confidently identify and quantify axonal injury and degeneration associated with vascular, neurodegenerative, and traumatic brain injury processes. Future studies that incorporate neuroimaging and quantitative pathological outcomes, in addition to detailed and highly structured clinical assessments that include items critical for TBI-related outcomes, are sorely needed to increase power to detect subtle or mixed pathologic processes associated with remote TBI exposure.

Conclusion

We found that TBI with LOC, but not milder forms of head trauma including RHI, was associated with increased risk of cerebral cortical atrophy. We found no associations of TBI of any severity with AD neuropathology. We used selection weights, three sources of TBI ascertainment, and self- and/or other-report RHI exposure history data to address weaknesses in earlier studies, and we still found no association with any of the AD-related neuropathologic outcomes among people who survived to at least age 65 without dementia. This finding adds to a growing body of research that suggests the pathophysiological processes underlying post-traumatic neurodegeneration are distinct from the hallmark pathologies of AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY

Data cannot be made publicly available for ethical and legal reasons. In order to replicate our findings, a researcher must have access to personal health identifiers (PHI) including dates of birth and death, dates of diagnoses, and ages over 89. These are required variables for the analysis and we cannot publicly release this information without IRB approval and a Data Use Agreement with interested researchers. However, external researchers can request these data with proper IRB and HIPAA approvals. If a researcher is interested in requesting data, the process is available on the Adult Changes in Thought (ACT) website: actagingresearch.org.

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Table 1

Description of the study samples

		ACT brain donors, with baseline TBI-LOC and APOE ε4 data		
	Full Cohort (*n* = 5,546) *n* (%)	**No baseline TBI with LOC[a] (*n* = 626) *n* (%)**	**Baseline TBI with LOC[b] (*n* = 154) *n* (%)**	**Total (*n* = 780) *n* (%)**
Male	2,318 (42%)	246 (39%)	87 (56%)	333 (43%)
Age at last visit				
68–84	3,442 (62%)	242 (39%)	62 (40%)	304 (39%)
85–89	1,170 (21%)	181 (29%)	47 (31%)	228 (29%)
90–94	697 (13%)	149 (24%)	29 (19%)	178 (23%)
95–106	237 (4%)	54 (9%)	16 (10%)	70 (9%)
Completed college	3,978 (72%)	433 (69%)	111 (72%)	544 (70%)
APOE ε4 alleles				
None	3,329 (60%)	447 (71%)	114 (74%)	561 (72%)
1–2	1,179 (21%)	179 (29%)	40 (26%)	219 (28%)
Unknown	1,038 (19%)			
Any dementia, last visit	1,270 (23%)	286 (46%)	69 (45%)	355 (46%)
ACT study cohort				
1994–1996	2,581 (47%)	391 (62%)	101 (66%)	492 (63%)
Subsequent	2,965 (53%)	235 (38%)	53 (34%)	288 (37%)

[a] No TBI with LOC based on ACT study data, or, when available, on BISQ self-report or proxy or chart review.

[b] At least one report of TBI with LOC as of ACT study entry, based on ACT study data, or, when available, on BISQ self-report or proxy or chart review.

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Table 2

Age at death, TBI risk factors, and neuropathology outcomes by TBI-LOC in the analytic sample who had *APOE ε*4 data and underwent autopsy

	No baseline TBI with LOC[a] (*n* = 626) *n* (%) or mean (SD)	**Baseline TBI with LOC[b] (*n* =154) *n* (%) or mean (SD)**	**Total (*n* = 780) *n* (%) or mean (SD)**
Age at death, mean (SD)			
68–84	152 (24%)	42 (27%)	194 (25%)
85–89	157 (25%)	48 (31%)	205 (26%)
90–94	194 (31%)	38 (25%)	232 (30%)
95–106	123 (20%)	26 (17%)	149 (19%)
Maximum length of LOC at baseline			
None	626 (100%)	0 (0%)	626 (81%)
Hour or less	0 (0%)	126 (87%)	126 (16%)
Over an hour	0 (0%)	19 (13%)	19 (2%)
Any TBI with LOC after baseline[c]			
Yes	72 (12%)	24 (16%)	96 (12%)
No	442 (71%)	106 (69%)	548 (70%)
Unknown	112 (18%)	24 (16%)	136 (17%)
Any baseline TBI with or without LOC (*n* = 332)[d]	9 (5%)	154 (100%)	163 (49%)
Years of contact sports (*n* = 212)[e]			
None	143 (92%)	46 (81%)	189 (89%)
1–3	4 (3%)	5 (9%)	9 (4%)
4–13	8 (5%)	6 (11%)	14 (7%)
Military service (*n* = 216)[f]	44 (28%)	25 (43%)	69 (32%)
Neuropath outcomes			
Braak stage V or VI	223 (37%)	57 (38%)	280 (37%)
CERAD score 2 or 3	330 (54%)	73 (48%)	403 (53%)
Thal phase A2 or A3 (score 3–5)	186 (70%)	37 (69%)	223 (70%)
LATE stage			
0	314 (52%)	83 (55%)	397 (52%)
1	138 (23%)	35 (23%)	173 (23%)

	No baseline TBI with LOC[a] (*n* = 626) *n* (%) or mean (SD)	Baseline TBI with LOC[b] (*n* =154) *n* (%) or mean (SD)	Total (*n* = 780) *n* (%) or mean (SD)
2–3	157 (26%)	33 (22%)	190 (25%)
Any Amyloid Angiopathy (Occipital Lobe)	227 (38%)	57 (38%)	285 (38%)
Any cerebral or deep microinfarcts	302 (50%)	78 (51%)	380 (50%)
Any cerebral microinfarcts	220 (36%)	55 (36%)	275 (36%)
Any deep microinfarcts	192 (32%)	47 (31%)	239 (32%)
Any macroinfarcts	169 (27%)	45 (29%)	214 (27%)
Any Lewy bodies in any of the 4 regions	121 (20%)	23 (15%)	144 (19%)
Substantia Nigra	80 (14%)	15 (10%)	95 (13%)
Locus Ceruleus	73 (12%)	12 (8%)	85 (12%)
Amygdala	99 (17%)	18 (13%)	117 (16%)
Frontal Cortex	48 (8%)	9 (6%)	57 (8%)
Any hippocampal sclerosis	76 (13%)	17 (11%)	93 (13%)
Ratio of fixed brain weight to expected weight[g]	0.95 (0.11)	0.95 (0.12)	0.94 (0.12)
Centimeters cerebral cortical atrophy [h]	1.29 (1.07)	1.42 (1.10)	1.32 (1.08)
Any cerebral cortical atrophy [h]	374 (70%)	106 (77%)	480 (71%)

[a]No baseline TBI with LOC based on ACT study data, or, when available, on BISQ self-report or proxy or chart review.

[b]At least one report of TBI with LOC as of ACT study entry, based on ACT study data, or, when available, on BISQ self-report or proxy or chart review.

[c]At least one report of TBI with LOC after ACT study entry, based on ACT study data, or, when available, on BISQ self-report or proxy or chart review.

[d]The 244 people who completed the BISQ, which asked about TBI without LOC, as well as 88 additional people with a baseline TBI with LOC based on ACT study data or chart review.

[e]212 people completed a version of the BISQ that included questions on sports participation.

[f]216 people completed a version of the BISQ that included questions on military service.

[g]Mean (SD). Total fixed brain weight divided by the expected brain weight, where the expected brain weight was calculated as 200 + the posteriorfossacontents weight/0.15.

[h]Atrophy defined by dilatation in the lateral ventricles at the level of the temporal tip.

Table 3

Baseline TBI with LOC status by ascertainment source (ACT legacy item, Chart review, or BISQ)

ACT Legacy item		N			
No TBI with LOC		BISQ			
	Chart review	No TBI with LOC	TBI with LOC	Not assessed	Total
	No TBI with LOC	164	6	429	599
	TBI with LOC	4	2	21	27
	Not reviewed	14	0	19	33
	Total	182	8	469	659
TBI with LOC		*BISQ*			
	Chart review	No TBI with LOC	TBI with LOC	Not assessed	Total
	No TBI with LOC	30	19	62	111
	TBI with LOC	1	2	5	8
	Not reviewed	2	0	0	2
	Total	33	21	67	121

Table 4

Risk of select neuropathological endpoints for TBI with LOC at baseline [a], compared with no TBI with LOC at baseline

Neuropath outcome	N	RR[b] (95% CI)	*p*
Braak stage V or VI	759	1.01 (0.75, 1.32)	0.96
CERAD score 2 or 3	761	0.86 (0.67, 1.09)	0.22
Thal phase A2 or A3 (score 3–5)	320	0.91 (0.66, 1.21)	0.53
LATE stage (0, 1, or 2–3)	760	0.96 (0.74, 1.21)	0.74
Any Amyloid Angiopathy (Occipital Lobe)	759	0.84 (0.61, 1.13)	0.26
Any cerebral or deep microinfarcts	758	1.01 (0.79, 1.29)	0.96
Any cerebral microinfarcts	758	0.96 (0.71, 1.29)	0.81
Any deep microinfarcts	758	0.95 (0.66, 1.36)	0.78
Any macroinfarcts	780	1.05 (0.73, 1.47)	0.77
Any Lewy bodies in any of the 4 regions	748	0.80 (0.48, 1.38)	0.43
Substantia Nigra	748	0.78 (0.39, 1.59)	0.49
Locus Ceruleus	739	0.63 (0.30, 1.31)	0.24
Amygdala	731	0.69 (0.37, 1.23)	0.23
Frontal Cortex	750	0.63 (0.23, 1.53)	0.37
Any hippocampal sclerosis	744	0.88 (0.50, 1.55)	0.68
Ratio of fixed brain weight to expected weight[c]	628	1.00 (0.97, 1.02)	0.88
Centimeters of cerebral cortical atrophy[d]	675	1.20 (0.98, 1.45)	0.06
Any cerebral cortical atrophy[d]	675	1.22 (1.02, 1.42)	0.017

[a] At least one report of TBI with LOC as of ACT study entry, based on ACT study data, or, when available, on BISQ self-report or proxy or chart review.

[b] Adjusted rate ratios (RR) and 95% confidence intervals (CI) are from Poisson regressions modified with robust standard errors, adjusting for age at death, sex, education, any Apoe4 alleles, TBI with LOC after baseline, and ACT study cohort. Results were weighted back to the full cohort in a bootstrapping procedure that accounted for the error in estimating the weights, resulting in wider confidence intervals and higher *p*-values than in unweighted results.

[c] Total fixed brain weight divided by the expected brain weight, where the expected brain weight was calculated as 200 + the posterior fossa contents weight/0.15.

[d] Atrophy defined by dilatation in the lateral ventricles at the level of the temporal tip.

Table 5

Risk of select neuropathological endpoints among those with baseline TBI with LOC [a] ≤1 hour or >1 hour at baseline, compared to those with no TBI with LOC at baseline.

		Hour or less (*n* = 126)		Over an hour (*n* = 19)	
Neuropath outcome[b]	**N**	**RR[c] (95% CI)**	***p***	**RR[c] (95% CI)**	***p***
Braak stage V or VI	750	1.01 (0.74, 1.36)	0.96	1.12 (0.49, 2.04)	0.77
LATE stage >0	751	1.00 (0.75, 1.31)	0.99	1.01 (0.52, 1.64)	0.97
Any cerebral or deep microvascular lesions	749	0.97 (0.73, 1.27)	0.81	1.20 (0.55, 1.96)	0.53
Any cerebral microvascular lesions	749	0.92 (0.66, 1.28)	0.65	1.06 (0.45, 2.00)	0.88
Any deep microvascular lesions	749	0.87 (0.58, 1.31)	0.53	1.58 (0.66, 2.90)	0.21
Any Macroinfarcts	771	1.04 (0.70, 1.51)	0.83	0.97 (0.37, 1.94)	0.94
Ratio of fixed brain weight to expected weight[d]	621	1.00 (0.97, 1.02)	0.96	0.99 (0.93, 1.06)	0.88
Centimeters of cerebral cortical atrophy[e]	669	1.16 (0.94, 1.43)	0.16	1.53 (0.86, 2.80)	0.17

[a] At least one report of TBI with LOC as of ACT study entry, based on ACT study data, or, when available, on BISQ self-report or proxy or chart review.

[b] Some outcomes were too rare to assess by LOC duration.

[c] Adjusted rate ratios (RR) and 95% confidence intervals (CI) are from Poisson regressions modified with robust standard errors, adjusting for age at death, sex, education, any Apoe4 alleles, TBI with LOC after baseline, and ACT study cohort. Results were weighted back to the full cohort in a bootstrapping procedure that accounted for the error in estimating the weights, resulting in wider confidence intervals and higher *p*-values than in unweighted results.

[d] Total fixed brain weight divided by the expected brain weight, where the expected brain weight was calculated as 200 + the posterior fossa contents weight/0.15.

[e] Atrophy defined by dilatation in the lateral ventricles at the level of the temporal tip.

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Table 6

Risk of select neuropathological endpoints for TBI *with* **or** *without* LOC at baseline, compared to no TBI at baseline, in the $n = 244$ with the BISQ.

Neuropath outcome[a]	N	RR[b] (95% CI)	*p*
Braak stage V or VI	233	1.54 (0.88, 2.46)	0.10
CERAD score 2 or 3	234	1.08 (0.64, 1.68)	0.75
Thal phase A2 or A3 (score 3–5)	131	1.12 (0.64, 1.69)	0.65
LATE stage (0, 1, or 2–3)	243	0.63 (0.32, 1.09)	0.14
Any Amyloid Angiopathy (Occipital Lobe)	234	1.15 (0.69, 2.01)	0.61
Any cerebral or deep microinfarcts	233	0.83 (0.44, 1.34)	0.52
Any cerebral microinfarcts	233	0.63 (0.22, 1.38)	0.40
Any deep microinfarcts	233	1.00 (0.49, 1.82)	0.99
Any macroinfarcts	244	1.23 (0.64, 2.21)	0.51
Any Lewy bodies in any of the 4 regions	233	0.93 (0.40, 2.12)	0.46
Ratio of fixed brain weight to expected weight[c]	190	1.01 (0.95, 1.07)	0.85
Centimeters of cerebral cortical atrophy[d]	207	1.34 (0.97, 1.79)	0.06
Any cerebral cortical atrophy[d]	207	1.27 (0.99, 1.62)	0.055

[a] Some outcomes were too rare to assess in this subsample.

[b] Adjusted rate ratios (RR) and 95% confidence intervals (CI) are from Poisson regressions modified with robust standard errors, adjusting for age at death, sex, education, any Apoe4 alleles, TBI with LOC after baseline, and ACT study cohort. Results were weighted back to the full cohort in a bootstrapping procedure that accounted for the error in estimating the weights, resulting in wider confidence intervals and higher *p*-values than in unweighted results.

[c] Total fixed brain weight divided by the expected brain weight, where the expected brain weight was calculated as 200 + the posterior fossa contents weight/0.15.

[d] Atrophy defined by dilatation in the lateral ventricles at the level of the temporal tip.