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Association between Traumatic Brain Injury and Late Life Neurodegenerative Conditions and Neuropathological Findings

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Abstract

IMPORTANCE—There is great interest in the late effects of traumatic brain injury (TBI).

OBJECTIVE—To determine whether TBI with loss of consciousness (LOC) is associated with increased risk for clinical and neuropathological findings of Alzheimer's disease, Parkinson's

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disease, and other dementias. Our primary hypothesis was that TBI with LOC would be associated with increased risk for Alzheimer's disease and neurofibrillary tangles.

DESIGN—Prospective cohort studies which follow all participants (Religious Orders Study and the Memory and Aging Project, ROS and MAP) or all consenting participants (Adult Changes in Thought, ACT) to autopsy. Studies performed annual (ROS and MAP) or biennial (ACT) cognitive and clinical testing to identify incident cases of dementia and Alzheimer's disease.

SETTING—Members of a Seattle-area healthcare delivery system (ACT); priests and nuns living in orders across the US (ROS), and Chicago-area adults in retirement communities (MAP).

PARTICIPANTS—7,130 older adults; 1,589 came to autopsy.

EXPOSURE—Self reported TBI reported when free of dementia, categorized as <1 hour vs. > 1 hour of LOC.

MAIN OUTCOMES AND MEASURES—Clinical: incident all-cause dementia, Alzheimer's disease, and Parkinson's disease (all studies), and incident mild cognitive impairment and progression of parkinsonian signs (ROS and MAP). Neuropathology: neurofibrillary tangles, neuritic plaques, microinfarcts, cystic infarcts, Lewy bodies, and hippocampal sclerosis (all studies).

RESULTS—865 participants reported a history of TBI with LOC. In >45,000 person-years of follow-up, there were 1,537 incident dementia and 117 incident Parkinson's disease cases. There was no association between TBI with LOC and incident dementia or Alzheimer's disease. There were associations between TBI with LOC and incident Parkinson's disease and progression of parkinsonian signs. There was no association between TBI with LOC and neurofibrillary tangles or neuritic plaques. There was an association between TBI with LOC and Lewy bodies, and with microinfarcts, though numbers of people with these findings were small.

CONCLUSIONS AND RELEVANCE—Pooled clinical and neuropathology data from three prospective cohort studies indicate that TBI with LOC is associated with risk of Lewy body accumulation, progression of parkinsonism, and Parkinson's disease, but not dementia, Alzheimer's disease, neuritic plaques, or neurofibrillary tangles.

Each year, many people experience a traumatic brain injury (TBI). Most TBIs are mild, and most people return to prior levels of functioning. Worry about late effects of TBI has magnified in recent years with media coverage of chronic traumatic encephalopathy (CTE) in athletes with repetitive head trauma[1,2]. Head injury is the signature injury of recent military conflicts[3]. Many TBIs are not sports- or combat-related. Characterizing late life effects of nonrepetitive TBIs in non-athlete civilians is important[4].

Studies assessing TBI's late effects have been limited with few exceptions[2,5] to outcomes observed during life. Several studies reported associations between TBI with loss of consciousness (TBI with LOC) and Alzheimer's disease[6]; the Institute of Medicine concluded moderate or severe TBI was an Alzheimer's disease risk factor[7]. We sought to determine whether there were associations between TBI with LOC and late life dementia, including Alzheimer's disease, and between TBI with LOC and Alzheimer's related neuropathologic changes. We hypothesized that TBI with LOC causes accumulation of

neurofibrillary tangles and increased Alzheimer's disease risk. We also assessed associations with Parkinson's disease, parkinsonism, Lewy bodies, and other neuropathologic changes.

Methods

Overview

We evaluated data from three prospective cohort studies, the Adult Changes in Thought (ACT) study, the Religious Orders Study (ROS), and the Memory and Aging Project (MAP). ROS and MAP were designed to have consistent data acquisition and processing and are analyzed jointly in numerous manuscripts. ROS and MAP TBI exposure rates were similar; we combined their data. For all participants, we evaluated associations between TBI and late life clinical outcomes including dementia and Alzheimer's disease (all 3 studies), mild cognitive impairment (MCI; ROS and MAP), Parkinson's disease (all 3 studies), and change in parkinsonian signs (ROS and MAP). For those who consented and came to brain autopsy, we evaluated associations between TBI and neuropathologic findings (all 3 studies).

Parent Studies

ROS started in 1994 and enrolled older religious clergy from >40 groups across the United States. MAP started in 1997 and enrolled older residents from Chicago-area retirement facilities and subsidized housing, and through church groups and social service agencies. ACT started in 1994 and enrolled older Seattle-area Group Health members. Detailed study design and data collection procedures are published.[8–12]

TBI Ascertainment

All studies assessed head injuries at enrollment and every study visit, and all captured TBI with LOC; exposure data were collected when participants were known not to have dementia. In ACT, an initial item ascertains whether participants had "an injury so severe that you lost consciousness." If that item is endorsed, subsequent items address type of injury including head injury and LOC duration. In ROS and MAP, participants are asked whether they have ever had a head injury, and if so, whether they ever lost consciousness and LOC duration. We provide further details in Supplemental Methods S1.

Dementia and Alzheimer's Disease Ascertainment, ACT

Methods for identifying dementia cases are published[10–12]. Participants were screened every two years with the Cognitive Abilities Screening Instrument (CASI)[13], a 100-point brief cognitive assessment. Participants with CASI scores <86 underwent a standardized diagnostic evaluation, including physical and neurological examinations and a neuropsychological test battery. Dementia diagnoses were determined at consensus conferences using DSM-IV criteria[14], and Alzheimer's disease using NINCDS-ADRDA criteria[15]. Additional details are provided in Supplemental Methods S2.

Mild Cognitive Impairment (MCI), Dementia, and Alzheimer's Disease Ascertainment, ROS and MAP

Cognitive function in ROS and MAP was assessed annually using a battery of 21 tests with 19 tests in common.[16] Computer-scored results were reviewed by a neuropsychologist to diagnose cognitive impairment. Participants were then evaluated by a clinician who used cognitive and clinical data to identify Alzheimer's disease and other dementias.[17] MCI was defined as cognitive impairment in the absence of dementia. Detailed methods are published[17,18] and are provided in Supplemental Methods S2.

Parkinsonian Features and Parkinson's Disease Ascertainment

We used pharmacy and ICD9 data in ACT and self-report data from ROS and MAP to identify Parkinson's disease; see Supplemental Methods S3. In ROS and MAP, parkinsonian features are assessed at every study visit using a modified version of the motor section of the Unified Parkinson's Disease rating Scale (mUPDRS[19]); see Supplemental Methods S4.

Neuropathology Protocols

Neuropathology protocols are published for ACT[20,21] and ROS and MAP[9,18,22,23]; details are provided in Supplemental Methods S5. We evaluated neurofibrillary degeneration as measured by Braak stage[24], neuritic plaque frequency according to Consortium to Establish a Registry for Alzheimer's Disease (CERAD)[25], presence of cerebral amyloid angiopathy, presence of macroscopic infarcts, presence of hippocampal sclerosis, presence and location of cerebral microinfarcts categorized as deep (basal ganglia or thalamus) vs. cortical, and presence and location of Lewy bodies categorized as present in the substantia nigra or locus ceruleus, in the frontal or temporal cortex, or in the amygdala. We dichotomized each neuropathologic measure as high vs. low/none based on associations with dementia[21]. High measures included Braak stage V or VI, intermediate or frequent CERAD scores, any amyloid angiopathy, any macroscopic infarcts, any microinfarcts, and any Lewy body.

Covariate Ascertainment

Age, sex, and years of education were self-reported. *APOE* genotype was obtained from consenting individuals. We adjusted models for *APOE* genotype as presence of ≥1 *APOE* ε4 alleles, and tested for interactions with APOE genotype and with sex.

Standard Protocol Approvals, Registrations, and Patient Consents

Studies were approved by Group Health, University of Washington, and Rush University Medical Center Institutional Review Boards. Participants provided written informed consent. ROS and MAP participants sign an Anatomic Gift Act donating their brain, and 25–30% of ACT participants consent to brain donation.

Statistical Analysis

We used Stata 13.1 for all analyses. We categorized duration of LOC as none vs. ≤1 hour vs. >1 hour. We adjusted models for age at study entry, sex, education, and study cohort. Proportional hazards and other model assumptions were tenable for incident Parkinson's disease, so we used Cox models for that outcome. We used Weibull models for analyses of

dementia, MCI, and Alzheimer's disease. We used ordinal mixed effects models to analyze parkinsonian signs; see Supplemental Methods S4 for additional details. We used Poisson regression models for neuropathology outcomes.

We noted that most of the participants who reported TBI with LOC > 1 hour were younger than age 25 at the time of their TBI, so we repeated analyses comparing individuals with TBI with LOC before age 25 to people who never reported a TBI with LOC; for these sensitivity analyses we censored people who had a TBI with LOC after age 25.

Results

There were 7,130 people with head injury data at enrollment; 4,265 (60%) from ACT and 2,865 (40%) from ROS and MAP. In ACT, there were 643 (15%) people who reported a TBI with LOC at enrollment, and in ROS and MAP, there were 222 (8%). Proportions of people reporting TBI with LOC >1 hour were more similar, with 94 from ACT (2.2%) and 48 from ROS and MAP (1.7%). These rates of TBI exposure are intermediate between those reported based on hospital data[26] and based on extensive injury history questionnaires[27]. Demographic characteristics stratified by history of TBI and duration of LOC are shown in Tables 1 and 2.

Incident MCI, Dementia, and Alzheimer's Disease

In ACT, people with prevalent dementia were not enrolled. One participant was missing educational attainment data. There were 4,626 participants. Of these, 3,666 (86%) had ≥1 follow-up visit. They had a median of 6.2 years of follow-up (interquartile range, IQR, 3.9–11.1 years), with a mean (standard deviation, SD) of 7.8 (5.0) years. We identified 921 incident cases of dementia and 759 of Alzheimer's disease in 28,664 person-years of follow-up. There was no statistically significant relationship between TBI with LOC and dementia risk. Compared with people with no TBI with LOC, people with LOC < 1 hour had an adjusted hazard ratio (HR) of 1.03 (95% confidence interval, CI, 0.83, 1.27) and those with a TBI with LOC >1 hour had an adjusted HR 1.18 (0.77, 1.78).

In ROS and MAP, 2 participants were missing educational attainment data, and 174 had prevalent dementia. There were 2,689 remaining participants. Of these, 2,452 (92%) had ≥1 follow-up visit. They had a median (IQR) of 4.7 (2.0–8.0) years of follow-up, with a mean (SD) of 5.5 (4.1) years. We identified 616 incident dementia cases and 563 of Alzheimer's disease in 16,526 person-years of follow-up. There was no statistically significant relationship between TBI with LOC and dementia risk. The HR (95% CI) for TBI with LOC < 1 hour was 0.87 (0.58, 1.29), and for TBI with LOC ≥ 1 hour it was 0.84 (0.44, 1.57).

Including *APOE* genotype did not change findings in either study and there were no significant interactions with *APOE* genotype (Supplemental Results S1) or sex (Supplemental Results S2). Results for Alzheimer's disease were similar to those for dementia (Supplemental Results S1). There was no association between TBI with LOC and incident MCI in ROS and MAP (Supplemental Results S1). When we grouped by age at TBI exposure, there was no statistically significant association between TBI with LOC and MCI, dementia, or Alzheimer's disease (Supplemental Results S1). It made little difference when

we used the most recent rather than earliest TBI with LOC in ACT (Supplemental Results S1).

Incident Parkinson's Disease and Progression of Parkinsonian Signs

We excluded 39 people with prevalent Parkinson's disease at enrollment in ACT, leaving 3,627 with ≥1 follow-up. We identified 83 incident Parkinson's disease cases in 22,800 person-years of follow-up. The adjusted HR (95% CI) for a TBI with <1 hour LOC was 0.66 (0.28, 1.52), while that for TBI with >1 hour LOC was 3.56 (1.52, 8.28).

We excluded 29 people with prevalent Parkinson's disease at enrollment in ROS and MAP, leaving 2,437 with ≥1 follow-up. We identified 34 incident Parkinson's disease cases in 18,156 person-years of follow-up. Only 3 of those who developed incident Parkinson's disease had reported exposure to TBI with LOC, all of whom had duration of LOC <1 hour. Regression results were unstable for TBI with LOC <1 hour, and undefined for TBI with LOC>1 hour.

For evaluation of the progression of parkinsonian signs, we controlled analyses for baseline age, sex, and time since baseline, and used the 8-point ordinal variable described in Supplemental Methods S3. The adjusted OR for increasing scores for a history of TBI-LOC was 1.75 (1.33, 2.29).

Neuropathological Findings at Autopsy

Of the 4,265 ACT participants who had TBI data from study enrollment, autopsy data were available for 525 of 2,022 deaths. Of the 2,643 ROS and MAP participants who had TBI data at study enrollment, autopsy data were available for 1,064 of 1,332 deaths. Demographic characteristics were similar to those for the entire cohorts; see Supplemental Results S3. The frequency of neuropathological findings is shown in Supplemental Results S4. Regression results for ACT and ROS and MAP separately are shown in Table 3. There was no association between TBI with LOC <1 hour and any neuropathological finding except Lewy bodies in frontal or temporal cortex in ROS and MAP. People with TBI with LOC>1 hour had increased risk for cerebral microinfarcts in ROS and MAP and hippocampal sclerosis and Lewy bodies in ACT. There were no interactions with *APOE* genotype (Supplemental Results S5) or sex (Supplemental Results S6).

Regression results from pooled analyses are shown in Table 4. In pooled analyses, TBI with LOC<1 hour was associated with increased risk for Lewy bodies in frontal or temporal cortex, and TBI with LOC>1 hour was associated with increased risk of cerebral microinfarcts.

More than a third of TBI with LOC<1 hour and nearly half of TBI with LOC>1 hour occurred at age<25. Among people with TBI with LOC before age 25, TBI with LOC>1 hour was associated with increased risk of microinfarcts and Lewy bodies, especially in frontal or temporal cortex (Table 5).

Discussion

In three prospective cohort studies of older adults free of dementia at baseline and followed for nearly 45,000 person-years, we did not find associations between TBI with LOC and risk of incident MCI, AD, or dementia. There were 1,537 incident dementia cases across the three studies, of which 1,322 were incident Alzheimer's disease; we had substantial power for these outcomes. We did not find associations between TBI with LOC and neurofibrillary degeneration or neuritic plaques, though Braak stage V or VI (30% in ACT, 24% in ROS and MAP) and intermediate or frequent neuritic plaques by CERAD (50% in ACT, 66% in ROS and MAP) were common. Including *APOE* genotype had negligible impact on our results, and we did not find different risk among *APOE* ε4 carriers. Our total autopsy sample size (1,652 autopsies) is nearly 7 times a previous evaluation of associations between TBI exposure and Alzheimer's pathology; those investigators found relationships with neocortical plaques and sex differences that are not confirmed in our study[5].

Parkinson's disease (total of 117 incident cases) and parkinsonian signs are less common than dementia. Despite lower power, we found associations between TBI with LOC > 1 hour and progression of parkinsonian signs (in ROS and MAP) and risk for incident Parkinson's disease (in ACT); there were no Parkinson's disease cases with that exposure in ROS and MAP.

Lewy bodies are less common (17% in ACT, 22% in ROS and MAP) than neuritic plaques, neurofibrillary tangles, or microinfarcts, but we found associations between TBI with LOC and Lewy body accumulation. Despite lower power, we found associations between TBI with LOC>1 hour and Lewy body accumulation in substantia nigra or locus ceruleus in ACT and in frontal or temporal cortex in ACT. We found associations between TBI with LOC < 1 hour and frontal or temporal cortex Lewy bodies in ROS and MAP, and the point estimate was similar for ACT, though ACT's confidence interval included 1. In pooled analyses, we found associations between TBI with LOC>1 hour and cerebral cortical Lewy bodies. A recent paper showed an association between TBI in mid life with development of Parkinson's disease a few years later[28]. Some features of synucleinopathies have been identified decades in advance of clinical disease, so it is possible that the higher rates of TBI with LOC in this group are the result of, rather than the cause of, Parkinson's disease. We suspect that explanation may be less likely here, where for many individuals exposure was four or more decades preceding Parkinson's disease. A prior study of TBI exposure and neuropathological outcomes excluded people with diffuse Lewy bodies from analyses.[5]

Cerebral microinfarcts were common (43% in ACT and 36% in ROS and MAP). TBI with LOC > 1 hour was associated with an increased risk of cortical microinfarcts in ACT. The point estimate was elevated in ROS and MAP, though the confidence interval included 1. The pooled analyses showed an association between TBI with LOC > 1 hour and cerebral cortical microinfarcts. Microinfarcts were identified on hematoxylin and eosin stained sections; more may have been identified if other stains had been used.

Limitations to this study warrant consideration. The study cohorts may not be broadly representative of the more ethnically diverse United States population. As in all cohort

studies, unmeasured and residual confounding are always possibilities. Data from the three studies were carefully harmonized, autopsies were performed by highly experienced neuropathologists using standard research protocols, and dementia diagnoses were obtained by expert clinicians using research quality guidelines; still, systematic differences may be present. TBI ascertainment methods varied across studies and were limited to self-report. Nevertheless, TBI exposure was ascertained at a time when participants were known not to be demented, and before the development of incident conditions and neuropathological evaluations described here. For Parkinson's disease diagnosis we were limited to self-report in two studies and medications and ICD9 codes in the other. We performed many tests, and did not alter our threshold for statistical significance, so it may be prudent to consider our results to be hypothesis generating. Some potentially important confounders were omitted, such as occupational history, smoking, physical activity, body mass index, risk taking, and alcohol intake. There is substantial interest in effects of repetitive TBI, but numbers of participants with >1 TBI with LOC were too small to analyze. We did not have data on athletic or military exposures, and the autopsy protocol did not include specific evaluation of chronic traumatic encephalopathy (CTE)[29]. The ACT neuropathology protocol did not specifically include evaluation of diffuse plaques, and none of the protocols were not designed specifically for detection of TBI-related neuropathology. The parent studies were designed to study late-onset Alzheimer's disease, and do not provide information about possible relationships between TBI and early-onset Alzheimer's disease. Reverse causation may be a concern in cohort studies with short intervals between exposure and outcome. This is less of a concern here as in sensitivity analyses we limited exposure to people younger than age 25. Even in that case, we found increased risk of Lewy body accumulation and microinfarcts among people enrolled after age 65 and thus had >40 years lag between exposure and outcome (see Supplemental eFigure 2).

Several previous studies have suggested associations between TBI with LOC and Alzheimer's disease.[30] To our knowledge this is by far the largest study ever on this topic. With more than adequate power to detect an association between TBI with LOC and Alzheimer's disease, we found no such association. We found that TBI with LOC was associated with Lewy body accumulation, progression of parkinsonian features, and risk for incident Parkinson's disease. These results suggest that a single TBI with LOC is not associated with increased risk for clinical Alzheimer's disease or the accumulation of neuritic plaques or neurofibrillary degeneration, but rather that the late life effects of TBI may include Lewy bodies, microinfarcts, Parkinson's disease, and parkinsonism. TBI with LOC sustained early in life is not innocuous, and appears to be associated with neurodegenerative conditions, though not Alzheimer's disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and functional characteristics of the ACT sample stratified by presence vs. absence of TBI and duration of loss of consciousness at baseline*

Variable	No TBI with LOC (n=3622)		TBI with LOC <1 hour (n=470)		TBI with LOC > 1 hour (n=94)		TBI with LOC, duration unknown (n=79)		Total (n=4,265)	
Demographics	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Age at study entry										
65–74	2,005	55	290	62	59	63	48	61	2,402	56
75–84	1,282	35	150	32	29	31	25	32	1,486	35
85–	335	9	30	6	6	6	6	8	377	9
Female sex	2,194	61	196	42	36	38	37	47	2,463	58
Education										
Up to 12 years	1,082	30	115	24	31	33	22	28	1,250	29
13–16 years	1,509	42	191	41	38	40	25	32	1,763	41
At least 17 years	1,030	28	164	35	25	27	32	41	1,251	29
Self-reported white race	3,288	91	445	95	89	95	76	96	3,898	92
Function	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
IRT CASI score	0.29	0.72	0.39	0.69	0.24	0.66	0.45	0.66	0.31	0.72
IADL score	0.35	0.83	0.36	0.85	0.48	0.95	0.36	0.72	0.35	0.83
ADL score	0.24	0.66	0.22	0.65	0.24	0.61	0.21	0.54	0.24	0.66

*One person was missing data on years of formal education, 8 people were missing data on self-reported race, 137 people were missing valid IRT CASI scores, 22 people were missing IADL scores, and 20 were missing ADL scores.

Abbreviations: TBI, traumatic brain injury. LOC, Loss of consciousness. IRT CASI, item response theory Cognitive Abilities Screening Instrument. IADL: instrumental activities of daily living. ADL, activities of daily living. SD, standard deviation.

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Table 2

Demographic and functional characteristics of the ROS and MAP sample stratified by presence vs. absence of TBI and duration of loss of consciousness at baseline

Variable	No TBI with LOC (n=2643)		TBI with LOC <1 hour (n=148)		TBI with LOC > 1 hour (n=48)		TBI with LOC, duration unknown (n=26)		Total (n=2,865)	
Demographics	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Age at study entry										
50–64	94	4	11	7	1	2	0	0	106	4
65–74	792	30	61	41	17	35	13	50	883	31
75–84	1222	46	60	41	22	46	7	27	1311	46
85–	535	20	16	11	8	17	6	23	565	20
Female sex	1917	73	94	64	31	65	16	62	2058	72
Education										
Up to 12 years	577	22	32	22	6	13	4	15	619	22
13–16 years	953	36	51	34	17	35	11	42	1032	36
At least 17 years	1111	42	65	44	25	52	11	42	1212	42
Self-reported white race	2439	92	139	94	47	98	25	96	2650	93
Function	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Global cognitive score	−0.01	0.65	0.14	0.61	−0.06	0.78	−0.03	0.60	−0.01	0.65
IADL score	1.02	1.58	0.81	1.21	1.23	1.78	1.12	1.51	1.02	1.56
ADL score	0.18	0.67	0.12	0.45	0.21	0.55	0.38	0.80	0.18	0.66
Rosow-Breslau scale	0.73	0.97	0.58	0.82	0.79	0.93	0.92	1.02	0.72	0.96

*2 people were missing data on years of formal education, 3 were missing data on self-reported race, 6 were missing data on cognition, 12 on IADLs, 9 on ADLs, and 12 on Rosow-Breslau scale scores.

Abbreviations: TBI, traumatic brain injury. LOC, loss of consciousness. IADL, instrumental activities of daily living; ADL, activities of daily living, SD, standard deviation

Table 3

Adjusted associations between traumatic brain injury with loss of consciousness and neuropathological findings separately in ACT and in ROS and MAP*

	ACT n=418 with no TBI with LOC exposure				ROS and MAP n=1,021 with no TBI with LOC exposure			
	TBI with LOC < 1 hour (n=80)		TBI with LOC ≥1 hour (n=14)		TBI with LOC < 1 hour (n=96)		TBI with LOC ≥1 hour (n=23)	
Outcome	**RR (95% CI)**	**P value**	**RR (95% CI)**	**P value**	**RR (95% CI)**	**P value**	**RR (95% CI)**	**P value**
Braak Stage 5 or 6	1.22 (0.86, 1.73)	0.26	1.11 (0.61, 2.00)	0.74	0.87 (0.55, 1.37)	0.54	0.85 (0.35, 2.06)	0.71
CERAD intermediate or frequent	1.01 (0.79, 1.29)	0.92	0.67 (0.36, 1.25)	0.21	1.01 (0.78, 1.31)	0.93	1.16 (0.73, 1.85)	0.54
Amyloid angiopathy	1.08 (0.73, 1.59)	0.71	1.02 (0.47, 2.20)	0.96	1.10 (0.88, 1.39)	0.41	1.11 (0.72, 1.71)	0.63
Cystic infarcts	0.83 (0.56, 1.24)	0.37	1.05 (0.52, 2.12)	0.88	0.95 (0.68, 1.33)	0.77	1.24 (0.71, 2.15)	0.45
Hippocampal sclerosis	0.93 (0.41, 2.10)	0.86	2.34 (1.02, 5.30)	0.042	0.84 (0.37, 1.93)	0.68	0.49 (0.07, 3.52)	0.48
Cerebral Microinfarcts								
Any	0.87 (0.64, 1.19)	0.39	1.23 (0.73, 2.09)	0.44	1.03 (0.72, 1.46)	0.88	1.18 (0.63, 2.21)	0.61
Any cortical	0.92 (0.65, 1.31)	0.64	1.12 (0.57, 2.18)	0.74	0.89 (0.53, 1.48)	0.66	2.12 (1.12, 4.01)	0.021
Any deep	0.89 (0.60, 1.33)	0.58	1.67 (0.95, 2.93)	0.075	1.16 (0.77, 1.76)	0.48	1.07 (0.47, 2.40)	0.88
Lewy bodies								
Any	0.93 (0.55, 1.59)	0.80	2.64 (1.40, 4.99)	0.003	1.04 (0.67, 1.62)	0.85	0.95 (0.39, 2.31)	0.91
Substantia Nigra / Locus Ceruleus	0.96 (0.51, 1.80)	0.89	3.30 (1.71, 6.38)	<0.001	1.09 (0.69, 1.71)	0.82	0.82 (0.31, 2.22)	0.70
Frontal or temporal cortex	1.49 (0.61, 3.64)	0.38	5.73 (2.18, 15.0)	<0.001	1.64 (1.00, 2.70)	0.051	0.74 (0.18, 3.00)	0.67
Amygdala / limbic‡	1.30 (0.75, 2.24)	0.35	1.89 (0.69, 5.19)	0.22	1.16 (0.73, 1.84)	0.91	0.91 (0.34, 2.44)	0.85

Models were adjusted for age at death, sex, years of education, and in the ACT study for study enrollment cohort

‡Lewy bodies were evaluated in the amygdala in the ACT study and in the limbic region in ROS and MAP. See methods section and supplemental methods for further details.

Abbreviations: TBI, traumatic brain injury. LOC, loss of consciousness. RR, relative risk. CERAD: Consortium to Establish a Registry for Alzheimer's Disease.

Table 4

Adjusted associations between traumatic brain injury with loss of consciousness at any age and neuropathological findings from analysis of pooled data from all three studies*

	TBI with LOC < 1 hr (n=176)		TBI with LOC ≥1 hr (n=37)	
Outcome	**RR (95% CI)**	**P value**	**RR (95% CI)**	**P value**
Braak Stage 5 or 6	1.02 (0.79, 1.33)	0.88	0.98 (0.58, 1.65)	0.93
CERAD intermediate or frequent	1.01 (0.89, 1.15)	0.88	1.00 (0.79, 1.27)	0.98
Amyloid angiopathy	1.08 (0.99, 1.19)	0.09	1.09 (0.93. 1.27)	0.28
Cystic infarcts	0.90 (0.73, 1.12)	0.35	1.17 (0.84, 1.62)	0.34
Hippocampal sclerosis	0.91 (0.51, 1.61)	0.75	1.34 (0.62, 2.89)	0.45
Cerebral Microinfarcts				
Any	0.94 (0.76, 1.15)	0.54	1.18 (0.85, 1.66)	0.32
Any cortical	0.90 (0.68, 1.19)	0.47	1.58 (1.06, 2.35)	0.026
Any deep	1.02 (0.78, 1.33)	0.90	1.30 (0.83, 2.05)	0.25
Lewy bodies				
Any	1.00 (0.73, 1.37)	0.99	1.44 (0.87, 2.39)	0.16
Substantia Nigra / Locus Ceruleus	1.04 (0.74, 1.45)	0.84	1.48 (0.86, 2.55)	0.16
Frontal or temporal cortex	1.59 (1.06, 2.39)	0.025	1.75 (0.82, 3.77)	0.15
Amygdala / limbic	1.22 (0.88, 1.69)	0.24	1.16 (0.59, 2.27)	0.67

* See footnotes to Table 3. Across the three studies there were 1,439 people with no reported TBI with LOC. These models adjusted for age at death, sex, years of education, and indicator terms for ROS, MAP, and three different enrollment groups for ACT

Table 5

Adjusted associations between traumatic brain injury with loss of consciousness younger than age 25 and neuropathological findings from joint analysis of data from all three studies*

	TBI with LOC < 1 hr (n=67)		TBI with LOC ≥1 hr (n=19)	
Outcome	**RR (95% CI)**	**P value**	**RR (95% CI)**	**P value**
Braak Stage 5 or 6	1.00 (0.66, 1.52)	0.99	1.03 (0.50, 2.14)	0.94
CERAD intermediate or frequent	1.09 (0.89, 1.32)	0.41	0.91 (0.62, 1.35)	0.65
Amyloid angiopathy	1.07 (0.89, 1.29)	0.44	0.86 (0.62, 1.20)	0.38
Cystic infarcts	0.83 (0.58, 1.21)	0.33	0.84 (0.45, 1.60)	0.60
Hippocampal sclerosis	1.42 (0.68, 2.97)	0.35	1.33 (0.37, 4.76)	0.66
Cerebral Microinfarcts				
Any	1.04 (0.78, 1.40)	0.77	1.66 (1.19, 2.32)	0.003
Any cortical	1.10 (0.77, 1.57)	0.60	1.29 (0.71, 2.35)	0.41
Any deep	1.06 (0.72, 1.58)	0.76	1.24 (0.64, 2.40)	0.53
Lewy bodies				
Any	0.95 (0.56, 1.62)	0.86	1.86 (1.03, 3.35)	0.040
Substantia Nigra or Locus Ceruleus	1.03 (0.59, 1.80)	0.91	1.84 (0.94, 3.60)	0.08
Frontal or temporal cortex	1.53 (0.77, 3.03)	0.23	2.53 (1.02, 6.24)	0.045
Amygdala / limbic	1.09 (0.60, 1.98)	0.78	1.77 (0.86, 3.64)	0.12

*See footnotes to Tables 3 and 4. Across the three studies there were 1,439 people with no reported TBI with LOC. These models adjusted for age at death, sex, years of education, and indicator terms for ROS, MAP, and three different enrollment cohorts for ACT. Note that only 6 people with TBI with LOC>1 hour had at least one microinfarct, and only 4 people with TBI with LOC > 1 hour had at least one Lewy body, so those results may be unstable.