**Supplemental materials**

This document provides supporting documentation to Crane, Gibbons, et al., “Association between traumatic brain injury and late life neurodegenerative conditions and neuropathological findings.”

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**Supplemental Methods S1. Details of head injury exposure ascertainment**

In ACT, participants were asked at study entry, “Have you ever had an injury so severe that you lost consciousness?” If an injury was reported, participants were further queried to determine whether the injury was a head injury or other type of injury (e.g., near drowning, electric shock), and the age at which this injury was sustained. At study entry, all lifetime injuries leading to loss of consciousness are recorded. Duration of loss of consciousness had response options shown in the left column of the table below. A person who reported a history of multiple head injuries leading to loss of consciousness would have all of those head injuries reported. Only head injuries that involved loss of consciousness are recorded.

From these data, age at injury and duration of loss of consciousness can be derived for every head injury with loss of consciousness reported by ACT participants.

Questions at every follow-up visit focused on injuries leading to loss of consciousness in the intervening period since the baseline evaluation. Follow-up questionnaires had the same format and response options as at baseline.

Not all head injuries lead to medical attention, and in many cases head injuries preceded Group Health membership by many years, so we could not validate self-reported TBI with LOC with medical records.

In ROS and MAP, participants are asked “Have you EVER had a head injury?” If they endorse a history of a head injury, the participant is asked “What year was the last time?” If they endorse ever having had a head injury, the participant is asked “Have you ever lost consciousness because of a head injury?” If the participant endorses loss of consciousness, they are asked, “How many times?” Subsequent questions relate only to the most recent head injury. They are asked, “What year was the last time?” The duration of loss of consciousness is assessed for the most recent head injury with a loss of consciousness, with response options of less than 5 seconds, between 5 seconds and 5 minutes, between 5 minutes and 1 hour, between 1 hour and 2 days, and more than 2 days.

From these data, for the most recent head injury with loss of consciousness, age at injury and duration of loss of consciousness can be derived from ROS and MAP data.

Not all head injuries lead to medical attention, and in many cases head injuries preceded study enrollment for many years, so we could not validate self-reported TBI with LOC with medical records.

|  |  |
| --- | --- |
| **eTable 1. Response options for duration of loss of consciousness in the three studies** | |
| **ACT** | **ROS and MAP** |
| A few seconds | Less than 5 seconds |
| A few seconds – 1 minute | 5 seconds – 5 minutes |
| 1-9 minutes | 5 minutes – 1 hour |
| 10 minutes-1 hour | **1 hour – 2 days\*** |
| **>1 hour\*** | **>2 days\*** |

\* Response categories grouped together as “LOC >1 hour” in analyses; these are also indicated by bold font

Subsequent analyses with the ACT cohort using a more sensitive indicator of TBI confirmed 100% of reported TBI with LOC along with additional cases. There are no other TBI indicators available from the ROS and MAP cohorts.

**Supplemental Methods S2. Detailed methods of dementia, Alzheimer’s disease, and MCI detection procedures.**

Methods for ACT have been published previously[1](#_ENREF_1) and we borrow from that source and its supplemental materials. Study participants were assessed every two years with the Cognitive Abilities Screening Instrument, for which scores range from 0 to 100 and higher scores indicate better functioning.[2](#_ENREF_2) The CASI assesses attention, concentration, orientation, memory, language, visual construction, verbal fluency, and judgment. Participants with scores of 85 or less underwent further clinical and psychometric evaluation, including a battery of neuropsychological tests (see below). The results of these evaluations and laboratory testing and imaging records were then reviewed in a consensus conference. Diagnoses of dementia[3](#_ENREF_3) and of probable or possible Alzheimer’s disease[4](#_ENREF_4) were made on the basis of research criteria. Dementia-free participants continued with scheduled follow-up visits. The incidence date was recorded as the halfway point between the study visit at which dementia was diagnosed and the previous visit.[5](#_ENREF_5)

The dementia psychometric battery includes clock drawing[6](#_ENREF_6), verbal fluency[7](#_ENREF_7), Mattis Dementia Rating Scale[8](#_ENREF_8), Boston naming[7](#_ENREF_7), verbal paired associations and recall, logical memory and recall[9](#_ENREF_9), Word List Memory[7](#_ENREF_7), Constructional Praxis and recall[7](#_ENREF_7), Trails A and B[10](#_ENREF_10), and Information and Comprehension subtest items[9](#_ENREF_9). All clinical data are reviewed at a consensus conference. If dementia is diagnosed, clinical laboratories and imaging results are considered in assigning dementia subtype (e.g. Alzheimer’s disease, thyroid disease, normal pressure hydrocephalus, vascular dementia, etc.). When these results are not available from medical records, they are requested to be ordered by the delivery system, results are obtained, and then reviewed again at a subsequent consensus conference.

These procedures have been used since 1986. ACT incidence rates are consistent with those found worldwide[5](#_ENREF_5), supporting the validity of our case definitions. Furthermore, forest plots of associations between single nucleotide polymorphisms and dementia from Alzheimer’s disease suggest similar strength of association for cases and controls ascertained by the ACT study as those from more than a dozen other research studies of dementia from Alzheimer’s disease[11](#_ENREF_11).

The ACT neuropsychological battery is characterized by good assessment of executive functioning (Mattis initiation and concept scales, comprehension, Trails, fluency, and clock drawing) which would aid in identification of vascular cognitive impairment / vascular dementia and fronto-temporal dementia. There is good assessment of spatial ability (clock and Mattis construction) that would help with the diagnosis of Lewy body dementia and Parkinson’s disease with dementia. It should be emphasized that the diagnostic process is based not only on psychometric test results but also on historical and clinical elements, all of which are considered by an expert consensus of clinicians and neuropsychologists using all available data including results from the psychometric tests.

In Table 1 we summarize cognitive functioning at baseline in the ACT study with an item response theory (IRT) CASI score. Methods and the rationale for scoring CASI responses using IRT have been published.[12](#_ENREF_12) Here we quote from that source. In prior analyses of data from the ACT study, we found that the CASI had curvilinear scaling properties such that a given number of standard CASI points was associated with a variable amount of cognitive ability at different parts of the ability spectrum. In that same analysis, we performed some simulation studies and demonstrated that use of standard scores with curvilinear tests produced biased estimates of rates of change compared with using IRT scores.[13](#_ENREF_13)

In IRT, tests are conceptualized as collections of items measuring a common underlying ability or trait. Each item has a difficulty level. Cognitive tests such as the CASI have several items with difficulty levels appropriate for individuals with moderate levels of impairment but few very hard questions appropriate for those with excellent cognition. Therefore, for an individual with excellent cognitive ability, a 5-point decline from 100 to 95 represents a relatively large cognitive decline because there are relatively few test items at risk. An individual with moderate impairment whose score declines from 80 to 75 points would have relatively less cognitive decline because there are many more test items at risk. The distribution of item difficulties is not uniform across all ability levels, so standard scores that sum the number of items answered correctly have a curvilinear relationship with the underlying ability measured by the test.

IRT scores analyze item-level data, so they have a linear relationship with the underlying ability measured by the test and should be preferred to standard scores for analyses of change over time.[13](#_ENREF_13)

We used data about the CASI items (item difficulty and discrimination parameters) from our previously published analyses[13](#_ENREF_13) to generate scores at baseline. We used the IRT computer program Parscale[14](#_ENREF_14" \o "Muraki, 2003 #176) (Scientific Software International Inc, Chicago, Illinois) and an IRT model called the graded response model[15](#_ENREF_15),[16](#_ENREF_16) which is appropriate for items with multiple response categories.

As in previous publications,[12](#_ENREF_12) the scale for IRT scores was defined such that the mean score was 0 and standard deviation was 1 among individuals without dementia at their most recent study visit.

The ACT study does not identify people with MCI; no exclusions of people with MCI were made for dementia or Alzheimer’s disease analyses.

Methods for ROS and MAP have been published previously[17](#_ENREF_17) and are provided here quoted from that source.

At baseline, each subject underwent a uniform structured evaluation that included the procedures recommended by the Consortium to Establish a Registry for AD (CERAD[7](#_ENREF_7)). Follow-up evaluations, identical in all essential details, were performed annually by examiners blinded to previously collected data. The evaluation included a medical history, complete neurologic examination, 20 neuropsychological performance tests (see below), and review of a brain scan when available. Clinical diagnoses were performed in a three-stage process. First, neuropsychological tests were administered by trained technicians and scored by a computer. Because neuropsychological tests do not measure cognition uniformly across different levels of education, an education-adjusted impairment rating for 11 tests commonly used for the clinical classification of AD was assigned based on review of the literature and extensive pilot testing; specific cut points can be found in Table 1 in a previous publication[17](#_ENREF_17). Second, an experienced, board-certified clinical neuropsychologist, blinded to subject age, sex, and race, reviewed the results of all cognitive tests, computer generated impairment ratings, and data on education, occupation, sensory and motor deficits, and effort. Based on review of these data, the neuropsychologist rendered a clinical judgment regarding the presence of cognitive impairment. Third, all participants were evaluated, in person, by a neurologist or geriatrician with expertise in the evaluation of older persons with and without dementia. Based on review of all available data, the clinician determined whether the subject met the clinical criteria for dementia and AD recommended by the joint working group of the National Institute of Neurologic and Communicative Disorders and Stroke/AD and Related Disorders Association (NINCDS/ADRDA).[4](#_ENREF_4) There were no consensus criteria for the clinical classification of MCI at the time ROS and MAP were launched.[18-20](#_ENREF_18) In this study, the group with MCI represented those persons who were judged to have cognitive impairment by the neuropsychologist but did not meet accepted criteria for dementia by the clinician. It should be emphasized that the neuropsychological tests were used to guide clinical judgment in order to enhance uniformity of clinical decisions across examiners and over time and to reduce bias based on age, sex, or race. However, both the neuropsychologist’s and clinician’s decisions were the result of clinical judgment.

People with MCI at baseline were included for analyses of dementia and AD risk to be parallel to the ACT study. People with MCI at baseline were included in analyses of risk for incident MCI.

**Supplemental Methods S3. Parkinson’s disease ascertainment**

Identification of Parkinson’s disease in ACT relied on pharmacy data and ICD-9 codes. ACT participants are drawn from Group Health, a stable health maintenance organization serving people in the greater Seattle area. Group Health includes a pharmacy benefit, and almost all (>95%) of older adults at Group Health fill almost all (>95%) of their prescriptions at a Group Health pharmacy. Group Health pharmacy data are available for all ACT participants since 1977. We considered dopaminergic agents with only an indication for Parkinson’s disease (e.g. levodopa, cabergoline) to indicate Parkinson’s disease treatment. Some dopamine agonists have an indication for Parkinson’s disease and for restless leg syndrome (pramipexole, ropinirole, rotigotine). For people where this was the only category of PD drugs they had received, we reviewed ICD9 codes for restless leg syndrome (333.99, 333.94) and related codes (750.58, sleep-related movement disorder, unspecified, and 780.59, other sleep disturbances). We considered any of these drugs in the absence of such an ICD9 code to indicate Parkinson’s disease treatment. We considered the mono-amine oxidase (MAO) inhibitor rasagiline to indicate PD treatment, as its only indication is Parkinson’s disease. The MAO inhibitor selegiline in the transdermal patch form has an indication for depression. We considered oral selegiline to indicate Parkinson’s disease treatment. Finally, amantadine can also be used to treat acute influenza as well as PD. We identified chronic amantadine treatment (defined by 3 or more fills) along with Parkinson’s disease ICD9 codes to indicate Parkinson’s disease treatment.

The identification of Parkinson’s disease in ROS and MAP was based on self-report. Participants at baseline were asked “Have you been told by a doctor, nurse, or therapist that you had Parkinsonism or Parkinson’s disease?” and “Are you currently taking any medication for your Parkinsonism or Parkinson’s disease (some examples are sinemet, Symmetrel, Parlodel, bromocriptine, etc.” Incident Parkinson’s disease was based on similar questions, e.g. “Since your last evaluation on (date), have you been told…” and the same “are you currently taking” item. We required affirmative responses to both items to identify prevalent (baseline) and incident (follow-up) Parkinson’s disease cases.

**Supplemental methods S4: Parkinsonian assessment in ROS and MAP and statistical methods**

The quantification of parkinsonian features in ROS and MAP has been previously published.[21](#_ENREF_21) This section borrows extensively from that source. Parkinsonism is assessed by trained nurses at study entry and is based on 26 items from a modified version of the motor section of the Unified Parkinson’s Disease rating Scale (mUPDRS).[22](#_ENREF_22) Four previously established parkinsonian sign scores (bradykinesia, rigidity, tremor, and gait disturbance) were derived from these 26 items, and a summary global parkinsonian sign score was constructed by averaging those 4 scores, as detailed in prior publications.[22](#_ENREF_22),[23](#_ENREF_23)

The distribution of the summary global parkinsonian sign score was very skewed and kurtotic in the combined ROS and MAP cohorts. The mean value (standard deviation) was 9.2 (8.5), with skewness of 1.7 and kurtosis 7.1. The histogram in eFigure 1 shows the global score across all time points (total = 16,152).

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| **eFigure 1. Histogram of global parkinsonian summary scores across all time points in ROS and MAP** |
|  |

Poisson regression is one valid analytic approach for longitudinal models of skewed and kurtotic data. Poisson regression models did not converge even after rounding each score to the nearest whole number. We therefore recoded scores into ordinal categories (see below), and performed mixed effects ordinal logistic regression, using multivariate adjusted Gauss-Hermite integration with 7 integration points, which is another appropriate analytic approach to analyze the longitudinal mUPDRS data to evaluate progression of parkinsonian features.

eTable 2 provides the original range of scores and their recoded category:

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| **eTable 2. Original global parkinsonian scores recoded into 8 ordinal categories** | |
| **Score range** | **Recoded ordinal score** |
| 0 | 0 |
| 0.625 – < 2.68 | 1 |
| 2.68 – < 6.96 | 2 |
| 6.96 – <13.21 | 3 |
| 13.21 – <20.35 | 4 |
| 20.35 – <25.71 | 5 |
| 25.71 – <38.08 | 6 |
| 38.08 – 100 | 7 |

These categories were determined on the basis of the distribution of scores to ensure adequate numbers in each category. That determination was done before looking at any associations with exposure.

In previous publications the parkinsonian score was analyzed by taking its square root; the square root of the score was then used as the dependent variable in mixed effects models. We did the same thing here, using an unstructured covariance matrix, and the findings were essentially the same; the coefficient was 0.21 (95% confidence interval, 0.10, 0.32, p<0.001).

**Supplemental Methods S5. Details of neuropathological assessment and harmonization.**

Neuropathology workup for ACT has been reported; we quote here from Li et al.[24](#_ENREF_24) and Sonnen et al.[25](#_ENREF_25) Neuropathologic examinations were performed in the UW Division of Neuropathology and the UW AD Research Center (ADRC) Neuropathology Core. All neuropathologic assessments were performed blind to clinical diagnosis and status of risk factors. Brains were immersion-fixed in formalin for at least 2 weeks prior to dissection. Following fixation, all brains were evaluated (wholly and after coronal sectioning) for any gross lesions, including the extent of atherosclerosis (“mild” when restricted to branch points in the circle of Willis, “moderate” when also in other regions at the base of the brain, and “severe” when present on the convexity of cerebrum) and the number of gross (macroscopic) cystic infarcts (including lacunar infarcts). We limited our evaluation to remote (estimated at least several months old) cystic (including lacunar) infarcts, as acute and subacute infarcts were thought unlikely to have contributed to longstanding cognitive decline. Lateral ventricle enlargement was estimated by measuring the maximal cross-section of the lateral ventricles following a coronal section at the temporal tips. Tissue sections were dissected from middle frontal gyrus, superior and middle temporal gyri, inferior parietal lobule, anterior cingulate gyrus, primary visual cortex, basal ganglia at the level of the anterior commissure, thalamus, hippocampus at the level of the uncus and lateral geniculate nucleus, amygdala, midbrain including substantia nigra, pons at the level of the locus ceruleus, medulla, cerebellar hemisphere, and pituitary gland. These tissue sections were processed and embedded in paraffin prior to sectioning and staining. Neuritic plaques (NPs) were scored according to the criteria of the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD). [26](#_ENREF_26),[27](#_ENREF_27) Neurofibrillary tangles (NFTs) were scored according to the methods of Braak and Braak.[28](#_ENREF_28),[29](#_ENREF_29) Amyloid angiopathy was scored according to the method of Vonsattel.[30](#_ENREF_30) Microvascular lesions (MVLs) were evaluated in bilateral sections of frontal lobe, temporal lobe, parietal lobe, occipital lobe, caudate nucleus, putamen, internal capsule, and thalamus similarly to the protocol published by the Honolulu Asia Aging Study. [31](#_ENREF_31) A MVL (microinfarct) was defined as an encephalomalacic lesion, 2 mm or smaller in its greatest dimension, which was not visible on gross inspection of the brain. Hematoxin and eosin-stained sections were evaluated for hippocampal sclerosis; TDP-43 immunostains were not routinely performed.

Immunohistochemistry for α-synuclein is performed in sections from frontal cortex and amygdala and evaluated in brainstem (substantia nigra and locus ceruleus) on H&E / luxol fast blue stained sections. A classification of neocortical Lewy body disease was made if immunohistochemically confirmed Lewy bodies were identified in mid-frontal cortex, and was typically associated with brainstem and amygdala Lewy bodies.[32](#_ENREF_32),[33](#_ENREF_33)

Neuropathology workup for ROS and MAP have been reported; we quote here from Yu et al.[34](#_ENREF_34) and Bennett et al.[35](#_ENREF_35) Postmortem brains are processed following a standard procedure. Brains of deceased subjects were removed, weighed, and cut coronally into 1-cm slabs and fixed for at least 72 hours in 4% paraformaldehyde, blocked, and embedded in paraffin. Paraffin-embedded tissue blocks were sectioned at 6 µm. One block was dissected from each of 5 regions (midfrontal cortex, middle/superior temporal cortex, inferior parietal, hippocampus, and entorhinal cortex) and stained with modified Bielschowsky technique to assess for AD pathology. These blocks (except the hippocampus), the midbrain, and anterior cingulate cortex were also stained with antibodies to alpha-synuclein to assess for Lewy bodies. These 7 regions plus 2 others (anterior basal ganglia and thalamus) were stained with hematoxylin and eosin to assess for microscopic infarctions. Investigators also dissected blocks for histological confirmation of macroscopic infarctions. Separately, tissue blocks from each 1 cm slab from 2 regions (entorhinal cortex, CA1/subiculum of the hippocampus) and 2 tissue blocks from 5 regions (superior frontal cortex, dorsolateral prefrontal cortex, inferior temporal cortex, angular gyrus, and anterior cingulate cortex) were cut into 20 µm sections to assess amyloid load and paired helical filament (PHF) tau tangle density. Two or more blocks from each region were taken to reduce random variability.

Fixed slabs and/or pictures from both hemispheres were examined for macroscopic infarcts, followed by histological confirmation.[36](#_ENREF_36) Microinfarcts, defined as infarcts not seen grossly but discovered using microscopy, were identified by examining at least 9 sections stained with hematoxylin and eosin.[37](#_ENREF_37) We considered only presence vs. absence of chronic infarcts in the analysis. We only considered neocortical Lewy body as presence of alpha-synuclein immunoreactive Lewy bodies in either mid-frontal, or middle or superior temporal cortex; we excluded inferior parietal cortex to be harmonized with ACT.[38](#_ENREF_38) Hippocampal sclerosis was evaluated unilaterally in a coronal section of the midhippocampus at the level of the lateral geniculate body, and graded as absent or present based on severe neuronal loss and gliosis in CA1 and/or subiculum[39](#_ENREF_39" \o "Nag, 2015 #5417). TDP-43 immunostaining is also performed but was not used to determine the presence or absence of hippocampal sclerosis.

For this project, investigators performed additional analyses to ensure that data for ROS and MAP could be harmonized with data for ACT. Microinfarct data were collected by both studies but general locations were recorded differently. The locations of the microinfarcts are recorded in the electronic database as one of 70 possible regions in the brain; investigators classified these as cortical or deep to align with the ACT classification. Cortical infarcts included infarcts in the cortex and underlying white matter; with deep microinfarcts including those in the basal ganglia and thalamus. From this reclassification, we programmed comparable variables for analyses.

ROS and MAP autopsy procedures have not routinely included evaluation of the amygdala for Lewy bodies in particular. Rather slides are reviewed enabling a rating of whether Lewy bodies are seen in the entorhinal cortex. Recently, Lewy body assessments have begun in the amygdala as well as in the entorhinal cortex. **eTable 3** below shows agreement between data for the amygdala and entorhinal cortex from a sample of brains from ROS, MAP, and from the metholodogically similar Minority Aging Research Study (MARS); the same pathologists perform the vast majority of neuropathologic evaluations for all three studies.

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| **eTable 3. Agreement between Lewy body findings for amygdala and entorhinal cortex in ROS, MAP, and MARS** | | | |
|  | Entorhinal cortex Lewy bodies absent | Entorhinal cortex Lewy bodies present | Total |
| Amygdala Lewy bodies absent | 183 | 1 | 184 |
| Amygdala Lewy bodies present | 5 | 101 | 106 |
| Total | 188 | 102 | 290 |

These data enabled us to compute a kappa coefficient to measure agreement beyond that expected by chance alone, which was 0.96 (95% confidence interval, 0.92-0.99). This excellent agreement reinforced our choice to examine Lewy bodies in the amygdala from ACT alongside Lewy bodies from the entorhinal cortex from ROS and MAP.

Detailed methods for amyloid angiopathy evaluation have been recently published[40](#_ENREF_40). Here we quote from that source. “For CAA assessment, we expanded on a previously published methodology[41](#_ENREF_41) similar to a recently proposed protocol.[42](#_ENREF_42) For each region, meningeal and parenchymal vessels were assessed for amyloid deposition and scored from 0 to 4, where 0 5 no deposition, 1 5 scattered segmental but no circumferential deposition, 2 5 circumferential deposition up to 10 vessels, 3 5 circumferential deposition up to 75% of the region, and 4 5 circumferential deposition over 75% of the total region. The CAA score for each region was the maximum of the meningeal and parenchymal CAA scores. Scores were averaged across regions and summarized as a continuous measure of CAA pathology for analyses. In addition, for illustration of findings and supporting analyses, we classified CAA scores into a 4-level severity rating including none, mild, moderate, and severe using cutoffs determined by the neuropathologist. Finally, capillary CAA was rated as present or absent.” For these analyses we used the 4-level severity CAA rating, and as in ACT used present vs. absent in analyses.

**Supplemental Methods S6. Authorship roles.**

The ACT study was designed by Eric Larson with Walter Kukull and Gerald van Belle. Dr. Larson and Paul Crane serve as multiple PIs of the ACT study. ROS and MAP were designed by David Bennett. MARS was designed by Lisa Barnes.

The present analyses were designed by Paul Crane, Laura Gibbons, Kristen Dams-O’Connor, and Emily Trittschuh, and all analyses performed by Dr. Gibbons.

Neuropathology evaluations for ROS, MAP, and MARS were performed by Julie Schneider. Neuropathology evaluations for ACT were performed by Thomas Montine, Joshua Sonnen, and C. Dirk Keene. Discussions around harmonizing ACT neuropathology data with ROS and MAP data were conducted by Drs. Keene, Schneider, Leurgans, and Crane. Recoding of ROS and MAP neuropathology data based on these discussions were performed by Drs. Leurgans and Schneider, who also performed additional analyses of Lewy bodies in the amygdala and entorhinal cortex using data from ROS, MAP, and MARS. Parkinson’s expertise was provided by Drs. Bennett and James Leverenz.

Dr. Crane wrote the first draft of the paper. All authors supplied critical intellectual content to the first draft, which Dr. Crane incorporated in subsequent drafts of the paper. All authors approved the final manuscript. The decision to publish the paper was mutual by all authors.

The National Institutes of Health (the sponsor of the ACT, ROS, MAP, and MARS studies) had no influence on the decision to publish the paper and no requirements to keep any aspect of the data confidential.

**Supplemental Results S1. Sensitivity analyses for dementia, Alzheimer’s disease, and MCI.**

**eTable 4** below shows dementia outcomes with and without *APOE* genotype entered in the model stratified by duration of loss of consciousness associated with the traumatic brain injury. For both ACT and ROS and MAP, results in the left column are as reported in the body of the paper. Due to missing data on *APOE* genotype, sample size is somewhat smaller when including that covariate. In this table, people with TBI with LOC of unknown duration are excluded. When stratifying by duration of loss of consciousness, including *APOE* genotype in the models had a negligible effect on point estimates for the hazard ratios, and the pattern of findings was the same.

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| **eTable 4. Dementia outcomes with and without *APOE* genotype, stratified by duration of LOC** | | | | |
|  | **ACT** | | **ROS and MAP** | |
|  | **Excluding *APOE*** | **Including *APOE*** | **Excluding *APOE*** | **Including *APOE*** |
| N | 3,666 | 3,176 | 2,452 | 2,036 |
| Person-years | 28,664 | 25,607 | 16,526 | 14,880 |
| N dementia cases, known duration LOC | 921 | 806 | 612 | 572 |
| N TBI with <1 hour LOC | 394 | 334 | 122 | 98 |
| N TBI with ≥ hour LOC | 79 | 73 | 41 | 29 |
| HR, <1 hour LOC (95% CI) | 1.03 (0.83, 1.27) | 0.97 (0.77, 1.23) | 0.87 (0.58, 1.29) | 0.80 (0.53, 1.20) |
| HR, ≥1 hour LOC (95% CI) | 1.18 (0.77, 1.78) | 1.25 (0.81, 1.93) | 0.84 (0.45, 1.57) | 0.81 (0.43, 1.53) |

For ACT, the model with interaction terms between *APOE* ε4 carrier status and duration of TBI with LOC had a chi squared value of 1.04 on 2 degrees of freedom, which results in a p value of 0.60. The hazard ratio for *APOE* ε4 carriers with a TBI with LOC < 1 hour was 1.13 (95% CI 0.69, 1.84), and for *APOE* ε4 carriers with a TBI with LOC > 1 hour the HR was 0.55 (0.13, 2.37).

For ROS and MAP, the model with interaction terms between *APOE* ε4 carrier status and duration of TBI with LOC had a chi squared value of 2.43 on 2 degrees of freedom, which results in a p value of 0.30. The hazard ratio for *APOE* ε4 carriers with a TBI with LOC<1 hour was 0.57 (95% CI 0.24, 1.37), and for *APOE* ε4 carriers with a TBI with LOC>1 hour the HR was 0.55 (95% CI 0.15, 1.97).

**eTable 5** shows dementia outcomes with and without *APOE* genotype entered in the model stratified by reported age at time of TBI. Here we included people with a TBI whose duration of loss of consciousness was unknown or not reported. Including *APOE* genotype in these models had a negligible effect on point estimates for the hazard ratios, and the pattern of findings was similar, with the exception that the direction of effect for people in ROS and MAP who reported a TBI with LOC at age ≥55 was insignificantly elevated without *APOE* genotype in the model and insignificantly reduced when including *APOE* genotype in the model.

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| **eTable 5. Dementia outcomes with and without *APOE* genotype, stratified by age at TBI** | | | | |
|  | **ACT** | | **ROS and MAP** | |
|  | **Excluding *APOE*** | **Including *APOE*** | **Excluding *APOE*** | **Including *APOE*** |
| N dementia cases, any duration LOC | 934 | 818 | 616 | 576 |
| N TBI with LOC, age < 25 | 339 | 293 | 78 | 63 |
| N TBI with LOC, age 25-54 | 89 | 72 | 42 | 29 |
| N TBI with LOC, age ≥ 55 | 178 | 165 | 65 | 56 |
| HR, age <25 | 1.14 (0.91, 1.44) | 1.05 (0.82, 1.36) | 0.63 (0.37, 1.07) | 0.65 (0.38, 1.11) |
| HR, age 25-54 | 1.05 (0.69, 1.58) | 1.00 (0.64, 1.55) | 0.84 (0.40, 1.77) | 0.92 (0.44, 1.93) |
| HR, age ≥ 55 | 0.82 (0.62, 1.08) | 0.91 (0.68, 1.21) | 1.11 (0.70, 1.78) | 0.88 (0.54, 1.44) |

For ACT, the model including interaction terms between *APOE* ε4 carrier status and age-group exposure categories had a chi squared value of 0.37 on 3 degrees of freedom, which results in a p value of 0.95. The hazard ratio (95% CI) for *APOE* ε4 carriers who sustained a TBI with LOC younger than age 25 was 1.10 (0.65, 1.85), the HR for *APOE* ε4 carriers who sustained a TBI with LOC from age 25-55 was 1.28 (95% CI 0.50, 3.24), and for *APOE* ε4 carriers who sustained a TBI with LOC after age 55 the HR was 1.04 (95% CI 0.52, 2.07).

For ROS and MAP, the model including interaction terms between *APOE* ε4 carrier status and age-group exposure categories had a chi squared value of 5.74 on 3 degrees of freedom, which results in a p value of 0.12. The hazard ratio (95% CI) for *APOE* ε4 carriers with TBI with LOC exposure sustained before age 25 was 0.83 (95% CI 0.26, 2.68); for *APOE* ε4 carriers with TBI with LOC sustained age 25-55, the HR was 0.74 (95% CI 0.14, 3.86), and for *APOE* ε4 carriers with TBI with LOC sustained after age 55, the HR was 0.31 (95% CI 0.11-0.82). The Wald p value for the last category was 0.019. There is little biological plausibility that sustaining a TBI after age 55 would be protective for people with 1 or more APOE ε4 alleles, and across all 3 age groups the LR test (as reported above) was non-significant.

**eTable 6** shows probable or possible Alzheimer’s disease by NINCDS-ADRDA criteria[4](#_ENREF_4) stratified by the duration of loss of consciousness. Findings are similar to those reported for all-cause dementia in the body of the paper (left columns for both ACT and ROS and MAP; compare with the left columns of **eTable 4** above). Including *APOE* genotype had a negligible effect on risk estimates for probable or possible Alzheimer’s disease. Numbers of people and person-years are different from those for the dementia outcome because of censoring at time of non-Alzheimer’s disease dementia.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **eTable 6. Alzheimer’s disease outcomes with and without *APOE* genotype, stratified by duration of LOC** | | | | |
|  | **ACT** | | **ROS and MAP** | |
|  | **Excluding *APOE*** | **Including *APOE*** | **Excluding *APOE*** | **Including *APOE*** |
| N | 3,666 | 3,176 | 2,445 | 2,030 |
| Person-years | 28,664 | 25,607 | 16,461 | 14,817 |
| N AD cases, known duration LOC | 749 | 656 | 559 | 521 |
| N TBI with LOC <1 hour | 394 | 334 | 122 | 98 |
| N TBI with LOC ≥ hour | 79 | 73 | 41 | 29 |
| HR, <1 hour LOC (95% CI) | 0.99 (0.77, 1.26) | 0.96 (0.74, 1.25) | 0.81 (0.52, 1.25) | 0.74 (0.47, 1.16) |
| HR, ≥1 hour LOC (95% CI) | 1.16 (0.72, 1.85) | 1.26 (0.78, 2.06) | 0.82 (0.43, 1.59) | 0.79 (0.41, 1.54) |

For ACT, models including interaction terms for *APOE* genotype were unstable. The model had a chi squared value of 5.91 on 2 degrees of freedom, which results in a p value of 0.052. The hazard ratio (95% CI) for *APOE* ε4 carriers with a TBI with LOC < 1 hour was 1.10 (0.63, 1.90), while for *APOE* ε4 carriers with a TBI with LOC>1 hour the HR (95% CI) was 0 (undefined confidence interval) due to very small cell sizes.

For ROS and MAP, the model with interaction terms between *APOE* ε4 carriers and duration of TBI with LOC had a chi squared value of 0.73 on 2 degrees of freedom, which results in a p value of 0.70. The hazard ratio (95% CI) for *APOE* ε4 carriers with a TBI with LOC < 1 hour was 0.76 (95% CI 0.30, 1 91), and for *APOE* ε4 carriers with a TBI with LOC > 1 hour, the HR (95% CI) was 0.65 (0.17, 2.46).

**eTable 7** shows probable or possible Alzheimer’s disease stratified by reported age at time of TBI. Patterns of findings are similar to those shown in **eTable 5** above. Including *APOE* genotype did not have a marked impact on estimates.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **eTable 7 Alzheimer’s disease outcomes with and without *APOE* genotype, stratified by age at TBI** | | | | |
|  | **ACT** | | **ROS and MAP** | |
|  | **Excluding *APOE*** | **Including *APOE*** | **Excluding *APOE*** | **Including *APOE*** |
| N AD cases, any duration LOC | 759 | 666 | 563 | 525 |
| N TBI with LOC, age < 25 | 339 | 293 | 78 | 63 |
| N TBI with LOC, age 25-54 | 89 | 72 | 42 | 29 |
| N TBI with LOC, age ≥ 55 | 178 | 165 | 65 | 56 |
| HR, age <25 | 1.17 (0.90, 1.51) | 1.11 (0.84, 1.47) | 0.69 (0.40, 1.17) | 0.71 (0.42, 1.21) |
| HR, age 25-54 | 0.90 (0.55, 1.49) | 0.92 (0.55, 1.53) | 0.67 (0.28, 1.61) | 0.73 (0.30, 1.76) |
| HR, age ≥55 | 0.70 (0.50, 0.97) | 0.77 (0.55, 1.09) | 1.03 (0.62, 1.73) | 0.80 (0.47, 1.37) |

For ACT, the model including interaction terms between *APOE* ε4 carrier status and each age-group exposure category had a chi squared value of 0.12 on 3 degrees of freedom, which results in a p value of 0.99. The hazard ratio for a TBI with LOC sustained younger than age 25 among those with 1 or more copies of the *APOE* ε4 allele was 1.00 (95% CI 0.56, 1.78), for those with a TBI with LOC sustained at age 25-55 years, the HR (95% CI) was 1.16 (0.39, 3.44), and for those with a TBI with LOC sustained at age >55, the HR (95% CI) was 0.91 (0.39, 2.13).

For ROS and MAP, the model with interaction terms between *APOE* ε4 carrier status and each age group exposure category had a chi squared value of 2.61 on 3 degrees of freedom, which results in a p value of 0.46. The hazard ratio for a TBI with LOC sustained younger than age 25 among those with 1 or more copies of the *APOE* ε4 allele was 0.84 (95% CI 0.26, 2.74), for those with a TBI with LOC sustained at age 25-55 years, the HR (95% CI) was 1.21 (0.20, 7.35), and for those with a TBI with LOC sustained at age >55, the HR (95% CI) was 0.42 (0.14, 1.21).

**eTable 8** shows results for MCI in ROS and MAP with and without including *APOE* genotype. There was no increased risk of MCI associated with TBI with LOC.

|  |  |  |
| --- | --- | --- |
| **eTable 8. MCI outcomes with and without *APOE* genotype, stratified by duration of LOC and by age at TBI, in ROS and MAP** | | |
|  | **Excluding *APOE*** | **Including *APOE*** |
| **Duration of LOC** |  |  |
| N | 1,790 | 1,447 |
| Person-years | 10,172 | 9,083 |
| N AD cases, known duration LOC | 888 | 819 |
| N TBI with LOC <1 hour | 104 | 83 |
| N TBI with LOC ≥ hour | 30 | 21 |
| HR, <1 hour LOC (95% CI) | 1.08 (0.81, 1.44) | 1.04 (0.77, 1.40) |
| HR, ≥1 hour LOC (95% CI) | 0.52 (0.29, 0.95) | 0.51 (0.27, 0.95) |
| Age at TBI with LOC |  |  |
| N |  |  |
| Person-years |  |  |
| N AD cases, any duration LOC | 899 | 830 |
| N TBI with LOC, age < 25 | 67 | 53 |
| N TBI with LOC, age 25-54 | 32 | 20 |
| N TBI with LOC, age ≥ 55 | 53 | 48 |
| HR, age <25 | 0.68 (0.46, 1.00) | 0.66 (0.44, 0.98) |
| HR, age 25-54 | 1.09 (0.66, 1.82) | 1.37 (0.82, 2.29) |
| HR, age ≥55 | 1.18 (0.82, 1.70) | 1.03 (0.71, 1.49) |

The model including *APOE* genotype interactions with exposure defined by the duration of LOC had a chi squared value of 0 on 2 degrees of freedom, with a p value of 1.00. The hazard ratio (95% CI) for *APOE* ε4 carriers with TBI with LOC < 1 hour was 1.01 (0.54, 1.89), and for *APOE* ε4 carriers with TBI with LOC > 1 hour the HR was 0.96 (95% CI 0.27, 3.44).

The model including *APOE* genotype interactions with exposure defined by age at TBI with LOC had a chi squared value of 0.43 on 3 degrees of freedom, with a p value of 0.93. The HR (95% CI) for *APOE* ε4 carriers with TBI with LOC sustained younger than age 25 was 1.00 (0.41, 2.45), for *APOE* ε4 carriers who sustained a TBI with LOC from age 25 to 55 the HR was 1.09 (0.34, 3.46), and for *APOE* ε4 carriers who sustained a TBI with LOC after age 55 the HR was 0.78 (95% CI 0.36, 1.67).

To make the TBI with LOC operational definitions more comparable between studies, we considered the most recent TBI with LOC rather than the first lifetime TBI with LOC for the ACT study. We did not see an association between TBI with LOC and either dementia or AD risk, whether excluding or including APOE genotype data, as shown in **eTable 9.**

|  |  |  |
| --- | --- | --- |
| **eTable 9. Sensitivity analysis using most recent TBI with LOC from ACT.** | | |
|  | **Excluding *APOE*** | **Including *APOE*** |
| **Dementia** |  |  |
| N dementia cases, any duration LOC including unknown | 934 | 818 |
| N TBI with LOC, age < 25 | 310 | 267 |
| N TBI with LOC, age 25-54 | 100 | 89 |
| N TBI with LOC, age ≥ 55 | 131 | 113 |
| HR, age <25 | 1.20 (0.95, 1.51) | 1.09 (0.84, 1.41) |
| HR, age 25-54 | 1.10 (0.74, 1.64) | 1.09 (0.71, 1.67) |
| HR, age ≥ 55 | 0.74 (0.50, 1.10) | 0.84 (0.56, 1.26) |
| **Alzheimer’s disease** |  |  |
| N AD cases, any duration LOC including unknown | 759 | 666 |
| N TBI with LOC, age < 25 | 310 | 267 |
| N TBI with LOC, age 25-54 | 100 | 89 |
| N TBI with LOC, age ≥ 55 | 131 | 113 |
| HR, age <25 | 1.21 (0.94, 1.58) | 1.15 (0.86, 1.52) |
| HR, age 25-54 | 0.99 (0.62, 1.58) | 1.05 (0.64, 1.70) |
| HR, age ≥55 | 0.67 (0.42, 1.05) | 0.77 (0.48, 1.24) |

The model for dementia including *APOE* genotype interactions with exposure defined by age at TBI with LOC had a chi squared value of 0.27 on 3 degrees of freedom, with a p value of 0.97. The HR (95% CI) for *APOE* ε4 carriers with TBI with LOC sustained younger than age 25 was 1.14 (0.67, 1.93), for *APOE* ε4 carriers who sustained a TBI with LOC from age 25 to 55 the HR was 1.10 (0.42, 2.85), and for *APOE* ε4 carriers who sustained a TBI with LOC after age 55 the HR was 1.02 (95% CI 0.40, 2.61).

The model for AD including *APOE* genotype interactions with exposure defined by age at TBI with LOC had a chi squared value of 0.17 on 3 degrees of freedom, with a p value of 0.98. The HR (95% CI) for *APOE* ε4 carriers with TBI with LOC sustained younger than age 25 was 1.05 (0.59, 1.88), for *APOE* ε4 carriers who sustained a TBI with LOC from age 25 to 55 the HR was 0.88 (0.28, 2.75), and for *APOE* ε4 carriers who sustained a TBI with LOC after age 55 the HR was 1.18 (95% CI 0.42, 3.37).

**Supplemental Results S2. Interactions with sex for dementia outcomes.**

eTable 10 shows overall and sex-stratified results for dementia (top) and Alzheimer’s disease (bottom) analyses.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **eTable 10. Overall and sex-stratified results for all-cause dementia (top) and for AD (bottom)** | | | | |
| **Study and Group** | **TBI with LOC <1 hour** | | **TBI with LOC > 1 hour** | |
|  | **HR (95% CI)** | **p value** | HR (95% CI) | **p-value** |
| **All-cause dementia** |  |  |  |  |
| ACT, overall | 1.03 (0.83, 1.27) | 0.81 | 1.18 (0.78, 1.78) | 0.44 |
| ACT, males | 0.88 (0.64, 1.21) | 0.44 | 1.10 (0.63, 1.93) | 0.73 |
| ACT, females | 1.19 (0.65, 1.21) | 0.25 | 1.30 (0.69, 2.42) | 0.42 |
| ROS / MAP, overall | 0.87 (0.58, 1.29) | 0.48 | 0.84 (0.45, 1.57) | 0.59 |
| ROS / MAP, males | 0.93 (0.49, 1.77) | 0.82 | 2.03 (0.75, 5.50) | 0.17 |
| ROS/MAP, females | 0.85 (0.51, 1.42) | 0.53 | 0.60 (0.27, 1.34) | 0.21 |
| **Probable or possible Alzheimer’s disease** | | | | |
| ACT, overall | 0.99 (0.77, 1.26) | 0.92 | 1.16 (0.72, 1.85) | 0.61 |
| ACT, males | 0.97 (0.68, 1.37) | 0.84 | 1.14 (0.60, 2.15) | 0.69 |
| ACT, females | 1.01 (0.72, 1.41) | 0.97 | 1.22 (0.61, 2.46) | 0.57 |
| ROS/MAP, overall | 0.81 (0.52, 1.25) | 0.34 | 0.82 (0.43, 1.59) | 0.56 |
| ROS/MAP, males | 0.83 (0.40, 1.69) | 0.60 | 2.22 (0.81, 6.03) | 0.12 |
| ROS/MAP, females | 0.82 (0.47, 1.43) | 0.48 | 0.54 (0.22, 1.31) | 0.17 |

The p value for the interaction term for sex for all-cause dementia in ACT was 0.39, and for ROS and MAP it was 0.21. The p value for the interaction term for sex for probable or possible AD in AC was 0.97, and for ROS and MAP it was 0.14.

**Supplemental Results S3. Demographic characteristics of the autopsy cohorts.**

**eTable 11** shows characteristics of the ACT cohort stratified by autopsy status.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **eTable 11. Demographic and functional characteristics of the ACT sample stratified by autopsy status\*** | | | | | |
| **Variable** | **No Autopsy** | | **Autopsy** | |  |
| **Demographics** | **N** | **%** | N | **%** | **p-value** |
| Age at study entry |  |  |  |  |  |
| 65–74 | 2,231 | 60 | 171 | 33 | < 0.001 |
| 75–84 | 1,223 | 33 | 263 | 50 |  |
| 85– | 286 | 8 | 91 | 17 |  |
| Female sex | 2,178 | 58 | 285 | 54 | 0.090 |
| Education |  |  |  |  | < 0.001 |
| Up to 12 years | 1,076 | 29 | 174 | 33 |  |
| 13–16 years | 1,529 | 41 | 234 | 45 |  |
| At least 17 years | 1,134 | 30 | 117 | 22 |  |
| Self-reported white race | 3,394 | 91 | 504 | 96 | < 0.001 |
| **Function** | **Mean** | **SD** | **Mean** | **SD** |  |
| IRT CASI score | 0.32 | 0.72 | 0.21 | 0.68 | 0.001 |
| IADL score | 0.34 | 0.82 | 0.47 | 0.95 | 0.001 |
| ADL score | 0.22 | 0.63 | 0.36 | 0.78 | < 0.001 |

\* 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. P values are from Fisher’s exact test or ANOVA as appropriate. 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.

**eTable 12** shows characteristics of the ROS and MAP cohorts stratified by autopsy status.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **eTable 12. Demographic and functional characteristics of the ROS and MAP sample stratified by presence vs. absence of TBI and duration of LOC** | | | | | |
| **Variable** | **No autopsy** | | **Autopsy** | |  |
| **Demographics** | **N** | **%** | **N** | **%** | **p-value** |
| Age at study entry |  |  |  |  | < 0.001 |
| 50–64 | 101 | 6 | 5 | 0 |  |
| 65–74 | 639 | 37 | 244 | 21 |  |
| 75–84 | 721 | 42 | 590 | 51 |  |
| 85– | 247 | 14 | 318 | 27 |  |
| Female sex | 1,310 | 77 | 748 | 65 | < 0.001 |
| Education |  |  |  |  |  |
| Up to 12 years | 389 | 23 | 230 | 20 | 0.037 |
| 13–16 years | 627 | 37 | 405 | 35 |  |
| At least 17 years | 691 | 40 | 521 | 45 |  |
| Self-reported white race | 1,527 | 90 | 1,123 | 97 | <0.001 |
| **Function** | **Mean** | **SD** | **Mean** | **SD** |  |
| Global cognitive score | 0.10 | 0.60 | -0.18 | 0.68 | <0.001 |
| IADL score | 0.72 | 1.29 | 1.45 | 1.82 | <0.001 |
| ADL score | 0.12 | 0.54 | 0.26 | 0.80 | <0.001 |
| Rosow-Breslau scale | 0.56 | 0.89 | 0.95 | 1.02 | <0.001 |

\* 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

**eTable 13** shows the demographic characteristics of the ACT autopsy sample by duration of TBI.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **eTable 13. Demographic characteristics of the ACT autopsy sample stratified by presence vs. absence of TBI and duration of LOC** | | | | | | | | | | |
|  | No TBI (n=418) | | TBI, <1 hour LOC (n=80) | | TBI, >1 hour LOC (n=14) | | TBI, LOC duration unknown (n=13) | | Total | |
|  | N | % | N | % | N | % | N | % | N | % |
| Age at death |  |  |  |  |  |  |  |  |  |  |
| 68–84 | 121 | 29 | 29 | 36 | 4 | 29 | 3 | 23 | 157 | 30 |
| 85–90 | 138 | 33 | 30 | 38 | 4 | 29 | 4 | 31 | 176 | 34 |
| 91–103 | 159 | 38 | 21 | 26 | 6 | 43 | 6 | 46 | 192 | 37 |
| Female sex | 244 | 58 | 30 | 38 | 4 | 29 | 7 | 54 | 285 | 54 |
| Education |  |  |  |  |  |  |  |  |  |  |
| Up to 12 | 141 | 34 | 24 | 30 | 5 | 36 | 4 | 31 | 174 | 33 |
| 13–16 | 184 | 44 | 36 | 45 | 7 | 50 | 7 | 85 | 234 | 45 |
| At least 17 | 93 | 22 | 20 | 25 | 2 | 14 | 2 | 15 | 117 | 22 |
| Self-reported White race | 401 | 96 | 78 | 98 | 13 | 93 | 12 | 92 | 504 | 96 |

**eTable 14** shows the demographic characteristics of the ROS and MAP autopsy samples by duration of TBI

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **eTable 14. Demographic characteristics of the ROS and MAP autopsy sample stratified by presence vs. absence of TBI and duration of LOC\*** | | | | | | | | | | |
|  | No TBI (n=1021) | | TBI, <1 hour LOC (n=96) | | TBI, >1 hour LOC (n=23) | | TBI, LOC duration unknown (n=17) | | Total | |
|  | N | % | N | % | N | % | N | % | N | % |
| Age at death |  |  |  |  |  |  |  |  |  |  |
| 68–84 | 298 | 29 | 30 | 31 | 3 | 13 | 5 | 29 | 336 | 29 |
| 85–90 | 356 | 35 | 37 | 39 | 11 | 48 | 5 | 29 | 409 | 35 |
| 91–103 | 367 | 36 | 29 | 30 | 9 | 39 | 7 | 41 | 412 | 36 |
| Female sex | 664 | 65 | 60 | 63 | 14 | 61 | 10 | 59 | 748 | 65 |
| Education |  |  |  |  |  |  |  |  |  |  |
| Up to 12 | 208 | 20 | 14 | 15 | 4 | 17 | 4 | 24 | 230 | 20 |
| 13–16 | 355 | 35 | 36 | 38 | 8 | 35 | 6 | 35 | 405 | 35 |
| At least 17 | 457 | 45 | 46 | 48 | 11 | 48 | 7 | 41 | 521 | 45 |
| Self-reported White race | 991 | 97 | 93 | 97 | 22 | 96 | 17 | 100 | 1123 | 97 |

\* 1 person was missing data on education and self-reported race.

**Supplemental Results S4. Prevalence of neuropathology findings for ACT, ROS, and MAP.**

**eTable 15** shows the prevalence of neuropathology findings at autopsy in the ACT study

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **eTable 15. Prevalence of neuropathology findings at autopsy in the ACT study** | | | | | | | | | | |
|  | No TBI (n=418) | | TBI, <1 hour LOC (n=80) | | TBI, >1 hour LOC (n=14) | | TBI, LOC duration unknown (n=13) | | Total  (n=525) | |
|  | N | % | N | % | N | % | N | % | N | % |
| Braak Stage 5 or 6 | 123 | 31 | 123 | 29 | 5 | 36 | 7 | 54 | 160 | 30 |
| CERAD intermediate or frequent | 214 | 51 | 39 | 49 | 5 | 36 | 5 | 38 | 263 | 50 |
| Amyloid angiopathy | 118\* | 28 | 22 | 28 | 4 | 29 | 3 | 93 | 147\* | 28 |
| Cystic infarcts | 137† | 33 | 21 | 26 | 5 | 36 | 6 | 46 | 169† | 32 |
| Hippocampal sclerosis | 38‡ | 9 | 6 | 8 | 4 | 29 | 0 | 0 | 48 | 10 |
| Microinfarcts |  |  |  |  |  |  |  |  |  |  |
| Any | 182 | 44 | 29 | 36 | 8 | 57 | 7 | 54 | 226‡ | 43 |
| Any cortical | 149\*\* | 36 | 25 | 31 | 6 | 43 | 7 | 54 | 187‡ | 36 |
| Any deep | 129†† | 31 | 21 | 26 | 7†† | 54 | 5 | 38 | 162†† | 31 |
| Lewy bodies |  |  |  |  |  |  |  |  |  |  |
| Any | 69‡‡ | 17 | 13 | 16 | 6 | 43 | 1 | 8 | 89‡‡ | 17 |
| Substantia Nigra or locus ceruleus | 52‡‡ | 12 | 10 | 12 | 6 | 43 | 0 | 0 | 68‡‡ | 13 |
| Frontal or temporal cortex | 20\*\*\* | 5 | 6 | 8 | 4 | 29 | 0 | 0 | 30\*\*\* | 6 |
| Amygdala (any) | 52††† | 7 | 13††† | 18 | 3††† | 23 | 1 | 8 | 69††† | 14 |

\* Missing for 4 people, all of whom did not report history of TBI with LOC

† Missing for 9 people, all of whom did not report history of TBI with LOC

‡ Missing for 16 people, of whom 13 did not report history of TBI with LOC, 2 reported TBI with LOC < 1 hour, and 1 was missing LOC duration.

\*\*Missing for 2 people, both of whom did not report history of TBI with LOC

†† Missing for 4 people, of whom 3 did not report history of TBI with LOC and 1 reported history of TBI with LOC>1 hour; 2 of had data on cerebral microinfarcts

‡‡Missing for 1 person, who did not report a history of TBI with LOC

\*\*\*2 Missing for 2 people, both of whom did not report a history of TBI with LOC

†††Missing for 26 people, of whom 18 did not report a history of TBI with LOC, 7 reported TBI with LOC < 1 hour, and 1 reported TBI with LOC > 1 hour

**eTable 16** shows the prevalence of neuropathology findings at autopsy in the ROS and MAP cohorts.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **eTable 16. Prevalence of neuropathology findings at autopsy in the ROS and MAP cohorts** | | | | | | | | | | |
|  | No TBI (n=1021) | | TBI, <1 hour LOC (n=96) | | TBI, >1 hour LOC (n=23) | | TBI, LOC duration unknown (n=17) | | Total | |
|  | N | % | N | % | N | % | N | % | N | % |
| Braak Stage 5 or 6 | 249 | 24 | 20 | 21 | 5 | 22 | 1 | 6 | 275 | 24 |
| CERAD definite or probable | 668 | 65 | 63 | 66 | 18 | 78 | 10 | 59 | 759 | 66 |
| Any amyloid angiopathy | 811\* | 85 | 80\* | 93 | 21\* | 95 | 14 | 82 | 926 | 86 |
| Presence of gross cystic infarcts | 445 | 44 | 38 | 41 | 13 | 57 | 11 | 65 | 507 | 44 |
| Presence of microinfarcts | 363† | 36 | 34 | 37 | 10 | 43 | 6 | 35 | 413 | 36 |
| Hippocampal sclerosis | 78‡ | 8 | 6‡ | 6 | 1 | 4 | 1 | 6 | 86 | 8 |
| Lewy bodies |  |  |  |  |  |  |  |  |  |  |
| Any | 225 | 22 | 22 | 23 | 5 | 22 | 2 | 12 | 254 | 22 |
| Substantia Nigra | 206\* | 20 | 21 | 22 | 4 | 17 | 2 | 12 | 233 | 20 |
| Limbic | 185 | 18 | 20 | 21 | 4 | 17 | 2 | 12 | 211 | 18 |
| Neocortex | 116 | 11 | 18 | 19 | 2 | 9 | 2 | 12 | 138 | 12 |

\* Missing for 76 people, of whom 65 reported no TBI with LOC, 10 reported TBI with LOC < 1 hour, and 1 reported TBI with LOC > 1 hour

† Missing for 11 people, of whom 8 reported no TBI with LOC and 3 reported TBI with LOC < 1 hour

‡ Missing for 11 people, of whom 9 reported no TBI with LOC and 2 reported TBI with LOC < 1 hour

\*\* Missing for 1 person who did not report history of TBI with LOC

†† Missing for 3 people who did not report history of TBI with LOC

**Supplemental Results S5. APOE genotype interactions with neuropathology outcomes.**

**eTable 17** shows *APOE* genotype interactions with TBI with LOC exposures for neuropathological findings at autopsy. We combined durations of loss of consciousness because there was only 1 person with APOE ε4 and TBI with LOC > 1 hour in the ACT neuropathology sample.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **eTable 17. Interactions between *APOE* genotype and neuropathological findings at autopsy** | | | | |
|  | **ACT** | | **ROS and MAP** | |
|  | **RR, 95% CI** | **P value** | **RR (95% CI)** | **P value** |
| Braak Stage 5 or 6 | 0.65 (0.31, 1.38) | 0.26 | 0.76 (0.33, 1.73) | 0.51 |
| CERAD intermediate or frequent | 0.70 (0.41, 1.18) | 0.18 | 0.80 (0.50, 1.29) | 0.37 |
| Amyloid angiopathy | 1.06 (0.52, 2.14) | 0.87 | 0.96 (0.63, 1.47) | 0.86 |
| Cystic infarcts | 0.92 (0.40, 2.10) | 0.83 | 0.99 (0.55, 1.78) | 0.98 |
| Hippocampal sclerosis | 0.19 (0.03, 1.30 | 0.09 | 0.99 (0.23, 4.27) | 0.99 |
| Cerebral Microinfarcts |  |  |  |  |
| Any | 1.20 (0.66, 2.20 | 0.56 | 1.28 (0.68, 2.44) | 0.44 |
| Any cortical | 1.06 (0.53, 2.11) | 0.87 | 0.60 (0.25, 1.42) | 0.24 |
| Any deep | 1.46 (0.68, 3.16) | 0.34 | 1.02 (0.50, 2.06) | 0.96 |
| Lewy bodies |  |  |  |  |
| Any | 1.00 (0.36, 2.83) | 0.99 | 0.99 (0.42, 2.35) | 0.98 |
| Substantia Nigra / Locus Ceruleus | 0.52 (0.11, 2.46) | 0.41 | 1.06 (0.43, 2.62) | 0.90 |
| Frontal or temporal cortex | 1.00 (0.16, 6.12) | 1.00 | 0.69 (0.24, 1.98) | 0.49 |
| Amygdala / limbic | 1.01 (0.33, 3.09) | 0.99 | 0.67 (0.26, 1.71) | 0.40 |

**Supplemental Results S6. Sex interactions with neuropathology outcomes.**

**eTable 18** shows sex interactions with TBI with LOC exposures for neuropathological findings at autopsy for ACT. The p values in the top row for each outcome are for the interaction term between sex and each exposure in a single model. For example, for Braak stage, the p value for the interaction term between sex and TBI with LOC<60 minutes was 0.69, and for the interaction term between sex and TBI with LOC>60 minutes, the p value was 0.79.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **eTable 18. Sex interactions for neuropathological findings at autopsy, ACT** | | | | |
|  | **<60 minutes LOC** | | **>60 minutes LOC** | |
|  | **RR, 95% CI** | **P value** | **RR (95% CI)** | **P value** |
| Braak Stage 5 or 6 |  | 0.69 |  | 0.79 |
| Overall | 1.22 (0.86, 1.73) | 0.26 | 1.11 (0.61, 2.00) | 0.74 |
| Males | 1.13 (0.67, 1.90) | 0.64 | 1.14 (0.48, 2.67) | 0.77 |
| Females | 1.31 (0.83, 2.08) | 0.25 | 1.02 (0.45, 2.31) | 0.96 |
| CERAD intermediate or frequent |  | 0.82 |  | 0.08 |
| Overall | 1.01 (0.79, 1.29) | 0.92 | 0.67 (0.36, 1.25) | 0.21 |
| Males | 1.04 (0.75, 1.44) | 0.81 | 0.40 (0.13, 1.22) | 0.11 |
| Females | 0.97 (0.67, 1.41) | 0.89 | 1.24 (0.73, 2.13) | 0.43 |
| Amyloid angiopathy |  | 0.54 |  | 0.48 |
| Overall | 1.08 (0.73, 1.59) | 0.71 | 1.02 (0.47, 2.20) | 0.96 |
| Males | 0.96 (0.55, 1.68) | 0.88 | 0.77 (0.24, 2.49) | 0.67 |
| Females | 1.20 (0.72, 1.99) | 0.49 | 1.42 (0.56, 3.60) | 0.46 |
| Cystic infarcts |  | 0.39 |  | 0.60 |
| Overall | 0.83 (0.62, 1.24) | 0.37 | 1.05 (0.52, 2.12) | 0.88 |
| Males | 0.68 (0.38, 1.21) | 0.19 | 0.89 (0.33, 2.40) | 0.82 |
| Females | 1.02 (0.61, 1.72) | 0.94 | 1.37 (0.55, 3.41) | 0.50 |
| Hippocampal sclerosis |  |  |  |  |
| Overall | 0.93 (0.41, 2.10) | 0.86 | 2.34 (1.02, 5.30) | 0.042 |
| Males | 1.09 (0.42, 2.85) | 0.85 | 1.75 (9.50, 6.16) | 0.38 |
| Females | 0.48 (0.06, 3.59) | 0.47 | 4.03 (1.07, 15.17) | 0.039 |
| Cerebral Microinfarcts |  |  |  |  |
| Any |  | 0.29 |  | 0.21 |
| Overall | 0.87 (0.64, 1.19) | 0.39 | 1.23 (0.73, 2.09) | 0.44 |
| Males | 0.98 (0.68, 1.43) | 0.92 | 1.62 (1.00, 2.62) | 0.05 |
| Females | 0.70 (0.39, 1.27) | 0.24 | 0.44 (0.06, 3.25) | 0.42 |
| Any cortical |  | 0.72 |  | 0.38 |
| Overall | 0.92 (0.65, 1.31) | 0.64 | 1.12 (0.57, 2.18) | 0.74 |
| Males | 0.94 (0.60, 1.47) | 0.79 | 1.37 (0.70, 2.66) | 0.36 |
| Females | 0.85 (0.47, 1.56) | 0.61 | 0.54 (0.07, 4.10) | 0.55 |
| Any deep |  | 0.44 |  | 0.18 |
| Overall | 0.89 (0.60, 1.33) | 0.58 | 1.67 (0.95, 2.93) | 0.08 |
| Males | 1.01 (0.61, 1.68) | 0.97 | 2.29 (1.35, 3.89) | 0.002 |
| Females | 0.74 (0.37, 1.50) | 0.41 | 0.63 (0.10, 3.80) | 0.61 |
| Lewy bodies |  |  |  |  |
| Any |  | 0.10 |  | 0.41 |
| Overall | 0.93 (0.55, 1.59) | 0.80 | 2.64 (1.40, 4.99) | 0.003 |
| Males | 1.34 (0.74, 2.46) | 0.34 | 3.22 (1.58, 6.57) | 0.001 |
| Females | 0.40 (0.10, 1.58) | 0.19 | 1.58 (0.48, 5.20) | 0.45 |
| Substantia Nigra / Locus Ceruleus |  | 0.34 |  | 0.53 |
| Overall | 0.96 (0.51, 1.80) | 0.89 | 3.30 (1.71, 6.38) | 0.001 |
| Males | 1.29 (0.62, 2.68) | 0.50 | 3.80 (1.82, 7.92) | <0.001 |
| Females | 0.61 (0.15, 2.39) | 0.47 | 2.19 (0.73, 6.55) | 0.16 |
| Frontal or temporal cortex |  | 0.32 |  | 0.82 |
| Overall | 1.49 (0.61, 3.64) | 0.38 | 5.73 (2.18, 15.0) | <0.001 |
| Males | 2.51 (0.74, 8.56) | 0.14 | 6.80 (2.08, 22.2) | 0.002 |
| Females | 0.80 (0.11, 6.08) | 0.83 | 4.52 (1.70, 12.0) | 0.002 |
| Amygdala / limbic |  | 0.12 |  | 0.98 |
| Overall | 1.30 (0.75, 2.24) | 0.35 | 1.89 90.69, 5.19) | 0.22 |
| Males | 1.81 (0.95, 3.42) | 0.07 | 1.93 (0.51, 7.33) | 0.33 |
| Females | 0.59 (0.15, 2.31) | 0.45 | 1.93 (0.63, 5.91) | 0.25 |

eTable 19 shows the same thing for the ROS and MAP studies. There were too few people with hippocampal sclerosis to divide by sex. As in eTable 18, the p values in the top row for each outcome are for the interaction term between sex and each exposure in a single model.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **eTable 19. Interactions between sex and neuropathological findings at autopsy, ROS and MAP studies** | | | | |
|  | **<60 minutes LOC** | | **>60 minutes LOC** | |
|  | **RR, 95% CI** | **P value** | **RR (95% CI)** | **P value** |
| Braak Stage 5 or 6 |  | 0.21 |  | 0.67 |
| Overall | 0.87 (0.55, 1.37) | 0.54 | 0.85 (0.35, 2.06) | 0.71 |
| Males | 0.45 (0.14, 1.43) | 0.18 | 0.60 (0.08, 4.34) | 0.62 |
| Females | 1.03 (0.63, 1.70) | 0.90 | 0.95 (0.35, 2.58) | 0.93 |
| CERAD intermediate or frequent |  | 0.36 |  | 0.42 |
| Overall | 1.01 (0.78, 1.31) | 0.93 | 1.16 (0.73, 1.85) | 0.54 |
| Males | 0.86 (0.53, 1.39) | 0.54 | 1.47 (0.72, 2.97) | 0.29 |
| Females | 1.10 (0.81, 1.49) | 0.55 | 1.01 (0.54, 1.88) | 0.99 |
| Amyloid angiopathy |  | 0.93 |  | 0.72 |
| Overall | 1.10 (0.88, 1.39) | 0.41 | 1.11 (0.72, 1.71) | 0.63 |
| Males | 1.10 (0.75, 1.61) | 0.64 | 1.22 (0.63, 2.37) | 0.55 |
| Females | 1.11 (0.93, 1.48) | 0.48 | 1.04 (0.59, 1.85) | 0.88 |
| Cystic infarcts |  | 0.66 |  | 0.95 |
| Overall | 0.95 (0.68, 1.33) | 0.77 | 1.24 (0.71, 2.15) | 0.45 |
| Males | 1.01 (0.59, 1.73) | 0.96 | 1.28 (0.52, 3.11) | 0.59 |
| Females | 0.90 (0.59, 1.38) | 0.63 | 1.20 (0.59, 2.42) | 0.62 |
| Cerebral Microinfarcts |  |  |  |  |
| Any |  | 0.83 |  | 0.96 |
| Overall | 1.03 (0.72, 1.46) | 0.88 | 1.18 (0.63, 2.21) | 0.61 |
| Males | 1.07 (0.61, 1.86) | 0.81 | 1.16 (0.43, 3.14) | 0.77 |
| Females | 1.00 (0.63, 1.58) | 0.99 | 1.19 (0.53, 2.680 | 0.68 |
| Any cortical |  | 0.50 |  | 0.50 |
| Overall | 0.89 (0.53, 1.48) | 0.66 | 2.12 (1.12, 4.01) | 0.02 |
| Males | 0.70 (0.28, 1.72) | 0.43 | 1.54 (0.48, 4.89) | 0.46 |
| Females | 1.01 (0.55, 1.88) | 0.97 | 2.46 (1.14, 5.30) | 0.022 |
| Any deep |  | 0.75 |  | 0.82 |
| Overall | 1.16 (0.77, 1.76) | 0.48 | 1.07 (0.47, 2.40) | 0.88 |
| Males | 1.25 (0.64, 2.41) | 0.51 | 0.92 (0.24, 3.91) | 0.95 |
| Females | 1.11 (0.65, 1.89) | 0.70 | 1.16 (0.43, 3.13) | 0.77 |
| Lewy bodies |  |  |  |  |
| Any |  | 0.56 |  | 0.39 |
| Overall | 1.04 (0.67, 1.62) | 0.85 | 0.95 (0.39, 2.31) | 0.91 |
| Males | 1.21 (0.62, 2.33) | 0.58 | 0.48 (0.07, 3.48) | 0.47 |
| Females | 0.94 (0.52, 1.69) | 0.83 | 1.28 (0.47, 3.48) | 0.62 |
| Substantia Nigra / Locus Ceruleus |  | 0.55 |  | 0.51 |
| Overall | 1.09 (0.69, 1.71) | 0.71 | 0.82 (0.31, 2.22) | 0.70 |
| Males | 1.26 (0.65, 2.44) | 0.49 | 0.50 (0.07, 3.60) | 0.49 |
| Females | 0.97 (0.52, 1.80) | 0.92 | 1.08 (0.34, 3.39) | 0.90 |
| Frontal or temporal cortex |  | 0.66 |  | 0.76 |
| Overall | 1.64 (1.00, 2.70) | 0.05 | 0.74 (0.18, 3.00) | 0,67 |
| Males | 1.91 (0.89, 4.08) | 0.09 | 0.95 (0.13, 6.89) | 0.96 |
| Females | 1.50 (0.77, 2.90) | 0.23 | 0.63 (0.09, 4.55) | 0.65 |
| Amygdala / limbic |  | 0.70 |  | 0.65 |
| Overall | 1.16 (0.73, 1.84) | 0.53 | 0.91 (0.34, 2.44) | 0.85 |
| Males | 1.30 (0.62, 2.71) | 0.49 | 0.64 (0.09, 4.63) | 0.66 |
| Females | 1.09 (0.60, 1.97) | 0.78 | 1.09 (0.35, 3.44) | 0.88 |

eTable 20 shows the same thing for the two studies combined. As in eTable 18 and eTable 19, the p values in the top row for each outcome are for the interaction term between sex and each exposure in a single model.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **eTable 20. Interactions between sex and neuropathological findings at autopsy, Combined** | | | | |
|  | **<60 minutes LOC** | | **>60 minutes LOC** | |
|  | **RR, 95% CI** | **P value** | **RR (95% CI)** | **P value** |
| Braak Stage 5 or 6 |  | 0.40 |  | 0.85 |
| Overall | 1.02 (0.79, 1.33) | 0.88 | 0.98 (0.58, 1.65) | 0.93 |
| Males | 0.85 (0.54, 1.33) | 0.47 | 0.92 (0.41, 2.09) | 0.85 |
| Females | 1.11 (0.81, 1.53) | 0.51 | 1.01 (0.51, 2.00) | 0.97 |
| CERAD intermediate or frequent |  | 0.37 |  | 0.73 |
| Overall | 1.01 (0.89, 1.15) | 0.88 | 1.00 (0.79, 1.27) | 0.98 |
| Males | 0.95 (0.77, 1.19) | 0.67 | 0.97 (0.66, 1.42) | 0.86 |
| Females | 1.06 (0.91, 1.23) | 0.45 | 1.06 (0.79, 1.43) | 0.70 |
| Amyloid angiopathy |  | 0.31 |  | 0.88 |
| Overall | 1.08 (0.99, 1.19) | 0.09 | 1.09 (0.93, 1.27) | 0.28 |
| Males | 1.06 (0.89, 1.26) | 0.54 | 1.13 (0.89, 1.43) | 0.31 |
| Females | 1.12 (1.02, 1.24) | 0.023 | 1.09 (0.89, 1.33) | 0.40 |
| Cystic infarcts |  | 0.74 |  | 0.77 |
| Overall | 0.90 (0.73, 1.12) | 0.35 | 1.17 (0.84, 1.62) | 0.34 |
| Males | 0.86 (0.61, 1.21) | 0.38 | 1.11 (0.66, 1.87) | 0.70 |
| Females | 0.94 (0.71, 1.23) | 0.65 | 1.19 (0.80, 1.76) | 0.39 |
| Hippocampal sclerosis |  | 0.31 |  | 0.28 |
| Overall | 0.91 (0.51, 1.61) | 0.75 | 1.34 (0.62, 2.89) | 0.45 |
| Males | 1.12 (0.51, 2.46) | 0.78 | 1.97 (0.68, 5.67) | 0.21 |
| Females | 0.68 (0.28, 1.66) | 0.40 | 0.87 (0.28, 2.70) | 0.81 |
| Cerebral Microinfarcts |  |  |  |  |
| Any |  | 0.50 |  | 0.34 |
| Overall | 0.94 (0.76, 1.15) | 0.54 | 1.18 (0.85, 1.66) | 0.32 |
| Males | 1.01 (0.76, 1.34) | 0.96 | 1.40 (0.94, 2.07) | 0.10 |
| Females | 0.87 (0.64, 1.19) | 0.39 | 0.96 (0.52 ,1.78) | 0.90 |
| Any cortical |  | 0.75 |  | 0.63 |
| Overall | 0.90 (0.68 1.19) | 0.46 | 1.58 (1.06, 2.35) | 0.026 |
| Males | 0.86 (0.58, 1.27) | 0.44 | 1.43 (0.84, 2.42) | 0.19 |
| Females | 0.94 (0.2, 1.41) | 0.76 | 1.71 (0.92, 3.17) | 0.087 |
| Any deep |  | 0.62 |  | 0.28 |
| Overall | 1.02 (0.78, 1.33) | 0.90 | 1.30 (0.83, 2.05) | 0.25 |
| Males | 1.10 (0.76, 1.61) | 0.60 | 1.67 (0.96, 2.89) | 0.07 |
| Females | 0.96 (0.65, 1.41) | 0.83 | 0.97 (0.44, 2.14) | 0.94 |
| Lewy bodies |  |  |  |  |
| Any |  | 0.14 |  | 0.72 |
| Overall | 1.00 (0.73, 1.37) | 0.99 | 1.44 (0.87 2.39) | 0.16 |
| Males | 1.28 (0.85, 1.94) | 0.24 | 1.60 (0.79, 3.24) | 0.19 |
| Females | 0.77 (0.47, 1.27) | 0.31 | 1.32 (0.63, 2.76) | 0.46 |
| Substantia Nigra / Locus Ceruleus |  | 0.32 |  | 0.52 |
| Overall | 1.04 (0.74, 1.45) | 0.84 | 1.48 (0.86, 2.55) | 0.16 |
| Males | 1.25 (0.80, 1.96) | 0.32 | 1.76 (0.86, 3.62) | 0.12 |
| Females | 0.86 (0.51, 1.45) | 0.57 | 1.23 (0.52, 2.88) | 0.64 |
| Frontal or temporal cortex |  | 0.40 |  | 0.30 |
| Overall | 1.59 (1.06, 2.39) | 0.025 | 1.75 (0.82, 3.77) | 0.15 |
| Males | 2.02 (1.15, 3.57) | 0.015 | 2.59 (1.00, 6.66) | 0.049 |
| Females | 1.34 (0.75, 2.39) | 0.33 | 1.11 (0.30, 4.10) | 0.88 |
| Amygdala / limbic |  | 0.14 |  | 0.90 |
| Overall | 1.22 (0.88, 1.69) | 0.24 | 1.16 (0.59, 2.27) | 0.66 |
| Males | 1.59 (1.02, 2.48) | 0.040 | 1.11 (0.38, 3.82) | 0.86 |
| Females | 0.95 (0.58, 1.56) | 0.83 | 1.22 (0.52, 2.86) | 0.64 |

**Supplemental eFigure 2. Time lag between exposure younger than age 25 and late life brain outcomes**

**eFigure 2** shows a cartoon of exposure and outcome windows

|  |
| --- |
| eFigure 2. Time lag between exposure younger than age 25 and late life brain outcomes |
|  |
| This figure shows a hypothetical study participant who had an exposure younger than age 25 to be included in analyses whose results are shown in Table 4; the exposure window is shown in the blue box ranging from age 0 to 25. Study entry began in late life, as depicted by the blue box beginning at age 65 (though study entry could have been later than age 65). As pointed out in the middle of this figure, this design implies at least a 40 year window between exposure to TBI with LOC and ascertainment of outcomes. |

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