A population-based study of head injury, cognitive function and pathological markers

Sarah-Naomi James1,2, Jennifer M. Nicholas2,3, Christopher A. Lane2, Thomas D. Parker2, Kirsty Lu2, Ashvini Keshavan4, Sarah M. Buchanan2, Sarah E. Keuss2, Heidi Murray-Smith2, Andrew Wong2, David M. Cash2, Ian B. Malone2, Josephine Barnes2, Carole H. Sudre1,2,4,5, William Coath2, Lloyd Prosser2, Sebastien Ourselin4, Marc Modat2,4, David L. Thomas5, Jorge Cardoso6, Amanda Heslegrave6,7, Henrik Zetterberg6,7,8,9, Sebastian J. Crutch2, Jonathan M. Schott2, Marcus Richards1,a & Nick C. Fox2,6,a

1MRC Unit for Lifelong Health and Ageing at UCL, University College London, London, United Kingdom
2Dementia Research Centre, UCL Queen Square Institute of Neurology, University College London, London, United Kingdom
3Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom
4School of Biomedical Engineering and Imaging Sciences, King’s College London, Institute of Nuclear Medicine, University College London Hospitals, London, United Kingdom
5Centre for Medical Image Computing, Department of Computer Science, University College London, London, United Kingdom
6UK Dementia Research Institute at UCL, University College London, London, United Kingdom
7Department of Neurodegenerative Disease, UCL Institute of Neurology, London, United Kingdom
8Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden
9Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden

Correspondence
Sarah-Naomi James, MRC Lifelong health and Ageing at UCL, Floor 5, 1–19 Torrington Place, London WC1E 7HB, United Kingdom.
Tel: +44(0)2076705712; E-mail: sarah.n.james@ucl.ac.uk

Abstract

Objective: To assess associations between head injury (HI) with loss of consciousness (LOC), ageing and markers of later-life cerebral pathology; and to explore whether those effects may help explain subtle cognitive deficits in dementia-free individuals. Methods: Participants (n = 502, age = 69–71) from the 1946 British Birth Cohort underwent cognitive testing (subtests of Preclinical Alzheimer Cognitive Composite), 18F-florbetapir Aβ-PET and MR imaging. Measures include Aβ-PET status, brain, hippocampal and white matter hyperintensity (WMH) volumes, normal appearing white matter (NAWM) microstructure, Alzheimer’s disease (AD)-related cortical thickness, and serum neurofilament light chain (NFL). LOC HI metrics include HI occurring: (i) >15 years prior to the scan (ii) anytime up to age 71. Results: Compared to those with no evidence of an LOC HI, only those reporting an LOC HI >15 years prior (16%, n = 80) performed worse on cognitive tests at age 69–71, taking into account premorbid cognition, particularly on the digit-symbol substitution test (DSST). Smaller brain volume (BV) and adverse NAWM microstructural integrity explained 30% and 16% of the relationship between HI and DSST, respectively. We found no evidence that LOC HI was associated with Aβ load, hippocampal volume, WMH volume, AD-related cortical thickness or NFL (all p > 0.01). Interpretation: Having a LOC HI aged 50’s and younger was linked with lower later-life cognitive function at age ~70 than expected. This may reflect a damaging but small impact of HI; explained in part by smaller BV and different microstructure pathways but not via pathology related to AD (amyloid, hippocampal volume, AD cortical thickness) or ongoing neurodegeneration (serum NFL).
Population Head Injury, Cognition and Pathology

S.-N. James et al.

Wolfson Experimental Neurology Centre (JMS, NCF, MM, DT). JB is supported by an Alzheimer’s Research UK Senior Fellowship. TP is supported by a Wellcome Trust Clinical Research Fellowship (200109/Z/15/Z). AK was supported by a Wolfson Foundation Clinical Research Fellowship. CS is supported by an Alzheimer’s Society Junior Fellowship (AS-JF-17-011). MM is supported by an Alzheimer’s Society Project Grant (AS-PG-15-025). SC is supported by an Alzheimer’s Research UK Senior Research Fellowship (ARUK-SRF2013-8). SO receives funding from the EPSRC (EP/H046410/1, EP/J020990/1, EP/K005278), the MRC (MR/J01107X/1), the EU-FP7 project VPH-DARE@IT (FP7-ICT-2011-9-601055), and NIHR BRC UCLH/UCL High Impact Initiative. HZ acknowledges support from the UCL/UCLH NIHR Biomedical Research Centre, the UK Dementia Research Institute at UCL and a Wellcome Trust Multi-User Equipment Grant. JMS acknowledges the EPSRC (EP/J020990/1) and European Union’s Horizon 2020 research and innovation programme (Grant 666992) and a Weston Brain Institute and Selfridges Group Foundation award (176724). NCF acknowledges support from the UCL/UCLH NIHR Biomedical Research Centre, an NIHR Senior Investigator award and the UK Dementia Research Institute at UCL.

Received: 4 February 2021; Accepted: 12 February 2021

doi: 10.1002/acn3.51331

These authors contributed equally to the manuscript.

Introduction

Head injury (HI) is implicated as a risk factor for all-cause dementia and Alzheimer’s disease (AD).1–3 HI has been associated with pathological measures of increased β-amyloid (Aβ),3 cerebral atrophy,1 reduced hippocampal volume,3 white matter damage and reduced connectivity,6,7 tau pathology8 and shorter term axonal damage indexed by increased neurofilament light protein in blood (NFL),9,10 which may confer risk of cognitive impairment.

Studies of the effects of HI have largely been focused on populations at risk of severe or repetitive head injury at younger ages, such as military personnel and athletes, and often have relatively short follow-up periods. Longer term cognitive and pathological effects of minor HI that may occur in the general population have been less well-studied, particularly in older people. This has limited our understanding of the long-term cognitive and pathological effects of an injury and the interplay between injury and ageing processes; whereby, as part of normal ageing, cognitive decline and brain atrophy changes occur. Given that studies of HI in older populations are at risk of reverse causality, where cognitive impairment or ageing processes such as frailty may cause HI,14 the timing of HI needs to be taken into account to help establish long-term effects from HI incidents, or effects from HI coupled with ageing processes. Establishing long-term associations between HI and pathological markers observed in dementia-free individuals may further help explain subtle cognitive deficits observed or indicate potential future decline.11–13
The MRC National Survey of Health and Development (NSHD, 1946 British Birth cohort) has followed individuals since their birth. Using this population-based study we previously demonstrated that HI with LOC at least 15 years prior was associated with lower word learning memory by age 69, but we did not show evidence of faster cognitive decline.15 Recently, 502 members aged 69–71 underwent extensive cognitive examination and imaging as part of the neuroimaging sub-study (Insight 46), as well as updating a HI-related questionnaire. We now assess associations between HI with LOC at cognitive function at age 69–71, and the extent to which any associations are explained by pathology measures at this age (cerebral Aβ-PET, whole brain and hippocampal volume, AD-related cortical thickness signature, white matter hyperintensity (WMH) volume, measures of white matter microstructural integrity in normal appearing white matter (NAWM), and greater axonal injury indexed by serum NFL). We use two indicators of HI to differentiate potential effects of LOC HI (i) occurring >15 years prior to the scan, which limits the possibility of reverse causality; and (ii) occurring at any time across the life course, which may be coupled with ageing-related processes.

**Methods**

Study participants were from Insight 46, a sub-study of the NSHD which initially comprised 5362 individuals born throughout mainland Britain in one week of March 1946. Eligibility criteria16 and an overview of recruitment for Insight 4617 are outlined in detail elsewhere. Briefly 502 participants aged 69–71 were assessed with detailed and consistent clinical, cognitive, and brain imaging protocols (https://doi.org/10.5522/NSHD/Q103). Ethical approval for the neuroscience sub-study was granted by the National Research Ethics Service (NRES) Committee London (14/ LO/1173). All participants gave written informed consent.

**Head injury**

In this analysis we used two indicators of HI to differentiate potential effects of LOC HI occurring (i) >15 years prior to the scan and (ii) occurring at any time across the life course:

i"LOC HI >15 years prior to the scan"; At age 53, history of HI was ascertained by the response to the following question “Have you ever been knocked unconscious?”. The responses at age 53 were coded into a single HI variable with two levels: 0) no evidence of a HI with loss of consciousness (LOC) up to age 53; 1) evidence of at least one LOC HI in the life course up to age 53.

ii"LOC HI any time in life course"; At age 53 and 60–64, history of HI was ascertained by the response to the following question “Have you ever been knocked unconscious?”. At age 69–71, history of HI was ascertained by the response to the following question "Have you ever had a loss of consciousness", participants positive responses were followed up with: “Have you ever had a loss of consciousness following a head injury?” , “Have you ever had an admission to hospital following a head injury?” and “Have you ever had a skull fracture?”. We used the response to “Have you ever had a loss of consciousness following a head injury?” as the main variable at age 69–71. The responses at each age were combined into a single HI variable with two levels: (0) no evidence of a LOC HI up to age 71; (1) evidence of at least one LOC HI in the life course at any age.

**Cognitive function**

As previously described18 we used cognitive performance on the Preclinical Alzheimer Cognitive Composite (PACC) as the main outcome. This composite consists of the Mini Mental State Examination (MMSE) assessing cognitive state; logical memory delayed score from the Wechsler Memory Scale-Revised (WMS-R) – a test of verbal episodic recall; digit-symbol substitution test (DSST) from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) – a test of executive function and psychomotor speed; and the 12-item Face-Name test (FNAME-12) – a measure of free memory recall.

**Pathological measures**

Imaging was performed on a single Biograph mMR 3T PET/MRI scanner (Siemens Healthcare, Erlangen), with simultaneous acquisition of dynamic PET/MR data; the full imaging protocol has been described previously16 and published papers have used these derived variables accordingly.

PET data were acquired following injection of 370 MBq florbetapir F18 (Amyvid). Aβ burden was assessed over a 10-min period, ~50 min after injection. Global standardized uptake value ratios (SUVRs) were calculated from cortical regions of interest, normalized to eroded subcortical white matter. Aβ status (+/−) was determined by taking the 99th percentile of the lower Aβ-/+ Gaussian as the cut-point (0.6104), whereby Aβ+ indicates greater Aβ load.

Volumetric T1-weighted and FLAIR images underwent visual QC, before processing using automated pipelines16; whole-brain segmentation using Multi-Atlas Propagation and Segmentation19 and hippocampal volume using Similarity and Truth Estimation for Propagated Segmentations20 with appropriate manual editing. Models including brain

---

© 2021 The Authors. Annals of Clinical and Translational Neurology published by Wiley Periodicals LLC on behalf of American Neurological Association
volume were all adjusted for total intracranial volume (TIV), as calculated using Statistical Parametric Mapping (SPM) 12.

Cortical thickness estimation from T1-weighted images was performed using Freesurfer version 6.0 as previously described.21 Cortical thickness regions of interest (ROIs) included a proposed composite signatures of AD cortical thinning: “ADsig Mayo”25 which is comprised of select temporal cortex regions (entorhinal, fusiform, inferior and middle temporal).

A validated, unsupervised automated algorithm, BaMoS (Bayesian Model Selection)23 was used to segment WMH from T1/FLAIR images, followed by visual QC, generating a global WMH volume including subcortical grey matter but excluding infratentorial regions. Higher WMHV indicates worse small vessel disease.

Diffusion MRI enables sensitive estimation of tissue microstructure environments and typically includes parameters of fractional anisotropy (FA) and mean diffusivity (MD). NODDI (neurite orientation dispersion and density imaging) is a multicompartmental modelling technique that further estimates microstructural complexity parameters including neurite density index (NDI) and orientation dispersion index (ODI).24 To generate these parameters, diffusion-weighted images underwent automated processing pipelines,16 followed by visual QC. NAWM masks were generated from GfI-generated by the GIF pipeline eroded by one voxel to avoid CSF and grey matter cerebrospinal fluid contamination, followed by subtraction of corresponding BaMoS-derived lesion map25 using FSL Maths.26 Mean values of NAWM microstructural integrity metrics (fractional anisotropy (FA), mean diffusivity (MD), neurite density index (NDI), orientation dispersion index (ODI)) were extracted from T1-registered diffusion maps using FSL26 and NODDI toolbox.24 Higher values for FA and NDI represent high directionality whereas lower values for MD and ODI indicate more constrained diffusion.

Serum NFL is a marker of axonal injury whereby higher values reflect greater neuronal damage,27 and has previously been implicated in head injury.9,10 A single 500 μL aliquot of serum for each individual was thawed at room temperature over 1 h and vortexed. 130 μL of the supernatant was pipetted onto a 96-well plate for analysis in duplicate, using commercially available Simoa immunoassay kits of the same batch (Quanterix, Billerica, MA). Serum NFL value was quantified with an intra-assay CV <15%, and inter-assay CV were <30%.

Confounders

Based on previous work examining predictors of later-life cognitive function28 the following variables were treated as potential confounders: gender, age, childhood cognitive ability, educational attainment, childhood socioeconomic position (SEP); high affective (depression and anxiety) symptoms near the time of testing; and APOE-ε4 status.

Childhood cognitive ability was measured at age 8 and standardized. The highest educational attainment achieved by 26 years was grouped as: no qualifications; education up to age 16; education from age 17 onwards. Childhood SEP was derived from paternal occupational class and coded according to the UK Registrar General’s Standard Occupational Classification. Affective case-level problems were generated using a validated threshold for the 28-item General Health Questionnaire (GHQ-28) at age 69.29 Genotyping of the two single nucleotide polymorphisms, rs49358 and rs7412, were used to determine APOE-ε4 genotype and categorised as no ε4; heterozygous ε4 and homozygous ε4.

Statistical analysis

Sample

To be included in this analysis participants had to: be dementia-free at the time of scanning based on expert consensus, informed by clinical history, informant history, MMSE (score ≥26) and cognitive performance (WMS-R Logical Memory test and WAIS-R digit-symbol substitution test); have complete HI data; and have acceptable quality for the imaging modality of interest (Fig. 1). Differences in characteristics between those with and without HI were investigated using t-tests and χ² tests for continuous and categorical characteristics, respectively.

Analysis

Multivariable linear regression models were conducted to examine the association between both LOC HI indexes (used as a binary variable) and cognitive function measures, whole brain volume, hippocampal volume, cortical thickness measures and NAWM microstructural integrity measures derived at age 69–71. Due to the non-normal distribution of WMH and NFL, generalized linear models using the gamma distribution and log link were used to investigate relationships between history of HI and WMH volume, and NFL. Multivariable logistic regression models were conducted to examine the association between both LOC HI indexes and Aβ status (as a dichotomous variable) at age 69–71. A differential influence of HI by APOE-ε4 status on Aβ was additionally tested.

We tested the extent to which specific pathological measures explained the effect between LOC HI on later-life cognition. This was tested by re-fitting regression models between LOC HI and later-life cognition, adjusting for brain pathology measures of interest and estimating the
effect difference between models. To reduce multiple testing, only the cognitive and cerebral pathology variables that showed prior associations with an HI index were used for further testing.

**Adjustments**

For all analyses, Model 1 was adjusted for gender and age at scan; Model 2 further adjusted for childhood cognitive ability, educational attainment and childhood SEP. All models which included brain, hippocampal or WMH volume as outcomes were additionally adjusted for TIV. Results are shown as mean difference in cognitive scores with 95% confidence intervals; adjustments were not made for multiple comparisons in line with previous studies.30

As sensitivity analyses, all models including pathological measures as outcomes were additionally re-run, adjusting for affective problems; APOE-ε4 status; additionally adjusting for other concurrent pathology; and excluding those who met criteria for (MCI) mild cognitive impairment at the time of the scan (n = 13). All analyses were conducted using Stata version 15.1.

**Data availability**

Anonymized data will be shared by request from qualified investigators (skylark.ucl.ac.uk/NSHD/doku.php).

---

**Results**

**Demographics**

Of 502 individuals assessed, 499 were dementia-free and 471 completed the imaging protocol; 49% were female; age at scan ranged from 69.3 to 71.9 years. 80 individuals (16%) reported LOC HI >15 years prior; 104 (21%) participants reported having suffered at least one LOC HI at any time in the life course (Table 1). Compared to those with no evidence of LOC HI, those who reported LOC HI at any time were more likely to be male (68% of cases). There were no statistical differences between LOC HI groups for age at testing, childhood cognitive ability, education, childhood SEP, affective problems or APOE-ε4 status (Table 1).

**Cognitive function**

Compared to those without evidence of LOC HI, those who reported a LOC HI>15 years prior had lower digit-symbol substitution scores (DSST) and trend-level lower MMSE and PACC scores at age 69–71, even when adjusting for known common predictors of later-life cognition including childhood cognition and education (Table 2, Fig. 2). This pattern remained in sensitivity analyses (Table S1). However, for those who reported LOC HI at any time in the life course up to age 71, associations with
cognitive scores at age 69–71 were attenuated with adjustments for known common predictors of later-life cognition (Table 2, Fig. 2).

Pathological markers

There was no evidence that LOC HI was associated with Aβ status on PET imaging, smaller AD-related cortical thickness, increased WMH or increased NFL (Table 3, Fig. 3). A differential influence of any LOC HI by APOE-ɛ4 status on Aβ was tested but interactions were not significant; Aβ status $p = 0.41$.

Compared to those without evidence of LOC HI, those with LOC HI>15 years prior and LOC HI anytime in the life course, was associated with smaller whole brain volume relating to an observed decrease of 12 mL (1%) and 14 mL (1%), respectively; and associated with altered NAWM microstructure measures at age 69–71 (decreased mean FA and decreased NDI and higher MD and higher ODI) (Table 3, Fig. 3). The pattern of results remained with adjustments sensitivity analyses (Table S1). There were trend-level associations between LOC HI at any time in the life course and smaller hippocampal volume at age 69–71. However, the associations were largely attenuated when adjusting for whole brain volume (Table S1), implying hippocampal reduction was not disproportionate to brain volume reduction.

As the strongest associations with LOC HI>15 years prior were DSST scores (cognition); and whole brain volume and lower FA (pathology markers), we tested to what extent the association observed between LOC HI occurring >15 years before and DSST at age 69–71 was explained by brain volume or FA-related pathways. As previously noted, the estimate of the total effect of LOC HI>15 years prior on DSST in later-life in the fully adjusted model was negative ($n = 445$ with available brain volume data; $-0.29$ [95% CI $-0.51$, $-0.05$], $p < 0.01$, $R^2 = 0.17$). This effect was attenuated and became non-significant when additionally adjusting for TIV-adjusted brain volume ($-0.18$ [95% CI $-0.42$, 0.04], $p = 0.09$, $R^2 = 0.24$). This demonstrates that brain volume explained approximately 38% of the relationship between LOC HI<15 years prior and DSST. In contrast, the effect between LOC HI and DSST was only slightly attenuated when FA was additionally adjusted (changing from $-0.25$ [95% CI $-0.50$, $-0.02$], $p < 0.03$, $R^2 = 0.18$ with $n = 398$ available FA data to $-0.21$ [95% CI $-0.47$, 0.05], $p = 0.11$, $R^2 = 0.20$ with adjustment of FA), demonstrating that FA explains 16% of the relationship between LOC HI<15 years prior and DSST.

---

**Table 1.** Characteristics of participants reporting a head injury with loss of consciousness at any point before age 71.

<table>
<thead>
<tr>
<th>LOC HI occurring &gt;15 years prior to scan</th>
<th>All ($n = 499$)</th>
<th>Scanned only ($n = 471$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOC HI occurring at any age up to age 71</td>
<td>80 (16%)</td>
<td>77 (17%)</td>
</tr>
<tr>
<td>LOC HI occurring &gt;15 years prior to scan</td>
<td>104 (21%)</td>
<td>99 (21%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All</th>
<th>No HI up to 71</th>
<th>HI up to 71</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max n</td>
<td>499 (100%)</td>
<td>395 (79%)</td>
<td>104 (21%)</td>
<td></td>
</tr>
<tr>
<td>Childhood cognition (mean, SD)$^1$</td>
<td>0.39 (0.7)</td>
<td>0.38 (0.7)</td>
<td>0.46 (0.7)</td>
<td>0.37</td>
</tr>
<tr>
<td>Male</td>
<td>255 (51%)</td>
<td>173 (47%)</td>
<td>67 (68%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>244 (49%)</td>
<td>196 (53%)</td>
<td>32 (32%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Educational attainment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>76 (15%)</td>
<td>60 (16%)</td>
<td>12 (12%)</td>
<td></td>
</tr>
<tr>
<td>Up to GCE</td>
<td>151 (30%)</td>
<td>119 (32%)</td>
<td>23 (23%)</td>
<td></td>
</tr>
<tr>
<td>A-level and above</td>
<td>272 (55%)</td>
<td>190 (52%)</td>
<td>64 (65%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Childhood SEP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual</td>
<td>214 (44%)</td>
<td>160 (44%)</td>
<td>36 (36%)</td>
<td></td>
</tr>
<tr>
<td>Non-manual</td>
<td>280 (56%)</td>
<td>205 (56%)</td>
<td>63 (64%)</td>
<td></td>
</tr>
<tr>
<td>APOE-ɛ4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no ɛ4</td>
<td>351 (72%)</td>
<td>258 (72%)</td>
<td>69 (73%)</td>
<td></td>
</tr>
<tr>
<td>ɛ4 Heterozygous</td>
<td>122 (25%)</td>
<td>94 (26%)</td>
<td>22 (23%)</td>
<td></td>
</tr>
<tr>
<td>ɛ4 Homozygous</td>
<td>13 (3%)</td>
<td>9 (2%)</td>
<td>3 (3%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Affective problems, 69</td>
<td>38 (8%)</td>
<td>23 (6%)</td>
<td>9 (9%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Age at testing (mean, SD)</td>
<td>70.7 (0.6)</td>
<td>70.7 (0.4)</td>
<td>70.6 (0.6)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Abbreviations: HI, head injury; LOC, loss of consciousness; SD, standard deviation; SEP, socioeconomic position.

$^1$Childhood cognition Z-scores were based on the full National Survey of Health and Development cohort of $N = 5362$, so the mean for Insight 46 participants indicates that they had higher childhood cognitive ability on average than their peers not recruited to this study.
Table 2. Association between reported head injury (HI) and later-life cognitive function at age 69–71.

<table>
<thead>
<tr>
<th>LOC HI occurring ≥15 years prior</th>
<th>Standardized mean difference*</th>
<th>p</th>
<th>95% CI</th>
<th>Model 1 (gender and age)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit-symbol substitution test</td>
<td>−0.23</td>
<td>0.04</td>
<td>[−0.48, −0.01]</td>
<td>−0.28</td>
<td>0.02</td>
</tr>
<tr>
<td>Logical memory</td>
<td>0.01</td>
<td>0.93</td>
<td>[−0.23, 0.25]</td>
<td>−0.02</td>
<td>0.85</td>
</tr>
<tr>
<td>FNAMES</td>
<td>−0.05</td>
<td>0.71</td>
<td>[−0.29, 0.20]</td>
<td>−0.09</td>
<td>0.41</td>
</tr>
<tr>
<td>MMSE</td>
<td>−0.17</td>
<td>0.18</td>
<td>[−0.42, 0.08]</td>
<td>−0.22</td>
<td>0.07</td>
</tr>
<tr>
<td>PACC</td>
<td>−0.13</td>
<td>0.28</td>
<td>[−0.38, 0.11]</td>
<td>−0.20</td>
<td>0.07</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LOC HI occurring at anytime up to age 71</th>
<th>Standardized mean difference*</th>
<th>p</th>
<th>95% CI</th>
<th>Model 2 (gender, age, childhood cognition, education, childhood SEP)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit-symbol Substitution test</td>
<td>−0.03</td>
<td>0.78</td>
<td>[−0.27, 0.20]</td>
<td>−0.12</td>
<td>0.27</td>
</tr>
<tr>
<td>Logical memory</td>
<td>0.09</td>
<td>0.43</td>
<td>[−0.14, 0.32]</td>
<td>0.03</td>
<td>0.77</td>
</tr>
<tr>
<td>FNAMES</td>
<td>0.04</td>
<td>0.73</td>
<td>[−0.19, 0.27]</td>
<td>−0.04</td>
<td>0.71</td>
</tr>
<tr>
<td>MMSE</td>
<td>−0.06</td>
<td>0.63</td>
<td>[−0.29, 0.17]</td>
<td>−0.13</td>
<td>0.26</td>
</tr>
<tr>
<td>PACC</td>
<td>0.02</td>
<td>0.84</td>
<td>[−0.20, 0.25]</td>
<td>−0.08</td>
<td>0.44</td>
</tr>
</tbody>
</table>

HI, head injury; FNAME, Face-Name test; SEP, socioeconomic position; MMSE, mini mental state examination; PACC, Preclinical Alzheimer’s Cognitive Composite;
Model 1 adjusts for gender and age; Model 2 adjusts for gender, age, childhood cognition, education and childhood SEP. All outcome measures are standardized so estimates reflect differences in mean of the standardized cognitive outcome between HI groups, whereby those without evidence of head injury with loss of consciousness are the reference group. Bold reflects p < 0.05.
*estimates reflect differences in mean of the standardized cognitive outcome between HI groups.

Discussion

We found that reporting a HI with LOC is fairly common in a population-based birth study (21%) and is most likely to occur in men (68% of cases). Compared to those who had never reported a LOC HI, those with a LOC HI at least 15 years prior, when participants were aged 53 or younger, performed worse on a digit-symbol substitution test (DSST) at age 69–71 than expected based on known predictors of later-life cognition such as their childhood cognitive performance. The relationship between LOC HI and DSST was partly explained by smaller brain volume (38%) and worse microstructural integrity (16%). We found no strong evidence that those with a LOC HI at any time was associated with pathology linked to AD (amyloid burden, cortical thickness in AD-related signature region), axonal injury (NFL) or WMH at age 69–71 years. These findings may suggest that LOC HI that occur aged 50’s and earlier is associated with subtly worse cognition at age ~70 years, partly via diffuse brain volume-related pathways, but not via pathology related to AD (amyloid, hippocampal volume, AD signature regions cortical thickness) or ongoing neurodegeneration (NFL). Yet, given that brain volume and NAWM differences occur in normal ageing trajectories it is unclear whether HI relates to an acute but stable loss of volume, interacts with normal ageing processes or reflects ongoing neurodegeneration, to infer susceptibility for dementia.

Our findings show that LOC HI is associated with lower cognitive function on a DSST at least 15 years later. This test measures a range of cognitive domains including speed, motor skills and attention and is sensitive to cognitive impairment and brain damage. Notably, DSST scores were only lower in those with LOC HI occurring at least 15 years prior, not in those with a HI occurring at anytime in the life course. Whilst the relationship between HI and ageing processes are still unclear, given that our participants are born in the same week limiting age-effects between groups, and we take into account participants’ own prior cognition limiting reverse causation, finding subtle associations only with HI 15 years prior is a potentially elucidating finding. It could be a spurious association or suggests the importance of: (i) a longer duration of life following exposure; (ii) a temporal effect amplification of early exposure or (iii) age of HI. Growing research provides evidence that greater time since injury is associated with greater cognitive decline and older brain ageing, suggesting that HI accelerates brain atrophy and cognitive decline ageing trajectories. It is also known that the likely causes of HI are different across age groups, for example occupational, road accidents and sports-related injuries in younger populations and falls in older populations, which may infer different risk and
Figure 2. Forest plot of estimates from a linear regression model showing the mean difference in cognitive outcomes at age 69–71 by (A) LOC HI occurring >15 years prior, and (B) LOC HI occurring at anytime up to age 71 using no LOC HI as the reference group. Estimates are standardized and adjusted for gender, childhood cognition, education, childhood socioeconomic position, age at testing, APOE-ɛ4 status. FNAME, face name test; MMSE, mini mental state examination; PACC, Preclinical Alzheimer Cognitive Composite.
interact with ageing processes differently. It is plausible that later-life injuries occurring closer to the scan may be due to ageing processes linked to susceptibility to falls, comorbidities and related medication or as a consequence of prodromal cognitive impairment and therefore the measure of HI across the life course may have potential cases of reserve causation. Further work with better characterization of HI will help to elucidate the relationship between features of HI (i.e. duration, frequency, timing) and later-life cognitive function and brain health.

Our finding that HI is associated with lower whole brain volume is in line with well-documented evidence of traumatic brain injury-associated brain volume loss, estimated around 4% after 1 year. We also demonstrated that the smaller brain volume is partly explained lower DSST scores in HI participants, suggesting that HI-associated cerebral volume loss is likely on the mechanistic pathway from HI to lower cognitive performance.

Our evidence that HI is associated with lower NAWM FA and NDI is in accordance with the main findings of recent meta-analyses, demonstrating impaired structural integrity in all severities of TBI and that FA, a metric of directionality, is a stronger correlate of LOC HI than mean diffusivity. It is not possible to directly infer the underlying microstructural changes related to diffusion metrics without supporting histology, however post-mortem work in cerebral amyloid angiopathy has shown that decreased FA can be caused by tissue rarefaction and reduction in neuronal density, while increasing MD can reflect decreasing myelination. Notably, FA did not explain much of the variance between HI and lower DSST score, indicating that it is not a big explanatory influence, or it is a noisier measure; regional measures may closely relate to cognitive performance.

Acute disruptions to biochemical and cytoskeletal functions are thought to happen in all HI events, even in the...
Figure 3. Forest plot of estimates from a linear regression model showing the mean difference in continuous neuroimaging outcomes at age 69–71 by (A) LOC HI occurring >15 years prior, and (B) LOC HI occurring at anytime up to age 71. Estimates are standardized and adjusted for gender, age at testing, childhood cognition, education and childhood socioeconomic position. Volumetric measures additionally adjusted for total intracranial volume. NAWM, normal appearing white matter; FA, fractional anisotropy; MD, mean diffusivity; NDI, neurite density index; ODI, orientation dispersion index.
mild HI that is likely expected here, and could explain how HI-related changes affect whole brain volume and NAWM microstructural indexes.\textsuperscript{2} Given the existing wider evidence, it is feasible that acute HI-induced brain volume loss and different microstructure occurs as a direct effect of the initial pathological response and may reduce brain reserve and neuroplasticity, HI-induced atrophy and microstructural changes could also be the basis of a long-latency or temporal amplification effects, whereby it makes the brain more vulnerable to ageing, inflammation, and neurodegenerative effects many years after the initial injury, and consequently at greater risk of cognitive impairment.

Despite studies reporting links between HI and Alzheimer's disease, and a few studies providing evidence that HI is associated with AD-related pathology markers including increased β-amyloid (A\textsubscript{β})\textsuperscript{3} and reduced hippocampal volume,\textsuperscript{5} we find a lack of strong associations between LOC HI and a range of AD-biomarkers (A\textsubscript{β}-PET, disproportional hippocampal volume loss, AD-signature region cortical thickness\textsuperscript{43}). Our findings suggest that HI does not increase cognitive impairment risk via earlier development of pathology typically associated with the AD, at least not at this relatively early stage of the pathophysiological continuum of AD.\textsuperscript{44} Instead our findings suggest that HI is linked to diffuse brain volume-related pathways at this age, and may interact with normal ageing processes, or reflect ongoing neurodegeneration, which may infer susceptibility for dementia.

We did not observe greater cerebral global WMH indicative of small vessel disease or find differences in serum NFL, a marker of axonal injury. NFL may be a more suitable biomarker as an acute index of neuronal damage instead of chronic damage\textsuperscript{45}; and worse in those with pre-existing neurological conditions.\textsuperscript{46} In addition, as the severity of head injury in this cohort is expected to be mild it is possible that the neuronal injury is too low after adjusting for prior education and childhood cognitive ability. The effect was partly explained by the presence of smaller global brain volumes and microstructural changes, although other pathological underpinnings may be present. Continued follow-up will provide greater insight into whether the negative effects of HI on pathological markers and cognitive function are static or dynamic. If replicated, these findings suggest experiencing a LOC HI earlier in life may have implications for cognitive and brain health lasting decades later, into later life.

**Acknowledgements**

We are very grateful to those study members who helped in the design of the study through focus groups, and to the participants both for their contributions to Insight 46 and for their commitments to research over the last seven decades.

**Author Contributions**

MR, NCF and JMS conceived and obtained funding for the study. CAL, TP, AK, SB, SK, HMS, MB, AW, KM, JC
and SNJ had a major role in the acquisition of data. CAL, DC, IM, CS, WC, LP performed imaging processing and QC. JMN provided statistical support. SNJ performed the analysis and drafted the initial manuscript. All authors contributed to revision, interpretation and editing of the manuscript.

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Role</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarah-Naomi James</td>
<td>University College London</td>
<td>Author</td>
<td>Interpreted the data; revised the manuscript for intellectual content.</td>
</tr>
<tr>
<td>Jennifer M. Nicholas</td>
<td>London School of Hygiene and Tropical Medicine</td>
<td>Author</td>
<td>Provided statistical support. Interpreted the data; revised the manuscript for intellectual content.</td>
</tr>
<tr>
<td>Christopher A. Lane</td>
<td>University College London</td>
<td>Author</td>
<td>Major role in the acquisition of data. Interpreted the data; revised the manuscript for intellectual content.</td>
</tr>
<tr>
<td>Thomas D. Parker</td>
<td>University College London</td>
<td>Author</td>
<td>Major role in the acquisition of data. Interpreted the data; revised the manuscript for intellectual content.</td>
</tr>
<tr>
<td>Kirsty Lu</td>
<td>University College London</td>
<td>Author</td>
<td>Major role in the acquisition of data. Interpreted the data; revised the manuscript for intellectual content.</td>
</tr>
<tr>
<td>Ashvini Keshavan</td>
<td>University College London</td>
<td>Author</td>
<td>Major role in the acquisition of data. Interpreted the data; revised the manuscript for intellectual content.</td>
</tr>
<tr>
<td>Sarah M. Buchanan</td>
<td>University College London</td>
<td>Author</td>
<td>Major role in the acquisition of data. Interpreted the data; revised the manuscript for intellectual content.</td>
</tr>
<tr>
<td>Sarah E. Keuss</td>
<td>University College London</td>
<td>Author</td>
<td>Major role in the acquisition of data. Interpreted the data; revised the manuscript for intellectual content.</td>
</tr>
<tr>
<td>Heidi Murray-Smith</td>
<td>University College London</td>
<td>Author</td>
<td>Major role in the acquisition of data. Interpreted the data; revised the manuscript for intellectual content.</td>
</tr>
</tbody>
</table>
Conflicts of Interest

HZ is a co-founder of Brain Biomarker Solutions, a GU Ventures-based platform company at the University of Gothenburg, has served on advisory boards of Roche Diagnostics, Wave, Samumed and CogRx and has given lectures in symposia sponsored by Biogen and Alzecure. NCF has received research funding from Eisai, Elan, Eli Lilly, GE, IXICO, Janssen, Lundbeck, Pfizer, Roche Sanofi-Aventis and Wyeth. NCF has served on a Data Safety Monitoring Committee for Biogen. JS has received research funding from Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly), has consulted for Roche Pharmaceuticals, Biogen, and Eli Lilly, given educational lectures sponsored by GE, Eli Lilly and Biogen, and serves on a Data Safety Monitoring Committee for Axon Neuroscience SE. All other authors have no conflicts of interest to declare.

References


41. van Veluw SJ, Reijmer YD, van der Kouwe AJ, et al. Histopathology of diffusion imaging abnormalities in...


Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Means of cognitive and neuroimaging data available.

Table S2. Association between reported head injury (HI) and later-life cognitive function at age 69–71 with additional sensitivity analyses.

Table S3. Association between reported head injury (HI) and pathology at age 69–71 with additional sensitivity analyses.