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How Traumatic Brain Injury History Relates to Brain Health MRI Markers and Dementia Risk: Findings from the 3C Dijon Cohort

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Abstract.

Background: The long-term effects of traumatic brain injury (TBI) with loss of consciousness (LOC) on magnetic resonance imaging (MRI) markers of brain health and on dementia risk are still debated.

Objective: To investigate the associations of history of TBI with LOC with incident dementia and neuroimaging markers of brain structure and small vessel disease lesions.

Methods: The analytical sample consisted in 4,144 participants aged 65 and older who were dementia-free at baseline from the Three City – Dijon study. History of TBI with LOC was self-reported at baseline. Clinical Dementia was assessed every two to three years, up to 12 years of follow-up. A subsample of 1,675 participants <80 years old underwent a brain MRI at baseline. We investigated the associations between history of TBI with LOC and 1) incident all cause and Alzheimer's disease (AD) dementia using illness-death models, and 2) neuroimaging markers at baseline.

Results: At baseline, 8.3% of the participants reported a history of TBI with LOC. In fully-adjusted models, participants with a history of TBI with LOC had no statistically significant differences in dementia risk (HR = 0.90, 95% CI = 0.60–1.36) or AD risk (HR = 1.03, 95% CI = 0.69–1.52), compared to participants without TBI history. History of TBI with LOC was associated with lower white matter volume ($\beta = -4.58$, $p = 0.048$), but not with other brain volumes, white matter hyperintensities volume, nor covert brain infarct.

Conclusion: This study did not find evidence of an association between history of TBI with LOC and dementia or AD dementia risks over 12-year follow-up, brain atrophy, or markers of small vessel disease.

Keywords: Alzheimer's disease, brain MRI, dementia, traumatic brain injury

INTRODUCTION

Dementia is a burdensome syndrome with around 43.8 million cases estimated worldwide and 878,000 cases in France in 2016 [1]. In the absence of curative treatments, identifying modifiable factors that may reduce dementia risk and maintain cognitive

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functions is critical to establish prevention strategies. Recently, there has been an increased interest regarding traumatic brain injury (TBI) as a potential risk factor for neurodegenerative diseases [2]. TBI is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force [3]. It varies in severity from mild TBI (concussion) that may result in an alteration of mental status and/or brief loss of consciousness (LOC) (less than 30 min) [4, 5], to moderate and severe TBI that can result in prolonged disorders of consciousness or death. TBIs represent an important economic burden and are often associated with psychological and physical disabilities [6, 7]. A 3.6% increase in incidence rates worldwide from 1990 to 2016 has been reported by the Global Burden of Disease study [8], and the annual prevalence rate of TBI in France in 2016 has been estimated to be between 535 and 593 per 100,000 people [8].

Several reports from prospective studies have shown an association between history of TBI and increased risk of dementia [9–18] or Alzheimer’s disease (AD) dementia [9, 11, 12, 15–17, 19, 20], especially for severe TBI. Two recent cohort studies using nationwide hospitalization records from Denmark and Sweden reported strong increased risk of dementia in the first year following TBI (Hazard Ratio (HR)<6 months = 4.06 (95% Confidence Interval (CI): 3.79–4.34) in the Danish study and HR <1 year = 3.53 (95% CI: 3.23–3.84) in the Swedish study). These associations became weaker with increasing time from TBI (HR 10–12 years = 1.21 (95% CI: 1.10–1.32) in the Danish study and HR 10–20 years = 1.48 (95% CI: 1.39–1.58) in the Swedish study) [17, 18]. However, no association was evidenced in other studies, most of which were population-based studies with self-reported TBIs [21–26]. Self-reported TBIs include TBIs of milder severity that did not result in hospitalization or other medical treatment and this could lead to lower risk estimates compared to study that identified TBI history only based on medical records. In terms of physiopathology, the potential mechanisms that could link TBI to dementia are still unclear. One hypothesis states that TBI induces axonal injury that could accelerate both propagation of AD-related pathological proteins and neuronal loss [27]. This hypothesis is supported by studies reporting associations between TBI and markers of neuronal loss and brain atrophy such as hippocampal volume or brain volume loss, suggesting that TBI may promote neurodegeneration [27–29]. The con-

tribution of TBI to neurodegeneration may in part be explained by TBIs being linked to AD-related pathology, but results on this association are inconsistent [25, 26, 30–35]. Another hypothesis is that TBI may induce cerebrovascular pathology, such as small vessel disease, which could accelerate dementia onset [36, 37].

The primary aim of this work was thus to investigate the association between history of TBI with LOC and risk of all dementia and AD dementia in the Three City (3C) – Dijon study, a French population-based cohort. A secondary aim was to examine the associations between history of TBI with LOC and MRI markers of neurodegeneration and cerebrovascular disease.

METHODS

Study population

The 3C – Dijon study is a population-based cohort including 4,931 participants from Dijon, France. To be eligible for recruitment into the study, persons had to be 1) registered on the electoral rolls of Dijon city, 2) aged 65 years and over, and 3) not institutionalized. Baseline examinations took place between March 1999 and March 2001. Participants were then followed over 12 years, every 2 or 3 years. Repeated cognitive evaluations, as well as active assessment of dementia cases have been realized at each follow-up. At each study wave, a standardized questionnaire assessing socio-demographic, medical, cognitive, and functional characteristics was administered at home by trained neuropsychologists during face-to-face interviews. At baseline, MRI scans were proposed to participants aged ≤ 80 years; the MRI scan consent rate was 83%. A total of 1,923 baseline MRI examinations have been performed. Full details of the study have been previously published [38]. This research adhered to the principles of the Declaration of Helsinki. The ethics committee of the Kremlin-Bicêtre University Hospital and Sud-Méditerranée III (France) approved the 3C study protocol. All participants gave written informed consent.

Among the 4,862 dementia-free participants included in the 3C – Dijon study, 4,144 participants had non-missing data on TBI status at baseline and covariates. Among those, 1,675 participants underwent MRI examination before age 80, and have at least one of the studied MRI markers (Supplementary Figure 1). For analyses of incident dementia, partici-

140 pants were followed until death, dropout or until the
141 end of follow-up (12 years).

142 *Outcomes of interest*

143 *Dementia and its subtypes*

144 Dementia diagnosis was ascertained using a stan-
145 dardized three-step procedure [38]. The first step
146 was a cognitive evaluation by trained neuropsy-
147 chologists using a series of psychometric tests.
148 Participants who were suspected of dementia, based
149 on their neuropsychological performance or decline
150 relative to a previous examination were then exam-
151 ined for further medical assessments. Finally, each
152 case was discussed by a validation committee com-
153 posed of neurologists and geriatricians to classify
154 etiology. The diagnosis of dementia was based
155 on the Diagnostic and Statistical Manual of Men-
156 tal Disorders - Fourth Edition (DSM-IV) criteria.
157 Dementia subtyping was based on the National Insti-
158 tute of Neurological and Communicative Disorders
159 and Stroke–Alzheimer’s Disease and Related Disor-
160 ders Association (NINDS-ADRDA) criteria for AD,
161 and on the National Institute of Neurological Dis-
162 orders and Stroke–Association Internationale pour
163 la Recherche et l’Enseignement en Neurosciences
164 (NINDS-AIREN) criteria for vascular dementia.
165 Mixed dementia was defined as a diagnosis of AD
166 with either cerebrovascular lesions on brain imaging
167 when available or a documented history of stroke and
168 the presence of prominent executive function deficits
169 in addition to an AD-type cognitive profile. We con-
170 sidered all incident cases that occurred during the
171 12-year follow-up period for the current analyses.

172 *Brain MRI markers*

173 The protocol for brain MRI, using a 1.5-T Mag-
174 netom (Siemens, Erlangen, Germany), has been
175 described in detail previously [39]. We selected
176 five image-derived biomarkers: gray and white mat-
177 ter volumes (GM and WM, respectively), brain
178 parenchymal fraction (BPF), hippocampal volume,
179 white matter hyperintensities volume (WMHV), and
180 covert brain infarct (CBI). Using voxel-based mor-
181 phometry techniques, total intracranial volume (TIV)
182 was computed by summing GM, WM, and cere-
183 brospinal fluid (CSF) volumes. BPF was calculated
184 as the sum of GM and WM volumes divided by TIV.
185 Hippocampal volume was defined as the sum of left
186 and right hemisphere volume [40]. A fully automatic
187 image processing software was developed to detect
188 and quantify WMH [39]. WMHV was calculated by

189 summing the volumes of all the lesions detected.
190 CBI of presumed vascular origin were visually rated
191 on T1-, T2-, and proton density-weighted images.
192 Characteristics of lesions were visualized simulta-
193 neously in axial, coronal, and sagittal planes. They
194 were defined as focal lesions 3 to 15 mm in diam-
195 eter with the same signal characteristics as CSF on
196 all sequences, located in basal ganglia, brainstem, or
197 cerebral WM [41].

198 *Exposure of interest*

199 TBI was assessed at baseline with the following
200 question: “In your life, have you ever had a traumatic
201 brain injury with loss of consciousness?”. The expo-
202 sure was thus defined as history of TBI with LOC:
203 yes/no.

204 *Covariates*

205 At baseline, sociodemographic information was
206 collected and included date of birth, sex, height (mea-
207 sured), and education level (categorized as less than
208 high school level versus high school level and higher).
209 Potential confounding factors of interest included:
210 APOE $\epsilon 4$ status, history of stroke, history of car-
211 diovascular disease (CVD), hypertension, diabetes,
212 physical impairment, and depressive symptoms lev-
213 els. APOE $\epsilon 4$ status was defined as at least one $\epsilon 4$
214 allele carried versus none. The measurement meth-
215 ods for the APOE genotype have been described
216 previously [39]. History of stroke and CVD were
217 self-reported. Hypertension was defined by either
218 measured systolic blood pressure ≥ 140 mmHg or
219 diastolic blood pressure ≥ 90 mmHg, or antihyper-
220 tensives drug intake. Diabetes was defined as either
221 the presence of fasting blood glucose ≥ 7 mmol/L or
222 antidiabetic drug intake. Depressive symptomatology
223 was assessed with the Center for Epidemiological
224 Studies-Depression (CESD) scale, using scores of
225 >16 as indicators of a clinically relevant level of
226 depressive symptomatology [42]. Finally, fractures
227 within two years prior to baseline were self-reported.
228 Instrumental activities of daily living (IADL) impair-
229 ment was defined as having difficulty with at least
230 one activity. Low Mini-Mental State Examination
231 (MMSE) score was defined as a MMSE score <24 .

232 *Statistical analysis*

233 Regarding the dementia outcome, the analytical
234 sample comprised 4,144 participants. Comparison of

participants included vs excluded due to missing TBI status and covariates was performed. Regarding the MRI outcomes, 1,675 participants were included in the analytical sample and participants included vs excluded due to missing MRI assessment, TBI status or covariates were compared. Participants excluded from analyses were older, were less educated, and had more vascular diseases, more IADL disability, and lower MMSE scores (Supplementary Tables 1 and 2). Participants' characteristics at baseline according to history of TBI with LOC status were reported using median and interquartile range, or mean and standard deviation. Comparisons were tested using t tests for continuous variables and χ^2 statistics for categorical variables. Incidence rates of dementia according to history of TBI with LOC status were also computed.

The relationship between history of TBI with LOC and dementia incidence over 12-year follow-up was investigated using an illness-death model [43]. This model has the advantage to take into account interval censoring of age at dementia owing to the fact that dementia is assessed only at the study visits and dementia onset could have occurred between visits. It also accounts for competing risk of death, right censoring, and left truncation due to the selection of subjects alive and non-demented at inclusion. In this multistate model, individuals start out as healthy (state 0), they may become demented (move to state 1), and afterward they may die (state 2). Individuals may also die without first becoming demented (transition from state 0 to state 2). Transition intensity 01 from state 0 (healthy) to state 1 (dementia) represents the age-specific incidence adjusted for covariates.

In this analysis, participants' age was considered as the time scale, and we applied a parametric approach with a Weibull distribution on the baseline transition intensities. Participants who remained free of dementia were censored at the age of their last follow-up before drop-out or at the end of follow up. To examine the association between history of TBI with LOC and the risk of dementia, two models were computed: a model only adjusted for sex and a second model additionally adjusted for APOE ϵ 4 status, height, hypertension, stroke history, cardiovascular disease history, diabetes, and high depressive symptoms. Similar models were performed with AD dementia as the outcome (non-AD dementia cases were censored at the last visit seen). Then, effect modification by sex, APOE ϵ 4 status, and education level were tested using interactions, and stratified analyses were further presented. To further explore potential selection bias due to exclusion of participants with missing

data, missing values of TBI history and covariates were imputed by multiple imputation (MI) using chained equations with a fully conditional specification (10 imputed data sets) [44], and the primary analysis was rerun on complete datasets. In a sensitivity analysis, the primary analysis was rerun after excluding participants with a MMSE <27 at baseline in order to assess the impact of potential misclassification on the exposure of interest, as recall bias may arise from subclinical dementia.

The relationship between history of TBI with LOC and the different brain MRI markers (BPF, WM and GM volume, hippocampal volume, log-transformed WMHV, and CBI) was investigated using linear or logistic regression models, as appropriate. The basic model included age at baseline, delay between baseline and MRI assessment, sex, and TIV (except when BPF and CBI were the outcomes of interest). An adjusted model additionally included APOE ϵ 4 status, height, hypertension, stroke history, cardiovascular disease history, diabetes, and high depressive symptoms. Effect modification by sex, APOE ϵ 4 status, and education level was also examined using interaction terms and stratified analyses were further presented. To account for selection into the MRI subsample, we also applied inverse probability of attrition weighting. The weight (assessing the probability of being included in the analysis) of each participant was obtained by fitted values of a multivariable logistic regression modelling inclusion status (yes/no) as a dependent variable and including history of TBI status, the covariates used in the primary analysis, as well as other covariates (IADL dependency, fracture history), and cognitive test (MMSE and Benton tests [45]). Linear and logistic regressions between history of TBI with LOC and MRI markers were then weighted by the inverse of the stabilized probability of remaining in the sample.

Analyses were conducted in R (version 3.6.0) using SmoothHazard (version 1.4.1) [43].

RESULTS

Baseline characteristics of the analytic samples are presented overall and according to TBI status in Table 1. Among the 4,144 participants, 343 (8.3%) reported a history of TBI with LOC. Overall, mean age was 74.3 years old, with 61.4% women. Compared to unexposed participants, participants reporting a history of TBI with LOC had less often hypertension, and more often non-stroke CVD

Table 1
Baseline characteristics of study participants according to TBI status at study entry, the Three City – Dijon study, 1999–2000

	Total Sample (<i>n</i> = 4,144)	No TBI with LOC (<i>n</i> = 3,801)	History of TBI with LOC (<i>n</i> = 3,43)	<i>p</i>
Women, <i>n</i> (%)	2,543 (61.4)	2,370 (62.4)	173 (50.4)	<0.001
Age, mean (SD)	74.3 (5.5)	74.3 (5.5)	74.0 (5.3)	0.42
Education level				0.68
Less than high school, <i>n</i> (%)	2,634 (63.6)	2,412 (63.5)	222 (64.7)	
High school and above, <i>n</i> (%)	1,510 (36.4)	1,389 (36.5)	121 (35.3)	
<i>APOE</i> ϵ 4, <i>n</i> (%)	869 (21.0)	800 (21.0)	69 (20.1)	0.74
Height (cm), mean (SD)	162 (0.9)	162 (0.9)	163 (0.9)	0.03
Hypertension, <i>n</i> (%)	3,296 (79.5)	3,037 (79.9)	259 (75.5)	0.06
Stroke history, <i>n</i> (%)	192 (4.6)	175 (4.6)	17 (5.0)	0.87
CVD history, <i>n</i> (%)	605 (14.6)	532 (14.0)	73 (21.3)	<0.001
Diabetes, <i>n</i> (%)	387 (9.3)	356 (9.4)	31 (9.0)	0.92
High depressive symptoms, <i>n</i> (%)	865 (20.9)	786 (20.7)	79 (23.0)	0.34
IADL dependency, <i>n</i> (%)	370 (8.9)	337 (8.9)	33 (9.7)	0.72
Low baseline MMSE score, <i>n</i> (%)	193 (4.7)	175 (4.6)	18 (5.3)	0.68

TBI, traumatic brain injury; LOC, loss of consciousness; CVD, cardiovascular disease; MMSE, Mini-Mental State Examination.

Table 2
Associations* between history of TBI and risk of dementia and Alzheimer's disease, the Three City – Dijon study, 1999–2011

	All Dementia		Alzheimer's disease dementia	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Model 1				
TBI history versus not	0.98 (0.68–1.43)	0.94	1.14 (0.74–1.74)	0.55
Model 2				
TBI history versus not	0.90 (0.60–1.36)	0.62	1.03 (0.69–1.52)	0.90

TBI, traumatic brain injury. Model 1 adjusted for sex. Model 2: model 1+ education, *APOE* ϵ 4 status, height, stroke history, non-stroke CVD history, diabetes, hypertension, and high depressive symptoms. *Using illness-death models.

336 history. The incidence rate of dementia within the
337 group with history of TBI was 12.3 per 1000 person-
338 years (95%CI: 7.9, 16.7) compared to 12.7 per 1000
339 person-years (95%CI: 11.3, 14.0) in the group with-
340 out history of TBI ($p = 0.87$).

341 In both sex adjusted and fully adjusted models,
342 we did not observe any association between history
343 of TBI with LOC and dementia risk (HR = 0.98
344 (95% CI: 0.68, 1.43) and HR = 0.90 (95%CI: 0.60,
345 1.36), respectively) (Table 2). When AD demen-
346 tia was the outcome, a slightly higher hazard in
347 the sex adjusted model was observed but remained
348 non-significant (HR = 1.14 (95%CI: 0.74, 1.74)), and
349 there was no evidence of an association in fully
350 adjusted models (HR = 1.03 (95%CI: 0.69, 1.52)).
351 Results using imputed missing variables are pre-
352 sented in Supplementary Table 3 and yielded similar
353 estimates for dementia risk and estimates closer to
354 the null for AD risk. After exclusion of participants
355 with MMSE scores lower than 27, estimates were
356 slightly higher than for the main findings (demen-

357 tia HR = 0.99 (95%CI: 0.45–2.18); AD dementia
358 HR = 1.21 (95%CI: 0.65–2.27) for fully adjusted
359 models), yet still non-significant (Supplementary
360 Table 4).

361 Stratified analysis presenting the association of
362 TBI with dementia or AD dementia by sex, *APOE*
363 ϵ 4 status, and education level are presented in Fig. 1.
364 Interaction was not significant across sex and edu-
365 cation level. For *APOE* ϵ 4 status, interaction was
366 significant ($p < 0.05$), yet with non-significant point
367 estimates in the harmful direction among *APOE*
368 ϵ 4 carriers for dementia risk (HR = 1.62 (95%CI:
369 0.90–2.92)) and AD dementia (HR = 1.69 (95%CI:
370 0.97–2.94)).

371 Associations between history of TBI with LOC
372 and brain MRI markers are reported in Table 3 for
373 unweighted and weighted models. Individuals with
374 history of TBI with LOC presented on average signif-
375 icantly lower WM volume compared with individuals
376 without (adjusted unweighted model: beta = -4.58
377 (95%CI: -9.12, -0.04), $p = 0.048$). BPF, GM volume,

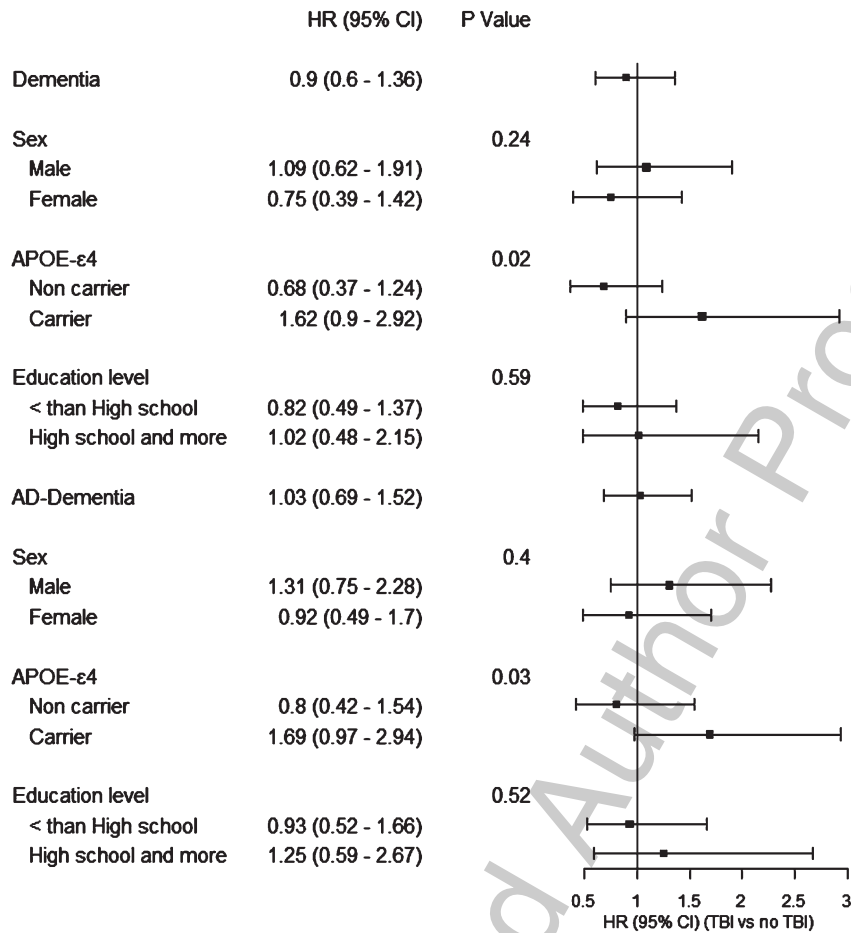


Fig. 1. Association between history of TBI and risk of dementia, stratified by sex, *APOE* ε4 status, and education level, the Three City – Dijon study, 1999–2011.

378 hippocampal volume, WMHV, and CBI did not differ
 379 according to history of TBI with LOC status, in
 380 both sex and fully adjusted models. Weighted analyses
 381 yielded similar results. We did not find evidence
 382 any significant effect modification by sex, education,
 383 or *APOE* ε4 in analyses of neuroimaging markers
 384 (Supplementary Table 5).

385 DISCUSSION

386 In a French prospective cohort of older adults free
 387 of dementia at baseline, we did not find support for an
 388 association between history of TBI with LOC and risk
 389 of dementia or AD over 12 years of follow-up. Our
 390 data showed a trend for an increased risk of dementia
 391 and AD dementia limited to *APOE* ε4 carriers.
 392 Moreover, history of TBI with LOC was only related
 393 to lower WM volume, but not with hippocampal volume,
 394 nor with markers of small vessel disease, as

395 measured by brain MRI; these associations were not
 396 modified by *APOE* ε4 status.

397 Our results are consistent with several studies [22,
 398 24–26, 30]. In particular, Crane et al. found no association
 399 between TBI with LOC and incident dementia,
 400 incident AD, or AD neuropathologic outcomes from
 401 autopsy in a pooled analysis of over 7,000 participants
 402 from three US cohort studies [25]. A recent study among
 403 autopsy subjects from the National Alzheimer's Coordinating
 404 Center also did not show association between TBI history
 405 and neither dementia nor AD neuropathologic changes [26].
 406 Finally, our previous work on 2,718 participants of the
 407 Health and Retirement Study also failed to evidence an
 408 association between TBI and dementia incidence [24].
 409 This body of literature is conflicting with other well-
 410 powered studies showing higher risks of dementia or
 411 AD for individuals with history of TBI [9, 10, 16–18,
 412 46].
 413

Table 3
Associations between history of TBI and MRI brain markers, the Three City – Dijon study, 1999–2011 (N = 1,675)

	Model 1		Model 2		Weighted* model 1		Weighted* model 2	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
BPF								
TBI history versus not	-0.36 (-0.88, 0.16)	0.17	-0.34 (-0.86, 0.17)	0.19	-0.41 (-0.92, 0.11)	0.12	-0.36 (-0.87, 0.15)	0.16
White matter volume								
TBI history versus not	-4.91 (-9.46, -0.38)	0.03	-4.58 (-9.12, -0.04)	0.05	-4.94 (-9.39, -0.49)	0.03	-4.59 (-9.04, -0.14)	0.04
Grey matter volume								
TBI history versus not	0.21 (-4.66, 5.08)	0.93	0.11 (-4.71, 4.92)	0.96	-0.24 (-5.02, 4.54)	0.92	-0.04 (-4.77, 4.68)	0.99
Hippocampal volume								
TBI history versus not	0.003 (-0.10, 0.11)	0.95	0.006 (-0.10, 0.11)	0.90	0.05 (-0.06, 0.16)	0.36	0.05 (-0.05, 0.16)	0.32
WMHV								
TBI history versus not	-0.07 (-0.19, 0.04)	0.19	-0.07 (-0.18, 0.04)	0.20	-0.10 (-0.21, 0.01)	0.08	-0.10 (-0.21, 0.01)	0.09
CBI**								
TBI history versus not	1.02 (0.55–1.77)	0.94	0.97 (0.51–1.71)	0.91	1.27 (0.76–2.04)	0.34	1.19 (0.69–1.95)	0.52

BPF, brain parenchymal fraction; WMHV, white matter hyperintensities volume; CBI, covert brain infarct. Model 1 adjusted for sex, age at baseline, and delay between age at baseline and age at MRI. Model 2: model 1 + education, APOE ϵ 4 status, height, stroke history, non-stroke CVD history, diabetes, hypertension, fracture, and high depressive symptoms. Each model was adjusted for total intracranial volume, except for brain parenchymal fraction and covert brain infarct. Brain volumes unit is cm^3 , WMHV was log-transformed. * Analysis using IPW to account for selection into the MRI subsample. ** Estimates shown are odd ratios with 95% confidence intervals.

These inconsistent associations' reports may be related to heterogeneous definition of TBI exposure across studies. Indeed, in most studies that reported links between TBI and higher dementia risk, TBI exposure status was attributed from hospitalization/medical records, i.e., restricted to more severe TBI cases that require hospitalization or other medical treatment. TBI exposure defined from medical records may miss some self-reported TBI cases that did not seek any medical care and were therefore milder. This is in line with the higher prevalence of TBI observed in population-based studies with self-reported definition of TBI exposure in comparison with studies relying on national registries or medical claims [21, 22, 24–26]. Yet, mild TBIs have also been shown to be associated with higher dementia risk [46, 47], even if these studies were also often based on clinically-diagnosed TBIs, identifying mild TBIs that are severe enough to require hospitalization or notable care. Definitions for mild TBI often vary across studies, which may further contribute to inconsistencies in the literature. Moreover, the two nationwide studies reported the highest risk of dementia in the first year after TBI, suggesting claims datasets could conflate acute TBI-related cognitive change with the progressive development of dementia. For studies based on self-reported TBIs, information most often lacks regarding severity, delay since the exposure and number of TBIs sustain, therefore preventing to explore the specific impact of TBI types on dementia risk. In addition, differences across studies may also be related to the different types of assessment of dementia, with studies identifying dementia cases using medical records potentially missing undiagnosed cases among non TBI cases, thus potentially overestimating the associations. Studies settings may also influence results. History of TBI has consistently been showed to be associated with higher dementia risk among US military veterans [12–14], who are more likely to have severe TBI history. However, focus on this specific population also raise concerns about unmeasured confounding. For example, psychiatric comorbidities, such as post-traumatic stress disorder, depression, or presence of multiple traumas, are frequent among veterans and are also risk factors for dementia, and could account partly for the observed increased risk.

We found a non-significant increased risk of dementia and AD dementia in TBI participants carrying APOE ϵ 4. This trend is in agreement with previous evidence of an impact of genetic factors on

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466 TBI-related neurodegenerative diseases [48–51]. The
467 non-significance of our result may be due to a limited
468 power due to the APOE ϵ 4 subsample size ($n = 801$).
469 In addition, our results did not show significant differ-
470 ences according to educational level nor sex, although
471 previous studies reported mixed results regarding a
472 potentially higher risk of dementia in men with TBI
473 [10, 14, 19, 52].

474 Investigating the impact of TBI exposure on inter-
475 mediate markers of dementia risk, such as AD
476 pathology, neurodegeneration, or cerebrovascular
477 lesions, is essential to better understand the impact
478 of TBI on pathological aging. In this work, we evi-
479 denced lower WM brain volume for participants
480 reporting a history of TBI with LOC, while we
481 did not find any significant associations or trends
482 with GM volume, hippocampal volume, nor cere-
483 brovascular lesions. TBI can result in focal brain
484 injury such as contusions. Our findings of an asso-
485 ciation between TBI with LOC history and lower
486 WM volumes are in line with diffusion tensor
487 imaging studies that are more sensitive than stan-
488 dard magnetic resonance techniques to WM damage
489 following TBI [53]. These studies suggest cortical
490 contusion can be followed by axonal damage.
491 Tissue injury evolves over time with the develop-
492 ment of macrophage infiltration, tissue edema, and
493 demyelination [53]. These WM changes could lead
494 to WM tract and neural network disruptions that
495 could increase dementia risk. Whether TBI may also
496 trigger AD-specific neuropathological processes or
497 cerebrovascular disease development need further
498 investigations. Indeed, results from well powered
499 autopsy-based studies have been mixed regarding
500 the cross-sectional association between TBI history
501 and neuropathological measures [25, 26, 31, 35].
502 Although some studies reported lower hippocampal
503 volume [54], higher amyloid deposition [32–35], as
504 well as higher cerebrovascular load following a TBI
505 with LOC [25, 35, 55], others did not evidence higher
506 hippocampal atrophy [25, 30–32, 35], higher AD neu-
507 ropathological changes [25, 26, 30, 31] or higher
508 WM lesions load or more frequent brain infarcts
509 among participants with history of TBI with LOC
510 [26, 30, 31, 35].

511 The principal limitation of this study lies in the
512 definition of TBI exposure, which is self-reported,
513 with missing information regarding the duration of
514 the LOC, as well as the date and severity of the TBIs.
515 Our TBI exposure relies on participants recall and
516 may be subject to misclassification bias. Some par-
517 ticipants with no self-reported TBI with LOC may

518 have had TBI without LOC, possibly driving the
519 associations toward the null as a few studies evi-
520 denced negative effect of concussive TBI without
521 LOC [46]. Studies using self-reported TBIs may thus
522 under-estimate the true TBI prevalence. However,
523 the sensitivity analysis excluding participants with
524 low cognitive performances at baseline led to similar
525 results, limiting concerns about differential misclas-
526 sification. Finally, the number of TBI sustained was
527 not collected in the 3C study, and individuals report-
528 ing a history of TBI may have sustained a single
529 mild TBI, potentially explaining the lack of asso-
530 ciations. These differences in TBI definitions may
531 explain the conflicting findings across the literature,
532 and future studies should attempt to address this
533 gap by using more accurate TBI assessment. Selec-
534 tion bias is another potential limitation of our study,
535 especially within the MRI subsample. However, anal-
536 ysis using multiple imputation and IPW to account
537 for selection yielded similar results. In addition, our
538 study included participants aged 65 years and older
539 (mean age at baseline = 74), leading to a sample of
540 older age compared to many studies reporting signif-
541 icant associations between TBI history and dementia.
542 The inclusion of older participants may have led to
543 the selection of people with history of TBI who sur-
544 vived longer and were free of dementia before the
545 age of 65, had milder TBI, and are therefore health-
546 ier. In the sample, participants with history of TBI
547 only differed from participants with no TBI regard-
548 ing higher history of cardiovascular disease, whereas
549 other health characteristics did not differ. The selec-
550 tion of healthier participants with history of TBI with
551 LOC could lead to an underestimation of the asso-
552 ciation of history of TBI with LOC with dementia.
553 Finally, although major risk factors for dementia were
554 adjusted for in these analyses, residual confounding
555 may remain.

556 Despite these limitations, this study has differ-
557 ent strengths. Our study population is a prospective,
558 population-based cohort with sufficient follow-up
559 and sample size, providing an adequate setting to
560 detect the long-term association between history of
561 TBI with LOC and risk of dementia. Additionally, this
562 work relies on well-defined dementia cases, where
563 each participant was evaluated at home for cognitive
564 and physical impairment, and each case was reviewed
565 by a validation committee. Finally, the availability of
566 MRI markers of brain health allowed us to investigate
567 different intermediate markers which could further
568 our understanding of the long-lasting effect of TBI
569 with LOC exposure.

In conclusion, our results did not evidence a global association between history of TBI with LOC and dementia, AD risk, or MRI markers of brain health, yet with a trend toward higher risk of dementia associated with history of TBI among APOE ϵ 4 carriers only. Future studies in the general population with a more comprehensive assessment of TBI exposure would be needed to confirm those results, and determine whether other potential risk factors may influence the association of TBI with dementia.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

Data will be made available upon request to E3C.CoordinatingCenter@gmail.com through a specific research proposal.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <https://dx.doi.org/10.3233/JAD-220658>.

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