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Head injury and 25-year risk of dementia

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Abstract

Introduction: Head injury is associated with significant morbidity and mortality. Long-term associations of head injury with dementia in community-based populations are less clear.

Methods: Prospective cohort study of 14,376 participants (mean age 54 years at baseline, 56% female, 27% Black, 24% with head injury) enrolled in the Atherosclerosis Risk in Communities (ARIC) Study. Head injury was defined using self-report and International Classification of Diseases, Ninth/Tenth Revision (ICD-9/10) codes. Dementia was defined using cognitive assessments, informant interviews, and ICD-9/10 and death certificate codes.

Results: Head injury was associated with risk of dementia (hazard ratio [HR] = 1.44, 95% confidence interval [CI] = 1.3–1.57), with evidence of dose-response (1 head injury: HR = 1.25, 95% CI = 1.13–1.39, 2+ head injuries: HR = 2.14, 95% CI = 1.86–2.46). There was evidence for stronger associations among female participants (HR = 1.69, 95% CI = 1.51–1.90) versus male participants (HR = 1.15, 95% CI = 1.00–1.32), *P*-for-interaction < .001, and among White participants (HR = 1.55, 95% CI = 1.40–1.72) versus Black participants (HR = 1.22, 95% CI = 1.02–1.45), *P*-for-interaction = .008.

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CONFLICT OF INTEREST

Dr. Ling serves as a consultant on the BrainScope Scientific Advisory Board (unpaid position), the National Football League Players Association Mackey-White Health Committee (unpaid position), the National Football League Health Foundation, the National Institutes of Health National Center for Advancing Transitional Sciences, and the Veterans Administration Research Advisory Council. For the other authors, no competing financial interests exist.

SUPPORTING INFORMATION

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

Discussion: In this community-based cohort with 25-year follow-up, head injury was associated with increased dementia risk in a dose-dependent manner, with stronger associations among female participants and White participants.

Keywords

cohort study; dementia; head injury

1 | BACKGROUND

Head injury in the United States is common, with over 23 million adults age 40 or older reporting a history of head injury with loss of consciousness.[1] Age-adjusted rates of emergency department visits for head injury increased by 54% between the years of 2006 and 2014, whereas age-adjusted rates of head injury–related deaths decreased 6% over this time,[2] suggesting that there are more survivors of head injury than ever before as a result of both increased awareness of head injury and improved survival.[3] It has become increasingly recognized that the sequelae from head injuries are long-lasting and several studies have reported increased cognitive impairment and higher rates of dementia among persons with head injuries,[4–11] although mechanisms linking traumatic brain injury (TBI) to cognitive decline and dementia remain poorly understood.[12] Prior studies on head injury and dementia associations are limited by selected populations (eg, military, medical claims databases) with limited sex and race representation, a lack of information on number of head injuries, and follow-up time <10 years.[4–10] In addition, literature from the dementia field has suggested that women are at higher risk of dementia compared to men[13] and that Blacks are at higher risk for dementia compared to Whites,[14] but few prior studies have evaluated for possible differences in associations of head injury with dementia risk by sex and race.[15]

The Atherosclerosis Risk in Communities (ARIC) Study is an ongoing community-based prospective cohort study that is uniquely positioned to investigate the associations between head injury and incident dementia over a median of 25 years of follow-up in a biracial population. We hypothesized that head injury would be associated with increased risk of dementia and that there would be a dose-dependence to the association.

2 | METHODS

2.1 | Study population

The ARIC Study is an ongoing, community-based cohort that recruited 15,792 participants ages 45–65 years of age at study visit 1 in 1987 to 1989 from the four U.S. communities of the suburbs of Minneapolis, Minnesota; Washington County, Maryland; Forsyth County, North Carolina; and Jackson, Mississippi.[16] Participants have attended up to six subsequent in-person visits and participate in annual/semi-annual telephone follow-up calls (Figure 1).

Of the 15,792 ARIC participants, we excluded 103 participants who were of non-Black and non-White race and Black participants at the Minnesota and Maryland field centers (in accordance with ARIC study analysis recommendations due to race-site aliasing): one participant with an International Classification of Diseases (ICD) code for dementia

occurring prior to study baseline, 365 participants missing head injury data or self-reported head injury year (no participants were excluded based on neurological sequelae from head injuries occurring prior to study baseline), and 947 participants missing data on statistical model covariates, leaving a total of 14,376 participants included in the present analyses (mean age 54 years at study baseline, 56% female, and 27% Black) (Figure 1).

The ARIC Study is approved by the institutional review boards of all participating institutions. All participants gave written informed consent at each study visit.

2.2 | Head injury

Head injury (with or without loss of consciousness) was defined using a combination of self-report questions and data from emergency department visits and hospitalizations. In total, 1866 participants had head injury/injuries identified from self-report only, 1081 participants had head injury/injuries identified from hospitalization data only, and 493 had head injury/injuries ascertained from both sources. Self-report questions were asked to participants at multiple visits (Figure 1). The text of self-reported questions asked changed over the course of the study (eTable 1). Self-reported questions inquired about head injury requiring physician/hospital care, loss of consciousness, number of head injuries, and year of head injury. Month and date for each self-reported head injury was imputed randomly using the random point method, which has been shown to be superior to mid-point imputation methods due to the minimization of the introduction of systematic bias.[17]

Hospitalization records were available from ARIC Study surveillance of all community hospitals study (1987 through December 31, 2018), and linked Centers for Medicare & Medicaid claims for hospitalizations and emergency department visits were available for participants ≥65 years of age enrolled in Medicare fee-for-service part B (1991 and December 31, 2015). Month, date, and year for each hospitalization were available. Hospitalized head injury was defined using the Centers for Disease Control and Prevention (CDC) ICD code definition[18–20] (eTable 2).

2.3 | Incident dementia

Detailed descriptions of the definition of incident dementia and its validation in ARIC have been described previously.[21–23] Briefly, there were three levels of ascertainment (eTable 3). Level 1 is adjudicated dementia defined using data from in-person evaluations at ARIC visits 5 and 6. Level 2 adds telephone data from participants who were alive but did not attend ARIC visit 5 and/or 6 and also adds data from informants of participants who were deceased prior to ARIC visit 5 and/or 6. Level 3, the main outcome in the present analysis, adds dementia cases identified by hospitalization ICD codes or death certificate codes occurring from baseline through December 31, 2018 (eTable 4); it is important to note that no participants were classified as having dementia based on codes for mild cognitive disorder or dementia with delirium alone. This Level 3 outcome is not dependent on visit attendance and thus minimizes potential biases due to attrition and the competing risk of death. However, in sensitivity analyses, we additionally used the adjudicated Level 1 outcome in a subset of participants who attended in-person visits 5 and 6 who did not have

dementia at visit 5. In this subpopulation we also investigated distributions of dementia etiologies (defined using previously described standardized criteria[22]).

2.4 | Covariates

All statistical models included the following covariates (assessed at ARIC visit 1): age (years, self-reported), sex (male; female, self-reported), race/center (Minnesota Whites; Maryland Whites; North Carolina Whites; North Carolina Blacks; Mississippi Blacks, self-reported), education (< high school; high school/GED/vocational school; college/graduate/professional school, self-reported), family income (≤ $35,000/year; > $35,000/year; not reported, self-reported), physical activity index (score range 1- to 5, modified Baecke Physical Activity Questionnaire[24]), cigarette smoking (current; former; never, self-reported), alcohol consumption (current; former; never, self-reported), hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of blood pressure medications), diabetes (fasting glucose ≥126 mg/dL or non-fasting glucose ≥200 mg/dL or use of diabetes medications), coronary heart disease (self-reported or silent myocardial infarction on electrocardiography[25]), stroke (self-reported[26]), apolipoprotein E (*APOE*) ε4 genotype (0 *APOE* ε4 alleles; 1/2 *APOE* ε4 alleles, TaqMan assay; Applied Biosystems, Foster City, CA), and military veteran status (self-reported). In sensitivity analyses we additionally adjusted for hospitalized depression (ICD codes 296.2, 296.3, and 311)[9] and post-traumatic stress disorder (ICD code 309.81)[9] occurring during study follow-up. When using the Level 1 dementia outcome, we additionally adjusted for depression (11-item Center for Epidemiologic Studies Depression score administered at ARIC visit 5; score <9 vs ≥9[27]).

2.5 | Statistical analyses

Head injury was defined as a time-varying exposure, allowing person-time to be allocated to no head injury and head injury groups (1 or 2+ head injuries) over follow-up (defined by date of first and second head injuries). Participant characteristics are shown overall and stratified by head injury status using means and standard deviations (SDs) or median (interquartile interval [25thth to 75th percentiles]) for continuous variables and using n's and proportions for categorical variables. Characteristics were compared head injury groups using *t* tests for comparing means of continuous variables, the Wilcoxon rank-sum test for comparing medians of continuous variables, and chi-square tests for categorical variables.

To calculate cumulative incidence of dementia by head injury status we used Kaplan-Meier analyses. We used Cox proportional hazards models employing Efron's approximation[28] to handle ties to obtain hazard ratios (95% confidence intervals [CIs]) to estimate the associations of head injury and head injury frequency with incident dementia. We verified that the proportional hazards assumption was met using Schoenfeld residuals (*P*-value for test of the null hypothesis that the log hazard ratio function is constant over time from our primary model = .758). In analyses of the association of head injury frequency with incident dementia, we additionally report *P*-values-for-linear-trend across head injury frequency categories (obtained by programming the categorical variable as a continuous variable). A priori, formal testing for interactions by age, sex, race, and *APOE* ε4 genotype was performed. When possible interactions by race were identified, we additionally performed

analyses restricted to participants from the Forsyth County, North Carolina field center, as this center recruited both black and white participants as a way to disentangle race versus field center effects. We additionally explored three-way interactions with *APOE ε*4 genotype as a way to explore *APOE ε*4 genotype as a potential driving factor for observed interactions by race and sex in the association of head injury with dementia. We additionally calculated the population attributable risk (95% CI) of head injury on dementia in our population by estimating attributable hazard fractions from the Cox proportional hazards model.[29]

In sensitivity analyses, we performed Fine-Gray models[30] to account for the competing risk of death. We additionally conducted sensitivity analyses implementing 1-year and 2-year "washout" periods, where persons with a dementia diagnosis occurring within 1 year of head injury diagnosis were excluded from the analysis to reduce the possible influence of reverse causality or misdiagnosis of head injury–related symptoms as dementia. We also conducted sensitivity analyses for the associations of head injury with incident dementia by timing of first head injury (prior to study baseline versus during follow-up) and by head injury defined by self-report versus by hospitalization data (only assessed during study follow-up) to assess the possible influences of survival bias and time since head injury. For head injuries defined by hospitalization data, we used Department of Defense[31] head injury severity classification (eTable 5) to investigate associations of head injury severity with incident dementia.

A *P*-value <.05 was considered statistically significant based on two-sided tests. All analyses were performed using Stata SE (Version 15, StataCorp, College Station, Texas).

3 | RESULTS

3.1 | Population characteristics

Participants were followed for a median of 25.0 years (interquartile interval: 17.9–28.2 years) for incident dementia. Twenty-four percent ($n = 3440$) of participants had at least one head injury occurring either before study baseline or by the end of follow-up. Of the 3440 with head injury, 1726 participants had head injury/injuries occurring only prior to study baseline, 120 participants had head injuries both occurring prior to study baseline and during study follow-up, and 1594 participants had head injury/injuries occurring only during study follow-up.

Compared to participants who never experienced a head injury, participants with head injury were of similar baseline age (54.4 years vs 54.2 years, $P = .055$), were more likely to be male (50.7% vs 42.6%, $P < .001$), White (80.5% vs 71.4%, $P < .001$), and be military veterans (28.9% vs 18.9%, $P < .001$) (Table 1). Participants with head injury were also more likely to be current/former alcohol consumers (77.8% vs 73.7%, $P < .001$) and be current/former cigarette smokers (60.7% vs 57.7%, $P < .001$) than participants without head injury.

3.2 | Association of head injury with incident dementia

There were 2350 incident dementia cases (1620 among persons without head injury, 730 among persons with a history of head injury) occurring over 320,306 person-years (PYs) of follow-up. The crude incidence rate for dementia per 1000 PYs was 6.2 (95% CI = 5.9–6.5)

among persons without head injury and was 12.5 (95% CI = 11.7–13.5) among persons with head injury. Overall, head injury was associated with 1.44 (95% CI = 1.32–1.57) times increased risk for incident dementia over a median of 25 years in adjusted models (Table 2). After further adjustment for hospitalized depression and post-traumatic stress disorder, the association remained significant (HR = 1.32, 95% CI = 1.21–1.44). In models accounting for the competing risk of death, the magnitude of association was stronger (HR = 1.72, 95% CI = 1.57–1.89) (eTable 6). The population attributable risk of head injury on dementia risk was 9.5% (95% CI = 7.5–11.4%).

In stratified analyses, there was evidence for a stronger association of head injury with incident dementia among females (HR = 1.69, 95% CI = 1.51–1.90) compared to among males (HR = 1.15, 95% CI = 1.00–1.32), *P*-for-interaction < .001. The crude rates of dementia per 1000 PYs were similar between female (6.0, 95% CI = 5.7–6.4) and male (6.4, 95% CI = 5.9–6.9) participants without head injury. There was also evidence for a stronger association of head injury with incident dementia among White (HR = 1.55, 95% CI = 1.40–1.72) compared to among Black participants (HR = 1.22, 95% CI = 1.02–1.45), *P*-for-interaction = .008. The crude rate of dementia per 1000 PYs was lower among White (5.5, 95% CI = 5.1–5.8) than among Black (8.2, 95% CI = 7.5–8.8) participants without head injury (Table 2). It is notable that analyses restricted to the Forsyth County, North Carolina field center (which recruited both White and Black participants) showed similar patterns, where the association of head injury with dementia was stronger among White compared to among Black participants (eTable 7). Furthermore, although three-way interactions of sex or race*head injury**APOE* ε4 genotype were significant, there was no evidence for any clear patterns by which *APOE* ε4 genotype explained the observed sex or race differences (eTable 8). The patterns whereby females only have higher crude rates of dementia than males in the head injury group (similar crude rates by sex in no head injury group) and Blacks have greater crude rates of dementia across all head injury and sex groups is shown in more detail in eFigure 1.

In sensitivity analyses implementing 1-year and 2-year “washout” periods, results were attenuated but head injury remained significantly associated with dementia risk (1-year “washout” period HR = 1.30, 95% CI = 1.19–1.43; 2-year “washout” period HR = 1.20, 95% CI = 1.10–1.32) (eTable 9). In sensitivity analyses investigating the possible influences of survival bias and time since head injury (eTable 10), associations of head injury with dementia were stronger in the subpopulation including participants with first head injury occurring during study follow-up (HR = 1.83, 95% CI = 1.64–2.04) compared to in the subpopulation including participants with first head injury occurring prior to study baseline (HR = 1.05, 95% CI = 0.93–1.19). Similarly, associations were stronger for head injury defined by hospitalization ICD codes (HR = 1.99, 95% CI = 1.80–2.21) compared to head injury defined by self-report (HR = 1.07, 95% CI = 0.96–1.19) (eTable 11). In analyses restricted to hospital ICD code–defined head injury, we found dementia risk increased with head injury severity (mild head injury: HR = 1.38, 95% CI = 1.24–1.55, moderate/severe/penetrating head injury: HR = 1.57, 95% CI = 1.27–1.94, *P*-value-for-linear-trend < .001) (eTable 12). There were no differences in the distribution of mild injury versus moderate/severe/penetrating injury by sex or race (both $P > .05$) observed in this subpopulation.
In sensitivity analyses using the Level 1 dementia definition ($N = 3399$ participants who

attended ARIC visits 5 and 6 and who did not have dementia at visit 5), analyses were limited by lower power, but overall were similar to the main analyses using the Level 3 dementia definition (odds ratio [OR] = 1.31, 95% CI = 0.92–1.86; further adjustment for depression did not appreciably alter these results) (eTable 13) and the distribution of dementia etiologies (Alzheimer's disease, vascular dementia, mixed dementia/other) did not differ by head injury status ($P = .367$).

3.3 | Association of head injury frequency with incident dementia

Of the 3440 with head injury, 2620 had one head injury, and 820 had 2+ head injuries, occurring either before study baseline or by the end of follow-up (eTable 14). Overall, 1 head injury was associated with a 1.25 (95% CI = 1.13–1.39) times increased risk and 2+ head injuries was associated with a 2.14 (95% CI = 1.86–2.46) times increased risk of incident dementia compared to no head injury (*P*-value-for linear-trend < .001 and *P*-value comparing 2+ versus 1 head injury < .001) (Figure 2, Figure 3A, and eTable 15). In adjusted models accounting for the competing risk of death, the magnitude of association was stronger (1 head injury: HR = 1.50, 95% CI = 1.35–1.67; 2+ head injuries: HR = 2.53, 95% CI = 2.19–2.94) (eTable 6).

We found evidence for multiplicative interaction by sex (*P*-value for interaction < .001), whereby female participants had stronger associations of head injury frequency with dementia than male participants. We also found evidence for multiplicative interaction by race (*P*-value for interaction = .043) whereby Whites had stronger associations of head injury frequency with dementia than Blacks (Figure 3B and 3C, eTable 15).

In sensitivity analyses implementing a 1-year and a 2-year "washout" period," results were somewhat attenuated, but remained significant for all except for the one head injury category in the 2-year "washout" period analysis (1-year "washout" period: 1 head injury: HR = 1.14, 95% CI = 1.03–1.27; 2+ head injuries: HR = 1.81, 95% CI = 1.56–2.10; 2-year "washout" period: 1 head injury: HR = 1.05, 95% CI = 0.943–1.17; 2+ head injuries: HR = 1.81, 95% CI = 1.56–2.10) (eTable 9). In sensitivity analyses investigating the possible influences of survival and time since head injury, associations of head injury with dementia were stronger in the subpopulation including participants with first head injury occurring during study follow-up compared to in the subpopulation including participants with first head injury occurring prior to study baseline (eTable 10).

4 | DISCUSSION

In this large biracial community–based population, we found that head injury was associated with a 1.44 times increased risk of dementia over 25 years and that this risk increased in a dose-dependent manner with increasing numbers of head injuries. We also found evidence for stronger associations of head injury with dementia risk among female compared to male participants and among White compared to Black participants.

A recent systematic review[32] of head injury with dementia risk in military veterans suggested a possible dose-response relationship, but this was based on sparse data.[7,8] Our results expand the evidence for a dose-response relationship between number of head

injuries and dementia risk to community-based populations and support the notion that prevention of head injuries is an important public health priority.[11,33]

There are limited data about sex differences in the association of head injury with dementia. One meta-analysis[34] found an increased risk of Alzheimer's dementia associated with head injury among male but not among female participants, whereas another meta-analysis[35] found that females have worse outcomes after head injury than males, including in areas of impaired memory. Our findings showed a higher risk of dementia associated with head injury among females as compared to among males. These heterogenous results may be attributable to different populations and the possibility that the types and severities of head injuries sustained in different settings among males and females may be different. Further investigation of sex differences in dementia risk after head injury in diverse populations is warranted.

There are few existing studies on racial differences in the association of head injury with dementia. Importantly, a recent study of military veterans reported stronger associations of head injury with dementia among Whites compared to Blacks.[15] Similarly, in our community-based study, we found that Whites were at higher risk for dementia after head injury compared to Blacks. This interaction may be partially driven by the higher crude baseline rates of dementia in Blacks compared to Whites without head injury as Blacks are at higher risk for dementia at baseline, so head injury may not confer as much extra risk among Blacks as it does among Whites. More research is needed to better understand the potential race differences in the association of head injury with dementia risk, with a particular focus on contributions from socioeconomic and vascular risk factors for dementia, which may contribute to the different baseline rates of dementia by race.

Certain limitations should be considered in the interpretation of this study. First, our definition of head injury was derived from self-report and hospitalization ICD code data. We did not have detailed information on the type and severity of head injury for all injuries and it is possible that the severity of injury ascertained by self-report and by hospitalization ICD code data may differ. The self-reported head injury questions focused on injuries in which there was a loss of consciousness or in which medical care was sought, so very mild injuries may not be captured in our head injury definition. However, self-report has been shown to be reliable in assessing head injury[36] and standard definitions were used to identify hospitalizations with ICD codes for head injury.[18–20] In addition, we were able to investigate the impact of head injury severity in the subset of hospitalized cases using standardized criteria.[31] It is also important to consider the impact of a head injury diagnosis on a dementia diagnosis[37] as well as the timing of dementia diagnosis after head injury diagnosis, as head injury-related symptoms may be misdiagnosed as dementia, particularly in the time following the head injury. We addressed this by performing 1- and 2-year wash-out analyses in which associations were somewhat attenuated, but remained significant, which suggests that part of the association between head injury and dementia may be driven by dementia diagnoses occurring close to the time of head injury. In addition our study population is biracial and does not include other races or ethnicities (eg, Hispanics, Asians). In the ARIC Study, Black participants were recruited at two of the four field centers, so we are not able to fully separate effects of race from effects of geography, although analyses restricted to

participants at the Forsyth County, North Carolina site showed patterns similar to those of the overall race-stratified analyses, suggesting that race is more of a driving factor than site. Finally, our study design did not allow for detailed investigation into associations of head injury with dementia subtypes, although we were able to look at clinically defined etiologies in a subset of our population. Future studies with neuropathological correlates are warranted.

In conclusion, head injury was associated with an increased risk for dementia over 25 years of follow-up and this increased risk was dose-dependent and stronger for a higher number of prior head injuries. There was evidence for greater risk of dementia after head injury among female compared to male and among White compared to Black participants. The robust and dose-dependent long-term associations of head injury with dementia risk demonstrated in this study support a possible role for increased cognitive monitoring among head injury survivors and suggest that prevention of head injury could mitigate risk of dementia later in life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Schneider ALC, Wang D, Ling G, Gottesman RF, Selvin E. Prevalence of self-reported head injury in the United States. N Engl J Med. 2018;379(12):1176–1178. [PubMed: 30231228]
2. Centers for Disease Control and Prevention. Surveillance Report of Traumatic Brain Injury-related Emergency Department Visits, Hospitalizations, and Deaths - United States, 2016–2014. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services; 2019.
3. Hsia RY, Markowitz AJ, Lin F, Guo J, Madhok DY, Manley GT. Ten-year trends in traumatic brain injury: a retrospective cohort study of California emergency department and hospital revisits and readmissions. BMJ Open. 2018;8(12):e022297.
4. Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K. Association of mild traumatic brain injury with and without loss of consciousness with dementia in US Military Veterans. JAMA Neurol. 2018;75(9):1055–1061. [PubMed: 29801145]
5. Barnes DE, Kaup A, Kirby KA, Byers AL, Diaz-Arrastia R, Yaffe K. Traumatic brain injury and risk of dementia in older veterans. Neurology. 2014;83(4):312–319. [PubMed: 24966406]
6. Gardner RC, Burke JF, Nettiksimmons J, Kaup A, Barnes DE, Yaffe K. Dementia risk after traumatic brain injury vs nonbrain trauma: the role of age and severity. JAMA Neurol. 2014;71(12):1490–1497. [PubMed: 25347255]

7. Nordstrom P, Michaelsson K, Gustafson Y, Nordstrom A. Traumatic brain injury and young onset dementia: a nationwide cohort study. Ann Neurol. 2014;75(3):374–381. [PubMed: 24812697]
8. Fann JR, Ribe AR, Pedersen HS, et al. Long-term risk of dementia among people with traumatic brain injury in Denmark: a population-based observational cohort study. Lancet Psychiatry. 2018;5(5):424–431. [PubMed: 29653873]
9. Yaffe K, Lwi SJ, Hoang TD, et al. Military-related risk factors in female veterans and risk of dementia. Neurology. 2019;92(3):e205–e211. [PubMed: 30541865]
10. Lee YK, Hou SW, Lee CC, Hsu CY, Huang YS, Su YC. Increased risk of dementia in patients with mild traumatic brain injury: a nationwide cohort study. PLoS One. 2013;8(5):e62422. [PubMed: 23658727]
11. Nordstrom A, Nordstrom P. Traumatic brain injury and the risk of dementia diagnosis: a nationwide cohort study. PLoS Med. 2018;15(1):e1002496. [PubMed: 29381704]
12. Mendez MF. What is the relationship of traumatic brain injury to dementia?. J Alzheimers Dis. 2017;57(3):667–681. [PubMed: 28269777]
13. Rahman A, Jackson H, Hristov H, et al. Sex and gender driven modifiers of Alzheimer's: the role for estrogenic control across age, race, medical, and lifestyle risks. Front Aging Neurosci. 2019;11:315. [PubMed: 31803046]
14. Weuve J, Barnes LL, Mendes de Leon CF, et al. Cognitive aging in black and white Americans: cognition, cognitive decline, and incidence of Alzheimer disease dementia. Epidemiology. 2018;29(1):151–159. [PubMed: 28863046]
15. Kornblith E, Peltz CB, Xia F, Plassman B, Novakovic-Apopain T, Yaffe K. Sex, race, and risk of dementia diagnosis after traumatic brain injury among older veterans. Neurology. 2020;95(13):e1768–e1775. [PubMed: 32887780]
16. ARIC Study Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. Am J Epidemiol. 1989;129(4):687–702. [PubMed: 2646917]
17. Vandormael A, Dobra A, Barnighausen T, de Oliveira T, Tanser F. Incidence rate estimation, periodic testing and the limitations of the mid-point imputation approach. Int J Epidemiol. 2018;47(1):236–245. [PubMed: 29024978]
18. Langlois JA, Kegler SR, Butler JA, et al. Traumatic brain injury-related hospital discharges. Results from a 14-state surveillance system, 1997. MMWR Surveill Summ. 2003;52(4):1–20.
19. Burke JF, Stulc JL, Skolarus LE, Sears ED, Zahuranec DB, Morgenstern LB. Traumatic brain injury may be an independent risk factor for stroke. Neurology. 2013;81(1):33–39. [PubMed: 23803315]
20. Hedegaard H, Johnson R, Warner M, Chen L. Proposed framework for presenting injury data using the International Classification of Diseases, Tenth Revision, Clinical Modification diagnosis codes. Hyattsville, MD: National Center for Health Statistics; 2016.
21. Gottesman RF, Albert MS, Alonso A, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort. JAMA Neurol. 2017;74(10):1246–1254. [PubMed: 28783817]
22. Knopman DS, Gottesman RF, Sharrett AR, et al. Mild cognitive impairment and dementia prevalence: the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). Alzheimers Dement (Amst). 2016;2:1–11. [PubMed: 26949733]
23. Walker KA, Sharrett AR, Wu A, et al. Association of midlife to late-life blood pressure patterns with incident dementia. JAMA. 2019;322(6):535–545. [PubMed: 31408138]
24. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr. 1982;36(5):936–942. [PubMed: 7137077]
25. Rosamond WD, Chambless LE, Heiss G, et al. Twenty-two-year trends in incidence of myocardial infarction, coronary heart disease mortality, and case fatality in 4 US communities, 1987–2008. Circulation. 2012;125(15):1848–1857. [PubMed: 22420957]
26. Koton S, Schneider AL, Rosamond WD, et al. Stroke incidence and mortality trends in US communities, 1987 to 2011. JAMA. 2014;312(3):259–268. [PubMed: 25027141]
27. Sonsin-Diaz N, Gottesman RF, Fracica E, et al. Chronic systemic inflammation is associated with symptoms of late-life depression: the ARIC Study. Am J Geriatr Psychiatry. 2020;28(1):87–98. [PubMed: 31182350]

28. Hertz-Picciotto I, Rockhill B. Validity and efficiency of approximation methods for tied survival times in Cox regression. Biometrics. 1997;53(3):1151–1156. [PubMed: 9333345]
29. Samuelsen SO, Eide GE. Attributable fractions with survival data. Stat Med. 2008;27(9):1447–1467. [PubMed: 17694507]
30. Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association. 1999;94:496–509.
31. Defense and Veterans Brain Injury Center. TBI Severity Classifications - DoD Worldwide Numbers for TBI. http://dvbic.dcoe.mil/dod-worldwide-numbers-tbi. Published 2015. Accessed October 26, 2020.
32. Peterson K, Veazie S, Bourne D, Anderson J. Association between traumatic brain injury and dementia in veterans: a rapid systematic review. J Head Trauma Rehabil. 2020;35(3):198–208. [PubMed: 31996602]
33. Baldwin G, Breiding M, Sleet D. Using the public health model to address unintentional injuries and TBI: a perspective from the Centers for Disease Control and Prevention (CDC). NeuroRehabilitation. 2016;39(3):345–349. [PubMed: 27497467]
34. Fleminger S, Oliver DL, Lovestone S, Rabe-Hesketh S, Giora A. Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. J Neurol Neurosurg Psychiatry. 2003;74(7):857–862. [PubMed: 12810767]
35. Farace E, Alves WM. Do women fare worse: a metaanalysis of gender differences in traumatic brain injury outcome. J Neurosurg. 2000;93(4):539–545. [PubMed: 11014529]
36. Wilmoth K, LoBue C, Clem MA, et al. Consistency of traumatic brain injury reporting in older adults with and without cognitive impairment. Clin Neuropsychol. 2017:1–6.
37. Pradeep T, Bray MJC, Arun S, et al. History of traumatic brain injury interferes with accurate diagnosis of Alzheimer's dementia: a nationwide case-control study. Int Rev Psychiatry. 2020;32(1):61–70. [PubMed: 31707905]

RESEARCH IN CONTEXT

1. **Systematic review:** The authors reviewed the literature using standard (eg, PubMed) databases. Although sequelae from head injuries are long-lasting and several studies have reported increased cognitive impairment and higher rates of dementia among persons with head injuries, many of these prior studies are limited by selected populations (eg, military, clinic-based, claims databases) with limited sex and race representation, a lack of information on number of head injuries, and follow-up time <10 years. These relevant citations are appropriately cited.
2. **Interpretation:** Our findings confirm the association between head injury and dementia risk and expand the literature by providing evidence for a dose-dependent relationship and evidence that the association is stronger among women versus men and among Whites versus Blacks.
3. **Future directions:** There remains much to be learned about possible demographic differences in the association of traumatic brain injury (TBI) with dementia, and this study provides a framework for further investigation of sex/race differences and possible factors driving these differences.

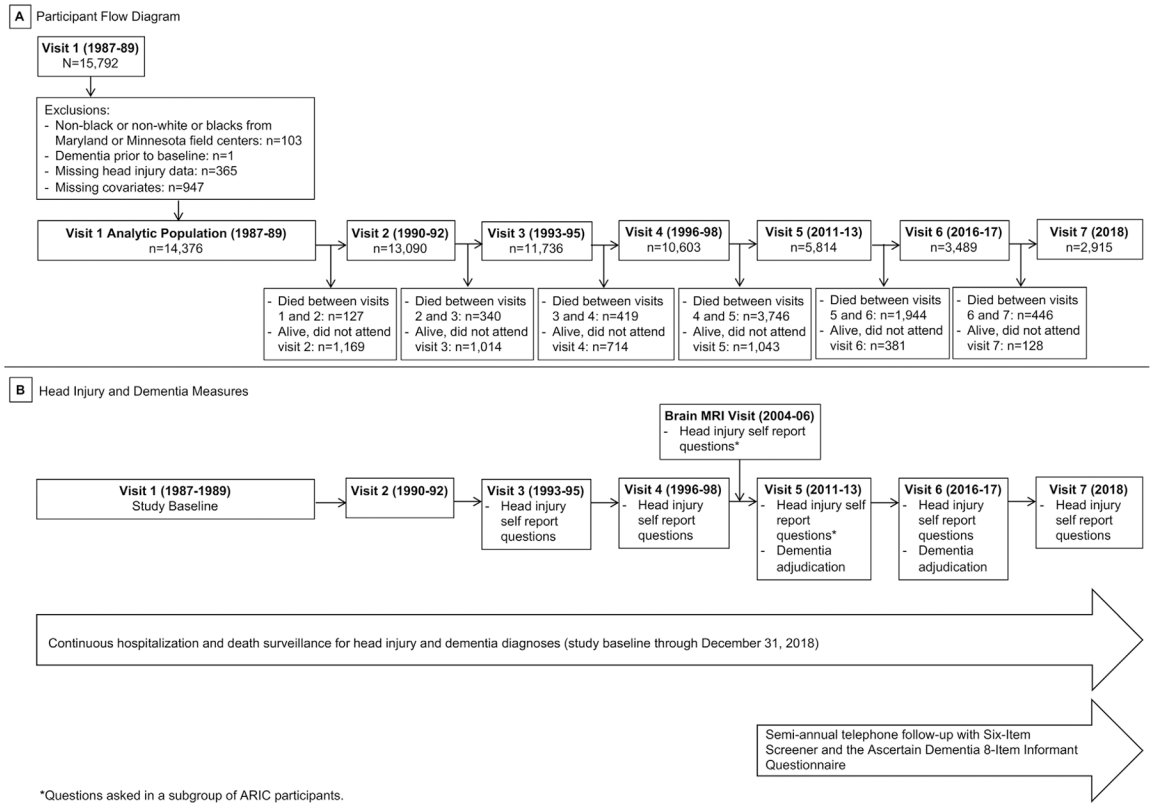

FIGURE 1.

Study timeline and measures (A: participant flow diagram; B: head injury and dementia measures)

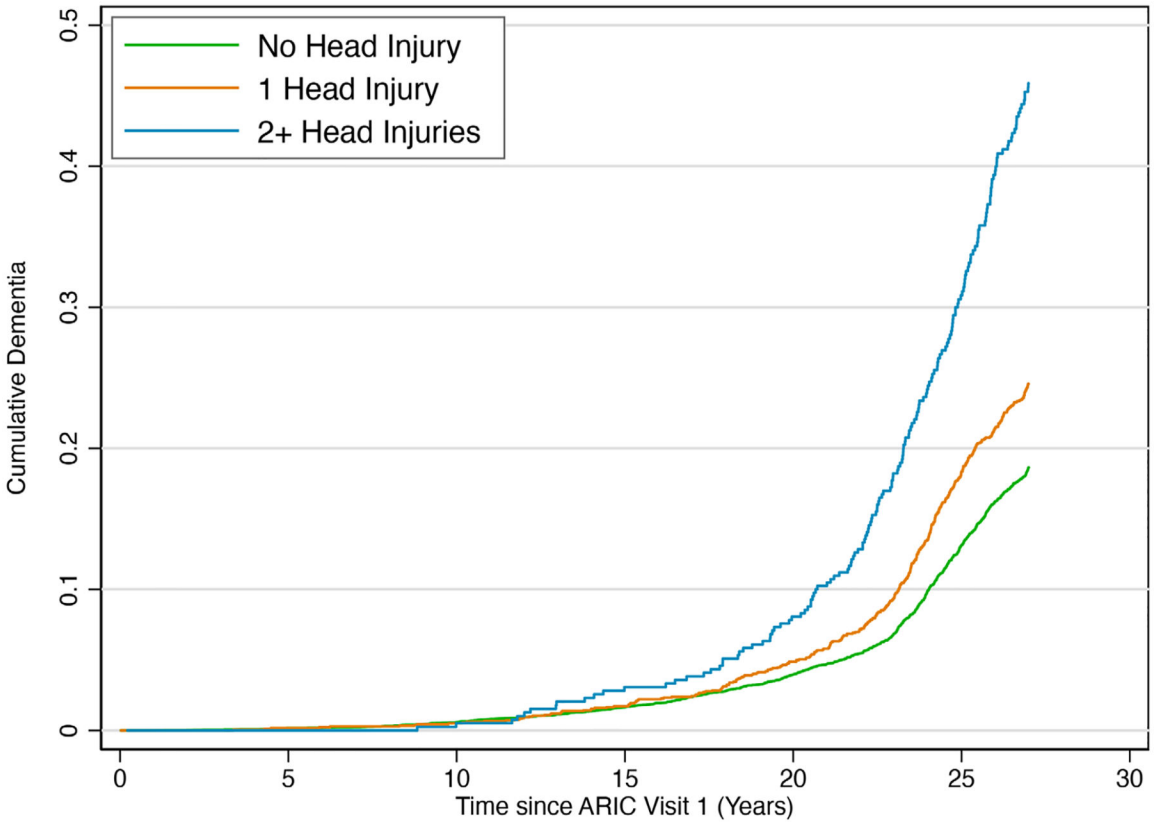

FIGURE 2.

Kaplan-Meier curve for cumulative dementia incidence by head injury frequency, $N =$ 14,376. Log-rank P-value < .001

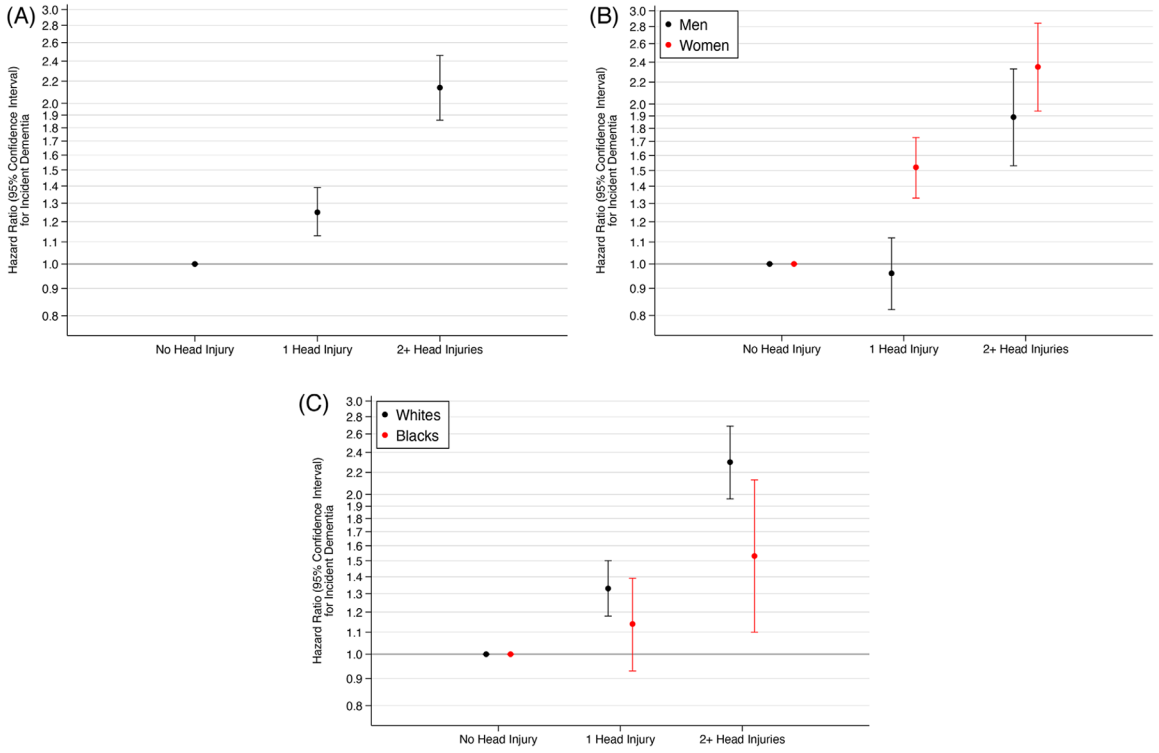

FIGURE 3.

Adjusted* hazard ratios (95% confidence intervals) for incident dementia (A: overall;B: by sex; C: by race) by head injury frequency, *N* = 14,376. *Model adjusted for age (years; continuous), sex (male; female), race/center (Minneapolis, Minnesota Whites; Washington County, Maryland Whites; Forsyth County, North Carolina Whites; Forsyth County North Carolina Blacks; Jackson, Mississippi Blacks), education (< high school; high school, GED, or vocational school; college, graduate, or professional school), income (< $35,000 per year; ≥ $35,000 per year; not reported), physical activity index (score; continuous) cigarette smoking (current; former; never), alcohol consumption (current; former; never), hypertension (yes; no; defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of blood pressure medications), diabetes (yes; no; defined as fasting glucose ≥126 mg/dL or non-fasting glucose ≥200 mg/dL or use of diabetes medications), coronary heart disease (yes; no), stroke (yes; no), military veteran status (yes; no), and *APOE ε*4 genotype (0 *APOE ε*4 alleles; 1 or *APOE ε*4 alleles). *P*-value for interaction by sex < .001. *P*-value for interaction by race = .043

TABLE 1

Baseline (ARIC visit 1, 1987–1989) participant characteristics by head injury status[a], *N* = 14,376

	Overall (N = 14,376)	No Head Injury (n = 10,936)	Head Injury (n = 3440[a])	*P* [b]
Age (years), mean (SD)	54.2 (5.8)	54.2 (5.8)	54.4 (5.7)	.055
Female, *n* (%)	7975 (55.5)	6280 (57.4)	1695 (49.3)	<.001
Race/center, *n* (%)				<.001
Minneapolis, Minnesota Whites	3611 (25.1)	2701 (24.7)	910 (26.5)	
Washington County, Maryland Whites	3684 (25.6)	2670 (24.4)	1014 (29.5)	
Forsyth County, North Carolina Whites	3274 (22.8)	2428 (22.2)	846 (24.6)	
Forsyth County, North Carolina Blacks	460 (3.2)	388 (3.5)	72 (2.1)	
Jackson, Mississippi Blacks	3347 (23.3)	2749 (25.1)	598 (17.4)	
Education, *n* (%)				<.00
< High school	3412 (23.7)	2713 (24.8)	699 (20.3)	
High School, GED, or vocational school	5886 (40.9)	4504 (41.2)	1382 (40.2)	
College, graduate, or professional school	5078 (35.3)	3719 (34.0)	1359 (39.5)	
Family income, *n* (%)				<.001
< $35,000 per year	7578 (52.7)	5838 (53.4)	1740 (50.6)	
≥ $35,000 per year	5972 (41.5)	4430 (40.5)	1542 (44.8)	
Not reported	826 (5.7)	668 (6.1)	158 (4.6)	
Physical activity index, median (IQR)	2.3 (1.8–3.0)	2.3 (1.8–3.0)	2.5 (1.8–3.0)	<.001
Cigarette smoking, *n* (%)				<.001
Current	3775 (26.3)	2933 (26.8)	842 (24.5)	
Former	4628 (32.2)	3383 (30.9)	1245 (36.2)	
Never	5973 (41.5)	4620 (42.2)	1353 (39.3)	
Alcohol consumption, *n* (%)				<.001
Current	8020 (55.8)	5997 (54.8)	2023 (58.8)	
Former	2723 (18.9)	2069 (18.9)	654 (19.0)	
Never	3633 (25.3)	2870 (26.2)	763 (22.2)	
Hypertension, *n* (%)	5025 (35.0)	3888 (35.6)	1137 (33.1)	.007
Diabetes, *n* (%)	1722 (12.0)	1316 (12.0)	406 (11.8)	.720
Coronary heart disease, *n* (%)	692 (4.8)	536 (4.9)	156 (4.5)	.380

	Overall (N = 14,376)	No Head Injury (n = 10,936)	Head Injury (n = 3440[a])	P [b]
Stroke, *n* (%)	262 (1.8)	182 (1.7)	80 (2.3)	.011
*APOE ε*4 genotype, *n* (%)				.240
0 *APOE ε*4 alleles	9935 (69.1)	7530 (68.9)	2405 (69.9)	
1 or 2 *APOE ε*4 alleles	4441 (30.9)	3406 (31.1)	1035 (30.1)	
Military Veteran, *n* (%)	3062 (21.3)	2067 (18.9)	995 (28.9)	<.001

[a] Of the *n* = 3440 total with head injury, *n* = 1726 participants had head injury/injuries occurring only prior to study baseline (ARIC visit 187–1989), *n* = 120 participants had head injuries both occurring prior to study baseline and during follow-up through December 31, 2018, and *n* = 1594 participants had head injury/injuries occurring only during follow-up through December 31, 2018 (median time from baseline to first head injury among those with head injury/injuries only occurring during follow-up: 16.9 years [interquartile interval: 7.8–21.9 years]).

[b] *P*-value comparing no head injury to head injury using *t* tests or Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables.

TABLE 2

Adjusted[a] hazard ratios (95% confidence intervals) for the association of head injury with incident dementia, *N* = 14,376

	No Head Injury			Head Injury			
	No. events/PYs	**Crude Rate per 1000 PYs (95% CI)**	**Adjusted[a] HR (95% CI)**	**No. events / PYs**	**Crude Rate per 1000 PYs (95% CI)**	**Adjusted[a] HR (95% CI)**	***P* for Interaction**
Overall (*N* = 14,376)	1620 / 262,057	6.2 (5.9, 6.5)	1 (Reference)	730 / 58,249	12.5 (11.7, 13.5)	1.44 (1.32, 1.57)	
By Baseline Age							.697
<54 y (n = 6776)	479/135,035	3.5 (3.2, 3.9)	1 (Reference)	197 / 30,945	6.4 (5.5, 7.3)	1.38 (1.16, 1.64)	
≥54 y (*n* = 7600)	1141 / 127,022	9.0 (8.5, 9.5)	1 (Reference)	533 / 27,304	19.5 (17.9, 21.3)	1.45 (1.31, 1.61)	
By Sex							<.001
Male (n = 6401)	664/103,929	6.4 (5.9, 6.9)	1 (Reference)	311 / 31,564	9.9 (8.8, 11.0)	1.15 (1.00, 1.32)	
Female (*n* = 7975)	956/158,128	6.0 (5.7, 6.4)	1 (Reference)	419 / 26,684	15.7 (14.3, 17.3)	1.69 (1.51, 1.90)	
By Race							.008
White (*n* = 10,569)	1049 / 192,013	5.5 (5.1, 5.8)	1 (Reference)	568 / 48,449	11.7 (10.8, 12.7)	1.55 (1.40, 1.72)	
Black (*n* = 3807)	571/70,044	8.2 (7.5, 8.8)	1 (Reference)	162 / 9,800	16.5 (14.2, 19.3)	1.22 (1.02, 1.45)	
By *APOE* ε4 Genotype							.866
0 *APOE* ε4 Alleles (*n* = 9935)	916/182,429	5.0 (4.7, 5.4)	1 (Reference)	416 / 41,184	10.1 (9.2, 11.1)	1.44 (1.28, 1.62)	
1 or 2 *APOE* ε4 alleles (*n* = 4441)	704/79,628	8.8 (8.2, 9.5)	1 (Reference)	314 / 17,064	18.4 (16.5, 20.6)	1.45 (1.27, 1.66)	

[a]Model adjusted for age (years; continuous), sex (male; female), race/center (Minneapolis, Minnesota Whites; Washington County, Maryland Whites; Forsyth County, North Carolina Whites; Forsyth County North Carolina Blacks; Jackson, Mississippi Blacks), education (< high school; high school, GED, or vocational school; college, graduate, or professional school), income (<$35,000 per year; ≥$35,000 per year; not reported), physical activity index (score; continuous) cigarette smoking (current; former; never), alcohol consumption (current; former; never), hypertension (yes; no; defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or use of blood pressure medications), diabetes (yes; no; defined as fasting glucose ≥ 126 mg/dL or non-fasting glucose ≥ 200 mg/dL or use of diabetes medications), coronary heart disease (yes; no), stroke (yes; no), military veteran status (yes; no), and *APOE* ε4 genotype (0 *APOE* ε4 alleles; 1 or 2 *APOE* ε4 alleles).