Association of Head Injury With Late-Onset Epilepsy

Results From the Atherosclerosis Risk in Communities Cohort

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Abstract

Background and Objectives

Late-onset epilepsy (LOE; i.e., epilepsy starting in later adulthood) affects a significant number of individuals. Head injury is also a risk factor for acquired epilepsy, but the degree to which prior head injury may contribute to LOE is less well understood. Our objective was to determine the association between head injury and subsequent development of LOE.

Methods

Included were 8,872 participants enrolled in the Atherosclerosis Risk in Communities (ARIC) study with continuous Centers for Medicare Services fee-for-service (FFS) coverage (55.1% women, 21.6% Black). We identified head injuries through 2018 from linked Medicare fee for service claims for inpatient/emergency department care, active surveillance of hospitalizations, and participant self-report. LOE cases through 2018 were identified from linked Medicare FFS claims. We used Cox proportional hazards models to evaluate associations of head injury with LOE, adjusting for demographic, cardiovascular, and lifestyle factors.

Results

The adjusted hazard ratio (HR) for developing LOE after a history of head injury was 1.88 (95% confidence interval [CI] 1.44–2.43). There was evidence for dose–response associations with greater risk for LOE with increasing number of prior head injuries (HR 1.37, 95% CI 1.01–1.88 for 1 prior head injury and HR 3.55, 95% CI 2.51–5.02 for 2+ prior head injuries, compared to no head injuries) and with more severe head injury (HR 2.53, 95% CI 1.83–3.49 for mild injury and HR 4.90, 95% CI 3.15–7.64 for moderate/severe injury, compared to no head injuries). Associations with LOE were significant for head injuries sustained at older age (age ≥67 years: HR 4.01, 95% CI 2.91–5.54), but not for head injuries sustained at younger age (age < 67 years: HR 0.98, 95% CI 0.68–1.41).

Discussion

Head injury was associated with increased risk of developing LOE, particularly when head injuries were sustained at an older age, and there was evidence for higher risk for LOE after a greater number of prior head injuries and after more severe head injuries.

Classification of Evidence

This study provides Class I evidence that an increased risk of late-onset epilepsy is associated with head injury and that this risk increases further with multiple and more severe head injuries.

Glossary

ARIC = Atherosclerosis Risk in Communities; **BMI** = body mass index; **CI** = confidence interval; **FFS** = fee-for-service; **HR** = hazard ratio; **ICD-9** = International Classification of Diseases–9; **ICD-10** = International Classification of Diseases–10; **LOE** = late-onset epilepsy; **PTE** = posttraumatic epilepsy; **TBI** = traumatic brain injury.

Late-onset epilepsy (LOE; i.e., epilepsy starting in later adulthood[1]) affects a large and growing number of individuals worldwide. The yearly incidence of first seizure is higher in the elderly than at any other time of life,[2] at 40–110 per 100,000 people after age 60 years and 175 per 100,000 people after age 80 years.[3,4] In comparison, the incidence of epilepsy is lower in earlier adulthood (20 per 100,000 from ages 20 through 60 years).[2] In older adults without a prior history of seizures, the cumulative incidence of epilepsy is 1.85% in those 80–84 years old and 3.25% in those who live to 90–94 years.[4] Stroke and neurodegenerative diseases account for a portion of LOE diagnoses[5]; we previously showed that vascular risk factors such as hypertension and diabetes are also risk factors for LOE, even in the absence of stroke or dementia.[6] However, a significant number of LOE cases remain unexplained by these potential etiologies.

Head injury is also a risk factor for acquired epilepsy,[7] but the degree to which prior head injury may contribute to LOE is less well understood. Traumatic brain injury (TBI) affects an estimated 2.8 million persons in the United States every year,[8] with the highest incidence occurring among individuals aged 65 years and older.[9] Post-traumatic epilepsy (PTE) accounts for 5%–20% of all cases of epilepsy.[10,11] The 30-year cumulative incidence of PTE after TBI ranges from 2.1% for mild TBIs to 16.7% for severe injuries.[10,11] The timing of PTE onset ranges from weeks to years after the initial TBI.[12,13] Several prior studies have found that the risk of PTE is increased among older individuals (i.e., age >65 years) who sustain head injuries compared to younger individuals,[12,14] whereas other studies have found no association of PTE risk with age.[15] In addition, the effect of the number and severity of prior head injuries on the risk for LOE is less well characterized in older populations.

The Atherosclerosis Risk in Communities (ARIC) study provides a unique opportunity to evaluate associations between head injury and LOE in an older community-based population with 30 years of follow-up and data collected since midlife. The primary objective of this study was to determine the association between head injury and development of epilepsy at age 67 or later (allowing for a 2-year seizure-free period after reaching Medicare eligibility, to identify incident epilepsy), adjusting for demographics and other risk factors for LOE. Our secondary objectives included evaluating the association of head injury frequency (0, 1, or 2+ prior head injuries) and head injury severity (mild vs moderate/severe) with LOE and evaluating whether the association between head injury and LOE differed by the timing of the first head injury (<age 67 vs ≥67 years, the age at which incident LOE started being ascertained).

Methods

Study Population

The ARIC study initially enrolled 15,792 mostly White and Black women and men (baseline visit: 1987–1989). Participants were identified through population sampling from 4 US communities (Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and suburbs of Minneapolis, Minnesota).[16] Study participants have been followed with up to 7 in-person visits through 2019 and have been contacted annually (semiannually since 2012) with telephone calls. If a participant was unable to answer self-report questions at in-person visits or during telephone follow-up, a proxy was used. ARIC has conducted surveillance of all death certificates and collected hospital discharge records on all participants since study initiation. Participants aged ≥65 years have also had Centers for Medicare and Medicaid Services Medicare claims data linked to ARIC records since 1991.[17] Figure 1 shows the ARIC study design as well as when variables of interest were collected.

### Standard Protocol Approvals, Registrations, and Patient Consents

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

Identification of Head Injuries

History of 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, as previously described.[18,19] Self-report questions were asked at select study visits. Self-report questions inquired about prior head injury requiring physician/hospital care, loss of consciousness, number of prior head injuries, and year of head injury (text and timing of questions are shown in eTable 1, links.lww.com/WNL/B704). Month and date for each self-reported head injury was randomly imputed using the random point method.[20]

Hospitalization records were available for all ARIC cohort participants and linked Medicare fee-for-service (FFS) data for inpatient hospitalizations, emergency department visits, and outpatient visits were available for participants aged ≥65 years enrolled in Medicare FFS part B. Hospitalization surveillance data were available over the entire duration of the ARIC study (1987 through December 31, 2018, for the Maryland, Minnesota, and North Carolina field centers and through December 31, 2017, for the Mississippi field center) and Medicare FFS claims were available for participants aged

Figure 1 Timeline of Atherosclerosis Risk in Communities Visits and Data Collection
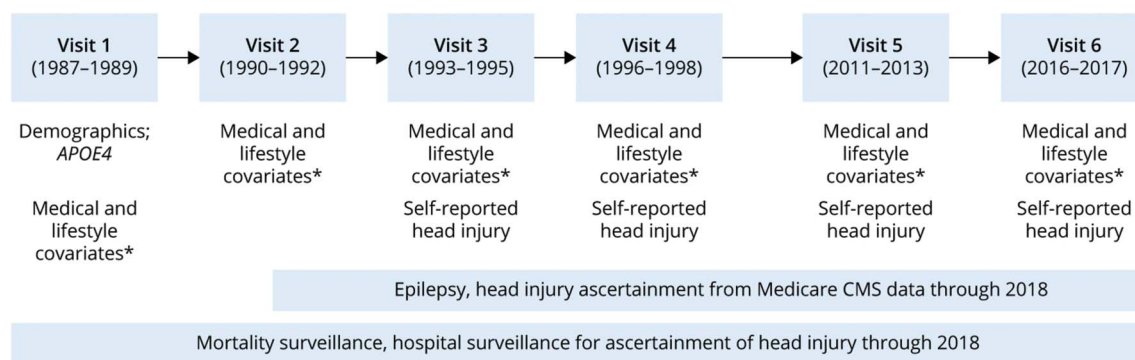
*Used data from the visit immediately prior to 67th birthday. CMS = Centers for Medicare Services.

≥65 years between January 1, 1991, and December 31, 2018. Dates of discharge were available for each hospitalization and emergency department visit. Head injury was defined using the Centers for Disease Control and Prevention ICD-9[21,22] and ICD-10[23] code definition (eTable 2, links.lww.com/WNL/B704). In a secondary analyses, we also categorized the subset of head injury cases identified using ICD-9 codes into head injury severity categories (mild vs moderate/severe) using Department of Defense criteria (eTable 3 and eTable 4).[24]

Identification of LOE

As previously described,[6] to identify incident epilepsy, we used Medicare FFS claims from 1991 to 2018 from ambulatory care visits, inpatient hospitalizations, observations, and emergency department visits. We defined epilepsy as 2 or more claims for epilepsy or seizure-related ICD-9 and ICD-10 codes (eTable 5 and eTable 6, links.lww.com/WNL/B704) in the first 5 diagnosis positions on separate visits.[25] We included only those with at least 2 years of FFS coverage without a seizure-related code to identify incident epilepsy (as defined in prior studies[26,27]). Thus, by definition, the first seizure in these participants had to occur at age 67 or later, to allow for the 2 years of seizure-free coverage after reaching Medicare eligibility at age 65. We also excluded cases of first seizure that occurred in the acute postinjury phase (within 1 week of a head injury event).

Study Inclusions and Exclusions

A total of 1,516 participants died prior to age 67 and were excluded. We excluded participants without at least 2 years of Medicare FFS coverage (n = 1,231) or with gaps in coverage (n = 3,185). Of the 9,860 eligible participants, we excluded 147 with less than 2 years of coverage prior to the first seizure and 772 with missing covariate data. To exclude those with seizures in the acute postinjury phase, we excluded participants whose first seizure diagnosis was within 1 week of head injury (n = 6; 3 would otherwise have developed LOE). As is standard in ARIC due to race/site aliasing, we included Black participants in North Carolina and Mississippi and White participants in North Carolina, Minnesota, and Maryland.

Black participants in Minnesota and Maryland were excluded, as were participants of other races, due to small numbers (n = 60),[16] leaving 8,872 included in the analysis.

Covariates

Demographic information and genetic data were collected at the first ARIC visit in 1987–1989. Birth date, sex (male, female), and race (White, Black) were self-reported. To address the race/site aliasing in the ARIC study,[16] race/field center was categorized as North Carolina White, North Carolina Black, Mississippi Black, Maryland White, and Minnesota White. Education was categorized as less than high school, high school graduate or GED or vocational school, and some college, college graduate, or professional school. The number of *APOE* ε4 alleles was categorized as 0 ε4 alleles vs 1 or 2 ε4 alleles (TaqMan assay; Applied Biosystems).[28]

Vascular risk factor data were collected at all ARIC study visits and data from the last ARIC visit prior to age 67 (the origin for analysis in this study) were used. Body mass index (BMI) was calculated from height and weight. Self-reported smoking status and alcohol use was collected at each visit (current, former, never use). Blood pressure was measured 3 times at each visit (except at visit 4, where it was measured 2 times), and the average of the last 2 measurements were recorded; we defined prevalent hypertension as use of an antihypertensive medication, mean systolic pressure ≥140 mm Hg, or mean diastolic pressure ≥90 mm Hg. We defined prevalent diabetes as use of diabetes medications or insulin, fasting blood glucose ≥126 mg/dL, nonfasting blood glucose ≥200 mg/dL, or self-report of diabetes diagnosed by a physician.

Stroke and dementia were evaluated as time-varying covariates. Participants self-reported prevalent strokes at visit 1. Incident strokes are identified continuously in ARIC using surveillance of hospital discharge records and algorithm classification of events with adjudication by independent physician reviewers.[29] Participants with dementia in ARIC are identified via adjudication incorporating cognitive testing conducted at visits 2, 4, 5, and 6; telephone interviews of the

participant or an informant; and surveillance of hospital discharge records and death certificate data.[30,31]

Statistical Analyses

Head injury was defined as a time-varying exposure in all analyses, allowing person-time to be allocated to no head injury and head injury groups defined by date of head injury. Follow-up time for the present study started at age 67 years. Among participants having diagnoses of both head injury and LOE, only head injuries prior to LOE were considered. Participant characteristics are shown stratified by head injury status using means and SDs for continuous variables and using frequencies and proportions for categorical variables. Characteristics were compared between those with and without head injury using t tests for continuous variables and chi-square tests for categorical variables.

To calculate cumulative incidence of LOE by head injury status, we used Kaplan-Meier analyses and compared between head injury groups using log-rank tests. To estimate the hazard ratio (HR) for developing LOE, we used a Cox proportional hazards model with the 67th birthday as the origin (the earliest time at which participants could be identified as having LOE using Medicare FFS claims) and first seizure-related diagnosis as the event (censoring for death and at the end of follow-up on December 31, 2017/2018). We confirmed that the proportional hazards assumption was met for our Cox models 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 = 0.858). We performed unadjusted as well as two adjusted statistical models. Model 1 was adjusted for visit 1 age, sex, race/field center, and education. Model 2 was adjusted for variables in model 1 plus BMI, smoking, alcohol use, *APOE* ε4 genotype, hypertension, diabetes, stroke, and dementia. In a sensitivity analysis, we additionally included adjustment for number of outpatient encounters. A priori, formal testing for interactions by age, sex, race, and study site was performed. In sensitivity analyses, we performed Fine-Gray models[32] to account for the competing risk of death. We also calculated the population attributable risk (95% confidence interval [CI]) of head injury on LOE in our population by estimating attributable hazard fractions from the Cox proportional hazards model.[33]

In secondary analyses, we evaluated the association of time-varying head injury frequency (0, 1, or 2+) with LOE. In these analyses, we report p values for linear trend across head injury frequency categories obtained by programming the categorical variable as a continuous variable. In sensitivity analyses, we repeated our main analyses excluding 737 individuals who were later diagnosed with dementia in order to minimize the potential contribution of early dementia (i.e., before clinical diagnosis) to LOE. We in addition evaluated the association of head injury severity (defined as the most severe injury if multiple head injuries) and a combination of head injury frequency and severity with LOE among the subset of 1,345 head injury cases identified using ICD-9 codes (mild vs moderate/severe (no penetrating injuries existed in this sample), severity definition shown in eTable 3 and eTable 4, links.lww.com/WNL/B704). We also evaluated whether the association between head injury and LOE differed by the timing of first head injury (age <67 vs ≥67 years, as 67 years is the age of origin for our analysis of LOE) by performing stratified analyses. Because the majority of first head injuries occurring prior to age 67 years were ascertained from self-report and the majority of first head injuries occurring at or after 67 years were ascertained by ICD codes, we performed a sensitivity analysis stratified by the timing of first head injury and the method of head injury identification (ICD code vs self-report) to help distinguish between potential effects of age at time of initial head injury vs method of head injury ascertainment.

We considered a 2-sided p value of <0.05 as significant. Stata SE version 16.0 was used to perform all statistical analyses.

Data Availability

ARIC data are available through the NIH National Heart, Lung, and Blood Institute–sponsored Biologic Specimen and Data Repository Information Coordinating Center.

Results

Participant Characteristics

The median follow-up time for analysis (starting at age 67) was 11.2 years (25th and 75th percentile 6.8–15.9). Of the 8,872 participants, 6,173 had no history of head injury, while 2,699 (30.4%) had at least one head injury either before age 67 years or at any time during the follow-up period. A total of 249 participants had a diagnosis of LOE at any time during study follow-up (n = 160 without a prior head injury and n = 89 with a prior head injury [median time between head injury and LOE 6.4 years]).

Compared to participants without head injury, participants with head injury were slightly older at ARIC study baseline in 1987–1989 (55.4 years vs 55.1 years, $p = 0.031$), more likely to be men (50.9% vs 42.2%, $p < 0.001$), be of white race (83.9% vs 76.1%, $p < 0.001$), and have greater than high school education (40.9% vs 35.5%, $p < 0.001$). By age 67 years, individuals with head injury occurring anytime were more likely to be an ever smoker (63.0% vs 59.1%, $p < 0.001$), be a current alcohol drinker (54.8% vs 51.9%, $p = 0.022$), and have a history of diabetes (16.3% vs 14.5%, $p = 0.027$) compared to individuals without head injury (Table 1). Participants with head injury were also more likely to have a history of stroke (8.5% vs 5.8%, $p < 0.001$) and a history of dementia (10.6% vs 7.0%, $p < 0.001$) by age 67 years compared to individuals without head injury.

The incidence rate of LOE was higher among those with a prior head injury, 3.76 (95% CI 3.12–4.54) per 1,000 person-years, than among those without a prior head injury, 1.50 (95% CI 1.27–1.77) per 1,000 person-years.

Table 1 Characteristics of Participants With and Without Head Injury

	No head injury (n = 6,173)	Head injury[a] (n = 2,699)	*p* Value
Age at visit 1, y	55.1 (5.7)	55.4 (7.0)	0.03
Female	3,567 (57.8)	1,323 (49.1)	<0.001
Race/field center			
White: North Carolina	1,288 (20.9)	589 (21.8)	<0.001
Black: North Carolina	179 (2.9)	40 (1.5)	
Black: Mississippi	1,299 (21.0)	394 (14.6)	
White: Maryland	1,792 (29.0)	936 (34.7)	
White: Minnesota	1,615 (26.2)	740 (27.4)	
Education level			
Less than high school	1,389 (22.5)	531 (19.7)	<0.001
High school graduate, GED, or vocational school	2,590 (42.0)	1,062 (39.3)	
College, graduate, or professional school	2,194 (35.5)	1,106 (41.0)	
BMI[b]	28.4 (5.6)	28.6 (5.4)	0.18
Smoking[b]			
Current	1,169 (18.9)	449 (16.6)	<0.001
Former	2,479 (40.2)	1,251 (46.4)	
Never	2,525 (40.9)	999 (37.0)	
Alcohol use[b]			
Current	3,201 (51.9)	1,480 (54.8)	0.021
Former	1,591 (25.8)	674 (25.0)	
Never	1,381 (22.4)	545 (20.2)	
***APOE4* ε4 Genotype**			
0 *APOE* ε4 alleles	4,339 (70.3)	1,861 (68.9)	0.44
1 *APOE* ε4 allele	1,683 (27.3)	769 (28.5)	
2 *APOE* ε4 alleles	151 (2.4)	69 (2.6)	
Hypertension[b]	2,729 (44.2)	1,209 (44.8)	0.61
Diabetes[b]	896 (14.5)	440 (16.3)	0.03
History of stroke[b]	355 (5.8)	231 (8.5)	<0.001
History of dementia[b]	435 (7.0)	287 (10.6)	<0.001

Abbreviation: BMI = body mass index.
Values are mean (SD) or n (%).
[a] n = 1,023 with first head injury at or after age 67.
[b] Hypertension, diabetes status, BMI, smoking, alcohol use, history of stroke, and history of dementia obtained from last visit prior to age 67 years or at age 67 years.

Association of Head Injury With LOE

Head injury was significantly associated with increased risk of LOE (Kaplan-Meier cumulative incidence by head injury status shown in Figure 2). The unadjusted HR for development of LOE in association with prior head injury was 2.23 (95% CI 1.73–2.87) (Table 2). This association remained significant after adjustment for other risk factors for LOE (model 2 HR 1.88, 95% CI 1.44–2.43). With further adjustment for number of outpatient encounters, the association remained significant (HR 1.80, 95% CI 1.38–2.34). There were no significant interactions by age, sex, race, or study site (all *p* > 0.05). In models accounting for the competing risk of death, the magnitude of the association was slightly, but not appreciably, stronger than in our main analysis (model 2 HR 1.99, 95% CI 1.53–2.58) (Table 2). The population

Kaplan-Meier Estimates of the Cumulative Incidence of Late-Onset Epilepsy Among Participants With and Without a History of Head Injury (Log-Rank *p* < 0.001)
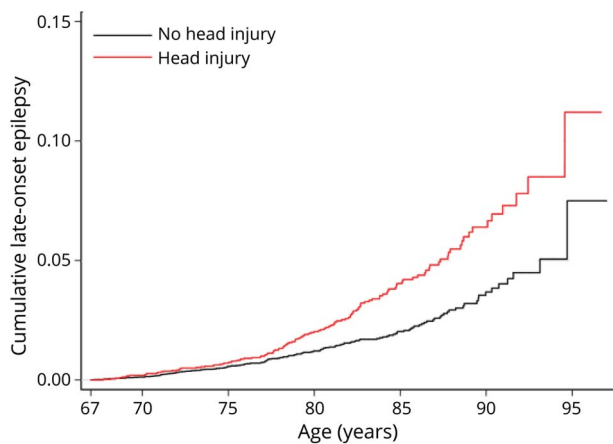
The origin is age 67, the earliest age at which participants are eligible for a diagnosis of late-onset epilepsy using Medicare claims data with a 2-year seizure-free period to identify incident epilepsy.

attributable risk of head injury on LOE risk in this population was 20.2% (95% CI 13.9%–26.0%). To put this in context, we also calculated the population attributable risks of stroke and dementia on LOE in this population, which were 17.0% (95% CI 15.0%–18.9%) and 26.3% (95% CI 24.6%–27.9%), respectively. In sensitivity analyses excluding individuals with a later diagnosis of dementia, results were similar to our main analyses (eTable 7, links.lww.com/WNL/B704).

Association of Head Injury Frequency and Severity With LOE

Of the 2,705 with head injury occurring prior to study baseline, prior to LOE, or prior to the end of study follow-up, 1,990 had 1 head injury and 715 had 2+ head injuries. We found evidence for a dose-dependent association, with an increased risk of LOE following 2+ head injuries, compared to 1 and no head injuries (Table 3). The fully adjusted HR for development of LOE in those with 2+ head injuries compared to no head injuries was 3.55 (95% CI 2.51–5.02), with HR

1.37 (95% CI 1.01–1.88) for 1 head injury compared to no head injuries (*p* trend<0.001). In sensitivity analyses excluding individuals with a later diagnosis of dementia, results were slightly attenuated, but remained significant (eTable 7, links. lww.com/WNL/B704). Of the 1,345 incident head injury cases identified using ICD-9 codes, 1,081 were classified as mild injuries and 264 were classified as moderate/severe injuries. In fully adjusted models, compared to no head injuries, mild head injury was associated with a 2.53 (95% CI 1.83–3.49) times increased risk of LOE and moderate/severe injuries were associated with a 4.90 (95% CI 3.15–7.64) times increased risk of LOE compared to no head injuries (Table 4). In analyses evaluating the effects of both head injury frequency and severity, there was evidence for increasing risk with both increasing number of head injuries and with increasing severity (eTable 8).

Association of Head Injury With LOE Stratified by Age at First Head Injury

Of the 2,699 participants with head injury, 1,017 had first head injury occurring at age 67 years or older and 1,682 had first head injury occurring prior to age 67 years. In analyses including only participants with a first head injury occurring at age 67 years or later, the risk of LOE associated with head injury (versus no head injury) was elevated, with a fully adjusted HR of 2.99 (95% CI 2.21–4.07) (Table 5). Among the 50 participants with a first head injury occurring at age 67 or later who later developed LOE, the median time from head injury to first seizure was 2.3 years. In contrast, in analyses including only participants with first head injury occurring prior to age 67 years, the association of head injury with risk of LOE was not significant (fully adjusted HR 0.98, 95% CI 0.68–1.41). Among the 39 participants with a first head injury occurring prior to age 67 years who later developed LOE, the median time from head injury to first seizures was 36.4 years. In sensitivity analyses stratified by method of head injury ascertainment, similar patterns with age at first head injury were seen where a significant association of head injury with LOE was observed for individuals with first head injury occurring at age 67 years or later but not for individuals with first head injury occurring before age 67 years both for head injury cases identified by ICD codes and by self-report (Table 5).

Table 2 Unadjusted and Adjusted Models of the Hazard Ratio for Risk of Late-Onset Epilepsy After Head Injury, With and Without Adjustment for the Competing Risk of Death

Model	Not accounting for competing risk of death			Accounting for competing risk of death		
	Hazard ratio	95% Confidence interval	*p* Value	Hazard ratio	95% Confidence interval	*p* Value
Unadjusted	2.23	1.73–2.87	<0.001	2.22	1.72–2.86	<0.001
Model 1[a]: adjusted for demographics	2.30	1.78–2.97	<0.001	2.32	1.80–3.00	<0.001
Model 2[b]: fully adjusted	1.88	1.44–2.43	<0.001	1.99	1.53–2.58	<0.001

The hazard ratio is compared to the no head injury reference group.
[a] Model 1 is adjusted for visit 1 age, sex, race/field center, and education level.
[b] Model 2 is adjusted for variables in model 1 + body mass index, smoking, alcohol use, *APOE* ε4 genotype, hypertension, diabetes, history of stroke, and history of dementia.

Table 3 Unadjusted and Adjusted Models of the Hazard Ratio for Risk of Late-Onset Epilepsy After 0, 1, and 2+ Head Injuries

Model	Hazard ratio	95% Confidence interval	p Value for linear trend
Unadjusted			<0.001
0 Head injuries	1	Reference	
1 Head injury	1.51	1.11–2.05	
2+ Head injuries	5.16	3.72–7.15	
Model 1[a]: adjusted for demographics			<0.001
0 Head injuries	1	Reference	
1 Head injury	1.55	1.13–2.11	
2+ Head injuries	5.54	3.98–7.72	
Model 2[b]: fully adjusted			<0.001
0 Head injuries	1	Reference	
1 Head injury	1.37	1.01–1.88	
2+ Head injuries	3.55	2.52–5.02	

[a] Model 1 is adjusted for visit 1 age, sex, race/field center, and education level.
[b] Model 2 is adjusted for variables in model 1 + body mass index, smoking, alcohol use, *APOE* ε4 genotype, hypertension, diabetes, history of stroke, and history of dementia.

This study provides Class I evidence that an increased risk of late-onset epilepsy is associated with head injury and that this risk increases further with multiple and more severe head injuries.

Discussion

In this community-based study, we found a nearly 2-fold increased risk of LOE among older adults with a history of head injury compared to adults without head injury. This amounts to approximately 1 in 5 LOE cases being attributable to prior head injury in this cohort. Moreover, we found a dose-dependent relationship, whereby a higher number of prior head injuries and increased severity of injury was associated with a higher risk of LOE. These relationships persisted after adjusting for other known risk factors for LOE.[6] We also found increased risk among individuals with first head injury occurring in later life (i.e., at or after age 67 years), but not among individuals with first head injury occurring earlier in life (i.e., before age 67 years), compared to individuals without head injury. Taken together, these results suggest that head injury is a substantial, dose-dependent risk factor for LOE, particularly among individuals sustaining a head injury at an older age.

Prior studies have shown that the increased annual risk of PTE for moderate TBI is around 0.1% annually, and is 1% annually for severe injuries, with between 9% and 17% cumulative risk over 20 years from injury.[7,34,35] In this study, we found that 1.9% of those with prior head injury developed LOE over a median of 11 years, likely reflecting the mixed severity of head injuries in this population. Indeed, in our secondary analysis investigating TBI severity among the subset of head injuries identified by ICD-9

code data, 80% of head injuries were of mild severity whereas only 20% were of moderate or greater severity. Consistent with the literature across the age span, we found increased risk of

Table 4 Unadjusted and Adjusted Models of the Association of Head Injury Severity (Among Subpopulation of 1,345 Head Injury Cases Identified Using ICD Codes) With Risk of Late-Onset Epilepsy

Model	Hazard ratio	95% Confidence interval
Unadjusted		
No head injuries	1	Reference
Mild head injury	3.55	2.60–4.84
Moderate/severe head injury	6.41	4.17–9.86
Model 1[a]: adjusted for demographics		
No head injuries	1	Reference
Mild head injury	3.70	2.71–5.05
Moderate/severe head injury	6.84	4.44–10.56
Model 2[b]: fully adjusted		
No head injuries	1	Reference
Mild head injury	2.53	1.83–3.49
Moderate/severe head injury	4.90	3.15–7.64

[a] Model 1 is adjusted for visit 1 age, sex, race/field center, and education level.
[b] Model 2 is adjusted for variables in model 1 + body mass index, smoking, alcohol use, *APOE* ε4 genotype, hypertension, diabetes, history of stroke, and history of dementia.

Table 5 Unadjusted and Adjusted Models of the Hazard Ratio for Risk of Late-Onset Epilepsy After Head Injury, Stratified by Age at First Head Injury (<67 Versus ≥67 years)

Model	Age at first head injury <67 years			Age at first head injury ≥67 years		
	Hazard ratio	95% Confidence interval	*p* Value	Hazard ratio	95% Confidence interval	*p* Value
Including all head injury cases	N with head injury = 1,682			N with head injury = 1,017		
Unadjusted	1.05	0.73–1.49	0.799	4.06	3.02–5.45	<0.001
Model 1[a]: adjusted for demographics	1.09	0.76–1.57	0.632	4.02	2.99–5.40	<0.001
Model 2[b]: fully adjusted	0.98	0.68–1.41	0.895	2.99	2.21–4.07	<0.001
Including ICD code identified head injury cases	N with head injury = 58			N with head injury = 919		
Unadjusted	1.35	0.19–9.67	0.765	6.43	4.67–8.83	<0.001
Model 1[a]: adjusted for demographics	1.18	0.16–8.48	0.871	6.65	4.83–9.14	<0.001
Model 2[b]: fully adjusted	0.64	0.09–4.70	0.662	4.44	3.18–6.20	<0.001
Including self-report identified head injury cases	N with head injury = 1,624			N with head injury = 104		
Unadjusted	0.86	0.56–1.32	0.485	4.56	1.13–18.41	0.033
Model 1[a]: adjusted for demographics	0.90	0.58–1.39	0.644	4.61	1.12–18.92	0.034
Model 2[b]: fully adjusted	0.87	0.56–1.35	0.543	3.49	0.84–14.56	0.086

The hazard ratio is compared to the no head injury reference group.
[a] Model 1 is adjusted for visit 1 age, sex, race/field center, and education level.
[b] Model 2 is adjusted for variables in model 1 + body mass index, smoking, alcohol use, *APOE* ε4 genotype, hypertension, diabetes, history of stroke, and history of dementia.

epilepsy with increasing head injury severity in our population of older individuals.[13,35] Furthermore, we observed a dose–response relationship with number of head injuries and LOE, whereby a higher number of prior head injuries was associated with higher risk of LOE.

We found a strong relationship between head injury occurring after age 67 and LOE but not between head injury occurring prior to age 67 and LOE. This difference may in part reflect the time course of PTE, whereby the highest risk of seizures is within the first 6 months after injury, although the risk remains increased for well over 10 years postinjury.[13] For example, epilepsy occurring 3 years after an injury at age 50 would be considered PTE but would not be considered LOE and would not be identified as incident epilepsy in this study, whereas epilepsy occurring 3 years after an injury at age 67 would be considered both PTE and LOE in this study. Therefore, our results looking at head injury occurring before age 67 are conservatively biased by immortal person time. However, our findings are consistent with several prior studies, which have also reported higher risk of PTE after head injuries sustained at older compared to younger age.[13,14] Taken together, these results suggest that an emphasis on both primary and secondary prevention of head injuries may help to decrease cases of epilepsy in older populations. Indeed, older individuals (i.e., age 75 years or greater) have the highest rates of head injury–related emergency visits, hospitalizations, and deaths.[9] A large proportion of head injuries among older populations are due to falls, which are potentially preventable.[9,36]

We did not observe any significant differences in the association of head injury with LOE by sex or race in our population of older individuals. One prior study including individuals aged 15 years and older reported a higher risk of PTE among men as compared to women,[37] but similar to our study, the majority of prior studies did not report any differences by sex.[15,37] One prior study found increased risk of PTE among Black compared to White participants,[38] a finding that was replicated in a recent study, which reported that the risk of epilepsy after both traumatic and nontraumatic subdural hematomas is stronger among Black compared to White patients.[39] The majority of prior studies did not evaluate for possible interaction by race in associations of head injury with PTE. It is possible that the heterogeneity in study population, especially regarding factors such as age and injury type and severity, may account for these observed differences between studies; indeed, our population was limited to individuals aged 67 years and older, whereas most other studies included individuals across the lifespan.

PTE is a well-known disorder, accounting for 5%–20% of all cases of epilepsy, and is a focus of considerable ongoing study. There are many hypothesized mechanisms for the development of epilepsy following head injury, including neuroinflammation[40] leading to loss of interneurons and resulting hyperexcitability, impairment of $GABA_A$ activity, increased glutamate signaling, blood–brain barrier disruption, and altered mechanistic target of rapamycin 1c (mTOR1c) phosphorylation.[10]

Certain limitations should be considered in the interpretation of the results of this study. Our definition of LOE relied on Medicare claims rather than medical record reviews for the identification of cases. However, similar ICD code-based definitions validated by medical record review have 94.4% sensitivity and 91.7% for epilepsy.[25] This definition necessarily limited our analysis to those with LOE starting at age 67 or later, preventing us from examining the association in younger people. Similarly, our definition of head injury was derived from self-report and hospitalization/emergency department ICD codes and we did not have detailed information on the type and severity of head injury, but we were able to assess number of prior head injuries and assess injury severity in the subset of cases identified by ICD code data. Furthermore, self-report has been shown to be reliable in assessing head injury[41] and we used the standard Centers for Disease Control and Prevention definition[21-23] to identify hospitalizations and emergency visits with ICD codes for head injury. It is important to note that our definition likely does not capture head injuries that did not require medical care. As the majority of first head injuries occurring prior to age 67 years were ascertained from self-report and the majority of first head injuries occurring at or after 67 years were ascertained by ICD codes, this study is unable to fully distinguish between age vs method of head injury ascertainment driving the strong observed association seen with head injury occurring at or after 67 years with LOE. However, we performed a sensitivity analysis stratifying by method of head injury ascertainment and found similar results whereby head injury occurring at or after 67 years was strongly associated with LOE while head injury occurring prior to age 67 was not, suggesting that age is driving the association, not method of head injury ascertainment. In addition, while head injuries occurring after a code for seizure were not included, there is the potential for reverse causality if an unrecognized seizure caused a fall leading to a head injury. As we used time-invariant covariate data for certain confounders (including comorbidities such as hypertension, which are related to LOE and accumulate with age) from the visit closest to age 67, the time interval prior to age 67 (and age) at which the data were collected could vary substantially; the possibility of residual confounding remains. Our study also has a number of important strengths, including a large population with over 10 years of follow-up for LOE events and detailed assessments of comorbidity data at multiple time points over follow-up, allowing for ascertainment of participant characteristics from the last ARIC visit prior to the origin for analysis in this study at age 67 and for time-varying adjustment for certain confounders (dementia, stroke).

Head injury, particularly occurring in later life, is an independent, dose-dependent risk factor for the development of late-onset epilepsy. We found that head injury accounts for approximately 20% of LOE cases in this older population. Our results highlight the significant burden of epilepsy observed among individuals sustaining a head injury at an older age. Further work, such as in a cohort study with incident epilepsy determined across the age spectrum as well as with more detailed information about the mechanisms and characteristics of the head injury event(s), is needed to identify and refine potentially modifiable risk factors (e.g., alcohol consumption) for head injury–related LOE with the goal of preventing a subset of future cases of LOE in older populations.

Disclosure
This article was partially prepared while R.F. Gottesman was employed at the Johns Hopkins University School of Medicine. The opinions expressed in this article are the author's own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the United States Government. A.L.C. Schneider reports no disclosures relevant to the manuscript. R.F. Gottesman is a former Associate Editor for *Neurology*®. G.L. Krauss, J. Gugger, R. Diaz-Arrastia, A. Kucharska-Newton, J. Huang, and E.L. Johnson report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Appendix Authors

Name	Location	Contribution
Andrea L.C. Schneider, MD, PhD	Department of Neurology, University of Pennsylvania, Philadelphia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

Appendix *(continued)*

Name	Location	Contribution
Rebecca F. Gottesman, MD, PhD	Stroke Branch, National Institutes of Neurological Disorders and Stroke Intramural Research Program, Bethesda, MD	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Gregory L. Krauss, MD, PhD	Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
James Gugger, MD, PharmD	Department of Neurology, University of Pennsylvania, Philadelphia	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Ramon Diaz-Arrastia, MD, PhD	Department of Neurology, University of Pennsylvania, Philadelphia	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Anna Kucharska-Newton, PhD, MPH	Department of Epidemiology, University of North Carolina at Chapel Hill	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Juebin Huang, MD	Department of Neurology, University of Mississippi Medical Center, Jackson	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Emily L. Johnson, MD	Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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