Predictors of incident epilepsy in older adults

The Cardiovascular Health Study

Hyunmi Choi, MD, MS
Alison Pack, MD, MPH
Mitchell S.V. Elkind,
MD, MS
W.T. Longstreth, Jr.,
MD, MPH
Thanh G.N. Ton, MPH,
PhD
Frankline Onchiri, PhD

Correspondence to
Dr. Choi:
hc323@columbia.edu

ABSTRACT

Objective: To determine the prevalence, incidence, and predictors of epilepsy among older adults in the Cardiovascular Health Study (CHS).

Methods: We analyzed data prospectively collected in CHS and merged with data from outpatient Medicare administrative claims. We identified cases with epilepsy using self-report, antiepileptic medication, hospitalization discharge ICD-9 codes, and outpatient Medicare ICD-9 codes. We used Cox proportional hazards regression to identify factors independently associated with incident epilepsy.

Results: At baseline, 42% of the 5,888 participants were men and 84% were white. At enrollment, 3.7% (215 of 5,888) met the criteria for prevalent epilepsy. During 14 years of follow-up totaling 48,651 person-years, 120 participants met the criteria for incident epilepsy, yielding an incidence rate of 2.47 per 1,000 person-years. The period prevalence of epilepsy by the end of follow-up was 5.7% (335 of 5,888). Epilepsy incidence rates were significantly higher among blacks than nonblacks: 4.44 vs 2.17 per 1,000 person-years ($p < 0.001$). In multivariable analyses, risk of incident epilepsy was significantly higher among blacks compared to nonblacks (hazard ratio [HR] 4.04, 95% confidence interval [CI] 1.99–8.17), those 75 to 79 compared to those 65 to 69 years of age (HR 2.07, 95% CI 1.21–3.55), and those with history of stroke (HR 3.49, 95% CI 1.37–8.88).

Conclusions: Epilepsy in older adults in the United States was common. Blacks, the very old, and those with history of stroke have a higher risk of incident epilepsy. The association with race remains unexplained. *Neurology*® 2017;88:870–877

GLOSSARY

CHF = congestive heart failure; **CHS** = Cardiovascular Health Study; **CI** = confidence interval; **CMS** = Centers for Medicare & Medicaid Services; **HR** = hazard ratio; **ICD-9** = *International Classification of Diseases, ninth revision*; **TIA** = transient ischemic attack.

The most rapidly growing segment of the US population comprises those ≥ 65 years of age, and it is projected to almost double from 43.1 million in 2012 to 83.7 million by 2050.¹ Epilepsy, defined as at least 2 unprovoked seizures occurring > 24 hours apart,² is a common neurologic disorder in this age group.³ While multiple studies have reported the prevalence and incidence of epilepsy in older adults,^{4–6} their findings have limited generalizability. One recent study addressed the limited generalizability of prior studies by using outpatient administrative claims codes from the Centers for Medicare & Medicaid Services (CMS), which includes use data for $> 95\%$ of the older adult US population.⁷ Prior validation studies of the epilepsy diagnosis showed a higher positive predictive value when outpatient claims data were combined with additional clinical data such as medication use.⁸ The Cardiovascular Health Study (CHS) is a large, geographically and racially diverse, population-based cohort of 5,888 well-characterized older adult participants followed up for > 15 years. The CHS data have been merged with outpatient CMS claims data. Using these combined data, we sought to define more precisely than in prior studies the rates and risk factors for epilepsy. On the basis of existing literature,⁷ we

Supplemental data
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From the Department of Neurology (H.C., A.P., M.S.V.E.), Columbia University, New York, NY; Departments of Neurology (W.T.L.) and Epidemiology (W.T.L., F.O.), University of Washington, Seattle; Precision Health Economics (T.G.N.T.), Oakland, CA; and Seattle Children's Research Institute (F.O.), WA.

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hypothesized that the prevalence and incidence rates of epilepsy among older adults increase with age and are higher in blacks than whites and in those with comorbid conditions.

METHODS **Description of the cohort and sources of data.** The CHS is a prospective cohort study of coronary heart disease and stroke in adults ≥ 65 years of age in whom data were collected prospectively over 15 years of follow-up.^{9,10} Starting in 1989, members of the original CHS cohort were recruited from a random sample of men and women on the Health Care Financing Administration Medicare eligibility lists in 4 US communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh (Allegheny County), PA. Participants had to be ≥ 65 years of age, able to give informed consent, and able to respond to questions without the aid of a surrogate respondent. To enhance the minority representation in the original cohort of 5,201 men and women, an additional 687 black men and women were recruited from the centers in North Carolina, California, and Pennsylvania, bringing the total size of the cohort to 5,888 people. Extensive in-person evaluations were performed at baseline and at follow-up visits that occurred every 12 months. Recently, CHS merged its data with those from the CMS, a social insurance program that provides insurance to nearly 40 million older Americans. The CMS program provides coverage for in-patient care in hospitals and skilled nursing facilities, hospice care, and postacute home health care, as well as outpatient services, including physician visits, outpatient hospital care, and selected preventive services. By the final follow-up date of this study (December 31, 2010), 5,546 of 5,888 participants (94.2%) had been hospitalized, suggesting that the vast majority of the cohort have available healthcare use information from administrative claims.

Standard protocol approvals, registrations, and patient consents. Human subjects review committees at each study site approved the study, and all participants provided informed consent.

Adjudication for epilepsy. We used multiple data sources to identify potential cases with epilepsy, summarized in table 1. We developed a priori criteria to screen participants for epilepsy based on data available in CHS and CMS. Using these definitions, we implemented a formal adjudication process with 2 reviewers (H.C. and A.P.) evaluating independently all potential cases with epilepsy who screened positive for epilepsy on the basis of self-report, medication use, ICD-9 hospitalization diagnosis code, or CMS claims. Similar to a previously published study,¹¹ we placed greater credibility of an epilepsy diagnosis on ICD-9 claims submitted by a neurologist than a nonneurologist. Reviewers preliminarily classified participants as having probable epilepsy, possible epilepsy, or no epilepsy according to the criteria summarized in table 2. We assessed agreement between reviewers (interrater reliability) using κ statistics. Reviewers discussed all discordant classifications and came to a consensus. Final adjudicated assignments were probable epilepsy, possible epilepsy, and not epilepsy.

We first defined cases of epilepsy as those participants who were adjudicated as probable epilepsy and noncases as those who were adjudicated as either possible epilepsy or not epilepsy. Following the methods of others,⁷ we regarded cases with incident epilepsy as a subset of cases with probable epilepsy who had a period of at least 2 years since enrollment in the CHS, during which time they had no claims with the ICD-9 codes of 345.xx or 780.3x. Thus, we excluded from incidence analyses and defined as prevalent probable epilepsy those cases with ICD-9 claims during the first 2 years.

Measures. Study endpoints. The primary study outcomes were point prevalence at baseline, incident epilepsy, and period prevalence over the entire course of the study.

Table 1 Sources of data from the Cardiovascular Health Study (CHS) and Centers for Medicare & Medicaid Services (CMS) used for classification of epilepsy

Data source	Description
CHS data source	
Self-report of prior seizures	During yearly follow-up, participants were asked about any sudden episodes such as dizziness, loss of balance, spinning sensation, double vision, numbness/tingling, paralysis/weakness, change in speech, or loss of vision in the past year. If response was yes, participants were then asked whether seizures or convulsions occurred during such symptoms.
MRI screening questionnaire eliciting history of seizures	The 3,660 participants who had a brain MRI during CHS were given a prescan interview form, which included a question about whether they had ever had a seizure or convulsion. If response was yes, participants were then asked whether seizures or convulsions occurred only during childhood or whether seizures or convulsions occurred within the last 5 years.
Indicator of any AEDs	Prescription medications recorded at each visit were searched electronically to determine whether participants had at any point during the CHS taken one or more AEDs (listed in table e-1 at Neurology.org). We counted the number of CHS study visits that patients had while taking one or more AEDs.
Number of hospitalization discharges with ICD-9 codes of 345.xx or 780.3x	We determined the number of distinct hospital discharges with ICD-9 codes for epilepsy (345.xx) or ICD-9 codes for convulsions (780.3x) during enrollment in the CHS.
CMS data source	
Number of claims filed for ICD-9 codes of 345.xx or 780.3x	Total number of distinct ICD-9 claims filed for 345.xx or 780.3x
Specialty of the physician filing the claims	Number of distinct ICD-9 claims of 345.xx or 780.3x submitted by neurologists vs nonneurologists
Eligibility for CMS fee for service	For each participant we reviewed, information on periods of enrollment in CMS was determined.

Abbreviations: AED = antiepileptic drug; CHS = Cardiovascular Health Study; CMS = Centers for Medicare & Medicaid Services; ICD-9 = *International Classification of Diseases, ninth revision*.

Table 2 Criteria for case adjudication of epilepsy

Category	Criteria
Probable epilepsy	Any one of the following
	If both CHS and CMS data are available and minimum of one source each from CHS and CMS supportive of epilepsy, then:
	Total number of distinct ICD-9 claims ≥ 1
	If both CHS and CMS data available but evidence of epilepsy exists only in CMS, then the following criterion must be met:
Possible epilepsy	Total number of distinct ICD-9 claims (345.xx or 780.3x) ≥ 3 if submitted by nonneurologist or ≥ 2 if submitted by neurologist
	Data sources suggest epilepsy but evidence to adjudicate epilepsy status is insufficient or conflicting, with any one of the following:
	If both CHS and CMS data available but evidence of epilepsy exists in only CMS, then the following criterion must be met:
	Total number of distinct ICD-9 claims (345.xx or 780.3x) is ≤ 2 made by nonneurologist or only one made by neurologist
Not epilepsy	If CHS and CMS data available but evidence exists only in CHS, then the following criterion must be met:
	≥ 2 Sources of CHS must exist to suggest epilepsy
	If CHS data available but not CMS data, namely no period of enrollment in Medicare fee for service, and evidence of epilepsy exists in CHS, then the following criterion must be met:
	≥ 2 Sources of CHS must exist to suggest epilepsy
	Does not meet criteria for either probable epilepsy or possible epilepsy and any one of the following:
	No suggestion of epilepsy from any source
	If CHS and CMS data are available, with evidence of epilepsy in CHS only:
Not epilepsy	Only one source of CHS data suggesting epilepsy
	If CHS data available but not CMS data, namely no period of enrollment in Medicare fee for service, with evidence of epilepsy in CHS, then the following criterion must be met:
	Only one source of CHS data source must exist

Abbreviations: CHS = Cardiovascular Health Study; CMS = Centers for Medicare & Medicaid Services; ICD-9 = *International Classification of Diseases, ninth revision*.

Independent variables. Variables tested for association with study outcomes were defined in previous CHS articles^{9,12,13} and are categorized in tables e-2 and e-3. They included age; sex; race; marital status; education; life occupation; body mass index (underweight, normal, overweight, obese); self-reported health (excellent, very good, good, fair, poor); and comorbidities present at baseline and during CHS follow-up but before the occurrence of incident epilepsy. Race was dichotomized as black and non-black, the latter being entirely white except for 15 American Indians/Alaska Natives, 4 Asian/Pacific Islanders, and 20 in the “other” race category. The few participants with Hispanic ancestry are included in the nonblack group. Comorbidities included hypertension status; diabetes mellitus; chronic obstructive pulmonary disease; left ventricular hypertrophy; congestive heart failure (CHF); claudication; stroke; transient ischemic attack (TIA); myocardial infarction; and coronary heart disease.

Statistical analysis. We performed a cross-sectional comparison between cases with prevalent epilepsy and those without epilepsy to determine any significant differences in baseline demographic and clinical characteristics using unadjusted and adjusted logistic regression. Because of the known limitations of using bivariate analysis to screen variables for inclusion in the adjusted analysis,¹⁴ we built a multivariable logistic regression model to

assess independent correlates of epilepsy, including carefully selected variables based on a priori knowledge and previous studies. In adjusted analyses, we included all of the variables that were individually assessed in unadjusted analyses.

Analysis of incident epilepsy. For each case of incident epilepsy, we determined the time from entry into the CHS cohort until an incident diagnosis of epilepsy. Participants without epilepsy were all censored on the date of their last encounter with medical facilities. We estimated the incidence of epilepsy as the number of cases divided by the number of person-years of follow-up. We used unadjusted and adjusted Cox proportional hazards regression to assess the associations between demographic and clinical factors and incident epilepsy. We constructed 2 different multivariable Cox proportional hazards models to evaluate associations between (1) incident epilepsy and comorbid conditions present at baseline such as a history of prevalent stroke and (2) incident epilepsy and comorbid conditions that developed after enrollment in CHS but before the onset of incident epilepsy. In the second model, participants with comorbid conditions present at baseline were excluded ($n = 1,517$). We evaluated the proportional hazards assumption for each covariate using log-log plots of survival curves and formal significance test based on the unscaled and scaled Schoenfeld residuals.¹⁵ Hazard ratios (HRs) and their 95% confidence intervals (95% CIs) are reported.

Sensitivity analysis. In sensitivity analyses, we examined to see whether the results of the incident analyses were altered by excluding from the analyses those participants classified as having possible epilepsy. In the main analysis, those with possible epilepsy were grouped with those who did not have epilepsy. We hypothesized that associations may be stronger once participants with possible epilepsy were removed from the no epilepsy group. Analyses were conducted with Stata 13.1 (StataCorp, College Station, TX), and statistical significance was set at 2-sided $p < 0.05$.

RESULTS The overall agreement between reviewers in assigning epilepsy categories was 99.8% with a corresponding chance-corrected κ of 99.2% ($p < 0.001$). After consensus was reached for all conflicting cases, the final adjudication resulted in 335 with probable epilepsy, 323 with possible epilepsy, and 5,230 with no epilepsy.

With probable epilepsy ($n = 335$) used as the primary case definition, the period prevalence of epilepsy by the end of follow-up was 5.7% (95% CI 5.1–6.3). We identified a subset of 120 participants who met the criteria for incident epilepsy. Thus, 215 individuals had prevalent epilepsy at enrollment, yielding a point prevalence at baseline of 3.7% (95% CI 3.2–4.2).

When baseline characteristics were compared between those with prevalent epilepsy and those without epilepsy, using unadjusted and adjusted logistic regression analysis, we found no significant associations except TIA. The adjusted odds of having prevalent epilepsy at CHS enrollment was 2.2 times greater for participants with history of TIA at the baseline examination (odds ratio 2.2, 95% CI 1.1–4.8).

The overall incidence rate was 2.47 per 1,000 person-years for the 120 incident cases identified over 48,651 person-years of follow-up. In unadjusted Cox

regression analysis (table e-2), significant risk factors for incident epilepsy were ages of 75 to 79 years, black race, a graduate/professional level of education (post-college), self-perceived fair/poor health status, CHF, stroke, and TIA. The incidence rates were significantly higher among black than nonblack participants: 4.44 vs 2.17 per 1,000 person-years. The incidence rates also differed by age, with those 75 to 79 years of age having the highest incidence rate of 3.28 and those ≥ 80 years of age having a relatively lower incidence rate of 2.07. In the Cox analysis adjusted for the effects of all other covariates (figure 1, table e-2), the risk factors for incident epilepsy included age of 75 to 79 years (HR 2.07, 95% CI

1.21–3.55), black race (HR 4.04, 95% CI 1.99–8.17), and history of stroke (HR 3.49, 95% CI 1.37–8.88). Of note, significantly reduced risks of developing epilepsy were observed with coronary heart disease (HR 0.26, 95% CI 0.08–0.85) and obesity (HR 0.2, 95% CI 0.04–0.95).

The results of unadjusted and adjusted Cox regression models, including time-dependent covariates for CHF, claudication, stroke, TIA, myocardial infarction, and coronary heart disease in participants who developed these after CHS enrollment but before the development of epilepsy, are provided in table e-3. Similar to the adjusted model using covariates measured at baseline and based on 120 incident cases,

Figure 1 Risk factors for incident epilepsy with baseline comorbidities

Forest plot of adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of risk factors for incident epilepsy with comorbidities at baseline. Increased risk of incident epilepsy is to the right of the vertical axis. Table e-2 provides specific incidence rate, referent group, and *p* value. BMI = body mass index; CHD = coronary heart disease; CHF = congestive heart failure; CLD = claudication; IFG = impaired fasting glucose; MI = myocardial infarction; TIA = transient ischemic attack.

the adjusted model based on 87 incident cases showed that black race (HR 3.61, 95% CI 1.61–8.11) and incident stroke (HR 2.94, 95% CI 1.71–5.06) were independently associated with incident epilepsy (figure 2). CHF was significantly associated with a 61% lower incidence of epilepsy compared to those without CHF.

Sensitivity analysis. In sensitivity analyses, when the 323 participants with possible epilepsy were not included in the no epilepsy group and the analyses for incident epilepsy were repeated, results were not substantially different (tables e-4 and e-5).

DISCUSSION Using data from both CHS and CMS, we found that epilepsy in older adults was common, prevalent in 3.7% of individuals at baseline and affecting 5.7% of the cohort by the end of 14 years of follow-up. The overall incidence of epilepsy in this cohort was 2.47 per 1,000 person-years, making it 1.5 times more common than what has been reported for Parkinson disease in older adults.¹⁶ We confirmed that independent predictors of developing epilepsy after age 65 included advanced age, black race, and history of both prevalent and incident stroke. Prevalent coronary heart disease, obesity at baseline, and incident congestive heart failure diagnosed

Figure 2 Risk factors for incident epilepsy with incident comorbidities before onset of epilepsy

Forest plot of adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of risk factors for incident epilepsy with comorbidities occurring after baseline but before onset of epilepsy (n = 87). Increased risk of incident epilepsy is to the right of the vertical axis. Table e-3 provides specific incident rates, referent group, and p values. BMI = body mass index; CHD = coronary heart disease; CHF = congestive heart failure; CLD = claudication; IFG = impaired fasting glucose; MI = myocardial infarction; TIA = transient ischemic attack.

during the CHS follow-up were independently associated with a reduced risk of incident epilepsy. Reduced risk of incident epilepsy in patients with obesity, also reported by others¹⁷ and called the obesity paradox,^{18,19} raises the possibility for neuroprotective effects of metabolic syndromes against epilepsy in older adults. Reduced risk of incident epilepsy in those with prevalent coronary heart disease and incident congestive heart failure during CHS were unanticipated findings because these conditions are common causes of stroke.^{20,21} The role of medical treatments for these conditions such as statins, a class of medication associated with reduced risk of incident epilepsy in older adults, is uncertain.¹⁷

Our estimated point prevalence of epilepsy at baseline was higher than previously reported for community-dwelling older adults,^{17,22} possibly reflecting differences in methods of case ascertainment. However, our incidence rate was nearly identical to that in a study that used CMS outpatient diagnosis codes.⁷ A review of methods for identifying epilepsy with administrative and claims data showed that positive predictive values can vary across studies.²³ A prior study examining the validity of different algorithms for identifying cases with epilepsy in administrative data found that the probability of detecting epilepsy increased with increasing numbers of ICD-9 codes. The ability to detect cases with epilepsy increased even further when prescription data were combined with ICD-9 codes.⁸ Our criteria required multiple diagnosis codes and took into account whether they were submitted by neurologists or nonneurologists. Additionally, our criteria required other sources of data such as hospitalization discharge ICD-9 codes, use of antiepileptic medications, and self-report, likely further improving the detection of participants with epilepsy. A recent study examining all sectors of the US population found a prevalence estimate of 8.5 cases per 1,000 persons and documented age-specific estimates of epilepsy incidence similar to those of other studies, with higher rates in persons <5 or >60 years of age.²⁴

Disparity in risk by race was the most salient finding in our study. Blacks had a greater likelihood of having prevalent epilepsy and increased risk of developing incident epilepsy after age 65. Both population-based and tertiary care center studies have shown that older black persons have nearly double the incidence rate of epilepsy compared to whites,^{7,22} a finding consistent with our estimates. In fact, the higher prevalence and incidence of epilepsy in black persons of all ages, including children, have been reported in previous studies.^{25–27} Stroke is the most common known cause of epilepsy in the older adult population, and blacks have a >2-fold increased risk of stroke compared with whites living in the same community.²⁸ However, we found that black race is a risk factor for epilepsy in

older adults independent of stroke, as seen in a prior study of 1,919 community-dwelling elderly in the Bronx followed up in a prospective aging study.²² Because other risk factors of epilepsy such as Alzheimer disease disproportionately affect blacks,²⁹ whether other factors explain the relationship between black race and incidence of epilepsy in our study is not entirely clear. Emerging data from genetic studies suggest that ethnicity may have a role in genetic causes of epilepsy in specific populations.^{30,31} Although genetic epilepsy would be unlikely to begin in older age, other genetic mutations may be associated with increased susceptibility to incident epilepsy in older age among different ethnic groups.

In contrast to previous studies in which the incidence rate of epilepsy among older adults increased linearly with age,⁵ we found that the risk was nonlinear, being highest in the 75- to 79-year-old group compared to other 5-year groups ranging from 65 to >80 years of age. The incidence rate for the >80-year-old group actually decreased, similar to other studies that found the lowest risk among the oldest age group (≥ 85 years old).^{17,32} These findings raise the question of the specific age range in which susceptibility to incident epilepsy may be higher or lower. On the other hand, lower risk in the oldest age groups may be an effect of survivor bias, a selection bias whereby healthy people are selectively retained while unhealthy people, say those with epilepsy, die.³³

A number of sociodemographic and clinical factors were significantly associated with incident epilepsy. Participants with a highest level of education (graduate/professional) had the lowest incidence of epilepsy in the unadjusted analysis. We do not believe that this is a result of reverse causality, in which epilepsy leads to lower educational attainment, because participants' education was completed long before enrollment in CHS or age 65. This particular finding raises the question of socioeconomic status serving as an independent risk factor or a proxy for some other risk factor for epilepsy in older adults, not confounded by other risk factors such as cerebrovascular disease.³⁴ In a population-based case-control study in Iceland, low socioeconomic status, as measured by low education level, was found to be a risk factor for epilepsy in adults of all ages.³⁵ In that study, the association was not explained by established risk factors for epilepsy such as stroke.

We also found no sex differences, similar to what others have reported in the past.¹⁷ In another study of epilepsy in older adults, women were slightly more likely to have incident epilepsy than men.⁷ However, this finding was confounded by women living longer than men. When adjusted for age difference, the incidence rates for women were in fact slightly lower than for men.

While hypertension is an established risk factor for clinically detected stroke, like others,¹⁷ we did not find hypertension to be an independent risk factor for incident epilepsy. However, a case-control study found that severe, uncontrolled hypertension, defined as left ventricular hypertrophy without diuretic treatment, had an 11-fold increased risk of unprovoked seizure.³⁶ As shown in table e-2, left ventricular hypertrophy detected by ECG at baseline was not an independent risk factor of incident epilepsy in our study, although we did not examine whether those with left ventricular hypertrophy were on diuretic treatment.

In the second model of risk factor analysis examining participants with incident epilepsy and comorbid conditions that developed during the study follow-up but before the onset of epilepsy, a limited number of risk factors were identified. Only black race and incident stroke remained as independent risk factors of incident epilepsy in older adults. Congestive heart failure was associated with reduced risk. Measured or unmeasured confounders not included in our analysis likely resulted in the change in the directionality of risk.

Our study had several methodological strengths, notably the inclusion of population-based data from racially, demographically, and geographically diverse settings. We also used multiple sources of data, including self-report of seizures, use of antiepileptic medications, and hospitalization discharge diagnostic codes from a prospective study, in addition to outpatient diagnostic codes from CMS.

However, our study also had some important limitations. First, older adults destined to develop epilepsy may have succumbed to some other disease before their epilepsy ever manifested; hence, we may have underestimated the incidence of epilepsy if such older adults had survived. Second, history of TIA was more likely to be present in those with prevalent epilepsy compared to those without epilepsy at baseline, raising the possibility of misdiagnosis of TIA.^{16,37} Because history of stroke or TIA reported at CHS study entry was not confirmed beyond self-reporting,⁹ it is possible that individuals reporting TIA might have had a seizure instead. Third, we were not able to interview those with suspected epilepsy or to review the hospitalization medical records of those with epilepsy ICD-9 hospital discharge codes during the CHS follow-up, which were not feasible within the scope of this study. Furthermore, medical records associated with CMS outpatient ICD-9 codes were not available for review. Review of medical records could have served to validate our case ascertainment method. We have likely underestimated the incidence of epilepsy in the cohort because some of those with claims in the first 2 years who were excluded and

some of those classified as having possible epilepsy may in fact have had incident epilepsy. Additionally, the relatively small number of incident cases of epilepsy during the study period could have resulted in limited statistical power, a problem that could be addressed by collaboration with other cohort studies. Finally, we were unable to examine in this study other risk factors of epilepsy such as brain tumor, traumatic brain injury, dementia, or psychiatric risk factors.³²

Epilepsy in older adults in the United States was common, affecting $\approx 4\%$ of the cohort. We confirmed that significant, independent predictors of developing epilepsy after age 65 included black race and stroke. Additional study is needed to determine neurologic or medical conditions raising the risk of epilepsy among older adults and to identify mechanisms by which race affects this risk.

AUTHOR CONTRIBUTIONS

Hyunmi Choi: study concept, design, analysis and interpretation of data, drafting of the manuscript. Alison Pack: analysis, interpretation of data, drafting of the manuscript. Mitchell S.V. Elkind: study concept, interpretation of data, drafting of the manuscript. W.T. Longstreth, Jr: study concept, interpretation of data, drafting of the manuscript. Thanh G.N. Ton: study concept, design, interpretation of data, drafting of the manuscript. Frankline Onchiri: study concept, statistical analysis, interpretation of data, drafting of the manuscript.

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