RESEARCH ARTICLE

Late-Onset Seizures

Etiology and Demographics in US Tertiary Care Epilepsy Centers

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Abstract

Background and Objectives

Adults older than age 55 years have the highest incidence rate and are the fastest-growing population among people with epilepsy. The aim of this study was to characterize the etiologies of new-onset seizures in older adults and to examine how seizure etiology varies across demographic groups. We used data from 7 US epilepsy centers from 2021 to 2025 and compared findings with those of previous population-based studies, providing an updated view and highlighting opportunities for prevention and improved risk stratification.

Methods

We retrospectively reviewed medical charts of 2,052 patients aged ≥55 years at the time of a first seizure, who were evaluated at 7 epilepsy centers between 2021 and 2025. We categorized seizures by etiology as follows: ischemic stroke, hemorrhagic stroke, tumor, neurodegeneration, provoked seizures, traumatic brain injury, and unknown. We examined differences in etiology by demographic strata (age, sex, race, and primary language) using chi-square tests, Kruskal-Wallis tests, analysis of variance, and Cuzick tests.

Results

The most frequent seizure etiologies among older adults were unknown (29.9%), ischemic stroke (15.4%), and provoked seizures (14.9%). Neurodegenerative disease was the etiology for 5.3% of cases overall but increased in prevalence with age, accounting for 18.5% among patients aged 85–89 years. Seizure etiologies also differed by sex and race. Men more commonly had seizures caused by cerebrovascular disease and traumatic brain injury, while women more commonly had seizures due to neurodegenerative disease. Black patients had higher proportions of ischemic stroke and neurodegenerative disease, while unexplained epilepsy was more common among White patients.

Discussion

The causes of late-onset seizures vary based on age, sex, and race. Nearly one-third of cases of epilepsy in older adults remain unexplained despite advances in imaging techniques, underscoring the need for further research on the mechanisms and health implications of late-onset unexplained epilepsy. Improved prevention of cerebrovascular disease and optimized management of provoked seizures may reduce the growing burden of epilepsy in older adults.

Introduction

Epilepsy is a leading cause of neurologic disability. Adults older than 55 years not only have the highest incidence rate of epilepsy but also are the fastest-growing population with epilepsy.[1-3] Much of our understanding of seizure etiology in older adults is based on decades-old data with small sample sizes and limited racial and linguistic diversity, which may not reflect current

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Glossary

ELUCID = Epilepsy of Late-onset Unknown etiology as a Risk Factor for Cognitive Impairment and Dementia; **EMR** = electronic medical record; **IPH** = intraparenchymal hemorrhage; **MGB** = Mass General Brigham; **NAEC** = National Association of Epilepsy Center; **OR** = odds ratio; **SAH** = subarachnoid hemorrhage; **SDH** = subdural hematoma.

diagnostic techniques[4] and do not include all first seizures (i.e., provoked seizures were excluded).[4,5] The goals of this study were to (1) provide an updated view on the causes of late-onset seizures in a large cohort of patients treated at tertiary care epilepsy centers; (2) expand understanding of the association between demographic factors such as age, race, sex, and linguistic preference and seizure etiology; and (3) compare seizure etiologies in the 2021–2025 time frame with those described in previous studies.

Methods

Population

This is an analysis of retrospectively collected data obtained during record screening for the Epilepsy of Late-onset Unknown etiology as a risk factor for Cognitive Impairment and Dementia (ELUCID) study. ELUCID is a prospective multicenter cohort study (NIH R01 NS130119), with the goals of accurately phenotyping late-onset unexplained epilepsy and identifying risk factors of cognitive decline and dementia in this population. ELUCID has 7 primary recruitment sites, all of which are designated as Level IV Epilepsy Centers by the National Association of Epilepsy Centers (NAECs), including Massachusetts General Hospital, Brigham and Women's Hospital, and Beth Israel Deaconess Medical Center in Boston, MA; Icahn School of Medicine at Mount Sinai in New York City, NY; Johns Hopkins Medical Institutions in Baltimore, MD; University of Alabama–Birmingham in Birmingham, AL; and University of Texas–Southwestern in Dallas, TX. These centers serve broad and diverse catchments that encompass both rural and urban populations in the Northeast, Mid-Atlantic, South, and Southwestern United States (eTable 1). As Level IV epilepsy centers, these sites receive referrals of persons with epilepsy or seizures from other clinics and hospitals and also provide care to the populations surrounding the medical systems. Standard workup for first seizure in these systems includes documenting a thorough history, physical examination, brain imaging, EEG, and laboratory evaluation.

Each ELUCID study site identified the medical records of patients for screening using the criteria of patient age ≥55, diagnosis of seizure or epilepsy during the study time frame, and provider affiliated with the epilepsy centers. This involved searching first seizure, epilepsy, and neurology clinics; persons undergoing EEGs; epilepsy monitoring unit admissions; and other presentations for seizure.

As part of standardized screening procedures to identify people eligible for ELUCID, clinical research coordinators were trained in screening procedures, including how to review medical records, and diagnostic and etiologic categorization, which was verified by a site primary investigator or second reviewer. Researchers at each site then reviewed the medical records (including all available clinic notes, imaging and EEG findings, and laboratory results) of all patients aged 55 years or older who had at least 1 episode concerning for seizure and were evaluated at each institution between February 1, 2021, and January 31, 2025. To identify incident cases only, patients with first seizure before February 1, 2021, were excluded. If there was diagnostic or etiologic uncertainty, the images and/or raw EEG tracings were reviewed when available, and all uncertain cases were discussed in consensus conferences with board-certified and practicing epileptologists from the 7 centers.

This analysis includes data from screened individuals who had a first-time seizure between 2021 and 2025 at age ≥55 years. All persons categorized as having a definite or probable first seizure were included in this study, whereas persons categorized as being "unlikely" to have had a seizure were not included. Inclusion criteria for the subsequent ELUCID study require the etiology for the seizure(s) to be unknown.

Classification of Seizure Etiologies

Researchers determined whether the likelihood of seizure in each patient was definite, probable, or unlikely and whether there was evidence of definite, probable, or unlikely epilepsy (eTable 2). Patients classified as unlikely to have had seizures were excluded from this analysis. This study reports seizure etiologies in all screened patients with definite or probable seizures starting at age 55 years or older. From these patients, researchers recorded demographic information and seizure etiology (eTable 3). Persons without a known cause for seizures were deemed eligible for ELUCID.

From the medical records, the etiologies were categorized as follows: ischemic stroke (cortical), hemorrhagic stroke, vascular malformation, infection, autoimmune, head trauma, supratentorial surgery, neurodegeneration, neoplasm, provoked seizure, other known etiology, and unknown etiology. The "hemorrhagic stroke" etiology included subdural, subarachnoid, intraparenchymal (cortical), and/or intraventricular hemorrhages. The "provoked" etiology included alcohol withdrawal, toxic ingestion, and metabolic disturbances, following the International League Against Epilepsy acute symptomatic seizure classification.[6] The "neurodegeneration" etiology included diagnosis of Alzheimer disease, Lewy body disease, frontotemporal dementia, vascular dementia, Parkinson disease, amyotrophic lateral sclerosis, Huntington disease, or other neurodegenerative diseases. Patients with any focal

cortical imaging findings on brain MRI that were believed to be a potential seizure focus were classified in the appropriate lesional or "other known etiology" groups. White matter hyperintensities, hippocampal sclerosis, microhemorrhages, and global cortical volume loss were not considered causative lesions. Etiologies were determined from the medical record.

If there was diagnostic or etiologic uncertainty, cases were discussed and adjudicated at a consensus conference attended by researchers at each site and all study site principal investigators, all of whom are practicing epileptologists with board certification in epilepsy and/or clinical neurophysiology.

Data Analysis

Population statistics are presented as means ± SDs, unless stated otherwise. We used *t* tests, chi-square tests with Pearson residuals, Kruskal-Wallis tests, analysis of variance, and Cuzick test as appropriate to compare study population age, sex, race, and primary language distributions by site and by etiology, and regression models to adjust distributions for age. Analysis was conducted using Stata 19.0 (College Station, TX). A two-sided p value of 0.05 was considered significant.

Standard Protocol Approvals, Registrations, and Patient Consents

All study procedures were performed under an approved institutional review board (IRB) protocol (#2023P001566), with the Mass General Brigham (MGB) IRB serving as the single IRB of record, and all other sites ceding IRB review to the MGB IRB. Consent was waived by the sIRB for patient screening procedures; participants who were eligible for ELUCID were contacted and consented as part of that study.

Data Availability

Deidentified data will be made available to qualified researchers on reasonable request.

Results

Study Population Characteristics

A total of 2,052 patients, screened across 7 NAEC Level IV epilepsy centers, had a definite or probable first seizure at the age of 55 years or older, between February 1, 2021, and January 31, 2025, and are described here. The mean age at the time of screening was 70 years, with 25th and 75th quartiles of 63 and 77 years and a maximum age of 101 years (Table 1). Women comprised 47.4% of screened patients. Women were slightly older at the time of screening (mean age of 71.4 ± 9.67 years in women vs 70.1 ± 8.75 years in men, $p = 0.004$). A total of 3 patients whose sex was unclear from the medical record were excluded from sex-based analyses. All other participants had equivalent biological sex at birth and current sex according to the medical records.

Patients screened were 63.5% White, 17.2% Black, and 2.5% Asian (Table 1). A total of 180 patients reported Hispanic ethnicity (8.8%). The mean age at the time of screening was 69.9 ± 9.56 in Black, 70.9 ± 9.12 in White, and 71.2 ± 9.34 in Asian patients ($p = 0.06$).

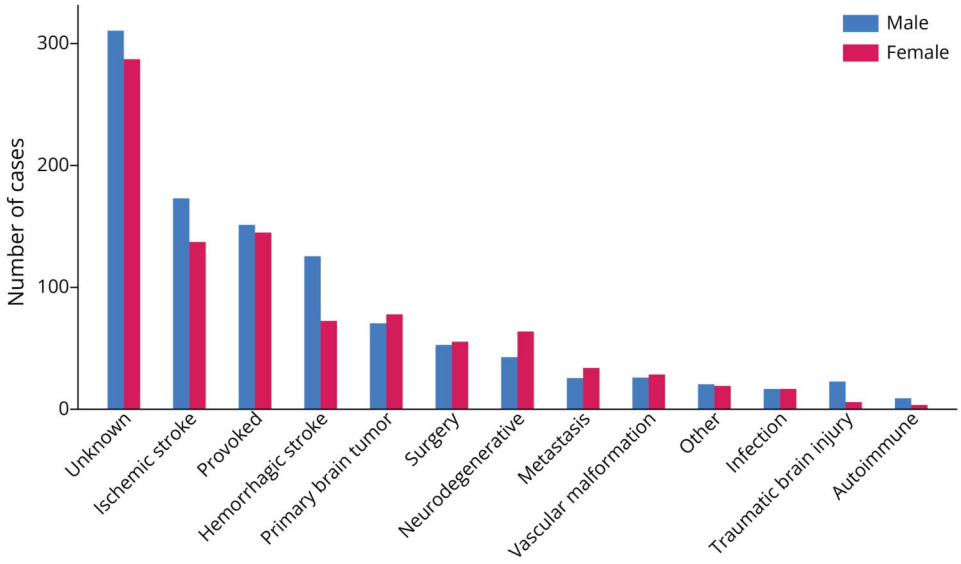
Figure 1 and Table 2 present demographic information on the most common seizure etiologies identified in our cohort. The most common classification was "unknown," accounting for nearly one-third of all patients with late-onset seizure(s) (601, 29.9%; these patients with unexplained seizure(s) were considered potentially eligible for ELUCID). Among patients

Table 1 Demographics of Screened Patients With First Seizure at Age 55 or Older Within the Past 3 Years

N	2052
Age, median (IQR)	70 (63–77)
Sex, (%)	
Men	1,070 (52.3)
Women	971 (47.4)
Other/unknown	6 (0.3)
Race (%)	
Not reported	321 (16.0)
More than 1	8 (0.4)
White	1,277 (63.5)
NHOPI	3 (0.1)
Black/AA	346 (17.2)
Asian	51 (2.5)
AIAN	4 (0.2)
Primary language (%)	
English	1,677 (81.7)
Spanish	112 (5.5)
Other	263 (12.8)
Institution (%)	
BIDMC	143 (7.1)
BWH	499 (24.8)
ISMMS	606 (30.1)
JHMI	142 (7.1)
MGH	221 (11.0)
UAB	300 (14.9)
UTSW	99 (4.9)

Abbreviations: AA = African American; AIAN = American Indian or Alaska Native; BWH = Brigham and Women's Hospital; Institutions: BIDMC = Beth Israel Deaconess Medical Center; ISMMS = Icahn School of Medicine at Mount Sinai; IQR = interquartile range; JHMI = Johns Hopkins Medical Institutions; MGH = Massachusetts General Hospital; NHOPI = Native Hawaiian/Other Pacific Islander; UAB = University of Alabama–Birmingham; UTSW = University of Texas–Southwestern.

Figure 1 Etiologies of New-Onset Seizures in Adults Aged 55 Years and Older Across 7 US Tertiary Care Epilepsy Centers



"Other" refers to another identified etiology.

with a known etiology for seizures, the most common etiology was ischemic stroke (15.4% of all patients), followed by acute provoked seizure (14.9%; Figure 1). Hemorrhagic stroke was the cause in 9.9%, followed by primary brain tumor in 7.4%.

Differences in Etiology of Late-Onset Seizures Across Age Groups

Figure 2 presents the relative proportion of seizure etiologies across different age groups, whereas Figure 3 shows the age

Table 2 Demographics of Screened Patients With First Seizure at Age Older Than 55 Within the Past 3 Years, by 7 Most Common Etiologies

	Unknown	Ischemic stroke	Provoked	Hemorrhagic	Neoplasm	CNS surgery	Neurodegenerative	*p* Value
N, (%)	601 (29.9)	310 (15.4)	300 (14.9)	199 (9.9)	149 (7.4)	109 (5.4)	107 (5.3)	
Age, median (IQR)	70 (63–76)	71 (64–79)	68 (62–75)	73 (66–79)	68.5 (61–76)	66 (60–73)	80.5 (74–87)	<0.001
Sex (%)								
Men	311 (51.9)	173 (55.8)	151 (50.5)	126 (63.3)	71 (47.7)	53 (48.6)	43 (40.2)	0.002
Women	288 (48.1)	137 (44.2)	145 (48.5)	72 (36.2)	78 (52.3)	56 (51.4)	64 (59.8)	
Race (%)								
Unknown/not recorded	79 (13.1)	78 (25.2)	52 (17.3)	26 (13.1)	19 (12.8)	11 (10.1)	25 (23.4)	<0.001
More than 1	3 (0.5)	3 (1.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	
White	423 (70.4)	142 (45.8)	187 (62.3)	136 (68.3)	101 (67.8)	80 (73.4)	48 (44.9)	
NHOPI	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.7)	0 (0.0)	0 (0.0)	
Black/AA	80 (13.3)	79 (25.5)	54 (18.0)	30 (15.1)	22 (14.8)	16 (14.7)	28 (26.2)	
Asian	14 (2.3)	7 (2.3)	5 (1.7)	6 (3.0)	6 (4.0)	2 (1.8)	4 (3.7)	
AIAN	1 (0.2)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	
Primary language (%)								
English	514 (85.5)	239 (77.1)	259 (86.3)	170 (85.4)	127 (85.2)	97 (89.0)	81 (75.7)	<0.001
Spanish	22 (3.7)	28 (9.0)	22 (7.3)	9 (4.5)	3 (2.0)	2 (1.8)	12 (11.2)	
Other	65 (10.8)	43 (13.9)	19 (6.3)	20 (10.1)	19 (12.8)	10 (9.2)	14 (13.1)	

Abbreviations: AA = African American; AIAN = American Indian or Alaska Native; IQR = interquartile range; NHOPI = Native Hawaiian/Other Pacific Islander.

distribution for each seizure etiology. Even among older adults, the relative distribution of seizure etiologies differed across age strata (Figures 2 and 3). "Unexplained" etiology accounted for 30%–32% of patients consistently between ages 55 and 84 years, although the proportion was less than 20% after age 85 years. Conversely, neurodegenerative etiology accounted for an increasing proportion of seizure etiology with increasing age, accounting for 2.4% of cases in patients aged 55–59 years and 18.5% of cases in patients older than 85 years. After age 60, each additional 5-year increase in age had a nearly 60% increase in the odds of neurodegeneration as the seizure etiology (odds ratio [OR] 1.58, 95% CI 1.40–1.77, $p < 0.001$).

Hemorrhagic stroke also became more common as a cause of seizure with increasing age, through age 80 (OR 1.27 for hemorrhagic etiology for each 5-year age category, 95% CI 1.11–1.45, $p < 0.001$). Patients with neurodegenerative disease as the seizure etiology had the oldest median age (80.5).

Sex, Race, and Language-Based Differences in Etiology of Late-Onset Seizures

Sex-based differences in seizure etiologies were also present (Figure 1). Hemorrhagic stroke was a more common etiology in men than in women (14.5 vs 8.9%, $p < 0.001$), as was traumatic brain injury (2.2% vs 0.63%, $p = 0.002$). Neurodegenerative disease was a more common etiology in women (6.7% in women vs 4.1% in men, OR 1.68 for women (95% CI 1.13–2.51)). However, after adjusting for age, this relationship was attenuated (OR 1.47, 95% CI 0.97–2.22).

The 2 largest reported racial groups were Black and White, and seizure etiologies also differed between these 2 groups (Figure 4). Ischemic stroke was more common in Black than in White patients (22.8% vs 11.1%, respectively, $p < 0.001$). "Unknown" etiology was more common in White than in Black patients (33.1% vs 23.1% respectively, $p < 0.001$). The lower number of Asian patients (51) limited comparisons, although the proportions with ischemic stroke as an etiology (13.7%) and with unknown etiology (27.5%) fell between the respective percentages observed in Black and White groups. After adjusting for age, the finding of higher likelihood of ischemic stroke as the etiology for Black patients persisted (OR 1.55, 95% CI 1.33–1.82, $p < 0.001$), as did the higher likelihood of unknown etiology in White patients (OR 1.65, 95% CI 1.25–2.18, $p < 0.001$).

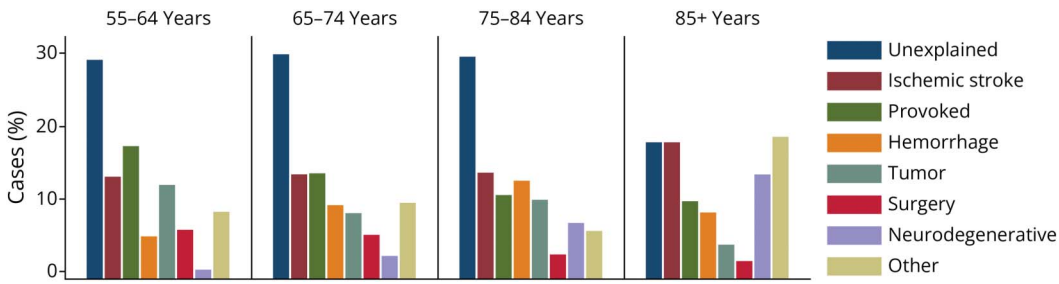
Seizure etiologies also differed by primary language. Compared with English-speaking patients, Spanish-speaking patients were more likely to have neurodegenerative disease (10.7% vs 4.8%, $p = 0.025$) or ischemic stroke as the cause of seizure (25.0% vs 14.25%, $p = 0.007$), and less likely to have unknown etiology as the cause of seizure (19.6% vs 30.6%, $p = 0.010$). After adjusting for age, the higher likelihood of neurodegenerative cause (OR 1.99, 95% CI 1.01–3.92, $p = 0.045$) or ischemic stroke (OR 1.95, 95% CI 1.25–3.07, $p = 0.003$) and lower likelihood of unexplained seizures (OR 0.56, 95% CI 0.35–0.91, $p = 0.018$) in Spanish-speaking patients persisted. Results for ethnicity were similar, with a higher percentage of ischemic stroke (23.3% vs 14.1%, $p = 0.001$) and lower percentage of unknown etiology (24.4% vs 31.1%, $p = 0.07$) in Hispanic compared with non-Hispanic participants. However, after adjusting for age, the relationships between Hispanic ethnicity and ischemic stroke and unknown etiologies were mitigated (OR 1.01, 95% CI 1.00–1.03, $p = 0.062$, and OR 0.99, 95% CI 0.98–1.00, $p = 0.109$).

Differences in Hemorrhagic Stroke Etiology Subtype Across Age

Among patients with hemorrhagic stroke as their seizure etiology, 47.3% had subdural hematoma (SDH), 28.3% had intraparenchymal hemorrhage (IPH), 23.6% had subarachnoid hemorrhage (SAH), and less than 1% had IV hemorrhage (Table 3). Patients with subdural hemorrhage as their seizure etiology had an older age at screening compared with those with other hemorrhage subtypes (mean 75.2 ± 8.91 years for SDH, 69.9 ± 8.98 years for SAH, and 71.6 ± 8.00 years for IPH; $p = 0.001$) (eTable 4, eFigure 1).

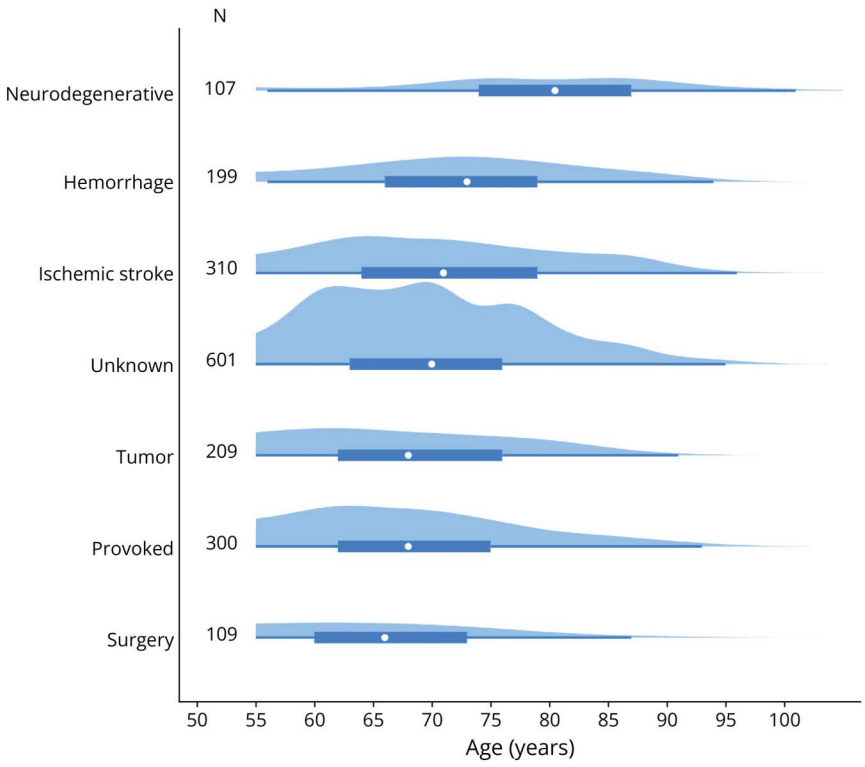
There were no sex differences in hemorrhagic subtype (eFigure 1B). SDH comprised 53% of hemorrhages in men but only 38% of the hemorrhages in women, although this difference was not statistically significant ($p = 0.196$). Only the Black and White racial groups had sufficient hemorrhagic

Figure 2 Distribution of 7 Most Common Seizure Etiologies by Age Group



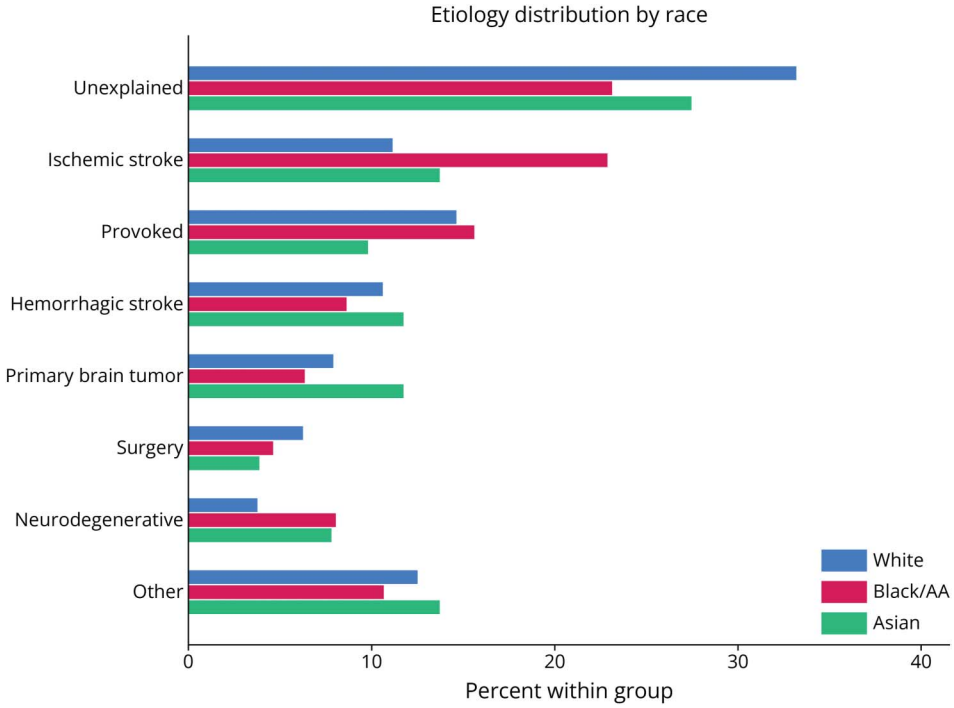
The percent of cases refers to the percent of new-onset seizures attributed to a given etiology within each age group.

Figure 3 Age Distribution of 7 Most Common Seizure Etiologies in Adults Older Than Age 55 Years



Violin plots show the distribution of ages at seizure onset, for all patients whose seizures were attributed to a given seizure etiology. Plots are ordered (from bottom to top) by increasing median age of seizure onset for each etiology. The number of cases is provided next to each etiology. The area under the curve for each violin plot is scaled in proportion to the total number of cases for each etiology. In the violin plot, the boxes with central dot represent the 25th, 50th, and 75th percentiles.

Figure 4 Distribution of 7 Most Common Seizure Etiologies Within the 3 Largest Racial Groups



"Other" refers to other identified etiology.

Table 3 Demographics of Hemorrhage Subtypes

		Subdural	Subarachnoid	Intraparenchymal	Intraventricular	*p* Value
N (%)	237	112 (47.3)	56 (23.6)	67 (28.3)	2 (0.8)	
Sex (%)						
Male		80 (71.4)	32 (57.1)	39 (59.1)	1 (50.0)	0.2
Female		32 (28.6)	24 (42.9)	27 (40.9)	1 (50.0)	
Race (%)						
Asian		5 (4.5)	2 (3.6)	1 (1.5)	0 (0.0)	0.47
Black/AA		13 (11.6)	10 (17.9)	13 (19.4)	1 (50.0)	
NHOPI		1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	
White		75 (67.0)	42 (75.0)	46 (68.7)	1 (50.0)	
Unknown/NR		18 (16.1)	2 (3.6)	7 (10.4)	0 (0.0)	
Age, mean (SD)		75.2 (8.8)	69.9 (8.8)	71.6 (8.0)	73.5 (21.9)	0.001

Abbreviations: AA = African American; AIAN = American Indian or Alaska Native; NHOPI = Native Hawaiian/Other Pacific Islander; NR = not reported.

stroke etiology cases (fewer than 10) to allow comparison (eTable 4). Although the proportions of hemorrhage subtypes varied between racial groups (SDH comprised 46% in White vs 36% in Black, and IPH comprised 36% in Black vs 28% in White; eFigure 1C), these differences were not significant.

Demographic Differences in Patients With Unknown Seizure Etiology

Compared with those with a known seizure etiology, patients with unknown etiology were overall more likely to be White and less likely to be Black (33% of White persons, 23% of Black persons, $p = 0.004$), and more likely to be English speaking than non–English speaking (31% of English speakers, 23% of non-English speakers, $p = 0.014$). However, there was no difference in sex (52% men, 48% women, $p = 0.768$), and the mean age was similar between those with unexplained seizures and those with all other causes (Table 2).

Discussion

In this large, multicenter study of new-onset seizure(s) in older adults, we found that seizures were most commonly of unknown causes (29.9%), followed by ischemic stroke (15.4%) and provoked seizures (14.9%). This study fills a gap in the literature because recent studies examining both provoked and unprovoked first seizures in older adults are lacking. By examining patients across geographically, linguistically, and racially diverse academic centers, we identified important demographic variations in seizure etiology: neurodegenerative disease increased markedly with advancing age (from 2.4% in ages 55–59 years to 18.5% in ages older than 85 years); men had higher rates of cerebrovascular and traumatic causes while women had more neurodegenerative etiologies; and Black patients showed higher proportions of ischemic stroke and neurodegenerative disease compared with White patients.

Our findings are consistent with earlier work on the incidence of late-onset epilepsy in the United States in the late 20th century, which reported that "idiopathic" or unknown cause was also the most common epilepsy etiology (accounting for approximately 50% of cases), followed by cerebrovascular etiology (accounting for approximately 30% of cases).[4] However, we found lower proportions of both of these etiologies in our cohort, perhaps reflecting differences between seizure and epilepsy etiology and/or improvements in diagnosis and/or treatment of seizures and associated conditions. It is notable that, despite many changes in diagnostic techniques, including the advent of MRI and other advanced imaging techniques, almost one-third of new seizures in older adults remain unexplained.

Our study also shows that among possibly preventable causes of seizures, cerebrovascular disease—including ischemic and hemorrhagic strokes—are major contributors to new seizures, accounting for 15.4% and 9.9% of cases, respectively. As the population ages and the numbers of older adults with epilepsy continue to grow,[7] prevention of cerebrovascular disease should continue to remain a focus for the primary prevention of epilepsy in older adults.[8] Among those with hemorrhagic etiology of seizure, we found that subdural hemorrhages accounted for an increasing proportion of seizures with advancing age, reinforcing the importance of preventing falls and head injuries in older adults. Neurodegenerative disease accounted for 5.3% of cases, and there is increasing evidence that amyloid and tau, proteins related to neurodegeneration that accumulate with age, are proepileptogenic.[9,10] In this cohort, other commonly identified seizure causes included primary CNS tumors (7.4%) and brain metastases (3%). As

treatments, and hopefully prevention, of cancer and neurodegenerative disease continue to improve, there may be additional opportunities for the prevention of epilepsy in these groups.

Notably, we found that the third most common cause of seizure in older adults was "provoked" (14.9%). Some of these provoked seizures are likely to be due to substance use including alcohol. Substance use among older adults is difficult to identify and is believed to be increasing.[11] Comprehensive treatment of substance use disorder in older adults may decrease seizures in this age group. In addition, a significant proportion of these "provoked" seizures may be iatrogenic. Older adults are known to be more sensitive to medication adverse effects,[12] which may include seizures. Moreover, metabolic derangements such as hyponatremia and hypoglycemia may be more common in this population and may also result from medication side effects.[13] Future work to understand the causes of provoked seizures in older adults and whether interventions to improve prescribing may reduce iatrogenic seizures is needed.

Understanding how seizure etiology varies across groups is important both for planning health care delivery systems and for identifying populations where preventive strategies may be most effective. Accordingly, we examined differences by sociodemographic groups and found differences in the identified cause of seizures by age, sex, race, and language spoken. Gender differences have previously been noted in risk of cerebrovascular disease[14] and traumatic brain injury,[15] and these were also present in our cohort. We found that ischemic stroke, hemorrhagic stroke, and traumatic brain injury were all more common in men than in women. Our finding that stroke accounts for the etiology of new-onset seizures in a greater proportion of men compared with women was unexpected because women have a higher lifetime risk of stroke than men do.[14] This finding may be due to the higher risk of stroke death in women, such that more men survive their stroke and are, therefore, able to go on to develop seizures. Alternatively, there may also be biological sex differences in poststroke epileptogenesis.[16]

Our cohort was mostly male (52.3%), which is consistent with previous studies showing a higher incidence of epilepsy in older men compared with older women.[4] However, despite the larger proportion of men in this cohort, there were more women with seizures due to neurodegenerative disease (and older age at time of first seizure in women). This finding is consistent with work showing higher incidence of dementia in women.[17] Of interest, there was no difference in the proportion of unknown etiology by sex (29.0% in men and 29.6% in women).

We also found differences in seizure etiology by race. In Black patients, cerebrovascular disease (specifically, ischemic stroke) and neurodegenerative disease accounted for a higher proportion of seizure etiologies compared with that in White patients. These findings are consistent with studies showing that Black patients have a disproportionately higher burden of vascular risk factors, an almost two-fold higher risk of first stroke,[18] and a higher incidence of neurodegenerative disease[19] compared with White patients. These findings of differences by race, ethnicity, and language spoken are not biologically based[20] and are presumed to reflect differences in exposure to social determinants of health, including access to care over the individual's lifetime, and may present high-yield avenues for epilepsy prevention.

Late-onset epilepsy is often considered a distinct clinical entity compared with epilepsy that presents earlier in life, and there has been considerable debate regarding what age is the appropriate cutoff to use for this clinical group.[21] Our findings in late-onset seizures strongly caution against considering late-onset seizures or epilepsy as a single clinical entity. Instead, our study reveals substantial heterogeneity among patients with late-onset seizures, with diverse underlying etiologies that vary significantly across age, sex, and race. Recognizing and accounting for this variability will be essential for advancing our understanding of seizures in older adults and for developing more precise diagnostic, therapeutic, and preventive strategies in this population.

The strengths of this study include collection of data from 7 large US medical centers that are geographically distributed with diverse multistate catchments to examine the etiology of new seizures in older adults. Moreover, we studied a large sample of older adults (N = 2,052), each of whom had access to a thorough evaluation as to the cause of their epilepsy from a tertiary academic center with specialized epilepsy care. This study has several limitations. First, the data were extracted from electronic medical records (EMRs) and, therefore, may be subject to misclassification, and not all patients had the same clinically available data (e.g., patients without MRI), although we used a standardized case definition with trained abstractors. Second, because this is based on EMR documentation, sex and race are self-reported but at an unknown time before data extraction and so may not reflect their current self-report. In addition, age was recorded at the time of data abstraction, which could vary by up to 3 years from the time of first seizure. Third, although our study cohort was derived from large health care systems with diverse multistate catchments, this sample was not designed to be generalizable to the entire US population. Persons with better access to care and those who had preexisting neurologic care are also more likely to be represented, which may have artificially reduced the proportion of unexplained seizures. Similarly, the study design focused on screening epilepsy and first seizure clinics and, therefore, may not represent patients who have had a first seizure but do not see a specialist. In addition, because this study focused on the underlying etiology of seizures, immediate poststroke (or post-traumatic) seizures were classified as seizures due to ischemic stroke (or head injury), rather than as acute symptomatic seizures. Because we studied patients after a first seizure, some patients may not go on to develop

recurrent seizures, particularly those with provoked seizures or acute symptomatic seizures. Therefore, this study is a description of the etiologies and demographics in late-onset seizures rather than specifically late-onset epilepsy. Finally, subtle imaging findings including global cortical atrophy and hippocampal sclerosis were treated as nonspecific but may represent unrecognized stages of specific pathology such as early neurodegeneration and traumatic brain injury.

New-onset seizures in older adults are expected to be increasingly common as the population ages and the incidence rate of epilepsy in older adults rises independently.[3,4] Cerebrovascular diseases, including ischemic and hemorrhagic stroke, CNS tumors, and neurodegenerative disease, remain common causes of new seizures in older adults. Approximately 15% of new seizures in older adults are provoked, suggesting room for improvement in medication prescribing and management of comorbid disorders in older adults. Despite improvements in diagnostic technologies and improvement in the treatment of disorders that predispose to seizures, 30% of seizures cases in older adults remain unexplained. Finally, our finding that seizure etiologies among older adults vary significantly across age, sex, and race highlights that epilepsy in older adults is a highly heterogeneous entity, underscoring the need for more nuanced research approaches that capture this complexity to advance understanding and epilepsy care in this population.

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Author Contributions

L.J. Blank: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. E.L. Johnson: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. K.R. Pellerin: major role in the acquisition of data. R.A. Sarkis: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. T.E. Gaston: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M.M. Shafi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. R. Zepeda: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. M. Camitan: major role in the acquisition of data. T. Anderson: major role in the acquisition of data. A. Hankerson: major role in the acquisition of data. A. Jan: major role in the acquisition of data. K. Jung: major role in the acquisition of data. M. Leake: major role in the acquisition of data. M.B. Westover: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. A.D. Lam: 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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