Mortality in Patients With Late-Onset Epilepsy

Results From the Atherosclerosis Risk in Communities Study

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Abstract

Background and Objectives
To determine the risk of mortality and causes of death in persons with late-onset epilepsy (LOE) compared to those without epilepsy in a community-based sample, adjusting for demographics and comorbid conditions.

Methods
This is an analysis of the prospective Atherosclerosis Risk in Communities study, initiated in 1987–1989 among 15,792 mostly Black and White men and women in 4 US communities. We used Centers for Medicare & Medicaid Services fee-for-service claims codes to identify cases of incident epilepsy starting at or after age 67. We used Cox proportional hazards analysis to identify the hazard of mortality associated with LOE and to adjust for demographics and vascular risk factors. We used death certificate data to identify dates and causes of death.

Results
Analyses included 9,090 participants, of whom 678 developed LOE during median 11.5 years of follow-up after age 67. Participants who developed LOE were at an increased hazard of mortality compared to those who did not, with adjusted hazard ratio 2.39 (95% confidence interval 2.12–2.71). We observed excess mortality due to stroke, dementia, neurologic conditions, and end-stage renal disease in participants with compared to without LOE. Only 4 deaths (1.1%) were directly attributed to seizure-related causes.

Conclusions
Persons who develop LOE are at increased risk of death compared to those without epilepsy, even after adjusting for comorbidities. The majority of this excess mortality is due to stroke and dementia.

Glossary

Late-onset epilepsy (LOE; i.e., starting at age 65 or older[1]) affects a large and growing number of persons worldwide. The yearly incidence of first seizure is higher in the elderly than at any other time of life,[2] at 175–250 per 100,000 people after age 80.[3-5]

Numerous population-based studies have shown that people with epilepsy (diagnosed at any age) have an increased mortality rate compared to those without epilepsy,[6,7] and are at an increased a risk of injuries associated with seizures, such as fractures, drownings, and motor vehicle accidents. People diagnosed with epilepsy are also at risk for sudden unexplained death in epilepsy.[6,8-10] The increased mortality rate observed in those with epilepsy is especially marked in persons under age 50,[6,11] and is up to 13 times higher in children.[7] Standardized mortality ratios of adults with epilepsy vary between 1.6 and 3.0[7] and are higher in those with drug-resistant epilepsy or frequent seizures.[12]

Whether mortality is also increased in persons with LOE, and what may be the causes of mortality in this population, remain unknown. Antecedent stroke and neurodegenerative diseases are common causes of LOE, yet persons with LOE also have an elevated risk of developing subsequent stroke[13] and dementia.[14,15] We previously demonstrated that the *APOE4* genotype and vascular risk factors are independent risk factors for LOE, even in the absence of prior stroke or dementia.[16,17] It is unknown whether any differences in mortality for people with vs without LOE are simply due to differences in these vascular comorbidities, which also increase mortality risk.

Using data from the Atherosclerosis Risk in Communities (ARIC) study cohort, we compared mortality rates among older adults with and without LOE. We hypothesized that the mortality rate would be higher among individuals with LOE as compared to those without LOE.

Methods

ARIC Study

The ARIC study was initiated with a baseline visit conducted in 1987–1989 among 15,792 mostly Black and White men and women, ages 45–65, selected through population sampling from 4 US communities (Jackson, Mississippi; Forsyth County, North Carolina; Washington County, Maryland; and suburbs of Minneapolis, Minnesota).[18] Study participants have been followed with 7 in-person visits through 2019 and contacted annually (and since 2012, semi-annually) with telephone calls. ARIC collects hospital discharge records on all participants and conducts surveillance of all death certificates. Participant data are also linked to Centers for Medicare & Medicaid Services (CMS) Medicare claims data.[19] Participants were selected using probability sampling (regardless of medical comorbidities) from community-dwelling adults age 45–64 in these urban and rural areas, and are thought to be representative of Black and White noninstitutionalized adults in these communities.[20,21]

Identification of LOE

To identify incident epilepsy, we used CMS Medicare fee-for-service (FFS) claims from 1991 to 2015 from inpatient, outpatient, and carrier files, linked to ARIC participant data. We defined epilepsy as 2 or more claims for epilepsy or seizure-related primary diagnostic codes (345.00–345.91, 780.39, G40.0–G40.919, and R56.9) on separate visits (1 outpatient and 1 inpatient, 2 separate inpatient, or 2 claims for separate outpatient visits from carrier and outpatient files). To identify incident epilepsy, we used only data from participants with at least 2 years of claims data prior to the first seizure-related code. Previous studies (validated using chart review) have shown that the use of ≥2 *ICD* codes has 94.4% sensitivity and 91.7% specificity for the identification of epilepsy.[22] This and similar claims-based definitions are commonly used in research on epilepsy in this population.[4,5]

Covariates

Demographic information was collected at the baseline visit in 1987–1989. We defined diabetes as nonfasting blood glucose ≥200 mg/dL, fasting blood glucose ≥126 mg/dL, use of diabetic medications or insulin, or self-report of diabetes diagnosed by a physician. Blood pressure was measured 3 times, and the second 2 measurements averaged and recorded; we defined hypertension as mean systolic pressure ≥140 mm Hg, mean diastolic pressure ≥90 mm Hg, or use of an antihypertensive medication. Body mass index (BMI) was calculated from weight and height at each visit. At visit 1, the number of *APOE4* alleles was measured (TaqMan assay; Applied Biosystems).[23] Self-reported smoking status and alcohol use was collected at each visit.

Participants self-reported prevalent strokes at visit 1. Incident strokes are identified in ARIC using surveillance hospital discharge records, which are adjudicated by computer algorithm and independent physician reviewers.[24]

Participants with dementia in ARIC were identified via cognitive testing conducted at visits 2 and 4, with adjudicated diagnoses from a more extensive cognitive battery at visits 5 and after; telephone interviews of the participant or an

informant; and surveillance of hospital discharge records and death certificate data.[25,26]

Outcome
Death certificate data are collected on all ARIC participants, and the causes of death recorded by *ICD-9* and *ICD-10* codes. Follow-up for this analysis consisted of all deaths occurring through December 31, 2018.

Causes of Death
We examined the causes of death by *ICD-9* and *ICD-10* classification and grouped those into the following categories: cancer, cardiovascular (excluding cerebrovascular accidents), cerebrovascular accident (ischemic and hemorrhagic), respiratory, dementia, neurologic (excluding dementia), endocrine, external and accidental causes, and other. *ICD* codes corresponding to each classification are included in Table 1.

Exclusions
Participants with noncontinuous FFS coverage and without at least 2 years of FFS coverage were excluded. Due to the definition used for LOE, we included only those with age at onset 67 or older to allow for the 2 years of seizure-free codes after reaching Medicare eligibility at age 65 to define LOE; those with epilepsy onset prior to age 67 were excluded. Those with less than 2 years of claims data prior to the first seizure code were also excluded, as they did not meet our definition of incident epilepsy. As is standard in ARIC, we included Black participants in Mississippi and North Carolina, and White participants in Minnesota, Maryland, and North Carolina, and excluded those of other races due to small numbers and those with missing covariates.

Statistical Analysis
We used STATA 15.0 for statistical analysis. We considered a 2-sided *p* value of 0.05 significant.

To estimate the hazard ratio (HR) for mortality in those with LOE compared to those without 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 CMS Medicare claims), and date of death as the event time. We adjusted for baseline (visit 1) age, a combined field center–race variable, sex, *APOE4* genotype, and education level. We adjusted for diabetes, hypertension, smoking history, BMI, and alcohol use collected at the last visit prior to the participant's 67th birthday (the origin for survival time analysis). To specifically examine deaths due to cardiovascular causes (due to the elevated rate of LOE in those with cardiovascular risk factors),[16] we used a competing risk model to take into account deaths due to other causes.[27] We checked the proportional hazards assumption using Schoenfeld residuals.

We used time-varying variables for LOE, stroke, and dementia (with 0 prior to the date of onset and 1 after).

We compared causes of death between those with and without LOE using χ^2 analyses, with Bonferroni correction for multiple comparisons.

Effects of Stroke and Dementia
Stroke is a common cause of seizures in older adults.[16,28] The risk of incident stroke is elevated in persons with LOE.[29,30] Similarly, preexisting dementia can be a cause of LOE[31,32] and dementia develops after LOE with an increased risk compared to that in persons without LOE.[14,15,33] Because of these strong associations and the increased mortality independently associated with stroke and with dementia, we considered these conditions both as confounders (when occurring prior to LOE) and as modifiers (when occurring after LOE). We stratified by stroke and dementia status and performed several analyses to examine these effects and adjusted for stroke and dementia in models when stroke or dementia preceded LOE.

Modification by Sex and Race
We examined potential effect measure modification by sex and race by including a sex-by-LOE term and a race-by-LOE term in the proportional hazards models to check for multiplicative interaction.

Table 1 *ICD-9* and *ICD-10* Codes for Categories of Cause of Death

	ICD-9	ICD-10
Cancer	140–239	C00–C99, D00–D49
Cardiovascular (excluding stroke)	390–459, excluding cerebrovascular codes	I00–99 excluding cerebrovascular codes
Respiratory	460–519	J00–J99
Dementia	294, 295, 290, 291, 331, 332	F01, F02, F03, G30
Cerebrovascular	430–438	I60–69
Endocrine	240–279	E00–E99
Other neurologic	320–389, excluding dementia codes	G00–99, excluding dementia codes
External and accidental	800–999	V00–99, U00–99, X00–99, Y00–99
Other	All others	All others

Standard Protocol Approvals, Registrations, and Patient Consents

Each participating institution's institutional review board approved the study. All participants provided written informed consent at each study visit. For those with dementia, diminished capacity, or impaired mental status, designated surrogates provided consent along with the participant's assent. The ARIC study is registered on clinicaltrials.gov (NCT00005131).

Data Availability

A public-use ARIC dataset is available through BioLINCC. Additional data are available to researchers who submit a manuscript proposal to the ARIC publications committee; due to participant consent and privacy, the full data are not publicly available. CMS Medicare claims data are governed by Data Use Agreement specific to the user (here: ARIC study) and cannot be shared.

Results

A total of 9,090 participants (55% female, 22% Black) had sufficient CMS data available without gaps in coverage or other exclusions and were included in the final analysis (Figure 1). Of those, 678 qualified as developing LOE during the time of follow-up, with an incidence of 29 per 1,000 person-years (similar to that observed in other studies[4,5,16]). Characteristics of participants are presented in Table 2.

Persons with LOE were at an increased risk of death over study follow-up time (Figure 2 and Table 3). By December 31, 2018, 54.0% of participants with LOE had died, compared to 34.9% of those without LOE ($p < 0.005$). The median survival time after the first seizure code in those with LOE was 4.79 years. The mortality rate in those with LOE was 49.76 (45.64–54.26) per 1,000 after age 67; the mortality rate in those without LOE was 33.68 (32.67–34.72) after age 67, with an incident rate ratio (IRR) of 1.48 (1.35–1.62) in those with LOE.

Mortality, Stroke, and Dementia

ARIC participants with LOE (and without stroke or dementia following LOE) had a mortality rate of 51.27 (45.85–57.34) per 1,000 after age 67, compared to a mortality rate of 33.68 (32.67–34.72) per 1,000 after age 67 in participants without LOE, with an IRR of 1.52 (1.35–1.71). This translated to an HR of 2.39 (2.12–2.71) for mortality in those with LOE, after adjusting for demographics, medical comorbidities, and prior stroke or dementia (Table 3). Prior stroke and prior dementia were also associated with increased mortality: HR for stroke 2.10 (1.92–2.30) and dementia 3.71 (3.39–4.06).

When we considered only ARIC participants with LOE who never had a diagnosis of stroke or dementia, those with LOE had an increased IRR of mortality at 1.57 (1.36–1.81) and adjusted HR of mortality of 3.11 (2.69–3.62).

When we examined all ARIC participants together, including those with stroke or dementia following LOE, those with LOE had an increased IRR of mortality at 1.48 (1.35–1.62) and adjusted HR for mortality of 1.72 (2.12–2.71; the proportional hazards assumption is violated for this group).

Figure 1 Inclusion and Exclusion of Study Participants
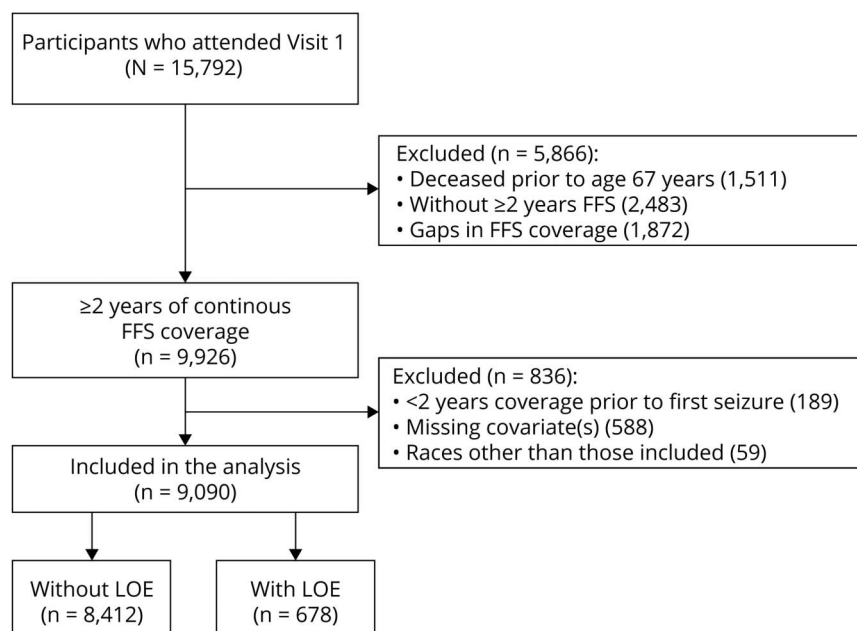
FFS = Centers for Medicare & Medicaid Services fee-for-service; LOE = late-onset epilepsy.

Table 2 Characteristics of Atherosclerosis Risk in Communities (ARIC) Participants With and Without Late-Onset Epilepsy (LOE)

Characteristics	No LOE (n = 8,412)		LOE (n = 678)		p Value
	N or mean	SD or %	N or mean	SD or %	
Visit 1 age	55.1	5.7	56.8	56.4	<0.001
Female	4,628	55.0	392	57.8	0.158
Black	1830	21.8	159	23.5	0.304
HS+ education	6,617	78.7	519	76.6	0.198
Hypertension	3,705	44.0	346	51.0	<0.001
Diabetes	1,230	14.6	145	21.4	<0.001
BMI	28.5	5.5	28.8	5.6	0.116
Smoking status					0.350
Never	3,329	39.6	274	40.4	
Former	3,544	42.1	295	43.5	
Current	1,439	18.3	109	16.1	
Alcohol use					0.327
Never	1814	21.6	159	23.5	
Former	2,139	25.4	179	26.4	
Current	4,459	53.0	340	50.2	
APOE4					0.028
1 allele	2,320	27.6	205	30.2	
2 alleles	202	2.4	25	3.7	
Ever diagnosed with					
Stroke	803	9.6	166	24.5	<0.001
Dementia	1,397	16.6	285	42.0	<0.001

Abbreviations: BMI = body mass index; HS = high school.
Characteristics are taken from the last ARIC visit prior to age 67, except age, which is visit 1.

In those participants with both stroke and dementia, there was no difference in mortality between those with and without LOE (IRR 1.09, 0.81–1.45).

When participants with stroke or dementia (who have known increased risks of mortality) that followed a diagnosis of LOE were excluded, the proportional hazards assumption was met ($p = 0.77$). The proportional hazards assumption was also met when those who ever had stroke or dementia were excluded ($p = 0.31$), but violated when those who had incident stroke or dementia following LOE were included ($p < 0.01$), as these comorbidities increase the risk of mortality.

Neither race nor sex modified the observed association of LOE with mortality (p interaction 0.221 for sex, $p = 0.079$ for race).

Causes of Death

Participants with LOE had proportionally more deaths due to stroke and dementia than did participants without LOE (Table 4). The leading cause of death in participants without LOE was cancer; the leading cause of death in participants with LOE was cardiovascular.

After Bonferroni correction for multiple comparisons, those with LOE had a higher proportion of death than those without LOE for stroke, dementia, "other neurologic," and "other" causes. The most common diagnosis for primary cause of death in those with LOE and other neurologic diseases was Parkinson disease. The most common diagnosis for primary cause of death in those with LOE in the other category was end-stage renal disease.

Among participants with LOE, there were 2 deaths in which the primary cause was epilepsy (0.5% of deaths in persons with LOE) and 2 deaths in which the primary cause was status epilepticus (0.5% of deaths in persons with LOE).

Figure 2 Survival of Participants With and Without Late-Onset Epilepsy (LOE)

Number at risk:

—	8,412	6,184	1,521
—	678	518	146
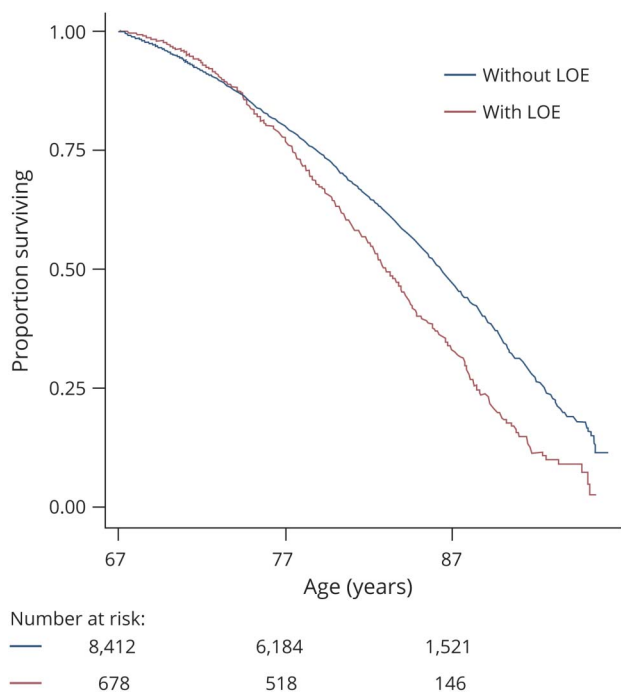
Kaplan-Meier survival estimates of participants with and without LOE. Origin for survival is age 67, the earliest age at which participants were eligible for a diagnosis of LOE using Centers for Medicare & Medicaid Services codes.

comparator group of those who never had stroke, dementia, or LOE, and had relatively longer survival.

Our findings are similar to previous studies showing that persons with epilepsy (diagnosed at any age) are at an elevated risk of mortality compared to persons without epilepsy.[6,7,12] However, the causes of death in persons with LOE, compared to those with epilepsy at younger ages, appear to be different. Studies estimating the risk of mortality due to external causes such as drowning, vehicle accidents, falls, and other causes demonstrate increased mortality risks of 1.8–13.8 times higher in those with epilepsy compared to those without epilepsy.[6,8] In studies of persons with severe epilepsy (e.g., those with frequent seizures, refractory to medication), seizure-related deaths account for up to 40% of mortality.[12] In a cohort study of 558 persons with epilepsy (with median age at diagnosis 24 years [interquartile range 14–56]), external causes such as drowning accounted for 4.2% of deaths, while seizure-related deaths occurred among 3.2% of persons.[34] Another cohort study of persons diagnosed with convulsive epilepsy at any age found that accident and injury-related deaths accounted for half of the observed deaths.[10] In a population-based study examining US mortality data, 6% of deaths in persons with epilepsy were seizure/epilepsy-related, while the relative risk of fatal vehicle accidents for people with seizures was 2.3–4.6 times higher than for people with other chronic medical conditions.[8] In contrast, our study (which

Cardiovascular Mortality

Persons with LOE have increased cardiovascular risk factors such as hypertension and diabetes.[16] When we restricted analysis to nonstroke cardiovascular mortality (using a competing-risk model to account for noncardiovascular deaths), the unadjusted HR for mortality in those with LOE compared to those without LOE was 1.42 (95% confidence interval 0.53–3.83) and the HR adjusted for demographics and comorbidities was 0.78 (0.18–3.33). Thus, the risk of mortality from cardiovascular causes did not differ significantly between those with and without LOE.

Discussion

In this longitudinal cohort study, we found that adults with LOE were more than twice as likely to die compared to those without LOE, with an adjusted HR for mortality of 2.39 (2.12–2.71). Excess deaths were observed due to stroke or dementia, conditions which are highly comorbid with seizures. Participants with LOE were not at a significantly elevated risk of death due to cardiac causes.

When only participants who never had a diagnosis of stroke or dementia were considered, those with LOE had an increased HR of mortality (3.11) that was higher than when all participants were considered (1.72). This initially seems counterintuitive, but is likely explained by the relatively healthier

Table 3 Adjusted Hazard Ratios (HRs) and Incidence Rate Ratios (IRRs) for Mortality Associated With Late-Onset Epilepsy (LOE)

	HR	95% CI	p Value	IRR	95% CI
Participants without any diagnosis of stroke or dementia					
LOE	3.11	2.69–3.62	<0.001	1.57	1.36–1.81
Participants without stroke or dementia following LOE					
LOE	2.39	2.12–2.71	<0.001	1.52	1.35–1.71
Stroke (prior to LOE)	2.10	1.92–2.30	<0.001		
Dementia (prior to LOE)	3.71	3.39–4.06	<0.001		
All participants[a]					
LOE	1.72	1.55–1.90	<0.001	1.48	1.35–1.62
Stroke (at any time)	2.05	1.89–2.24	<0.001		
Dementia (at any time)	3.66	3.36–3.99	<0.001		
Participants with stroke and dementia					
LOE	1.16	0.85–1.59	0.341	1.09	0.81–1.45

Abbreviation: CI = confidence interval.
Adjusted for baseline age, sex, race, field center, education level, diabetes, hypertension, body mass index, smoking history, alcohol use, and *APOE4* genotype. Models including stroke and dementia adjust for those diagnoses (as time-varying variables).
[a] Proportional hazards assumption not met due to increased risk of stroke, dementia following LOE.

Table 4 Causes of Death in Atherosclerosis Risk in Communities (ARIC) Participants With and Without Late-Onset Epilepsy (LOE) December 31, 2018

	Without LOE	%	With LOE	%	All	%
N	8,412		678		9,090	
Total deceased[a]	2,935	34.9	366	54.0	3,301	36.3
Cancer	981	33.4	72	19.7	1,053	31.9
Cardiovascular (excluding stroke)	742	25.3	76	20.8	818	24.8
Respiratory	281	9.6	32	8.7	313	9.5
Dementia[a]	260	8.9	58	15.8	318	9.6
Cerebrovascular[a]	126	4.3	34	9.3	160	4.8
Endocrine	115	3.9	17	4.6	132	4.0
Other neurologic[a]	88	3.0	25	6.8	113	3.4
External and accidental	85	2.9	9	2.5	94	2.8
Other[a]	257	8.8	43	11.7	300	9.1

For each cause of death, % shows % of total deceased.
[a] p Value < 0.005 (level of significance after Bonferroni correction for multiple comparisons).

consists of older participants than the preceding studies) found persons with LOE had no elevated risk of death from external and accidental causes (2.4% of deaths in persons with LOE). Moreover, only 1.1% of deaths in persons with LOE were related to epilepsy or status epilepticus, which may reflect the lower rate of tonic-clonic seizures in the older population[35] and relatively pharmacoresponsive nature of seizures reported in LOE.[36] While an elevated risk of cardiac disease has been observed in persons with epilepsy compared to those without (mostly in those with a history of stroke as the cause of their epilepsy),[37] we did not observe such a relationship after adjusting for underlying vascular comorbidities.

The majority (56%) of the excess mortality that we observed in participants with LOE was due to stroke or dementia, 2 conditions that are known to be causes of LOE, as well as conditions that can develop after the onset of LOE.[13,14] The incidence of stroke is elevated in older adults with LOE, who have a 3-fold risk of stroke compared to peers without LOE.[29,38] In another study, 10% of those with LOE had a stroke within 5 years of LOE onset.[29] New diagnoses of dementia are also more common in persons with LOE, with a 2–3-fold increased risk compared to those without LOE (demonstrated in multiple cohorts including ARIC).[14,15] Mortality is known to be elevated after incident stroke, with mortality rates 2–3 times that of those without stroke, and with nearly 50% of stroke victims deceased by 5 years.[39] Dementia is also associated with increased mortality, with an up to 3-fold increase in mortality seen in persons with Alzheimer disease (and varying rates in different dementias). Survival after dementia diagnosis is estimated to be an average of approximately 3–4.5 years, with survival depending on age at diagnosis and particular type of dementia.[40-42] Taken together, stroke and dementia account for the majority of excess mortality in persons with LOE, though other neurologic (primarily Parkinson disease, which is known to have an increased risk of acquired epilepsy[43]) and other (primarily end-stage renal disease) deaths were also elevated in those with LOE compared to those without. Other possible causes of increased mortality include the effects of enzyme-inducing antiseizure medications, which are associated with elevated lipid levels in older patients with epilepsy.[44]

The strengths of this study include the large number of participants, community-based sampling, and multidecade follow-up time. A limitation is the reliance on CMS Medicare claims for the definition of LOE. This definition and similar definitions, however, are generally accepted and independently validated in other studies in this population,[4,5] with chart-validated sensitivity and specificity of >90%.[22] Claims data do not include information regarding the severity of participants' epilepsy such as seizure frequency, seizure type, or type or number of medications used, which have been associated with increased mortality[7] and stroke[30] among persons with epilepsy; therefore, we could not evaluate the effects of these factors on mortality. We also relied on death certificate *ICD* codes for the causes of death, which may be inaccurate in some cases. However, the possibility of misclassification of the cause of death was true for participants both with and without LOE, and the potential bias in outcome ascertainment would likely have been nondifferential by exposure. In addition, we are not able to differentiate between different types of dementia, which may have varying implications for mortality. The population studied was drawn from US Medicare participants; therefore, there may be limited generalizability to low- and middle-income countries.

Adults who develop LOE are at increased risk of mortality compared to those who do not, being over 2.5 times more likely to die during the 30 years of this study follow-up. The majority of this excess risk is attributable to stroke and dementia. These mortality risks suggest that clinicians should address modifiable vascular risk factors with lifestyle and medication changes as appropriate. Future studies with additional clinical data available regarding the type of epilepsy, seizure frequency, and medication treatment to determine the effects of these factors on mortality would be of great importance in this population.

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Study Funding

Disclosure

Publication History

Appendix Authors

Name	Location	Contribution
Emily L. Johnson, MD	Johns Hopkins School of Medicine, Baltimore, MD	Designed and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Gregory L. Krauss, MD	Johns Hopkins School of Medicine, Baltimore, MD	Revised the manuscript for intellectual content
Anna Kucharska-Newton, PhD, MPH	University of North Carolina at Chapel Hill; University of Kentucky, Lexington	Interpreted the data; revised the manuscript for intellectual content
Alice D. Lam, MD, PhD	Massachusetts General Hospital, Boston	Revised the manuscript for intellectual content

Appendix *(continued)*

Name	Location	Contribution
Rani A. Sarkis, MD, MSc	Brigham and Women's Hospital, Boston, MA	Revised the manuscript for intellectual content
Rebecca F. Gottesman, MD, PhD	Johns Hopkins School of Medicine, Baltimore, MD	Major role in acquisition of data; interpreted the data; revised the manuscript for intellectual content

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