Antiseizure medications and cardiovascular events in older people with epilepsy

Li, J.; Shlobin, N.A.; Thijs, R.D.; Sylvestre, M.P.; Josephson, C.B.; Deacon, C.; Keezer, M.R.

JAMA Neurology | Original Investigation

Antiseizure Medications and Cardiovascular Events in Older People With Epilepsy in the Canadian Longitudinal Study on Aging

Jimmy Li, MD; Nathan A. Shlobin, MD; Roland D. Thijs, MD, PhD; Marie-Pierre Sylvestre, PhD; Colin B. Josephson, MD; Charles Deacon, MD; Mark R. Keezer, MD, PhD

Supplemental content

IMPORTANCE How epilepsy may promote cardiovascular disease remains poorly understood.

OBJECTIVE To estimate the odds of new-onset cardiovascular events (CVEs) over 6 years in older people with vs without epilepsy, exploring how enzyme-inducing antiseizure medications (EIASMs) and traditional cardiovascular risk factors mediate these odds.

DESIGN, SETTING, AND PARTICIPANTS This was a prospective cohort study using the comprehensive cohort of the Canadian Longitudinal Study on Aging (CLSA), with 6 years of follow-up (2015-2021, analysis performed in December 2023). The CLSA is an ongoing, national study of 51 338 adults aged 45 to 85 years at baseline who are recruited in Canada. The comprehensive cohort includes 30 097 individuals living near 1 of 11 data collection centers. Participation in the CLSA was voluntary; participation rate was 45%. Among those in the comprehensive cohort, individuals reporting no previous history of CVEs (ie, stroke, transient ischemic attack [TIA], or myocardial infarction [MI]) at baseline were excluded. No other exclusion criteria were applied. A total of 86% of participants completed follow-up.

EXPOSURE Lifetime history of epilepsy.

MAIN OUTCOMES AND MEASURES The primary outcome was new-onset CVEs over 6 years. Secondary outcomes were new-onset strokes, TIAs, and MIs. Logistic models were fitted for these outcomes as a function of epilepsy, age, sex, household income, and education level. Mediation analyses were conducted for strong EIASM use, weak EIASM use, Framingham score, Physical Activity Scale for the Elderly (PASE) score, and waist to hip ratio.

RESULTS Among the 30 097 individuals in the comprehensive cohort, a total of 27 230 individuals (mean [SD] age, 62.3 [10.1] years; 14 268 female [52.4%]) were included, 431 with a lifetime history of epilepsy. New-onset CVEs were more likely in epilepsy, with an adjusted odds ratio of 2.20 (95% CI, 1.48-3.27). The proportion of the effect of epilepsy on new-onset CVEs was mediated as follows by each of the following variables: strong EIASM use, 24.6% (95% CI, 6.5%-54.6%), weak EIASM use, 4.0% (95% CI, 0.8%-11.0%), Framingham score, 1.4% (95% CI, −1.6% to 4.5%), PASE score, 3.3% (95% CI, 1.4%-6.8%), and waist to hip ratio, 1.6% (95% CI, 0.4%-3.7%).

CONCLUSIONS AND RELEVANCE Results of this cohort study reveal that epilepsy was associated with new-onset CVEs. Nearly one-third of this association can be explained by EIASMs. These findings should be considered when choosing an antiseizure medication for a person at risk for cardiovascular disease.

JAMA Neurol. 2024;81(11):1178-1186. doi:10.1001/jamaneurol.2024.3210
Published online September 30, 2024. Corrected on January 13, 2025.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Mark R. Keezer, MD, PhD, Centre de Recherche du Centre Hospitalier de l'Université de Montréal, 1000 Rue Saint-Denis, Montréal, QC H2X 0C1, Canada (mark.keezer@umontreal.ca).

Approximately 1 in 10 people will have at least 1 epileptic seizure in their lifetime.[1] Epilepsy often occurs in younger individuals, but the greater number of people with epilepsy (PWE), both new onset and long-standing, is among adults 60 years and older.[1] The prevalence of older PWE is expected to increase substantially as populations continue to age worldwide.[2,3] Epilepsy impacts individuals not only through seizures but also through its association with numerous comorbidities. This is particularly relevant in older adults who are already at risk for developing chronic diseases.[4]

There is a strong cross-sectional association between epilepsy and cardiovascular disease (CVD).[4] At least some of this association is due to shared risk factors given that stroke is a major cause of epilepsy.[5] Several studies have shown, however, that even among people whose epilepsy is not due to cerebrovascular disease, the risk of developing CVD is high.[6] The reasons underlying this risk are under investigation. In a large retrospective cohort study[7] using linked electronic health records, the use of enzyme-inducing antiseizure medications (EIASMs) was associated with incident CVD in PWE. Some authors have also suggested that the heart and coronary vasculature may be incrementally damaged by repeated seizures; this concept has been coined the *epileptic heart*.[8]

Further characterizing the cardiovascular risk seen in epilepsy as well as the mechanisms underlying this risk may help inform the screening and management of CVD in PWE. We aimed to determine the odds of new-onset cardiovascular events (CVEs) in people with vs without epilepsy over 6 years. We also aimed to investigate the mediation effects of EIASM use and traditional cardiovascular risk factors (CVRFs) on this association, thereby deciphering the relative contribution of each factor on CVD risk in epilepsy.

Key Points

Question Are older adults with epilepsy more likely to develop cardiovascular events (CVEs) than their counterparts without epilepsy, and how much of this results from enzyme-inducing antiseizure medication (EIASM) use?

Findings This cohort study included 27 230 individuals and, using the Canadian Longitudinal Study on Aging, found that adults with a lifetime history of epilepsy were approximately 2 times more likely to report new CVEs, including strokes, transient ischemic attacks, and myocardial infarctions, over 6 years. Almost one-third of this association may result from EIASM use.

Meaning Results suggest that clinicians should be careful when prescribing EIASMs to older adults with epilepsy, especially in the presence of other cardiovascular risk factors.

Methods

Data Source

Ethics approval was obtained from the CRCHUM Review Board (#2022-10274). This article follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[9]

The Canadian Longitudinal Study on Aging (CLSA) is an ongoing, national, prospective study of 51 338 adults aged 45 to 85 years at baseline and recruited in Canada. Participation was voluntary, and all participants provided written informed consent.[10] The exclusion criteria were as follows: resident of a long-term care facility, cognitive impairment, resident of a First Nations reserve, full-time member of the Canadian Armed Forces, and inability to communicate in English or French.[10] Participants self-identified with the following ethnicities as codified by CLSA investigators: Arab, South Asian, Southeast Asian, West Asian, Black, Chinese, Filipino, Japanese, Korean, Latin Amerian, White, or other. In this study, ethnicities from Chinese to Korean were all categorized within one level (Asian). Participants responding as other described belonging to ethnicities such as Caribbean, Native American, or multiple ethnicities. The CLSA is divided into the tracking cohort and the comprehensive cohort. The tracking cohort comprises approximately 20 000 individuals who complete self-report questionnaires through telephone interviews. The comprehensive cohort includes approximately 30 000 individuals who are evaluated in person at 1 of 11 data collection centers. Only people living within 25 to 50 km of one such urban center were eligible for the comprehensive cohort.[10] Currently, data from the baseline, the first follow-up at 3 years, and the second follow-up at 6 years are available (2015-2021). Study analyses focused on the comprehensive cohort, in which data from clinical/physical tests and biospecimens are collected in addition to self-report data.[10] In this study, we excluded all participants who reported at baseline having previously had a stroke, a transient ischemic attack (TIA), or a myocardial infarction (MI).

Variables

The primary outcome of this study was the self-reported occurrence of a CVE at the first or second follow-up. CVE was a composite outcome that included stroke, TIA, and MI. Secondary outcomes were the occurrence of each CVE component (ie, stroke, TIA, or MI). Exposure was a lifetime history of epilepsy at baseline, determined with a modified version of a previously validated diagnostic algorithm (sensitivity >97%, specificity >98%).[11] More information on this algorithm can be found in the eMethods in Supplement 1.

Other variables of interest, all measured at baseline, included sociodemographic variables (eg, age and sex), comorbidity/lifestyle variables (eg, history of diabetes and smoking status), medication variables (eg, use of EIASMs), clinical/physical test variables (eg, Physical Activity Scale for the Elderly [PASE] score and waist to hip ratio), and biospecimen variables (eg, high-density lipoprotein and total cholesterol). The PASE score reflects the intensity and duration of physical activity in older adults, with a higher score being attributed to a more active individual.[12] All sociodemographic, comorbidity/lifestyle, and medication variables were self-reported (for medication data, a list of active medications was consulted), whereas other variables were measured during a clinical examination. EIASMs were divided into 2 categories: strong EIASMs (ie, carbamazepine, phenytoin, phenobarbital, and primidone) and weak EIASMs (ie, oxcarbazepine, eslicarbazepine, topiramate, and rufinamide).[7,13] Using available data, the Framingham risk score (FRS) was calculated, which has been validated to predict MI and coronary death at 10 years.[14]

Statistical Analyses

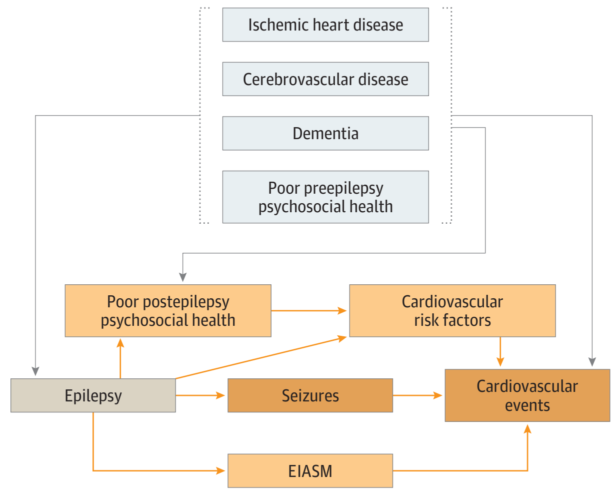
All statistical analyses were performed using R (R Project for Statistical Computing).[15] Significance level was set at 2-sided *P* value ≤.05. We performed descriptive analyses on the full study sample and stratified by epilepsy status. Binary/categorical data are presented as count (proportion), and continuous data are presented as mean (SD).

Missing data were handled using multiple imputations (200 iterations).[16] Technical details pertaining to this process are available in the eMethods in Supplement 1. Estimates from the subsequent regression models were pooled using Rubin rules.[17]

Logistic regression models were fitted for new-onset CVEs (as well as for each type of CVE) as a function of epilepsy, age, sex, household income, and education level. A directed acyclic graph (DAG), the simplified version of which is available in the **Figure** and the complete version of which is available in eFigure 1 in Supplement 1,[18] was used to determine the minimal set of variables to adjust for confounding. These variables were cerebrovascular disease, ischemic heart disease, dementia, and psychosocial health preepilepsy onset. We attempted to eliminate confounding due to cerebrovascular disease and ischemic heart disease by excluding people with a history of stroke, TIA, or MI at baseline. Little to no confounding due to dementia was expected, as cognitive impairment was an exclusion criterion for recruitment into the CLSA.[19] We adjusted for baseline household income and education level to account for confounding due to preepilepsy-onset psychosocial health. The regression formulas were weighted using analytic weights provided by the CLSA (eMethods in Supplement 1).

From the DAG (Figure and eFigure 1 in Supplement 1),[18] several mediators were identified, for which mediation analyses were performed using the mediation R package (R Project for Statistical Computing).[20,21] In sum, it is possible to decompose the effect of an exposure on an outcome into a natural direct effect (independent of the mediator) and a natural indirect effect (passing through the mediator). The natural direct effect captures the effect of an exposure on an outcome holding the mediator at the value it would naturally take in the absence of the exposure. The natural indirect effect captures the effect of an exposure on an outcome that operates through a mediator variable. This indirect effect can be obtained by multiplying the coefficients of 2 regression models, one regressing the mediator on the exposure and the other regressing the outcome on both the exposure and the mediator (ie, product of coefficients approach). The direct effect can then be calculated by subtracting the indirect effect from the total effect. The proportion mediated corresponds to the natural indirect effect divided by the total effect. The mediation R package uses a simulation-based approach (eg, Monte Carlo or bootstrapping) instead of a simple product of coefficients approach to measure these effects.[20,21] These 2 approaches do not change

Figure. Simplified Directed Acyclic Graph (DAG) Depicting the Hypothesized Causal Mechanisms Underlying the Association Between Epilepsy and Cardiovascular Events



A DAG is a powerful graphical tool that uses a priori knowledge on biological and behavioral pathways to guide research design and statistical analysis.[18] This DAG depicts the hypothesized causal relationships (arrows) between variables (rectangles) involved in the association between epilepsy and cardiovascular events. The 4 variables in blue-gray represent the minimal set of variables that must be adjusted to eliminate exposure-outcome, exposure-mediator, and mediator-outcome confounding. Cerebrovascular disease, ischemic heart disease, and dementia were operationalized by the following variables in the Canadian Longitudinal Study on Aging, respectively: history of stroke or transient ischemic attack, history of myocardial infarction, and history of dementia at baseline. Enzyme-inducing antiseizure medication (EIASM) and cardiovascular risk factors represent mediators of interest between epilepsy and cardiovascular events. As we do not have access to data on poor preepilepsy psychosocial health, we use poor postepilepsy psychosocial health as a proxy, the adjustment of which possibly causes some overadjustment bias because it is presumed to lie in the causal pathway between epilepsy and cardiovascular events. A more detailed version of this DAG is available in eFigure 1 in Supplement 1.

the interpretation of the natural effects. For these effects to be truly causal, the sequential ignorability assumption must hold true.[20] This assumption essentially requires that the exposure-mediator, mediator-outcome, and exposure-outcome associations are not confounded, and that there is no mediator-outcome confounder that is affected by the exposure. This assumption cannot be directly tested from observed data and is therefore nonrefutable. The proportion mediated (95% CI) was calculated for 5 mediators: strong EIASM use, weak EIASM use, FRS, PASE score, and waist to hip ratio. The PASE score and waist to hip ratio were chosen as measures of physical activity and obesity, respectively. Exposure-mediator interactions were tested for each outcome, and if such an interaction was statistically significant, we would perform additional mediation analyses where the direct effect, indirect effect, and proportion mediated were allowed to differ between levels of exposure. Mediation analysis was also conducted for a set of non-EIASMs (ie, levetiracetam, lamotrigine, lacosamide, and valproic acid) for control purposes. Mediation analysis was performed for all outcomes. More details on the methodology and assumptions used in the mediation analyses are available in the eMethods in Supplement 1.

Sensitivity analyses

Regression analyses were repeated for new-onset CVEs (and for each individual type of CVE) using complete cases only rather than imputed data.

Performing multiple imputations requires that the missing data are at least missing at random (MAR). If data are missing not at random (MNAR), multiple imputations may generate biased results.[17] Tipping point analyses were performed to determine if new-onset CVEs were MNAR.[22] In other words, we calculated how much the odds ratios (ORs) would change if imputed datasets were used in which the outcomes were more/less likely to occur in people who were lost to follow-up vs those who were not lost to follow-up. Details on these analyses are provided in the eMethods in Supplement 1.

For each exposure-outcome OR calculated in the regression analyses, an E-value was calculated.[23] An E-value represents the minimum strength of association that would be required by an unmeasured confounder to render an exposure-outcome association insignificant.[24]

Results

Of 30 097 participants in the CLSA's comprehensive cohort, 2867 were excluded for having a history of CVEs at baseline. In total, 27 230 individuals (mean [SD] age, 62.3 [10.1] years; 14 268 female [52.4%]; 12 962 male [47.6%]) were included, 431 with a lifetime history of epilepsy. Participants self-identified with the following ethnicities: 97 Arab (0.4%), 658 Asian (2.4%), 237 Black (0.9%), 117 Latin American (0.4%), 25 664 White (94.4%), and 426 other (1.6%).

Descriptive Analyses

Table 1 provides a general description of the study sample. New-onset CVEs were more likely in epilepsy and occurred over 6 years in 1260 individuals (5.5%), including 43 PWE (11.9%) and 1217 people (5.4%) without epilepsy. In total, 3793 people (13.9%) did not complete all 6 years of follow-up (these people had their outcomes imputed). Of note, 49 people (0.18%) without a lifetime history of epilepsy took strong EIASMS, and 63 people (0.24%) without a lifetime history of epilepsy took weak EIASMs. The explanation for this may be 2-fold: most EIASMs have indications outside of epilepsy (eg, primidone for essential tremor), and the algorithm used to identify people with a lifetime history of epilepsy may not have been perfectly accurate. The exact distribution of different types of ASMs among people with vs without a lifetime history of epilepsy is provided in eTable 1 in Supplement 1.

Multiple Imputations and Multivariable Analyses

Standard diagnostic plots for multiple imputations are provided in eFigures 2 to 5 in Supplement 1, showing no obvious assumption violations.

Table 2 depicts the results of the multivariable analyses using imputed data.[23,24] Over 6 years, the odds of new-onset CVEs, TIAs, and MIs were significantly higher in people with vs without epilepsy (OR for any CVE, 2.20; 95% CI, 1.48-3.27) when adjusting for age, sex, household income, and education level. eTable 2 in Supplement 1 presents the results of the multivariable analyses using complete cases only. Results were similar, although epilepsy did not reach statistical significance in the TIA and MI models. eTable 3 and eFigure 6 in Supplement 1 confirm that logistic regression assumptions were met for the models.

Mediation Analyses

Table 3 presents the results of the mediation analyses presuming no exposure-mediator interactions (eTable 4 in Supplement 1). The proportion of the effect of epilepsy on new-onset CVEs mediated by strong EIASM use was 24.6% (95% CI, 6.5%-54.6%) when adjusting for age, sex, household income, and education level. Weak EIASM use, the PASE score, and waist to hip ratio were significant mediators, with proportion-mediated point estimates as follows: weak EIASM, 4.0% (95% CI, 0.8%-11.0%); PASE score, 3.3% (95% CI, 1.4%-6.8%); and waist to hip ratio, 1.6% (95% CI, 0.4%-3.7%). The FRS (1.4%; 95% CI, −1.6% to 4.5%) and non-EIASM (0.2; 95% CI, −8.3 to 12.6) use did not show significant mediation effects.

eTable 5 in Supplement 1 shows the results of significance tests for exposure-mediator interactions. No significant interactions were found. Therefore, the mediation analyses were not repeated with exposure-mediator interaction terms.

Sensitivity Analyses

eFigures 7 to 10 in Supplement 1 detail the tipping point analyses performed for new-onset CVEs, strokes, TIAs, and MIs, respectively. As the log-odds of a CVE occurring more often in people with missing data increased up to 5, the exposure-outcome OR decreased but remained statistically significant. Because log-odds of 5 equate to an OR of approximately 150, we consider the multiple imputations to have been robust to MNAR CVE data. The models for strokes, TIAs, and MIs were generally less robust against departures from a MAR mechanism.

Table 2 presents the E-values for each regression model.[23,24] An unmeasured confounder would have had to generate an OR of 2.32 or greater to render the association between epilepsy and new-onset CVEs not statistically significant.

Discussion

In this prospective cohort study, we measured the association between a lifetime history of epilepsy at baseline and new-onset CVEs over 6 years. We investigated the mediation effects of EIASM use and CVRF on this association. Results reveal that epilepsy was associated with new-onset CVEs in older adults and that almost one-third of this association can be explained by EIASM use.

Conceptually, epilepsy and CVD share risk factors, at least in older adults. Because epilepsy may be caused by stroke and stroke may result from an underlying CVD, it is unsurprising that PWE may experience more CVD.[5] New-onset CVEs may

Table 1. Cohort Characteristics, All Participants, as Well as Lifetime History of Epilepsy vs No Lifetime History of Epilepsy

Variable	All participants (n = 27 230)		History of epilepsy[a] Lifetime (n = 431)		No lifetime (n = 26 797)	
	No. (%)	Miss	No. (%)	Miss	No. (%)	Miss
Age, mean (SD), y	62.25 (10.07)	0	61.22 (9.41)	0	62.27 (10.08)	0
Sex						
Female	14 268 (52.40)	0	235 (54.52)	0	14 032 (52.36)	0
Male	12 962 (47.60)		196 (45.48)		12 765 (47.64)	
Province						
AB	2679 (9.84)	0	45 (10.44)	0	2634 (9.83)	0
BC	5688 (20.89)		99 (22.97)		5588 (20.85)	
MB	2812 (10.33)		40 (9.28)		2772 (10.34)	
NL	1993 (7.32)		29 (6.73)		1964 (7.33)	
NS	2774 (10.19)		39 (9.05)		2734 (10.20)	
ON	5774 (21.20)		97 (22.51)		5677 (21.19)	
QC	5510 (20.24)		82 (19.03)		5428 (20.26)	
Household income, $						
<20 000	1306 (5.12)	1711	50 (12.41)	28	1256 (5.00)	1683
20 000-50 000	5527 (21.66)		102 (25.31)		5424 (21.60)	
50 000-100 000	8976 (35.17)		126 (31.27)		8849 (35.24)	
100 000-150 000	5159 (20.22)		70 (17.37)		5089 (20.26)	
>150 000	4551 (17.83)		55 (13.65)		4496 (17.90)	
Ethnicity[b]						
Arab	97 (0.36)	31	0 (0)	0	97 (0.36)	31
Asian	658 (2.42)		7 (1.62)		651 (2.43)	
Black	237 (0.87)		5 (1.16)		232 (0.87)	
Latin American	117 (0.43)		1 (0.23)		116 (0.43)	
White	25 664 (94.36)		410 (95.13)		25 252 (94.34)	
Other[c]	426 (1.57)		8 (1.86)		418 (1.56)	
Level of education						
No PS education	1976 (8.47)	3899	36 (10.29)	81	1940 (8.44)	3817
PS but no university	7645 (32.77)		134 (38.29)		7510 (32.68)	
Undergraduate	7723 (33.10)		94 (26.86)		7629 (33.20)	
Postgraduate	5987 (25.66)		86 (24.57)		5901 (25.68)	
Single unmarried (vs not single)	8363 (30.67)	8	151 (35.03)	0	8211 (30.65)	8
Strong EIASM use (vs none)	149 (0.55)	0	100 (23.20)	0	49 (0.18)	0
Weak EIASM use (vs none)	71 (0.26)	0	8 (1.86)	0	63 (0.24)	0
Warfarin use (vs none)	437 (1.60)	0	9 (2.09)	0	428 (1.60)	0
Framingham score, mean (SD)	12.23 (4.66)	3099	12.26 (4.47)	58	12.22 (4.66)	3041
PASE score, mean (SD)	143.29 (73.99)	1390	136.60 (73.67)	20	143.39 (73.99)	1370
Waist to hip ratio, mean (SD)	0.900 (0.097)	199	0.904 (0.095)	5	0.900 (0.097)	194
New-onset CVEs (vs none)	1260 (5.52)	4419	43 (11.91)	70	1217 (5.42)	4347
New-onset strokes (vs none)	287 (1.26)	4424	14 (3.88)	70	273 (1.22)	4352
New-onset TIAs (vs none)	539 (2.37)	4461	19 (5.26)	70	520 (2.32)	4389
New-onset MIs (vs none)	569 (2.49)	4409	16 (4.44)	71	553 (2.46)	4336
Death (vs alive at follow-up)	1343 (4.93)	0	24 (5.57)	0	1318 (4.92)	0
Lost to follow-up (vs not)	3793 (13.93)	0	62 (14.39)	0	3730 (13.92)	0

Abbreviations: AB, Alberta; BC, British-Columbia; CLSA, Canadian Longitudinal Study on Aging; CVE, cardiovascular event; EIASM, enzyme-inducing antiseizure medication; MB, Manitoba; MI, myocardial infarction; miss, missing data; NL, Newfoundland and Labrador; NS, Nova Scotia; ON, Ontario; PASE, Physical Activity Scale for the Elderly; PS, postsecondary; QC, Quebec; TIA, transient ischemic attack.

[a] Some people without a lifetime history of epilepsy took EIASMs. The explanation for this may be 2-fold: most EIASMs have indications outside of epilepsy (eg, primidone for essential tremor), and the algorithm used to identify people with a lifetime history of epilepsy may not have been perfectly accurate. The exact distribution of different types of ASMs among people with vs without a lifetime history of epilepsy is provided in eTable 1 in Supplement 1. Details on the algorithm used to identify people with a lifetime history of epilepsy are provided in the eMethods in Supplement 1. Only 4 people taking strong EIASMs and 3 people taking weak EIASMs took warfarin.

[b] The levels of categorization for ethnicity were adapted from the initial codification used by CLSA investigators.

[c] Other ethnicity includes, eg, Caribbean, Native American, and multiple ethnicities.

Table 2. Multivariable Analyses With E-Values, New-Onset Cardiovascular Events (CVEs), Strokes, Transient Ischemic Attacks (TIAs), and Myocardial Infarctions (MIs) Over 6 Years, Lifetime History of Epilepsy vs No Lifetime History of Epilepsy, After Multiple Imputation[a]

	New-onset, OR (95% CI)			
Variable	CVEs	Strokes	TIAs	MIs
Lifetime history of epilepsy (vs none)	2.20 (1.48-3.27)	1.76 (0.96-3.23)	2.11 (1.07-4.15)	1.85 (1.04-3.27)
Age	1.07 (1.06-1.08)	1.08 (1.06-1.11)	1.08 (1.07-1.09)	1.06 (1.03-1.08)
Female sex (vs male)	0.51 (0.45-0.58)	0.61 (0.44-0.83)	0.67 (0.50-0.88)	0.32 (0.25-0.40)
Household income, $				
<20 000	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
20 000-50 000	0.54 (0.43-0.69)	0.83 (0.52-1.33)	0.54 (0.34-0.84)	0.49 (0.37-0.66)
50 000-100 000	0.49 (0.41-0.59)	0.67 (0.32-1.38)	0.49 (0.33-0.72)	0.40 (0.31-0.52)
100 000-150 000	0.31 (0.23-0.42)	0.37 (0.19-0.71)	0.29 (0.18-0.46)	0.25 (0.17-0.38)
>150 000	0.38 (0.27-0.54)	0.52 (0.25-1.09)	0.35 (0.22-0.55)	0.28 (0.16-0.46)
Level of education				
No PS education	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
PS education but no university	0.80 (0.67-0.95)	0.69 (0.48-1.00)	0.89 (0.66-1.21)	0.73 (0.57-0.93)
Undergraduate education	0.74 (0.63-0.88)	0.58 (0.41-0.81)	0.78 (0.60-1.03)	0.72 (0.56-0.92)
Postgraduate education	0.59 (0.47-0.74)	0.52 (0.35-0.77)	0.59 (0.38-0.93)	0.56 (0.39-0.82)
E-value for the point estimate/ E-value for the CI[b]	3.82/2.32	2.92/1.00	3.64/1.34	3.10/1.24

Abbreviations: CLSA, Canadian Longitudinal Study on Aging; OR, odds ratio; PS, postsecondary.

[a] Models were adjusted for age, sex, baseline household income, and level of education. ORs were calculated from the weighted logistic regression models' estimates. Analytic weights provided by the CLSA were used. Regression analyses were performed after multiple imputations, and Rubin rules were used to pool ORs. The same sample of individuals who reported no previous history of stroke, TIA, or MI at baseline was used for all models.

[b] E-values are presented for each model and represent the OR that would be needed by an unmeasured confounder to explain away the association between lifetime history of epilepsy and the outcome.[24] The E-value for point estimate is measured based on the point estimate of the exposure-outcome OR, whereas the E-value for the CI is measured based on the lower bound of the CI of the exposure-outcome OR.[23] The E-value for the CI is therefore the minimum OR needed by an unmeasured confounder to render the exposure-outcome OR insignificant.

Table 3. Proportions Mediated by Different Variables of the Effect of Lifetime History of Epilepsy With New-Onset Cardiovascular Events (CVEs), Strokes, Transient Ischemic Attacks (TIAs), and Myocardial Infarctions (MIs)[a]

	Proportion mediated, % (95% CI)			
Variable	New-onset CVEs	New-onset strokes	New-onset TIAs	New-onset MIs
Strong EIASM use (vs none)	24.6 (6.5 to 54.6)	15.8 (−14.2 to 98.9)	13.3 (−5.9 to 46.9)	59.1 (26.3 to 126.9)
Weak EIASM use (vs none)	4.0 (0.8 to 11.0)	0.3 (−5.4 to 19.0)	7.7 (2.1 to 22.5)	−2.8 (−3.7 to 7.8)
Framingham score	1.4 (−1.6 to 4.5)	2.2 (−3.0 to 14.6)	0.7 (−0.7 to 2.9)	2.0 (−2.3 to 7.2)
PASE score	3.3 (1.4 to 6.8)	7.8 (2.3 to 28.2)	3.3 (1.2 to 8.2)	3.7 (1.3 to 11.0)
Waist to hip ratio	1.6 (0.4 to 3.7)	0.3 (−3.7 to 2.1)	1.4 (0.2 to 4.1)	3.3 (0.6 to 8.4)
Non-EIASM use (vs none)	0.2 (−8.3 to 12.6)	−9.7 (−46.1 to 21.7)	8.0 (−4.3 to 33.4)	−2.8 (−16.3 to 16.8)

Abbreviations: EIASM, enzyme-inducing antiseizure medication; PASE, Physical Activity Scale for the Elderly.

[a] Models were adjusted for age, sex, baseline household income, and level of education. An effect between an exposure and an outcome can be decomposed into an average mediated effect (ie, the indirect effect explained by the mediator) and an average direct effect (ie, the direct effect of an exposure on an outcome). The proportion mediated refers to the proportion of the exposure-outcome effect that can be explained by the mediator and is calculated by dividing the average mediated effect by the total effect. Quasi-bayesian 95% CI are supplied. The upper bound of the CI for the proportion mediated can surpass 1 if the CIs for the average mediated effect and average direct effect have different signs, as is the case for strong EIASM use in the model for new-onset MIs. We used binary probit models for binary outcomes or mediators and gaussian models for continuous mediators. We presumed there were no exposure-mediator interactions; the estimates shown here are, therefore, common between both levels of exposure. Mediation analysis was performed for a set of non-EIASMs for control purposes. Tables detailing the average direct, average indirect, and total effects for each mediator and outcome can be found in eTable 4 in Supplement 1.

be a manifestation of an underlying, progressive CVD, rather than of epilepsy itself. Several observational studies have investigated the occurrence of CVEs in people whose epilepsy was presumably not due to cerebrovascular disease. A 2019 systematic review of 6 such population-based cohort studies showed that the risk of stroke and MI was higher in people with vs without epilepsy.[6] Five studies[25-29] reported hazard ratios (HRs) between 1.09 (95% CI, 1.00-1.19) and 3.30 (95% CI, 2.46-4.43) for strokes, and 2 studies[28,30] reported HRs between 1.09 (95% CI, 1.00-1.19) and 1.48 (95% CI, 1.31-1.67) for MIs. None of these studies explicitly investigated the role of EIASMs and lifestyle factors in the association between epilepsy and CVEs.[6] Our multivariable analyses support the notion that the risk of new-onset CVEs is higher in people with vs without epilepsy, even in a cohort restricted to individuals who had no history of CVEs.

Why PWE experience more CVD, beyond shared risk factors, is not well understood. Sudden cardiac death, for instance, has been observed more often in people taking ASMs.[31] Which ASMs carry the highest risk for cardiac death is under investigation. The use of EIASMs, which can lead to dyslipidemia and increased homocysteine and C-reactive protein levels, has been proposed to promote atherosclerosis.[32-36] Switching from EIASMs to non–enzyme-inducing agents has been shown to result in a lasting decrease in serum lipid and C-reactive protein levels and can lead to a 3.2- to 5.7-fold decrease in sudden cardiac death risk.[35] A 2021 retrospective cohort study[7] of approximately 30 000 PWE yielded an HR of incident CVD of 1.21 (95% CI, 1.06-1.39) when comparing people who took EIASMs vs those who did not. After the first 8 to 10 years, the cumulative hazard of incident CVD began to prominently diverge between both groups, with people taking EIASMs experiencing ever greater hazards. Surprisingly, only 4% of the effect of EIASMs on incident CVD was mediated by incident dyslipidemia. A few other cohort studies[37,38] found no significant association between EIASMs and CVD but were either underpowered or had shorter follow-up periods. Our study results suggest that EIASMs may mediate almost one-third of the association between epilepsy and new-onset CVEs. In turn, more than two-thirds of this association may be due to other factors, such as more prevalent CVRF or a direct effect of epilepsy on CVD.

One hypothesis is that, due to socioeconomic disparities, epilepsy itself leads to worse CVRF and thereby promotes CVD. It is well accepted that a diagnosis of epilepsy may be associated with alterations in social determinants of health through various mechanisms.[39] It is also well accepted that the social determinants of health play an important role in the development of CVRF and, subsequently, CVD.[40,41] The current study supports the notion that PWE may develop more important/prevalent CVRF (ie, PASE score and waist to hip ratio), leading to CVEs. The FRS had no significant mediation effect, but this effect was probably artificially lowered by adjusting models for baseline psychosocial health variables. In sum, CVRF appear to mediate the effect of epilepsy on new-onset CVEs, albeit less than EIASMs do.

A final hypothesis is that chronic epilepsy may somehow directly cause CVD. This has led some authors to coin the term epileptic heart to describe the cardiac and coronary impacts of repeated seizures.[8] The epileptic heart is presumably due to structural and electromechanical cardiac dysfunction secondary to seizure-related catecholamine surges and episodes of hypoxemia.[8] The vascular impacts of seizures are probably not limited to the coronary system. For example, a 2017 systematic review[42] identified 15 studies of carotid intima-media thickness (CIMT) in PWE, demonstrating an increased CIMT in PWE as compared with those without epilepsy. Some experts recommend monitoring lipid levels in people with chronic epilepsy to detect epilepsy-related changes in CVRF.[43] Given that our mediators could not explain the entirety of the association between epilepsy and new-onset CVEs, this implies that either other mediators exist, or epilepsy has a direct effect on CVD.

Strengths and Limitations

Our study features many strengths. In contrast to a prior analysis of CVEs in people with epilepsy,[7] the current study relied on prospective data collection and included formal mediation analyses. Confounders and mediators were identified using a DAG, promoting transparency and reproducibility. As the CLSA is a research database, we had access to high-quality and standardized clinical testing data, including data on blood work, which allowed us to study numerous CVRF. We pushed beyond the FRS and investigated measures of physical activity and obesity. Using sample weights in our analyses rendered study findings more generalizable to the Canadian population at large. Although we studied a composite outcome of CVEs to enhance statistical power, analyses were also performed on the individual components of this outcome. Finally, we provided several sensitivity analyses, including E-values, to address assumptions in the main analyses.

Several limitations must be addressed. First, many of the data used in this study were self-reported, which may have led to misclassification errors. For strokes and potentially TIAs, a 2015 systematic review[44] showed that the specificity of self-report was excellent (96%-99.6%), although the sensitivity was variable (36%-98%). Likewise, we used a modified version of a diagnostic algorithm to identify PWE at baseline. Although the original algorithm has been shown to be accurate (sensitivity >97%, specificity >98%), the accuracy of the version used in this study is unknown.[11] Fortunately, misclassification errors were likely nondifferential, biasing toward the null (ie, the reported association is weaker than the true association). Second, approximately 14% of participants were lost to follow-up, which may have induced selection bias. The only scenario, however, in which this would have biased our results away from the null would have been if among the losses to follow-up, the association between epilepsy and new-onset CVEs was weaker or inverted, which seems unlikely. In any event, we used multiple imputation to replace missing data, including outcomes. Ascertainment bias, another form of selection bias, was possible if PWE reported more CVEs due to more frequent contacts with the health care system. Third, missing outcome data may have followed an MNAR mechanism rather than a MAR mechanism. We have provided tipping point analyses showing that our findings were mostly robust to MNAR data. Fourth, we could not perfectly adjust for variables shown in the DAG due to temporality issues. For example, our DAG suggested that only strokes occurring before epilepsy onset required adjustment, but all people who had strokes at baseline were excluded. Removing people who developed stroke after epilepsy may have biased results toward the null. Adjusting for baseline psychosocial health may have also biased results toward the null, given that psychosocial health was a potential mediator in the DAG. Fifth, due to confounding variables being self-reported, residual confounding was possible. History of stroke and TIA were used as proxy variables to adjust for cerebrovascular disease, but if small vessel disease was somehow a cause of epilepsy, this may have also resulted in residual confounding. We provided E-values to quantify how much residual confounding would be needed to challenge our results. Sixth, we did not differentiate between ischemic strokes and hemorrhagic strokes. This may be relevant as hemorrhagic strokes may be less due to atherosclerosis. Seventh, the causal nature of our mediation analyses can only be asserted if there is no confounding at all, which we cannot guarantee. Furthermore, we chose to estimate natural mediation effects instead of controlled mediation effects. Calculating controlled effects requires less strong assumptions but yields findings that may be less generalizable to real-world circumstances. Last, participants may have begun or stopped EIASMs during their follow-up. These dynamic features of EIASM use could not be analyzed, as we only had access to baseline EIASM data.

Conclusions

Results from this prospective cohort study reveal that epilepsy was associated with new-onset CVEs in older adults. Nearly one-third of this association can be explained by EIASMs. Of note, EIASMs appear to play a more important role than many traditional CVRF in explaining this association. Our findings should be considered when choosing an antiseizure medication for a person at risk for CVD.

ARTICLE INFORMATION

Accepted for Publication: July 31, 2024.

Published Online: September 30, 2024. doi:10.1001/jamaneurol.2024.3210

Correction: This article was corrected on January 13, 2025, to add Canadian Longitudinal Study on Aging to the title and short title and to fix the project identification number in the Additional Contributions section. The supplements were also updated with the new title.

Author Affiliations: Neurology Division, Centre Hospitalier de l'Université de Sherbrooke, Sherbrooke, Québec, Canada (Li, Deacon); Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada (Li, Sylvestre, Keezer); Department of Neurosurgery, Columbia University, New York, New York (Shlobin); Stichting Epilepsie Instellingen Nederland, Heemstede, the Netherlands (Thijs); Department of Neurology, Leiden University Medical Centre, Leiden, the Netherlands (Thijs); NIHR University College London Hospitals Biomedical Research Centre, UCL Queen Square Institute of Neurology, London, United Kingdom (Thijs, Keezer); School of Public Health, Université de Montréal, Montréal, Québec, Canada (Sylvestre, Keezer); Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada (Josephson); O'Brien Institute for Public Health, University of Calgary, Calgary, Alberta, Canada (Josephson); Centre for Health Informatics, University of Calgary, Calgary, Alberta, Canada (Josephson); Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada (Josephson).

Author Contributions: Dr Keezer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Li, Shlobin, Josephson, Deacon, Keezer.
Acquisition, analysis, or interpretation of data: Li, Shlobin, Thijs, Sylvestre, Keezer.
Drafting of the manuscript: Li, Josephson.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Li, Sylvestre, Josephson, Deacon, Keezer.
Obtained funding: Keezer.
Administrative, technical, or material support: Shlobin, Keezer.
Supervision: Deacon, Keezer.

Conflict of Interest Disclosures: Dr Li reported receiving funding support from Fonds de Recherche du Québec—Santé Support outside the submitted work. Dr Thijs reported receiving personal fees from Xenon, Theravance, Novartis, Eisai, Angelini Pharma, LivAssured, and UCB Pharma, all paid to employer, outside the submitted work. Dr Sylvestre reported receiving a salary award from Fonds Recherche Québec and consulting fees from Montreal Heart Institute outside the submitted work. Dr Josephson reported receiving grants from Jazz Pharma outside the submitted work. Dr Keezer reported receiving grants from UCB, Eisai, Jazz Pharmaceuticals, and Paladin outside the submitted work. No other disclosures were reported.

Disclaimer: The opinions expressed in this article are our own and do not reflect the views of the Canadian Longitudinal Study on Aging.

Data Sharing Statement: See Supplement 2.

Additional Contributions: This research was made possible using the data/biospecimens collected by the Canadian Longitudinal Study on Aging (CLSA). Funding for the CLSA is provided by the Government of Canada through the Canadian Institutes of Health Research under grant reference: LSA 94473 and the Canada Foundation for Innovation, as well as the following provinces, Newfoundland, Nova Scotia, Quebec, Ontario, Manitoba, Alberta, and British Columbia. This research has been conducted using the CLSA Baseline Comprehensive Dataset version 7.0, Follow-up 1 Comprehensive Dataset version 3.2 and Follow-up 2 Comprehensive Dataset version 2.0, under Application ID 2104036. The CLSA is led by Drs Parminder Raina, Christina Wolfson and Susan Kirkland.

REFERENCES

1. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. *Neurology*. 2017;88(3):296-303. doi:10.1212/WNL.0000000000003509

2. Ferrucci L, Giallauria F, Guralnik JM. Epidemiology of aging. *Radiol Clin North Am*. 2008;46(4):643-652. doi:10.1016/j.rcl.2008.07.005

3. Sen A, Jette N, Husain M, Sander JW. Epilepsy in older people. *Lancet*. 2020;395(10225):735-748. doi:10.1016/S0140-6736(19)33064-8

4. Keezer MR, Sisodiya SM, Sander JW. Comorbidities of epilepsy: current concepts and future perspectives. *Lancet Neurol*. 2016;15(1):106-115. doi:10.1016/S1474-4422(15)00225-2

5. Brodie MJ, Elder AT, Kwan P. Epilepsy in later life. *Lancet Neurol*. 2009;8(11):1019-1030. doi:10.1016/S1474-4422(09)70240-6

6. Brigo F, Lochner P, Nardone R, Manganotti P, Lattanzi S. Increased risk of stroke and myocardial infarction in patients with epilepsy: a systematic review of population-based cohort studies. *Epilepsy Behav*. 2020;104(pt B):106307. doi:10.1016/j.yebeh.2019.05.005

7. Josephson CB, Wiebe S, Delgado-Garcia G, et al. Association of enzyme-inducing antiseizure drug use with long-term cardiovascular disease. *JAMA Neurol*. 2021;78(11):1367-1374. doi:10.1001/jamaneurol.2021.3424

8. Verrier RL, Pang TD, Nearing BD, Schachter SC. The epileptic heart: concept and clinical evidence. [Review]. *Epilepsy Behav*. 2020;105:106946. doi:10.1016/j.yebeh.2020.106946

9. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453-1457. doi:10.1016/S0140-6736(07)61602-X

10. Raina P, Wolfson C, Kirkland S, et al. Cohort Profile: The Canadian Longitudinal Study on Aging (CLSA). *Int J Epidemiol*. 2019;48(6):1752-1753j. doi:10.1093/ije/dyz173

11. Keezer MR, Pelletier A, Stechysin B, Veilleux M, Jette N, Wolfson C. The diagnostic test accuracy of a screening questionnaire and algorithm in the identification of adults with epilepsy. *Epilepsia*. 2014;55(11):1763-1771. doi:10.1111/epi.12805

12. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol*. 1993;46(2):153-162. doi:10.1016/0895-4356(93)90053-4

13. Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: general features and interactions between antiepileptic drugs. *Lancet Neurol*. 2003;2(6):347-356. doi:10.1016/S1474-4422(03)00409-5

14. D'Agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care. *Circulation*. 2008;117(6):743-753. doi:10.1161/CIRCULATIONAHA.107.699579

15. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2013.

16. Van Buuren S, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. *J Stat Softw*. 2011;45:1-67. doi:10.18637/jss.v045.i03

17. Van Buuren S. *Flexible Imputation of Missing Data*. Vol 1. 2nd ed. CRC press; 2018:415. Interdisciplinary Statistics Series. doi:10.1201/9780429492259

18. Digitale JC, Martin JN, Glymour MM. Tutorial on directed acyclic graphs. *J Clin Epidemiol*. 2022;142:264-267. doi:10.1016/j.jclinepi.2021.08.001

19. Raina PS, Wolfson C, Kirkland SA, et al. The Canadian Longitudinal Study on Aging (CLSA). *Can J*

Aging. 2009;28(3):221-229. doi:10.1017/S0714980809990055

20. Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. *Psychol Methods*. 2010;15(4):309-334. doi:10.1037/a0020761

21. Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. Mediation: R package for causal mediation analysis. *J Stat Softw*. 2014;59(5):1-38. doi:10.18637/jss.v059.i05

22. Tompsett DM, Leacy F, Moreno-Betancur M, Heron J, White IR. On the use of the not-at-random fully conditional specification (NARFCS) procedure in practice. *Stat Med*. 2018;37(15):2338-2353. doi:10.1002/sim.7643

23. Mathur MB, Ding P, Riddell CA, VanderWeele TJ. Web site and R package for computing E-values. *Epidemiology*. 2018;29(5):e45-e47. doi:10.1097/EDE.0000000000000864

24. VanderWeele TJ, Ding P. Sensitivity Analysis in observational research: introducing the E-value. *Ann Intern Med*. 2017;167(4):268-274. doi:10.7326/M16-2607

25. Chang CS, Liao CH, Lin CC, Lane HY, Sung FC, Kao CH. Patients with epilepsy are at an increased risk of subsequent stroke: a population-based cohort study. *Seizure*. 2014;23(5):377-381. doi:10.1016/j.seizure.2014.02.007

26. Cleary P, Shorvon S, Tallis R. Late-onset seizures as a predictor of subsequent stroke. *Lancet*. 2004;363(9416):1184-1186. doi:10.1016/S0140-6736(04)15946-1

27. Hsu SPC, Yeh CC, Chou YC, et al. Stroke risk and outcomes in epilepsy patients: 2 retrospective cohort studies based on national health insurance in Taiwan. *Atherosclerosis*. 2019;280:147-154. doi:10.1016/j.atherosclerosis.2018.11.009

28. Olesen JB, Abildstrøm SZ, Erdal J, et al. Effects of epilepsy and selected antiepileptic drugs on risk of myocardial infarction, stroke, and death in patients with or without previous stroke: a nationwide cohort study. *Pharmacoepidemiol Drug Saf*. 2011;20(9):964-971. doi:10.1002/pds.2186

29. Wannamaker BB, Wilson DA, Malek AM, Selassie AW. Stroke after adult-onset epilepsy: a population-based retrospective cohort study. *Epilepsy Behav*. 2015;43:93-99. doi:10.1016/j.yebeh.2014.11.028

30. Wilson DA, Wannamaker BB, Malek AM, Selassie AW. Myocardial infarction after epilepsy onset: a population-based retrospective cohort study. *Epilepsy Behav*. 2018;88:181-188. doi:10.1016/j.yebeh.2018.09.009

31. Hookana E, Ansakorpi H, Kortelainen ML, et al. Antiepileptic medications and the risk for sudden cardiac death caused by an acute coronary event: a prospective case-control study. *Ann Med*. 2016;48(1-2):111-117. doi:10.3109/07853890.2016.1140225

32. Lopinto-Khoury C, Mintzer S. Antiepileptic drugs and markers of vascular risk. *Curr Treat Options Neurol*. 2010;12(4):300-308. doi:10.1007/s11940-010-0080-y

33. Mintzer S, Maio V, Foley K. Use of antiepileptic drugs and lipid-lowering agents in the US. *Epilepsy Behav*. 2014;34:105-108. doi:10.1016/j.yebeh.2014.03.008

34. Brodie MJ, Mintzer S, Pack AM, Gidal BE, Vecht CJ, Schmidt D. Enzyme induction with antiepileptic drugs: cause for concern? *Epilepsia*. 2013;54(1):11-27. doi:10.1111/j.1528-1167.2012.03671.x

35. Mintzer S, Miller R, Shah K, et al. Long-term effect of antiepileptic drug switch on serum lipids and C-reactive protein. *Epilepsy Behav*. 2016;58:127-132. doi:10.1016/j.yebeh.2016.02.023

36. Mintzer S, Trinka E, Kraemer G, Chervoneva I, Werhahn KJ. Impact of carbamazepine, lamotrigine, and levetiracetam on vascular risk markers and lipid-lowering agents in the elderly. *Epilepsia*. 2018;59(10):1899-1907. doi:10.1111/epi.14554

37. Gao J, Seki T, Usami K, Fan D, Ikeda A, Kawakami K. Complications associated with the use of enzyme-inducing and non–enzyme-inducing antiseizure medications in the Japanese population: a retrospective cohort study. *Epilepsy Behav*. 2022;129:108610. doi:10.1016/j.yebeh.2022.108610

38. Lee-Lane E, Torabi F, Lacey A, et al. Epilepsy, antiepileptic drugs, and the risk of major cardiovascular events. *Epilepsia*. 2021;62(7):1604-1616. doi:10.1111/epi.16930

39. Szaflarski M. Social determinants of health in epilepsy. *Epilepsy Behav*. 2014;41:283-289. doi:10.1016/j.yebeh.2014.06.013

40. Powell-Wiley TM, Baumer Y, Baah FO, et al. Social determinants of cardiovascular disease. *Circ Res*. 2022;130(5):782-799. doi:10.1161/CIRCRESAHA.121.319811

41. Teshale AB, Htun HL, Owen A, et al. The role of social determinants of health in cardiovascular diseases: an umbrella review. *J Am Heart Assoc*. 2023;12(13):e029765. doi:10.1161/JAHA.123.029765

42. Lai Q, Shen C, Zheng Y, Zhang Y, Guo Y, Ding M. Effects of antiepileptic drugs on the carotid artery intima-media thickness in epileptic patients. *J Clin Neurol*. 2017;13(4):371-379. doi:10.3988/jcn.2017.13.4.371

43. Verrier RL, Pang TD, Nearing BD, Schachter SC. Epileptic heart: a clinical syndromic approach. *Epilepsia*. 2021;62(8):1780-1789. doi:10.1111/epi.16966

44. Woodfield R, Group UKBSO, Follow-up UKB, Outcomes Working G, Sudlow CL. Accuracy of patient self-report of stroke: a systematic review from the UK Biobank stroke outcomes group. *PLoS One*. 2015;10(9):e0137538. doi:10.1371/journal.pone.0137538