RESEARCH ARTICLE

Associations of Late-Onset Epilepsy With Myocardial Infarction and Nonstroke Vascular Death

Evan L. Thacker,[1] Hyunmi Choi,[2] Kevin Strobino,[2] Minghua Liu,[2] Sylwia Misiewicz,[2] John D. Beard,[1] Marco R. Di Tullio,[3] Tatjana Rundek,[4] Mitchell S.V. Elkind,[2,5] and Jose Gutierrez[2]

Correspondence
Prof. Thacker
elt@byu.edu

Neurology® 2025;105:e214292. doi:10.1212/WNL.0000000000214292

Abstract

Background and Objectives

Cerebrovascular disease is associated with increased risk of late-onset epilepsy (LOE). Because vascular disease is often systemic, coexisting in multiple vascular beds, LOE may be a marker of increased systemic vascular risk outside the brain. We sought to determine whether stroke-free middle-aged and older adults with incident myocardial infarction (MI) subsequently have increased risk of LOE and whether those with incident LOE subsequently have increased risks of incident MI and nonstroke vascular death.

Methods

The Northern Manhattan Study (NOMAS) is a population-based cohort study of participants aged 40 years and older enrolled from 1993 to 2008, with follow-up through May 2023 for the present analysis. Participants free of a history of stroke, MI, or epilepsy at enrollment were followed prospectively for up to 30 years (mean 14 years). We used Cox proportional hazards regression with censoring at incident stroke to assess the associations of (1) incident MI with subsequent incident LOE; (2) incident LOE with subsequent incident MI; and (3) incident LOE with nonstroke cardiovascular death, adjusting for demographics, health behaviors, and comorbid diagnoses.

Results

The mean (SD) age of 3,174 participants at enrollment was 69.1 (10.4) years, and 63.5% were women. We identified 296 participants (9.3%) who developed incident MI, 120 (3.8%) who developed incident LOE, and 794 (25.0%) who died of nonstroke vascular causes. Incident LOE occurred at a rate of 7.02 cases per 1,000 person-years (PYs) after incident MI compared with 2.49 per 1,000 PYs without MI (adjusted hazard ratio [aHR] 2.12; 95% CI 1.06–4.25; p = 0.035). Incident MI occurred at a rate of 17.68 cases per 1,000 PYs after incident LOE compared with 6.46 per 1,000 PYs without LOE (aHR 1.99; 95% CI 0.98–4.05; p = 0.059). Nonstroke vascular death occurred at a rate of 99.24 deaths per 1,000 PYs after incident LOE compared with 16.29 per 1,000 PYs without LOE (aHR 2.82; 96% CI 2.09–3.80; p < 0.001). Sensitivity analyses yielded similar results.

Discussion

The bidirectional associations we observed suggest that LOE might be a marker of increased systemic vascular risk. This warrants further study in additional populations.

RELATED ARTICLE

Editorial
Seizing the Heart: Late-Onset Epilepsy and Cardiovascular Disease in Older Adults
Page e214391

Introduction

Manifestations of cerebrovascular disease, including symptomatic stroke and covert vascular abnormalities on brain MRI, are associated with increased risk of late-onset epilepsy (LOE).[1-5] Furthermore, older adults with LOE are at increased risk of subsequent stroke,[6-9] likely due to covert cerebrovascular disease that first causes seizures and later progresses to symptomatic

[1]Department of Public Health, Brigham Young University, Provo, UT; [2]Department of Neurology, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY; [3]Division of Cardiology, Department of Medicine, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY; [4]Department of Neurology, University of Miami Miller School of Medicine, FL; and [5]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY.

Glossary

ΔMSE = delta mean squared error; **AIC** = Akaike information criterion; **ASM** = antiseizure medication; **BMI** = body mass index; **CUIMC** = Columbia University Irving Medical Center; **HR** = hazard ratio; **ICD-9** = International Classification of Diseases, Ninth Revision; **ICD-10** = International Classification of Diseases, 10th Revision; **LOE** = late-onset epilepsy; **MI** = myocardial infarction; **NOMAS** = Northern Manhattan Study; **PYs** = person-years.

stroke. Hence, LOE and symptomatic stroke share a bidirectional association in the adult life course, each becoming more common after the other first occurs.

It is less clear whether LOE also has a bidirectional association with vascular disease outside the brain. In middle-aged and older adults, vascular disease is often systemic, coexisting in multiple vascular beds.[10,11] As shown in the conceptual scheme that guided our hypotheses (Figure),[12] a plausible mechanism underlying a bidirectional association of LOE with nonstroke vascular events such as myocardial infarction (MI) is that systemic vascular disease contributes simultaneously to increased risk of LOE and increased risk of vascular events outside the brain. According to the conceptual scheme, individuals who experience incident MI as their first incident event are likely to have a higher burden of covert systemic vascular disease, including covert cerebrovascular disease, which would increase the risk of subsequent LOE. Likewise, individuals who experience incident LOE as their first incident event are likely to have a higher burden of covert systemic vascular disease, including coronary artery disease or disease in other vascular beds, which would increase the risks of subsequent MI, other vascular events, and ultimately nonstroke vascular death (Figure).

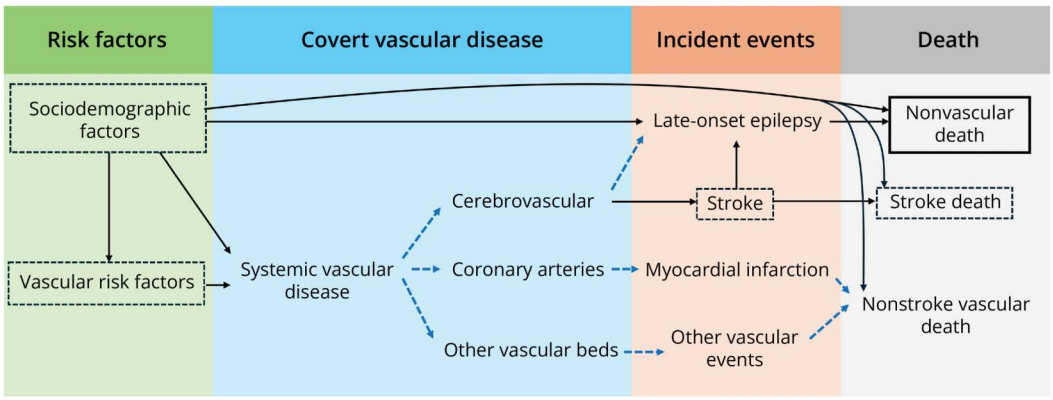
Thus, we analyzed relationships of incident LOE, incident MI, and nonstroke vascular death in stroke-free middle-aged and older adults. We hypothesized that stroke-free individuals who experienced incident MI and remained stroke free subsequently had increased risk of LOE, and that stroke-free individuals who experienced LOE and remained stroke free subsequently had increased risks of incident MI and nonstroke vascular death.

Methods

Study Design, Setting, and Participants

The Northern Manhattan Study (NOMAS) is a prospective cohort study of stroke risk factors, incident stroke, and cognitive decline in the multi-ethnic community of northern Manhattan, New York City. The study recruited adults aged 40 years or older with no history of self-reported stroke who had resided in northern Manhattan for at least 3 months. Recruitment was performed through random digit dialing between 1993 and 2001, with a 68% response.[13,14] Additional participants were enrolled between 2001 and 2008 in the NOMAS MRI substudy if they were stroke free, were aged 50 years or older, and lived in the household of a NOMAS participant. Enrolled individuals were followed annually by telephone to screen for changes in vital status, detect

Figure Conceptual Scheme or Directed Acyclic Graph Relating LOE to Myocardial Infarction and Nonstroke Vascular Death



This conceptual scheme or directed acyclic graph[12] guided our hypotheses and statistical analyses. Arrows in the diagram represent hypothesized cause-and-effect relationships. Dashed boxes in the diagram indicate adjustment for confounding (risk factors) or accounting for censoring (incident stroke, stroke death, and nonstroke vascular death). Dashed blue arrows represent "open" or "unblocked" paths linked by systemic vascular disease by which LOE is associated with myocardial infarction and nonstroke vascular death. There is no arrow leading from incident myocardial infarction to incident LOE, and there are no arrows leading from incident LOE to incident myocardial infarction or nonstroke vascular death, because we do not think epilepsy directly causes the vascular events or vice versa. Rather, LOE is associated with myocardial infarction and nonstroke vascular death because they share an underlying common cause: systemic vascular disease (the dashed blue arrow pathways). LOE = late-onset epilepsy.

neurologic and cardiac events, and review hospitalizations. For this analysis, all who had a history of epilepsy, seizures, or MI at enrollment were excluded. Study follow-up extended through May 2023, with <2% of participants lost to follow-up.

Standard Protocol Approvals and Participant Consents

The Institutional Review Boards of Columbia University and the University of Miami approved the study. All participants provided written informed consent.

Outcome Measures

Incident LOE

Study participants screened positive for possible epilepsy in 3 ways: (1) participants responded "yes" to the question "Have you ever had seizures, convulsions or epilepsy?" at enrollment or during annual telephone follow-up; (2) mention of seizure or epilepsy was found during review of hospitalization records at Columbia University Irving Medical Center (CUIMC, where most of the NOMAS participants receive medical care) or medical records collected from other sources when a possible medical event alert was triggered during the annual telephone survey; or (3) 1 or more ICD-9 codes (345.xx and 780.3x, excluding 345.6x) or ICD-10 codes (G40.xxx and R56.x, excluding G40.82x and R56.0x) were found in the New York Statewide Planning and Research Cooperative System claims data linked to NOMAS.[15] Once participants with possible epilepsy were identified, a research coordinator reviewed their CUIMC electronic medical records to confirm the epilepsy diagnosis. If clinical workup for epilepsy or seizure was mentioned in the medical record but no epilepsy diagnosis was stated, a study neurologist adjudicated the presence of epilepsy. We defined LOE cases as those with confirmed or adjudicated epilepsy during follow-up who did not have a history of seizures or epilepsy at enrollment.

Incident MI

During annual telephone follow-up, participants were screened for new cardiac or neurologic symptoms, hospitalizations, medical conditions, or death. Study physicians assessed participants who screened positive for possible vascular events with an in-person visit. MI was adjudicated by a study cardiologist using criteria adapted from the Cardiac Arrhythmia Suppression Trial and the Lipid Research Clinics Coronary Primary Prevention Trial.[16]

Nonstroke Vascular Death

Death and cause of death were ascertained through phone discussion with the participant's family, review of medical records, and, when available, a copy of the death certificate. Nonstroke vascular death was defined as death due to MI; heart failure; pulmonary embolism; cardiac arrhythmia/sudden death; or other vascular causes including aortic aneurysm, aortic stenosis, mitral stenosis, or left ventricular hypertrophy. Participants who had experienced incident MI (mentioned above) and later died were not necessarily classified as having died due to MI; their cause of death classification was based on adjudication of all available evidence for the cause of death.

Incident Stroke

Neurologic events that were possible strokes were adjudicated by 2 study vascular neurologists who were blinded to risk factor data, using all available diagnostic data and a modified National Institute of Neurological Disorders and Stroke classification scheme.[17,18] Discordance between the 2 vascular neurologists was resolved by a third vascular neurologist.

Independent Variables

Sociodemographic Characteristics

Participants self-reported their age, sex, race, ethnicity, attained education, occupation type, health insurance status, and marital status during the enrollment interview. Based on the 2000 US census classifications of race and ethnicity,[19] participants were classified into 4 categories: non-Hispanic White, non-Hispanic Black, Hispanic (any race), and non-Hispanic other race. Participants were classified into categories of attained education (high school or less vs some college or higher), occupation type (professional or skilled vs other), health insurance (Medicare or private insurance vs Medicaid or no health insurance), and marital status (married vs other).

Vascular Risk Factors

Standardized questions adapted from the Behavioral Risk Factor Surveillance System[20] were used to assess prevalent hypertension, diabetes, and hypercholesterolemia at enrollment. Standard techniques were used to measure blood pressure, fasting serum glucose, and blood lipids. Hypertension was defined as self-reported history of hypertension; use of antihypertensive medication; or blood pressure ≥140/90 mm Hg, measured as the average of 2 measurements taken at the beginning and end of the in-person examination. Diabetes was defined as self-reported history of diabetes, use of insulin or oral antidiabetic medication, or fasting blood glucose ≥126 mg/dL. Hypercholesterolemia was defined as self-reported history of hypercholesterolemia, use of cholesterol-lowering medication, or total cholesterol >240 mg/dL.[21] Smoking status was categorized as current (within the past year); former; or never smoker of cigarettes, cigars, or pipes. Body mass index (BMI) was calculated from measured height and weight and categorized as normal weight or underweight (<25 kg/m^2), overweight (25–29 kg/m^2), or obesity (≥30 kg/m^2).

Data Analysis

We calculated descriptive statistics for sociodemographic characteristics and vascular risk factors, by incident LOE, incident MI, and nonstroke vascular death.

To address our hypothesis that stroke-free individuals who experienced incident MI and remained stroke free subsequently had increased risk of LOE, we used Cox regression with incident MI as the time-varying exposure; incident LOE as the outcome event of interest; and incident stroke, death,

loss to follow-up, or end of study follow-up as censoring events. To address our hypothesis that stroke-free individuals who experienced incident LOE and remained stroke free subsequently had increased risks of incident MI and nonstroke vascular death, we constructed models similar to that described above, but with incident LOE as the time-varying exposure and incident MI or nonstroke vascular death as the outcome of interest.

For each hypothesis, we constructed Cox models to estimate hazard ratios (HRs) and 95% CIs: model 0 was unadjusted; model 1 was adjusted for age, sex, and race/ethnicity; and model 2 was adjusted for sociodemographic and vascular risk factors, backward-selected through the delta mean squared error (ΔMSE) method from the following set of potential confounders: age, sex, race/ethnicity, attained education, occupation type, health insurance status, marital status, hypertension, diabetes, hypercholesterolemia, smoking, and BMI category. The ΔMSE method quantifies the tradeoff between bias reduction and variance inflation from adjustment for each potential confounder when estimating the HR and 95% CI for the association of the exposure with the outcome. The process leads to sequentially simpler models until all variables retained in the final model achieve bias reduction of greater magnitude than variance inflation.[22] Individuals with missing covariate values were excluded from model 2. For the incident LOE outcome event, model 2 was adjusted for age, sex, race/ethnicity, occupation types, health insurance status, diabetes, smoking status, and BMI category. For the incident MI outcome event, model 2 was adjusted for age, sex, race/ethnicity, hypertension, and diabetes. For the nonstroke vascular death outcome event, model 2 was adjusted for age, sex, attained education, marital status, hypertension, diabetes, hypercholesterolemia, smoking status, and BMI category.

We anticipated a priori that model 2, adjusted for backward-selected confounders, would be the best model for addressing our research questions because it would optimize the bias/variance tradeoff in estimating the HRs of interest. To assess the robustness of the observed associations by exploring confounding adjustment more thoroughly, we conducted the following sensitivity analyses: model 3, in which we adjusted for all potential confounders, including those that had been omitted from model 2 by backward selection; and model 4, in which we adjusted for a propensity score for exposure that was calculated using all potential confounders. For the analysis of incident LOE as an outcome before or after incident MI, we calculated each participant's propensity for incident MI using an unconditional logistic regression model with incident MI as the dependent variable and all potential confounders as independent variables and then adjusted for the propensity of incident MI in Cox model 4. For the analyses of incident MI and non-stroke vascular death as outcomes before or after incident LOE, we calculated each participant's propensity for incident LOE using an unconditional logistic regression model with incident LOE as the dependent variable and all potential confounders as independent variables and then adjusted for the propensity of incident LOE in Cox model 4.

We compared the Akaike information criterion (AIC) across different Cox models for a given outcome, where lower AIC values indicate better model fit.[23]

Data Availability

Deidentified data will be shared through the NOMAS by request from any qualified investigator.

Results

Participant Characteristics

The NOMAS cohort included 3,298 participants enrolled between 1993 and 2001 and an additional 199 participants enrolled in the MRI substudy between 2001 and 2008, for a total of 3,497 participants. For this study, 323 participants with a history of epilepsy, seizures, or MI at enrollment were excluded, leaving 3,174 participants for inclusion. The mean age at enrollment was 69.1 years (SD 10.4), and 63.5% were women (Table 1). Over a follow-up of up to 30 years (mean 14 years), we identified 120 participants who developed incident LOE, 296 who developed incident MI, and 794 who died of nonstroke vascular causes. Of the 120 incident LOE cases, 95% were aged 65 years or older at epilepsy onset, and the youngest age at onset was 59 years. Incident LOE cases were older on average; less likely to be female, Hispanic, married, or overweight or obese; and more likely to be non-Hispanic Black, be college educated, have diabetes or hypercholesterolemia, or be current smokers than noncases. Incident MI cases were older on average and less likely to be female, non-Hispanic Black, Hispanic, or uninsured; they were more likely to be college educated; have hypertension, diabetes, or hypercholesterolemia; or be former smokers than noncases. Nonstroke vascular decedents were older on average and less likely to be Hispanic, insured, married, or overweight. They were more likely to be female, non-Hispanic Black, or college educated; have a skilled/professional occupation, hypertension, diabetes, or hypercholesterolemia; be former smokers; or have obesity compared with those who remained alive or died of other causes.

Risk of Incident LOE After Incident MI

During 1,282 person-years (PYs) of follow-up after incident MI, 9 individuals developed incident LOE (unadjusted incidence rate 7.02 per 1,000 PYs). By contrast, during 44,596 PYs without incident MI, 111 individuals developed incident LOE (unadjusted incidence rate 2.49 per 1,000 PYs). In the Cox model adjusted for backward-selected confounders, participants after incident MI were 2.12 times as likely to develop incident LOE as those without incident MI (95% CI 1.06–4.25; $p = 0.035$; Table 2, model 2). In sensitivity analyses, further adjustment for all potential confounders (Table 2, model 3) or for a propensity score for incident MI

Table 1 Characteristics of Participants Who Had No History of Stroke, MI, or Epilepsy/Seizure at Enrollment in the Northern Manhattan Study

Characteristic[a]	Full cohort (n = 3,174)	Incident LOE		Incident MI		Nonstroke vascular death[b]	
		Yes LOE (n = 120)	No LOE (n = 3,054)	Yes MI (n = 296)	No MI (n = 2,878)	Yes death (n = 794)	No death (n = 2,380)
Age at enrollment, y, mean ± SD	69.1 ± 10.4	70.2 ± 10.2	69.0 ± 10.4	72.3 ± 9.9	68.8 ± 10.4	74.1 ± 9.4	67.4 ± 10.1
Female, n (%)	2,016 (63.5)	73 (60.8)	1,943 (63.6)	176 (59.5)	1,840 (63.9)	531 (66.9)	1,485 (62.4)
Race/ethnicity, n (%)							
Non-Hispanic white	631 (19.9)	25 (20.8)	606 (19.8)	89 (30.1)	542 (18.8)	222 (28.0)	409 (17.2)
Non-Hispanic Black	745 (23.5)	41 (34.2)	704 (23.1)	56 (18.9)	689 (23.9)	233 (29.4)	512 (21.5)
Non-Hispanic other	71 (2.2)	3 (2.5)	68 (2.2)	6 (2.0)	65 (2.3)	21 (2.6)	50 (2.1)
Hispanic	1,727 (54.4)	51 (42.5)	1,676 (54.9)	145 (49.0)	1,582 (55.0)	318 (40.0)	1,409 (59.2)
College education, n (%)	874 (27.5)	41 (34.2)	833 (27.3)	86 (29.1)	788 (27.4)	235 (29.6)	639 (26.9)
Skilled/professional occupation, n (%)	1,054 (33.2)	38 (31.9)	1,016 (33.3)	100 (33.9)	954 (33.2)	286 (36.1)	768 (32.3)
Medicaid or no health insurance, n (%)	1,394 (44.2)	52 (43.7)	1,342 (44.2)	112 (38.0)	1,282 (44.8)	275 (35.0)	1,119 (47.3)
Married, n (%)	1,071 (33.8)	35 (29.2)	1,036 (33.9)	99 (33.5)	972 (33.8)	209 (26.4)	862 (36.2)
Hypertension, n (%)	2,292 (72.2)	85 (70.8)	2,207 (72.3)	247 (83.5)	2,045 (71.1)	620 (78.1)	1,672 (70.3)
Diabetes, n (%)	663 (20.9)	29 (24.2)	634 (20.8)	82 (27.7)	581 (20.2)	179 (22.7)	484 (20.4)
Hypercholesterolemia, n (%)	1,964 (61.9)	79 (65.8)	1,885 (61.7)	197 (66.6)	1,767 (61.4)	504 (63.5)	1,460 (61.3)
Smoking status, n (%)							
Never smoker	1,501 (47.3)	52 (43.3)	1,449 (47.5)	125 (42.2)	1,376 (47.8)	384 (48.4)	1,117 (47.0)
Former smoker	1,144 (36.1)	37 (30.8)	1,107 (36.3)	120 (40.5)	1,024 (35.6)	298 (37.5)	846 (35.6)
Current smoker	527 (16.6)	31 (25.8)	496 (16.3)	51 (17.2)	476 (16.6)	112 (14.1)	415 (17.4)
Body mass index category, n (%)							
Normal weight or underweight	927 (29.2)	41 (34.2)	886 (29.0)	91 (30.7)	836 (29.1)	252 (31.7)	675 (28.3)
Overweight	1,439 (45.3)	52 (43.3)	1,387 (45.4)	127 (42.9)	1,312 (45.6)	326 (41.1)	1,113 (46.8)
Obesity	808 (25.5)	27 (22.5)	781 (25.6)	78 (26.4)	730 (25.4)	216 (27.2)	592 (24.9)

Abbreviations: LOE = late-onset epilepsy; MI = myocardial infarction.
[a] Column percentages were calculated for each characteristic among participants with valid data for that characteristic. There were 20 participants missing health insurance status, 2 missing marital status, 1 missing attained education, 3 missing occupation type, 6 missing diabetes, and 2 missing smoking status.
[b] The 794 nonstroke vascular deaths included 76 deaths due to MI (9.6%); 85 due to heart failure (10.7%); 20 due to pulmonary embolism (2.5%); 419 due to cardiac arrhythmia/sudden death (52.8%); and 194 due to other vascular causes including aortic aneurysm, aortic stenosis, mitral stenosis, and left ventricular hypertrophy (24.4%).

based on all potential confounders (Table 2, model 4) yielded HRs similar to those from model 2. Model 2 had the lowest AIC, evidence of the best model fit.

Risk of Incident MI After Incident LOE

During 452 PYs of follow-up after incident LOE, 8 individuals developed incident MI (unadjusted incidence rate 17.68 per 1,000 PYs). By contrast, during 44,600 PYs without incident LOE, 288 individuals developed incident MI (unadjusted incidence rate 6.46 per 1,000 PYs). In the Cox model adjusted for backward-selected confounders, participants after incident LOE were 1.99 times as likely to develop incident MI as those without incident LOE (95% CI 0.98–4.05; $p = 0.059$; Table 3, model 2). In sensitivity analyses, further adjustment for all potential confounders (Table 3, model 3) yielded a lower HR of 1.78 (95% CI 0.83–3.82; $p = 0.136$) while adjustment for a propensity score for incident epilepsy (Table 3, model 4) yielded a higher HR of 2.38 (95% CI 1.12–5.07; $p = 0.025$), demonstrating that this association estimate was more influenced by methods of confounding adjustment. Model 3 had the lowest AIC, evidence of the best model fit, while model 4 had a higher AIC, evidence of relatively poor model fit.

Risk of Nonstroke Vascular Death After Incident LOE

During 474 PYs of follow-up after incident LOE, 47 individuals died of nonstroke vascular causes (unadjusted cause-

Table 2 Incidence of LEO Before and After Incident MI Among 3,174 Stroke-Free Participants in the Northern Manhattan Study

Exposure: incident MI	Outcome: incident LOE	PYs	Unadjusted incidence rate per 1,000 PYs	Model	HR (95% CI)	*p* Value	AIC
No MI	111	44,596	2.49	—	1.00 (reference)	—	—
After incident MI	9	1,282	7.02	Model 0	2.62 (1.32–5.20)	0.006	1,811
				Model 1	2.23 (1.12–4.44)	0.023	1,783
				Model 2	2.12 (1.06–4.25)	0.035	1,747
				Model 3	2.15 (1.07–4.33)	0.032	1,752
				Model 4	2.22 (1.10–4.46)	0.026	1,772

Abbreviations: AIC = Akaike information criterion; HR = hazard ratio; LOE = late-onset epilepsy; MI = myocardial infarction; PYs = person-years.
Model 0: unadjusted. Model 1: adjusted for age, sex, and race/ethnicity. Model 2: considered a priori to be the best model, adjusted for age, sex, race/ethnicity, occupation type, health insurance status, diabetes, smoking status, and body mass index category after backward selection using the delta mean squared error method. (Attained education, marital status, hypertension, and hypercholesterolemia were removed from the model by backward selection.) Model 3: sensitivity analysis, adjusted for all potential confounders including age, sex, race/ethnicity, attained education, occupation type, health insurance status, marital status, hypertension, diabetes, hypercholesterolemia, smoking status, and body mass index category. Model 4: Sensitivity analysis, adjusted for a propensity score for incident MI that was calculated using all potential confounders.

specific mortality rate 99.24 per 1,000 PYs). By contrast, during 45,845 PYs without incident LOE, 747 individuals died of nonstroke vascular causes (unadjusted cause-specific mortality rate 16.29 per 1,000 PYs). In the Cox model adjusted for backward-selected confounders, participants after incident LOE were 2.86 times as likely to experience nonstroke vascular death as those without incident LOE (95% CI 2.10–3.89; $p < 0.001$; Table 4, model 2). In sensitivity analyses, further adjustment for all potential confounders (Table 4, model 3) yielded a HR similar to that from model 2 and the lowest AIC, whereas adjustment for a propensity score (Table 4, model 4) yielded a higher HR but also a much higher AIC, suggesting poorer model fit. All models consistently showed a substantially higher risk of nonstroke vascular death after incident LOE regardless of the confounders for which we adjusted or the methods we used for confounding adjustment.

Discussion

In this prospective multi-ethnic cohort study of stroke-free middle-aged and older adults, we found evidence for bidirectional associations of incident LOE with incident MI and nonstroke vascular death. We observed (1) elevated risk of incident LOE after incident MI, (2) elevated risk of incident MI after incident LOE, and (3) elevated risk of nonstroke vascular death after incident LOE. The findings for post-MI LOE and post-LOE nonstroke vascular death remained statistically significant after adjustment for confounders in several different models. The finding for post-LOE MI suggested a higher risk of MI after LOE, but the association estimate varied across different methods of adjustment for confounding and was not statistically significant in some of the confounder-adjusted models. These findings suggest that LOE, in absence of stroke, may be an initial symptomatic

Table 3 Incidence of MI Before and After Incident LOE Among 3,174 Stroke-Free Participants in the Northern Manhattan Study

Exposure: incident LOE	Outcome: incident MI	PYs	Unadjusted incidence rate per 1,000 PYs	Model	HR (95% CI)	*p* Value	AIC
No epilepsy	288	44,600	6.46	—	1.00 (reference)	—	—
After incident LOE	8	452	17.68	Model 0	2.82 (1.39–5.75)	0.004	4,514
				Model 1	2.04 (1.00–4.16)	0.049	4,387
				Model 2	1.99 (0.98–4.05)	0.059	4,348
				Model 3	1.78 (0.83–3.82)	0.136	4,318
				Model 4	2.38 (1.12–5.07)	0.025	4,471

Abbreviations: AIC = Akaike information criterion; HR = hazard ratio; LOE = late-onset epilepsy; MI = myocardial infarction; PYs = person-years.
Model 0: unadjusted. Model 1: adjusted for age, sex, and race/ethnicity. Model 2: considered a priori to be the best model, adjusted for age, sex, race/ethnicity, hypertension, and diabetes after backward selection using the delta mean squared error method. (Attained education, occupation type, health insurance status, marital status, hypercholesterolemia, smoking status, and body mass index category were removed from the model by backward selection.) Model 3: Sensitivity analysis, adjusted for all potential confounders including age, sex, race/ethnicity, attained education, occupation type, health insurance status, marital status, hypertension, diabetes, hypercholesterolemia, smoking status, and body mass index category. Model 4: sensitivity analysis, adjusted for a propensity score for incident MI that was calculated using all potential confounders.

Table 4 Occurrence of Nonstroke Vascular Death Before and After Incident LOE Among 3,174 Stroke-Free Participants in the Northern Manhattan Study

Exposure: incident LOE	Outcome: nonstroke vascular death[a]	PYs	Unadjusted mortality rate per 1,000 PYs	Model	HR (95% CI)	*p* Value	AIC
No epilepsy	747	45,845	16.29	—	1.00 (reference)	—	—
After incident LOE	47	474	99.24	Model 0	4.23 (3.14–5.70)	<0.001	11,572
				Model 1	2.73 (2.03–3.69)	<0.001	10,755
				Model 2	2.82 (2.09–3.80)	<0.001	10,667
				Model 3	2.89 (2.13–3.92)	<0.001	10,529
				Model 4	4.02 (2.98–5.43)	<0.001	11,267

Abbreviations: AIC = Akaike information criterion; HR = hazard ratio; LOE = late-onset epilepsy; MI = myocardial infarction; PYs = person-years.
Model 0: unadjusted. Model 1: adjusted for age, sex, and race/ethnicity. Model 2: considered a priori to be the best model, adjusted for age, sex, attained education, marital status, hypertension, diabetes, hypercholesterolemia, smoking status, and body mass index category after backward selection using the delta mean squared error method. (Race/ethnicity, occupation type, and health insurance status were removed from the model by backward selection.) Model 3: Sensitivity analysis, adjusted for all potential confounders including age, sex, race/ethnicity, attained education, occupation type, health insurance status, marital status, hypertension, diabetes, hypercholesterolemia, smoking status, and body mass index category. Model 4: sensitivity analysis, adjusted for a propensity score for incident MI that was calculated using all potential confounders.
[a] The 794 nonstroke vascular deaths included 76 deaths due to MI (9.6%); 85 due to heart failure (10.7%); 20 due to pulmonary embolism (2.5%); 419 due to cardiac arrhythmia/sudden death (52.8%); and 194 due to other vascular causes including aortic aneurysm, aortic stenosis, mitral stenosis, and left ventricular hypertrophy (24.4%).

manifestation of cerebrovascular disease, and that LOE may be a marker of systemic vascular disease.

Based on the conceptual scheme that guided our hypotheses (Figure),[12] the associations we observed were unlikely to be due to incident MI directly causing subsequent LOE or due to incident LOE directly causing subsequent MI or nonstroke vascular death. Rather, we postulated that systemic vascular disease led to increased risks of LOE, MI, and nonstroke vascular death in the same individuals, causing these conditions to be associated with each other, even after adjusting for vascular risk factors. Future studies using brain MRI data to assess the role of covert cerebrovascular disease may shed further light on these relationships.

Previous studies show that vascular disease tends to affect multiple vascular beds, coronary artery disease is linked to covert cerebrovascular disease, and they share common risk factors.[24-27] In a clinical sample of 208 stroke-free patients, 46% of those with coronary artery disease had 3 or more covert brain infarcts on MRI, compared with 21% of those who had hypertension but no coronary artery disease.[28] Among those with coronary artery disease, each additional stenosed coronary artery was associated with double the odds of having an infarct in the deep perforator region, including the basal ganglia, which can be involved in seizure propagation and control.[29] Similarly, in a clinical sample of 78 stroke-free patients with coronary artery disease, those with 3 stenosed coronary arteries had higher mean scores on scales of intracranial atherosclerosis severity, covert infarct multiplicity, and maximal infarct size than those with zero stenosed coronary arteries.[30] In a clinical trial sample of 308 stroke-free patients with noncerebral atherosclerotic vascular disease, 17% had covert brain infarcts,[31] distributed mostly in the white matter, basal ganglia, and cerebral cortex, all of which may be involved in seizures.[32-34] Additional studies in community-based samples and a genetically high-risk sample have shown that higher levels of coronary artery plaque or calcification are associated with higher levels of white matter hyperintensity and covert brain infarcts.[35-37] Finally, in a clinical trial sample, higher levels of white matter hyperintensity were associated with higher risk of vascular disease outcomes.[38]

Covert cerebrovascular disease is prevalent among individuals with LOE. For example, in a clinical sample of 93 stroke-free LOE patients, 61% had covert cerebrovascular disease vs 33% of age-matched controls who had headache.[39] In another clinical sample, 16 stroke-free LOE patients had a mean white matter hyperintensity volume of 1,339 mL compared with a mean of 541 mL among age-matched controls.[40] Among 1,526 participants in the Atherosclerosis Risk in Communities cohort who underwent brain MRI, including 77 who developed LOE during follow-up in the absence of stroke or dementia, each SD increment in the white matter hyperintensity score was associated with 33% higher risk of LOE.[4]

Because vascular disease tends to be systemic, we would expect a greater degree of coronary artery disease among adults with LOE than among those without LOE. Owing to the heterogeneity of the study population and study designs across studies, it has been difficult to quantitatively synthesize the risks of MI and vascular death among those with LOE.[41] Previous studies examined individuals across wide ranges of ages at epilepsy onset, which limits the applicability of their findings to the LOE population. For example, in a population-based cohort study of 39,203 individuals aged 18 years or older with epilepsy diagnosis and without previous vascular

disease, the incidence rate of MI was 40.4 per 10,000 PYs, compared with 11.8 per 10,000 PYs in a comparison cohort of 80,469 individuals with migraine.[42] In another population-based cohort study of 48,602 individuals aged 10 years or older with epilepsy diagnosis and without previous stroke, those treated with antiseizure medication (ASM) were 9% more likely to have a new MI and 64% more likely to have vascular death, and those not treated with an ASMwere 15% more likely to have a new MI and 42% more likely to have vascular death than 4,481,132 control individuals who did not have epilepsy.[9] Comparable studies reporting findings specifically for LOE are lacking.

Medication use may play a role in the bidirectional relationship between LOE and vascular events. First, several ASMs are associated with increased vascular risk by their adverse effects on blood lipid levels and other vascular biomarkers, particularly the cytochrome P450 enzyme-inducing ASMs and also the non–enzyme-inducing ASM valproate, which have declined in use over time.[43] Other non–enzyme-inducing ASMs that have increased in use over time have minimal effects on blood lipid levels and would be expected to have less effect on vascular risk. NOMAS participants included in this analysis were enrolled and followed over the course of 3 decades from 1993 to 2023, during which interval epilepsy treatment in adults in the United States shifted strongly toward the use of non–enzyme-inducing ASMs.[44] However, we did not have data on NOMAS participants' ASM use available for our analyses. Second, emerging evidence from large pharmacoepidemiologic studies suggests that angiotensin receptor blockers, an antihypertensive medication class often used by MI survivors, may reduce seizure risk relative to other antihypertensive medication classes.[45,46] More than 70% of NOMAS participants in this analysis and more than 80% of those who experienced incident MI had hypertension at study entry. However, the relatively small number of post-MI incident LOE cases in our analysis precluded investigation of the role of antihypertensive medication.

Our study had methodological strengths. NOMAS is a racially and ethnically diverse sample with many years of follow-up, little missing data, and limited participant attrition. MI and nonstroke vascular death events were adjudicated by cohort investigators based on all available medical information rather than identified solely through health insurance billing codes. By restricting the cohort to participants who were free of prevalent epilepsy and history of MI at enrollment and analyzing incident events, we could determine the time sequence of different incident events in our analyses. Fourth, we optimized the bias/variance tradeoff in adjusted models by using the ΔMSE method to select confounders, and we conducted sensitivity analyses to further explore different methods of adjustment for confounding.

A limitation of our study was that the small numbers of post-MI incident LOE cases and post-LOE incident MI cases limited the precision of our estimates of bidirectional associations and did not allow for reliable investigation of effect measure modification by other factors such as age, other demographic characteristics, cardiovascular medication use, or time elapsed between the 2 incident events. Another limitation was that our ascertainment of epilepsy cases did not include determination of seizure type, underlying vascular or nonvascular causes of individual participants' seizures, or information about ASM use. Finally, our analysis may be limited by residual confounding due to imperfect measures of risk factors in our models or confounding by unmeasured, unknown, or unincluded risk factors, which could be an alternative explanation for the associations observed, instead of the common pathway of covert systemic vascular disease that we hypothesized.

Our findings highlight the interconnectedness of heart and vascular health with brain health in middle-aged and older adults. The bidirectional associations we observed suggest that LOE might be a marker of increased systemic vascular risk that warrants further study in additional populations. Highlighting the latent increased vascular risk among people who present first with LOE in the absence of vascular event history may enable more accurate assessment of the societal burden of vascular disease by including LOE in such assessments in addition to traditional outcomes such as stroke and MI. In people without any vascular event history, it is plausible that LOE occurring as the first incident event could indicate elevated incremental risk of vascular events and, therefore, improve the accuracy of risk prediction for vascular events, spur vascular risk factor reduction, and thereby improve vascular event prevention.[47] If LOE is confirmed as a risk marker of coronary artery disease, this knowledge could lead to improved vascular risk reduction in LOE. In addition, the incremental benefit and cost-effectiveness of screening patients with LOE for coronary artery disease may warrant investigation. Just as evidence has supported the inclusion of stroke as an outcome and risk equivalent in risk scores for vascular disease,[48,49] our present findings highlight the potential significance of LOE as a vascular risk equivalent or an indication for more aggressive vascular risk factor control. Future research is needed to determine whether LOE should be included as an incremental factor in risk equations.

Author Contributions

E.L. Thacker: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. H. Choi: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. K. Strobino: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. M. Liu: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. S. Misiewicz: drafting/revision of the manuscript for content, including medical writing for content. J.D. Beard: drafting/

revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. M.R. Di Tullio: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. T. Rundek: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M.S.V. Elkind: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J. Gutierrez: 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.

Study Funding

This work was supported by the NIH (grants R01AG074355, R01AG057709, R01AG066162, and R56NS029993).

Disclosure

E.L. Thacker, H. Choi, and J. Gutierrez were supported by the National Institute on Aging (R01AG074355). T. Rundek, M.S.V. Elkind, and J. Gutierrez were supported by the National Institute on Aging and the National Institute of Neurological Disorders and Stroke (R01AG057709, R01AG066162, and R56NS029993). The other authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology*® February 14, 2025. Accepted in final form August 15, 2025. Submitted and externally peer reviewed. The handling editors were Associate Editor Emily Johnson, MD, MPH, and Associate Editor Barbara Jobst, MD, PhD, FAAN.

References

1. Choi H, Pack A, Elkind MS, Longstreth WT Jr, Ton TG, Onchiri F. Predictors of incident epilepsy in older adults: the Cardiovascular Health Study. *Neurology*. 2017;88(9):870-877. doi:10.1212/wnl.0000000000003662
2. Johnson EL, Krauss GL, Lee AK, et al. Association between midlife risk factors and late-onset epilepsy: results from the Atherosclerosis Risk in Communities Study. *JAMA Neurol*. 2018;75(11):1375-1382. doi:10.1001/jamaneurol.2018.1935
3. Galovic M, Ferreira-Atuesta C, Abraira L, et al. Seizures and epilepsy after stroke: epidemiology, biomarkers and management. *Drugs Aging*. 2021;38(4):285-299. doi:10.1007/s40266-021-00837-7
4. Johnson EL, Krauss GL, Lee AK, et al. Association between white matter hyperintensities, cortical volumes, and late-onset epilepsy. *Neurology*. 2019;92(9):e988-e995. doi:10.1212/wnl.0000000000007010
5. Gibson LM, Hanby MF, Al-Bachari SM, Parkes LM, Allan SM, Emsley HC. Late-onset epilepsy and occult cerebrovascular disease. *J Cereb Blood Flow Metab*. 2014;34(4):564-570. doi:10.1038/jcbfm.2014.25
6. 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
7. 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
8. 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
9. 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
10. Razzouk L, Rockman CB, Patel MR, et al. Co-existence of vascular disease in different arterial beds: peripheral artery disease and carotid artery stenosis: data from Life Line Screening. *Atherosclerosis*. 2015;241(2):687-691. doi:10.1016/j.atherosclerosis.2015.06.029
11. Duvall WL, Vorchheimer DA. Multi-bed vascular disease and atherothrombosis: scope of the problem. *J Thromb Thrombolysis*. 2004;17(1):51-61. doi:10.1023/B:THRO.0000036029.56317.d1
12. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999;10(1):37-48. doi:10.1097/00001648-199901000-00008
13. Boden-Albala B, Sacco RL, Lee HS, et al. Metabolic syndrome and ischemic stroke risk: Northern Manhattan Study. *Stroke*. 2008;39(1):30-35. doi:10.1161/strokeaha.107.496588
14. Sacco RL, Boden-Albala B, Abel G, et al. Race-ethnic disparities in the impact of stroke risk factors: the Northern Manhattan Stroke Study. *Stroke*. 2001;32(8):1725-1731. doi:10.1161/01.str.32.8.1725
15. *Classification of Diseases, Functioning, and Disability*. National Center for Health Statistics. Accessed December 18, 2024. cdc.gov/nchs/icd/
16. Willey JZ, Rodriguez CJ, Moon YP, et al. Coronary death and myocardial infarction among Hispanics in the Northern Manhattan Study: exploring the Hispanic paradox. *Ann Epidemiol*. 2012;22(5):303-309. doi:10.1016/j.annepidem.2012.02.014
17. White H, Boden-Albala B, Wang C, et al. Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study. *Circulation*. 2005;111(10):1327-1331. doi:10.1161/01.Cir.0000157736.19739.D0
18. Special report from the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III. *Stroke*. 1990;21(4):637-676. doi:10.1161/01.str.21.4.637
19. Grieco EM, Cassidy RC. *Overview of Race and Hispanic Origin*. 2001. Accessed December 18, 2024. www2.census.gov/library/publications/decennial/2000/briefs/c2kbr01-01.pdf
20. *BRFSS Questionnaires*. Behavioral Risk Factor Surveillance System. Accessed December 18, 2024. cdc.gov/brfss/questionnaires/index.htm
21. Gardener H, Della Morte D, Elkind MS, Sacco RL, Rundek T. Lipids and carotid plaque in the Northern Manhattan Study (NOMAS). *BMC Cardiovasc Disord*. 2009;9:55. doi:10.1186/1471-2261-9-55
22. Greenland S, Daniel R, Pearce N. Outcome modelling strategies in epidemiology: traditional methods and basic alternatives. *Int J Epidemiol*. 2016;45(2):565-575. doi:10.1093/ije/dyw040
23. Akaike H. A new look at the statistical model identification. *IEEE Trans Autom Control*. 1974;19(6):716-723. doi:10.1109/TAC.1974.1100705
24. Suh JW, Floud S, Reeves GK, Cairns BJ, Wright FL. Multimorbidity of cardiovascular disease subtypes in a prospective cohort of 1.2 million UK women. *Open Heart*. 2023;10(2):e002552. doi:10.1136/openhrt-2023-002552
25. Nakai M, Iwanaga Y, Sumita Y, et al. Associations among cardiovascular and cerebrovascular diseases: analysis of the nationwide claims-based JROAD-DPC dataset. *PLoS One*. 2022;17(3):e0264390. doi:10.1371/journal.pone.0264390
26. Soler EP, Ruiz VC. Epidemiology and risk factors of cerebral ischemia and ischemic heart diseases: similarities and differences. *Curr Cardiol Rev*. 2010;6(3):138-149. doi:10.2174/157340310791658785
27. Fernández-Friera L, Peñalvo JL, Fernández-Ortiz A, et al. Prevalence, vascular distribution, and multiterritorial extent of subclinical atherosclerosis in a middle-aged cohort: the PESA (Progression of Early Subclinical Atherosclerosis) study. *Circulation*. 2015;131(24):2104-2113. doi:10.1161/circulationaha.114.014310
28. Hoshide S, Kario K, Mitsuhashi T, et al. Different patterns of silent cerebral infarct in patients with coronary artery disease or hypertension. *Am J Hypertens*. 2001;14(6 pt 1):509-515. doi:10.1016/s0895-7061(00)01293-0
29. Vuong J, Devergnas A. The role of the basal ganglia in the control of seizure. *J Neural Transm (Vienna)*. 2018;125(3):531-545. doi:10.1007/s00702-017-1768-x
30. Uekita K, Hasebe N, Funayama N, et al. Cervical and intracranial atherosclerosis and silent brain infarction in Japanese patients with coronary artery disease. *Cerebrovasc Dis*. 2003;16(1):61-68. doi:10.1159/000070117
31. Giele JL, Witkamp TD, Mali WP, van der Graaf Y; SMART Study Group. Silent brain infarcts in patients with manifest vascular disease. *Stroke*. 2004;35(3):742-746. doi:10.1161/01.Str.0000117572.56058.2a
32. Doerrfuss JI, Hebel JM, Holtkamp M. Epileptogenicity of white matter lesions in cerebral small vessel disease: a systematic review and meta-analysis. *J Neurol*. 2023;270(10):4890-4902. doi:10.1007/s00415-023-11828-6
33. Bentes C, Pimentel J, Ferro JM. Epileptic seizures following subcortical infarcts. *Cerebrovasc Dis*. 2001;12(4):331-334. doi:10.1159/000047730
34. Ferreira-Atuesta C, Döhler N, Erdélyi-Canavese B, et al. Seizures after ischemic stroke: a matched multicenter study. *Ann Neurol*. 2021;90(5):808-820. doi:10.1002/ana.26212
35. Kneihsl M, Gattringer T, Hofer E, et al. Cerebral white matter hyperintensities indicate severity and progression of coronary artery calcification. *Sci Rep*. 2024;14(1):4664. doi:10.1038/s41598-024-55305-0
36. Johansen MC, Gottesman RF, Kral BG, et al. Association of coronary artery atherosclerosis with brain white matter hyperintensity. *Stroke*. 2021;52(8):2594-2600. doi:10.1161/strokeaha.120.032674
37. Bos D, Ikram MA, Elias-Smale SE, et al. Calcification in major vessel beds relates to vascular brain disease. *Arterioscler Thromb Vasc Biol*. 2011;31(10):2331-2337. doi:10.1161/atvbaha.111.232728
38. Sheibani N, Wong KH, Turan TN, et al. White matter hyperintensity and cardiovascular disease outcomes in the SPRINT MIND trial. *J Stroke Cerebrovasc Dis*. 2021;30(6):105764. doi:10.1016/j.jstrokecerebrovasdis.2021.105764
39. Maxwell H, Hanby M, Parkes LM, Gibson LM, Coutinho C, Emsley HC. Prevalence and subtypes of radiological cerebrovascular disease in late-onset isolated seizures and epilepsy. *Clin Neurol Neurosurg*. 2013;115(5):591-596. doi:10.1016/j.clineuro.2012.07.009
40. Hanby MF, Al-Bachari S, Makin F, Vidyasagar R, Parkes LM, Emsley HC. Structural and physiological MRI correlates of occult cerebrovascular disease in late-onset epilepsy. *Neuroimage Clin*. 2015;9:128-133. doi:10.1016/j.nicl.2015.07.016

41. 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
42. 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
43. Abbasi A, Abbasi B, Mintzer S, LoPinto-Khoury C. Antiseizure medications and their differing effects on cardiovascular risk. *Epilepsy Behav Rep*. 2025;29:100746. doi: 10.1016/j.ebr.2025.100746
44. Sánchez Fernández I, Gaínza-Lein M, Amengual-Gual M, et al. Evolution of antiseizure medication use and cost in the United States of America 2006-2021. *Seizure*. 2023;112:128-138. doi:10.1016/j.seizure.2023.10.005
45. Wen X, Otoo MN, Tang J, et al. Angiotensin receptor blockers for hypertension and risk of epilepsy. *JAMA Neurol*. 2024;81(8):866-874. doi:10.1001/jamaneurol.2024.1714
46. Doege C, Luedde M, Kostev K. Association between angiotensin receptor blocker therapy and incidence of epilepsy in patients with hypertension. *JAMA Neurol*. 2022; 79(12):1296-1302. doi:10.1001/jamaneurol.2022.3413
47. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11):e596-e646. doi:10.1161/CIR.0000000000000678
48. Dhamoon MS, Elkind MS. Inclusion of stroke as an outcome and risk equivalent in risk scores for primary and secondary prevention of vascular disease. *Circulation*. 2010; 121(18):2071-2078. doi:10.1161/circulationaha.109.921072
49. Lackland DT, Elkind MS, D'Agostino R Sr, et al. Inclusion of stroke in cardiovascular risk prediction instruments: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2012;43(7): 1998-2027. doi:10.1161/STR.0b013e31825bcdac