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Late-Onset Epilepsy and 25-Year Cognitive Change: The Atherosclerosis Risk in Communities (ARIC) Study

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Summary

Objective: To define the association between late-onset epilepsy (LOE) and 25-year change in cognitive performance.

Methods: The Atherosclerosis Risk in Communities (ARIC) study is a multicenter longitudinal cohort study with participants from 4 U.S. communities. From linked Medicare claims, we identified cases of LOE, defined as ≥2 seizure-related diagnostic codes starting at age ≥67. The ARIC cohort underwent evaluation with in-person visits at intervals of 3–15 years. Cognition was evaluated 4 times over >25 years (including before the onset of seizures) using the delayed word recall (DWRT), digit symbol substitution (DSST), and word fluency (WFT) tests; a global z score was also calculated. We compared the longitudinal cognitive changes of participants with and without LOE, adjusting for demographics and LOE risk factors.

Results: From 8,033 ARIC participants with midlife cognitive testing and Medicare claims data available (4523 [56%] female, 1392 [17%] black), we identified 585 cases of LOE. The rate of cognitive decline was increased on all measures in the participants who developed LOE compared to those without LOE. On the measure of global cognition, participants with LOE declined by −0.43 z-score points more over 25 years than did participants without epilepsy (95% CI −0.59, −0.27). Prior to the onset of seizures, cognitive decline was more rapid on the DWRT, DSST, and

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Ethical Publication Statement
We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

global z-scores in those who would later develop LOE than it was in non-LOE participants. Results were similar after excluding data from participants with dementia.

Significance: Global cognition, verbal memory, executive function, and word fluency declined faster over time in persons developing LOE than without LOE. Declines in cognition preceding LOE suggests these are linked; it will be important to investigate causes for midlife cognitive declines associated with LOE.

Keywords

Epilepsy; Late-onset; Cognition; Dementia; Longitudinal

Introduction

New-onset epilepsy is more common in older adults than at any other time in life[1–4], affecting 15 to 50 per 1000 older adults, and over 700,000 people in the U.S. Medicare population alone[4]. Stroke and neurodegenerative disease are major causes of late-onset epilepsy (LOE; i.e., epilepsy starting at age 60 or later)[3,5–7], as well as causes of cognitive impairment. However, many cases of LOE occur in persons without a known history of these conditions. We previously showed that LOE is associated with vascular risk factors such as hypertension and diabetes[8] and with the apolipoprotein E4 genotype (APOE4; the major genetic risk factor for Alzheimer's disease[9], AD), even in non-demented persons[8]. However, the cognitive course in persons with LOE without dementia or stroke is unknown.

Some studies of cognition in patients with epilepsy (of all ages) suggest declines in memory over time[10–13], but there are few longitudinal studies of cognition in LOE. Given the relatively common co-occurrence of epilepsy with dementia[14–17] and recently reported increased risk of dementia in persons with LOE[18], longitudinal studies of cognition in patients with acquired LOE would be particularly informative to determine the relationship of LOE to cognitive decline. Risk factors for LOE such as ischemic stroke, hypertension, and diabetes[8] are associated with steeper declines in cognition over time[19–21], but the cognitive trajectory of persons with LOE without stroke or dementia is unclear.

To characterize longitudinal cognitive changes in persons with LOE, we analyzed cognitive scores from ages 45–64 to 72–94 among participants of the Atherosclerosis Risk in Communities (ARIC) study, which included testing prior to the first seizure. Because of the known association between epilepsy and dementia[14–16,18] and our previous studies linking LOE with the APOE4 genotype and with vascular risk factors[8], we hypothesized that persons who develop LOE would have a more rapid decline in cognitive scores than those without LOE – even in the absence of clinically diagnosed dementia.

Methods

Study population

This is an analysis of prospectively collected longitudinal cohort study data. The Atherosclerosis Risk in Communities (ARIC) study conducted initial study visits in 1987–1989 among 15,792 black and white men and women, ages 45–64 years, selected through probability sampling from 4 U.S. communities (Jackson, MS; Forsyth County, NC; Washington County, MD; and suburbs of Minneapolis, MN). Cohort members participated in 6 in-person visits between 1987–2017 (Figure 1; with a seventh visit in process at the time of this analysis), and have been contacted annually (and since 2012, semiannually) by telephone to provide health status updates. In addition, Centers for Medicare and Medicaid Services (CMS) claims data have been linked with participants' data[22]. We included black participants in MS and NC and white participants in MN, MD, and NC, and excluded those of other races, as is standard in ARIC due to small numbers[8]. We excluded those who did not give permission for use of DNA. We excluded those with a known history (at any time) of brain tumor, brain radiation, brain surgery, or multiple sclerosis. To omit persons with prevalent cognitive impairment, we excluded participants who scored below the 5th percentile at the time of baseline cognitive testing.

Institutional Review Board Approval and Patient Consent

All participants provided written informed consent at each study visit. The institutional review boards at each participating institution approved the study.

Cognitive assessments

At ARIC Visits 2, 4, 5, and 6 (Figure 1), participants were administered the Delayed Word Recall Test (DWRT), a test of verbal memory; Digit Symbol Substitution Test (DSST), a measure of executive function; and Word Fluency Test (WFT), a measure of language fluency; which have been previously described[19,23]. In the DWRT, participants learn 10 common nouns by reading each word, and using it in a sentence. Participants are then asked to recall each of the words (after a 5-minute delay filled with distractors). In the DSST, participants are asked to convert as many numbers to symbols as possible in 90 seconds, using a key (maximum score 93). In the WFT, participants are asked to generate as many words as possible for the letters S, F, and A (with 60 seconds for each letter).

Individual scores were converted to z-scores using Visit 2 means and standard deviations as referents. We calculated a global measure of cognition for each participant from the individual z-scores, which was then converted to a global z-score using Visit 2 mean and standard deviation as referents[19,20,23,24].

Covariates

Seated blood pressure was measured 3 times, and the 2nd and 3rd values averaged; hypertension was defined as systolic blood pressure mean ≥140mmHg, diastolic blood pressure mean ≥90mmHg, or use of an antihypertensive medication. We defined diabetes as fasting blood glucose ≥126mg/dL, nonfasting blood glucose ≥200mg/dL, use of diabetic medications or insulin, or self-report of physician-diagnosed diabetes. We defined hyperlipidemia as total cholesterol ≥200 mg/dL, and calculated body mass index (BMI) from height and weight. Participants reported smoking and alcohol use at each visit (never, former, current). The APOE4 genotype was ascertained at Visit 1, and participants classified as having 0, 1, or 2 Apo ε4 alleles (TaqMan assay; Applied Biosystems, Foster City, CA)[25]. Depression was self-reported at Visit 5.

Identification of late-onset epilepsy

To identify LOE, we used an ICD screening method which has previously been validated in claims studies with chart review[26]. LOE was identified and defined as ≥2 seizure-related ICD-9 or ICD-10 primary diagnostic codes (345.00–345.91, 780.39, G40.0-G40.919, or R56.9) identified from CMS Medicare fee-for-service (FFS) claims from 1991 through 2015 (one outpatient and one inpatient claim, 2 separate inpatient claims, or 2 claims for separate outpatient visits from the Carrier and outpatient claims). To identify incident cases, we included only participants with at least two years of seizure-free claims data prior to the first seizure-related code, and participants with the first seizure-related code at age 67 or later (to allow for 2 years of seizure-free claims following Medicare eligibility at age 65). This and similar definitions have previously been used in claims-based research[4,5,8,27] and have been validated with chart review[26]. We excluded individuals with less than 2 years of FFS coverage or gaps in coverage.

Statistical analysis

We used Stata 15.0 (College Station, TX) for statistical analysis. To compare change in cognitive scores over time in participants ever diagnosed with LOE to those without LOE, we used a generalized estimating equation (GEE) with unstructured correlation matrix and robust variance. The GEE contains linear spline terms representing the time in years since the Visit 2 cognitive testing baseline, with a knot 6 years post Visit 2 (as is standard in ARIC analyses, due to the long interval between Visits 4 and 5)[19]. We adjusted the models for baseline age, baseline age squared, and interactions between time, baseline age, and baseline age-squared terms. We adjusted for hypertension, diabetes, hyperlipidemia, BMI, education, center-race, smoking status (current, former, never), and drinking status (current, former, never) ascertained at Visit 2 cognitive baseline, and APOE4 genotype which was ascertained at Visit 1. We used a LOE-by-time term to estimate the cognitive trajectories of participants with and without LOE, and then used this annualized change to estimate the excess 25-year change experienced by participants with LOE compared to those without LOE.

Effect of timing of seizure onset

To examine the effect of the timing of seizure development on cognitive change, we used GEEs as described above, and a time-LOE spline term with a knot at the visit prior to development of LOE (as defined by the first seizure-related code). We used marginal construction of the post-seizure spline term to statistically compare the change in slope from the pre-seizure spline term. Both terms were compared to individuals without LOE as the reference group.

Interactions

We examined the data for of interactions between LOE and race, and between LOE and sex, and conducted stratified analyses when an interaction was present.

Sensitivity analyses: effects of stroke, dementia, traumatic brain injury, and possible unrecognized seizures

Since stroke is a risk factor for LOE[7,8,28] and causes cognitive decline[21], we performed a sensitivity analysis adjusting for ischemic or hemorrhagic stroke to identify cognitive changes not due to stroke. In participants who developed a stroke, we introduced a time-varying variable to adjust for stroke, which was 0 prior to the date of stroke and 1 afterwards. Stroke information from hospitalization records and self-report is collected for all ARIC participants, and adjudicated by computer algorithm and physician reviewers[29].

Since dementia is a known risk factor for LOE[6,8], we conducted a sensitivity analysis excluding participants at the time of and after a diagnosis of dementia, which is ascertained from informant interviews and neurocognitive assessments from Visits 2–6, surveillance data, and telephone interviews with informants or participants[30]. We performed this analysis to determine whether cognitive decline in the setting of dementia was driving all the observed cognitive changes.

To focus solely on cognitive changes in participants without a known symptomatic etiology for LOE, we also conducted a sensitivity analysis excluding all visits after a diagnosis of stroke, dementia, or traumatic brain injury (obtained from ICD-9 and ICD-10 codes[31]). Those with known brain tumor, surgery, radiation, and multiple sclerosis are excluded from all analyses.

To investigate the possibility that undiagnosed seizures caused the observed pre-seizure cognitive decline, we also performed sensitivity analyses excluding data from visits that occurred ≤2 and ≤3 years prior to the first seizure code.

Effect of missing data

We used multiple imputations with chained equations (MICE) in a sensitivity analysis to account for attrition due to visit non-participation or death, as has been previously been described and validated in ARIC[32]. We used baseline (Visit 2) cognitive scores and participant covariates (as detailed above) to impute missing cognitive data.

Results

Baseline cognitive testing at Visit 2 and complete covariate data was available on 8,033 participants; 1721 (20.4%) were black, and 4851 (57%) female. 585 developed LOE during follow-up (incidence 3.62 per 1000 person-years; 95% confidence interval 3.33–3.92. This was similar to our previously-reported incidence of 3.33 per 1000 person-years in the full ARIC cohort[8]). Patient characteristics are summarized in Table 1, with the numbers and reasons for exclusions in Figure 1. All participants with LOE had baseline testing prior to the first seizure code, and testing 1–3 times after the first seizure code (Figure 1). At baseline (Visit 2), the correlation between z scores for all participants on the measure of verbal memory (DWRT) and executive function (DSST) was 0.39, between executive function (DSST) and verbal fluency (WFT) was 0.52, and between verbal memory (DWRT) and word fluency (WFT) was 0.30.

Participants who developed LOE had steeper global cognitive decline by −0.43 z-score points over 25 years (adjusted as above; 95%CI −0.56, −0.28; Figure 2) than did those without LOE (−0.017 z-score points annually; 95% CI −0.023, −0.011). We observed similar effects for all individual tests (Table 2). The excess decline associated with LOE is comparable to an age-associated difference of 6.5 years (i.e., a reduced z-score of −0.43 standard deviations in participants developing LOE corresponds to the difference in cognitive performance between a 55-year-old and a 61.5-year-old person at baseline).

Changes in cognitive decline before and after onset of LOE

When we examined cognitive decline occurring only before the first seizure-related code, those who would later develop LOE declined more rapidly on the measure of global cognition than did those without LOE by −0.21 z-score points over 14 years (the median time from baseline testing to the first seizure among those with LOE; 95% CI −0.35, −0.08). We observed similar results on the DWRT and DSST prior to the first seizure (Table 2).

After the first seizure, participants with LOE had more rapid decline on global cognition than did those without LOE by −0.19 z-score points over 8 years (the median time from first seizure to last cognitive testing among those who with LOE who attended Visit 6; 95% CI −0.32, −0.06). We observed similar results on the DSST and WFT after the first seizure (Table 2).

After the first seizure, participants' DSST and WFT performance declined more steeply than it did prior to their seizures, Table 2.

Interactions

The effect of LOE on the decline over time was greater in white participants than in black participants on the DSST. White participants with LOE declined by −0.36 (95% CI −0.48, −0.26) z-score points more over 25 years than did white participants without LOE, while black participants with LOE declined by −0.18 (95% CI −0.42, 0.05) z-score points more over 25 years than did black participants without LOE (p-interaction 0.003; Figure 3). There was no difference by race in the effect of LOE on the decline over time on the global, DWRT, or WFT z-scores.

The effect of LOE on cognitive change over time did not differ by sex.

Sensitivity analyses: effects of stroke, dementia, traumatic brain injury, and unrecognized seizures

In a sensitivity analysis adjusting for participants' history of stroke using a time-varying variable, the more rapid declines in cognition in all domains found in participants with LOE compared to without LOE persisted (Supplemental Table 1). In the sensitivity analysis excluding participants after dementia diagnosis, the more rapid cognitive changes in all domains demonstrated in participants with LOE compared to without LOE also persisted (Supplemental Table 2).

In a sensitivity analysis excluding all participants after a diagnosis of stroke, dementia, or traumatic brain injury (those with known brain tumor, surgery, radiation, and multiple sclerosis already excluded) focusing solely on cognitive changes in participants without a known symptomatic etiology for LOE, the excess cognitive change identified in all domains over 25 years was still present. Prior to the first seizure, the excess change in global z-score (−0.44, 95% CI −0.73, −0. 16) and DWRT z-score (−0.73, 95% CI −1.09, −0.37) persisted (Supplemental Table 3).

To exclude effects of delay in diagnosis of seizures, we performed a sensitivity analysis excluding data from 190 visits which occurred ≤2 years prior to the first seizure-related code. The more rapid decline in the DWRT observed in participants with LOE prior to the first seizure compared to those without LOE persisted, as did the more rapid overall declines in the global, DWRT, and DSST z-scores among those with LOE compared to those without LOE (Supplemental Table 4). Results were also similar after excluding data from the 219 visits from participants with LOE which occurred within 3 years prior to a first seizure.

We also performed a sensitivity analysis to adjust for a diagnosis of depression to evaluate the possible effects of depression in persons with epilepsy. This did not substantially alter the results. In this analysis, the adjusted global z-score change over 25 years in participants with LOE compared to those without was −0.42 z-scores (95% CI −0.60, −0.25).

Effect of Missing Data

ARIC participants with LOE were less likely to complete all visits than were participants without LOE (Figure 1). Therefore, to account for the effects of missing data, we used multiple imputations with chained equations (MICE) to impute the missing cognitive scores, a technique which has been previously validated in ARIC for cognitive scores[32]. The findings of more rapid annual cognitive change on global cognition and all subtests in participants with LOE persisted after using MICE to impute missing data from Visits 4, 5, and 6 (Supplemental Table 5). Using imputed values, there was no change in rate of cognitive decline between pre- and post-seizure intervals for any tests.

Discussion

In our study of 8,033 adults followed for up to 26 years, we found that those who developed LOE had faster cognitive decline over time than did those without LOE. Moreover, steeper cognitive decline occurred prior to the first seizure, and became more rapid after the development of seizures on some measures. The adjusted decline we observed for LOE (−0.43 excess global z-score points over 25 years) is larger than the observed adjusted effects of hypertension (−0.07 excess global z-score points over 25 years) or diabetes (−0.19 excess global z-score points over 25 years) measured in other studies[19,20].

To our knowledge, this is the first study examining cognitive changes prior to the development of LOE, and the first longitudinal study of cognition in LOE to be able to adjust for comorbidities such as hypertension and diabetes which also affect cognitive function. Our findings are consistent with prior longitudinal studies of patients diagnosed with epilepsy at any age which demonstrated possible “accelerated cognitive ageing[10,33].” Our findings for LOE are supported by a recent study showing a higher rate of progression to dementia after 3 years in patients with LOE compared to controls[34], and a large claims-based study of U.S. veterans found an elevated rate of incident dementia over the period of study follow-up[18]. We also found, however, that steeper declines in cognitive performance began prior to participants' first seizures (which persisted after we excluded measurements within 2 and 3 years of the first seizure, to minimize the effect of undetected seizures).

Vascular and metabolic disease are possible contributors to these findings. We observed declines even prior to the onset of seizures on the test of executive function (DSST), which is associated with small vessel disease[35]. Vascular risk factors such as hypertension and diabetes are also associated with LOE[8], as are white matter hyperintensities (a marker of cerebral small vessel disease)[27]. Vascular dementia is a leading cause of cognitive decline, and microvascular disease affecting subcortical networks could explain some of our findings[35]. Metabolic dysfunction, such as altered glucose metabolism that leads to synaptic dysfunction and neuronal injury, is another possible cause of cognitive impairment[36] that could also lead to seizures. Type 2 diabetes is a risk factor for AD[36], and we previously identified diabetes as a risk factor for LOE[8].

In our study, the steepest pre-seizure declines in participants with compared to without LOE occurred on the measure of verbal memory (DWRT); performance on this test is compromised in individuals with amnestic mild cognitive impairment and AD[37]. Our findings persisted after excluding participants with diagnosed dementia, suggesting LOE could be associated with early-stage, subclinical neuropathologic changes. There has been prior evidence that AD-related neuropathology may contribute to cognitive decline in some persons who develop LOE: LOE is associated with AD[38] and with having the APOE4 genotype[8]. Amyloid-β has previously been hypothesized as a possible cause of seizures in AD[14], and one small study found that patients with LOE (without dementia) had higher levels of pathologic CSF markers of amyloid-β and tau than did control patients without LOE[34]. The cognitive tests used in the current study are not sufficient to determine whether participants have Alzheimer's-type, vascular-type, or mixed cognitive changes. Most likely, there are subsets of LOE associated with each type of pathology, just as many individuals with dementia have mixed pathologies[39].

The major identified causes of LOE in other series are cerebrovascular disease, dementia, brain injuries, and tumors[3,40,41]. Another cause of new-onset epilepsy in adults (of all ages) is autoimmune-mediated epilepsy, which may account for a large share of unexplained cases (up to 35% of adults of all ages in one series[42]). One descriptive series of 32 patients autoimmune epilepsy included 15 adults with autoimmune epilepsy and seizures starting at age 60 or later[43]. These epilepsies may be associated with cognitive impairment as well as seizures, and are often difficult to diagnose[43]; some of the participants with LOE in this study may have had an autoimmune etiology. Further studies to understand the importance of autoimmune epilepsy in older adults and to describe the cognitive impact of these epilepsies are needed.

It will be important to determine the causes of cognitive decline in this population to identify risk factors that can be improved. Cognitive changes in persons with LOE should be investigated within the current framework of dementia pathophysiology and cognitive loss with aging, and possibly modifiable factors such as diet, exercise, and lifestyle[44] should be addressed. Clinicians must be aware of the potential for this impairment, as persons with LOE may develop difficulty with medication management and other daily tasks. Identification of this risk may also help clinicians and families in planning for future needs of patients with LOE.

The unique strengths of this study include the large number of participants and >25-year longitudinal follow up, which includes cognitive testing prior to the first seizure. This study also has several limitations. Diagnosis using ICD codes is a potential limitation due to the risk of misclassification; however, previous studies using this method have shown that the use of ≥2 ICD codes has 94.4% sensitivity and 91.7% specificity for the identification of epilepsy, validated using chart review[26]. Similar claims-based definitions are used and generally corroborated and accepted in research on epilepsy in the elderly population[4,5]. Seizures developing late in life are often mild focal unaware or focal sensory seizures, which may cause a delay in diagnosis[45]. However, we showed in a sensitivity analysis that delayed diagnosis of seizures was unlikely to account for the entirety of this cognitive decline; it seems likely, therefore, that shared pathologic mechanisms account for cognitive losses and later seizures. We also do not have information about the type and frequency of participants' seizures, and whether there was a difference between participants with and without medically refractory epilepsy. However, other studies of LOE have shown that new seizures in older patients new epilepsies are overwhelmingly focal rather than generalized onset seizures[2,46], and in characterized series the majority are temporal[47,48] or frontal[1] in origin; this cohort is likely to be similar. MRI was not available on many participants, precluding assessment for mesial temporal pathology. As there is an association between the severity of both hypertension[19] and diabetes[20] and increased cognitive decline (with benefits from treatment of these vascular risk factors[19,49]), greater detail about the severity of epilepsy to allow correlation with cognitive decline would be of great interest. Another limitation is the lack of information about whether and when antiseizure medications were prescribed (as specific medication data was not available on all participants), and whether some or all of the observed changes after LOE onset could be due to medication effect, and whether antiseizure treatment could alter the cognitive trajectory. However, the finding that cognitive decline started before seizure onset implies that a neuropathologic process beyond medication effects contributed to cognitive changes. In addition, while ARIC participants with LOE were less likely to complete all visits than were participants without LOE, adjustment for missing data using multiple imputations did not affect the main results. The finding that some increased cognitive decline precedes the first seizure is also unaffected by participant attrition. We do not have specific information about specific etiologies of epilepsy given the nature of the data, which would be vital to understanding an individual patient's course. To identify the cognitive changes in those without a known symptomatic etiology, we include a sensitivity analyses excluding participants after a diagnosis of stroke, dementia, or traumatic brain injury; those with known brain tumor, surgery, radiation, and multiple sclerosis are excluded from all analyses.

We identified steeper declines in cognitive performance in participants with LOE, who were tested up to 20 years prior to their first seizure. The fact that more rapid changes were observed even prior to the development of seizures suggests that at least some of the differences in some persons with LOE without a clear symptomatic etiology could be due to underlying neuropathology, rather than simply a medication or seizure effect.

Late-onset epilepsy is associated with excess cognitive decline during the 25-year ARIC study. Declines on global cognition, verbal memory, and executive function occur before the onset of seizures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points:

- Cohort study participants with late-onset epilepsy (LOE) had faster cognitive decline over 25 years than did participants without LOE
- Some cognitive decline in participants with LOE occurred prior to the first seizure
- We observed early changes on the measure of verbal memory, measure of executive function, and measure of global cognition

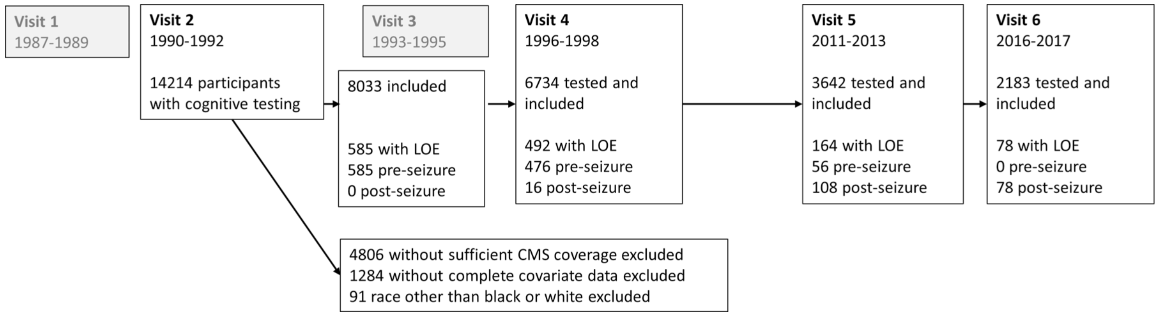

Figure 1: Timeline of Atherosclerosis Risk in Communities study and numbers of participants included from each visit.

Abbreviations: LOE, Late-onset epilepsy; CMS, Centers for Medicare and Medicaid Services. Participants were tested with the delayed word recall test, digit symbol substitution test, and word fluency test at visits 2, 4, 5, and 6. Numbers of participants with LOE are those ever determined to have LOE, broken down by pre-first seizure and post-first seizure.

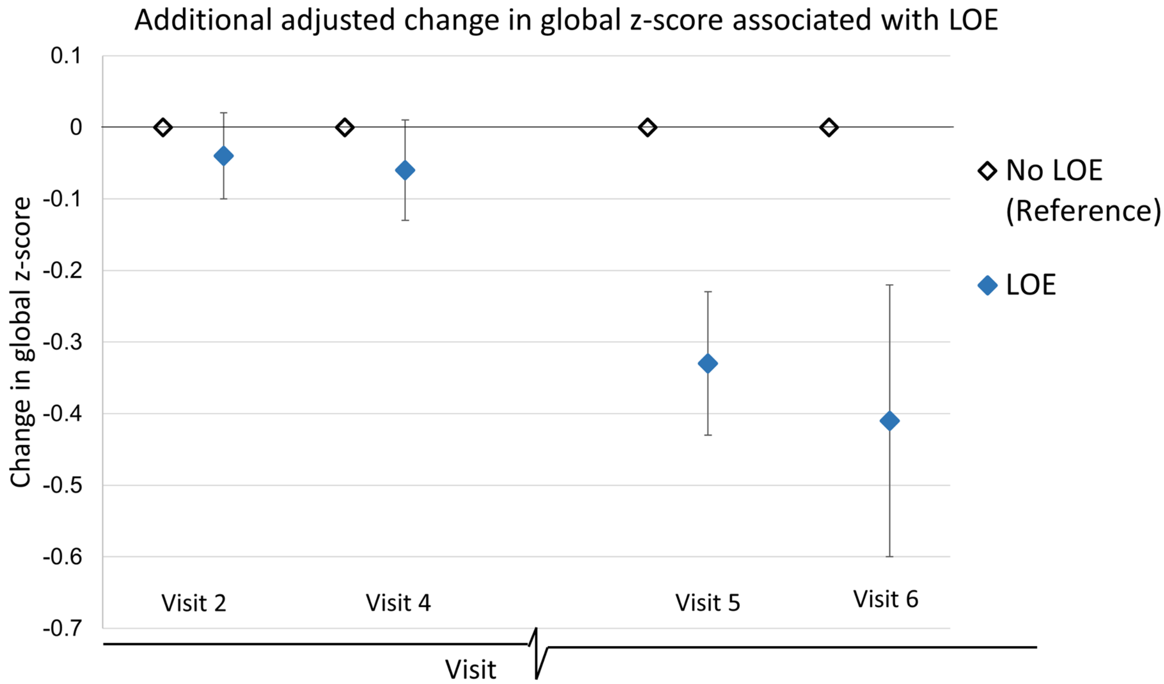

Figure 2: Adjusted excess change in global z-score in participants with late-onset epilepsy (LOE) compared to those without LOE.

Model adjusted for baseline age, age-squared, time since baseline (linear spline), age and age-squared-time interaction terms, sex, education, center/race, hypertension, diabetes, body mass index, hyperlipidemia, apolipoprotein E4 genotype, smoking history, and alcohol use history. Error bars represent 95% confidence interval.

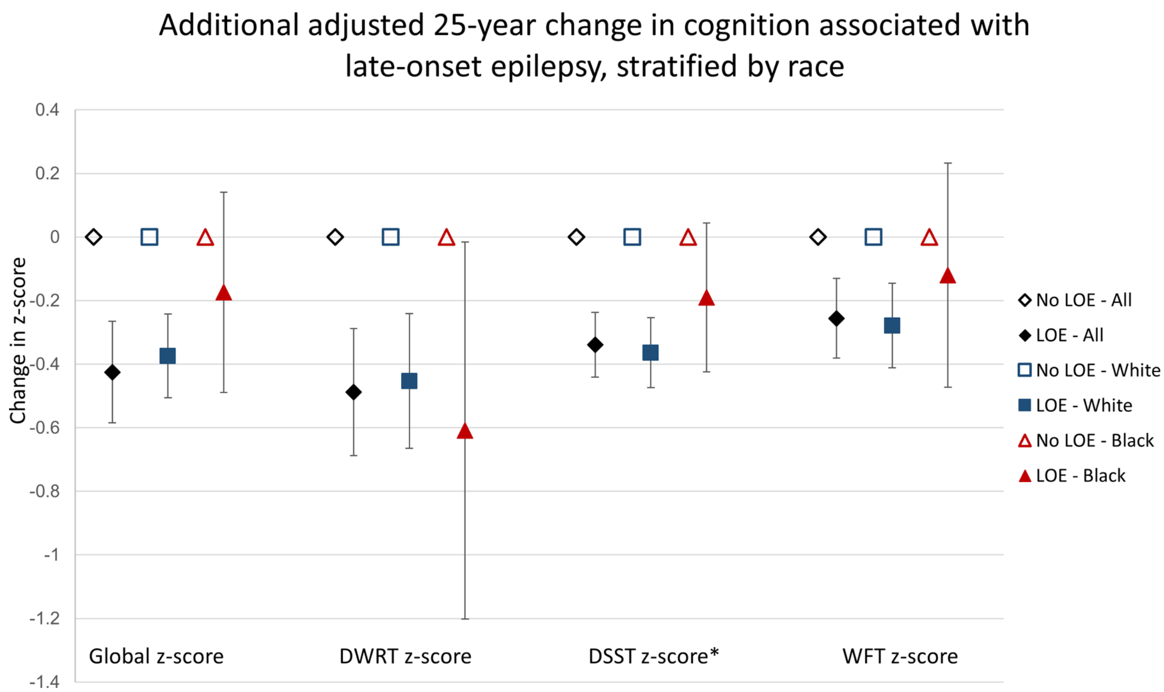

Figure 3: Additional adjusted 25-year change in cognition associated with late-onset epilepsy (LOE), stratified by race.

Stratified changes in z-scores for participants with LOE are compared to those of the same race without LOE. DWRT = delayed word recall test; DSST = digit symbol substitution test; WFT = word fluency test. Models adjusted for baseline age, age-squared, time since baseline (linear spline), age and age-squared-time interaction terms, sex, education, field center, hypertension, diabetes, body mass index, hyperlipidemia, apolipoprotein E4 genotype, smoking history, and alcohol use history. Error bars represent 95% confidence interval.

* = p-interaction <0.05 between race and effect of LOE.

Table 1:

Baseline (Visit 2) characteristics of ARIC participants included in study.

No. (%)	Without LOE n=7448	With LOE n=585	p-value
Age, mean (SD), years	**57.7 (5.7)**	**59.4 (5.3)**	**<0.001**
Female	4164 (56.2)	341 (58.3)	0.315
Black	1288 (17.3)	104 (17.8)	0.766
≥ HS education	6249 (83.9)	478 (81.7)	0.166
Hypertension *	**2035 (27.3)**	**192 (32.8)**	**0.004**
Diabetes *	**912 (12.2)**	**106 (18.1)**	**<0.001**
BMI, mean (SD)	27.7 (5.2)	27.9 (5.3)	0.350
Hyperlipidemia	410 (5.5)	34 (5.8)	0.754
APOE4 genotype *			**0.034**
1 allele	**2025 (27.2)**	**171 (29.2)**	
2 alleles	**170 (2.3)**	**22 (3.8)**	
Smoking Status			0.345
Former	2896 (38.9)	242 (41.4)	
Current	1497 (20.1)	105 (17.8)	
Alcohol Use			0.982
Former	1425 (19.1)	111 (19.0)	
Current	4444 (59.7)	349 (59.7)	

Number of participants with late-onset epilepsy (LOE) is those diagnosed at any time during study follow up. Abbreviations: ARIC, Atherosclerosis Risk in Communities; SD, standard deviation; HS, high school; BMI, body mass index; APOE4, apolipoprotein E4 genotype.

* = p<0.05.

Table 2:

Additional adjusted 25-year cognitive change associated with late-onset epilepsy (LOE).

	No LOE	LOE (all)	95% CI
	n=7448	n=585	
Global z score	0 (Reference)	**−0.43**	**(−0.59, −0.27)**
DWRT z score	0 (Reference)	**−0.49**	**(−0.69, −0.29)**
DSST z score	0 (Reference)	**−0.34**	**(−0.44, −0.24)**
WFT z score	0 (Reference)	**−0.26**	**(−0.38, −0.13)**
DWRT raw score	0 (Reference)	**−0.75**	**(−1.05, −0.44)**
DSST raw score	0 (Reference)	**−4.83**	**(−6.28, −3.37)**
WFT raw score	0 (Reference)	**−3.21**	**(−4.78, −1.64)**
	No LOE	**LOE (prior to first seizure only)**	**95% CI**
Global z score	0 (Reference)	**−0.38**	**(−0.62, −0.14)**
DWRT z score	0 (Reference)	**−0.67**	**(−0.98, −0.35)**
DSST z score	0 (Reference)	**−0.19**	**(−0.28, −0.00)**
WFT z score	0 (Reference)	−0.03	(−0.28, 0.21)
DWRT raw score	0 (Reference)	**−1.02**	**(−1.49, −0.54)**
DSST raw score	0 (Reference)	**−2.74**	**(−5.42, −0.06)**
WFT raw score	0 (Reference)	−0.41	(−3.50, 2.67)
	No LOE	**LOE (after first seizure only)**	**95% CI**
Global z score	0 (Reference)	**−0.60**	**(−1.01, −0.19)**
DWRT z score	0 (Reference)	−0.40	(−0.96, 0.16)
DSST z score *	0 (Reference)	**−0.62**	**(−0.89, −0.35)**
WFT z score *	0 (Reference)	**−0.62**	**(−0.93, −0.32)**
DWRT raw score	0 (Reference)	−0.62	(−1.47, 0.24)
DSST raw score *	0 (Reference)	**−8.80**	**(−12.60, −5.01)**
WFT raw score *	0 (Reference)	**−7.80**	**(−11.59, −4.01)**

Results are adjusted for age, age squared, time since baseline visit, sex, race/center, education, hypertension, diabetes, body mass index, hyperlipidemia, smoking status, alcohol use, and apolipoprotein E4 genotype. Comparisons are the additional decline attributable to LOE on global z scores, delayed word recall test (DWRT) z scores and raw number of words, digit symbol substitution test (DSST) z scores and raw number of symbols, word fluency test (WFT) z scores and raw number of words. Maximum raw score for the DWRT is 10 and for the DSST is 93, and maximum observed WFT score at baseline was 99.

* = significant change from pre-seizure trajectory, $p<0.05$.