

**ARIC Manuscript Proposal # 3181**

**PC Reviewed:** 6/12/18  
**SC Reviewed:** \_\_\_\_\_

**Status:** \_\_\_\_\_  
**Status:** \_\_\_\_\_

**Priority:** 2  
**Priority:** \_\_\_\_\_

**1.a. Full Title:** Cognitive trajectories and cognition in late-onset epilepsy

**b. Abbreviated Title (Length 26 characters):** Epilepsy and cognition

**2. Writing Group:**

Writing group members:

Emily Johnson, MD (first and corresponding author)

Rebecca Gottesman, MD, PhD

Greg Krauss, MD

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Thomas Mosley, PhD

Jason Brandt, PhD

Others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. EJ [please confirm with your initials electronically or in writing]

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**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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**3. Timeline:**

Months 1-4: data acquisition and analysis

Months 5-8: manuscript preparation

#### **4. Rationale:**

Late-onset epilepsy (i.e., starting at age 60 or older<sup>1</sup>) affects a large and growing number of persons worldwide. The yearly incidence of first seizure is higher in the elderly than at any other time of life<sup>2,3</sup>. In older adults without a prior history of seizures, the yearly incidence of epilepsy is 1.85% in those 80-84 yo and 3.25% in those who live to 90-94 yo<sup>3</sup>. Stroke and neurodegenerative diseases account for a share of late-onset epilepsy, but many patients have no obvious single cause of seizures.

There is a high incidence of seizures in patients with Alzheimer's disease (6-10%)<sup>4</sup>. We have previously shown that, after adjusting for demographics and other vascular and lifestyle risk factors, the apolipoprotein ε4 genotype is associated with late-onset epilepsy, with a dose-dependent effect (i.e., higher rates with 2 allele compared to 1 allele; under review). As apolipoprotein ε4 is associated with Alzheimer's disease and with cognitive decline, we hypothesize that some participants with late-onset epilepsy may also have early (preclinical) Alzheimer's-type pathology, and that their cognitive function will be lower than similar participants without late-onset epilepsy.

In addition, we have previously shown (using ARIC data) that hypertension, diabetes, smoking, physical activity, and alcohol use are associated with late-onset epilepsy (under review). In addition, we have previously shown that late midlife white matter hyperintensities are associated with the later development of epilepsy, and that lower cortical volumes are associated with a higher rate of late-onset epilepsy (manuscript in preparation). As these findings are also associated with lower cognitive scores, we have further reason to believe that participants with epilepsy will have lower cognitive scores than will similar participants without late-onset epilepsy.

#### **5. Main Hypothesis/Study Questions:**

We hypothesize that:

**H1.** Cognitive scores will be lower in participants diagnosed (at any point) with late-onset epilepsy than without late-onset epilepsy at each visit with cognitive testing, even in the absence of diagnosed dementia.

**H2.** Decline in cognitive scores over time will be larger in participants with late-onset epilepsy than without late-onset epilepsy.

**H3.** The rate of cognitive decline will change (increase) after the onset of seizures in participants with late-onset epilepsy, compared to the rate prior to that point and the rate in individuals who do not develop late-onset epilepsy.

**6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).**

**Study design:**

This will be a retrospective analysis of prospectively collected ARIC cohort data.

**Inclusions:**

Black and white ARIC participants with cognitive testing data available will be included.

Only participants with two or more cognitive assessments will be included in analyses of cognitive change over time.

**Exclusions:**

Participants missing cognitive testing from each visit (i.e., Visit 6) will be excluded from cross-sectional analyses using that visit (hypothesis H1).

Participants with cognitive testing available from only one visit will be excluded from longitudinal data analysis.

Participants with low cognition at baseline (<5<sup>th</sup> percentile on any cognitive test) will be excluded from analyses examining cognitive decline (H2 and H3).

We will address missing covariate data (i.e. hypertension) using multiple imputations.

**Primary Outcomes:**

Cognitive scores (delayed word recall test, DWRT; digit symbol substitution test, DSST; and word fluency test, WFT) measured at Visits 2, 4, 5, and 6;

Change in cognitive scores over time.

All tests will be standardized to z-scores to allow for the creation of a composite score and comparisons across tests.

**Independent variables:**

Epilepsy cases: We will identify cases of late-onset epilepsy using ICD-9 codes (from ARIC hospitalization data and from CMS data), identifying incident cases as those with  $\geq 2$  years of claims data available prior to the first seizure-related code, and limiting cases to those with a first seizure-related code at age 60 or later.

We will also include demographic factors (age, sex, a combined race-center variable, education) and risk factors for cerebrovascular disease and dementia: hypertension, diabetes, cholesterol, BMI, smoking history, alcohol use, and APOE $\epsilon$ 4 genotype.

Sex, race-center, and education history will be taken from Visit 1. The APOE $\epsilon$ 4 genotype was measured at Visit 1.

Hypertension, age, diabetes, cholesterol, BMI, smoking history, and alcohol use will be extracted from each visit for cross-sectional comparison of cognition in participants with and without late-onset epilepsy at that visit.

In longitudinal comparisons of cognitive change over time, hypertension, age, diabetes, cholesterol, BMI, smoking history, and alcohol will be extracted from the first visit used in the comparison of cognitive change (i.e., in a comparison of cognitive change from Visit 2 to Visit 6, independent variables that may vary over time will be extracted from Visit 2).

### **Summary of data analysis:**

H1. To compare cognitive scores in participants with and without late-onset epilepsy at each time point and to adjust for other variables related to cognition, we will use linear regression models with cognitive test z-score as the dependent variable, and late-onset epilepsy and the demographic and cerebrovascular risk factors listed above as independent variables. We will check for differing effects of epilepsy on cognition by race and sex, using interaction terms.

H2. As per ARIC-NCS Analysis Manual recommendations, generalizing estimating equations with an unstructured correlation matrix and robust variance will be used to estimate the difference in population-averaged trajectories of cognitive change over time by late-onset epilepsy status (ever diagnosed, never diagnosed). We will check for differing effects of epilepsy on cognition by race and sex, using interaction terms.

H3. We will identify the date of first seizure diagnosis in participants with late-onset epilepsy, and will compare cognitive trajectory prior to the development of epilepsy (i.e. change in cognition between visits prior to the development of epilepsy) to cognitive trajectory after the development of epilepsy (i.e. change in cognition between visits following the diagnosis of epilepsy); as per ARIC-NCS recommendations, we will use generalized estimating equations as above. We will use a model with a time-dependent variable for “post-seizure” set to 1 after the development of epilepsy and 0 before, to represent change in cognition after development of epilepsy (similar to methods previously described for analysis of post-stroke cognitive change<sup>5,6</sup>). We will also use a model with a spline with knot at time of epilepsy development to compare slopes before and after development of epilepsy.

We will check for differing effects of epilepsy on cognition by race, sex, and APOE  $\epsilon 4$  genotype, using interaction terms.

### *Sensitivity Analysis:*

We will use multiple imputation by chained equations (MICE) for missing covariates and to assess the potential effects of differential attrition due to death or dropout. Additionally, to determine whether the associations between late-onset epilepsy and cognition occur independent of stroke, we will repeat analyses censoring participants with incident clinical stroke between Visits 2 and 6.

### **Methodologic limitations or challenges:**

We are limited by the use of claims data, which can identify a first diagnosis of seizure but does not give us the actual date of a first seizure.

7.a. Will the data be used for non-CVD analysis in this manuscript?  Yes  No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES\_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES\_DNA = "CVD Research" would be used?  Yes  No

(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?  X Yes  No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES\_DNA = "No use/storage DNA"?  Yes  No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: <http://www.csc.unc.edu/ARIC/search.php>

Yes  No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

Systemic inflammation, cognitive decline, and dementia (1/2018) – Keenan Walker  
Blood pressure trajectory from Midlife to Late Life and Cognitive Change – (12/2017) – Yuichiro Yano

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  Yes  No

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number\* \_\_\_\_\_)

B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)\* 1999.01)

\*ancillary studies are listed by number at <http://www.csc.unc.edu/atic/forms/>

**12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.**

**12b. The NIH instituted a Public Access Policy in April, 2008** which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from <http://publicaccess.nih.gov/> are posted in <http://www.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to PubMed central.

### **References:**

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6. Dhamoon M, Moon Y, Paik M, Sacco R, Elkind M. Trajectory of Functional Decline Before and After Ischemic Stroke. *Stroke*. 2012;43(8):2180-2184. doi:10.1161/strokeaha.112.658922.