

ARIC Manuscript Proposal #3435

PC Reviewed: 7/9/19

Status: _____

Priority: 2

SC Reviewed: _____

Status: _____

Priority: _____

1.a. Full Title: Late-onset epilepsy and risk of later dementia or mild cognitive impairment

b. Abbreviated Title (Length 26 characters): LOE and dementia

2. Writing Group:

Writing group members:

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Others welcome

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

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3. Timeline:

Data analysis and manuscript preparation will take place over 1 year.

4. Rationale:

Late-onset epilepsy (LOE; i.e., starting at age 65 or older¹) 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 life² at 175 per 100,000 people after age 80³. In comparison, the incidence of epilepsy is low in earlier adulthood (20 per 100,000 from ages 20-60), and moderately high in infants under 1 year of age (100 per 100,000). In older adults without a prior history of seizures, the yearly incidence of epilepsy is 1.85% in those age 80-84 and 3.25% in those who live to 90-94³. Stroke and neurodegenerative diseases account for a share of late-onset epilepsy; we previously showed that vascular risk factors and the apolipoprotein ε4 (APOE4) genotype are risk factors for LOE, even in the absence of stroke or dementia⁴.

There is a relatively high incidence of seizures and subclinical seizure activity in patients with Alzheimer's disease (6-17%)⁵⁻⁸. We have previously shown that, after adjusting for demographics and other vascular and lifestyle risk factors, the APOE4 genotype is associated with late-onset epilepsy, with a dose-dependent effect (i.e., higher rates with 2 allele compared to 1 allele)⁴. As APOE4 is associated with Alzheimer's disease and with cognitive decline, we hypothesize that some participants with LOE will be at an elevated risk for mild cognitive impairment (MCI) and dementia. 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 LOE⁹. As these findings are also associated with cognitive impairment, we have further reason to believe that participants with LOE will have elevated rates of MCI and dementia. Lastly, we have demonstrated that participants with LOE have a steeper annualized decline in cognitive scores than do those participants without LOE (manuscript in preparation; manuscript proposal #3181), which also supports our reasoning that LOE will be associated with MCI and dementia.

5. Main Hypothesis/Study Questions:

H1: Late-onset epilepsy (LOE) will be associated with an increased risk of later dementia.

H2: Late-onset epilepsy (LOE) will be associated with an increased risk of later MCI.

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 is a prospective cohort study of data from Visit 1 (1987–1989) through Visit 6 (2016-2017).

Inclusion criteria (primary analysis):

Since the definition of LOE relies on Centers for Medicare Services fee-for-service (CMS FFS) claims codes, black (NC and MS) and white (MD, MN, and NC) participants with at least 2 years of continuous CMS FFS coverage will be included.

Exclusion criteria: Since the definition of LOE relies on CMS FFS claims codes, participants without 2 years of continuous CMS FFS coverage or with noncontiguous coverage periods will be excluded.

We will also exclude those who did not give consent for DNA to be used, those with identified epilepsy starting before age 67, and those with a known history of brain surgery, brain radiation, or multiple sclerosis.

As we are examining the relationship of LOE to incident dementia and MCI, we will also exclude those participants with a dementia or MCI diagnosis prior to the date of the first seizure-related code.

Outcome:

The primary outcome of interest, dementia (H1), will be taken from adjudicated diagnoses of dementia at any time, based on cognitive testing, participant and informant interviews, and ARIC surveillance (as per ARIC-NCS manual, version 4). We will use the variable *demdxl3_61* for dementia, and use the date of dementia diagnosis *date_demdxl3_61*.

For the outcome of MCI (H2), we will use the variable *cogdiag61* which has been adjudicated from Visit 5 and 6 cognitive testing.

Independent variables:

Our primary exposure variable of interest is late-onset epilepsy. This will be defined as 2 or more seizure- (or epilepsy-) related ICD-9 or ICD-10 codes from CMS FFS data, with the first code occurring at age 67 or later, and with at least 2 years of seizure-free code data prior to the first seizure-related code (to detect incident epilepsy).

Other independent variables will be: hypertension, defined as SBP \geq 140, DBP \geq 90, or antihypertensive use (measured at visit 1); diabetes, defined as fasting blood glucose \geq 126mg/dL, nonfasting glucose $>$ 200mg/dL, diabetes diagnosis, or current medication for diabetes (measured at visit 1); smoking status: self-reported from visit 1 (current, former, never); smoking pack-year history – visit 1; stroke – from adjudicated cohort stroke surveillance; APOE4 genotype – obtained at visit 1; alcohol use, self-reported at visit 1 (current, former, never); hyperlipidemia, measured at visit 1; and body mass index, obtained at visit 1.

Other variables of interest:

Sex, combined race-field center, age, educational level.

Planned data analysis:

We will examine the association between LOE and time to dementia onset (H1) using a Cox proportional hazard model, adjusting for covariates above. We will use the 67th birthday as the origin time (the earliest age at which LOE could be diagnosed), and the date of dementia onset ascertained from surveillance codes, telephone interviews, or testing (*date_demdxl3_61* as above) as the event time.

We will examine the association between LOE and MCI (H2) using logistic regression, adjusting for covariates above; for this analysis we will include only participants who attended visits 5 and/or 6 as suggested in the ARIC-NCS analysis manual (version 4).

We will also perform an analysis using multinomial regression examining the association between LOE and the outcomes of MCI or dementia.

Potential limitations:

The main limitation is the reliance on CMS codes for determination of the primary variable of interest, LOE. There is a risk of case misclassification; however, we expect misclassification bias to be towards the null. CMS code-based case identification for LOE has been used and accepted as a means of studying this population in other studies^{4,10,11}.

We also anticipate not being able to examine incident MCI and time to MCI, which is only possible in participants who attended both Visits 5 and 6, due to relatively small numbers of participants with LOE who attended both Visits 5 and 6 (n=70).

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? 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)?

- #3181 – Cognitive Trajectories and Cognition in Late-Onset Epilepsy (Johnson)
#2947 – Late-onset seizures and cardiovascular risk factors (Johnson)
#3361 – Genetic risk factors for Alzheimer’s Disease and risk of late onset epilepsy (George)

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* ARIC-NCS 2008.06)

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

*ancillary studies are listed by number at <http://www.csc.unc.edu/aric/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 shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript Yes No.

References:

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9. 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.00000000000007010
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11. Faught E, Richman J, Martin R, et al. Incidence and prevalence of epilepsy among older U.S. Medicare beneficiaries. *Neurology*. 2012;78(7):448-453. doi:10.1212/WNL.0b013e3182477edc