ARIC Manuscript Proposal #3436

PC Reviewed: 7/9/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Late-onset epilepsy and mortality

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

2. Writing Group:

Writing group members:
Emily Johnson, M.D.
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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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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:

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

4. Rationale:

Late-onset epilepsy (LOE; i.e., starting at age 65 or older[1]) 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[2] at 175 per 100,000 people after age 80[3]. 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 80-84 and 3.25% in those who live to 90-94[3]. Stroke and neurodegenerative diseases account for a share of late-onset epilepsy; we previously showed that vascular risk factors and the APOE4 genotype are risk factors for LOE, even in the absence of stroke or dementia[4].

LOE has also been associated with an elevated risk of later stroke[5]. Epilepsy is associated with an increased mortality rate in the general population[6], compared to those without epilepsy, with a risk of injuries associated with seizures including fractures, drownings, motor vehicle accidents, and sudden unexplained death in epilepsy (SUDEP). For these reasons, we anticipate that the mortality rate will be higher in participants with LOE than without LOE.

5. Main Hypothesis/Study Questions:

Our primary hypothesis (H1) is that participants with late-onset epilepsy (LOE; identified as below using CMS data) will have an increase in all-cause mortality compared to participants without LOE, after adjusting for comorbidities.

Our secondary hypothesis (H2) is that participants will have an increase in cardiovascular-related mortality compared to participants without LOE, after adjusting for comorbidities.

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 2017 (or the most recent available surveillance monitoring for date of death).

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, and those with a known history of brain surgery, brain tumor, brain radiation, or multiple sclerosis.

Outcome: The primary outcome (H1) is the date of death (in participants who are deceased). The secondary outcome (H2) is the date of death in participants with cardiovascular-related mortality.

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; apolipoprotein E4 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, age, educational level from baseline visit, combined field center-race variable, and cognitive impairment (using categories of normal cognition, MCI, and dementia as assigned after Visit 5[7]).

Planned data analysis:
To determine the hazard ratio for all-cause mortality (H1) in participants with vs. without LOE, we will use Cox proportional hazards modelling, adjusting for the covariates described above. The failure event will be the death date. Events will be censored at the time of the most recent mortality surveillance data available (currently 12/31/2017). The origin will be the participants' 67th birthday (the first available date at which LOE diagnosis could be made using our definition above).

We will perform a secondary analysis for cardiovascular-related mortality (H2), using competing risk proportional subhazards regression modelling and adjusting for the covariates above. We will use the death date for cardiovascular deaths as the failure event, and treat deaths from other causes as competing risks. The origin will be participants' 67th birthday.

We will perform a sensitivity analysis excluding participants with stroke, to test whether the observed differences in mortality are due to mediation by stroke.

We will also perform a sensitivity analysis censoring participants on 12/31/2015, the last date for which CMS data is currently available *(or censoring at the most recent date of CMS data at the time of analysis).*

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[4,8,9].

7.a. Will the data be used for non-CVD analysis in this manuscript? _x_ 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? _x_ 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"? __x__ 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.cscc.unc.edu/ARIC/search.php

___x___ 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? _x__ Yes ____ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* 2008.06)

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

*ancillary studies are listed by number at http://www.cscc.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.cscc.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 __x__ Yes ___ No.

References:

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9. 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