ARIC Manuscript Proposal #2947

PC Reviewed: 02/14/17 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Late-onset seizures and cardiovascular risk factors

b. Abbreviated Title (Length 26 characters): Late-onset seizures

2. Writing Group:
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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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3. Timeline:

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

4. Rationale:

Late-onset epilepsy (i.e., starting at age 55 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, but many patients have no obvious single cause of seizures. A large number of these patients are thought to have microvascular disease leading to seizures.

From case-control studies, it has been observed that patients who develop seizures in later years usually have risk factors that developed much earlier, including hypertension, elevated cholesterol, microvascular disease on imaging, and left ventricular hypertrophy. Sixty-five percent of late-onset seizure patients have a history of hypertension[4], which is significantly more common in adult-onset epilepsy patients than in those without seizures[5]. White matter changes on MRI (a marker of microvascular disease) are significantly more prevalent in patients with late-onset epilepsy than in age-matched controls[6]. Other vascular risk factors (including elevated cholesterol, left ventricular hypertrophy, and cardiac disease) are also elevated in patients with late-onset epilepsy[4,7]. Similarly, patients with adult-onset epilepsy may have an increased risk of later stroke compared to the general population[8]. Diabetes mellitus (DM) is another vascular risk factor that carries an increased risk of stroke[9]. Data from Medicare claims for patients with seizures found that approximately 30% also had claims for DM[10] indicating there is likely significant overlap in the populations; however, whether DM is a risk factor for later-life seizures in the absence of stroke has not been examined.

Diet is a risk factor for cardiovascular disease: the Mediterranean diet, rich in plant-based foods and olive oil with moderate meat and dairy intake, is known to be protective against stroke[11]. As treatment for epilepsy, low-carbohydrate, high-fat diets has been widely used in children for decades, and over the last decade have become more commonly used in adults[12]. In animal models of induced seizures, the ketogenic diet has been shown to have some neuroprotective effect in the hippocampus; protection against seizure development has been mixed[13,14]. There have been no studies examining the influence of diet on the development of late-onset epilepsy.

Physical activity has a beneficial effect in controlling blood pressure, but also may help preserve memory and stimulate neurogenesis during aging. In adult mice, running increases cell proliferation and neurogenesis in the dentate gyrus of the hippocampus[15]. In humans, moderate exercise increases the size of the hippocampus and improves memory in the elderly[16]. Adults in their 60s and 70s had an increase in total brain volume with 6 months of aerobic exercise in a study comparing aerobic exercise to toning and stretching exercises only[16]. In another study, older adults (mean age 65) had increased white matter fiber bundle thickness associated with improvement in their aerobic fitness after 1 year of an exercise intervention; short term memory also improved in those with improved aerobic fitness[17]. Higher levels of activity reduce the risk of ischemic stroke[18]; however, there are currently no studies showing links between activity level and late-life epilepsy.

5. Main Hypothesis/Study Questions:

1. The presence of hypertension and diabetes at Visit 1 will each be associated with risk of late-life seizure, even in the absence of prior stroke and neurodegenerative dementia. There will be no significant differences in the effects of hypertension and diabetes on adult-onset seizures by race or sex.

2. Smoking history, low activity level, and high typical glycemic load in diet (all at Visit 1) at will each be associated with an elevated risk of late-life seizure, even in the absence of prior stroke.

3. Relationships described in #1 and #2, above, will be present but weaker when risk factors are measured cross-sectionally, in late-life (visit 5 for those risk factors with available data).

4. A composite measure of vascular risk from midlife, defined through the ARIC stroke risk score, the American Heart Association's "Life Simple 7," or through a measure of number of risk factors present, will be associated with increased risk of late-life seizure.

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: Prospective cohort study of blood pressure, diabetes, smoking, activity level, and diet, measured at Visit 1 and Visit 5, and presence or absence of seizures starting at age $\geq$45 reported retrospectively between 2011-2013 (and at Visit 6, when available), or documented in Medicare CMS or hospitalization data. We chose $\geq$45 as the age cut off so that no ARIC participants with seizures prior to Visit 1 would be included in the late-onset seizure group.

Inclusion criteria (primary analysis): Participants queried about self-reported seizures or convulsions on the 2011-2013 ARIC-NCS questionnaire (only participants who attended stage 2 of ARIC-NCS were administered the Neurologic history form).

For secondary analysis, we will use Medicare CMS and hospitalization data to identify incident cases of epilepsy in the ARIC population (using procedures described by the ARIC CMS Committee). We will use a two-year look-back period to ensure preexisting cases of epilepsy are not included, and therefore ARIC participants enrolled in Medicare fee-for-service for a minimum of two years will be included. ICD-9 codes are reported to have a high validity for diagnosis of epilepsy (85-99% positive predictive value, 90-97% negative predictive value)[19].

We also plan to utilize the larger ARIC cohort in whom the TIA form was administered at visits 1-4, and which includes questions about specific neurologic symptoms and whether they were accompanied or related to seizures/ convulsions, for secondary analyses (as it is not available after visit 4). Participants treated with an anti-seizure medication will also be included in secondary analysis.

Exclusion criteria: clinical stroke (if prior to first seizure for participants with history of seizures); brain tumor or multiple sclerosis; insufficient data available on hypertension, diabetic

status, smoking, exercise, diet, or seizure status. In analysis of Medicare data, participants without at least 2 years of data prior to the first code for epilepsy or seizures will be excluded.

Outcome: The primary variable of interest for hypotheses 1 and 2 is the occurrence of a first lifetime seizure at age 45 or later; we will use self-reported seizures/convulsions from the ARIC-NCS questionnaire (NHX form) at Visit 5. Age at first seizure is a secondary outcome of interest. For secondary analysis using Medicare data, the outcome of interest is the occurrence of code for epilepsy or seizures, with at least two years of Medicare data prior to the first such occurrence. Participants with a history of seizure, but with onset before age 45, will be excluded from most analyses (so the reference group will be absence of any seizures).

Independent variables:

1. Hypertension: measured SBP and DPB, and categorical hypertension: hypertensive (SBP$\geq$140, DBP$\geq$90, or antihypertensive use), pre-hypertensive (SBP 120-139 or DBP 80-90 and not classified as hypertensive), or normotensive (SBP<120 and DBP<80, without anti-hypertensive medications) – visits 1, 5

2. Diabetes status: Fasting blood glucose $\geq$126mg/dL, nonfasting glucose >200mg/dL, diabetes diagnosis, or current medication for diabetes – visits 1, 5

3. Smoking status: self-reported from visits 1, 5 (current, former, never); smoking pack-year history – visits 1, 5

4. Exercise level: derived from modified Baecke questionnaire score (Visits 1), categorized into recommended (>75 minutes/week of vigorous or >150min/week moderate activity), intermediate (1-74 minutes/week vigorous or 1-149 minutes/week moderate activity), or poor (0 min/week vigorous or moderate activity).

5. Diet information from food questionnaire at Visit 1: carbohydrate quality (usual glycemic load = carbohydrate content per serving x average number of servings x glycemic index for that food), total fat, saturated fat; ARIC Healthy Food Score

Other variables of interest:
Sex, race, age at time of each measurement, educational level from baseline visit, alcohol abuse history, and cognitive impairment (using categories of normal cognition, MCI, and dementia as assigned after Visit 5[20]); we will also evaluate systolic and diastolic blood pressure from visits 1 and 5, in addition to the binary definitions provided in ARIC, as well as the ARIC stroke risk score from visits 1 and 5, and lipid levels and BMI from visits 1 and 5, to allow characterization of number of risk factors.

Planned data analysis:
We propose to use logistic regression to assess the association between the independent variables of interest and late-onset seizures (comparing individuals with seizures with onset after age 45 to individuals without any history of seizures; excluding individuals with seizures before age 45). We will first perform univariate analysis, then a combined multivariable analysis of variables

significant on univariate analysis. Exploratory analysis will include Cox regression for survival analysis to assess relationships between risk factors and the age of seizure onset. We will use multiplicative interaction terms, likelihood ratio tests, and stratified analyses to assess effect modification by sex, race. To evaluate the effect of midlife versus late-life risk factor status, we will evaluate an interaction term of time when risk factors were measured (mid versus late-life) by the risk factor.

Potential strengths:
This study will use prospectively collected cohort data to answer these important questions, and will allow longitudinal analysis of earlier-life risk factors and later-life seizures, which has not previously been studied. This study will draw on the large size and detailed data collected in the ARIC cohort.

Potential limitations:
One potential limitation is that the number of participants reporting seizures starting at age 45 or later may be low, which may limit power. The addition of Medicare, prescription drug data, and visit 6 data will allow ascertainment of seizures in a larger proportion of the cohort.

A second limitation is that participant-reported seizures may not be accurate, as in older patients seizures may be underdiagnosed (or, alternatively, other events may be misdiagnosed as seizure). In secondary analysis, inclusion of all patients treated with anti-seizure medications may include some patients who were taking the medication for other diagnoses. In addition, participant self-reported smoking status, food questionnaire, and activity level information all have potential for inaccuracy and misclassification; as activity level, food questionnaire, and initial smoking status were all assessed prospectively (Visit 1, prior to ascertainment of whether participants have had seizures), we expect inaccuracies to be similar in participants with and without adult-onset seizures and resulting bias to be towards the null.

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? ____ Yes __x_ 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.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)?

MS351: Population-based study of seizures in blacks and whites, Rich, submitted 5/22/2012

MS368: Prevalence of seizures in blacks and whites, Rich, submitted 5/22/2012

These studies use data from Visits 1-3 only, and only examine the differences in prevalence of seizures between race and in patients with and without a history of stroke. No mention is made of other risk factors. I do not see any publications from these proposals.

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

_x_ A. primarily the result of an ancillary study (list number* 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.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 ____ Yes _x__ No.

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