ARIC Manuscript Proposal # 3353

PC Reviewed: ___/___/19  Status: _____  Priority: ___
SC Reviewed: _________  Status: _____  Priority: ___

1.a. Full Title:

The Association between Gravidity, Parity, and Estrogen and Late-Onset Epilepsy

b. Abbreviated Title (Length 26 characters): Gravidity, Parity, and Epilepsy

2. Writing Group:

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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).
3. **Timeline:** Data to be used in this proposal are already available. Data analyses and manuscript preparation will be performed over 12 months.

4. **Rationale:**

The incidence of new-onset epilepsy is higher in older adults than in any other age group\(^1,2\). Late-onset epilepsy (i.e., recurrent unprovoked seizures starting at age 60 or later) is sometimes attributable to stroke or dementia, though 30-50% of cases are unexplained. Vascular risk factors such as hypertension and diabetes are associated with a higher risk of late-onset epilepsy\(^3,4\), however many other potential risk factors have yet to be investigated.

There is substantial evidence for the effects of neurosteroids (including estrogen and progesterone) and seizures. In general, estrogen has been shown to increase epileptiform activity in women with epilepsy\(^5\), while progesterone (and its metabolite, allopregnanolone) have anti-seizure properties\(^6,7\). The excitatory effects of estrogen are thought to help explain the catamenial seizure pattern seen in approximately one-third of women with epilepsy\(^8\).

Beyond catamenial epilepsy, the changes in estrogen levels during perimenopause, menopause, and when hormone therapy is used have effects on seizures. Some women report new-onset epilepsy around the time of menopause, or worsened seizures around menopause\(^9\). Hormone therapy is also reported to worsen seizures in women with preexisting epilepsy\(^10\).

Animal models have shown that increased estrogen levels during the estrus period of the rat correspond to increased epileptiform spike activity in the brain\(^11\), analogous to seizures in catamenial epilepsy. In addition, basic science research has shown that hippocampal dendritic spines are responsive to estrogen and pregnancy in animal models, and that some of the changes in dendritic morphology are permanent\(^12,13\).

It is clear that the neurosteroids estrogen and progesterone have effects on the brain and on seizures in women with preexisting epilepsy. We therefore propose to examine whether lifetime estrogen exposure (using gravidity, parity, and ages of menarche and menopause as surrogates) is associated with epilepsy developing in later adulthood.
5. Main Hypotheses/Study Questions:

Our study seeks to answer the following questions:

1. To determine whether higher numbers of gravidity and parity are associated with the risk of late-onset epilepsy. We hypothesize that participants with higher gravidity and parity (particularly grand multiparity, >5 births) will have an increased risk of late-onset epilepsy.

2. To determine whether age at menarche and menopause are associated with the risk of late-onset epilepsy. We hypothesize that participants with earlier menarche and later menopause will have an increased risk of 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:

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

Study Population:

Inclusion Criteria:
Female ARIC study participants with at least 2 years of Medicare FFS data will be included in the analysis.

Exclusion Criteria:
Males will be excluded from this study.
Non-black and non-white participants will be excluded due to small numbers, as is standard in ARIC.
Participants with known brain tumor, history of brain surgery, history of radiation, and history of head trauma with loss of consciousness will be excluded.
Participants missing information on gravidity and parity will be excluded from analysis for H1, and participants missing information on age at menarche and menopause will be excluded from analysis for H2.
We will address other missing covariate data (i.e. hypertension) using multiple imputations.
**Exposures:**

The exposures of interest are gravidity and parity (for H1), used as a partial representation of cumulative lifetime estrogen exposure. We will use the reported gravidity and parity from visit 1 for each woman. The exposures of interest for H2 are age at menarche and age at menopause (also reported at visit 1).

**Outcome:**

We will identify cases of late-onset epilepsy using ICD-9 and ICD-10 codes (from ARIC hospitalization data and from Medicare inpatient and outpatient CMS data), using the definition of 2 or more seizure-related ICD-9 or ICD-10 codes. We will identify incident cases as those with ≥2 years of ARIC hospitalization or Medicare data available prior to the first seizure-related code, and limit cases to those with a first seizure-related code at age 60 or later. We have previously used this definition to identify late-onset epilepsy cases. Similar claims-based codes have a reported sensitivity of 94-99% and specificity of 82-92% for epilepsy cases.

**Covariates:**

We will include demographic factors (age, a combined race-center variable, education) and risk factors for cerebrovascular disease and dementia: hypertension, diabetes, cholesterol, BMI, activity level, and APOEε4 genotype. We will use nested models to assess the contribution of these risk factors. Race-center, education history, hypertension, diabetes, cholesterol, and BMI will be taken from Visit 1. The APOEε4 genotype was measured at Visit 1. For Hypothesis 2, we will include a model adjusting for reported hormone replacement therapy from Visits 1-6. We will include cognitive status from Visit 5 in a sensitivity analysis.

**Statistical Analysis Plan:**

We will use Cox proportional hazards models to assess the relationship between our exposures and late-onset epilepsy, adjusting for covariates as above. We will use participants’ 60th birthday as the origin time for primary analyses, and a perform sensitivity analyses using the participants’ 67th birthday as origin time (the first age at which participants would be eligible for a diagnosis of late-onset epilepsy if only Medicare claims, and not ARIC hospitalization claims, are used).
We will also perform a sensitivity analysis excluding all participants with a diagnosis of dementia from Visit 5.

We will check for interactions between the effects of gravidity/parity and race, hypothesizing no interactions.
We will use chained multiple imputation by chained equations (MICE) to assess the effects of missing data.

**Limitations:**

Our sample size will be relatively small, as we are using only women with at least 2 years of CMS FFS data available, which may limit the power for some analyses. In addition, we are limited by the self-reported nature of the menarche and menopause variables, which may be inaccurate in some instances due to difficulty with recall.
As is true for any ICD-based outcome definition, there is the possibility of misclassification of epilepsy cases. However, claims-based epilepsy definitions have been accepted for use in similar studies\textsuperscript{4,14,18} with a reported sensitivity of 94-99\% and specificity of 82-92\% for epilepsy cases\textsuperscript{15-17}.
While observational and not prospective, we believe these analyses will be important as no previous studies of parity/gravidity and LOE exist.

7. Will the data be used for non-CVD analysis in this manuscript? __x__ Yes  __No

8. Will the DNA data be used in this manuscript? __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)?

_Late-onset seizures and cardiovascular risk factors_ (proposal #2946).
Reproductive history and late life health status among older African American and White Women (proposal #678)
Authors: S. Shreeniwas, C. Suchindran, E. Mutran

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

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.cscce.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:

4. Choi H, Pack A, Elkind MS V, Longstreth WT, Ton TGN, Onchiri F. Predictors of


