ARIC Manuscript Proposal #4007 (Amended)

PC Reviewed: 5/17/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority:**

Amendment

We would like to propose an additional aim to this manuscript proposal: To examine the relative strength of association between gray and white matter integrity and development of epilepsy in older adults. We hypothesize that incident epilepsy in older adults is associated positively with the burden of abnormalities in both gray and white matter structures. The relative importance of white vs. gray matter degeneration in epileptogenesis is unknown, but can be inferred from analysis of available derived neuroimaging variables from the ARIC Visit 5 MRI. To that end, we request the following derived variables to carry out this secondary aim: ROI-wise cortical thickness estimates from Visit 5 and ROI-wise brain volume estimates from Visit 5. We will derive a patient-specific summary measure from the ROI-wise estimates of each of the following neuroimaging parameters: cortical thickness, basal ganglia volume, thalamic volume, and hippocampal volume. We will enter these four variables as covariates in the Cox proportional hazards model described in the original proposal.

1.a. Full Title: Association between white matter microstructure and epilepsy

b. Abbreviated Title (Length 26 characters): White matter microstructure and epilepsy

2. Writing Group:

Writing group members:
James J. Gugger (first author) (University of Pennsylvania)
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Others Welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. JJG

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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 for analyses are currently available. Data analysis, conference abstract submission, and manuscript preparation and submission will take place over one year from manuscript proposal acceptance (2022-2023).

4. Rationale:

Emerging evidence suggests that epilepsy is a disorder of abnormal distributed brain networks.[1–3] The cerebral white matter is the structural scaffolding of brain networks and several studies utilizing diffusion MRI to characterize white matter microstructural integrity reveal widespread abnormalities in both focal and generalized epilepsies.[4] Recent work by the ENIGMA Epilepsy Working Group utilizing DTI to characterize white matter microstructure in 1249 individuals with epilepsy and 1068 healthy controls showed widespread abnormalities in white matter tracts across all forms of epilepsy, with the largest effect sizes in the corpus callosum, cingulum, and external capsule.[5] Whether these widespread white matter abnormalities represent a fundamental pathologic element underlying epileptogenesis or a consequence of epileptic seizures remains a critical knowledge gap in the field. If white matter abnormalities and the structural network abnormalities that follow are a cause of seizures, then diffusion MRI could be used as a biomarker for epilepsy risk stratification following various forms of brain injury.

Preliminary evidence from the ARIC cohort suggests that white matter abnormalities predate late onset epilepsy (LOE). Using ARIC Visit 3 MRI data, Johnson et al.[6] demonstrated that white matter hyperintensities (WMHs) are associated with LOE. Since the etiology of WMHs is diverse and can include cerebral small vessel disease and dementia, the authors carefully controlled for these covariates. In the model including vascular risk factors as covariates, the hazard ratio for LOE in association with WMH was 1.28 (95% confidence interval [CI] 1.06–1.54). When participants were censored at the time of stroke or dementia diagnosis, the association between WMH and LOE persisted (HR 1.34, 95% CI 1.07–1.67). To our knowledge, this is the first study to evaluate white matter structure prior to onset of epilepsy; however, WMHs provide only a crude estimate of white matter integrity and have multiple causes. WMHs are common in patients with vascular risk factors where they are thought to be the result of cerebral small vessel disease.[7] White matter lesions are also common in demyelinating diseases such as multiple sclerosis[8] and in neurodegenerative diseases where they reflect axonal degeneration.[9–12] The study by Johnson et al.[6] controlled for vascular risk factors and censored participants diagnosed with dementia suggesting that the association between white matter abnormalities and incident epilepsy is not dependent on concomitant neurodegenerative or

cerebral small vessel disease. Whereas WMHs provide a binary assessment for the presence or absence of white matter lesions, diffusion tensor imaging provides more specific data on white matter microstructural integrity with continuous variables such as fractional anisotropy and mean diffusivity, which would give a better view of the role of white matter abnormalities in epilepsy risk and thus provide a more robust link between white matter abnormalities and incident epilepsy.

The goal of the proposed study is to determine if measures obtained from the ARIC visit 5 diffusion MRI scan are associated with the development of epilepsy. Subjects enrolled in ARIC are extensively phenotyped for two factors known to influence white matter integrity: cerebrovascular disease and neurodegenerative diseases. Thus, ARIC offers a unique opportunity to understand the role of white matter microstructural abnormalities in epilepsy risk. By leveraging this large, well phenotyped cohort, we will be able to advance the field by understanding the role of white matter abnormalities underlying epileptogenesis.

5. Main Hypothesis/Study Questions:
Aim: To examine the longitudinal association between white matter microstructural integrity and development of epilepsy in older adults
Hypothesis: Incident epilepsy in older adults is associated positively with the burden of abnormalities in white matter structure.

Sub-Aim: To examine the effect of prevalent cerebrovascular disease and dementia on the longitudinal association of white matter microstructural integrity with incident epilepsy.
Sub-Hypothesis: Epilepsy in older adults is associated positively with the burden of abnormalities in white matter structure, independent of cerebrovascular disease or dementia.

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 participants with a visit 5 MRI.

Inclusion Criteria:
Participants who completed a visit 5 structural and diffusion weighted MRI. Since the definition of epilepsy that will be used in this study relies on diagnostic codes found in CMS fee-for-service (FFS) Medicare claims, Black (from NC and MS) and White (from MD, MN, and NC) participants with at least 2 years of continuous CMS FFS Medicare coverage from the date of the Visit 5 MRI will be included.

Exclusion criteria:
Participants with a seizure- (or epilepsy-) related ICD-9 or ICD-10 prior to visit 5 (prevalent epilepsy) and those missing data on covariates included in statistical models will be excluded. Clinical stroke or neurodegenerative disorder prior to first seizure; brain tumor or multiple sclerosis; no Visit 5 MRI of sufficient quality.

Outcome:

Primary outcome

Incident epilepsy after visit 5 MRI using CMS data: Epilepsy will be defined as 2 or more seizure- (or epilepsy-) related ICD-9 or ICD-10 codes from CMS FFS data (inpatient or outpatient), with no seizure- (or epilepsy-) related codes prior to the Visit 5 MRI.

ICD-9 and ICD-10 codes used to define epilepsy.

ICD-9 Codes	
345.0x	Generalized nonconvulsive epilepsy
345.1x	Generalized convulsive epilepsy
345.2	Petit mal status
345.3	Grand mal status
345.4x	Localization-related (focal) (partial) epilepsy with complex partial seizures
345.5x	Localization-related (focal) (partial) epilepsy with simple partial seizures
345.7x	Epilepsia partialis continua
345.8x	Other forms of epilepsy and recurrent seizures
345.9x	Epilepsy unspecified
780.39	Other convulsions
ICD-10 Codes	
G40.0xx	Localization-related (focal) (partial) epilepsy
G40.1xx	Localization-related (focal) (partial) epilepsy with complex partial seizures
G40.2xx	Localization-related (focal) (partial) epilepsy with simple partial seizures
G40.3xx	Generalized idiopathic epilepsy
G40.4xx	Other generalized epilepsy and epileptic syndromes
G40.8xx	Other epilepsy and recurrent seizures
G40.9xx	Epilepsy, unspecified
R56.9	Seizure (convulsive), convulsions NOS

Secondary outcome

Incident epilepsy after visit 5 MRI using CMS data, self-report, and hospitalization surveillance data: In addition to the criteria for the primary outcome using CMS data, incident epilepsy status will also be ascertained using self-report information from ARIC Visit 6 and Visit 7 as well as hospital surveillance data.

Independent Variables:

The primary independent variables of interest will be fractional anisotropy (FA) and mean diffusivity (MD) based summary scores representing the burden of white matter microstructural abnormality normalized to cognitively normal subjects. Derivation of this variable is described in more detail in the Statistical Analysis section below.

Covariates:

Model 1: Covariates included in this statistical model will include the following variables measured at ARIC visit 1: age (years, continuous), sex (male; female), race/field center (MN whites; MD whites; NC Whites; NC Blacks; MS Blacks), education (<HS, HS or equivalent, >HS), annual family income (<$35,000; ≥$35,000; not reported), and APOE ε4 genotype (0 ε4 alleles; 1 or 2 ε4 alleles).

Model 2: In addition to covariates included in Model 1, we will also consider the following covariates measured at the ARIC visit 5 MRI date: hypertension (SBP ≥140, DBP ≥90, or antihypertensive medication use), diabetes (fasting blood glucose ≥126mg/dL, non-fasting glucose ≥200mg/dL, HbA1c ≥6.5% physician diagnosis, or current medication for diabetes), and alcohol consumption (self-reported, current; former; never). Stroke and coronary heart disease status at the time of each participant's Visit 5 MRI will be determined from continuously collected adjudicated data. Presence of cerebral infarctions, WMHs, and microbleeds will be determined from the Visit 5 MRI. Dementia diagnosis will be determined by the visit 5 expert panel, using neurocognitive assessments, surveillance data, informant interviews, and telephone interviews.

Statistical Analyses:
Epileptic networks are anatomically/spatially heterogeneous between patients and thus analysis of individual brain regions of interest (ROI) is not ideal for analysis of group data. Prior work using normative modeling of diffusion MRI data has been shown to predict clinical outcomes such as epilepsy surgical outcome[13] and seizure semiology[14]. We propose to adopt this approach to normative modeling in this analysis. The proposed approach is described below:

The primary independent variables of interest will be fractional anisotropy (FA) and mean diffusivity (MD) based summary scores representing the overall burden of white matter microstructural abnormality for each participant normalized to cognitively normal participant. This measure will be derived from the DTI data obtained at ARIC Visit 5. Separately for FA and MD, we will first calculate the mean and standard deviation for each white matter ROI in the 2009 Johns Hopkins University atlas from the cohort of cognitively normal subjects without epilepsy completing Visit 5 DTI. This will serve as the control distribution. Next, for each participant with incident epilepsy we will calculate the number of standard deviations each ROI is away from the mean and standard deviation of the cognitively normal subjects without epilepsy (i.e., the control distribution):

$$z\ score\ ROI = \frac{mean\ patient - mean\ controls}{SD\ controls}$$

A z-score threshold above which is considered abnormal will be selected based on the best discrimination between ARIC Visit 5 participants with and without incident LOE. For each participant, the number of regions with a z-score above this threshold will be summed and this will represent the overall burden of white matter abnormalities relative to healthy aging. The summary score representing the overall burden of white matter microstructural abnormality will be calculated separately for FA and MD.

We will examine participant characteristics among those with and without incident epilepsy after Visit 5 and will compare distributions of continuous variables using *t*-tests and of categorical variables using chi-square tests. Time between Visit 5 and epilepsy onset will be calculated. To calculate cumulative incidence of epilepsy status we will use Kaplan-Meier analyses. We will examine associations between the DTI-based measures of burden of white matter microstructural abnormality with incident epilepsy risk using Cox proportional hazards models (reference: no epilepsy), adjusting for covariates listed above. The time of Visit 5 MRI of each participant will be the origin time (earliest age at which epilepsy could be diagnosed). The proportional hazards assumption will be checked using Schoenfeld residuals.

Limitations:
A limitation of this study is the reliance on ICD-9/10 codes to define epilepsy (primary outcome). The use of ICD-9/10 codes leads to a risk for misclassification; however, we expect misclassification bias to be towards the null as misclassification would minimize differences between groups. Another limitation is the potential for a small number of incident epilepsy cases. In the study by Johnson,[6] which was published in 2019 there were 28 participants identified with incident epilepsy after Visit 5. This would therefore represent the minimum number of participants we expect to identify. To mitigate this limitation, we have included a secondary outcome where incident epilepsy is ascertained using a combination of CMS data, self-report data from Visits 6 and 7, and hospital surveillance data. This will increase the number of cases of incident epilepsy.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes X No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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/mantrack/maintain/search/dtSearch.html

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)?

#3668: The Risk of Post-traumatic Epilepsy in the ARIC Study (Andrea Schneider)
#3181: Cognitive Trajectories and Cognition in Late-onset Epilepsy (Emily Johnson)
#3435: Late-onset Epilepsy and Risk of Later Dementia or Mild Cognitive Impairment (Emily Johnson)
#3354: Plasma Beta-amyloid and Late-onset Epilepsy: The ARIC Neurocognitive Study (Emily Johnson)
#2947: Late-onset Seizures and Cardiovascular Risk Factors (Emily Johnson)
#3898: Post-traumatic Epilepsy (PTE) and Dementia Risk (Andrea Schneider)
#3353: The Association between Gravidity, Parity, and Estrogen and Late-Onset Epilepsy (Emily Johnson)
#3436: Late-onset epilepsy and mortality (Emily Johnson)
#3851: Association of Obstructive Sleep Apnea with Late Onset Epilepsy among ARIC participants (Christopher M. Carosella)
#3075: Association between white matter microstructural integrity and cognitive decline, MCI, and incident dementia (Melinda Power)
#3153: Arterial stiffness and pressure pulsatility, white matter integrity and late-life depression: The ARIC-NCS study (Jingkai Wei)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes X 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)* _____ _____ _____)

*ancillary studies are listed by number https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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.

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