ARIC Manuscript Proposal Form

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Publication Committee Review Date: **02/13/24**
ARIC Manuscript Proposal Number: **#4399**

1.a. Full Title: Risk of Post-Stroke Epilepsy (PSE) and Associations of PSE with Dementia Risk

b. Abbreviated Title (Length 26 characters): PSE and Dementia

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
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Others Welcome	

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.
AAL **[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 (The ARIC author should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).

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3. Timeline:

Data for analyses are currently available. Data analysis and conference abstract submission will occur within one year of manuscript proposal approval with manuscript preparation and submission occurring within two years from manuscript proposal acceptance.

4. Rationale:

Stroke is one of the leading causes of death and disability in the United States.[1] Seizures are an important complication post-stroke and may occur immediately as a stroke symptom or manifest later as post-stroke epilepsy. It has been estimated that strokes account for approximately 11% of adult-onset epilepsy and up to 45% of epilepsy cases occurring in adults over 60 years of age.[2] A European study estimated similar incidence of post-stroke seizures in both large artery strokes and cardioembolic strokes with one third of the seizures occurring in the first 24 hours of the stroke and half of all seizures occurred within the first 30 days of the stroke.[3] The mechanisms of post-stroke epilepsy differ depending on when the seizure occurs. Earlier onset seizures are often secondary to acute neuronal injury, glutamate excitotoxicity and blood brain barrier dysfunction while later onset seizures are due to gliotic scarring and chronic inflammation leading to neurodegeneration.[4-6]

Both stroke and epilepsy have been shown to be associated with increased risk of dementia.[7,8] Prior studies estimate cognitive increased risk of dementia associated with epilepsy. Two large cohort studies performed among older adults (including one in ARIC) found that individuals with epilepsy had nearly 3 times the risk developing dementia compared to individuals without epilepsy.[8,9] The risk of developing dementia after a diagnosis of epilepsy is multi-factorial and has been associated with genetic background, vascular comorbidities, age at seizure onset, recurrent seizures as well as type and number of antiepileptic drugs.[10,11] Possible biologic mechanisms underlying associations of epilepsy with dementia risk include the co-occurrence of vascular risk factors and the aggregation of β-amyloid and tau prior to dementia onset resulting in altered synaptic transmission and increased network hyperexcitability, among others.[8]

The risk of dementia among individuals who develop post-stroke epilepsy is understudied. The extant literature is limited to either large studies using administrative data, with stroke, epilepsy, and dementia identified using ICD codes only or to small hospital-based studies with short follow-up time.[12,13] In a study of 23,680 younger (mean age <45 years) stroke patients identified in the 2005-2014 IBM Watson Health MarketScan Commercial Claims and Encounters database, Lekoubou et al.[12] found that stroke survivors who developed post-stroke seizures had a greater risk of dementia compared to individuals who did not develop post-stroke seizures (HR: 2.53, 95% CI: 1.84-3.48). Another small (N=169) study reported that stroke patients (mean age 72 years) recruited from the stroke unit at one university medical center who had early post-stroke seizures (within 7 days of stroke) were at increased risk of dementia over 3 years of follow-up.[13]

In the present ARIC Study proposal, we aim to investigate the risk of post-stroke epilepsy, with consideration of stroke type (ischemic/hemorrhagic) and severity (defined by NIHSS). We further aim to explore associations of post-stroke epilepsy with dementia risk over 30+ years of follow-up. We do not expect to have enough power to incorporate stroke type and severity in this dementia analysis but will consider if sample size allows.

5. Main Hypothesis/Study Aims:

Aim 1 - Risk of Post-Stroke Epilepsy: We hypothesize that individuals with incident stroke will have higher risk of subsequent epilepsy compared to individuals without stroke.

In secondary analyses, we hypothesize that individuals with incident hemorrhagic stroke (intracerebral hemorrhage; subarachnoid hemorrhage) will have greater risk of subsequent epilepsy compared to individuals with incident ischemic stroke and to individuals without stroke. We additionally hypothesize that individuals with greater incident stroke severity (as assessed by the NIHSS) will have greater risk of subsequent epilepsy compared to individuals with lesser stroke severity and to individuals without stroke.

Aim 2 - Associations of Post-Stroke Epilepsy with Dementia Risk: We hypothesize that individuals with post-stroke epilepsy will have greater risk of incident dementia compared to individuals without stroke and without seizure/epilepsy and compared to individuals with stroke alone and with seizure/epilepsy alone. We do not expect to have enough power to incorporate stroke type and severity in this analysis but will consider if sample size allows.

6. Design and analysis - please address the following aspects:

a) Inclusion/exclusion

We will include all ARIC Study participants without prevalent stroke or dementia at baseline (Visit 1) with complete data on covariates included in statistical models. In sensitivity analyses, we will also exclude individuals with seizure/epilepsy occurring in the first 2 year of follow-up in order to exclude potential cases of prevalent seizure/epilepsy.

b) Study design

Prospective cohort study using Visit 1 as baseline with follow-up through 12/31/2020 (or the most recent administrative censoring date at the time of journal submission).

c) Exposures, outcomes and other variables of interest with specific reference to the time of their collection

All exposures in this study will be time-varying with person-time allocated accordingly over study duration (Visit 1 to 12/31/2020 or the most recent administrative censoring date at the time of journal submission).

In **Aim 1**, we will create a 2-level time-varying exposure variable:

0 – No stroke
1 – Stroke

In sensitivity analyses, we will consider stroke types (ischemic versus hemorrhagic [subarachnoid hemorrhage and intracerebral hemorrhage]) as separate categories. We will also consider stroke severity (NIHSS ≤5; NIHSS 6-10; NIHSS ≥11) as separate categories.

In **Aim 2**, we will create a 4-level primary time-varying exposure variable:

0 – No stroke and no seizure/epilepsy
1 – Stroke only
2 – Seizure/epilepsy only (will also include participants with seizure/epilepsy followed by stroke)
3 – Post-stroke epilepsy (PSE; stroke followed by new epilepsy)

Participants can contribute person-time to category 0 (no stroke and no seizure/epilepsy) and subsequently category 1 (stroke only) and subsequently category 3 (PSE). Alternatively, participants can contribute person-time to category 0 (no stroke and no seizure/epilepsy) and subsequently category 2 (seizure/epilepsy only), but by definition, cannot go from category 2 (seizure/epilepsy only) to either category 1 (stroke only) or 3 (PSE).

In sensitivity analyses, we will also consider participants with seizure/epilepsy followed by stroke as a separate category.

Stroke Definition: Prior (prevalent) stroke is self-reported at visit 1 (these participants will be excluded from the present analyses). Incident stroke events are identified were identified through community surveillance of hospitalizations occurring in ARIC Study communities and telephone follow-up calls, after which medical records are obtained.[14-16] Stroke events are preliminarily classified by a computer-generated algorithm[15], and are then adjudicated by study physicians. Definite and probable stroke events will be used as the primary stroke definition in this analysis. In secondary analyses, stroke type (ischemic versus hemorrhagic [subarachnoid hemorrhage and intracerebral hemorrhage]) and stroke severity ascertained by trained reviewers based on data from hospitalization records for all definite or probable strokes using a validated algorithm for retrospective National Institutes of Health Stroke Scale

(NIHSS) scoring[17-19]. We will also consider incorporating the recurrence of stroke episodes during the follow up period in secondary analyses.

Seizure/Epilepsy Definition: Consistent with prior work[8,20], seizure/epilepsy will be defined from seizure or epilepsy-related ICD-9/10 codes from 1) ARIC study hospitalization data (1987-12/31/2020, obtained from community surveillance of hospitalizations occurring in ARIC Study communities and reported during telephone follow-up calls, after which medical records are obtained) and 2) linked Centers for Medicare and Medicaid Services (CMS) data for participants aged 65+ years who were enrolled in fee-for-service part B (1/1/1991-12/31/2018).

In primary analyses, we will define seizure/epilepsy as 1+ healthcare encounters with a seizure or epilepsy-related ICD-9/10 code and in sensitivity analyses, we will define epilepsy as 2+ encounters with a seizure or epilepsy-related ICD-9/10 code.

As there is not self-reported seizure/epilepsy data that can be used to define prevalent epilepsy at ARIC Visit 1, we will perform a sensitivity analysis excluding individuals with seizure/epilepsy occurring in the first 2 year of follow-up in order to exclude potential cases of prevalent seizure/epilepsy.

ICD-9 and ICD-10 codes used to define seizure/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

Post-Stroke Epilepsy Definition: In our primary analyses, post-stroke epilepsy will be defined as a diagnosis of seizure/epilepsy occurring >7 days after a stroke diagnosis. This definition is in accordance with prior studies which have specified post-stroke epilepsy as seizures/epilepsy occurring after the acute phase of stroke (i.e., after 7 days) based on the premise that early seizures are provoked and there is not consensus on whether or not to treat[21,22]. However, the definition of early "provoked" seizures is not clear; with other studies defining post-stroke epilepsy as occurring 14 days or 30 days after stroke presentation[23]. In sensitivity analysis, we will consider alternative definitions of post-stroke epilepsy (any seizure/epilepsy diagnosis occurring any time after stroke; occurring >14 days after stroke; occurring >30 days after stroke).

Dementia Definition: Detailed descriptions of the definition of incident dementia in ARIC have been described previously[24]. Briefly, there are three levels of ascertainment. Level 1 is adjudicated dementia defined using data from in-person evaluations at ARIC visits starting at Visit 5. Level 2 adds telephone data from participants who were alive but did not attend in-person visits (starting at Visit 5) and from informants of participants who were deceased prior to in-person visits (starting at Visit 5). Level 3, the main outcome in the present analysis, adds dementia cases identified by hospitalization ICD codes or death certificate codes occurring from baseline through 12/31/2020 (or the most recent data at the time of journal submission). This level 3 outcome is not dependent on visit attendance and thus minimizes potential biases due to attrition and the competing risk of death. If power allows, we will additionally consider sensitivity analyses using the Level 1 and 2 dementia definitions.

Covariates: Covariates included in our statistical model will include the following covariates measured at ARIC Visit 1: age (years, continuous), sex (male; female), race/field center (MN White; MD White; NC White; NC Black; MS Black), education (<high school; high school, GED, or technical school; some college, college, graduate, or professional school), occupation (full-time; part-time; retired; unemployed) hypertension (defined as self-report of physician diagnosis, systolic blood pressure ≥140, diastolic blood pressure ≥90, or antihypertensive medication use), diabetes (defined as self-report of physician diagnosis, fasting blood glucose ≥126mg/dL, non-fasting glucose ≥200mg/dL, or use of medication for diabetes), history of head injury (self-reported[20,25]), alcohol consumption (current; former; never), smoking (current; former; never), and APOE ε4 genotype (0 ε4 alleles; 1 or 2 ε4 alleles).

d) Summary of data analysis

Aim 1: Participant characteristics will be shown stratified by incident stroke status (exposure variable) using means (standard deviations) for continuous variables and numbers (proportions) for categorical variables. Kaplan-Meier analyses will be used to show the cumulative incidence of seizure/epilepsy by time-varying stroke status. In our primary analyses, Cox proportional hazard models with time since enrollment (Visit 1) as the timescale will be used to examine the association between the time-varying 2-level stroke exposure variable with seizure/epilepsy risk. Follow-up time will extend to date of seizure/epilepsy, study withdrawal/loss-to follow-up, or administrative censoring on 12/31/2020 (or the most recent date at the time of journal submission).The proportional hazards assumption will be evaluated by examining Schoenfeld residuals and complementary log-log plots.[26] Statistical models will be adjusted for age, sex, race/field center, education, occupation hypertension, diabetes, history of head, alcohol consumption, and smoking status. We will formally evaluate for interaction by age, sex, and race. In secondary analyses, we will Fine and Gray proportional hazard models to account for the competing risk of death.[27] In additional secondary analyses, we will conduct subgroup analysis to assess

and compare the risk of post-stroke seizure/epilepsy by stroke type (ischemic; hemorrhagic) and severity (NIHSS ≤5; NIHSS 6-10; NIHSS ≥11); each compared to no stroke.

Aim 2: Participant characteristics will be shown stratified by our 4-level exposure variable (no stroke and no seizure/epilepsy; stroke only; seizure/epilepsy only; post-stroke epilepsy) using means (standard deviations) for continuous variables and numbers (proportions) for categorical variables. The cumulative incidence of dementia by stroke and epilepsy status will be calculated using Kaplan-Meier analyses. In our primary analyses, Cox proportional hazard models with time since enrollment (Visit 1) as the timescale will be used to examine the association between the time-varying 4-level stroke and seizure/epilepsy exposure variable with dementia risk. Follow-up time will extend to date of dementia, study withdrawal/loss-to follow-up, or administrative censoring on 12/31/2020 (or the most recent date at the time of journal submission). To specifically determine if the risk of dementia associated with post-stroke epilepsy is significantly higher than the risk of dementia associated with either stroke or seizure/epilepsy alone, we will change the reference group to stroke and to seizure/epilepsy, respectively (instead of no stroke and no seizure/epilepsy). The proportional hazards assumption will be evaluated by examining Schoenfeld residuals and complementary log-log plots.[26] Statistical models will be adjusted for age, sex, race/field center, education, occupation hypertension, diabetes, head injury, alcohol consumption, smoking status and APOE ε4 genotype. We will formally evaluate for interaction by age, sex, race, and APOE ε4 genotype. In secondary analyses, we will Fine and Gray proportional hazard models to account for the competing risk of death.[27] In additional secondary analyses, we will consider stroke type and severity if power allows.

e) Any anticipated methodologic limitations or challenges if present

The definition of seizure/epilepsy and post-stroke epilepsy is based on ICD-9/10 codes and there is not a measure of self-reported seizure/epilepsy at study baseline. However, we plan to perform a sensitivity analysis excluding individuals with seizure/epilepsy occurring within the first 2 years of follow-up as a way to exclude prevalent seizure/epilepsy. While our primary definition of seizure/epilepsy is based on 1+ healthcare encounter with an epilepsy or seizure-related ICD-9/10 code in order to increase statistical power, we will also consider epilepsy defined as 2+ encounters with an epilepsy or seizure-related ICD-9/10 code, which has been shown to have a sensitivity of 94% and specificity of 91%.[28] We additionally do not have detailed location on type of epilepsy (focal versus generalized) or on the number and type of antiseizure medications used (although there is a self-reported question we could consider on having ever used antiseizure medications). Additionally, in our primary analysis for Aim 2, we will use the Level 3 definition of dementia to minimize the influence of study attrition and the competing risk of mortality, but we will also consider Level 1 and 2 dementia definitions among the subgroup of the population with these data. We will also have limited power to consider stroke type and stroke severity, which may preclude our ability to investigate these factors, particularly in Aim 2.

f) Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed (Provide a brief (2-3 sentences) justification for requesting PHI data) ☒ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.) ☐ **Yes** ☒ **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 is distributed to ARIC PIs annually, 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 - APOEε4 genotype** ☐ **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"? ☒ **Yes** ☐ **No**

9. The lead author or the "sponsoring" ARIC 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website Publications and Proposal Search] ☒ **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)?

Relevant Stroke, Epilepsy, and Dementia-Related Manuscript Proposals:
- **MSP #3181: Cognitive Trajectories and Cognition in Late-Onset Epilepsy (Johnson)**
- **MSP #3354: Plasma Beta-Amyloid and Late-Onset Epilepsy (Johnson)**
- **MSP #3435: Late-Onset Epilepsy and Risk of Later Dementia or MCI (Johnson)**
- **MSP #3436: Late-Onset Epilepsy and Mortality (Johnson)**
- **MSP #3668: The Risk of Post-Traumatic Epilepsy in the ARIC Study (Schneider)**
- **MSP #3672: Stroke Incidence and Severity as Risk Factors for Dementia and MCI (Koton)**
- **MSP #3800: Retrospective Evaluation of Severity of Stroke and Disability after Stroke in the ARIC Study: Objectives and Methodology (Koton)**
- **MSP #3801: The Association between Ischemic Stroke Subtype and Stroke Severity (Johansen)**
- **MSP #3898: Post-traumatic Epilepsy (PTE) and Dementia Risk (Schneider)**
- **MSP #4071: Cognitive Predictors in Late-Onset Epilepsy (Reyes)**

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)? ☒ **Yes** ☐ **No → Skip to question 12**

11.b. If yes to 11.a., is the proposal

☐ **A. primarily the result of an ancillary study**
☒ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)**

11.c. If yes to 11.a., list number*: Brain MRI Study 1999.01, ARIC-NCS 2008.06

*ancillary studies are listed by number
https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website Ancillary Studies 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.

Understood.

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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website, Publications, Publication Policies, Forms, and Guidelines].
http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

Understood.

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