ARIC Manuscript Proposal #3668

PC Reviewed: 7/14/20 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: **The risk of post-traumatic epilepsy in the ARIC study**

b. Abbreviated Title (Length 26 characters): **Post-traumatic epilepsy in ARIC**

2. Writing Group:
Writing group members:

Andrea L. C. Schneider – first author
Emily L. Johnson – last author
Anna Kucharska-Newton
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Rebecca F. Gottesman
Others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ALCS **[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 one year (2020-2021).

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 40-110 per 100,000 after age 60 and 175 per 100,000 people after age 80[3,4]. In comparison, the incidence of epilepsy is low in earlier adulthood (20 per 100,000 from ages 20 through 60 years). In older adults without a prior history of seizures, the yearly incidence of epilepsy is 1.85% in those 80-84 years old and 3.25% in those who live to 90-94 years[3]. Stroke and neurodegenerative diseases account for a share of late-onset epilepsy; we previously showed that vascular risk factors such as hypertension and diabetes are risk factors for LOE, even in the absence of stroke or dementia[5].

Traumatic brain injury (TBI) affects an estimated 1.7 million persons in the U.S. every year; 1.4 million require treatment in emergency departments, with 275,000 hospitalizations and 52,000 deaths due to TBI annually[6]. Among adults aged 40 year or older, the prevalence of prior head injury is 15.7%, which corresponds to nearly 23 million individuals[7].

TBI is known to be a risk factor for acquired epilepsy. Post-traumatic epilepsy (PTE) accounts for 5-20% of all cases of epilepsy[8,9]. The 30-year cumulative incidence of PTE after TBI ranges from 2.1% for mild TBIs to 16.7% for severe injuries. The timing of PTE ranges from weeks to years after the initial TBI, with more severe injuries raising the risk of PTE a longer period after the initial injury. One prior study found that persons with the Apolipoprotein ε4 (APOE ε4) genotype are at increased risk of PTE[10], though other studies have not confirmed this. We previously found that the APOE ε4 genotype is a risk factor for LOE, even in ARIC participants without dementia[5].

We will examine the association of head injury with LOE in the ARIC population, adjusting for demographics and other risk factors for acquired epilepsy. We will also examine the interaction between head injury and the APOE ε4 genotype to determine whether those with 1 or 2 APOE ε4 alleles and who also experience a head injury are at increased risk of PTE. We will specifically examine those without a history of stroke or dementia (known risk factors for epilepsy).

This study will add to our existing knowledge of the role of head injuries on the risk of later seizures, as we currently do not know how much head injuries contribute to otherwise unexplained epilepsy in the older population. We will also add to existing knowledge as we will be able to adjust for comorbidities that increase the risk of LOE, and to explore the previously described relationship between APOE4 and PTE[10]. We will also be able to exclude participants with adjudicated stroke or dementia to examine the effects of head injuries in those with otherwise unexplained LOE.

5. Main Hypothesis/Study Questions:

H1: We hypothesize that ARIC participants with prior head injury will be at increased risk of developing late-onset epilepsy (LOE), compared to participants without head injuries.

H1a. We further hypothesize that having 1 or 2 alleles of the APOE ε4 genotype will modify the risk of LOE after head injury (compared to those with 0 APOE ε4 alleles).

H2: We further hypothesize that those with more than 1 head injury will be at increased risk compared to those with 1 or 0 head injuries.

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).

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.

Outcome:
Our primary outcome of interest is late-onset epilepsy (LOE). 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) as previously used in ARIC[5,11]. We will exclude those with seizures only occurring within 1 week of initial head injury.

An additional outcome of interest will be the use of anti-seizure medication in persons with and without head injury.

Independent variables:
The main independent variable of interest will be head injury, defined as the occurrence of a related ICD-9 or ICD-10 code [800.xx (fracture of vault of skull), 801.xx (fracture of base of skull), 803.xx (other and unqualified skull fractures), 804.xx (multiple fractures involving skull or face with other bones), 850.xx (concussion), 851.xx (cerebral laceration and contusion), 852.xx (subarachnoid subdural and extradural hemorrhage following injury), 853.xx (other and unspecified intracranial hemorrhage following injury), 854.xx (intracranial injury of other and unspecified nature), and 959.01 (head injury, unspecified)] from ARIC hospitalization or CMS FFS data. We will also include self-reported TBI (from Visits 3, 4, 5, 6 and the brain MRI visit). Head injuries occurring before age 67 will be included. We are using all available sources to identify TBI, as head injuries prior to Medicare eligibility are of interest. Previous analysis by the first author has identified 4,287 reported head injuries in ARIC.

Other independent variables will include age, sex, combined race-field center, educational level (as collected at Visit 1); stroke – from adjudicated cohort stroke surveillance and self-reported stroke at Visit 1; APOE4 genotype – obtained at visit 1; and (as collected at the visit closest to the participant's 67th birthday): hypertension, defined as SBP$\geq$140, DBP$\geq$90, or antihypertensive

use; diabetes, defined as fasting blood glucose ≥126mg/dL, nonfasting glucose >200mg/dL, diabetes diagnosis, or current medication for diabetes; smoking status, self-reported (current, former, never); alcohol use, self-reported (current, former, never); hyperlipidemia; and body mass index. We will also examine dementia (as ascertained from testing at Visits 5-7 and Level 3 dementia as ascertained from testing and surveillance data), and stroke (as self-reported at Visit 1 and as adjudicated during follow up).

Planned data analysis:
We will examine the association between head injury and time to onset of LOE using a Cox proportional hazard model, adjusting for covariates listed above (H1). We will use the 67th birthday as the origin time (the earliest age at which LOE could be diagnosed), and the date of LOE onset ascertained from CMS codes.

Head injury will be included as a time-varying variable, split at the time of TBI onset (ascertained from ARIC hospitalization and CMS FFS codes and self-reported data from Visits 3-6 and the brain MRI visit). To explore the relationship of LOE and multiple head injuries (H2), we will perform an analysis using an additionally split time-varying variable for the second or greater TBI.

We will examine interactions between head injury and race, head injury and sex, and head injury and the APOE ε4 genotype.

Sensitivity analysis: 1.) exclude those with head injury prior to or origin at age 67 years, 2.) perform separate analyses using self-reported TBI data and using ARIC hospitalization and CMS FFS codes; 3) exclude those with stroke or dementia during follow up.

Potential limitations:
The main limitation is the reliance on CMS codes for determination of LOE and head injury. There is a risk of case misclassification; however, we expect misclassification bias to be towards the null. There is also a risk that head injuries may be underascertained, as some head injuries do not result in hospitalization and may be forgotten by the participant. However, we would expect this underascertainment to also bias our results towards the null. Additionally, for head injury, we do not have measures of severity or type of injury.

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)?
Cognitive trajectories and cognition in late-onset epilepsy (#3181) – Johnson PI
Late-onset epilepsy and mortality (#3436) – Johnson PI
The association of head injury and cognition, mild cognitive impairment, and Dementia – Schneider PI (#2768)
The association of head injury with risk of stroke, cardiovascular disease, and mortality – Schneider PI (#2769)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes – Brain MRI visit data for self-reported head injury data

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.

The authors agree.

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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