ARIC Manuscript Proposal #3898

PC Reviewed: _7/13/21___ Status: _____ Priority: 2___
SC Reviewed: _____ Status: _____ Priority: ____

1.a. Full Title:
Post-traumatic Epilepsy (PTE) and Dementia Risk

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

2. Writing Group Members:
Andrea L.C. Schneider (first author) (University of Pennsylvania)
Emily L. Johnson (last author) (Johns Hopkins University)
Rebecca F. Gottesman (NINDS)
Gregory Krauss (Johns Hopkins University)
Juebin Huang (University of Mississippi Medical Center)
Ramon Diaz-Arrastia (University of Pennsylvania)
James Gugger (University of Pennsylvania)
Frances Jensen (University of Pennsylvania)
Anna Kucharska-Newton (University of North Carolina)
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]**

First author: **Andrea Lauren Christman Schneider, MD, PhD**
Address: 51 North 39th Street, Andrew Mutch Building 416
Philadelphia, Pennsylvania 19104

Phone: 443-827-2352 Fax: 215-662-9858
E-mail: Andrea.Schneider@pennmedicine.upenn.edu

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).

First author: **Andrea Lauren Christman Schneider, MD, PhD**
Address: 51 North 39th Street, Andrew Mutch Building 416
Philadelphia, Pennsylvania 19104

Phone: 443-827-2352 Fax: 215-662-9858
E-mail: Andrea.Schneider@pennmedicine.upenn.edu

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 (2021-2022).

4. Rationale:

Traumatic brain injury (TBI) and epilepsy both affect a large and growing number of individuals, particularly at older ages[1, 2]. Further, TBI is a known risk factor for epilepsy in the form of post-traumatic epilepsy (PTE). It is estimated that PTE accounts for approximately 5-15% of all cases of epilepsy and PTE usually develops months to even years after TBI[3]. We previously showed that head injury (median time between head injury and first seizure: 2.9 years) is a significant risk factor for the development of late-onset epilepsy (i.e., starting at age 67 years or older[4]) in the ARIC Study (n=167 cases of PTE) (manuscript proposal #3668; manuscript under journal review).

In addition to TBI being a risk factor for epilepsy, our prior work in ARIC has also shown that both head injury[5] and late-onset epilepsy[6] are independently associated with dementia risk. Building on this prior work, we hypothesize that PTE acts as a "second-hit" which leads to significantly worse cognitive outcomes (i.e., higher risk of dementia) after TBI[7] compared to TBI (or epilepsy) alone. Few studies have specifically investigated this hypothesis and prior studies had short-term follow-up (i.e., ≤5 years) which limited the ability to look at dementia as an outcome (prior studies all looked at cognitive tests)[8-10]. Data from 182 TBI patients (91 with PTE) from the TBI Model Systems National Database found that individuals with TBI and PTE had worse functional independence measure (FIM) cognitive test sub-scores at 5 years post-TBI[9]. Another study of 210 TBI patients (38 with PTE) found that patients with TBI and PTE had worse cognitive outcomes at 1-year post-injury than those with TBI alone, however, after adjusting for the TBI severity, there were no differences between groups[10]. In one additional study of 143 severe TBI patients (27 with PTE) admitted to an inpatient rehabilitation center in Italy, there were no differences between TBI patients who did and did not develop PTE on measures of memory, intelligence, attention, and spatial cognition over 1-year[8]. Hence, there is currently no consistent data regarding the potential interaction of TBI and epilepsy/PTE with dementia risk. It is important to consider that the relatively short post-PTE follow-up time may also have limited these prior studies as PTE develops over months to years post-injury, so therefore the additional burden of the "second hit" from PTE may not have had sufficient time to manifest in some of these earlier studies with shorter follow-up time[8, 10].

In the present analysis, we propose to examine the association of PTE with dementia risk in the ARIC Study, with a particular focus on determining if the association of PTE with dementia risk is significantly stronger than the associations of TBI alone (or epilepsy alone). Importantly, due to the epilepsy definition in the ARIC cohort (defined using Centers for Medicare fee-for-service [CMS FFS] data), we will focus our analyses to look at late-onset epilepsy and late-onset PTE in participants with at least 2 years of FFS coverage prior to the first seizure code (i.e., occurring at age 67 years or older).

5. Main Hypothesis/Study Questions:

- Hypothesis 1: Post-traumatic epilepsy will be independently associated with an increased risk of incident dementia.
- Hypothesis 2: The association between post-traumatic epilepsy and dementia risk will be stronger than the associations of head injury alone or epilepsy alone with dementia risk.

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 with origin at age 67 years (i.e., when first eligible to receive an epilepsy, PTE diagnosis) and >10 years of follow-up.

Inclusion/Exclusion Criteria:
Since the definition of late-onset epilepsy / late-onset PTE relies on CMS FFS claims codes, Black (from NC and MS) and White (from MD, MN, and NC) participants with at least 2 years of continuous CMS FFS coverage will be included. Participants with prevalent dementia at baseline (age 67 years) and those missing data on covariates included in statistical models will be excluded.

Exposures:
All exposures in this study will be time-varying. We will create a 4-level primary time-varying exposure variable:

0-no head injury and no epilepsy
1-head injury only
2-epilepsy only (will also include participants with epilepsy followed by head injury)
3-PTE (head injury followed by epilepsy).

Participants can contribute person-time to category 0 and subsequently category 1 and subsequently category 3 (but by definition, cannot go from category 2 to either category 1 or 3).

1. Head Injury: Head injury will be defined as the occurrence of a head injury/TBI related ICD-9 or ICD-10 code from ARIC hospitalization or CMS FFS data. We will also include self-reported TBI (from Visits 3, 4, 5, 6, 7, and the brain MRI visit). This definition has been used previously in the ARIC cohort[5] (see below). Head injuries occurring before age 67 will be excluded from the primary analysis (but will be considered in sensitivity analyses).

Self-reported head injury questions.

ARIC Visit 3 (1993-1995)
1. Have you ever had a head injury which led you to see a physician or seek hospital care?
2. How many times has this happened?
3. How many of these head injuries resulted in your losing consciousness, no matter how briefly?
4.In what year was your head injury for which you sought medical care?
ARIC Visit 4 (1996-1998)
1. Have you ever had a major head injury? That is, one that resulted in your losing consciousness, no matter how briefly, or that led you to see a physician or seek hospital care?
2. How many times has this happened?
3. How many head injuries resulted in your losing consciousness, no matter how briefly?
4. In what year was your head injury for which you lost consciousness sought medical care?

ARIC Brain MRI Visit (2004-2006)*
1. Have you ever had a head injury that resulted in loss of consciousness (knocked out)?
2. How many times?
3. In what year or how old were you when this first occurred?
4. In what year or how old were you when this last occurred?
ARIC Visit 5 (2011-2013)*
1. Have you ever had a head injury that resulted in loss of consciousness?
2. Have you had a head injury with extended loss of consciousness (>5 minutes)?
3. Have you had a head injury that resulted in long-term problems or dysfunction?
ARIC Visit 6-7 (2016-2017 and 2018-2019)
1. Have you ever had a head injury that resulted in loss of consciousness?
2. Have you had a head injury with extended loss of consciousness (>5 minutes)?
3. Have you had a head injury that resulted in long-term problems or dysfunction?

*Questions asked in a subgroup of ARIC participants selected for brain magnetic resonance imaging (MRI) scans.

ICD-9 and ICD-10 codes used to define head injury.

ICD-9 Codes	
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
959.01	Head injury, unspecified
ICD-10 Codes	
S02.0	Fracture of vault of skull
S02.1X	Fracture of base of skull
S02.8	Fractures of other unspecified skull and facial bones
S02.91	Unspecified fracture of skull
S04.02	Injury of optic chiasm
S04.03X	Injury of optic tract and pathways
S04.04X	Injury of visual cortex
S06.X	Intracranial injuries, concussion, traumatic cerebral edema, diffuse and focal traumatic brain injury, traumatic epidural, subdural, and subarachnoid hemorrhage
S07.1	Crushing injury of skull

2. Late-onset Epilepsy: Late-onset epilepsy 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] (see below).

ICD-9 and ICD-10 codes used to define late-onset epilepsy (LOE).

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 spimple 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

3. Late-onset PTE: Late-onset PTE 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). By definition, all participants classified as late-onset PTE must have had a head injury occurring at some point prior to an epilepsy diagnosis. Individuals with seizures only occurring within 1 week of initial head injury will be excluded from this definition. This definition has been used previously in the ARIC cohort (manuscript proposal #3668; manuscript under journal review).

Outcome:
Detailed descriptions of the definition of incident dementia in ARIC have been described previously[11-13]. Briefly, there are three levels of ascertainment. Level 1 is adjudicated dementia defined using data from in-person evaluations at ARIC visits 5, 6, and 7. Level 2 adds telephone data from participants who were alive but did not attend ARIC visit 5 and/or 6 and/or 7 and also

adds data from informants of participants who were deceased prior to ARIC visit 5 and/or 6 and/or 7. 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 31 December 2019. This level 3 outcome is not dependent on visit attendance and thus minimizes potential biases due to attrition and the competing risk of death, but is limited by lack of outpatient data and the low sensitivity of ICD codes in the identification of dementia cases. In sensitivity analyses, we additionally will use the adjudicated level 1 outcome in a subset of participants who attended in-person visits 5, 6 and 7. In this subpopulation we will also investigate distributions of dementia etiologies (defined using previously described standardized criteria[12]).

Covariates:
Covariates included in our main 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). In supplemental models, we will also consider the following covariates measured at the ARIC visit closest to the participant's 67th birthday (origin for the present analyses): 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 67th birthday will be determined from continuously collected adjudicated data.

Statistical Analyses:
Our 4-level exposure variable (0-no head injury and no epilepsy, 1-head injury only, 2-epilepsy only, 3-PTE [head injury and epilepsy]) will be time-varying, split at the time of TBI, epilepsy, and PTE onset as described in the above exposure section. We will examine participant characteristics between these groups and will compare distributions of continuous variables using t-tests and of categorical variables using chi-square tests. Time between head injury/epilepsy/PTE onset and dementia onset will be calculated. To calculate cumulative incidence of dementia by head injury and epilepsy status we will use Kaplan-Meier analyses. We will examine associations between head injury alone, epilepsy alone, and PTE (head injury and epilepsy) with incident dementia risk using Cox proportional hazards models (reference no head injury and no epilepsy), adjusting for covariates listed above. To determine if the association of PTE with incident dementia is significantly stronger than the association of TBI alone and epilepsy alone with incident dementia, the TBI alone and epilepsy alone categories will be programmed as the reference group in separate analyses. The 67th birthday of each participant will be the origin time (earliest age at which late-onset epilepsy/PTE could be diagnosed). The proportional hazards assumption will be checked using Schoenfeld residuals. If power allows, we will examine interactions in the associations by sex, race, and APOE ε4 genotype.

Sensitivity Analyses:
In sensitivity analyses we will include individuals with a head injury occurring prior to age 67 years (these individuals are excluded from the main analysis as the time at risk does not start until age 67 years in this analysis and thus, it is possible that a diagnosis of PTE is missed in

these individuals due to not having follow-up starting at the time of injury). We additionally will perform separate analyses only using ICD-9/10 code identified head injury (excluding self-report) and will incorporate assessment of the impact of head injury severity (mild versus moderate/severe) (cannot assess head injury severity using self-reported data). We will also look at the impact of number of head injuries occurring after age 67 years on associations (0 versus 1 versus 2+ head injuries). Depending on available numbers/power, we will consider a sensitivity analysis where we will investigate the adjudicated level 1 dementia outcome in the subset of participants who attended in-person Visits 5, 6, and 7 and will investigate distributions of expert panel defined dementia etiologies (e.g., Alzheimer's, vascular, etc., defined using previously described standardized criteria[12]).

Limitations:
A limitation of this study is the reliance on ICD-9/10 codes to defined late-onset epilepsy/PTE and head injury. The use of ICD-9/10 codes leads to a risk for misclassification; however, we expect misclassification bias to be towards the null. There is also the possibility that milder head injuries may be under-ascertained, as the ICD-9/10 code and self-reported definition used in this study requires an individual to have sought medical attention for their head injury. However, we would expect this under-ascertainment to bias our results towards the null. Additionally, for head injury, we only have measures of severity in the subset of ICD-9/10 code defined cases (not for the self-reported cases).

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 __X__ N/A
(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
APOE ε4 genotype

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)?

#2768: The Association of Head Injury and Cognition, Mild Cognitive Impairment, and Dementia in the ARIC Study (Andrea Schneider)
#3668: The Risk of Post-traumatic Epilepsy in the ARIC Study (Andrea Schneider)
#2767: The Association of Head Injury with Brain MR and Brain PET Amyloid Imaging in the ARIC Study (Andrea Schneider)
#2769: The Association of Head Injury with Risk of Stroke, Cardiovascular Disease, and Mortality 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)

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

___ A. primarily the result of an ancillary study (list number* _____)
_X_ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* Brain MRI Study 1999.01)

*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.

References

1. Hesdorffer DC, Logroscino G, Benn EK, Katri N, Cascino G, Hauser WA. Estimating risk for developing epilepsy: a population-based study in Rochester, Minnesota. Neurology 2011;76:23-27.
2. Centers for Disease Control. TBI Data and Statistics [online]. Available at: https://www.cdc.gov/traumaticbraininjury/data/index.html. Accessed March 12, 2021.
3. Lucke-Wold BP, Nguyen L, Turner RC, et al. Traumatic brain injury and epilepsy: Underlying mechanisms leading to seizure. Seizure 2015;33:13-23.
4. Josephson CB, Engbers JD, Sajobi TT, et al. Towards a clinically informed, data-driven definition of elderly onset epilepsy. Epilepsia 2016;57:298-305.
5. Schneider ALC, Selvin E, Latour L, et al. Head injury and 25-year risk of dementia. Alzheimers Dement 2021.
6. Johnson EL, Krauss GL, Kucharska-Newton A, et al. Dementia in late-onset epilepsy: The Atherosclerosis Risk in Communities study. Neurology 2020;95:e3248-e3256.
7. Semple BD, Zamani A, Rayner G, Shultz SR, Jones NC. Affective, neurocognitive and psychosocial disorders associated with traumatic brain injury and post-traumatic epilepsy. Neurobiol Dis 2019;123:27-41.
8. Mazzini L, Cossa FM, Angelino E, Campini R, Pastore I, Monaco F. Posttraumatic epilepsy: neuroradiologic and neuropsychological assessment of long-term outcome. Epilepsia 2003;44:569-574.
9. Bushnik T, Englander J, Wright J, Kolakowsky-Hayner SA. Traumatic brain injury with and without late posttraumatic seizures: what are the impacts in the post-acute phase: a NIDRR Traumatic Brain Injury Model Systems study. J Head Trauma Rehabil 2012;27:E36-44.
10. Haltiner AM, Temkin NR, Winn HR, Dikmen SS. The impact of posttraumatic seizures on 1-year neuropsychological and psychosocial outcome of head injury. J Int Neuropsychol Soc 1996;2:494-504.
11. Gottesman RF, Albert MS, Alonso A, et al. Associations Between Midlife Vascular Risk Factors and 25-Year Incident Dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort. JAMA Neurol 2017;74:1246-1254.
12. Knopman DS, Gottesman RF, Sharrett AR, et al. Mild Cognitive Impairment and Dementia Prevalence: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). Alzheimers Dement (Amst) 2016;2:1-11.
13. Walker KA, Sharrett AR, Wu A, et al. Association of Midlife to Late-Life Blood Pressure Patterns With Incident Dementia. JAMA 2019;322:535-545.