ARIC Manuscript Proposal #2768

PC Reviewed: 6/7/16	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: **The Association of Head Injury and Cognition, Mild Cognitive Impairment, and Dementia in the ARIC Study**

b. Abbreviated Title (Length 26 characters): **Head Injury and Cognition/MCI/Dementia**

2. Writing Group:

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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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3. Timeline:
Data is currently available. We anticipate that analyses will be performed within 6-12 months of manuscript proposal approval with a goal to submit an abstract to a conference within this time period. We anticipate submitting the manuscript for publication within 1-2 years of manuscript proposal approval.

4. Rationale:
The burden of head injury (traumatic brain injury; TBI) in the United States is high. Each year, 1.7 million individuals sustain a TBI, 1.4 million of these individuals are treated in emergency departments with 275,000 hospitalizations and 52,000 deaths[1, 2]. The estimated cost of TBI in 2010 was estimated to be approximately $76.5 billion[2].

Several prior studies have investigated short and long-term associations between TBI and cognition and dementia[3-6]. One study found no association of TBI with cognitive test score or with incident MCI/dementia, but this study had only 2 years of follow-up[3]. Other studies with longer-term follow-up (median 6-33 years) have reported associations with dementia, but these studies were limited by the use of administrative datasets and by defining both TBI and dementia by ICD-9 codes[4-6]. Another recent study has suggested that a history of TBI is associated with acceleration of the age of onset of cognitive impairment by 1-2 years[7]. Mechanisms by which TBI is associated with cognitive dysfunction and MCI/dementia include both primary and secondary brain injury. Primary injury includes axonal injury, contusion, and hematoma and secondary injury occurs via oxidative stress, inflammation, excitotoxicity leading to axonal degeneration and cell death, all of which cumulatively are hypothesized to lead to cognitive dysfunction and MCI/dementia[8].

We propose to investigate prospective long-term associations of head injury with both cognitive change and adjudicated MCI/dementia in a community-based population.

5. Main Hypothesis/Study Questions:
We hypothesize that a history of head injury will be associated with greater cognitive decline over follow-up. We also hypothesize that a history of head injury will be associated with increased prevalence of MCI/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 to examine the association between history of head injury (data collected between 1993 and 2013) and cognition (data collected in 1996-1998 and 2011-2013). For this analysis, head injury will be defined using Visit 3 and Visit 4 data. We will additionally consider time-varying head injury (ever/never) to account for head injury events occurring after visit 4.

Cross-sectional study to examine the association between history of head injury (data collected between 1993 and 2013) and MCI/dementia (assessed in 2011-2013). For this analyses, head injury will be defined using data from Visit 3, Visit 4, and Visit 5.

Inclusion/Exclusion Criteria:

- Inclusion: All ARIC participants with head injury and cognition and MCI/dementia (will have two separate analysis populations – one for cognition data and one for MCI/dementia data).
- Exclusion: Non-white and non-black participants, black participants from the Washington County, Maryland or Minneapolis, Minnesota field centers, participants missing data on covariates included in statistical models.

Exposure: Head Injury:

Self-reported data on head injury was collected at ARIC visit 3 (1993-1995), visit 4 (1996-1998), and visit 5 (2011-2013, in the NCS subset). The following variables are available:

- Visit 3:
  - amha5: Have you ever had a head injury which led you to see a physician or seek hospital care?
  - amha5a: How many times has this happened?
  - amha5b: How many of these head injuries resulted in your losing consciousness, no matter how briefly?
  - amha5c In what year was your last head injury for which you sought medical care?
- Visit 4:
  - hhxd10: 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?
  - hhxd10a: How many times has this happened?
  - hhxd10b: How many head injuries resulted in your losing consciousness, no matter how briefly?
  - hhxd10c: In what year was your last head injury for which you lost consciousness sought medical care?
- Visit 5:
  - nhx2: Have you ever had a head injury that resulted in loss of consciousness?
  - nhx2a: Have you had a head injury with extended loss of consciousness (>5 minutes)?
  - nhx2b: Have you had a head injury that resulted in long-term problems or dysfunction?

The ARIC study also collects data on hospitalizations via annual telephone contact with study participants and through active surveillance of hospitalizations occurring in the study community hospitals. Hospitalization data is currently available through December 31, 2012. The CDC has previously used the following ICD-9 codes to define head injury[9, 10]:

- 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

Using the above self-reported and hospitalization data on head injury we will create the following exposure definitions:

- Ever/never head injury
- Counts of head injury events
- Length of time between head injury and cognition measurement (baseline) and MCI/dementia assessment

Outcome: Cognition:
Cognitive testing measured by DWRT, DSST, and WFT was performed at ARIC visit 4 (1996-1998) and visit 5 (2011-2013).

The DWRT[11] is a test of verbal learning and recent memory. Participants were given 10 common nouns that they were asked to learn by using each word in one or two sentences. After a five-minute delay, participants were given 60 seconds to recall the 10 words. The score is the number of words correctly recalled.

The DSST[12] is a test of executive function and processing speed. Participants were asked to translate numbers to symbols using a key. The score (range 0-93) is the total number of numbers correctly translated to symbols within 90-seconds.

The WFT[13] is a test of executive function and language, and tests the ability to spontaneously generate words beginning with a particular letter, excluding proper names or places. Participants were given 60 seconds for each of the letters "F", "A", and "S". The score is the total number of words generated across the three trials.

We will perform analyses using the raw cognitive test scores and using z-scores that were generated by the ARIC coordinating center for each cognitive test. We will also perform analyses using a global z-score. The coordinating center also averaged test z-scores to create global z-scores, which were then standardized using the visit 2 global z mean and standard deviation.

Outcome: Mild Cognitive Impairment (MCI) and Dementia:
Diagnoses of MCI and dementia were assigned at ARIC visit 5 (2011-2013) were based on an algorithm based on the formulation of MCI and dementia laid out in the National Institute on Aging - Alzheimer's Association workgroups. MCI was defined as at least one domain score worse than -1.5 Z, a CDR-SB >0.5 and <3, an FAQ <5 and decline below the 10^{th} percentile on one test or below the 20^{th} percentile on two tests in the ARIC cognitive test battery. Dementia was defined as >1 cognitive domain worse than -1.5 Z and a CDR-SB >3 and FAQ>5 and decline below the 10^{th} percentile on one test or below the 20^{th} percentile on two tests in the ARIC

cognitive test battery. In addition, a low MMSE score (<21 for whites or <19 for blacks), even in the absence of more complete cognitive testing, was regarded as diagnostic of dementia. A group of 8 ARIC clinicians (4 physicians [DK, BW, RG and GM] and 4 neuropsychologists [MA, OA, TM, and LC]) reviewed the full battery of testing and assessments on all of the discordant individuals, a subset of those with concordant assessments and examinations, and all dementia cases. For individuals in whom the reviewers disagreed, a third reviewer evaluated the protocol and rendered a deciding vote.

Etiological diagnoses were assigned and designated as primary or secondary diagnoses. The following etiological diagnoses were included: Alzheimer disease, cerebrovascular disease related, Lewy body disease, depression/psychiatric disorders, medication-related, alcohol-related, trauma-related, other neurodegenerative disorders (PSP, corticobasal syndrome, Huntington disease, HIV dementia, etc.), systemic disorder with major impact on brain function (e.g. severe heart failure, active cancer, severe connective tissue disease), and cognitive disorder of uncertain etiology.

Covariates:
The following covariates (assessed at ARIC visit 4 for cognition analyses and visit 5 for MCI/dementia analyses unless otherwise specified) will be included in statistical models: age (years; continuous), sex (male; female), race/center (Minnesota whites; Maryland whites; North Carolina whites; North Carolina blacks; Mississippi blacks), education (assessed at ARIC visit 1, <high school; high school, GED, vocational school; college, graduate, professional school), physical activity (assessed at ARIC visit 1, ordinal score); hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or medication use), diabetes (self-report physician diagnosis, medication use, fasting glucose ≥126 mg/dl, or HbA1c ≥6.5%), cardiovascular disease (adjudicated events), and APOE ε4 genotype (0, 1, or 2 ε4 alleles).

Potential Effect Modifiers:
We will formally test for interaction by age, sex, race, and APOE ε4 genotype. We will perform stratified analysis if we observe evidence for significant effect modification.

Data Analyses:
Characteristics of the included study population will be described overall and stratified by history of head injury. Characteristics will be compared between head injury groups using t-tests for continuous variables and chi-square tests for categorical variables.

We will use adjusted linear regression models to assess the association of head injury with change in cognition between Visit 4 and Visit 5. In this analysis, we will consider using a time-varying head injury (ever/never) variable to account for head injury events occurring after visit 4. We will use adjusted logistic regression models to assess the association of head injury with MCI and dementia outcomes (including subtypes). Given the attrition among the population at Visit 5, we will explore the use of multiple imputation and inverse probability of attrition weighting in our analyses.

We will perform three statistical models:

- Model 1: adjusted for demographic variables: age, sex, and race/field center.

- Model 2: adjusted for Model 1 + education, smoking status, and physical activity.
- Model 3: adjusted for Models 1 and 2 + hypertension, diabetes, cardiovascular disease, and APOE ε4 genotype.

Limitations:
A limitation of this study is the use of self-reported and hospitalization ICD-9 codes to define head injury. However, the CDC has previously used defined head injury using ICD-9 codes[9, 10]. We do not have details regarding the type of injury that occurred or details on treatment received. Additionally, as with any observational study, we will not be able to rule out the possibility of residual confounding in our analyses.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This 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 file ICTDER03 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/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)?

MSP Number	Lead Author	Title
2175	Rebecca Gottesman	Midlife blood pressure and 20-year cognitive change: The ARIC-Neurocognitive Study
2160	Andreea Rawlings	Diabetes and cognitive change over 20 years: the Atherosclerosis Risk in Communities Study
2169	Jennifer Deal	Association of retinal microvascular abnormalities with 23-year cognitive decline: The Atherosclerosis Risk in Communities Study
2120	David Knopman	Prevalence of Mild Cognitive Impairment and Dementia and Their Relationship to Diabetes and Hypertension in ARIC

2120b	David Knopman	Mid-life vascular risk factors for Mild Cognitive Impairment in the ARIC NCS Study
2120c	Rebecca Gottesman	Incidence of Dementia and its relationship to midlife vascular risk factors in ARIC
2628	Shelly-Ann Love	The Relationship of Central Adiposity and Cognitive Decline: The Atherosclerosis Risk in Communities Neurocognitive Study
2201	Melinda Power	Lipids, stains, and 20-year cognitive change: The ARIC-Neurocognitive Study
2357	Andrea Schneider	Vitamin D, Vitamin D Binding Protein Genetic Polymorphisms, C-3 epimer Vitamin D3 and Cognitive Change Over 20-years: the Atherosclerosis Risk in Communities (ARIC) Study
2632	Sai Korada	Parathyroid Hormone and Cognitive Change Over 20-years: the Atherosclerosis Risk in Communities (ARIC) Study

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 at http://www.cscc.unc.edu/aric/forms/

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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