ARIC Manuscript Proposal #2769

PC Reviewed: 6/7/16   Status: <u>A</u>   Priority: <u>2</u>
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title: **The Association of Head Injury with Risk of Stroke, Cardiovascular Disease, and Mortality in the ARIC Study**

b. Abbreviated Title (Length 26 characters): **Head Injury and Stroke, CVD, Mortality**

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. <u>ALCS</u> **[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].

The relationship between TBI and risk of subsequent stroke is not well studied. Two prior studies[3, 4] using administrative databases have suggested an increased risk of stroke among individuals who have sustained and survived a TBI. Chen et al found increased 5-year risk of incident stroke among TBI survivors (HR 2.32, 95% CI: 2.17-2.14) with suggestion that the risk of intracerebral hemorrhage is greater than the risk of ischemic stroke[4]. Similarly, Burke et al found an increased risk of ischemic stroke (HR: 1.31, 95% CI 1.25-1.36); hemorrhagic stroke was not investigated[3]. Limitations of these studies include reliance on administrative data (ICD-9 codes) and limited follow-up time[3, 4]. Further, many of the strokes occurring in these studies happened in the first month after TBI, so it is difficult to determine if some strokes were sequelae of the TBI itself, rather than independent events.

The long-term relationships between mild/moderate TBI and mortality and cardiovascular disease are also not well studied. In a population-based analysis of Olmsted County, Minnesota residents, Brown et al report a small, but statistically significant risk of increased mortality among those with mild/moderate TBI compared to those without TBI (HR 1.33, 95% CI: 1.05-1.65)[5]. TBI has been associated with endothelial dysfunction (blood-brain barrier and vasculature) as well as oxidative stress and these are mechanisms whereby TBI may be associated with cardiovascular disease[6, 7]. In a recent analysis of Veteran Health Administration data, Ahmadi et al[8] increased risk of both subclinical (coronary artery calcification) and clinical cardiovascular disease among those with mild/moderate TBI over a median of 4-years follow-up.

We propose to add to this body of literature by investigating prospective long-term associations of head injury with incident stroke, cardiovascular disease, and mortality in a community-based population.

5. Main Hypothesis/Study Questions:

We hypothesize that a history of head injury will be associated with increased risk of incident stroke and that the risk will be higher for hemorrhagic stroke compared to ischemic stroke.

We also hypothesize that a history of head injury will be associated with increased risk of both cardiovascular disease and mortality.

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 head injury (baseline defined at ARIC visit 4 [1996-1998]) and stroke, cardiovascular disease, and mortality risk after visit 4 (follow-up currently available through December 31, 2013).

Inclusion/Exclusion Criteria:
- Inclusion: All ARIC participants with head injury data available at ARIC visit 3 and/or 4.
- 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, and participants with prevalent stroke/cardiovascular disease at ARIC visit 4.

Exposure: Head Injury:
Self-reported data on head injury was collected at ARIC visit 3 (1993-1995) and visit 4 (1996-1998). 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?

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. We will use all hospital data prior to baseline (ARIC Visit 4) to supplement the self-report head injury data. The CDC has previously used the following ICD-9 codes to define head injury[3, 9]:
- 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
- Time between head injury and baseline (visit 4)

Outcome: Incident Stroke, Cardiovascular Disease and Mortality:
All stroke-related hospitalizations and deaths occurring through December 31, 2013 in ARIC participants were identified by annual telephone follow-up call and community surveillance of all ARIC hospitalizations. Hospital records for all possible stroke-related hospitalizations were obtained (ICD-9 codes 430-438 until 1997 and ICD-9 codes 430-436 afterwards). Definite/probable hospitalized strokes were classified by a combination of computer algorithm and physician review, using standardized criteria[10]. Strokes were sub-classified as ischemic versus hemorrhagic.

Cardiovascular events were ascertained via active surveillance of all participants in the study. Hospitalizations were identified through surveillance of hospitals within the study communities and reported by participants or their proxies during annual telephone calls. Study personnel abstracted potential cardiovascular events from hospital records. Coronary heart disease events were adjudicated by an endpoints committee and defined as definite or probable myocardial infarction or death from coronary heart disease.

All-cause mortality was determined by death surveillance using hospital discharge records, coroner reports, the National Death Index, and next-of-kin interviews.

Covariates:
The following covariates (assessed at ARIC visit 4 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), and diabetes (self-report physician diagnosis, medication use, or fasting glucose ≥126 mg/dl).

Potential Effect Modifiers:
We will formally test for interaction by age, sex, and race. 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 Cox proportional hazards models to assess the association of head injury at baseline (Visit 4: 1996-1998) with stroke, cardiovascular disease, and mortality risk (with follow-up through December 31, 2013). We will stratify by stroke type (ischemic versus hemorrhagic) in secondary analyses. In subsequent analyses, we will explore modeling head injury as a time-varying exposure to incorporate head injury events that occur after visit 4.

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 and diabetes.

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[3, 9]. We do not have details regarding the type of injury that occurred or details on treatment received. The power in analyses with hemorrhagic stroke will be lower due to the smaller number of events. 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
2030	Silvia Koton	Twenty-five year trends in stroke incidence and mortality in the Atherosclerosis Risk in Communities (ARIC) Study
2598	Andrea Schneider	Stroke and Risk of Subsequent Hospitalization: The Atherosclerosis Risk in Communities (ARIC) Study
2019	Erin Michos	25-hydroxyvitamin D levels and incident stroke: Twenty-year follow-up in a bi-ethnic cohort
1327	Souvik Sen	Association between initial etiological stroke subtype and recurrent etiological stroke subtype and vascular event type
2391	Logan Cowan	Hospitalized infection as a trigger for acute ischemic stroke in the ARIC study
2250	Amber Fyfe-Johnson	Heart Rate Variability and Incident Stroke: The Atherosclerosis Risk in Communities 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.

References

1.   Roozenbeek B, Maas AI, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. Nat Rev Neurol 2013;9:231-236.

2.   Centers for Disease Control and Prevention. Report to Congress on Traumatic Brain Injury in the United States: Epidemiology and Rehabilitation. Atlanta, GA: National Center for Injury Prevention and Control; Division of Unintentional Injury Prevention, 2015.

3.   Burke JF, Stulc JL, Skolarus LE, Sears ED, Zahuranec DB, Morgenstern LB. Traumatic brain injury may be an independent risk factor for stroke. Neurology 2013;81:33-39.

4.   Chen YH, Kang JH, Lin HC. Patients with traumatic brain injury: population-based study suggests increased risk of stroke. Stroke 2011;42:2733-2739.

5.   Brown AW, Leibson CL, Malec JF, Perkins PK, Diehl NN, Larson DR. Long-term survival after traumatic brain injury: a population-based analysis. NeuroRehabilitation 2004;19:37-43.

6.   Khan M, Sakakima H, Dhammu TS, et al. S-nitrosoglutathione reduces oxidative injury and promotes mechanisms of neurorepair following traumatic brain injury in rats. J Neuroinflammation 2011;8:78.

7.   Larson BE, Stockwell DW, Boas S, et al. Cardiac reactive oxygen species after traumatic brain injury. J Surg Res 2012;173:e73-81.

8.   Ahmadi N, Hajsadeghi F, Yehuda R, et al. Traumatic brain injury, coronary atherosclerosis and cardiovascular mortality. Brain Inj 2015;29:1635-1641.

9.   Langlois JA, Kegler SR, Butler JA, et al. Traumatic brain injury-related hospital discharges. Results from a 14-state surveillance system, 1997. MMWR Surveill Summ 2003;52:1-20.

10.   Rosamond WD, Folsom AR, Chambless LE, et al. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. Stroke 1999;30:736-743.