ARIC Manuscript Proposal #2767

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

1.a. Full Title: **The Association of Head Injury with Brain MR and Brain PET Amyloid Imaging in the ARIC Study**

b. Abbreviated Title (Length 26 characters): **Head Injury and Brain Imaging**

2. Writing Group:

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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].

The long-term brain-related consequences of TBI, especially those measured using advanced imaging techniques, have not been well studied. There have been a few small clinic/hospital-based PET amyloid-imaging studies performed on individuals with TBI[3-7], with sample sizes <50 participants. To our knowledge, there has only been one previously published community-based study of head trauma and PET amyloid imaging (Mayo Clinic Study of Aging)[8]. Methods and results from these previously published studies have been varied. The majority of prior studies have used ^{11}C-PiB-PET[3, 4, 6-8]; only the study by Yang et al.[5] used ^{18}F-Florbetapir PET. Some studies used both global and regional standardized uptake value ratios (SUVRs)[3-5], while others used only a global SUVR measure[6, 8]. Four studies showed that TBI was associated with increased amyloid[3-5, 8], whereas two studies found no association[6, 7].

There have been several studies looking at diffusion tensor imaging (DTI) among individuals with TBI. It has been hypothesized that TBI results in axonal injury, which is represented on DTI imaging as decreased fractional anisotropy (FA) and increased mean diffusivity (MD). A recent systematic review of these DTI studies found overall decreased FA and increased MD among those with TBI compared to controls, but specific locations varied between studies[9]. A few prior studies have also shown associations of TBI with decreased total and regional brain volumes[10, 11], increased white matter hyperintensities (WMH)[12] and increased microhemmorrhages[12, 13] on brain MRI.

We propose to investigate prospective long-term associations of head injury with both PET amyloid (global and regional SUVR) and brain MR imaging (including global and regional brain volumes, vascular pathology, and DTI) in a community-based population.

5. Main Hypothesis/Study Questions:
We hypothesize that a history of head injury will be associated with lower brain volumes, increased WMH volume, infarcts, microbleeds, and worse white matter integrity (lower fractional anisotropy and higher mean diffusivity) on brain MRI/DTI scans in late life. We also hypothesize that past head injury will be associated with increased amyloid deposition on brain PET scans in late life.

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:
Cross-sectional study to examine the association between past head injury (data collected between 1993 and 2013) and brain MRI and brain PET amyloid imaging markers (data collected in 2011-2013).

Inclusion/Exclusion Criteria:

- Inclusion: All ARIC participants with head injury and brain MRI/PET data (will have two separate analysis populations – one for MRI data and one for PET data).
- Exclusion: Participants with race other than black or white, 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?
- Brain MRI Visit:
  - nhxa1: Have you ever had an injury that resulted in loss of consciousness?
  - nhxa1a: How many times?
  - nhxa1b1: At what year did this first occur?
  - nhxa1b2: At what age did this first occur?
  - nhxa1c1: At what year did this last occur?
  - nhxa1c2: At what age did this last occur?
- 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[14, 15]:

- 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 brain imaging date

Outcome: Brain MRI:

A subsample of participants who attended visit 5 (2011-2013) was selected for brain MRI scans. Briefly, selection criteria for a visit 5 brain MRI scan included: 1) absence of MRI contraindications, 2) prior participation in the ARIC Brain MRI Ancillary Study[16], 3) all participants with evidence of cognitive impairment at visit 5 (low Mini-Mental State Exam [MMSE] score [<21 for whites and <19 for blacks] *or* low visit 5 domain z-scores on 2 or more cognitive domains [< -1.5 SD] *and* cognitive decline on the Delayed Word Recall Test, the Digit Symbol Substitution Test, or the Word Fluency Test [defined as visit 5 score minus highest previous score <20th percentile on 1 or more tests or <10th percentile on 2 or more tests]), and 4) a random sample of participants without evidence of cognitive impairment at visit 5.

The ARIC visit 5 brain MRI scans (2011-2013) were performed using 3=-Tesla scanners (Maryland: Siemens Verio [vb17 software]; North Carolina: Siemens Skyra [D11 software]; Minnesota: Siemens Trio [vb17 software]; Mississippi: Siemens Skyra [D13 software]. The following sequences were obtained: Localizer, MP-RAGE (1.2 mm slices), Axial T2*GRE (4 mm slices), Axial T2 FLAIR (5 mm slices), Field Mapping (3 mm slices), Axial DTI (2.7 mm slices for Skyra and Verio scanners and 3 mm slices for Trio scanners). Brain volume was measured from MP-RAGE sequences (FreeSurfer [http://surfer.nmr.mgh.harvard.edu][17] image analysis software), WMH volume and infarcts were assessed on T2 FLAIR sequences, and microhemorrhages were assessed on T2*GRE sequences.

The following vascular brain lesions will be used as outcomes in our analyses: lacunar infarcts (defined as non-cortical T2 FLAIR lesions of greater than 3 mm and less than or equal to 20 mm in maximum dimension located in the caudate, lenticular nucleus, internal capsule, thalamus, brainstem, deep cerebellar white matter, centrum semiovale, or corona radiata), cortical infarcts

(defined as T2 FLAIR lesions of greater than 20 mm in minimum diameter) WMH volume, and lobar and subcortical microhemorrhages (defined as T2*GRE lesions of less than or equal to 5 mm in maximum diameter).

The following brain volumes will be used as outcomes in our analyses: total brain volume, lobar volumes (frontal, parietal, temporal, and occipital), deep gray subcortical structure volume (defined as the total volume of the thalamus, caudate, putamen, and globus pallidum), total volume of an Alzheimer's Disease signature region (defined as the total volume of parahippocampal, entorhinal, and inferior parietal lobules, hippocampus, precuneus, and cuneus)[18] and hippocampal volume.

Using the MRI technique of diffusion tensor imaging (DTI), the following outcome measures will be used: fractional anisotropy (FA, defined as the directional constraint of water diffusion – lower FA is associated with worse white matter tract integrity), and mean diffusivity (MD, defined as the average rate of diffusion in any direction – higher MD is associated with worse white matter tract integrity). FA and MD will be measured both overall and in ROI. The Lobar-22 atlas will be used to define white matter ROI.

Outcome: Brain PET Amyloid Imaging:
Florbetapir PET scans were performed within one year of the brain MRI scans. MP-RAGE sequences from the brain MRIs were used for co-registration of PET images. Florbetapir isotope was injected through a butterfly needle, with images acquired from 50 to 70 minutes for a 20-minute (4x5 minute) uptake scan. Images were transferred to the PET image analysis center (Johns Hopkins), where they were reviewed qualitatively for incidental findings, image quality, and quantified for SUVR. Images were co-registered to the MRI images, spatially normalized, and 34 total regions of interest (ROI)[19] were manually drawn and applied to the SUVR images.

The primary outcome for the PET amyloid imaging analyses is a global cortical SUVR measure, which was calculated as a weighted average of the following regions: orbitofrontal, prefrontal, and superior frontal cortices, lateral temporal, parietal, and occipital lobes, precuneus, and anterior and posterior cingulate cortices. The SUVR value was dichotomized at the sample median of 1.2. Secondary outcomes for the PET amyloid imaging analyses are ROI SUVRs, dichotomized at the median SUVR of 1.2.

Covariates:
The following covariates (assessed at ARIC visit 5 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 scale); 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, MCI/dementia, and APOE ε4 genotype. We will perform stratified analysis if we observe evidence for significant effect modification.

Data Analyses:
All analyses with brain MRI outcomes will be performed incorporating sampling weights (derived by the ARIC coordinating center) to account for the visit 5 brain MRI selection process that was designed to oversample cognitively impaired individuals (see above).

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 brain volume (global; regional), WMH volume, and DTI FA/MD. The distributions of these volumes may be non-normal, so we will explore and transform distributions of these data as appropriate. We will use adjusted logistic regression models to assess the association of head injury with infarcts (lacunar; non-lacunar), microbleeds, and PET amyloid SUVR (global; regional).

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.

In sensitivity analyses, we will use inverse-probability of attrition weighting to account for participants who were lost to follow-up/died prior to visit 5.

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[14, 15]. 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
2466	Rebecca Gottesman	The ARIC-PET Amyloid Imaging Study: Differences in Brain Amyloid deposition by Age, Race, Sex, and APOE genotype
2511	Rebecca Gottesman	Vascular risk factors and brain amyloid deposition: The ARIC-PET Study
2544	Timothy Hughes	Arterial Stiffness and β-Amyloid Deposition in the ARIC-PET Study
2551	Melinda Power	Midlife and late life vascular risk factors and white matter integrity assessed using diffusion tensor imaging: the ARIC-NCS study
2315	Andrea Schneider	Association of Diabetes with Brain Magnetic Resonance Imaging
2351	Melinda Power	Association of blood pressure with neurodegenerative and cerebrovascular changes on brain MRI
2678	Elizabeth Fracica	Association of Depression with Neuroimaging Markers of Brain Vascular Disease: The Atherosclerosis Risk in Communities Study
2288	David Knopman	Associations of Brain Imaging with Cognitive Change over 20 Years

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

__X__ A. primarily the result of an ancillary study (list number* 2009.29)

___ 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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