ARIC Manuscript Proposal #4051

PC Reviewed: 5/17/22   **Status: _____**   **Priority: 2**
SC Reviewed: ___/___/___   **Status: _____**   **Priority: ____**

1.a. Full Title: Associations of Prior Head Injury and Hearing in ARIC-NCS

  b. Abbreviated Title (Length 26 characters): Head Injury and Hearing

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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 are currently available. Analyses and manuscript preparation will be performed over the next 6-12 months.

4. Rationale.

Each year, approximately 2.8 million individuals suffer a head injury requiring an emergency department visit or hospitalization.[1] The highest rates of head injury occur among older individuals (i.e., aged 75 years or older).[1] The sequelae from head injury can be long-lasting, and prior studies in ARIC (and other cohorts) have reported increased risk of dementia,[2,3] epilepsy,[4,5] and olfactory impairment[6] (ARIC MSP #3958; under journal review) years to decades after injury.

Head injury has also been associated with hearing impairment[7-13] and tinnitus[9,13-15] in prior studies, but the majority of prior studies were performed among military populations and were comprised of younger (i.e., <45 years) individuals. Thus, there is a clear need to investigate associations of head injury with hearing impairment and tinnitus among older community-dwelling individuals. Another important limitation of the existing literature is the lack of comprehensive audiometry and auditory processing testing in large samples of individuals with and without a history of head injury. Indeed, a recent systematic review[7] of 13 prior studies comprised of 773 participants (1 prospective cohort, 4 retrospective cohorts, 2 case-control studies, and 6 case reports) found that hearing loss was self-reported in 0.9% to 58% of individuals with a history of traumatic brain injury. Further, few studies have investigated associations of injury severity or number of prior head injuries with hearing impairment.[10]

It is widely known that severe traumatic brain injuries associated with temporal bone fractures are associated with increased risk of sensorineural and conductive hearing loss due to the proximity of the temporal bone to the vestibulocochlear nerve, inner and middle ear structures, the external auditory canal, and tympanic membrane.[16] However, mechanisms linking more mild head injuries to hearing impairment, auditory processing impairment, and tinnitus are less clear, but rotational/shearing injury to the brainstem and contusion/axonal injury in the temporal lobe have been proposed.

The ARIC Study provides a unique opportunity to comprehensively examine associations of prior head injury with hearing function in a large community-based cohort of older adults. Head injury information in ARIC was collected via self-report of head injuries requiring physician/hospital care, number of head injuries, and year of head injury. Additional head injury information is available from ICD-9/ICD-10 codes from Centers for Medicare/Medicaid records

and from hospitalization records from of all community hospitals through ARIC Study surveillance, allowing for additional analyses of TBI severity. Hearing is assessed in ARIC by self-reported hearing impairment, self-reported tinnitus, objective audiometric testing, and objective speech-in-noise testing. In the present proposal, we will examine associations of prior head injury with subjective and objective hearing measures and will investigate the influence of the number of prior head injuries and the severity of prior head injuries on measures of hearing performance.

5. Main Hypothesis/Study Questions.
The overarching objective of this manuscript proposal is to investigate associations of prior head injury with subjective (self-reported) and objective hearing measures.

Aim 1: To investigate associations of prior head injury with subjective hearing impairment and tinnitus. *Hypothesis*: Individuals with prior head injury will have higher prevalence of subjective hearing impairment and tinnitus than individuals without head injury. Prevalence will be higher among individuals with multiple prior head injuries compared to one prior head injury and among individuals with moderate/severe injury severity compared to individuals with mild injury severity.

Aim 2: To evaluate associations of prior head injury with objective audiometry and speech-in-noise assessment. *Hypothesis*: Individuals with prior head injury will perform worse on audiometry and speech-in-noise testing compared to individuals without head injury. Individuals with multiple prior head injuries will perform worse on audiometry and speech-in-noise testing compared to individuals with one prior head injury and individuals with moderate/severe injury severity will perform worse on audiometry and speech-in-noise testing compared to individuals with mild injury severity.

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 Population
The study population for this analysis will include ARIC Visit 6 participants with non-missing head injury, hearing, and covariate data. Participants self-identified as non-white or non-Black race and Black participants from the Minnesota and Maryland sites will also be excluded from this analysis. In sensitivity analyses, we will additionally exclude individuals with prior brain tumor, skull/brain surgery or radiation.

Exposure: Head Injury
Head injury occurring prior to Visit 6 will be defined using a combination of self-reported data (from Visits 3, 4, 5, 6 and the brain MRI visit) and ICD-9/10 code data from hospitalizations (ARIC hospitalization surveillance; Centers for Medicare and Medicaid Services [CMS] Fee-for-Service [FFS] data) and emergency department visits (CMS FFS data). As secondary exposures, we will also look at number of prior head injuries (0; 1; 2+) and in the subset identified using ICD-9/10 code data, we will look by head injury severity (mild; moderate/severe). This

definition has been used previously in the ARIC cohort[2,4] (see below for self-reported questions and ICD-9/10 codes). At the time of ARIC Visit 6, approximately 25-30% of participants have a history of prior head injury.

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 (2016-2017)
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
S04.03 X	Injury of optic tract and pathways
S04.04 X	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

Outcomes: Hearing Measures
Hearing was assessed at ARIC Visit 6. The hearing measures incorporate self-reported hearing, self-reported tinnitus, formal audiologic exam, and sound-in-noise testing.

Self-reported hearing
Self-reported hearing was assessed on the Self Reporting Hearing and Noise Exposure (HNE) form with the questions, "Which statement best describes your hearing in your right ear without hearing aid? Would you say your hearing is excellent, good, that you have a little trouble, moderate trouble, a lot of trouble, or are you deaf?" and "Which statement best describes your hearing in your left ear without hearing aid? Would you say your hearing is excellent, good, that you have a little trouble, moderate trouble, a lot of trouble, or are you deaf?". To align with categories created from audiometric data, for analysis, we will define self-reported hearing in the better and worse ears separately as: Normal / No functional loss ("excellent" or "good"), Mild ("that you have a little trouble"), Moderate ("moderate trouble") or Severe/Profound ("a lot of trouble" or "are you deaf"). Anticipated small numbers in the Severe/Profound group may necessitate collapsing with the Moderate group.

Tinnitus
Tinnitus was collected as part of the Hearing and Noise Exposure form at Visit 6 by the question, "In the past 12 months, have you been bothered by ringing, roaring, or buzzing in your ears or head that lasts for 5 minutes or more?" (yes/no). Participants who report "yes" are then asked, "How much of a problem is this ringing, roaring, or buzzing in your ears or head?" with possible responses, "No problem", "A small problem", "A moderate problem", "A big problem", and "A very big problem."

Audiometry
Pure tone air conduction audiometry was conducted at Visit 6 (2016-17). For participants who came to the clinic, audiometry was conducted in a soundproof booth in a quiet room with an Interacoustics AD-629 audiometer. For participants with a home visit or who were in a long-term

care facility, pure tone audiometry was conducted with a portable audiometer and supra aural headphones (Shoebox audiometry, Ottawa, Canada), after ensuring that the ambient levels of noise in the room were acceptable for valid testing. We will separately calculate a better-hearing ear and worse-hearing ear, 4-frequency pure tone average (PTA) in decibels hearing level (dB HL) using audiometric thresholds at the speech frequencies of 0.5, 1, 2, and 4 kHz. Hearing will be treated as a continuous variable. Additionally, we will define hearing impairment by categorizing PTA using a clinically defined ordinal variable: no hearing impairment, <25 dB HL; mild hearing impairment, 26-40 dB HL; and moderate or greater hearing impairment, >40 dB HL. Per VA guidelines, asymmetrical hearing loss will be defined as a difference in thresholds comparing left and right ears ≥20 dB HL across two contiguous frequencies, or of 10 dB HL across three contiguous frequencies. In sensitivity analysis, we will use alternate guidelines, those of the American Academy of Otolaryngology-Head and Neck Surgery [AAO-HNS], to define asymmetry as a difference between ears of 4 frequency PTA's comparing >15 dB HL.

Speech-in-Noise
Central auditory processing was measured using the Quick Speech-in-noise (QuickSIN) test. Following a practice session, participants completed two trials where they were presented with six sentences (different for each trial), in the presence of multi-talker babble such as might be experienced in a noisy restaurant, under successively more difficult listening conditions. The sentences were presented binaurally with a fixed presentation level for speech (70 dB HL), and with 5 dB incremental increases in noise level for each sentence, ranging from +25 dB speech-to-noise ratio (SNR) for the first sentence to no difference in volume between speech and noise for the final sentence (0 dB SNR). After each sentence, participants were instructed to repeat the sentence and to guess if unsure. Scoring for each sentence is on a scale of 0-5 based on correct identification of five target words. For the primary analysis, scores from the two trials will be averaged to give the mean number of words correctly identified, with a possible range from 0 to 30 (higher scores are better). In models for our primary inference, we will model the QuickSIN as a continuous variable. As there are no acceptable clinical cutpoints for the QuickSIN, for secondary analyses, we will categorize QuickSIN based on the statistical distribution in our sample (lowest quartile compared to top 3 quartiles), with sensitivity analysis to investigate robustness to chosen quantile (e.g., tertiles, quintiles, etc.)

Covariates
Covariates were assessed at ARIC Visit 6, unless otherwise specified, and will include: age (continuous), sex (male; female, assessed at Visit 1), race/center (Minnesota Whites; Maryland Whites, North Carolina Whites, North Carolina Blacks, Mississippi Blacks, assessed at Visit 1), education (assessed at ARIC Visit 1, <high school; high school, GED or vocational school; college, graduate, or professional school), military veteran status (yes; no), depression (defined by CES-D score ≥9), hypertension (yes; no), diabetes (yes; no), and cognitive status (normal; mild cognitive impairment; dementia).

Statistical Analyses
Characteristics of the study population will be shown stratified by prior head injury status (yes versus no). Continuous characteristics will be shown as means (SDs) and will be compared between head injury groups using t-tests. Categorical characteristics will be shown as n's (%'s) and will be compared between head injury groups using chi-square tests.

Log-binomial models will be used to estimate prevalence ratios (PRs and 95% CIs) for the associations of prior head injury with subjective (self-reported) hearing loss and tinnitus. We will use Poisson regression with robust standard errors if log-binomial models fail to converge. Ordinal logistic regression (audiometry categories, speech-in-noise tertiles/quartiles) and linear regression (4 frequency pure tone average [better and worse ears separately], speech-in-noise) will be used to estimate ORs (95% CIs) and beta-coefficients (95% CIs) for associations of prior head injury with audiometry and speech-in-noise measures. We will perform two statistical models: Model 1 will be adjusted for age, sex, race/center, and education and Model 2 will be adjusted for variables included in Model 1 + military veteran status, depression, hypertension, diabetes, and cognitive status. Models for speech-in-noise will also adjust for pure tone average. Analyses will be repeated using different head injury exposure definitions: number of prior head injuries (0, 1, 2+) and head injury severity (no head injury, mild injury, moderate/severe head injury; among the subset of head injuries identified using ICD code data). In sensitivity we will also repeat analyses using head injury defined by self-report and head injury defined by ICD codes separately.

Although ~70% of the variance in speech-in-noise performance is due to peripheral hearing, other factors, including cognitive function, play a role. Given the uniqueness of ARIC data to evaluate if head injury is one such factor, although not the primary research question for this proposal, in a secondary analysis, we will investigate if hearing injury modifies the association between PTA and speech-in-noise performance. Both peripheral hearing and speech-in-noise will be modeled continuously, and we will stratify results by head injury status. Models will be adjusted for demographic and clinical covariates.

All analyses will be performed using Stata SE (Version 17, StataCorp, College Station, Texas) and a two-sided p-value <0.05 will be considered statistically significant.

Limitations
A limitation of this study is the use of self-reported and hospitalization ICD codes to define head injury; therefore, we do not have details regarding the type of injury that occurred, location of injury, or details on treatment received. An additional limitation is that we do not have hearing measured at multiple time points and so will be unable to assess when hearing loss occurred relevant to head injury. Given that pure tone, but not bone conduction, audiometry was performed, we are also unable identify and exclude individuals with conductive, instead of sensorineural, hearing loss, although we expect the number with conductive loss to be small.

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? ____ Yes _X_ 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"? ____ 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/aricproposals/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)?

Head Injury-related MSPs:
- MSP #2767: The Association of Head Injury with Brain MR and Brain PET Amyloid Imaging in the ARIC Study (Andrea Schneider)
- MSP #2768: The Association of Head Injury and Cognition, Mild Cognitive Impairment, and Dementia in the ARIC Study (Andrea Schneider)
- MSP #2769: The Association of Head Injury with Risk of Stroke, Cardiovascular Disease, and Mortality in the ARIC Study (Andrea Schneider)
- MSP #3668: The Risk of Post-traumatic Epilepsy in the ARIC Study (Andrea Schneider)
- MSP #3916: Associations of Head Injury with Neuropsychiatric Symptoms (NPS) and Mild Behavioral Impairment (MBI) Domains (Lisa Richey)
- MSP #3958: Associations of Prior Head Injury with Olfactory Functioning (Andrea Schneider)
- MSP #3978: Associations between Head Injury and Mild Behavioral Impairment (MBI) Domains Across the Cognitive Spectrum (Nicholas Daneshvari)

Hearing-related MSPs:
- MSP #3204: Association between hearing loss and depression: A cross-sectional analysis from the Atherosclerosis Risk in Communities (ARIC) study (Frank Lin)
- MSP #3254: Hypertension and Age-Related Hearing Loss in the Atherosclerosis Risk in Communities Study (James Ting)
- MSP #3284: Association between hearing loss and frailty: A cross-sectional analysis from the Atherosclerosis Risk in Communities (ARIC) study (Aishwarya Shukla)
- MSP #3313: Smoking and Age-Related Hearing Loss in the Atherosclerosis Risk in Communities Study (James Ting)
- MSP #3359: Dementia, Hearing Loss, & Hearing Healthcare among Older Adults (Carrie Neiman)
- MSP #3630: Association of Hearing Loss with Dementia Severity (Carrie Neiman)
- MSP #3869: Hearing Loss and Subjective Cognitive Decline in the Atherosclerosis Risk in Communities Neurocognitive Study (Jennifer Deal)

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(s)* 2008.06, 2013.09, 2013.17)
　　___　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.

Understood.

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.

Understood.

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