ARIC Manuscript Proposal # 3316

PC Reviewed: 12/11/18 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: The association between hearing loss and white matter microstructure in the Atherosclerosis Risk in Communities Neurocognitive Study

b. Abbreviated Title (Length 26 characters): Hearing loss and DTI

2. Writing Group:
Writing group members:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. PHC

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- **3. Timeline**:

Manuscript will be completed in 6 months

4. Rationale:

Hearing loss is common in the middle aged and leads to impaired speech understanding and communication difficulties that have a large impact on a person's social, psychological, and physical well-being.(1-3) Recently, epidemiological studies have found that hearing loss in older adults might be a risk factor of cognitive decline and dementia.(4-7) These findings have led to an increased interest in the possible association between hearing loss and brain volumes in dementia-free individuals, as it is known that brain changes precede cognitive decline years before any cognitive impairment is present.(8) In the population-based Rotterdam Study it was found that age-related hearing loss was associated with smaller white matter volume in the brain.(1) However, apart from gross morphological changes, it is also known that white matter microstructure degenerates with aging.(9) Therefore the same researchers assessed the association between hearing loss and white matter microstructure and found that poorer white matter microstructure was associated with worse hearing acuity, specifically in the right superior longitudinal fasciculus and uncinated fasciculus.(10) However, since this previous study consists of a Dutch population, generalizability is limited. Therefore we need to replicate their findings to see whether hearing loss and white matter microstructure are also associated in different, more heterogeneous, populations.

5. Main Hypothesis/Study Questions:

Is hearing loss in older adults associated with white matter microstructure?

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).

Setting and study population
The Atherosclerosis Risk in Communities (ARIC) study is a population-based prospective cohort study of 15,792 men and women ages 45-64 years recruited in 1987 – 1989 from 4 US communities (Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and Minneapolis, Minnesota).(6)

Between 2016-17 (Visit 6), 3737 participants underwent pure-tone audiometry and N=3626 had complete audiometric data for the speech frequencies. Of those participants, XXX participants also had data available on white matter microstructure from Visit 5 (2011-13).

Hearing assessment
Pure tone air conduction audiometry was conducted in a sound-treated booth. Air conduction thresholds were obtained from 0.5 kHz to 8 kHz by trained technicians using insert earphones

(EARTone 3a; 3M, St. Paul, Minnesota) and an Interacoustics AD629 audiometer (Interacoustics A/S, Assens, Denmark). All thresholds were measured in decibel hearing level (dB HL). For each participant, hearing thresholds in the better hearing ear will be determined by averaging the threshold level for 4 pure tone frequencies (0.5, 1, 2, and 4 kHz), and average low frequency (0.5 and 1 kHz) and average high frequency (2 and 4 kHz) hearing thresholds will be determined. Moreover, hearing thresholds in dB will be determined for both the left and the right ear using the same method.(6) Hearing thresholds will be categorized to clinically defined cut points for hearing impairment (normal: ≤25 dB; mild: 26-40 dB; moderate/severe: >40 dB).(6)

White matter microstructure assessment

Each study site followed identical protocols for 3-T brain MRI. All scans included sagittal T1-weighted magnetization-prepared rapid gradient-echo imaging, axial T2 fluid attenuation inversion recovery, and axial diffusion tensor imaging (DTI).(11) Data were processed by the ARIC MRI Reading Center at the Mayo Clinic (Rochester, MN). From DTI, fractional anisotropy (FA) and mean diffusivity (MD) were derived as global measures of white matter microstructure. FA measures the directional constraint of water diffusion and ranges from 0 to 1 (unitless). MD is a scalar measure of how quickly water molecules diffuse overall (mm^2/s). A lower FA and higher MD indicate a worse white matter microstructure. White matter FA and MD are calculated for brain regions defined by an in-house atlas of lobar and dee white matter regions based on the STAND400 template.(11) Left and right white matter FA and MD will be averaged across atlas regions, after this we will take a weighted average to create white matter FA and MD measured for 7 regions of interest, namely frontal, temporal, occipital, and parietal lobes, anterior and posterior corpus callosum and an overall measure.(11)

Covariates

Covariates will include age (years), sex (male, female), race and center, education, body mass index (kg/m^2), smoking status, alcohol intake, hypertension, presence of diabetes mellitus, use of lipid-lowering medication, intracranial volume and total white matter volume.(6, 11)

Statistical methods

We will standardize region of interest white matter FA and MD. To assess the association between hearing loss and white matter microstructure we will use multivariable linear regression models. In the first model we will adjust for age, age^2 (to account for non-linear age effects), education, sex, race*center, and intracranial volume. In the second model we will additionally adjust for smoking status, alcohol intake, hypertension, presence of diabetes mellitus and use of lipid-lowering medications. We will explore for effect modification by sex by stratification and inclusion of an interaction between hearing and sex in the model.

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? ____ 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 file ICTDER03 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/aric/mantrack/maintain/search/dtSearch.html

_____ 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)?

MP#2417 Cross-sectional Association of Hearing Impairment and Region-Specific Brain Volumes in the Atherosclerosis Risk in Communities Hearing Pilot Study

MP#3075 Association between white matter microstructural integrity and cognitive decline, MCI, and incident dementia

MP#2551 Midlife and late life vascular risk factors and white matter integrity assessed using diffusion tensor imaging: the ARIC-NCS 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 https://www2.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.

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