**ARIC Manuscript Proposal # 3305**

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

**1.a. Full Title**: Relationship of hearing impairment with cognitive performance and β-amyloid deposition

**b. Abbreviated Title (Length 26 characters)**: Hearing and amyloid

**2. Writing Group (alphabetical)**:
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Others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _JAD_ **[please confirm with your initials electronically or in writing]**


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**3. Timeline**:
Manuscript will be completed in 6 months.

## 4. Rationale:

Hearing impairment in older adults has been consistently linked to cognitive impairment, accelerated cognitive decline[1] and increased risk of incident dementia[2] in population-based observational studies. Overall, hearing impairment is estimated to increase risk for dementia by 94%,[2] with risk increasing as hearing loss severity increases.[3-5] Because so many older adults have hearing impairment, prevention or treatment of hearing impairment is estimated to have the greatest potential for dementia prevention compared to any other modifiable dementia risk factor; up to 9% of dementia cases in the world could possibly be prevented with hearing treatment or prevention,[2] with the strong caveat that this estimate assumes a causal relationship between hearing impairment and dementia.

Whether hearing impairment is a cause or simply a marker of cognitive decline and dementia is unknown. Causal mechanisms that may link hearing impairment and cognitive decline and dementia include increased cognitive load and/or social isolation.[6] Additionally, neuroimaging studies suggest that hearing impairment may affect the brain, even in regions outside of the primary auditory cortex.[7] Individuals with hearing impairment appear to recruit executive networks[8] and show evidence of cross-modal plasticity between the somatosensory and auditory systems[9] for compensatory processing of degraded acoustic signals. Hearing impairment has also been associated with lower gray matter volume in the primary auditory cortex[8] and with faster rates of brain atrophy over time in the right temporal lobe and whole brain.[10]

Alternatively, both hearing impairment and cognitive decline/dementia may be caused by a common underlying pathology, such as microvascular disease or other processes typically ascribed to 'aging', or hearing loss may simply be a marker of socioeconomic disadvantage or poor health. Hearing loss is not thought to be related to amyloid deposition, which is felt to be a major pathogenic step in the development of Alzheimer's disease, although there are no population-based studies assessing this relationship. We propose to quantify the cross-sectional relationship between hearing impairment measured with pure tone audiometry and β-amyloid deposition using florbetapir positron emission tomography (PET).

## 5. Main Hypothesis/Study Questions:

Hearing impairment is cross-sectionally associated with cognitive performance but not with β-amyloid deposition.

## 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).

Analytic Sample

Biracial population of individuals without dementia in the Atherosclerosis Risk in Communities (ARIC)-PET Amyloid Imaging Study (Visit 5, 2011-13, 3 study sites: Washington County, MD; Forsyth County, NC; and Jackson, MS)[11] with hearing assessed at Visit 6 (2016-17, 43% African American). Of the 346 ARIC-PET participants, 2 will be excluded due to non-black or non-white race, and 1 will be excluded due to an dementia adjudication at Visit 5. Participants missing audiometric data (~N=3600 at Visit 6) will also be excluded from analysis.

Cognitive Test Performance

The primary analysis will use Visit 6 neurocognitive test performance. Latent variable methods were used to calculate cognitive domain-specific and global composite factor scores from 10

neurocognitive tests assessing the domains of memory, language and executive function/attention.[12] The primary outcome will be the global composite factor score. In secondary analyses, we will quantify the relationship between hearing impairment and domain-specific factor scores. Because cognitive impairment measured at one time is more susceptible to confounding due to education and other social factors than are analyses of cognitive change, we will also quantify the association of hearing impairment with recent prior cognitive decline from Visit 5-6. Although hearing was not assessed until Visit 6, we believe this approach is valid given that change in hearing generally progresses slowly over time (approximate rate of 1-2 dB/year) and that our measure of hearing impairment is based on the better hearing ear (most medical conditions that acutely affect hearing are rare and do not do so bilaterally). Additionally, we do not believe that subclinical cognitive impairment would affect the reliability of audiometric testing of peripheral hearing impairment (i.e., reverse causation) for several reasons: (1) PTA is a measure of the auditory periphery (i.e., it relies on cochlear transduction and neuronal afferents to brainstem nuclei without requiring significant higher auditory cortical processing),[13] (2) valid hearing thresholds can be obtained persons with dementia,[14] and (3) AD neuropathology has not been found in the peripheral auditory pathways.[15, 16]

β-Amyloid Deposition

Amyloid deposition will be measured from PET as the standardized uptake value ratio (SUVR), calculated as the standardized uptake value of florbetapir in a given region of interest divided by the standardized uptake value in the cerebellum. Global cortical SUVR will be the primary outcome of interest, calculated as an average of the precuneus, orbitofrontal cortex, prefrontal cortex, superior frontal cortex, lateral temporal lobe, parietal lobe, occipital lobe, anterior cingulate, and posterior cingulate, weighted based on region of interest size. Elevated SUVR will defined as SUVR>1.2 (the median value). [11]

Hearing Impairment

Pure tone air conduction audiometry was conducted at Visit 6 (2016-17) at all 4 study sites in a sound-treated booth within a quiet room. Pure tone audiometry is the gold-standard test to determine the faintest tones that a person can detect for a range of pitches. We will calculate a better-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.[17]

Additional independent Variables

Demographic information (Visit 1) includes birthdate (for calculation of age in years), sex, and education (highest grade or year of school completed). Education will be categorized according to standardized ARIC algorithms as less than high school, high school, or greater than high school. Smoking status will be defined using self-report current (Visits 5 and 6) and past (available at Visit 5 only) cigarette smoking status. Hypertension will be considered present based on a diastolic blood pressure ≥ 90 mmHg, systolic blood pressure ≥140 mmHg, or use of hypertensive medications. Diabetes will be considered present if fasting blood glucose level was ≥ 126 mg/dL, or the participant self-reported a diagnosis of diabetes or of medication use for diabetes. *APOE* e4 status will be defined using a binary variable for number of ε4 alleles (0 vs. ≥ 1).

Statistical Analysis

Multivariable linear and logistic regression will be used to estimate the average difference in cognitive factor scores at Visit 6 and amyloid deposition at Visit 5, respectively, comparing persons with and without hearing impairment.

Analyses for hearing impairment and amyloid deposition will adjust for age, education, and *APOE* e4 status; analyses will be stratified by race. Analyses for hearing impairment and cognitive impairment/decline will adjust for age, sex, race*center, education, Wide Range Achievement Test (WRAT, a test of premorbid intelligence measured at Visit 5) performance, smoking status (measured at Visit 6), diabetes (measured at Visit 6) and hypertension (measured at Visit 6). In a separate model, we will also adjust for global SUVR to determine if the relationship between hearing impairment and cognitive performance may be explained by β-amyloid deposition.

References:

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3. Lin FR, Metter EJ, O'Brien RJ, Resnick SM, Zonderman AB, Ferrucci L. Hearing loss and incident dementia. *Arch Neurol*. 2011;68:214-220.

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6. Lin FR, Albert M. Hearing loss and dementia - who is listening? *Aging Ment Health*. 2014;18:671-673.

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16. Sinha UK, Hollen KM, Rodriguez R, Miller CA. Auditory system degeneration in Alzheimer's disease. *Neurology*. 1993;43:779-785.

17. World Health Organization. Prevention of Blindness and Deafness Grades of Hearing Impairment. Available at: http://www.who.int/pbd/deafness/hearing_impairment_grades/en/. Accessed January 5, 2014.

**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? _X_ 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** n/a

**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

__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)?**

MP#3042 Rawlings et al. Association of midlife cognition, cognitive decline, and education with late-life cerebral β-amyloid deposition

MP#2466 Gottesman et al. The ARIC-PET Amyloid Imaging Study: Differences in Brain Amyloid deposition by Age, Race, Sex and ApoE genotype

**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 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.