ARIC Manuscript Proposal #3577

PC Reviewed: 3/10/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Role of hearing impairment in cognitive decline and progression to dementia in older adults

b. Abbreviated Title (Length 26 characters):

2. Writing Group (alphabetical):
Jennifer A. Deal (first author)
Josef Coresh
Rebecca F. Gottesman
David Knopman
Frank R. Lin
Thomas Mosley
Nicholas S. Reed
A. Richey Sharrett
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]**

First author: **Jennifer A. Deal, PhD**
Address: 2024 E. Monument Street, Suite 2-700
Baltimore, MD 21205

Phone: 410-955-1909 Fax: 410-614-9625
E-mail: jdeal1@jhu.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
Name: Frank Lin
E-mail: flin1@jhmi.edu

3. Timeline:
Manuscript will be completed in 1 year.

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, and assuming the observed associations reflect a causal relationship, 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.

However, whether hearing impairment is a cause or simply a marker of cognitive decline and dementia is unknown. 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'. Alternatively, 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 faster rates of brain atrophy over time in the right temporal lobe and whole brain[10] and in the ARIC cohort, is associated with smaller brain volumes in the superior temporal gyrus, the location of the primary auditory cortex (MP#2417, in preparation). Given this evidence, hearing loss has been described as a possible 'second hit' to the brain that may add to other brain pathologies (e.g., amyloid, cerebrovascular disease) to increase risk of cognitive decline and dementia, but this hypothesis has never been directly tested in an epidemiologic setting. We propose to address this research gap by quantifying the relationship between hearing impairment measured with pure tone audiometry and cognitive decline and progression to dementia over 8-9 years (visits 5-7/8).

5. Main Hypothesis/Study Questions:

Hearing impairment is associated with faster rates of cognitive change and with greater incidence of progression from unimpaired cognitive status or MCI at Visit 5 to dementia through Visit 7/8. We hypothesize that the magnitude of estimated associations increases with increasing levels of hearing impairment.

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 with hearing assessed at Visit 6 (2016-17, 43% African American) and at least one cognitive visit measured from Visits 5-7/8. Participants missing complete audiometric data needed calculate hearing in the better hearing ear will be excluded from analysis (N=375 at Visit 6).

Cognitive Test Performance

The primary outcome will be change in global factor cognitive score from Visits 5-7/8.[12] In secondary analyses, we will quantify the relationship between hearing impairment and change in domain-specific factor scores. Although hearing was not assessed until Visit 6, and our first

cognitive measure will be from Visit 5, 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] In a subset of Washington County participants with hearing measured at Visit 5 as part of the hearing pilot study (N~250), the average change in dB from visits 5-6 is 6 dB, a difference that is not clinically meaningful.

Dementia and Mild Cognitive Impairment

Dementia diagnosis ("level 3" dementia in the ARIC database) is performed using standardized algorithms incorporating longitudinal cognitive data and complete neuropsychological battery data, with algorithmic diagnoses confirmed by expert panel review. Dementia diagnoses for participants who do not attend clinic visits are based on supplementary cognitive information [Modified Telephone Interview for Cognitive Status (TICS) interview with the participant, on modified Clinical Dementia Rating (CDR) interviews with informants at visit 5, or the six-item screener (SIS) and the Alzheimer's disease 8 (AD8) at visits 6 and 7/8], or on hospital or death certificate dementia codes alone. For diagnosis ascertained by codes, the date of dementia onset is estimated to be 6 months before the hospitalization. Mild cognitive impairment (MCI) is adjudicated only for the subset of participants who attended each clinic visit.[17] Dementia and MCI status is currently available at visits 5-6. Visit 7/8 data will be utilized as part of this proposal as it becomes available.

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.[18]

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

Linear mixed models with random intercepts and slopes will be used to estimate the average difference in change in cognitive factor scores from Visits 5-7/8 by hearing impairment status. An interaction term between time and hearing will be used to test if rates of cognitive decline differ by hearing impairment status.

Progression to dementia by hearing impairment status will be modeled using multivariable-adjusted Cox proportional hazards models with the Efron method to handle ties; the proportionality assumption will be verified using Shoenfeld residuals. As per prior work in this cohort by Wu et al., the groups of interest in transition to dementia will be (1) all dementia-free participants; (2) participants without dementia with unimpaired cognition; and (3) participants without dementia with MCI.[19] Because MCI is only adjudicated at clinic visits, the transition from unimpaired cognitive status to MCI will be modeled using complementary log-log models.

Analyses will be adjusted for age, sex, education, race, smoking status (measured at Visit 5), *APOE* ε4, diabetes (measured at Visit 5) and hypertension (measured at Visit 5). We will explore for non-linear associations with age and adjust for age using flexible splines if warranted.

We will investigate for potential effect modification of the hearing loss-cognition relationship by sex and race by stratification and inclusion of an interaction term with hearing loss. We will also evaluate for possible modification by brain volumes in total cortex and in the superior temporal gyrus, the location of the primary auditory cortex.

Because participants must have attended visit 6 to have hearing measured, attrition prior to visit 7 would preclude measurement of cognitive function at that visit. Missing global factor scores at visit 7 will be imputed as described in Wu et al. (MP #3170).

References:

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

MP#3484 The Association of Hearing Impairment with dementia subtypes

MP#3514 Association between Dual Sensory Impairment and Cognitive Performance, Mild Cognitive Impairment and Dementia in Older Adults: The Atherosclerosis Risk in Communities Neurocognitive Study

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.