ARIC Manuscript Proposal #4145

PC Reviewed: 10/11/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Preventative Potential of Hearing Loss Control on Dementia Risk

b. Abbreviated Title (Length 26 characters):

Fraction of dementia from hearing loss

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

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3. Timeline:

Analysis and manuscript development will be completed in 12 months.

4. Rationale:

Associations between hearing loss and elevated dementia risk have been consistently documented in observational studies.[1] In 2020, these data led the Lancet dementia commission to add hearing loss as a novel modifiable risk factor for dementia.[2]

The commission[2] was the first to estimate a population attributable fraction (PAF; the upper bound of the number of dementia cases that could potentially be prevented if hearing loss were eliminated entirely) of dementia from hearing loss (8%), and one recent study quantified a smaller PAF of 2%.[3] However, there are several limitations to their approaches. The use of a systematic review, for example, that included several studies leveraging subjective measures of hearing (i.e., self-reported hearing loss)[4] for the relative measure of association between hearing and dementia might have led to an underestimation among older adults[5] of the true preventative potential of hearing loss control on dementia risk. Without individual-level follow-up data, these prior studies also could not use PAF formulas that account for potential confounding in association measures,[6,7] which can also downwardly bias PAF estimates in the presence of positive confounding of the exposure-outcome association.[8]

To address this gap in the literature, we aim to provide the first estimate—to our knowledge—of the PAF of dementia from objectively measured hearing loss among a well-characterized biracial, community-based cohort of older adults with longitudinal, individual-level follow-up data.

5. Main Hypothesis/Study Questions:

What is the proportion of dementia risk attributable to audiometric hearing loss? And does this vary by age and sex?

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 and sample

Our inclusion criteria will be all ARIC participants with race recorded at Visit 1 (1987-1989) as well as complete hearing data assessed at Visit 6 (2016-2017). For the primary analysis we will

exclude those with dementia diagnosis at Visit 5 and those with missing hearing and covariate data.

Given the expected minimal change in hearing between Visit 5 and 6, and to maximize the available follow-up data, the baseline for this analysis is Visit 5. In the primary analysis we will estimate longitudinal associations (hazard ratios and PAFs) between hearing loss and incident dementia at Visit 7. Data from Visit 8 will be incorporated as it becomes available.

Dementia diagnosis

We will define dementia diagnosis through Visit 7/8 using the standardized ARIC algorithm.[9,10] The algorithm leverages: a) longitudinal cognitive data and complete neuropsychological battery data among participants attending clinic visits; b) supplemental cognitive data obtained outside clinic visits, including the six-item screener (SIS) of Alzheimer's disease 8 (AD8) from Visit 6 and Visit 7; and c) ICD-9/10 claims-based definitions for dementia from hospitalizations or death certificates (with onset date estimated as 6 months pre-hospitalization).

Hearing impairment

Pure tone air conduction audiometry was conducted at Visit 6 at all 4 study sites in a sound-treated booth within a quiet room. If audiometry was collected at home or LTC visits, staff used portable audiometers. Pure tone audiometry is the reference-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.

We will define hearing impairment at Visit 6 as PTA >25 dB HL and categorize PTAs using predefined clinical cut points (normal hearing, ≤25 dB; mild hearing loss, 26-40 dB; moderate or greater hearing loss, >40 dB). This parameterization is consistent with previous analyses in ARIC (e.g.[11]).

Covariates

Demographic data from Visit 1 (1987-1989) will include date of birth (to derive age at Visit 5), sex, race/ethnicity, and education (< less than high school, high school or equivalent, > high school).

Clinical data will include *APOE* ε4 carrier status (0 alleles versus 1+), self-reported smoking history (never, former, current smoker), body mass index (calculated as weight kilograms/height $m^{2)}$, diabetes (yes [fasting glucose ≥126 mg/dL or nonfasting glucose ≥120 mg/dL or self-reported physician diagnosis of diabetes or use of oral diabetes medication or use of insulin] versus no [not meeting criteria]), hypertension (yes [≥140/≥90 mm Hg or use of antihypertension medication] versus no), self-reported prevalent stroke, and number of depressive symptoms (measured by the CES-D). All covariates were measured at Visit 5 and treated as time-invariant.

Statistical analysis

To characterize the sample, we will first describe the prevalence of demographic and clinical characteristics by hearing loss category. We will use t-tests, Mann-Whitney *U* tests, and chi-squared tests to compare groups by number of impairments using two sided tests with alpha of 0.05.

For the main analysis we will first estimate the association between hearing loss and dementia using multivariable Cox proportional hazards regression models adjusted for demographic covariates. Using the confounder-adjusted hazard ratios, we will then estimate adjusted PAFs of dementia from hearing loss.[6,7]

$$PAF = pd\ (\frac{HR-1}{HR})$$

Where pd is the prevalence of the *ith* level of hearing loss among dementia cases. This approach has been used in prior ARIC work (ARIC MS# 3965), however we will also consider alternative formulations of the PAF in subsequent analyses, if appropriate.

We will adjust for all demographic covariates outlined in the covariate section only in the primary analysis. To obtain 95% confidence intervals for the PAFs, we will use 5,000 bootstrapped samples.

In secondary analyses we will stratify models by age (<75 years, ≥ 75 years) and sex. We will also explore the potential impact of hearing aid use on dementia risk by estimating PAFs for dementia from no hearing aid use (reference group being hearing aid use).

Limitations and sensitivity analyses

To examine the robustness of our primary models, we will consider a) additional adjustment of the primary models for health-related and clinical covariates (*APOE* carrier status, depressive symptoms, smoking status, prevalent stroke, hypertension, and diabetes), and b) imputation of missing hearing and covariate data using multiple imputation with chained equations. Given that hearing status might be associated with phone-based ascertainment of dementia diagnosis, we will explore this as a possible source of measurement bias.

All analyses will be conducted in R version 4.0.2 (R Foundation for Statistical Computing, 2020)

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)?

#3577 Role of hearing impairment in cognitive decline and progression to dementia in older adults (Jennifer Deal)

MS #3965 Dementia occurring over a 32-year follow-up attributable to hypertension observed at different ages: Implications for dementia prevention (Jason Smith)

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)* 2014.38; 2018.07)

*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.

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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