1.a. Full Title: The Association of Hearing Impairment with dementia subtypes

b. Abbreviated Title (Length 26 characters): Hearing and dementia subtype

2. Writing Group:
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   Others Welcome

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

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3. **Timeline**: Manuscript to be completed within 1 year

4. **Rationale**:  
With the global aging of our population, the estimated 35.6 million individuals with dementia in 2010 is expected to grow to 65.7 million individuals by 2030\(^1\). This demographic transition necessitates that societies actively address risk factors for cognitive decline and dementia as recent reports indicate up to 35% of dementia cases could be prevented\(^2\). Those with hearing impairment have a two to five-fold increase in the risk of incident all-cause dementia and accelerated rates of cognitive decline\(^3\) compared to those with normal hearing. In addition, the prevalence of hearing impairment increases dramatically with age. Two-thirds of adults aged 70 years and older in the United States have a clinically meaningful hearing impairment in both ears\(^8\). Due to the high prevalence of dementia and high risk reported, it is estimated up to 9% of incident dementia cases could be prevented with the management of hearing impairment\(^2\). Despite this, less than 20% of adults who could benefit from amplification pursue hearing care\(^9\) indicating a striking opportunity to alter the course of dementia prevalence with management of hearing impairment.

To date, limited research has investigated the pathologic drivers of the known association between hearing impairment and dementia leaving an important research gap regarding the mechanism of this relationship\(^7\). \(^{10-11}\). The association seen may result from a common pathology such as Alzheimer’s disease related dementia (ADRD) or cerebrovascular disease (CVD) - the most common subtypes of dementia. Hearing could be a risk factor shared by each type. Alternatively, the association could result from mechanistic pathways independent of vascular or AD processes, for example, increased cognitive load allocating greater cognitive resources towards interpreting a degraded auditory signal\(^7\). \(^{10-14}\), a hearing-loss-associated change in brain structure and function which added to overall brain pathology\(^15-19\), or sensory deprivation leading to social isolation and its sequelae\(^20-23\).

Anatomical studies to date are limited when investigating pathology directly associated with hearing loss. One approach is to investigate the association of peripheral hearing with dementia subtypes where there is a paucity of large sample epidemiologic evidence. A study by Gallacher et al.\(^34\) of the Caerphilly cohort found an association with non-vascular related dementia but failed to maintain significance in fully adjusted models for vascular related dementia. If peripheral hearing impairment is an early biomarker of either subtype, we would expect to see a stronger association with one subtype over another and may allow for better targeting of a potential pathway for intervention and dementia prevention. On the other hand, if the cognitive loss is via mechanisms other than vascular or AD-related, hearing loss might be related to both AD and vascular dementias, simply by reducing the cognitive ability in persons who have either type of underlying pathogenesis. Our study will build upon previous ARIC hearing impairment literature\(^32-33\) supporting an association between hearing and cognitive impairment by allowing for further investigation of the association broken down by dementia/mild cognitive impairment subtype status. This determination may provide guidance toward dementia prevention options and further study by indicating if treating hearing impairment with hearing aids will reduce dementia cases.

5. **Main Hypothesis/Study Questions**: Determine the association between peripheral hearing impairment and etiologic subtype of dementia/Mild Cognitive Impairment (MCI) in older adults
  - We hypothesize that those with hearing impairment compared to normal hearing have a greater risk of both Alzheimer’s disease related MCI or dementia and cerebrovascular disease related MCI or dementia
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:** Cross-sectional analysis using Visit 6 hearing status and Visit 5 dementia ascertainment

**Study Population:** Our study sample originates from the full cohort of 15,792 participants and incorporates data from Visit 1 through Visit 6. Audiometry was completed in a subset of 250 participants from the Washington County, MD study site at Visit 5 and offered to all participants who attended Visit 6 (2016-2017). Participants received a full neurocognitive battery at Visit 5 (2011-2013) as part of the ARIC Neurocognitive Study. The study sample includes all participants who completed hearing measures at Visit 6 and the neurocognitive test battery leading to an analytic sample of 3,383 participants.

**Outcome:** Our primary outcome of interest is dementia or mild cognitive impairment subtyping status. Dementia status is ascertained for ARIC participants who attended clinic visit 5 (2011-13). Each was assigned a cognitive diagnosis via an adjudicated algorithm incorporating all available data (neurocognitive assessment, clinical dementia rating, functional activities questionnaire, and brain MRI) and verified by expert panel review. Etiologic diagnoses were additionally made based on examinations and sub classified into 1 of 11 etiologic subtype diagnosis. For this analysis, assigned dementia/MCI subtyping are categorized into three mutually exclusive categories: those with Alzheimer’s disease dementia/MCI (AD) without a primary or secondary diagnosis of cerebrovascular disease (CVD), those with a primary or secondary diagnosis of CVD related dementia or MCI (irrespective of Alzheimer’s disease), or those with dementia/MCI from other causes (excluded from analytic sample). These categories were selected as they are the most common subtypes within the population and provide a meaningful distinction between possible etiologies of dementia.

**Exposure:** Pure tone audiometry was completed in a sound-proof booth using insert earphones (EARTone 3a; 3M) and the Interacoustics AD629 audiometer (Interacoustics A/S, Assens, Denmark). Air conduction was completed at standard octaves from 500-8000 Hz. A four-frequency PTA in the better ear was calculated. Hearing impairment will be categorized along WHO standards: Normal hearing, PTA ≤25 dB; mild loss, 26-40 dB; moderate loss, 41-60 dB; severe or greater loss, >60 dB in the better hearing ear. We will also investigate the association treating PTA as continuous.

**Additional Independent Variables:** Basic demographic information was collected at Visit 1, including birthdate for calculating age at study visit, age at dementia diagnosis, sex, education, race, and study site. We will assess smoking status, diabetes, hypertension, and body mass index covariates as visit 5 status. Education will be categorized according to standardized ARIC algorithms as less than high school, high school, or greater than high school.

**Statistical Analysis:** We will explore differences in demographics by hearing status using chi square and t-tests as appropriate. The odds of dementia/MCI subtype by degree of hearing impairment will be estimated using multinomial logistic regression, adjusting for age, sex, race, study site, education, smoking, diabetes, hypertension, and body mass index. Multiple
imputation will be used to impute missing covariates. We will further explore the interaction of the association by race and sex as differences in both risk of hearing impairment and dementia exist by race and sex. Additionally, for those participants with hearing measured at visit 5 and 6 and normal cognition at visit 5, we will assess for incident mild cognitive impairment or dementia by hearing status using logistic regression, adjusting for the same covariates as above. For this secondary analysis, we do expect numbers to be small therefore power may be limited.

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
   _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)?

# 2797: Retinal signs and incident dementia in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC NCS)
#2327: Hearing Impairment and cognitive performance in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC NCS): cross-sectional and longitudinal results

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.

REFERENCES


