1.a. Full Title: Cross-sectional relationship of diabetes mellitus with hearing impairment in older adults

b. Abbreviated Title (Length 26 characters): Diabetes mellitus & hearing impairment

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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 will be completed in 6 months
4. **Rationale:**

Hearing health in older adults is a growing national priority. Prevalence of hearing impairment doubles with each age decade such that nearly two-thirds of adults over 70 years have clinically-meaningful hearing impairment. Hearing impairment is a known cause of communication difficulties and decreased health-related quality of life in older adults. An ever-increasing body of evidence has linked hearing impairment with broader health outcomes including dementia, cognitive decline, decreased mobility and physical disability, hospitalization, increased medical expenditures, and mortality. Several causal pathways are hypothesized to underlie these associations, including increased cognitive load, changes in brain structure/function, decreased awareness of the auditory environment and/or reduced social engagement. If these estimated relationships are causal, prevention of hearing impairment has the potential to have a substantial public health impact. For example, the Lancet Commission on Dementia, Prevention and Care estimated that 9% of dementia cases in the world could potentially be prevented if no one had hearing impairment (compared to 5% for smoking, 2% for hypertension and 1% for diabetes). Treatment of hearing impairment remains underutilized and its effect on these adverse functional (cognitive, physical) outcomes is unknown. Excluding noise exposure, the identification of modifiable risk factors for hearing loss has been controversial. The highly metabolic nature of the cochlea may make it susceptible to diseases that affect the vasculature, particularly at the basal (where high frequencies are localized) and apical (where low frequencies are localized) ends of the cochlea where blood supply is more restricted. Understanding of the specific frequency regions preferentially affected by diabetes will aid in clinical treatment and management of hearing loss.

Type 2 diabetes mellitus is prevalent and an established risk factor for cardiovascular disease, including stroke and hypertension, kidney disease and dementia. Histopathologic studies in animals and humans suggest that diabetes is associated with changes in the cochlea that could affect hearing, including hair cell loss and thickening of the vessels of the basilar membrane and stria vascularis.

The epidemiologic link between diabetes and hearing impairment in older adults is not well established. Several studies have found a positive association of diabetes with hearing loss, however others have been null. Cross-sectional studies have linked a diagnosis of diabetes to hearing loss and poorer hearing thresholds, however estimates varied, or evaluations were limited to middle-aged adults. One large cohort study (n=3,285) investigated risk factors for hearing loss yet only included non-Hispanic white participants. Two studies analyzing data from the National Health and Nutrition Examination Survey (NHANES) found odds ratios for the association of diabetes and hearing loss that ranged from 1.87 to 2.16, however these studies did not include diabetes as the primary risk factor or relied solely on self-reported diagnosis of diabetes without specific diagnosis measures. Hazard ratio estimates of hearing loss for those with diabetes have ranged from 1.04 to 2.71 in a small number of prospective studies, however other studies have again shown a weak or null associations. Only two studies have evaluated the association of diabetes and speech understanding measures which represent convergence of the different components of the hearing system. Limitations of these studies include small sample size (n=60), insensitive assessments, or unclear definition of speech...
measures.\textsuperscript{24,42} Prior studies investigating the relationship between poorer hearing at different frequencies have been inconsistent.\textsuperscript{23,25,27,28,30} Additionally, to our knowledge, all previous studies have treated adjacent frequency measures as independent when evaluating diabetes status on frequency region affected.

In this study, we will quantify the cross-sectional association between diabetes and glycemic measures and objective hearing impairment based on traditional pure tone audiometry (the gold standard for measuring peripheral hearing impairment) as well as speech-in-noise (a measure reflective of central auditory processing), in ARIC participants who underwent audiometry at Visit 6 (all study sites) and the 255 participants in the ARIC hearing pilot study (2013, Washington County). Although cross-sectional, this study will add to the literature by evaluating the association of diabetes with speech understanding, use objective measures of diabetes and HbA1c level, and include a biracial population from a large cohort. Additionally, our study will use appropriate methods to account for the dependence between hearing frequencies within an individual.

5. Main Hypothesis/Study Questions:

To quantify the cross-sectional association between diabetes and hearing measures. We hypothesize that:

- \textit{Individuals with diabetes have a higher prevalence of hearing impairment and poorer speech-in-noise performance as compared to persons without diabetes, and, among persons with diabetes, that the strength of this association is greatest in persons with higher HbA1c levels (HbA1c > 7\%)}

- \textit{Diabetes is preferentially associated with poorer hearing thresholds at higher frequencies (4 kHz to 8 kHz) compared to lower or mid frequencies (250 Hz to 3 kHz).}

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 Population:

3,625 participants have complete audiometry data in the interim Visit 6 data (Jan 2018); 23\% are African American with mean age 79.9±4.7 years (range 71.7-94.2 years). Of the interim data participants, 152 are missing diabetes status, 147 are missing HbA1c, and an additional 158 are missing covariate data (body mass index, hypertension, smoking, education), yielding a final analytic sample of 3,168. Even when using interim data, our study continues to be one of the largest cohort studies to quantify the association between hearing and glycemic measures.
We will also use data from the 226 participants from the ARIC hearing pilot study (Visit 5, 2013) who have complete audiometry and exposure data. A pilot study on hearing was initiated at the Washington County field site in 2013, and audiometric testing was offered to 307 ARIC participants who were presenting for a regularly-scheduled ARIC visit. Six declined participation, 46 did not complete the exam (45 because of impacted cerumen in one or both ears). Compared to other ARIC 2011-13 participants, those in the hearing pilot study were older [77.1(5.4) vs. 75.7(5.3) years, \( P<0.01 \)] and more likely to have \( \leq \) high school education (60% vs. 46%, \( P<0.01 \)). Of 255 participants with complete hearing data, 3 are non-white, 4 are missing diabetes status, and 22 are missing covariate data, yielding a final analytic sample of 226.

**Outcomes:**

Two physiologic processes are required for hearing and listening: peripheral transduction and encoding of sound in the cochlea followed by central processing of the auditory signal in the brain. Pure tone audiometry is considered a measure of peripheral auditory processing. Speech in noise measures, such as the QuickSIN, are thought to reflect central auditory processing.

I. Objective audiometry data obtained in a subset of 226 participants in Washington County in 2013 (the hearing pilot study).

Pure tone air conduction audiometry was conducted in 2013 in a quiet sound-treated booth. Pure tone audiometry is the gold-standard test to determine the faintest tones that a person can detect for a range of pitches (frequencies). We will calculate a speech frequency Pure Tone Average (PTA) in decibels hearing level (dB HL) using audiometric thresholds at 0.5, 1, 2, and 4 kHz in the better-hearing ear in accordance with the World Health Organization definition of hearing impairment. The primary analysis uses a clinical cut point of >25 dB HL to define presence of hearing impairment. Additionally, we will model PTA as a continuous variable.

I. Speech in Noise testing using the QuickSIN measure obtained in the subset of participants from Washington County in 2013

We will analyze the QuickSIN speech in noise measure as a continuous variable. The QuickSIN is a measure of speech understanding in the presence of progressively increasing background noise. It is a widely used clinical measure to estimate the impact of hearing loss (and sometimes cognitive decline) on speech understanding in a realistic setting and can be used as an estimate of functional difficulty on hearing in noise.

**Exposure:**

Diabetes will be defined as HbA1c \( \geq 6.5 \), self-reported doctor diagnosis or use of diabetes medication. For analysis, diabetes will be categorized as: no diabetes, diabetes with HbA1c \( <7\% \), or diabetes with HbA1c \( \geq 7\% \). Additionally, we will quantify the association of hearing loss and HbA1c levels modeled as a continuous variable.
**Additional independent variables:**

Demographic information was collected at Visit 1, including birthdate for calculating age at study visit (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. Audiometric testing was limited to Washington County, Maryland.

Self-reported information on current and past cigarette smoking status was collected at each study visit and recorded as never, former or current according to a standardized algorithm. Given the small sample size, smoking will be categorized as ever vs. never for this analysis. Body mass index (kg/m²) was calculated at each study visit and will be categorized according to clinical cut points: normal weight (<25 kg/m²), overweight (25-30 kg/m²) and obese (>30 kg/m²). History of noise exposure from employment, firearms or leisure activity was also collected at the hearing pilot visit and will be characterized as ever (vs. never) reporting a history of any noise exposure.

**Statistical analysis:**

The association of DM categories with hearing impairment will be estimated using multivariable-adjusted logistic or log-binomial (binary) and linear (PTA) regression. The difference in speech-in-noise performance by DM status will be modeled using multivariable linear regression.

The relationship between DM and individual hearing thresholds (0.5, 1, 2, 4, 8 kHz) will be modeled using generalized estimating equations (GEE), in order to account for the correlation between hearing thresholds in an individual. Fixed effects of frequency and DM status, as well as their interaction, will be used to test if the relationship between DM and audiometric thresholds vary by frequency.

A two-step model will be employed for adjustment. Model 1 will incorporate demographic covariates, including age, sex and education. We will include both a linear term for age and explore additional options to more flexibly model age (e.g., splines) in order to allow for the non-linear association of age with hearing. Model 2 will include covariates in Model 1, as well as additional vascular risk factors known to be associated with diabetes and with hearing impairment, including smoking status, body mass index (BMI) hypertension, and history of noise exposure.

7.a. Will the data be used for non-CVD analysis in this manuscript? ___ Yes     ____ No

7.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/search.php

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#2327 Deal et al. Hearing impairment and cognitive performance in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC NCS): cross-sectional and longitudinal results

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

MP#2418 Deal et al. Hearing Impairment and Physical Function in the Atherosclerosis Risk in Communities (ARIC) Hearing Pilot Study

ARIC MP #2623 Huddle et al. Association of Mid-Life Hypertension with Late-Life Hearing Loss

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 http://www.cscc.unc.edu/aric/forms/
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.cscce.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:


