ARIC Manuscript Proposal # 3254

PC Reviewed: 10/9/18	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Hypertension and Age-Related Hearing Loss in the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Hypertension and ARHL

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

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3. Timeline:
Manuscript will be completed in 12 months.

4. Rationale:
Hearing impairment currently affects over 5.8% of Americans and 9.8% of individuals worldwide [1,2]. Overall about 10% of people have hearing loss that impairs their ability to comprehend speech. This number increases to 40% when considering adults over the age of 65 [3]. In addition to its primary detrimental effects, hearing loss has also been associated with dementia, social isolation, and depression [4]. While age-related hearing loss is known to be a combination of genetic factors as well as acquired effects like trauma and environmental exposures, the exact mechanism has yet to be completely elucidated.

Current theories of age-related hearing loss describe circulatory insufficiency within the cochlea resulting in hair cell loss and action potential signal transduction weakening. In particular, the stria vascularis which is responsible for high frequency sounds appears to be most susceptible to circulatory insufficiency [5,6,7]. This structure may link the high frequency loss seen in presbycusis with associations to cardiovascular risk factors reported by some studies [5,6].

Better understanding the relationship between hypertension and hearing loss is important for two reasons. If hypertension is found to be related to hearing loss, it may provide clues to interventions for preventing hearing loss. In addition, understanding the casual relationship between hypertension, hearing loss, and other downstream effects may reveal new insight into the pathogenesis of these conditions. Current studies on hearing loss and other downstream effects adjust for hypertension at the time of the measurements. But given the extended amount of time required for cardiovascular disease to manifest, hypertension status adjusted during mid-life may be more revealing. And it will help to discern if hypertension is perhaps a cause of both hearing loss and other conditions currently associated with hearing loss.

Initially cross-sectional studies were ambivalent on the association. Through a cross-sectional analysis of a nationally representative dataset (NHANES) including 717 community-dwelling adults 70 years and older, there was no association between hearing loss and hypertension was observed [8]. But through a cross-sectional analysis of the Framingham dataset which included 1662 individuals (676 men and 996 women) over the age of 65, an association was demonstrated between hypertension and high-frequency hearing loss in women, in addition to hypertension and low-frequency hearing loss in men [9].

Longitudinal studies were undertaken to demonstrate an association over time. Through a 5-year longitudinal, prospective analysis of 1,984 Beaver Dam, WI community-dwelling residents between the ages of 21-84 (Beaver Dam Offspring Study dataset), no association was found between incident hearing loss and hypertension after adjusting for age and sex [10]. Similarly through a 15 year longitudinal, prospective analysis of 1,925 Beaver Dam, WI community-dwelling residents initially between the ages of 43-84, no association was found between incident hearing loss and hypertension after adjustment for age and sex [11]. However, limitations exist within both of these longitudinal studies. They both contain less than 2,000 participants, lack representation of minority participants, and have limited follow-up time (only allowing for up to 15 years of follow-up).

A prior ARIC study (under journal review) utilizing the hearing pilot study data (Visit 5, Washington County site only, N=250) found an association between mid-life (Visit 1) hypertension and hearing loss at Visit 5. Our current study will expand upon this work, assessing the association between past or current hypertension and hearing loss assessed at ARIC Visit 6 in a much larger sample (N=3420) from all 4 study sites, thus expanding study power and allowing for the inclusion of African American participants in the analysis.

5. Main Hypothesis/Study Questions:

Aim 1: To quantify the cross-sectional association between hypertension and age-related hearing impairment in older adults when hypertension is measured at the same time as hearing (Visit 6) as well as when hypertension is measured 20 years prior to hearing (Visit 4)

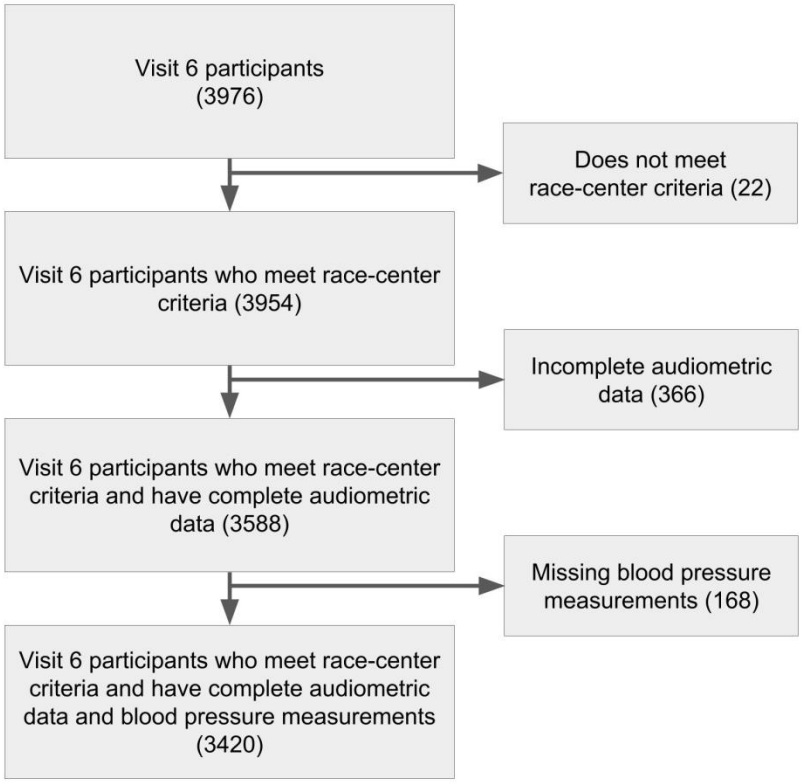
> *We hypothesize that hypertension is cross-sectionally associated with greater severity of hearing loss in older adults, and that hypertension is preferentially associated with poorer hearing thresholds at higher frequencies (4 - 8 kHz) compared to mid-frequencies (1 - 3 kHz).*

Aim 2: To quantify the association between trajectories of SBP and DBP measured from Visits 1-6 and hearing impairment measured at Visit 6.

> *We hypothesize that faster rates of change in blood pressure (in both directions) are associated with hearing impairment as compared to more stable rates of change in blood pressure over time.*

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: Biracial population of 3420 men and women (23% African American) aged 54-74 years at Visit 4, meet race-center criteria, with complete blood pressure measurement at Visits 4 & 6, who underwent audiometry testing at Visit 6, and have at least one blood pressure measurement from Visits 1-3.



There are 3976 participants who had complete blood pressure measurements at Visit 6. Twenty two participants are missing the race-center variable. An additional 366 participants are removed due to having incomplete audiometric testing, which we define as missing any hearing thresholds for 0.5, 1, 2, or 4 kHz. Finally, 168 more participants were excluded since they were either (1) missing any blood pressure measurements from Visit 4 or (2) missing all blood pressure measurements from Visits 1-3. This is performed so that at least one other timepoint (other than Visit 4) can be utilized to characterize a participant's blood pressure trajectory in mid-life.

Hearing Loss

Pure tone audiometry was offered to all ARIC participants at Visit 6 (2016-17). A four-frequency (0.5, 1, 2, and 4 kHz) pure tone average (PTA) will be calculated in the better-hearing ear and hearing impairment will be defined using clinically relevant PTA cutpoints as defined by the World Health Organization (WHO): (1) normal hearing: ≤25 decibels hearing loss (dB HL), (2) mild hearing loss: >25 dB HL and ≤40 dB HL, (3) moderate hearing loss: >40 dB HL and ≤60 dB HL, (4) severe or profound hearing loss: >60 dB HL [11]. PTA will also be modeled as a continuous variable (scaled so that one unit change equals a 10 dB HL increase).

In a secondary analysis, hearing thresholds at the higher frequencies (4, 6, and 8 kHz) will be modeled continuously in order to investigate the association between hypertension and high frequency hearing impairment. Higher hearing thresholds for a specific frequency correspond to higher volumes needed for participants to hear that frequency, thus corresponding to worse hearing.

Blood Pressure Variables

The primary analysis will categorize hypertension as normal blood pressure (SBP of <120 mm Hg, DBP of <80 mmHg, and no antihypertensive use), prehypertension or Stage 1 hypertension (SBP of 120-139 mm Hg or DBP of 80-89 mm Hg, and no antihypertensive use), or Stage 2 hypertension (SBP of ≥140 mm Hg, DBP of ≥90 mm Hg, or antihypertensive use).

The value of blood pressure used to determine categorization for hypertension is based on the average of multiple measurements at each visit. In Visits 1-3, blood pressure was measured three times with the final value calculated as an average of the second and third measurement. In Visit 4, blood pressure was measured twice and the final value is calculated as the average of those two measurements. In Visits 5-6, blood pressure is measured three times, and the final value is calculated as an average of all three measurements.

Additional independent variables

Demographic information was collected at Visit 1, including age (years), sex, race, 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 equivalent, or greater than high school.

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. Body mass index (kg/m2) was calculated at each study visit and will be categorized according to clinical cutpoints: normal weight (<25 kg/m2), overweight (25-30 kg/m2) and obese (>30

kg/m2). Diabetes will be considered present if fasting blood glucose level was ≥ 126 mg/dL, nonfasting level ≥ 200 mg/dL, or the participant self-reported a diagnosis of diabetes or of medication use for diabetes. Medications that may possibly be ototoxic (e.g., ibuprofen) will also be evaluated.

Noise exposure will be considered present if the participant self-reported a history of occupational or leisure loud noise exposure (5+ hours per week) or self-reported ever using firearms. Noise exposure will be modeled as ordinal variable with 0 being assigned to absence of all three types exposures, 1 to presence of any one type of exposure, and 2 to presence of two or more types of exposures

Statistical analysis

Ordinal logistic regression (hearing impairment categories) and linear regression (PTA) will be used to estimate the association of hypertension and blood pressure measured at Visit 6 (Aim 1) and Visit 4 (Aim 2) with hearing impairment measured at Visit 6. Prior studies have shown that hearing thresholds for similar frequencies are more correlated than more dissimilar frequencies. To account for these correlations, we will use linear mixed models with random intercept to estimate the association between hypertension and hearing thresholds at individual frequencies.

For the 2nd aim, we will utilize similar methods to those employed in Windham et al 2017 (The Importance of Mid-to-Late Life Body Mass Index Trajectories on Late-Life Gait Speed). [12] We will start by modeling the trajectories of blood pressure (systolic blood pressure, diastolic blood pressure, and pulse pressure) from Visits 1-6 using linear mixed models. Given the 16-year gap between Visits 4 and 5, we will use a two piece linear spline to allow blood pressure trajectories to differ between Visits 1-4 and Visits 4-6. Results from this model will be used to create blood pressure change groups according to baseline values (normotensive, Stage 1 hypertension, Stage 2 hypertension), changes from Visits 1-4 (Years 1-10 in the study; decrease/maintain/increase blood pressure) and Visits 4-6 (Years 10-30; decrease/maintain/increase). In the second phase of the analysis, we will then model the association between the blood pressure trajectory groups with hearing impairment at Visit 6 using linear models.

A two-step model will be employed for adjustment. Model 1 will incorporate demographic covariates, including age, sex, site-race, 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 functional performance. Model 2 will include those covariates in Model 1, as well as noise exposure and additional cardiovascular risk factors that are known to be associated with hearing impairment, including smoking status, body mass index (BMI), and prevalent diabetes. Missing covariate values will be imputed with 20 sets of multiple imputation using chained equations (MICE).

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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? ____ 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

_____ 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#2623 Deal et al. Association of mid-life versus late-life hypertension on hearing impairment

MP#3206 Powell et al. Cross-sectional relationship of diabetes mellitus with hearing impairment in older adults

MP#2254 Windham et al. Relationship of Adiposity Trajectories to Later Life Physical Function and Strength

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