ARIC Manuscript Proposal #2623

PC Reviewed: 9/8/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of mid-life versus late-life hypertension on hearing impairment

b. Abbreviated Title (Length 26 characters): Hypertension & hearing loss

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __MGH__ **[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 loss is highly prevalent in older adults, affecting two-thirds of the population ages 70 and older.[1] While hearing loss itself can lead to communication difficulties and decreased health-related quality of life,[2] an ever-increasing body of evidence has linked hearing impairment with a variety of poor health outcomes including cognitive decline,[3,4] physical disability,[5–7] falls,[8,9] hospitalization,[10,11] and mortality.[12] Hearing loss is responsible for an estimated $3.1 billion in additional medical expenditures in the United States alone.[13] This evidence has attracted the attention of the Institute of Medicine (IOM), which has held two workshops addressing hearing and healthy aging as a public health concern.[14]

While the treatment of hearing impairment remains underutilized,[15] another potential area of mitigation of the adverse public health effects of hearing loss is hearing loss prevention. Aside from noise exposure, the identification of modifiable risk factors for hearing loss has been controversial.[16–19] A 2011 report on the epidemiology of hearing loss using data from the National Health and Nutrition Examination Survey (NHANES) demonstrated age, race, and sex as being significantly associated with hearing loss. However, cardiovascular risk factors including stroke, smoking, diabetes, and hypertension were not found to be significantly associated with hearing loss.[20]

Prior studies have attempted to link hypertension and other cardiovascular risk factors to hearing loss. A 1993 study demonstrated an association between prevalent hypertension and hearing loss.[21] However, a 2005 cross sectional study using Epidemiology of Hearing Loss Study (EHLS) data found no association between hearing loss and self-reported hypertension at the time of hearing screening. It remains unclear whether hypertension is a risk factor for the development of hearing loss. Additionally, the effect of age of onset of hypertension on hearing loss is unknown.

Here we propose to quantify the association between hypertension and objective hearing impairment in the Atherosclerosis Risk in Communities (ARIC) study. Further, we propose to examine the possible differences in the estimated effect on hearing loss of hypertension measured in mid-life versus late-life. Using the wealth of longitudinal blood pressure data available in ARIC, we also propose to quantify the association between trajectories of change in blood pressure and hearing impairment measured at Visit 5. Paradoxically, low blood pressure in older adults is often cross-sectionally associated with adverse health outcomes (e.g., mortality, cognitive impairment, dementia). These associations may be true relationships (e.g., hypotension contributing to poor cognition), may reflect survival effects (with surviving hypotensives somehow no longer at higher risk for the outcome), or they may reflect a common cause of declining BP and declining cognitive ability (e.g., low blood pressure as a marker of preclinical dementia). Should

these relationships also be true for hearing loss, trajectory analysis of risk factor-outcome associations in adults over two decades can help to address these concerns.

5. Main Hypothesis/Study Questions:

Aim 1: To quantify the association between hypertension measured in mid-life and hearing impairment measured in late life.

Aim 2: To quantify the cross-sectional association between hypertension measured in late life and audiometric hearing impairment measured at the same time as hypertension status.

> *We hypothesize that using relative measures of association (e.g., odds ratio), hypertension measured in mid-life (Visit 1, Visit 4) will be more strongly associated with late-life hearing impairment than will hypertension measured in late life (Visit 5). We hypothesize that age will not attenuate (or will only mildly attenuate) the association between hypertension and hearing impairment when quantified using absolute measures of association (e.g., risk difference).*

Aim 3: To quantify the association between trajectories of SBP and DBP measured from Visits 1-5 and hearing impairment measured at Visit 5.

> *We hypothesize that faster rates of change in blood pressure (in both directions) will be 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:
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 their regularly-scheduled ARIC visit. Six declined participation, 46 did not complete the exam (45 of them because of impacted cerumen in one or both ears). Compared to other ARIC 2011-13 participants, participants 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 ≤ high school education (60% vs. 46%, $P<0.01$).[4]

Outcomes:

I. Objective audiometry data obtained in a subset of 250 participants in Washington County at visit 5 (the hearing pilot study).

Pure tone air conduction audiometry was conducted at Visit 5 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 speech frequency Pure Tone Average (PTA) in decibels hearing loss (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 loss.[22] The primary analysis will categorize hearing impairment using a clinically defined ordinal variable for hearing impairment: no HI: <25 dB HL, mild HI: 26-40 dB HL, moderate/severe HI: >40db HL. Additionally, we will model PTA as a continuous variable.

Exposure:

I. Hypertension

In keeping with previous work in this cohort,[23] the primary analysis will categorize hypertension as normal blood pressure (SBP of <120 mm Hg, DBP of <80 mmHg, and no antihypertensive use)), prehypertension (SBP of 120-139 mm Hg or DBP of 80-89 mm Hg), or hypertension (SBP of ≥140 mm Hg, DBP of ≥90 mm Hg, or antihypertensive use). For the first 2 aims, hypertension will be measured at the following study visits: Visits 1 and Visit 4 (mid-life hypertension) and Visit 5 (late-life hypertension). In secondary analyses, SBP and DBP across all 5 visits will be modeled continuously. For Aim 3, the exposure will be trajectories of SBP and DBP from all available visits (Visits 1-5).

Additional independent variables:

Demographic information was collected at Visit 1, including age (years), sex, and education (highest grade or year of school completed). Education will be categorized according to standardized ARIC algorithms as basic (≤ 11 years), intermediate (12-16 years), or advanced (≥ 17 years). Audiometric testing was limited to Washington County, Maryland. Because of the small number of non-white participants (N=1 Asian and N=1 Black), the analysis will be restricted to participants self-reporting white race.

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. Quantity of lifetime tobacco use (cumulative cigarette-years) among ever smokers was calculated at Visit 1 and 2 according to standardized algorithms. Body mass index (kg/m^2) was calculated at each study visit and will be categorized according to clinical cutpoints: normal weight (<25 kg/m^2), overweight (25-30 kg/m^2) and obese (>30 kg/m^2). 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.

Statistical analysis:

Separate multivariable logistic regression will be used to estimate the association of hypertension at Visit 1, hypertension at Visit 4, or hypertension at Visit 5 with

hearing impairment at Visit 5. The difference in PTA by hypertension status will be modeled using linear regression.

Although hearing impairment at Visit 5 is the outcome of interest, we will model the association between trajectories of SBP and DBP from Visits 1-5 with hearing impairment at Visit 5 using linear mixed models in which blood pressure is modeled as the dependent variable. In addition to adjustment covariates, hearing impairment, time and an interaction term between hearing and time will be included in the model as independent variables, similar to an published analysis looking at trajectories of blood pressure and dementia in the Honolulu-Asia Aging Study.[24]

Model building:

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 functional performance. Model 2 will include those covariates in Model 1, as well as additional cardiovascular risk factors that are known to be associated with hearing impairment, including smoking status, body mass index (BMI), and prevalent diabetes.

Our study will be limited in its generalizability, as the hearing pilot study was only conducted at the Washington County field center, but will make a valuable contribution to the literature on risk factors for hearing impairment in an aging context.

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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/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

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.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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __x__ No.