

ARIC Manuscript Proposal # 3317

PC Reviewed: ___/___/18

Status: _____

Priority: _____

SC Reviewed: _____

Status: _____

Priority: _____

1.a. Full Title: The association between carotid atherosclerosis and hearing loss: the ARIC study

b. Abbreviated Title (Length 26 characters): cIMT and hearing

2. Writing Group:

Writing group members:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **PHC**

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3. Timeline:

Manuscript will be completed in 6 months.

4. Rationale:

The ageing of the population,[1] is accompanied by a steep increase in the prevalence of age-related hearing loss.[2] Age-related hearing loss causes reduced hearing sensitivity and impaired speech understanding and has been associated with depression, social isolation, and even dementia.[3-6] However, no treatment is available to cure hearing loss. Therefore strategies to prevent or delay the onset or progression of age-related hearing loss are highly warranted. Moreover, it might shed more light on already established associations between hearing loss and several functional outcomes.

Age-related hearing loss is thought to be due to the degeneration of the cochlear sensory-neural structures and the stria vascularis. Given the high amount of vascularization of these parts of the inner ear, some epidemiologic studies have found cardiovascular risk factors to be associated with higher levels of hearing loss.[7-11] To date, few cross-sectional studies and one longitudinal study have found an association between atherosclerosis and hearing loss [12-14] in small to moderate sample sizes but have mainly assessed atherosclerosis [15] or hearing loss [13] by means of self-report. Therefore, direct evidence of the association between atherosclerosis and hearing loss, especially at a population-based level, remains scarce.

The authors of this paper assessed the association between atherosclerosis as measured by plaque score and intima media thickness and age-related hearing loss in the population-based Rotterdam Study (the Netherlands). In a cross-sectional sample of 3,724 participants (mean age 65.5 years (SD: 7.5); 55.4% female) they found that atherosclerosis was associated with age-related hearing loss (difference in Z-score hearing loss per 1-point increase in plaque score: 0.04 [95% CI: 0.02, 0.06], and difference in Z-score per 1-mm increase in IMT: 0.17 [95% CI: 0.01, 0.34]). Interestingly, it appeared that atherosclerosis was associated almost exclusively with hearing loss in the right ear, [16] suggesting a possible right-ear disadvantage for hearing thresholds. To our knowledge, this is the first study to report on left/right differences in hearing thresholds in association with atherosclerosis. Therefore, replication in other populations is highly warranted.

5. Main Hypothesis/Study Questions:

Is atherosclerosis associated with higher hearing thresholds in a large population-based sample? Specifically, is atherosclerosis associated with hearing loss in the right ear?

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).

Setting and study population

The Atherosclerosis Risk in Communities (ARIC) study is a population-based prospective cohort study of 15,792 men and women ages 45-64 years recruited in 1987 – 1989 from 4 US

communities (Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and Minneapolis, Minnesota).[17]

At Visit 6, 3737 participants underwent pure-tone audiometry and N=3626 had complete audiometric data for the speech frequencies. Of those 3626 participants, 1996 participants also had data available on carotid IMT and plaque from Visit 4 (1994-96).

Ultrasound measurement

To approximate atherosclerosis we will use measures of the presence of plaque and carotid intima media thickness (cIMT). To assess those, A Biosound ILSA system was used and images recorded on a VHS tape. The cIMT was measured centrally by trained readers at the ARIC Ultrasound Reading Center and was assessed in three segments: the distal common carotid, the carotid artery bifurcation, and the proximal internal carotid arteries. 11 measurements of the far wall were attempted at each of these segments. The mean of the mean measurements across these segments of both the right and left sides was estimated.[18]

Moreover, trained readers adjudicated either plaque presence or absence when 2 of the following 3 criteria were met: 1) an abnormal wall thickness defined as cIMT above 1.5 millimeter; 2) an abnormal shape (protrusion into the lumen, loss of alignment with adjacent arterial wall boundary); 3) an abnormal wall texture seen as brighter echoes than adjacent boundaries.[19]

Hearing assessment

Pure tone air conduction audiometry was conducted in a sound-treated booth at Visit 6. Air conduction thresholds were obtained from 0.5 kHz to 8 kHz by trained technicians using insert earphones (EARTone 3a; 3M, St. Paul, Minnesota) and an Interacoustics AD629 audiometer (Interacoustics A/S, Assens, Denmark). All thresholds were measured in decibel hearing level (dB HL). For each participant, hearing thresholds in the better hearing ear will be determined by averaging the threshold level for 4 pure tone frequencies (0.5, 1, 2, and 4 kHz), and average low frequency (0.5 and 1 kHz) and average high frequency (2 and 4 kHz) hearing thresholds will be determined. Moreover, hearing thresholds in dB HL will be determined for both the left and the right ear using the same method.[17] In a secondary analysis, hearing thresholds will be categorized to clinically defined cut points for hearing impairment (normal: ≤ 25 dB; mild: 26-40 dB; moderate/severe: >40 dB).[17] We will also quantify the association between hearing and low (0.5, 1) and high (4, 6, 8 kHz) frequency thresholds.

Statistical analysis

The association between subclinical atherosclerosis and hearing loss will be examined using a three-step strategy. First, we will assess associations of carotid plaque scores and IMT with hearing loss across all, high, and low hearing frequencies using multivariable linear regression models. In the first model we will adjust for age, age² (to account for non-linear age effects) sex, race*center, and level of education. In the second model we will additionally adjust for BMI, smoking, presence of hypertension, cholesterol levels (HDL and LDL), and lipid lowering medication use. In the third model we will additionally adjust for prevalent stroke, diabetes and CHD. Second, we will perform a similar multivariable linear regression analyses in which we study the association of side-specific atherosclerosis and hearing loss. Third, we will investigate the association of atherosclerosis with severity of hearing loss (none, mild, moderate/severe) using ordinal regression with similar multivariable adjusted models. For the ordinal regression,

the proportional-odds assumption will be checked. As prevalence of hearing loss increases substantially with age [7], we will further explore whether associations differ by sex.

7.a. Will the data be used for non-CVD analysis in this manuscript? 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? 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.csc.c.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 Association of mid-life versus late-life hypertension on hearing impairment
MP#3254 Hypertension and Age-Related Hearing Loss in the Atherosclerosis Risk in Communities Study
MP#3206 Cross-sectional relationship of diabetes mellitus with hearing impairment in older adults

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? 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.csc.c.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.csec.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

1. *World report on ageing and health*. Vol. <http://www.who.int/ageing/publications/world-report-2015/en/>. 2015, World Health Organization: Geneva.
2. Bernabei, R., et al., *Hearing loss and cognitive decline in older adults: questions and answers*. Aging Clin Exp Res, 2014. **26**(6): p. 567-73.
3. Lin, F.R., *Hearing loss in older adults: who's listening?* Jama, 2012. **307**(11): p. 1147-8.
4. Deal, J.A., et al., *Hearing Impairment and Incident Dementia and Cognitive Decline in Older Adults: The Health ABC Study*. J Gerontol A Biol Sci Med Sci, 2017. **72**(5): p. 703-709.
5. Cosh, S., et al., *The relationship between hearing loss in older adults and depression over 12 years: Findings from the Three-City prospective cohort study*. Int J Geriatr Psychiatry, 2018.
6. Mick, P., I. Kawachi, and F.R. Lin, *The association between hearing loss and social isolation in older adults*. Otolaryngol Head Neck Surg, 2014. **150**(3): p. 378-84.
7. Gates, G.A. and J.H. Mills, *Presbycusis*. Lancet, 2005. **366**(9491): p. 1111-20.
8. Gates, G.A., et al., *The relation of hearing in the elderly to the presence of cardiovascular disease and cardiovascular risk factors*. Arch Otolaryngol Head Neck Surg, 1993. **119**(2): p. 156-61.
9. Dhanda, N. and S. Taheri, *A narrative review of obesity and hearing loss*. Int J Obes (Lond), 2017. **41**(7): p. 1066-1073.
10. Hull, R.H. and S.R. Kerschen, *The influence of cardiovascular health on peripheral and central auditory function in adults: a research review*. Am J Audiol, 2010. **19**(1): p. 9-16.
11. Helzner, E.P., et al., *Hearing sensitivity in older adults: associations with cardiovascular risk factors in the health, aging and body composition study*. J Am Geriatr Soc, 2011. **59**(6): p. 972-9.
12. Fischer, M.E., et al., *Subclinical atherosclerosis and increased risk of hearing impairment*. Atherosclerosis, 2015. **238**(2): p. 344-9.
13. John, U., et al., *Associations of carotid intima-media thickness, tobacco smoking and overweight with hearing disorder in a general population sample*. Atherosclerosis, 2007. **195**(1): p. e144-9.
14. Nash, S.D., et al., *The prevalence of hearing impairment and associated risk factors: the Beaver Dam Offspring Study*. Arch Otolaryngol Head Neck Surg, 2011. **137**(5): p. 432-9.
15. Gong, R., et al., *Hearing loss prevalence and risk factors among older adults in China*. Int J Audiol, 2018. **57**(5): p. 354-359.
16. Croll, P.H., Bos, D., Vernooij, M.W., Arshi, B., Lin, F.R., Baatenburg de Jong, R.J., Ikram, M.A., Goedegebure, A., Kavousi, M., *Carotid atherosclerosis is associated with age-related hearing loss*. Submitted, 2018.
17. Deal, J.A., et al., *Hearing impairment and cognitive decline: a pilot study conducted within the atherosclerosis risk in communities neurocognitive study*. Am J Epidemiol, 2015. **181**(9): p. 680-90.
18. Pursnani, S., M. Diener-West, and A.R. Sharrett, *The effect of aging on the association between coronary heart disease risk factors and carotid intima media thickness: an analysis of the Atherosclerosis Risk in Communities (ARIC) cohort*. Atherosclerosis, 2014. **233**(2): p. 441-6.
19. Nambi, V., et al., *Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study*. J Am Coll Cardiol, 2010. **55**(15): p. 1600-7.