

ARIC Manuscript Proposal # 3190

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Priority: _____

1.a. Full Title: Retinal signs and hearing loss in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC NCS)

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

2. Writing Group:

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

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3. Timeline:

Manuscript will be completed in 6 months.

4. Rationale:

Age-related hearing loss is becoming an increasingly pervasive public health issue – prevalent in nearly two-thirds of adults aged 70 years and older in the US population.¹ In light of findings that suggest hearing impairment may be improved with rehabilitative interventions,¹ understanding the pathophysiology and finding early risk factors for hearing loss are important in developing effective interventions. Although a wide number of studies have investigated risk factors associated with hearing loss including noise exposure, smoking, and diabetes,³ the etiology of age-related hearing loss remains uncertain with a predominant cause yet to be identified. In previous efforts to identify etiologic factors, increasing evidence suggests microvascular disease⁴ as an underlying pathology. In addition, the association of hearing loss with diseases such as diabetes suggests that they may share a common microvascular pathology,⁵ providing further compelling evidence to investigate microvascular disease as an etiologic factor of age-related hearing loss.

To our purpose of investigating microvascular changes in hearing loss, retinal fundus photography may offer a non-invasive method of measuring changes in the systemic microvasculature extending to the cochlear microvasculature. Previous studies have already highlighted the potential to use retinal microvasculature as a reference for general cerebral microvascular health based on anatomic similarities and shared disease processes of the brain and retina.^{6 7 8} Hanff et al. found that retinopathy (OR 3.18; 95% CI 1.71-5.89) and its components: microaneurysms (OR 3.06; 95% CI 1.33-7.07), retinal hemorrhage (OR 3.02; 95% CI 1.27-7.20), arteriovenous (AV) nicking (OR 1.93; 95% CI 1.24- 3.02) and focal arteriolar narrowing (OR 1.76; 95% CI 1.19-2.59) were associated with a higher prevalence of new brain microvascular disease.⁹ Furthermore, retinal photography is also thought to be a measure of more systemic vascular disease, supported by retinal manifestations of non-ocular chronic diseases including diabetes,¹⁰ stroke,¹¹ hypertension,¹² and cardiovascular disease.¹³ In fact, changes to the retina may become apparent years before other systemic manifestations of disease in these chronic conditions.^{7 10 11 12 13} These studies provide compelling evidence to believe that fundus photography may capture vascular changes in the eye that are reflective of microvascular change not only in the cerebral microvasculature, but also in the cochlea as well. Retinal imaging offers clear visualization of vasculature using relatively simple instrumentation, and thus may potentially be used as an assessment tool in disease characterization and prognosis of hearing loss to identify individuals who may benefit from early intervention.¹⁴

In addition, previous ARIC studies have demonstrated the association between retinal signs and cognitive decline,¹⁵ as well as the association between hearing impairment and cognitive decline. Retinopathy was associated with lower scores on a variety of cognitive tests in previous studies,^{16 17 18} suggesting that microvascular contributions to cognitive decline may be detectable via retinal photography. Hearing loss is also associated with cognitive decline as indicated by recent epidemiologic studies.^{19 20 21} Moreover, a hearing pilot study conducted (N=250, Washington County site) within ARIC-NCS found associations between audiometric hearing impairment and cognitive performance in memory and executive function.²²

Thus, previous evidence has demonstrated that hearing loss is a risk factor for cognitive decline, and microvascular disease (as measured by retinal photography) is associated with cognitive decline. Drawing from the current literature, the association between hearing loss and cognitive decline can be explained in part if they are both sequelae of an underlying

etiology of microvascular disease. In a cross-sectional study of the Blue Mountains Study population, Liew et al. found that retinopathy was associated with hearing loss in women (adjusted OR, 2.10; 95% CI, 1.09 to 4.06, p 0.002), particularly with low-frequency losses (0.25 to 1.0 kHz).⁴ A potential explanation is that microvascular disease may affect hearing through a diminished cochlear blood supply^{23 24} and that vascular development in the retina and cochlear striae vascularis is controlled in part by the same genes.²⁵ The link between retinal microvasculature and hearing loss is further supported by findings from Klein et al. demonstrating the association of age-related macular degeneration with hearing impairment.²⁶ Additionally, there is increasing interest in understanding the role of microvascular disease in hearing loss as seen in the ASPREE-HEARING (ASpirin in Reducing Events in the Elderly) trial, which will investigate whether aspirin decreases the progression of age-related hearing loss and whether this progression is also associated with retinal microvascular changes and/or greater preservation of cognitive function.²⁷

Exploring the association of retinal microvasculature (as a reference for microvascular disease) and hearing impairment may help clarify the pathology of age-related hearing loss, particularly as the cochlear microvasculature is not amenable to direct measurement in vivo. As previous studies published on this relationship are few in number, this study will add to the current literature with its greater sample size compared to previous cross-sectional studies⁴ and relatively large proportion of African American participants.

5. Main Hypothesis/Study Questions:

We hypothesize that the microvascular retinal signs at Visit 5 are associated with hearing loss measured at Visit 6 due to an underlying shared pathology involving microvascular disease.

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: This cross-sectional study will involve analysis of retinal data collected at ARIC Visit 5 (2011-2013, N=2624) and hearing data collected at Visit 6 (2016-2017, N=3658). In secondary analyses, we will quantify the relationship between retinal data collected at Visit 3 (1993-95) and hearing data collected at Visit 6.

Inclusion/Exclusion: We will examine the data for all ARIC participants who underwent retinal photography at visit 5 who also completed hearing assessment at visit 6 with complete covariate data.

Primary Dependent Variable: The primary dependent variable/outcome will be hearing loss as measured with pure tone audiometry. Pure tone audiometry was offered to participants at all field centers at Visit 6. The Hearing Handicap Inventory for the Elderly (HHIE) and self-reported hearing and noise data were also collected at Visit 6, including self-reported hearing aid use. A pure tone average of air conduction thresholds at 0.5, 1, 2, and 4 kHz in the better ear will be used for analysis according to World Health Organization definitions (normal: ≤ 25 decibels

hearing level (dB HL); mild: 26-40 dB HL; moderate: 40-60 dB HL; severe: >61 dB HL) and a secondary analysis will use pure tone average as a continuous variable.

Primary Independent Variable: At Visit 5, two fundus photographs were taken of each eye using a digital camera. All photographs were graded by trained, certified graders at the Ocular Epidemiology Reading Center (OREC) at the University of Wisconsin-Madison who were masked to participant characteristics (including diabetes and hypertension status). The retinal variables of interest include measures related to loss of vascular integrity (e.g., retinopathy and its common components, including retinal hemorrhages, microaneurysms and soft exudates) and measures related to changes in the arteriolar wall [arteriovenous (AV) nicking, focal narrowing and generalized arteriolar narrowing, as measured by the central retinal arteriolar equivalent (CRAE)].

Retinopathy will be defined as the ‘definite’ presence of at least one of the following lesions: retinal microaneurysms, soft exudates, hard exudates, retinal hemorrhages, macular edema, intraretinal microvascular abnormalities, venous beading, new vessels, vitreous hemorrhage, disc swelling, or laser photocoagulation scars.

Focal arteriolar narrowing was defined as absent, definite or questionable based on the number and grading of arterioles estimated to be $\geq 50 \mu\text{m}$ in diameter that had a constricted area $\leq 2/3$ the width of proximal and distal vessel segments.²⁸ For the current analysis, arteriolar narrowing will be considered present given a grade of “definite”.¹⁶

AV nicking was defined as absent, definite or questionable based on the number and grading of at least one venous blood column(s) that was(were) tapered on both sides of its crossing underneath an arteriole.²⁸ For the current analysis, AV nicking will be considered present given a grade of “definite”.

Generalized arteriolar narrowing was evaluated using enhanced digital images and image processing software. Arteriolar diameters within a pre-specified zone surrounding the optic nerve were combined and quantified as the central retinal arteriolar equivalent (CRAE) using the following formula in order to adjust for branching:²⁸

$$\text{Arterioles } W_c = \sqrt{0.87 * W_a^2 + 1.01 * W_b^2 - 0.22 * W_a * W_b - 10.76}$$

where W_c = the caliber of the trunk vessel

W_a = the caliber of the smaller branch, and

W_b = the caliber of the larger branch

In keeping with previous analysis in this cohort, presence of generalized narrowing will be defined in this study as the lowest 25th percentile of CRAE.¹⁸

Additional Independent Variables:

Demographic information was collected at Visit 1, including birthdate (to calculate age in years), sex, education, race and study site.

Potential vascular confounding variables include disease and health behavior covariates collected at each study visit, including self-reported cigarette smoking status and body mass index (BMI) (kg/m²). Hypertension will be considered present based on the following ranges (Normal: <120 or <80 mm Hg; Hypertension Stage 1: 130-139 or 80-89 mm Hg; Hypertension Stage 2: ≥140 or ≥90 mm Hg; or anti-hypertensive medication use). Diabetes will be considered present if fasting blood glucose level was ≥ 126 mg/dL, or the participant self-reported a diagnosis of diabetes or of medication use for diabetes.

Statistical Analysis:

Multivariable-adjusted multinomial logistic regression and linear regression will be used to investigate the association of retinal signs with categories of hearing loss with continuous PTA, respectively. The primary models will use survey weights to account for selection factors for the Visit 5 retinal photography, so that inference from results will be generalizable to the entire ARIC population. Our models will adjust for potential demographic confounders including age, sex, education, and, because race is so tightly linked to study site in this cohort, a combination variable incorporating race and study site (Minneapolis whites, Jackson blacks, Washing Co whites, Forsyth blacks, Forsyth whites). Our models will also adjust for potential disease confounders measured at the time when the retinal photographs were taken, including hypertension status, diabetes status, smoking status, and body mass index. Stratification by diabetes status will also be considered in light of the substantial vascular impact of diabetes on retinal signs.

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7.a. Will the data be used for non-CVD analysis in this manuscript? Yes 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 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.unc.edu/ARIC/search.php>

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
ARIC MP #3068 Association of Retinal Microvascular Abnormalities and Cognitive Status: The Atherosclerosis Risk in Communities Neurocognitive Study

ARIC MP#2169 Association of retinal microvascular abnormalities
With 23-year cognitive decline: The Atherosclerosis Risk in Communities Study

ARIC MP# 2797 Retinal signs and incident dementia in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC NCS)

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.csc.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.csc.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.