

**ARIC Manuscript Proposal #3433**

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**SC Reviewed:** \_\_\_\_\_

**Status:** \_\_\_\_\_

**Priority:** \_\_\_\_\_

**1.a. Full Title:** Sensory Impairment and Missingness of Cognitive Test Scores in a Population-Based Study of Older Adults

**b. Abbreviated Title (Length 26 characters):**

**2. Writing Group:**

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **\_JAD\_ [please confirm with your initials electronically or in writing]**

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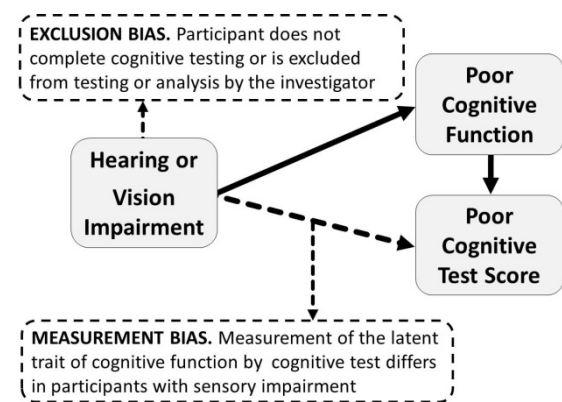
### 3. Timeline:

Manuscript will be completed within 12 months

### 4. Rationale:

Dementia is the “greatest global challenge for health and social care in the 21st century.”<sup>1</sup> To combat and plan for this challenge, valid estimates and projections of dementia prevalence are needed. Gold-standard neuropsychological batteries are used to derive these estimates and identify at-risk groups; however, these tests all involve either auditory or visual stimuli, and the majority of older Americans – 55% over 60 years old<sup>2</sup> – have either hearing or vision impairment. Despite the high prevalence of sensory loss, research examining the impact of hearing and vision impairment on cognitive testing is lacking. A recent NIA supported Bench-to-Bedside U13 conference, *Sensory Impairment and Cognitive Decline*, identified measurement of cognition in the face of sensory impairment as a future research priority.<sup>3</sup>

**Figure 1.** Conceptual Framework



An unbiased measurement tool should measure the latent trait (i.e., cognition) in the same way among subgroups of a population (e.g., persons with and without sensory impairment). However, because standard cognitive tests rely on hearing or seeing, older adults with hearing or vision impairment may possibly *perform* more poorly on cognitive tests than participants without sensory impairment despite intact cognitive ability leading to measurement bias (Fig. 1). This bias could potentially result in an overestimate of the relationship between sensory impairment and poor cognitive function.

On the other hand, both hearing and vision impairment have been linked to cognitive impairment and dementia risk, and mechanisms proposed by which this association could be causal. If hearing and vision impairment cause cognitive decline, exclusion of participants with sensory impairment from cognitive testing may potentially underestimate the prevalence of cognitive impairment (Fig. 1, exclusion bias).

To address these important research gaps, we will investigate if sensory impairment causes errors in measurements of cognitive function in older adults with sensory impairment in the ARIC-NCS.

### 5. Main Hypothesis/Study Questions:

- Identify and adjust for potential bias in measuring cognitive function that is due to hearing or vision impairment using item response theory (IRT) methods.
  - We hypothesize that older adults with hearing or vision impairment perform worse on tests that rely primarily on auditory or visual stimuli, respectively, than participants without impairment, after controlling for sensory-controlled cognitive performance as measured by tests that should be unaffected by mode of administration (e.g., for persons with hearing impairment, we will measure underlying cognitive function using tests that use visual, rather than auditory, stimuli)
- Quantify patterns of missingness in cognitive test scores by sensory impairment status, and investigate potential bias in estimates of cognitive performance that may be related to those missing cognitive test scores.
  - We have two competing, but not mutually exclusive, hypotheses for why persons with sensory impairment may have a greater proportion of missingness on cognitive tests. First, persons with hearing impairment may be more likely to fail to complete a test that relies on auditory stimuli, and similarly, persons with vision impairment may be more likely to fail to complete tests whose primary mode of administration is visual. If so, we

would hypothesize that persons with hearing impairment are primarily missing Logical Memory and Digits backwards (the two tests with a primarily auditory mode of administration, see Table 1), but not other tests. Similarly, for vision impairment, we hypothesize that participants have more missingness on tests that rely primarily on vision (Boston Naming Test, Trails A and B, Digit Symbol Substitution, Incidental Learning), but not other tests. In particular, we hypothesize that tests that rely on semantic knowledge are robust to sensory impairment, as is the Delayed Word Recall test, which ensures that participants have registered the words to recall through multiple means, including speaking the word, showing the printed word to the participants, and asking the participant to use the word in a sentence. We hypothesize that these associations are robust to MMSE stratification if due to the sensory loss as opposed to cognitive impairment.

- Alternatively, if hearing and vision impairment causally impacts cognitive function, we hypothesize, based on the conceptual frameworks for these associations,<sup>3,4</sup> that missingness on cognitive tests associated with sensory loss is on tests of working memory, attention and executive function,<sup>5</sup> particularly Digits Backwards, Trails A & B, Digit Symbol Substitution task.
- If we find that sensory loss is associated with greater missingness on cognitive tests, we will investigate whether the sensory impairment-cognitive function relationship is biased due to this missingness. We hypothesize that the association is underestimated in available case analyses as compared to analyses that impute missing cognitive data using available auxiliary cognitive information (e.g., Six-item screener, AD8)

## **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).**

**Design:** Cross-sectional analysis of participants with Visit 6 audiometric hearing data, Visit 6 vision data (as part of the EyeDoc Substudy, Washington County & Jacksonville sites only) and neurocognitive test data.

**Outcome:** 10 neurocognitive test scores measured at Visit 6 (Table 1).

### **Exposures:**

#### *Hearing*

Pure tone audiometry is the gold-standard test to determine the faintest tones that a person can detect for a range of pitches. For participants attending a clinic visit, pure tone air conduction audiometry was conducted in a sound-treated booth within a quiet room consistent with ANSI standards. For participants with a home or long term care facility visit, pure tone audiometry was conducted with a portable audiometer and supra aural headphones, after ensuring that the ambient levels of noise in the room were acceptable for valid testing. We will calculate a speech frequency pure tone average (PTA) 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. We will categorize hearing loss using a clinically-defined ordinal variable for hearing impairment – normal: <25 decibels hearing level (dB HL); mild: 26-40 dB HL; moderate: 41-70 dB HL; severe: >70dB HL.

#### *Vision*

Vision data will be from the EyeDoc ancillary study (Jackson and Washington County sites only). Measures of visual function assessed as part of EyeDoc for this proposal include visual acuity and contrast sensitivity. Visual acuity was measured using a backlit early treatment of diabetic retinopathy

study (ETDRS) chart with participants using their normal refractive correction (if any). Presenting visual acuity of 20/40 or worse underwent subjective refraction with trial lenses to determine best-corrected visual acuity. Contrast sensitivity was measured in participants using the MARS letter contrast sensitivity chart (presenting acuity).

**Additional independent variables:**

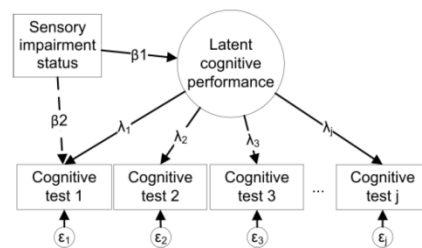
Demographic information was collected at Visit 1, including age (years), sex, race, and education (highest grade or year of school completed). Education will be categorized according to standardized ARIC algorithms (less than high school, high school or equivalent, greater than high school).

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. Disease covariates were collected at each study visit, and adjudicated according to standardized algorithms. Hypertension will be considered present based on a diastolic blood pressure  $\geq 90$  mmHg, systolic blood pressure  $\geq 140$  mmHg, or use of hypertensive medications. Diabetes will be considered present if fasting blood glucose level was  $\geq 126$  mg/dL, or the participant self-reported a diagnosis of diabetes or of medication use for diabetes. The Mini-Mental State Exam was collected at Visit 6 as part of the neurocognitive battery.

**Statistical Analysis:**

To test our first hypothesis, we will use an item response theory approach to disentangle true cognitive function, the true effect of sensory impairment on cognitive function, and potential bias that sensory impairment may have on cognitive test performance. If there is no bias on a cognitive test attributable to sensory impairment, then scores on that test should be related only to the level of underlying cognitive function (path  $\lambda_j$  in Fig. 2), and not to sensory impairment (path  $\beta_2$ ), after controlling for sensory impairment status (path  $\beta_1$ ). We will assess measurement invariance, or differential item functioning, for the cognitive battery by examining differences in two sets of parameters by sensory impairment status. (1) The item discrimination parameter for each test characterizes sensitivity of the test to measure cognitive functioning at a given level. High item discrimination (or factor loadings) indicates high sensitivity of a test to distinguish differences in cognitive function among people; if discrimination for a test is poorer in a sensory-impaired group, that would imply the test is a weaker measure of cognitive function in the sensory-impaired group than in the non-sensory impaired group. It is critical to evaluate equivalence of item discrimination parameters to be sure the tests are adequate measures of the underlying construct. (2) Item threshold parameters indicate if cognitive tests have the same level of difficulty by sensory impairment status. For example, if we observe that the sensory impaired have higher threshold parameters than the non-sensory impaired for a test, this would suggest differential difficulty on the cognitive test by sensory impairment status. Assessment of differences in item discrimination and threshold parameters is accomplished simultaneously while controlling for underlying cognitive function (path  $\beta_1$ ), which we acknowledge is complicated in older adults with sensory impairment as all cognitive tests require either seeing or hearing. We will thus assess for vision and hearing DIF separately, assuming that vision-only-dependent tests are not biased by hearing status, and vice versa. Together, results from the item discrimination and threshold parameter analyses will determine the presence of measurement differences by sensory impairment status. We will use propensity score weights to ensure sensory impairment groups are comparable across demographic and clinical characteristics. If we observe measurement bias by sensory impairment status, the next step is to correct for this bias; this is accomplished by retaining test-specific differences in parameters by sensory impairment status in a model to estimate cognitive performance (e.g., path  $\beta_2$  in Fig. 2).

**Figure 2.** Path analysis diagram for Aim 1



For our second aim, we will use Poisson regression with robust standard errors to estimate the prevalence of missingness for each cognitive test by sensory loss status, adjusting for demographics and vascular factors in a two-step model building process. We will stratify by education-stratified MMSE score ( $\geq 23$  vs.  $< 23$  for high school degree or less and  $\geq 25$  vs.  $< 25$  for some college or more) to determine if the prevalence of missingness by sensory loss status differs by level of cognitive function. We will compare results from available case analyses to results that impute missing cognitive data using multiple imputation using chained equations (MICE), in keeping with recommendations from the Analysis Workgroup.

### **Limitations:**

We will be unable to quantify the impact of dual sensory impairment on the measurement of cognitive function given differences in sample size between those who had hearing measured and those who had hearing measured (EyeDoc is a substudy at only 2 ARIC sites), the anticipated small number of participants with both hearing and vision impairment (prevalence in the NHANES population for the age of ARIC participants  $\sim 5\text{-}10\%$ ), and because all tests rely on either hearing or vision, it is unclear if we could successfully estimate 'unbiased' cognitive for the IRT analysis for this group.

Additionally, for aim 2, EyeDOC participants were selected based on MMSE scores ( $< 23$  in Washington and  $< 21$  in Jackson were excluded), which may limit our ability for inference based on the MMSE-stratified analysis.

An additional consideration for the discussion will be that examiners are asked to discontinue tests in the event that a physical limitation makes administration of a given test untenable.

### **References:**

1. Livingston, Sommerlad, Orgeta, Costafreda, Huntley, Ames, et al. Dementia prevention, intervention, and care. *Lancet*. 2017 Dec;390(10113):2673-2734.
2. Swenor, Ramulu, Willis, Friedman, Lin. *JAMA Intern Med*. 2013 Feb 25;173(4):312-313.
3. Whitson, Cronin-Golomb, Cruickshanks, Gilmore, Owsley, Peelle, et al. American Geriatrics Society and National Institute on Aging Bench-to-Bedside Conference: Sensory Impairment and Cognitive Decline in Older Adults. *JAGS*. 2018; 66:2052-2058.
4. Lin FR and Albert MA. Hearing Loss and Dementia - Who's Listening? Lin FR, Albert M. Hearing loss and dementia - who is listening? *Aging Ment Health*. 2014;18(6):671-673.
5. Tun PA, McCoy S, Wingfield A. Aging, hearing acuity, and the attentional costs of effortful listening. *Psychol Aging*. 2009 Sep;24(3):761-6.

**Table 1.** Neurocognitive tests administered as part of the Atherosclerosis Risk in Communities Study, by cognitive domain, Visit 6

| Test                           | Description  | Score   | Domain                       | Hearing or Vision? |
|--------------------------------|--|---|------------------------------|--------------------|
| Delayed Word Recall Test       | Participants are asked to learn 10 common nouns by reading each noun and using it in a sentence. After an interval filled with a different neurocognitive test, participants are asked to recall the 10 nouns.   | Total number of words correctly recalled; range 0-10; higher scores are better  | Memory                       | Both               |
| Incidental learning            | Participants are first asked to recall (in any order) as many symbols from the DSST as possible within 60 seconds. Participants are then asked to record the corresponding numbers for each symbol recalled; 60 seconds are allowed.   | Total number of symbols/digit-pairs recalled in 60 seconds ; higher scores are better                                     | Memory                       | Vision (writing)   |
| Logical Memory I & II          | As part of Logical Memory I, participants are instructed that the examiner will read a story and asked to listen and remember as many details as possible. After the completion of the reading (without repetition), participants are asked to begin at the beginning of the story and to recall everything that s/he can in up to 90 seconds. The process is then repeated with a second story. In Logical Memory II, after a filled interval, participants to again recall the two stories | Numbers of items/story elements correctly recalled.   | Memory                       | Hearing            |
| Word Fluency Test              | Consists of 3 consecutive 1-minute word-naming trials. Participants are asked to list as many words as possible (excluding proper nouns) that begin with the letter “F”, “A” and “S” in each trial, respectively.  | Total number of words generated during the 3 trials; higher scores are better.  | Language                     | --                 |
| Animals Naming                 | Participants are asked to name as many different types of animals as possible in 60 seconds.   | Numbers of animals correctly named in 60 seconds; higher scores are better.   | Language                     | --                 |
| Boston Naming Test             | Participants is asked to name a series of pictures (line drawings)   | Number of pictures correctly identified; possible range 0-30, higher scores are better.                                   | Language                     | Vision             |
| Trail Making Test Part A       | Without removing pen from paper, participants are asked to consecutively connect as quickly as possible the numbers 1-25, which are randomly distributed on a page. Up to 4 minutes (240 seconds) are allowed for test completion.   | Time to completion (sec); lower scores are better. Time is scored as 4 minutes (the maximum) if $\geq 5$ errors are made. | Psychomotor Speed            | Vision             |
| Digit Symbol Substitution Test | Participants are provided with a key that uniquely associates a number with a nonsense symbol and then asked to translate a series of numbers to the corresponding symbol.   | Total number of symbols correctly completed within 90 seconds; higher scores are better                                   | Executive function/attention | Vision             |
| Digit Span Backwards           | Participants are asked to recall in reverse order a sequence of numbers. Sequences increase in length as the test progresses. The test ends when participants incorrectly recall two sequences of the same length.   | Number of sequences correctly recalled in reverse order; higher scores are better.  | Executive function           | Hearing            |
| Trail Making Test Part B       | Without removing pen from paper, participants are asked to consecutively connect as quickly as possible an alternating series of 25 numbers and letters, which are randomly distributed on a page. Up to 4 minutes (240 seconds) are allowed for test completion.  | Time to completion (sec); lower scores are better. Time is scored as 4 minutes (the maximum) if $\geq 5$ errors are made. | Executive function           | Vision             |

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)?

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  Yes  No

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number\* 2017.25)

B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)\* 2014.38)

\*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.

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