1.a. **Full Title:** Association between Dual Sensory Impairment and Cognitive Performance, Mild Cognitive Impairment and Dementia in Older Adults: The Atherosclerosis Risk in Communities Neurocognitive Study

**b. Abbreviated Title (Length 26 characters):** DSI and cognition

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3. **Timeline:**

   Manuscript will be completed within 6 months.

4. **Rationale:**
Addressing dual sensory impairment (DSI) in the older population is an emerging public health imperative. The prevalence of DSI has been estimated to increase dramatically with increasing age, from 3% in those aged 60–69 years to 11.3–16.6% in those aged 80 years and older\textsuperscript{1-4}. DSI has been associated with mortality, poor physical health\textsuperscript{5}, low engagement in social activities\textsuperscript{6}, impaired activities of daily living (ADLs) and instrumental ADLs\textsuperscript{5}, and an increased estimated risk for depression and anxiety\textsuperscript{5,7,8,9}. Despite the relatively high frequency of DSI and its adverse effects on the health of older adults, its association with cognition is not clearly defined\textsuperscript{4,5}.

The sensory deprivation hypothesis postulates that impaired sensory function requires more cognitive reserve to interpret audible and/or visual information and simultaneously reduces cognitive capacity for other cognitively demanding tasks caused by neuronal atrophy\textsuperscript{10-14}. The mechanistic nature of this association might be particularly pronounced for older adults with DSI. Given that experiencing a decrease in both vision and hearing acuity interferes with communication abilities and the use of the compensatory coping strategies available when one sensory modality is impaired, there may be a synergistic impact on cognitive decline that extends beyond sensory impairment\textsuperscript{3}.

While there is some evidence to suggest a connection between vision\textsuperscript{11,13,15-19} or hearing loss\textsuperscript{20-25} and poor cognitive performance, research on the effects of DSI on cognitive function is still at a nascent stage\textsuperscript{26}. A small number of studies have previously examined the relationship between DSI and cognitive function among community-dwelling older adults with mixed results\textsuperscript{11,17,16,27,28}. In the cross-sectional Blue Mountains Eye Study\textsuperscript{27} of 3,509 participants aged 50 years and over, objective DSI was associated with an increased likelihood of cognitive impairment (OR = 4.0, 95% CI = 1.1–14.1), which was assessed using the Mini-Mental State Examination (MMSE). In the longitudinal study of 6,112 white women over 69 years of age (mean age = 76.1) from the Study of Osteoporotic Fracture\textsuperscript{17}, combined hearing and vision loss was associated with an increased risk of subsequent cognitive decline (OR = 2.19, 95% CI = 1.26–3.81) as measured by a modified version of the MMSE. In a longitudinal study of 4,612 white older adults (mean age = 64.9) from the English Longitudinal Study of Ageing\textsuperscript{11}, self-reported DSI was associated with worse cognitive performance (focusing on working memory and executive function) at 6-year follow-up (B = 2.30, 95% CI = 1.21–3.39). However, other studies have not found a significant relationship. In the longitudinal Blue Mountains Eye Study\textsuperscript{28} of 3,654 participants (mean age = 80.4), DSI was not correlated with poorer cognitive function assessed using ≥3 point decline on the MMSE over 5 years (OR = 1.41, 95% CI = 0.54–3.72) or 10 years (OR = 1.15, 95% CI = 1.04–1.10). Even fewer studies have quantified the relationship between DSI and mild cognitive impairment (MCI)/dementia. In the Health and Retirement Study\textsuperscript{18} of 19,618 male and female adults aged 50 years and over (mean age = 57.8), subjective DSI estimated the relative risk of incident possible cognitive impairment, no dementia (HR = 1.38, 95% CI = 1.25–1.54) over the course of 18 years, as measured by the Telephone Interview for Cognitive Status. Despite the importance of these, prior studies have several limitations, including a limited number of studies, particularly studies assessing risk of dementia\textsuperscript{18}, conducting in institutionalized populations (nursing home residents)\textsuperscript{29}, a failure to control for confounding factors affecting cognitive function such as hypertension\textsuperscript{17}, depression\textsuperscript{17,27}, smoking status\textsuperscript{27,28}, and self-reported health\textsuperscript{11,17,18,27,28}, relying on subjective DSI measures\textsuperscript{11,18}, a failure to investigate MCI/dementia using comprehensive and standardized measures for diagnosis\textsuperscript{11,17,18,27}, and the use of samples containing only whites\textsuperscript{11,17,18,27,28}.

To address these research gaps, we will use data from the Atherosclerosis Risk in Communities Study (ARIC), which is a large, well-characterized community-dwelling biracial population study. Specifically, we will use data from both the ARIC Neurocognitive Study (NCS) parent study and from the Eye Determinants of Cognition (EyeDOC) ancillary study. Using ARIC data will allow for a thorough and rigorous examination of the associations between DSI and cognitive performance, MCI, and dementia using objective hearing
(measured by pure-tone audiometry) and vision acuity (comprising distance visual acuity and contrast sensitivity). This study will complement and extend current knowledge about the association between DSI and cognition and is timely as projections of these conditions are climbing rapidly with global population aging. This will enable the development of public health efforts to address co-occurring DSI and cognitive decline and MCI/dementia in older adults in clinical practice.

5. Main Hypothesis/Study Questions:

The main objective of this study is to examine the associations between prevalent DSI and cognitive performance and between DSI and MCI/dementia in older adults. We hypothesize that older adults with DSI have worse cognitive performance and a greater prevalence of MCI/dementia diagnoses than participants without sensory impairments.

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

Cross-sectional analysis of the associations between DSI and cognitive performance, and MCI/dementia will be executed using hearing (visit 6), cognitive function (visits 5 and 6) and MCI/dementia diagnosis (visit 6) data from ARIC-NCS study and vision measurement data gathered during the EyeDOC study over visits 6 and 7 (2017-19).

Study Population & Inclusion/Exclusion Criteria

Participants with complete hearing and cognitive data from the ARIC study who also have vision data from the EyeDOC ancillary study (Jackson, Mississippi and Washington County, Maryland study sites only) will be included. Respondents will be excluded if non-whites are from the Washington site and non-blacks are from the Jackson site. It is estimated that 1,005 participants will be included into the final analytic sample (DSI=155).

Primary Measurements

1. Cognitive performance

A wide-ranging neuropsychological battery of tests that were measured at visit 5 and 6 will be used to assess overall cognitive function. The primary cognitive outcome will be the global composite factor scores for overall cognitive function derived using latent variable methods by Gross et al\(^{30}\), replicated with a factor score derived at the Coordinating Center. In secondary analysis, we will investigate the association between DSI and domain-specific cognitive performance using domain-specific factor scores derived from the following tests: (1) memory (delayed word recall, incidental learning, and logical memory); (2) executive function and speed of information processing (Trail Making Tests, parts A and B, the Digit Symbol Substitution Test); and (3) language (semantic and phonemic fluency, the Boston Naming Test).
2. Dementia/MCI diagnosis

An MCI/dementia diagnosis has been well described in previous studies\textsuperscript{31,32,33,34}. All participants who attended at sixth clinic visit (2016-17) were assessed for an MCI/dementia diagnosis using standardized algorithms, incorporating longitudinal and neuropsychological cognitive test data\textsuperscript{31,32}, with confirmation by expert panel review (e.g., neurologists, geriatricians, and neuropsychologists).

3. Hearing function

Peripheral hearing function was measured in the ARIC using pure-tone audiometry conducted in a sound-treated environment at all research sites at Visit 6 (2016-17). The pure tone average (PTA, measured in decibels) of participants’ hearing level will be calculated using as an average of air conduction thresholds at four frequencies (500, 1000, 2000, and 4000 Hz) in the ear with better hearing. Hearing impairment will be defined according to World Health Organization cutpoints\textsuperscript{35} and >25 decibel hearing level (dB HL).

4. Visual function

Contrast sensitivity and both presenting and autorefractor-corrected distance visual acuity were measured as a part of the EyeDOC study over visits 6 and 7 (2017-19) at two study sites. These data will be used as measures of overall visual function. Presenting distance visual acuity was assessed using an Early Treatment for Diabetic Retinopathy Study logarithm of the minimum angle of resolution (LogMAR) chart and contrast sensitivity was evaluated employing the MARS test. When presenting acuity was worse than 20/40 or worse in either eye, auto-refraction was performed and a corrected visual acuity obtained for the eye. Visual impairment will be defined per the American Academy of Ophthalmology\textsuperscript{36} as both presenting and corrected visual acuity worse than 20/40 or as a log contrast sensitivity (log CS) less than or equal to the mean + 1 standard deviation (SD) of the statistical distribution in our sample\textsuperscript{37}.

5. Dual sensory impairment

Dual sensory impairment will be considered present if the participant has both hearing impairment (pure tone average > 25 dB in their better ear) and vision impairment (visual acuity as worse than 20/40 in their better eye or their log CS as less than or equal to the mean + 1 SD of the statistical distribution in our sample. Based on this criterion, we will have a four-category exposure variable: no hearing and no vision impairment (reference group), hearing impairment only, vision impairment only, and DSI.

Other Variables of Interest

Participants’ demographic information include age, race (black or white) and sex (male or female). Consistent with standardized ARIC algorithms, education will comprise three categories: less than high school, high school, or greater than high school. Participants’ health status will be assessed using five variables, including body mass index (BMI), diabetes, hypertension, cigarette smoking, and self-reported health. Height (meters) and weight (kilograms) will be used to calculate (BMI and modeled as a continuous variable. Cigarette smoking will be dichotomized into ever (past or current) and never smoker groups. Hypertension will be considered present if participants’ diastolic blood pressure is ≥ 90 mmHg, their systolic blood pressure is ≥ 140 mmHg, or they reported antihypertensive medication use. Diabetes will be defined if fasting blood glucose level was ≥ 126 mg/dL or if the participant self-reported diagnosis of diabetes or the use of medications for diabetes.
Self-reported health was collected at the annual follow up calls by asking participants, “Over the past year, compared to other people your age, would you say that your health has been excellent, good, fair, or poor?” Depressive symptomatology was measured using the 11-item Center for Epidemiologic Studies Depression Scale (CES-D). Possible scores range from 0 to 22 with higher scores indicating greater depression.

Analysis

Descriptive analysis using chi-squared and analysis of variance tests will be used to examine differences in demographic variables (age, race, sex, and education), health status (BMI, cigarette smoking, hypertension, diabetes, and self-reported health), depression, and cognitive function among older adults with and without DSI. Multivariable-adjusted linear regression analysis will be performed to estimate the average cross-sectional differences in cognitive factor scores by DSI status after controlling for a comprehensive list of covariates (listed below). We will quantify the prevalence of combined MCI/dementia by DSI status using log binomial regression. We will perform regression analysis through a three-step model building approach. Model 1 will include demographic information, such as age, race, sex, and education. Additionally, because the measurement of cognitive performance at one point in time is susceptible to strong confounding effects related to education and social factors, we will also adjust for performance on the Wide Range Achievement Test (WRAT), a measure of premorbid intelligence. Model 2 will adjust for Model 1 covariates and will also incorporate health status (BMI, cigarette smoking, hypertension, diabetes, and self-reported health), which may confound the relationship between DSI and poor cognitive performance. Model 3 will be further adjusted for depressive symptoms. Model 2 will be the primary model for inference because depressive symptoms may mediate the association between DSI and MCI/dementia. Although sample size will be limited for the MCI/dementia analysis, we will explore for possible interaction by sex and race by including interaction terms with DSI in the models. All analyses will be performed using STATA, version 14.0.

Limitation

A key limitation of this proposed cross-sectional study is that we will be unable to determine the causality whereby DSI is associated with cognition, further warranting a future longitudinal study. Additionally, since the data collection occurred in areas where the population is almost exclusively restricted to white and black Americans, it may be difficult to disentangle race effects from location effects.

References:


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](http://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html)

   ___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)?

   # 2327 – “Hearing impairment and cognitive performance in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC NCS): cross-sectional and longitudinal results”
# 3305 – “Association of hearing impairment with cognitive performance and beta-amyloid deposition”
# 3346 – “Associations between Visual and Hearing Function in an Older Adult Population”
# 3433 – “Sensory Impairment and Missingness of Cognitive Test Scores in a Population-Based Study of Older Adults”

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.