ARIC Manuscript Proposal #2327

PC Reviewed: 3/11/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Hearing impairment and cognitive performance in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC NCS): cross-sectional and longitudinal results

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

2. Writing Group: (Alphabetical) : Marilyn Albert, Josef Coresh, David Knopman , Frank R. Lin (Senior author), Thomas Mosley, A. Richey Sharrett, Lisa Wruck

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 in 2 months.

4. Rationale:
There is a critical need to identify modifiable risk factors for cognitive decline and dementia in older adults. Hearing impairment is highly prevalent, increases with advancing age, and may be amenable to rehabilitative interventions.[1,2]

It may be that hearing loss and cognitive impairment are both sequalae of the same underlying (vascular) pathology. Alternatively, it may be that hearing impairment is causally associated with cognitive decline through mechanisms including (1) mediation through social isolation and loneliness, (2) an increase in cognitive load, and (3) changes in brain structure.

Several studies have suggested that hearing impairment is associated with greater levels of social isolation, including a recent cross-sectional analysis of data from the National Health and Nutrition Examination Survey (NHANES), in which hearing impairment was associated with an increased odds (Odds Ratio (OR) = 3.49; 95% Confidence Interval (CI): 1.91, 6.39) of social isolation in women aged 60 to 69 years.[3]

Hearing is a function both of peripheral transduction, or encoding of sound in the cochlea, and of central processing of sound. Poor or impaired encoding by the cochlea may require extra cognitive processing effort, limiting effort available for encoding speech in memory. This increase in cognitive load due to hearing impairment has been termed *effortful listening*[4,5] and was classically described in a study in which adults with normal hearing where shown to have poorer recall of a list of four spoken numbers that were heard in quiet when that list was followed by a second series of four numbers that were presented as noise-masked as compared to when the second series of four digits was heard in quiet. Conversely, there was no difference in recall of the second list by whether the first list was presented in noise or in quiet.[4]

Neuroimaging studies have suggested that structural changes within the brain may possibly occur in response to hearing impairment, both cross-sectionally[6] and longitudinally[7]. In 126 participants from the Baltimore Longitudinal Study on Aging, (BLSA) aged 56-86 years, hearing impairment was longitudinally associated with faster rate of atrophy in the right temporal lobe, a region associated with speech processing (difference in estimated average annual rate of change comparing participants with hearing impairment to participants without hearing impairment = -0.29 cm^3; 95% CI: -0.54, -0.04) as well as with whole brain atrophy (estimated average difference in annual rate of change associated with hearing impairment = 1.20 cm^3; 95% CI: -2.17, -0.22).[7]

In preliminary studies, audiometric hearing impairment has been associated with cross-sectional cognitive performance across multiple cognitive domains (memory, executive function, and global function) in several cohorts of older adults, including the BLSA[8] and NHANES.[9] In a longitudinal analysis in 1984 older adults (mean age 77.4 years) from the Health Aging and Body Composition Study (Health ABC), audiometric hearing impairment was associated with faster rates of decline on the Modified Mini-Mental State Exam (p=0.004) and the Digit Symbol Substitution Test (p=0.02) over 6 years of follow-up.[10] Hearing impairment has also been associated with increased risk for incident dementia; in 1,057 men from the Caerphilly Prospective Study, audiometric hearing impairment was associated with increased odds of incident dementia over 17 years of follow-up (OR = 2.67; 95% CI: 1.38-5.18)[11] and in 369 participants aged 36 to 90 years in the BLSA, baseline hearing impairment was associated with increased risk of all-cause dementia over approximately 12 years of follow-up (Hazard Ratio (HR) = 1.27 per every 10-decibell loss; 95% CI, 1.06-1.50).[12]

5. Main Hypothesis/Study Questions:

Aim 1: To test the hypothesis that audiometric hearing impairment is cross-sectionally associated with poorer cognitive function in community-dwelling older adults.

We hypothesize that, compared to persons with normal hearing, persons with hearing impairment score lower on cognitive tests in the domains of memory, language, speed of processing/executive function and global function.

Aim 2: To test the hypothesis that audiometric hearing impairment in older age is associated with a faster rate of 20-year longitudinal change in cognitive function that was measured from midlife into older age.

We hypothesize that compared to persons with normal hearing, persons with hearing impairment have a faster average rate of test- and domain-specific cognitive decline during follow-up in the domains of memory, language, executive function, and global function.

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: Prospective observational study of 253 men and women who underwent audiometric hearing testing (Washington County site only) and neurocognitive testing at Visit 5. Of those 253 participants, 252 also completed 3 neuropsychological tests at Visit 2 and up to 2 additional visits during up to 23 years of follow-up (1990-present).

Figure 1. Study design

Visit (Year):	**2** (1990-92)	**4** (1996-98)	**5** (2011-2013)
Hearing Data:			N=253
Cognitive Data:			
-Full battery:			N=253
-DWR, DSS, WFT:	N=252	N=243	N=249

Outcome:
Please see Table 1 for a summary of the neurocognitive tests included in this analysis.

Cross-sectional neurocognitive test scores measured at Visit 5. A comprehensive neuropsychological battery was administered at Visit 5 including the following cognitive tests: **Incidental learning**[13], **Animals Naming**[14], **Logical Memory I and II**[15], **Digit span backwards**[16], **Trail Making Test Part A (TMTA)**[17], **Trail Making Test Part B (TMTB)**[17], and the **Boston Naming Test**[18]. In order to facilitate comparisons of the effect of hearing impairment across tests, test- and domain-specific z-scores will be calculated for the domains of *memory*, *language*, *speed of processing/executive function*, and *global function* based on a priori categorization and previous work in this cohort (MP 2033, Rawlings et al.) (see Table 1).

Longitudinal 23-year trajectories of global and test-specific cognitive function. Cognitive function was measured in the entire cohort at up to 3 time points (Fig.1) using three standardized, neuropsychological tests: the **Delayed Word Recall Test (DWRT)**[19], the **Digit Symbol Substitution Test (DSST)**[16], and the **Word Fluency Test (WFT)**[20]. Consistent with the current recommendations of the ARIC NCS Analysis Workgroup, all tests will be standardized to z-scores in the primary analysis: z-score = (observed test score – mean test score)/ standard deviation of test score at baseline Visit 2. A *global* cognitive score, as described by Gottesman et al. (ARIC Manuscript Proposal (MP) 1982), will be created using the three neurocognitive tests.

Exposure: Pure tone air conduction audiometry and speech perception testing were conducted at Visit 5 in a sound-treated booth within a quiet room. Using that data, we will calculate the following hearing impairment variables:

(1) **Pure tone air conduction audiometry**:
   a. Pure tone average (PTA). 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 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.[21] The primary analysis for PTA will categorize hearing loss as a PTA exceeding 25 dB. In secondary analyses, we will test for possible dose-response relationship between hearing impairment and cognitive performance using a clinically defined ordinal variable for hearing impairment (normal: <25 dB, mild: 26-40 dB, moderate: 41-70db, severe: >70dB). Additionally, we will utilize PTA as a continuous variable to determine if there is a linear relationship with cognitive test performance overall, and within the clinically defined categories defined above.

(2) **Speech perception testing**:

a. Speech discrimination Score (SDS). SDS is used to evaluate how well the participant understands disyllabic words presented in an ideal, noise-free listening environment. A list of 25 pre-recorded words is played for the participant at a comfortable listening level, defined in this study as 60 dB. The participant is instructed to repeat each word as s/he hears it. Both ears are tested, with the right ear tested first. Clinically, SDS is scored as the percentage of the number of words correctly repeated. In analysis, we will utilize data from the better-hearing ear.

b. Signal to noise (SNR) ratio loss. In this study, SNR loss was measured using the *Quick Speech In Noise (QuickSIN)* test, which quantifies a participant's ability to hear and repeat speech in an increasingly noisy environment. A pre-recorded list of 6 sentences containing 5 key words per sentence is played at 70 dB for the participant; each sentence is contained within a recording of four-talker babble with an increasing SNR (25, 20, 15, 10, 5 and 0, respectively). SNR Loss is calculated as 25.5 – (Total number of key words correctly repeated). Two trials (of 6 sentences) are conducted.

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.

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 ≥ 90 mmHg, systolic blood pressure ≥140 mmHg, or use of hypertensive medications. 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. A participant will be considered to have prevalent coronary heart disease (CHD) or prevalent stroke at Visit 2 if CHD or stroke, respectively, was reported by the participant at Visit 1, or CHD or stroke events were adjudicated by Visit 2.

Apolipoprotein E (APOE) polymorphisms were sequenced by Taqman assay (Applied Biosystems, Foster City, CA). ABI 7900 and Sequence Detection System software (Applied Biosystems) were utilized for allele detection and genotype calling. APOE variants at codons 112 and 158 were detected separately during the assay, but later combined, resulting in six possible APOE genotypes: ε2/2, ε2/3, ε3/3, ε4/2, ε4/3, and ε4/4.[13] The primary analysis will utilize an ordinal variable for number of ε4 alleles (0, 1 or 2).

Self-reported hearing aid use and duration of daily use was collected at Visit 5.

Statistical analysis:

Cross-sectional analysis: Multivariable linear regression will be used to estimate the average difference in cognitive test performance at Visit 5 comparing persons with hearing loss to persons without hearing loss.

Longitudinal analysis: Generalizing estimating equations[14] with an unstructured correlation matrix (to account for the correlation between repeated cognitive measures in an individual over time) and robust variance will be used to estimate the average difference in the estimated average trajectories of cognitive change over time by hearing impairment status as measured at Visit 2. An interaction term between hearing impairment and time will be included in the models in order to test whether rates of cognitive change over time differ by hearing status. In addition to reporting the difference in rates of cognitive change by hearing impairment status (both before and after Visit 4), we will also test the global hypothesis that the average 20-year trajectory of cognitive decline differs by hearing status. Time on study will be used as the time scale, with a two-piece linear spline with knot at Year 6 in order to allow for differential rates of cognitive change before and after Year 6. Year 6 was chosen a priori as the knot for the spline, as year 6 is the mean follow-up time for participants at Visit 4, and the largest gap in time between study visits was between Visits 4 and 5, resulting in sparse outcome data between Year 6 and the start of Visit 5. Alternative splines will be explored. Model fit will be assessed using diagnostic plots, including residual plots, and through statistics such as the Bayesian Information Criterion (BIC), Akaike Information Criterion (AIC), and likelihood ratio tests.

Model building: For both the cross-sectional and longitudinal analyses, we will employ a two-step model building process for adjustment. Model 1 will incorporate demographic covariates, including age, sex, education and Wide Range Achievement Test (WRAT, a test of literacy) performance. Interaction terms between these variables and time will also be included based on a priori knowledge of the longitudinal relationship with the variable and cognitive decline or if shown to have statistical support for inclusion (e.g., significant p-value, improved model fit statistics). Based on previous analyses, we will include both a linear term and a quadratic spline for age, in order to allow for the non-linear association of age with cognitive performance. Model 2 will include those covariates in Model 1, as well as additional risk factors for cognitive decline, including smoking status, prevalent (at Visit 2) coronary heart disease, prevalent (at Visit 2) stroke, diabetes, and hypertension.

Limitations:

Audiometric hearing testing was performed in ARIC only at Visit 5. Given that the longitudinal analysis does not preserve temporality between the exposure and outcome, results will be interpreted cautiously, acknowledging this limitation. However, the longitudinal data in analyses of cognitive change are critical given the strong cross-sectional confounding effects of variables like education.

Participants who underwent audiometric testing comprise a very select group of individuals from the ARIC study (white race, Washington County site only who survived from baseline until Visit 5 and were willing to participate in a clinic site and to complete both the audiometric testing and the detailed neuropsychological battery). We will compare baseline (Visit 2) characteristics by participation status to quantify how those included in the analytic sample differ from those who did not participate. Because we hypothesize that those included in the sample are likely to have less comorbidity at baseline and were at lower risk of cognitive decline over time compared to the full ARIC NCS cohort, we hypothesize that any observed association of hearing impairment and cognitive decline is likely to be an underestimate of the association in the full cohort.

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Table 1. Neurocognitive tests administered as part of the Atherosclerosis Risk in Communities Study, listed in order of administration at Visit 5

Test	Description	Score	Domain	Measured
Digit Symbol Substitution Test (**DSST**)[16]	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	Visits 2,4,5
Delayed Word Recall Test (**DWRT**)[19]	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	Visits 2,4,5
Incidental learning[13]	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	Visit 5 only
Word Fluency Test (**WFT**)[20]	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	Visits 2,4,5
Animals Naming[14]	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	Visit 5
(Logical Memory I – see Logical Memory II)[15]				
Digit Span Backwards[16]	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	Visit 5
Trail Making Test Part A (**TMTA**)[17,22]	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 (seconds); lower scores are better. Time is scored as 4 minutes (the maximum) if ≥ 5 errors are made.	Psychomotor Speed	Visit 5
Trail Making Test Part B (**TMTB**)[17,22]	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 (seconds); lower scores are better. Time is scored as 4 minutes (the maximum) if ≥ 5 errors are made.	Executive function	Visit 5
Boston Naming Test[18]	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	Visit 5
Logical Memory II[15]	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	Visit 5

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? N/A
____ 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"? N/A
____ 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 1982. Estimation of cognitive change from repeat measures in observational studies; associations with education: the ARIC NCS. Gottesman R. et al.

MP 2033. Cognitive domain in elderly ARIC blacks and whites. Rawlings et al.

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 N/A
___ 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)* _1999.01____ _____)

*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.