ARIC Manuscript Proposal #4276

PC Reviewed: 6/13/23 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Effect of hearing intervention on reducing cognitive decline among older adults

b. Abbreviated Title (Length 26 characters): Hearing intervention and cognitive decline

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. __FRL___ **[please confirm with your initials electronically or in writing]**

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3. Timeline:

Proposal timeline	January 2023	April-May 2023	June 2023
Proposal approval	X		
Data Analysis		X	
Manuscript preparation and submission			X

4. Rationale:

Novel approaches for reducing cognitive decline in older adults are needed given the aging of the population and the personal, socioeconomic, and public health implications of cognitive impairment and dementia in older adults. Epidemiologic data now strongly suggest that age-related peripheral hearing loss in older adults is independently associated with accelerated cognitive decline and incident dementia. Mechanistic pathways that could underlie this observed association include the effects of poor audition and distorted peripheral encoding of sound on cognitive load, brain structure, and/or reduced social engagement. These pathways may be amenable to comprehensive hearing rehabilitative treatment consisting of the use of hearing assistive technologies (hearing aids, other integrated hearing assistive devices) and rehabilitative training. To date, however, there has never been a randomized trial that has investigated whether hearing loss treatment could reduce cognitive and other functional declines in older adults without dementia.

5. Main Hypothesis/Study Questions:

Study Question:

To determine the effect of a hearing intervention versus a successful aging health education control intervention on the primary outcome of global cognitive decline in 70-84 year-old well-functioning and cognitively-normal adults with hearing loss. An important secondary outcome is time until cognitive impairment. Additional secondary outcomes include decline in the cognitive domains of memory, executive function, and language.

Main Hypotheses:

Hearing intervention (versus successful aging health education control) reduces cognitive decline and incident cognitive impairment among older adults with hearing loss.

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: Randomized trial of 977 participants enrolled in the Aging and Cognitive Health Evaluation in Elders (ACHIEVE) trial from 2018-2019 and followed for 3 years. Participants were from four U.S. sites (Forsyth County, NC; Jackson, MS; Minneapolis, MN; Washington County, MD). 238 participants were recruited from the ongoing Atherosclerosis Risk in Communities Neurocognitive (ARIC-NCS) Study and the remaining 739 participants were recruited de novo from the community.

Inclusion/exclusion criteria: All eligible participants enrolled at baseline in the ACHIEVE study.

- Inclusion criteria: 1) age 70-84 years, 2) community-dwelling adults, 3) mild–to-moderate audiometric hearing impairment, defined as a better-hearing ear pure tone average (PTA) ≥30 and <70 dB hearing level (Deal et al., 2018), 4) MMSE ≥23 for those with high school degree or less, and ≥25 for those with some college education or more, 5) Word Recognition in Quiet score ≥60% correct in the better-hearing ear, 6) fluent English-speaker, 7) older adults who plan to remain in the area during the study period.
- Exclusion criteria: 1) self-reported difficulty in ≥2 activities of daily living, 2) prior dementia diagnosis, 3) vision impairment, 4) medical contraindication to hearing treatment, 5) untreatable conductive hearing impairment, 6) unwillingness to regularly wear hearing aids; 7) self-reported hearing aid use in the past year.

Outcome Variables

The primary outcome is cognitive decline, as measured by the change in a global cognitive function factor score.

An important secondary outcome is time until cognitive impairment defined as a composite of (1) adjudicated dementia or MCI diagnosis, (2) a 3-point drop in the 30-item MMSE administered in-person, or (3) a 3-point drop in a factor score derived from the 10-item MMSE orientation subscale and 11-item Blessed scale administered over the phone and rescaled to be equivalent to the 30-item MMSE.

Three additional secondary outcomes that will be examined include decline in the cognitive domain factor scores for memory, executive function, and language derived from in-person assessments.

Exposure Variables

Intervention group (hearing intervention vs. successful aging education) assigned at baseline randomization

Other Variables

The primary analysis may include adjustments for the baseline hearing loss, ARIC vs de novo status, center, age (years), sex (male/female), education (less than high school/ high school or equivalent/ greater than high school), and number of apolioprotein *(APOE)* ε4 alleles.

Analytic Plan

A statistical analysis plan (SAP) has previously been developed by the CC in conjunction with ACHIEVE invesigators and was approved by the NIA and ACHIEVE DSMB in June 2022. The primary analysis is briefly summarized below. Complete details of planned sensitivity and exploratory analyses and analyses of secondary outcomes are in the SAP. The Data Coordinating Center will re responsible for the analysis of this manuscript.

We will examine cognitive decline within each condition using mixed effects models that account for the correlation among repeated measures as well as the correlation between spouses or cohabitating partners. If a linear trend appears reasonable, we will fit a model with a linear slope. If a nonlinear trend is observed, the model will be adapted to include time splines. Continuous time in years from the baseline will be the time scale. An interaction term between treatment assignment and time will be used to test if rates of cognitive change differ by treatment assignment. Model fit will be assessed with residual plots and other statistics (Akaike Information Criterion, Bayesian Information Criterion, etc.). The primary analysis may include adjustments for the baseline hearing loss, ARIC vs de novo status, center, age, sex, education, and *APOE* ε4 alleles.

When examing the secondary outcome of time until cognitive impairment, we will use a discrete-time, cause-specific proportional-hazards model with a complimentary log-log link. The same baseline covariates specified for the mixed effects model will be integrated into the proportional-hazards model. Time on study will be the time scale.

Missing cognitive factor scores among ACHIEVE participants will be generated utilizing multiple imputation by chained equations. The number of imputations needed to generate valid parameter estimates will be determined by a two-stage analysis. The imputation model will include (1) in-person cognitive factor scores, (2) MMSE and Six-item Screener scores, (3) adjudicated incident MCI or dementia, (4) race, (5) time variables indicating when a participant with missing data might have completed an assessment based on time from randomization to missed visit, and (6) all previously listed covariates. Interactions between variables in the imputation model will be tested and added as necessary. The imputation will be conducted in stages so that concurrent and past measurements, but not future measurements, inform the imputed values. The validity of the imputation model will be assessed by

comparing observed values to imputed values among a 20% sample selected at random and a 20% sample selected based on the probability of missingness estimated from a logistic regression model.

The primary analysis will focus on cognitive factor scores imputed prior to death. An analysis comparing pre- and post-death cognitive factor scores will be performed using values generated from an imputation model in which death is included as an auxiliary variable. A similar procedure will be used to contrast pre- and post-dementia cognitive factor scores.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes _X___ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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? __X__ Yes ____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? _X___ 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

___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)?

Not applicable given that this manuscript is presenting the main results of the ACHIEVE trial

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

11.b. If yes, is the proposal
_X_ A. primarily the result of an ancillary study (list number* _2016.03_)
___ 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 https://sites.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.