ARIC Manuscript Proposal #H4350

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1.a. Full Title: Effects of Hearing Intervention on Fatigue Symptoms Over 3 Years: Findings from the ACHIEVE Study

b. Abbreviated Title (Length 26 characters): Hearing Intervention and Fatigue

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

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3. Timeline:

Proposal timeline	September 2023	October 2023	November 2023
Proposal approval	X		
Data Analysis		X	
Manuscript preparation and submission			X

4. Rationale:

Hearing loss may increase fatigue by draining cognitive resources through compensatory sustained, effortful listening along with the emotional toll of living with a hearing loss.[1–3] In turn, fatigue is associated with lower self-rated health, functional status, physical activity levels, loneliness, depression, and mortality.[4–6] Prior epidemiologic evidence has demonstrated that hearing loss is associated with higher frequency of hearing-loss-related fatigue. In a study by Jiang et al, hearing loss demonstrated a dose response relationship with likelihood of reporting near daily fatigue.[7]

However, the impact of treating hearing loss on fatigue is not well-understood, with the majority of prior studies limited to cross-sectional or small, non-randomized prospective studies. While some studies have demonstrated benefits of cochlear implantation in those with severe-profound hearing losses on fatigue,[8,9] relatively few have studied the potential benefits of hearing aid use, which would importantly focus on a broader population with less severe impairments. In one cross-sectional study, hearing aid users reported less fatigue, depressive symptoms, and forgetfulness compared to similar participants with untreated hearing loss.[10] Prospective data has suggested that hearing-aid fitting led to a significant decrease in listening-related fatigue, though not general fatigue, as well as an increase in social activity level.[3] To date, studies comparing groups of individuals with varying levels of hearing loss and use of different hearing devices have not demonstrated clear relationships between severity or treatment of hearing loss and fatigue.[3,11] Moreover, the magnitude of benefit of treating hearing loss on fatigue symptomatology is not well-understood.

Addressing hearing loss may represent a novel approach to reducing fatigue and its downstream sequelae among older adults. The Aging and Cognitive Health Evaluation in Elders (ACHIEVE) study is a multi-center randomized controlled trial of older adults with hearing loss. Participants were randomized to a best-practice hearing intervention versus a successful aging health education control and followed for a 3-year period (Clinicaltrials.gov Identifier: NCT03243422). In this study, we conduct a secondary analysis to investigate the effect of best-practice hearing care on fatigue symptomatology over a 3-year period (pre-specified exploratory outcome).

5. Main Hypothesis/Study Questions:

Study Question:
To determine the effect of a hearing intervention versus a successful aging health education control on change in fatigue symptomatology over 3 years in well-functioning and cognitively-normal adults with hearing loss aged 70 to 84 years.

Main Hypotheses:
Hearing intervention (versus successful aging health education control) is associated with reductions in self-reported fatigue among older adults with hearing loss over 3 years of follow up.

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 for ACHIEVE: All eligible participants enrolled at baseline in the ACHIEVE study.

- Inclusion criteria: 1) age 70-84 years, 2) community-dwelling adults, 3) audiometric hearing loss, 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.

Exposure Variables

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

Outcome Variables

The outcome of interest is fatigue symptomatology. Fatigue and exhaustion symptoms were measured during the ACHIEVE trial through questions on the the CES Depression, RAND SF36, and FAM Falls and Mobility (FAM) forms.

The primary fatigue outcome will be derived from the 5 questions collected on the FAM form, each selected from the PROMIS fatigue item banks. The PROMIS fatigue item banks assess a range of self-reported symptoms centered around the experience and impact of fatigue in terms of duration, frequency, and impact of fatigue on daily activities and has been previously validated across a variety of conditions.[12,13] Questions are asked using a Likert-type scale based on symptoms over the last 7 days (1-Never, 2-Rarely, 3-Sometimes, 4-Often, 5-Always). Answers to the following questions will be used in the present analysis:

a. How often did you feel tired?
b. How often did you experience extreme exhaustion?
c. How often did you run out of energy?
d. How often were you too tired to think clearly?
e. How often were you too tired to take a bath or shower?

PROMIS measures generate T-scores using a mean score of 50 and standard deviation of 10 in a relevant reference population, generally the US general population. For PROMIS measures, high scores indicate more of the concept being measured (e.g. greater fatigue).[14] The derived T-scores were generated and added to the ACHIEVE dataset by the coordinating center. Fatigue was assessed at 4 timepoints throughout the study—baseline, Year 1, Year 2, and Year 3.

A secondary exploratory analysis will use answers to fatigue symptom questions from the CES Depression and RAND SF36 forms. These questions have been used to study the association between hearing loss and exhaustion in a prior ARIC study.[15]

The SF RAND 36 form includes questions rated on a Likert-type scale (1-All of the time, 2- Most of the time, 3- A good bit of the time, 4- Some of the time, 5- A little of the time, 6-None of the time) asking "How much of the time during the past 4 weeks…"

1. Did you have a lot of energy?
2. Did you feel worn out
3. Did you feel tired?

The CES Depression form includes the questions on a Likert-type scale (0- Hardly ever or never (<1 day in the past week), 1- Some of the time (1-2 days in the past week), 2- Much or most of the time (3-7 days in the past week) asking "During the past week…"

1. I felt everything I did was an effort
2. I could not get "going"

Other Variables

The primary analysis may also include adjustments for baseline hearing loss, baseline speech-in-noise understanding (QuickSIN), baseline hearing-related quality of life (Hearing Handicap Inventory), ARIC vs de novo recruitment source, race and center (NC White, NC Black, MN White, MD White, and MS Black), age (years), sex (male/female), education (less than high school/ high school or equivalent/ greater than high school), marital status (married, not married), living alone (yes/no), global cognitive factor score, depressive symptoms (Center for Epidemiologic Studies Depression Scale), anti-depressant use (yes/no), COVID infection (yes/no), smoking (yes/no), alcohol use (yes/no), comorbidities (number of conditions).

Analytic Plan

A statistical analysis plan (SAP) has previously been developed by the CC in conjunction with ACHIEVE investigators and was approved by the NIA and ACHIEVE DSMB in June 2022. Complete details of the primary data analysis, and with planned sensitivity and exploratory analyses and analyses of secondary outcomes, are in the SAP. Mr. Wuyang Zhang will be the analysis lead for this manuscript.

Primary Analysis

We will examine the longitudinal change in fatigue symptomatology over 3 years within each intervention condition using linear mixed effects models that account for the correlation among repeated measures.

Model Specification

- An interaction term between time and intervention assignment will be used to test if the rate of change in the fatigue symptoms is associated with the intervention assignment.
- The linear mixed effects model will specify a random intercept and random time slope with an unstructured covariance matrix.
- When examining change over time, a two-level mixed effects model with assessments (level 1) nested within participants (level 2) will be employed.
- Continuous time in years from baseline will be the time scale. If a linear trend appears reasonable, we will fit a model with a linear slope. If a nonlinear trend is observed, particularly given the likely impact of COVID-19, the models will be adapted to include the appropriate time splines. Based on analytical practices from other ACHIEVE analysis, two approaches to account for non-linearity will be adopted and evaluated: (a) the addition of time splines at specific years (e.g., year 1, year 2, years 1 and 2); and (b) the addition of time splines at the beginning of COVID-19 lockdown (March 2020).
- Analysis may include adjustments for baseline hearing loss, baseline speech-in-noise understanding (QuickSIN), baseline hearing-related quality of life (Hearing Handicap Inventory), ARIC vs de novo recruitment source, race and center, age (years), sex (male/female), education (less than high school/ high school or equivalent/ greater than high school), marital status (married, not married), living alone (yes/no), global cognitive factor

score, depressive symptoms (Center for Epidemiologic Studies Depression Scale), anti-depressant use (yes/no), COVID infection (yes/no, from the COVID Impact Questionnaire), smoking (yes/no), alcohol use (yes/no), comorbidities (number of conditions).

Intervention effects will be examined in the total sample and stratified by subgroups of ARIC vs De novo participants. Three-way interaction among intervention condition, recruitment group, and time will also be tested.

Missing fatigue 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 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 fatigue scores imputed prior to death.

Secondary Analysis

In secondary analysis, we will follow the same analytical path to examine the longitudinal change in fatigue symptoms measured using the CES Depression and RAND SF36 forms. Similar model specifications will be adopted except for the exclusion of depressive symptoms when modeling fatigue measured with CES form. We expect similar intervention effect on the secondary fatigue measures.

Exploratory Analyses

- Complier Average Causal Effect (CACE): We will conduct CACE analyses (using instrumental variable or inverse probability weighting) to address intervention noncompliance by estimating the intervention effect on the subgroup of participants who complied with their treatment assignment.
- Subgroup analyses by demographics: Given the lower prevalence of hearing loss in women compared to men and blacks compared to other races, an exploratory analysis will be conducted stratifying by sex, race, and education. We will also conduct analyses stratifying by level of hearing loss, degree of difficulty understanding speech, and perceived hearing-related quality of life. Interactions between intervention condition and subgroups will be tested.
- Subgroup analyses by risk factors for social isolation and loneliness: We will investigate a further refinement of the primary analysis with subgroup analysis for known risk factors for social isolation and loneliness symptoms, including but not limited to baseline global cognitive factor score, marital and co-habitation status, and depressive symptoms.

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? ____ 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 current derived consent file ICTDER05 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

___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)?

Published: Huang AR, Reed NS, Deal JA, Arnold M, Burgard S, Chisolm T, Couper D, Glynn NW, Gmelin T, Goman AM, Gravens-Mueller L, Hayden KM, Mitchell C, Pankow JS, Pike JR, Sanchez V, Schrack JA, Coresh J, Lin FR; ACHIEVE Collaborative Research Group. Loneliness and Social Network Characteristics Among Older Adults with Hearing Loss in the ACHIEVE Study. J Gerontol A Biol Sci Med Sci. 2023 Aug 14:glad196. doi: 10.1093/gerona/glad196. Epub ahead of print. PMID: 37578190.

Proposal: Effect of best-practices hearing intervention on health-related quality of life: Findings from the ACHIEVE Study (Chisolm et al)

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.

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Association. Published online September 2023:S1525861023007478. doi:10.1016/j.jamda.2023.08.023