ARIC Manuscript Proposal #4284

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

1.a. Full Title: Effects of Hearing Intervention on Social Isolation and Loneliness Over 3 Years: Findings from the ACHIEVE Study

b. Abbreviated Title (Length 26 characters): ACHIEVE Social Loneliness

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

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3. Timeline:

Proposal timeline	June 2023	June - July 2023	August – September 2023
Proposal approval	X		
Data Analysis		X	
Manuscript preparation and submission			X

4. Rationale:

Social isolation and loneliness, while often discussed interchangeably, represent distinct concepts. Social isolation represents an objective characterization of frequency and quantity of social interactions while loneliness represents a subjective perception of unfulfillment with social relationships. In the United States (U.S.), nearly a quarter of older adults are socially isolated and more than a third feel lonely. Moreover, numerous epidemiologic studies report social isolation and loneliness associated with increased morbidity, health resource utilization, dementia, and mortality. The high prevalence and reported negative health impact has culminated in recent prioritization of addressing social isolation and loneliness among older adults by several high-profile U.S. health institutions including the U.S. National Academies, National Institute on Aging, and Office of the Surgeon General.

Importantly, addressing hearing loss may represent a novel approach to reducing social isolation and loneliness among older adults. Hearing plays a vital role in oral communication and engaging with others. A growing body of research suggests that both social isolation and loneliness are associated with hearing loss, and many have proposed that social isolation and loneliness represent mediators linking hearing loss to other poor health outcomes such as dementia. While some observational data analyses suggest a potential protective effect of hearing care, inferences are limited given the strong association between hearing aid access and socioeconomic factors (e.g., high income, more education) which may be equally protective against social isolation and loneliness among older adults. Moreover, it is possible that the exposures of interest (e.g., social isolation and loneliness) could affect propensity to access the treatment of interest (e.g., hearing aids). Randomized controlled trials are needed to balance the effect of confounders to characterize the effect of hearing care on social isolation and loneliness among older adults with hearing loss.

The Aging and Cognitive Health Evaluation in Elders (ACHIEVE) study is a multi-center randomized controlled trial of older adults with hearing loss randomized to a best-practice hearing intervention versus a successful aging health education control over a 3-year period (Clinicaltrials.gov Identifier: NCT03243422). While the primary outcome of the trial is cognitive decline over the course of 3 years, other exploratory outcomes were included measures of social isolation and loneliness. The aim of this study is to describe a secondary analysis of the ACHIEVE study to characterize the effect of best-practice hearing care on measures of social network characteristics and loneliness over a 3-year period.

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 social network characteristics and perceived loneliness over 3 years in 70-84 year-old well-functioning and cognitively-normal adults with hearing loss.

Main Hypotheses:

Hearing intervention (versus successful aging health education control) reduces declines in social network characteristics and reported loneliness 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 outcomes of interest are:

1. Social network characteristics as measured by the Cohen Social Network Index (SNI) which quantifies regular (at least once every two weeks) social engagement with individuals across 12 social roles and provides the following three summary characteristics of social networks:
    a. Number of Social Network Members (score range: 0-84)
        i. Absolute count of reported individuals in the entire network with whom the participant has regular contact with at least once every two weeks.
    b. Social Network Diversity (score range: 0-12)
        i. Number of social roles in which the participant has at least one individual with whom they have regular contact once every two weeks.
    c. Embedded Social Networks (score range: 0-8)
        i. Number of social network domains in which the participant remains active, defined as having contact with four or more individuals within each domain at least once every two weeks.
2. Loneliness as measured by self-report using the 20-item UCLA Loneliness Scale.

Exposure Variables

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

Other Variables

The primary analysis may also include adjustments for the 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, 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), and anti-depressant use (yes/no).

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. The current analysis will follow analysis of the primary outcome detailed in the SAP closely.

Primary Analysis

We will examine 3-year change in social network characteristics and loneliness 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 social network characteristics and loneliness is associated with the intervention assignment.
- The linear mixed effects model will specify a random intercept and random time slope and an unstructured covariance matrix.
- Correlation of repeated assessments within an individual as well as correlation between spouses or cohabitating partners will be accounted for by a two-level mixed effects model that accounts for the correlation among repeated assessments (level 1) adjusted for co-randomized spouse or cohabitating partner.
- 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 on social network characteristics and loneliness, the models will be adapted to include the appropriate time splines. We will test the addition of time splines at 6 months, year 1, year 2, years 1 and 2, and at March 2020 (beginning of COVID pandemic). We will also test for a spline in approximately Spring 2021 when Covid restrictions began to lift (although dates may differ slightly for different center locations and this will be taken into account via interaction variables considering location-covid restriction dates)
- Model fit will be assessed with residual plots and other statistics (Akaike Information Criterion, Bayesian Information Criterion, etc.).
- 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, 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)

Intervention effects will be examined in the total sample and stratified by subgroups of ARIC vs De novo participants. Interaction between intervention condition X recruitment group X time will also be tested.

Missing social network characteristics and loneliness 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 social network characteristics and loneliness scores imputed prior to death.

Sensitivity analyses

(a) Control-based multiple imputation, in which missing values of the primary outcome for the hearing aid condition are imputed based on the successful aging control intervention condition.

This analysis will investigate the strength of the primary analysis results to the missing at random assumption.

(b) An analysis comparing pre- and post-death social network characteristics and loneliness scores will be performed using values generated from an imputation model in which death is included as an auxiliary variable.

Exploratory Analyses

- Complier Average Causal Effect (CACE): We will conduct a CACE analysis using instrumental variables 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)?

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.