

ARIC Manuscript Proposal #3284

PC Reviewed: 11/13/18
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1.a. Full Title: Association between hearing loss and frailty: A cross-sectional analysis from the Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): Hearing loss and frailty

2. Writing Group (alphabetical):

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

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3. Timeline:

Manuscript will be completed in 6-9 months.

4. Rationale:

Frailty is a state of decreased physiological reserve and increased vulnerability to stressors in older adults.^{1,2} Frailty has been linked to increased cognitive decline, hospitalization, surgical complications, and mortality in older adults.^{1,3-6} A model for operationalizing phenotypic frailty was developed by Fried⁷ and includes the presence of three or more of the following components: weakness, low energy, slowed motor performance, low physical activity, or unintentional weight loss. The presence of one or two components constitutes a pre-frail state.

Hearing loss is an increasingly common condition among older adults, and two thirds of US adults over 70 have hearing loss significant enough to impair communication.⁸ A growing

body of evidence has shown that age-related hearing loss is also associated with negative cognitive and psychosocial health consequences.^{9,10} Several studies have shown that hearing loss is associated with declining physical and cognitive function, slower gait speed and falls.¹¹⁻¹⁶ but the relationship between hearing loss and the frailty phenotype is less clear. Potential mechanistic pathways linking hearing loss and frailty include increased cognitive load, social isolation and depression in older adults with hearing loss¹⁷⁻²⁰ leading to a predisposition for frailty. In addition, shared pathophysiological factors such as micro-vascular disease could lead to both hearing loss and frailty.^{21,22} Two studies of subjective hearing loss, one cross sectional and one longitudinal, have found an association between frailty and self-reported hearing loss.^{23,24} However, there have been no wide-scale epidemiological studies examining the association between objectively measured hearing loss and the frailty phenotype in a representative cohort of older adults.

Since Visit 5, the ARIC study has collected the data needed to construct a measure of phenotypic frailty. In Visit 6, objective hearing assessment was also added, thus providing a rich source of data to quantify the association between objective hearing status and frailty. Given this rich data resource, we propose to assess the cross-sectional relationship between objective hearing loss and phenotypic frailty for Visit 6 participants. We will examine the association between hearing loss and the construct of frailty, as well as each of its individual components.

Age related hearing loss progresses slowly at a rate of 1 to 2 dB per year²⁵ such that the change over the two years from Visit 5 to Visit 6 would be miniscule at best. Other studies have treated hearing loss as a time-fixed variable over longer periods of time.^{9,14} As a sub-analysis, we will investigate whether presence of hearing loss at Visit 6 (treated as a time-fixed variable) is associated with change in frailty from Visit 5 to Visit 6.

5. Main Hypothesis/Study Questions:

Aim 1: To quantify the cross-sectional association between hearing loss and frailty at Visit 6.

Hypothesis: We hypothesize that compared to persons with no hearing loss, persons who have hearing loss have higher odds of being pre-frail or frail, independent of age, demographic characteristics, and cardiovascular risk factors.

Aim 2: To investigate the association between hearing loss and the individual components of the frailty phenotype at Visit 6.

Hypothesis: Given the independent associations of hearing loss with decreased physical function and depression, we hypothesize that low physical activity and low energy will be most strongly associated with hearing loss.

Aim 3: To investigate whether presence of hearing loss at Visit 6 (measured at Visit 6 as a time fixed variable) is associated with change in frailty from Visit 5 to Visit 6.

Hypothesis: We hypothesize that those with hearing loss will have higher odds of worsened frailty status from Visit 5 to Visit 6.

6. Design and analysis

Study Design: Cross-sectional analysis within a prospective cohort study

Study population: Study population will be from ARIC visits 5 (2011-2013) and 6 (2015-2017). We will exclude participants for whom the frailty phenotype could not be calculated or for whom a better ear Pure Tone Average (PTA) was not obtained or could not be calculated.

For aim #3, we will include participants who completed both ARIC Visit 5 as well as ARIC Visit 6 and exclude participants for whom a frailty index score could not be calculated or for whom a better ear PTA could not be calculated.

We will examine descriptive characteristics of those included vs. those excluded from this study to explore whether our sample is representative of the overall study population.

Exposure: Hearing loss

Pure tone audiometry is the gold standard to determine the softest tones that can be detected for a range of frequencies. A Pure Tone Average (PTA) is calculated using audiometric thresholds at 0.5, 1, 2 and 4 kHz in the better hearing ear, per WHO definition of hearing loss.²⁶ Calculation of a PTA requires a threshold at 0.5, 1, 2, and 4kHz; if any of these values is missing a PTA cannot be calculated.

For primary analysis we will define hearing function categorically using the WHO criteria for PTA (18) as normal (<25dB) or hearing loss [mild (≥ 25 to <40dB), moderate or greater (≥ 40 dB)]. We will also consider PTA as a continuous variable for secondary analysis to explore the shape of the relationship between hearing and frailty status.

Outcome: Frailty syndrome

The frailty syndrome has been operationalized in the ARIC cohort²⁷ as below:

Table 1. Frailty syndrome in ARIC

Component of frailty	Definition within ARIC
Unintentional weight loss	10% of unintentional weight loss from Visit 4 to Visit 5 or BMI <18.5
Low energy expenditure	Gender-specific 20th percentile rank of the Baecke leisure sports activity index
Low walking speed	Gender- and height-adjusted time in seconds used to walk 4 meters. Slowest speed was defined using the cutoff values established from CHS.
Low energy	Responded “some of the time” or “most of the time” to either of the following CESD questions: CES3 (I felt everything I did was an effort) or CES11 (I could not get “going”)
Low grip strength	Gender- and BMI-specific grip strength. Lowest grip strength was defined using the cutoff values established from CHS.

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Frailty status will be categorized as frail (presence of three or more characteristics of frailty), pre-frail (presence of one or two characteristics of frailty) or non-frail (presence of none of the components of frailty).

For aim #3, change in frailty status between Visit 5 and Visit 6 will be categorized as:

- 1) No change
- 2) Improved frailty status
- 3) Worsened frailty status

Covariates:

Demographic data including: age (years), sex (male, female), field center/race, educational level (highest grade or year of school completed; education will be categorized consistent with standardized ARIC algorithm as <12 years, high school or vocational training, any college), and income.

Vascular risk factors and chronic medical conditions at Visit 6: smoking status (never, former, or current smoker), BMI (categorized as normal [<25], overweight [25-30], obese [>30]), hypertension (systolic BP >140 mmHg or diastolic BP >90 mmHg; or use of antihypertensive medication), diabetes (fasting blood glucose ≥ 126 mg/dl, non-fasting blood glucose >200 mg/dl, or use of diabetes medication), history of myocardial infarction and history of transient ischemic attack (TIA) or stroke. Cardiovascular disease including diabetes, hypertension and ischemic heart disease have been associated with both hearing loss and frailty^{21,22} and could be potential confounders in the relationship between hearing and frailty status.

Statistical analysis:

Demographic and clinical characteristics of participants will be compared using one-way analysis of variance or Chi-squared test.

Aim 1: To quantify the cross-sectional association between hearing loss and frailty status.

Primary analysis: We will examine the relationship between hearing loss (mild/moderate or greater versus normal hearing) and frailty (categories) using multinomial logistic regression. We will perform the following:

Unadjusted analysis

Model 1: Adjusted for demographic variables (age, sex, race/field center, education, income).

Model 2: Adjusted for model 1 + vascular risk factors and chronic medical conditions (smoking status, BMI, hypertension, diabetes, and history of MI, history of TIA or stroke).

Aim 2: To investigate the association between hearing loss and the individual components of the frailty phenotype.

We will repeat the above model-building approach for logistic regression analysis to examine the relationship between hearing loss (mild/moderate or greater vs normal hearing) and presence or

absence of each of the five components of the frailty index. We will have a separate logistic regression model for each component.

Aim 3: To investigate whether presence of hearing loss at Visit 6 is associated with worsening frailty status from Visit 5 to Visit 6

For this analysis, we will treat hearing loss at Visit 6 as a time fixed variable and assess the association between hearing loss and change in frailty status from Visit 5 to Visit 6. Age related hearing loss progresses slowly at a rate of 1 to 2 dB per year²⁵ such that the change over the two years from Visit 5 to Visit 6 would be miniscule at best. Other studies have treated hearing loss as a time-fixed variable in a similar fashion over longer periods of time.^{9,14}

We will perform multinomial logistic regression analysis (using the same model building approach as aim 1 above) to assess the relationship between hearing loss and change in frailty status between Visit 5 and Visit 6 for study population overall as well as stratified by frailty status at Visit 5. We will also consider using transition analysis to better control for starting state.

Limitations

This is a cross-sectional study so we will not be able to establish a temporal relationship between hearing loss and frailty status. We propose analyses using hearing status at Visit 6 as a time fixed variable to assess the association between hearing and change in frailty from Visit 5 to Visit 6. Although age-related hearing loss is a slowly progressing chronic disease that we do not expect to change in a meaningful way between Visit 5 and Visit 6, we do make the assumption that those with hearing impairment at Visit 6 also had impairment at Visit 5.

Finally, frailty at Visit 6 will be operationalized with a different criterion for unintended weight loss: at Visit 5 we could only look back to Visit 4 to determine change in weight. At Visit 6 we have an explicit question about weight loss in past year plus we have Visit 5 data. We have not yet arrived at the operationalization of the phenotype for change in frailty status given the discrepant definitions of frailty, and this may affect our analysis when comparing Visit 5 to Visit 6 frailty status.

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes 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 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
N/A

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.csc.unc.edu/ARIC/search.php>

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)?

2418: Deal et al, Hearing Impairment and Physical Function in the Atherosclerosis Risk in Communities (ARIC) Hearing Pilot Study

2671: Nadriz Junion et al, Cardiovascular characterization of frailty in the elderly: The ARIC study

2303. Godino et al. Diabetes, hyperglycemia, and the burden of frailty syndrome in the Atherosclerosis Risk in Communities Study

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

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (ARIC-NCS)

B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____)

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.csc.unc.edu/atic/index.php>, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes No.

References:

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