ARIC Manuscript Proposal #H4395

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1.a. Full Title: Effect of a hearing intervention among older adults at high risk of cognitive decline: ACHIEVE randomized trial

b. Abbreviated Title (Length 26 characters): ACHIEVE predicted risk

2. Writing Group:
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3. Timeline:

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Proposal approval	X		
Data Analysis		X	
Manuscript preparation and submission			X

4. Rationale:

Current projections indicate that 82 million individuals will be living with dementia by 2030 (Alzheimer's Disease International, 2023). By 2050 the estimated number rises to 152 million, underscoring the urgent need for scalable interventions that can modify known risk factors for dementia (Livingston, et al., 2020; World Health Organization, 2019). Among the known risk factors, hearing loss is a promising target (Livingston, et al., 2020). Meta-analyses of longitudinal observational studies have found that hearing loss is associated with greater risk of cognitive decline (Conceição Santos de Oliveira, et al., 2023), incident cognitive impairment (Lau, et al., 2022; Loughrey, Kelly, Kelley, Brennan, & Lawlor, 2018; Wei, et al., 2017), and incident dementia (Liang, Li, Xu, Qian, & Gao, 2021; Loughrey, Kelly, Kelley, Brennan, & Lawlor, 2018; Wei, et al., 2017). Meta-analyses also indicate that use of a hearing aid may reduce the risk of cognitive decline (Yeo, et al., 2023).

The Aging and Cognitive Health Evaluation in Elders (ACHIEVE) study (Lin, et al., 2023) was the first randomized trial to investigate the 3-year effects of a hearing intervention on cognitive change in older adults with untreated hearing loss. While a protective effect was not detected in the full cohort (n=977), effect heterogeneity was observed across the two populations that comprised the cohort. Among individuals recruited from the Atherosclerosis Risk in Communities (ARIC) study (n=238), the hearing intervention slowed cognitive decline by 48%. Among healthy community volunteers recruited de novo (n=739), there was no statistically significant effect.

Heterogeneity in the association between hearing loss and incident dementia has been previously reported (Gurgel, et al., 2014; Kim, Lim, Kong, & Choi, 2018; Liu & Lee, 2019). Consequently, it is not surprising that ACHIEVE participants with varying risk factors for cognitive decline (Lin, et al., 2023) responded differently to the hearing intervention. Yet, the precise factors that contribute to different levels of risk for cognitive decline and how predicted risk might interact with a hearing intervention is unknown.

To better understand how predicted risk for cognitive decline may moderate the effect of a hearing intervention on the rate of cognitive decline over three years, we will construct a parsimonious model utilizing data from 2,692 ARIC participants assessed between 2016 and 2022. The model will be applied to baseline measures from the ACHIEVE study to calculate a predicted risk score for each participant. Linear and nonlinear interactions between the predicted risk score and randomized treatment assignment will be tested to determine the types of individuals who may benefit the most from the use of hearing aids.

5. Main Hypothesis/Study Questions:

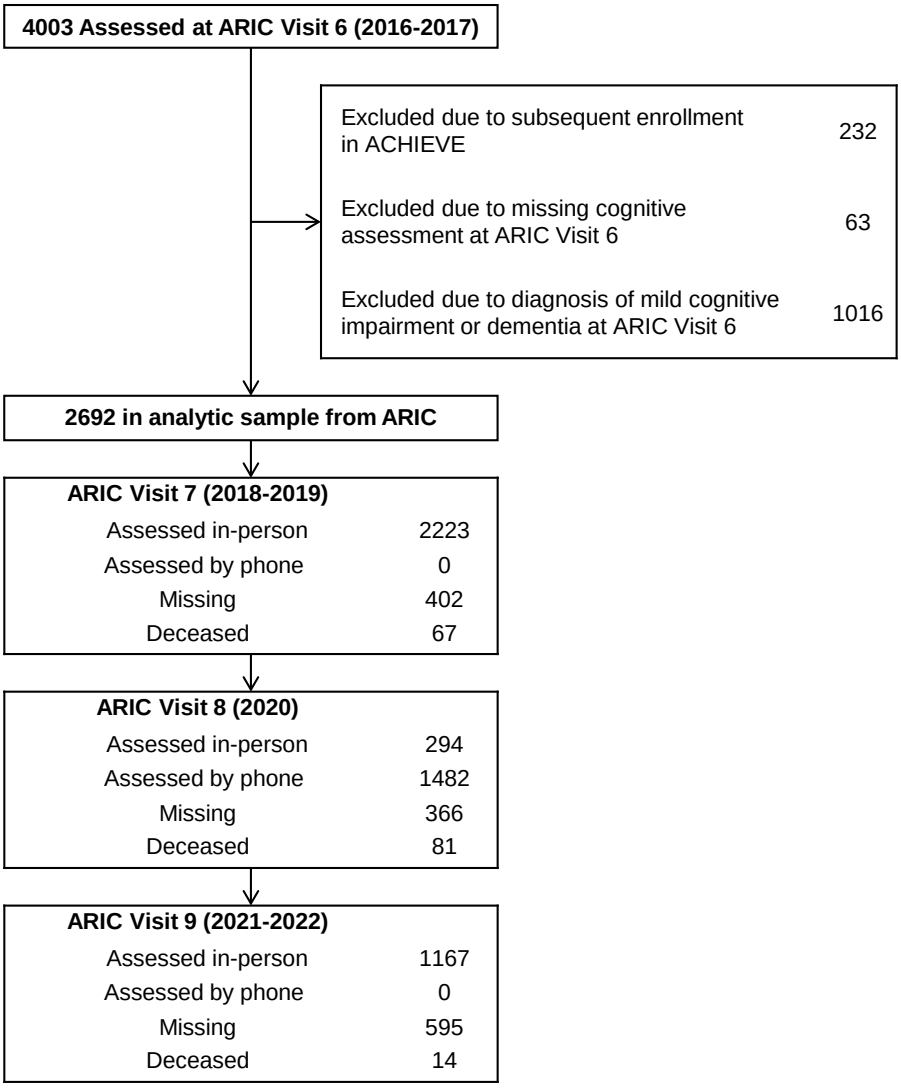
Study Question: Does the ACHIEVE hearing intervention have a protective effect among participants at high risk for cognitive decline?

- **Hypothesis 1.** Predicted risk scores will moderate the effect of the ACHIEVE hearing intervention such that participants with the *greatest risk* who were randomized to the hearing intervention will have the *greatest reduction* in cognitive decline compared to participants randomized to the successful aging health education control.
- **Hypothesis 2.** The interaction between the predicted risk score and randomized treatment assignment will be nonlinear. The nonlinear relationship will indicate that predicted risk scores *do not* moderate the effect of the ACHIEVE hearing intervention among participants with the *least risk* of cognitive decline.

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: The proposed investigation will use two analytic samples. The first sample will comprise participants from four U.S. sites (Forsyth County, NC; Jackson, MS; Minneapolis suburbs, MN; Washington County, MD) who participated in the ARIC study and completed neurocognitive examinations between Visit 6 (2016-17) and Visit 9 (2021-22). Participants will be included in the analytic sample if they completed a clinic-based assessment at Visit 6 (N=4,003). Participants will be excluded if they enrolled in ACHIEVE (N=232), did not complete a neurocognitive examination (N=63) at Visit 6, or were diagnosed with mild cognitive impairment or dementia (N=1,016) at Visit 6 (**Figure 1**).

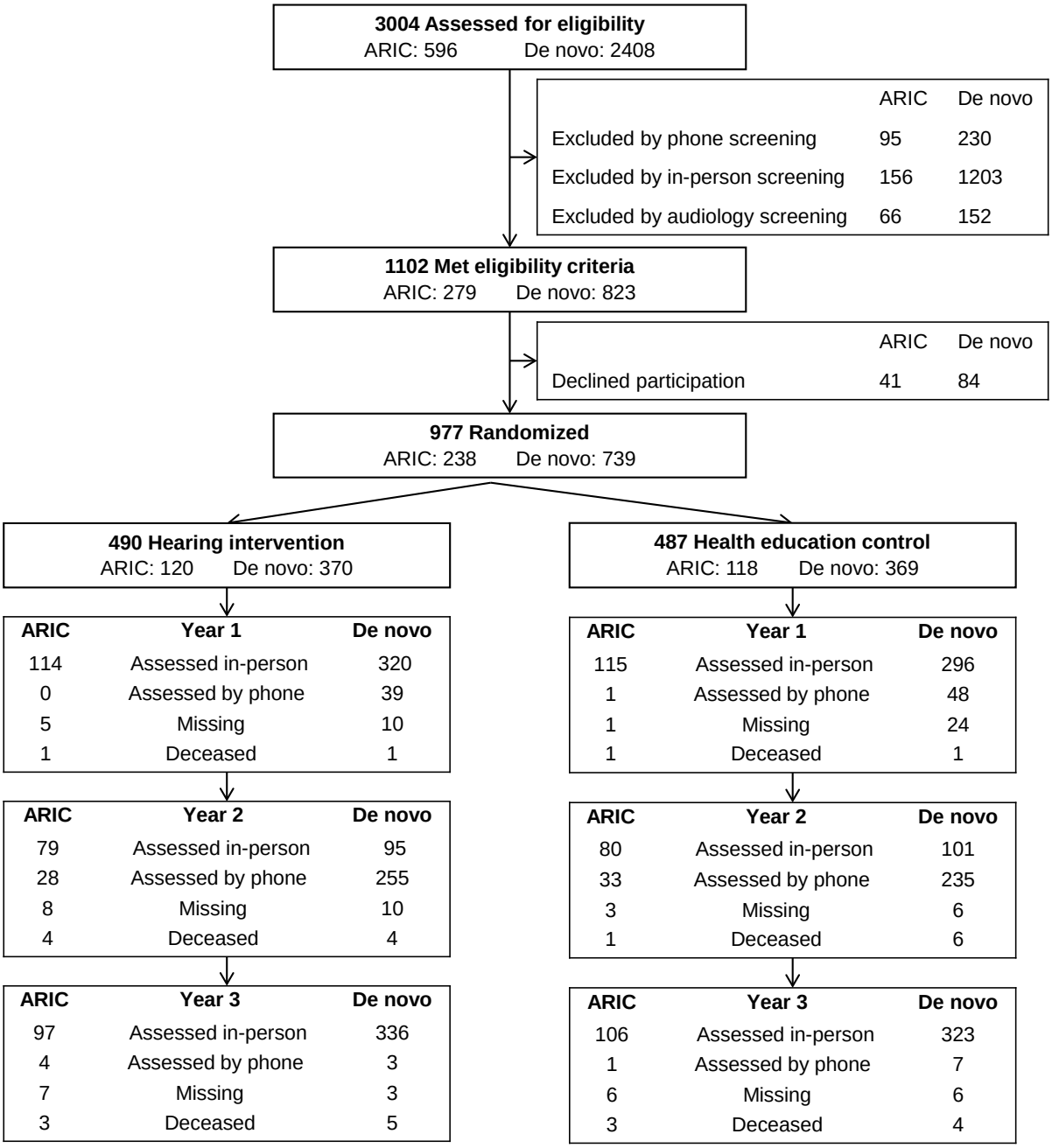
Figure 1. Flowchart of ARIC Participants Selected for Analysis



The second sample will comprise participants from the same four U.S. sites who enrolled in ACHIEVE and completed neurocognitive examinations between 2018 and 2022 (**Figure 2**). The inclusion criteria for the ACHIEVE trial were (1) aged 70-84 years, (2) being a community-dwelling adult who planned to stay in the area, (3) being a fluent English speaker, (4) adult-onset bilateral hearing loss with a better-ear 4-frequency (0·5–4·0 kHz) pure tone average (PTA) of 30 or more dB and less than 70 dB, (5) word-recognition score in quiet at least 60% correct in the better-hearing ear, and (6) free of substantial

cognitive impairment (mini-mental state examination [MMSE] score ≥23 for participants with a high-school degree or less and ≥25 for those with some college education or more). The exclusion criteria were (1) self-reported disability in two or more activities of daily living, (2) visual acuity worse than 20/63 on the MNREAD acuity chart (Precision Vision, Woodstock, IL, USA; corresponding to inability to comfortably read 14-point font), (3) permanent conductive hearing loss, (4) medical contraindication to hearing aid use, (5) self-reported hearing aid use in the past year, or (6) unwillingness to wear hearing aids on a regular basis.

Figure 2. Flowchart of ACHIEVE Participants Selected for Analysis



Predictors Tested for Inclusion in Predicted Risk Model: Measures administered by trained and certified staff during Visit 6 of the ARIC study and the baseline of the ACHIEVE randomized trial will be tested as predictors of cognitive decline.

Demographic. Date of birth, sex, and education (less than high school, high school or equivalent, or greater than high school) were self-reported. Date of birth was used to calculate age at ARIC Visit 6 or age at the ACHIEVE baseline.

Geographic. The site each participant was recruited by will function as a proxy for geographic differences.

Genetic. The Human Genetics Center at the University of Texas, Houston analyzed blood samples obtained during clinic visits (Blair, et al., 2005). The TaqMan assay (Applied Biosystems, Foster City, CA) detected APOE variants at codons 130 and 176 and determined the presence of 0, 1, or 2 ε4 alleles.

Hearing. Objective hearing was quantified by PTA measurements performed in single-walled, 7x7 sound attenuating WhisperRooms using Interacoustics Equinox 2.0 AC440 audiometer with E-A-R 3A insert earphones. Pure-tone air- and bone-conduction thresholds were assessed in each ear using a modified Hughson-Westlake (Hughson & Westlake, 1944) psychophysical bracketing method (Carhart & Jerger, 1959). The threshold in the better ear was defined as the lowest decibel hearing level at which a tone was recognized by the participant at least 50 percent of the time. Subjective hearing was quantified by the 10-item screening version of the Hearing Handicap Inventory for the Elderly (Tomioka, et al., 2013; Ventry & Weinstein, 1982). A measure of the auditory processes required for encoding sound and the cognitive processes required for decoding the signal and separating the speech from noise was obtained by administering the Quick Speech-in-Noise (Killion, Niquette, Gudmundsen, Revit, & Banerjee, 2004; Wilson, McArdle, & Smith, 2007). Two pre-recorded lists of 6 sentences per list containing 5 key words per sentence were presented binaurally with channel 1 and channel 2 routed to separate RadioEar SP90 speakers. Sentences were presented on channel 1 at 0 degrees azimuth using a fixed level of 70-dB SPL. Multi-talker babble was presented on channel 2 at 1800 azimuth, manually adjusting the signal-to-noise ratio from 25 dB to 0 dB in 5-dB increments. Participants were asked to repeat back the sentences to the best of their ability. Each sentence was graded on a score of 0-5 based on the number of key words correctly repeated by the participant. The score for each list was 0 to 30 and the average of both scores was computed.

Lifestyle. Current, former, or never use of cigarettes or alcohol were ascertained by self-report. Leisure-time and sport-related physical activity were measured by the Baecke questionnaire (Baecke, Burema, & Frijters, 1982).

Physical Function. Lower extremity function was quantified from repeated chair stands, balance tests (standing, semi-tandem, tandem), and a 4 meter walk (Guralnik, Ferrucci, Simonsick, Salive, & Wallace, 1995; Guralnik, et al., 1994). A value for each test was assigned based on population-based norms and summed into a composite Short Physical Performance Battery (SPPB) score. Upper body function was defined as grip strength (Bohannon, 2009) in kilograms of force in the participant's preferred hand measured by a Jamar Hydraulic Hand Dynamometer.

Anthropometric. Body weight was measured to the nearest 0.1 kilogram and height was recorded to the nearest centimeter. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured to the nearest centimeter using the smallest circumference between the lower ribs and iliac crests and hip circumference was measured using the greatest circumference between the iliac crest and thighs. The ratio of the waist to hip circumference was computed.

Cardiovascular. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using the Omron HEM-907 XL oscillometric automated sphygmomanometer (Omron Healthcare, Kyoto, Japan). Resting heart rate was calculated from a 2-minute supine 12-lead electrocardiogram recording using standardized methods (Liao, Barnes, Chambless, & Heiss, 1996).

Medical Conditions. The use of medication was ascertained by a questionnaire that cataloged all prescription and over-the-counter medications taken by the participant over the past four weeks. Hypertension was defined as SBP ≥140 mm/Hg, DBP ≥90 mm/Hg, use of anti-hypertensive medication, or self-reported physician diagnosis. Diabetes was defined as fasting glucose ≥ 126 mg/dL, non-fasting glucose ≥ 200 mg/dL, use of glucose-lowering medication, or self-reported physician diagnosis. Stroke, coronary heart disease, and myocardial infarction were determined by self-reported physician diagnosis on ACHIEVE. On ARIC, self-reported information was supplemented by data abstracted from medical records (Koton, et al., 2014; Rosamond, et al., 2012; Wright, et al., 2021). In both studies, the Neuropsychiatric Inventory (Cummings, et al., 1994; Kaufer, et al., 2000) was used to document self-reported physician diagnosis of Parkinson's disease, traumatic brain injury, and seizures.

Mental Health. Depressive symptomology was measured using the 11-item Center for Epidemiologic Studies Depression scale (Radloff, 1977; Kohout, Berkman, Evans, & Cornoni-Huntley, 1993) validated for older adults (Gellis, 2010).

Cognition. Cognition was assessed by the mini-mental state exam (MMSE) (Folstein, Folstein, & McHugh, 1975) and a 10-test cognitive battery administered in-person. The battery included the Digit Span Backwards (Wechsler, 1987), Boston Naming Test (Williams, Mack, & Henderson, 1989), Word Fluency Test (Benton & Hamsher, 1976), Animal Naming Score (Benton & Hamsher, 1976), Digit Symbol Substitution (Wechsler, 1987), Trail Making Tests A and B (Reitan, 1958), Incidental Learning (Ryan & Lopez, 2001), Logical Memory Test (Wechsler, 1987), and the Delayed Word Recall (Knopman & Ryberg, 1989).

Exposure: The primary exposure is random assignment (1:1) to either a hearing intervention or a successful aging health education control intervention using permuted block randomization, stratified by severity of hearing loss (PTA <40 dB or ≥40 dB), recruitment source (ARIC or de novo), and site. Eligible participants who were spouses or partners were randomly assigned as a unit. Participants assigned to the hearing intervention completed four 1 hour sessions with a study audiologist held every 1 to 3 weeks. During the intervention, participants received bilateral hearing aids and other hearing-assistive technologies as well as systematic orientation and instruction (Sanchez, et al., 2020). Participants assigned to the successful aging health education control met individually with a certified health educator who administered the 10 Keys to Healthy Aging program (Newman, et al., 2010), an evidence-based interactive health education program for older adults on topics relevant to chronic disease and disability prevention. Participants completed four 1 hour sessions with a health educator held every 1 to 3 weeks.

Outcome: Scores from the 10-test cognitive battery were used to compute a factor score of global cognitive function (Gross, et al., 2015) for each participant at each assessment. The factor score was standardized to either ARIC Visit 6 or the ACHIEVE baseline. A factor score was chosen over other summary measures, such as weighted averages, since it mitigates measurement error (Balsis, Unger, Benge, Geraci, & Doody, 2012), improves precision (Gross, et al., 2014), has interval-level properties (Lord, 1952), and has minimal floor or ceiling effects (Gross, Jones, Fong, Tommet, & Inouye, 2014). Select tests were used to compute separate factor scores (Gross, et al., 2015) for the domains of executive function (Digit Symbol Substitution, Trail Making Tests A and B), language (Boston Naming Test, Word Fluency Test, and Animal Naming Score), and memory (Incidental Learning, Logical Memory Test, Delayed Word Recall).

Auxiliary Variables for ARIC Imputation Model: To mitigate bias in the ARIC sample caused by informative attrition, we will use multiple imputation by chained equations (MICE) (Van Buuren, 2007). The MICE model will include time-invariant Visit 6 values of all measures plus time-varying measures of alcohol use, cigarette use, BMI, SBP, DBP, hypertension, diabetes, stroke, coronary heart disease, myocardial infarction, MMSE, the six-item screener (SIS) (Callahan, Unverzagt, Hui, Perkins, & Hendrie, 2002), self-reported health (Stewart, Hays, & Ware, 1988), the use of a proxy during in-person or phone-based assessments, the number of hospitalizations since the last in-person assessment, and incident dementia defined by adjudicated review, telephone interviews, informant interviews, hospitalization records, and death certificates (Knopman, et al., 2016).

Auxiliary Variables for ACHIEVE Imputation Model: Multiple imputation will also be used to imputed missing values in the ACHIEVE randomized trial. The MICE model will include random treatment assignment and the predicted risk score plus baseline measures of hearing loss severity (PTA <40 dB vs. ≥ 40 dB), recruitment source, site, age, sex, race, education, and the presence of APOE $\varepsilon 4$ alleles. Time-varying measures of the MMSE, SIS, and adjudicated mild cognitive impairment or dementia (Lin, et al., 2023) will also be integrated into the MICE model.

Analytic Plan: All measures administered during ARIC Visit 6 and the ACHIEVE baseline will be included in a linear regression model that examines change in global cognitive function from ARIC Visit 6 to Visit 9. Least absolute shrinkage and selection operator (LASSO) will be used to identify the minimum number of variables required. The variables selected and their interactions with time will be incorporated into a linear mixed effects model (LMEM) that estimates cognitive change in the ARIC sample. The LMEM will specify time in years from Visit 6 as the timescale, include a random intercept and time slope, employ an unstructured variance-covariance matrix, and use restricted maximum likelihood. The R^2 of the LMEM will be examined to ensure that the within participant variance explained by the variables exceeds 80%. If R^2 is less than 0.80, the LASSO selection criteria will be modified and the process will be repeated until an acceptable parsimonious LMEM of cognitive decline is developed.

MICE will be used to impute missing, pre-death factor scores of global cognitive function in the ARIC sample. The ARIC imputation model will include the measures previously described plus the interaction between time and time-varying measures of cognitive function or incident dementia. A similar process will be used to impute missing, pre-death factor scores of global cognitive function and the domains of executive function, language, and memory in the ACHIEVE sample. The ACHIEVE imputation model will include 2-way interactions between each measure and time, random treatment assignment, or recruitment source as well as 3-way interactions between each measure, time, and either random treatment assignment or recruitment source. The number of imputations needed for each sample will be determined using a quadratic formula (von Hippel, 2020).

The predicted risk LMEM will be fit to imputed data from the ARIC sample. The association between each measure and change in cognitive function over time will be estimated in separate models and collectively in a single model. Parameter estimates from the single model will be used to generate a predicted score for each ARIC participant. The difference between predicted and observed annualized change in cognition will be visualized (**Figure 3**). Parameter estimates from the single model will then be used to generate a predicted score for each ACHIEVE participant. The difference between predicted and observed annualized change in cognition will be visualized in the ACHIEVE sample and subsamples defined by random treatment assignment or recruitment source. Predicted risk scores in both samples will be standardized and presented in histograms that denote the proportion above or below a threshold defined by the discretizing predicted risk scores in the ACHIEVE sample (**Figure 4**).

Figure 3. Example Histogram of Difference Between Observed and Predicted Annualized Change in Cognition in ARIC (N=2,692)

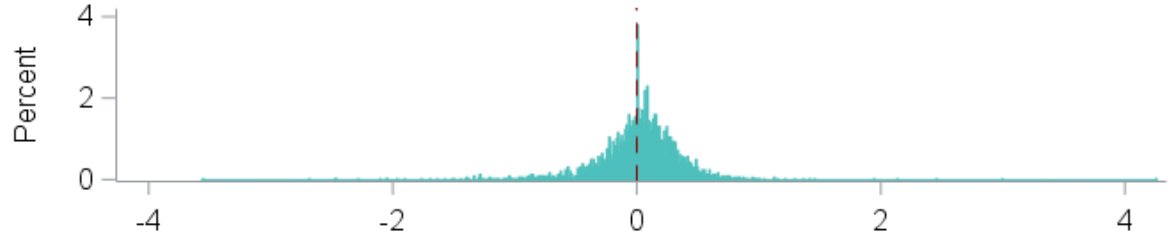
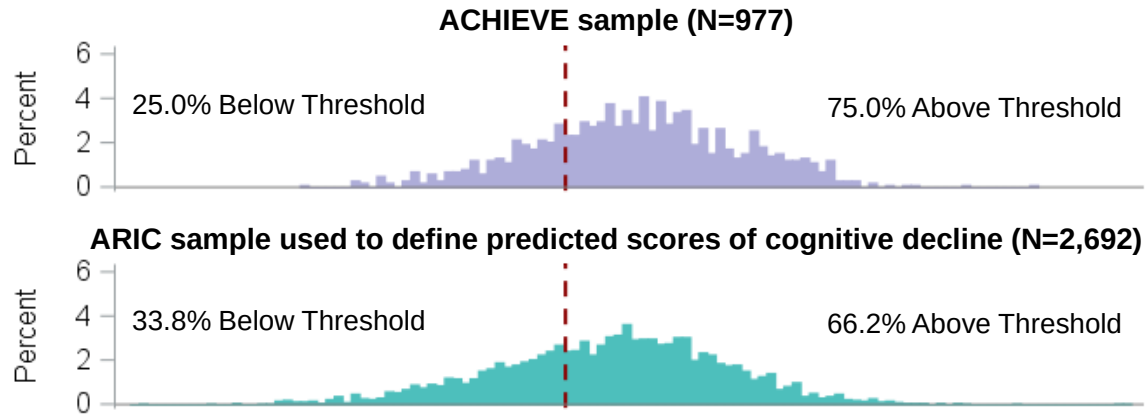
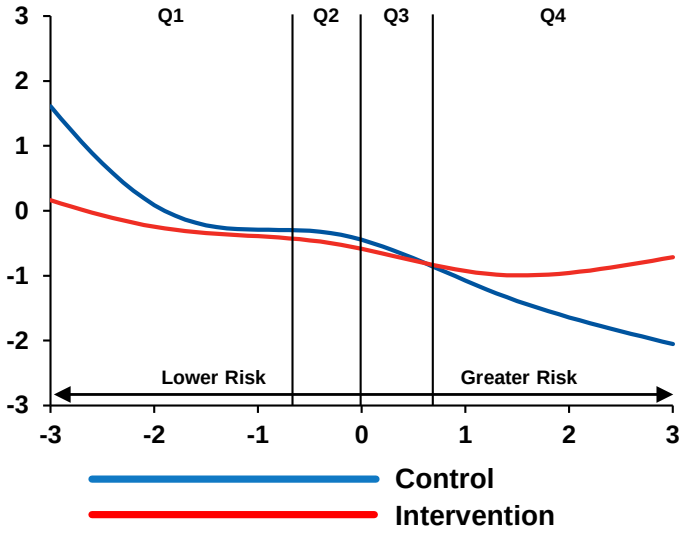


Figure 4. Example Histograms of Standardized Predicted Risk Scores in ACHIEVE and ARIC With a Line Demarcating the Threshold for the Quartile in ACHIEVE With the Greatest Risk of Cognitive Decline



Standardized predicted risk scores will be integrated into intention to treat (ITT) analyses previously performed for ACHIEVE (Lin, et al., 2023). The effect of random treatment assignment on 3-year change in cognition will be estimated using a three-level LMEM with an unstructured covariance matrix fit to imputed data from the baseline and the year three in-person assessment. The LMEM will use restricted maximum likelihood with a Kenward-Roger correction to generate parameter estimates, 95% confidence intervals, and p values. A random intercept and time slope will be specified at level two for participants and a random intercept will be specified at level three for spouses or partners randomly assigned as a unit. The LMEM will include baseline measures of hearing loss severity (PTA <40 dB vs. ≥40 dB), recruitment source, site, age, sex, race, education, and the presence of APOE ε4 alleles as time-invariant covariates. An interaction will be specified between continuous time from the baseline and each covariate except education. The LMEM will also incorporate the predicted risk score, a 2-way interaction between the predicted risk score and random treatment assignment, a 2-way interaction between the predicted risk score and time, a 2-way interaction between randomized treatment assignment and time, and a 3-way interaction between time, the predicted risk score, and random treatment assignment. The initial LMEM will use restricted cubic splines to test for a nonlinear interaction. Knots will be placed at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the predicted risk score. The unadjusted and covariate-adjusted effect of the interaction between the predicted risk score and random treatment assignment on cognitive function at the three-year follow-up assessment will be visualized (**Figure 5**).

Figure 5. Example Visualization of Covariate-Adjusted Nonlinear Interaction Between Baseline Predicted Risk Score and Random Treatment Assignment on Cognitive Function at the Three-Year Follow-Up Assessment With Lines Demarcating the Thresholds for Quartiles in ACHIEVE



Based on visualizations of the interaction, an appropriate threshold (e.g. top tertile, top quartile, etc.) will be selected and used to discretize the predicted risk score. Descriptive statistics of participant characteristics in the ARIC sample stratified by the discretized score will be generated and statistically significant differences will be calculated utilizing $\chi 2$ tests, t tests, and Cochran-Armitage trend tests. The same process will be used to generate descriptive statistics characterizing the ACHIEVE sample stratified by the discretized score and either random treatment assignment or recruitment source.

The first hypothesis that participants with the *greatest risk* who were randomized to the hearing intervention will have the *greatest reduction* in cognitive decline will be tested by fitting unadjusted and covariate-adjusted LMEMs. However, instead of using restricted cubic splines to estimate the nonlinear interaction, the discretized predicted risk score (e.g. quartile with *greatest* risk of cognitive decline versus remaining quartiles) will be included in the model. The second hypothesis that the interaction between random treatment assignment and the predicted risk score will *not* be statistically significant among participants with the *least risk* will be tested by inverting the discretized predicted risk score (e.g. quartile with *least* risk of cognitive decline versus remaining quartiles). A model that tests a linear interaction by incorporating a continuous version of predicted risk will also be fit to imputed data. This process will be implemented for the primary outcome of global cognitive function and repeated for the domains of executive function, language, and memory. In sensitivity analyses, the robustness of the results will be tested by moving the threshold (e.g. quartiles) used to discretize the predicted risk score to include more participants (e.g. tertiles) or less participants (e.g. quintiles). The ITT analyses of global cognition function will also be adapted into per protocol and complier average causal effect analyses. In supplemental analyses, measures tested for inclusion in the predicted risk model will be used to stratify the ACHIEVE sample and test for a 3-way interaction. These subgroup analyses will investigate the effect of individual factors independent of their role within the constellation of factors included in the predicted risk model.

Limitations: A strength of the proposed investigation is the development of a predicted risk model for the ACHIEVE randomized trial using a larger dataset provided by the ARIC cohort. Benefits of this approach include greater precision in parameter estimates and greater generalizability. A drawback is that the measures tested for inclusion in the model were limited to those administered in both the ACHIEVE

randomized trial and Visit 6 of the ARIC study. Some measures, such as depression, represent only one component of a critical construct (Shukla, et al., 2020) that is hypothesized to be a mechanism through which hearing loss may cause cognitive decline (Powell, Oh, Lin, & Deal, 2021). Other pertinent measures, such as brain structure and function (Powell, Oh, Lin, & Deal, 2021), were only measured in a subset of participants (Knopman, et al., 2015) and will therefore not be tested for inclusion in the predicted risk model. The measures that are included in the model should therefore be conceptualized as a first step toward identifying factors that may predict risk of cognitive decline rather than a definitive list.

Another limitation of the proposed investigation is that effect heterogeneity may not be limited to differences defined by the predicted risk of cognitive decline. If the analyses provide empirical support for the hypotheses and there is *minimal overlap* in the predicted risk scores between participants in ACHIEVE who were recruited from ARIC or recruited de novo, then this may explain prior findings (Lin, et al., 2023). However, if the analyses provide empirical support for the hypotheses and there is *significant overlap* in the predicted risk scores, then this may suggest that there are other individuals who may benefit from hearing aids and that recruitment source functions as a proxy for these measured or unmeasured factors. Thus, while the proposed investigation may offer insights into high risk individuals who may see greater cognitive benefits from hearing aid use, it does not exclude the possibility that there are cognitive benefits of hearing aid use among individuals with hearing loss who may appear to have a low risk of cognitive decline.

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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)?

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.