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Design and Methods of the Early Age-Related Hearing Loss Investigation (EARHLI) Randomized Controlled Trial

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Abstract

Objective: Hearing loss has been identified as a major modifiable risk factor for cognitive decline. The Early Age-Related Hearing Loss Investigation (EARHLI) study will assess the mechanisms linking early age-related hearing loss and cognitive impairment.

Study Design: Randomized, controlled, single-site, early phase II, superiority trial.

Setting: Tertiary academic medical center.

Participants: 150 participants aged 55 to 75 years with early age-related hearing loss (severity defined as borderline to moderate) and amnestic mild cognitive impairment will be included.

Interventions: Participants will be randomized 1:1 to a best practice hearing intervention or a health education control.

Main Outcome Measures: The primary study outcome is cognition measured by the Alzheimer Disease Cooperative Study-Preclinical Alzheimer Cognitive Composite (ADCS-PACC). Secondary outcomes include additional measures of cognition, social engagement, and brain organization/connectivity.

Results: Trial enrollment will begin in early 2024.

Conclusions: Following its completion in 2027, the EARHLI trial should offer evidence on the effect of hearing treatment versus a health education control on cognitive performance, social engagement, and brain organization/connectivity in 55–75-year-old community-dwelling adults with early age-related hearing loss and amnestic mild cognitive impairment.

Keywords

Clinical trials; Cognition; Dementia; Hearing loss; Memory; Presbycusis; Hearing Intervention

Introduction

Age-related hearing loss (ARHL) is the third most common chronic condition in older adults[1]. Studies by our group[2–5] and others[6–10] have shown associations between ARHL and cognitive impairment and dementia. We have recently extended this finding to subclinical levels of hearing loss[3,11,12], which are rarely treated with hearing aids.

The mechanisms linking ARHL and cognitive decline are unknown, but reduced socialization[13] and changes in brain organization/connectivity[14,15] have been proposed. Because ARHL is fundamentally a communication disorder, it may impair cognition through reduced social engagement[13,16], the process of maintaining social connections and participating in social activities[17]. Reduced social engagement may, in turn, chronically result in less cognitively stimulating activities[18,19]. Studies have also suggested that ARHL can lead to both structural[20,21] and functional[22–24] changes in the brain, including decreased auditory cortex volume[25] and increased activation of non-auditory regions due to the increased listening effort that ARHL demands[26]. ARHL may also cause cross-modal reorganization, a process by which the auditory cortex is taken over by visual processing

at the expense of auditory processing functionality. Cross-modal reorganization has been associated with worse cognitive function but may be reversible with hearing aid use[15].

A 2020 report of *The Lancet Commissions* estimated that eliminating ARHL would be associated with an 8% reduction in new dementia cases, more than other established risk factors[27]. While many studies have found evidence that treating ARHL (i.e., with hearing aids or cochlear implants) was associated with both short- and long-term cognitive benefit[28–33], there is a dearth of randomized controlled trials (RCTs). Moreover, while studies have suggested that hearing aids improve socialization[34] and brain organization/connectivity[15], there is no high quality RCT evidence. One RCT, the Aging and Cognitive Health Evaluation in Elders (ACHIEVE) study, was recently completed and focused on older adults (age 70-84 years old) with mid to late stage ARHL (30-70 dB pure tone average). However, the ideal time to intervene may be earlier, starting in midlife when both ARHL and the first detectable brain changes of cognitive decline may begin.

Here we detail the design of the Early Age-Related Hearing Loss Investigation (EARHLI) trial. This RCT is a single-center study aimed at evaluating the effect of hearing loss treatment on cognition in adults in midlife to early older age (55-75 years old) with early ARHL (20-55 dB) and amnestic mild cognitive impairment (MCI). This period in the adult lifespan is a time both critical for the development of cognitive decline and potentially ideal for intervention. Additionally, this study will evaluate the impact of hearing loss treatment on measures of social engagement and brain organization/connectivity.

Materials and Methods

Overall design

EARHLI (ClinicalTrials.gov ID NCT06174038) is a randomized, controlled, single-site, early phase II, superiority trial of 150 adults in midlife to early old age (55-75 years) with borderline to moderate hearing loss and amnestic mild cognitive impairment (MCI). Individuals are randomized to either a best practice hearing intervention based on Sanchez et al 2020[35], including prescription hearing aids, or a comparator health education program[36]. Participants are followed for one year, with a primary end point of better global cognition between the hearing intervention and comparator groups. Relevant timepoints across the study period can be found in Table 1.

Study objectives

The objective of the EARHLI trial is to determine the effect of a hearing intervention versus a health education comparator intervention on global (primary outcome) and domain-specific cognitive performance, social engagement, and brain organization/connectivity in 55–75-year-old well-functioning adults with early age-related hearing loss and amnestic mild cognitive impairment (MCI).

We will also explore whether social engagement and brain organization/connectivity mediate the effects of the intervention on cognitive outcomes, as well as exploring predictors of adherence, the relation of adherence with outcomes, and possible modifiers of the effect of the intervention (including sex, APOE genotype, baseline plasma amyloid positivity, and

cognitive diagnosis of early or late MCI). Ancillary outcome measures include depressive symptoms, communicative ability measures, quality of life measures, and the Pittsburgh Fatigability Scale.

Eligibility

Inclusion criteria are used to identify community-dwelling adults aged 55-75 years with borderline to moderate hearing-impairment and amnestic MCI. Amnestic MCI is an inclusion criterion as it is easier to study cognitive change in those who are at risk for cognitive change. This improves statistical power. This is also important in light of the recently published ACHIEVE randomized controlled trial, where significant cognitive findings were found only among those at greater risk for cognitive decline[37]. If recruitment efforts prove difficult, we would consider a protocol modification to additionally include those with subjective cognitive complaint. Borderline to moderate hearing loss is defined as a 4-frequency (0.5, 1, 2, and 4 kHz) pure tone average of 20-55 dB HL in the participant's better hearing ear. The lower cutpoint of 20 dB HL agrees with WHO criteria for defining hearing loss.[38] Amnestic MCI is defined by Mini-Mental State Exam 2 (MMSE-2) score > 23, Clinical Dementia Rating (CDR) equivalent global score equivalent = 0.5, and ADNI3 criteria of Logical Memory II score of ≤6 if 0-7 years of education, ≤9 if 8-15 years, and ≤11 if ≥16 years. Eligibility is determined through a telephone or in-person prescreening followed by an in-person screening visit including audiometry (or review of recent audiometric data). Confirmatory audiometric testing is conducted at the baseline visit. Figure 1 illustrates our screening and randomization procedure, and Table 2 lists specific inclusion and exclusion criteria. Notably, both English and Spanish speakers are included in our study.

Recruitment

Recruitment for EARHLI is scheduled to begin in February 2024 and is expected to be completed in June 2027. Participants are recruited from clinical practices affiliated with the Departments of Neurology and Otolaryngology—Head and Neck Surgery at the primary institution and local community institutions. Recruitment strategies include direct outreach using pre-existing research registries; listing on ClinicalTrials.gov (NCT06174038); advertising inside otolaryngology, audiology, and neurology practices; and advertising on the departmental website(s), a study-specific website (www.earhli.org), social media, newspapers, flyers, and public transportation.

Randomization

Randomization will be overseen by the EARHLI Data Coordinating Center. Eligible participants will be randomized in a 1:1 ratio to either the hearing intervention or comparator health education group using a block-type randomization procedure; groups with an even number of eligible participants will be randomized to achieve a balance of treatment assignment. Participants will be randomized 1:1 to receive MRI or not on a rolling basis.

Hearing and Covariate Measures

A standard hearing evaluation will be conducted in a sound-treated booth. This will include pure tone bone and air audiometry and word recognition. We will also measure speech recognition in background noise with the Words-in-Noise (WIN) test. We will also collect demographic information, medical history, hearing health history, and labs (APOE genotyping and plasma amyloid positivity). Hearing aid usage will be measured by self-report and by objective hearing aid data logs[39].

Blinding

Because blinding is not feasible for participants or technicians collecting outcome data, we will minimize bias through strategies based on recommendations for blinding in nonpharmacological trials[40] as well as previous work in the ACHIEVE trial. These precautions include using an attention control intervention, masking participants to the study hypothesis, standardizing data collection protocols, preventing access to prior cognitive testing results, and masking trial data from key staff.

Study interventions (hearing intervention vs health education)

Participants will be randomized to either a best practice hearing intervention or a health education comparator (control) program. The EARHLI hearing intervention is based on a best-practices intervention[35] developed in line with professional guidelines and past research[41] and used in the ACHIEVE Feasibility and Pilot studies[16,35,42], the ongoing ACHIEVE RCT[16,43], and piloted among Spanish-speakers and the target age group (55-75 years). The hearing intervention is designed to be delivered over 4 sessions (Table 3; A, B, C, D) across 8 weeks with a later booster session (Table 3; E). Each session takes ~75 minutes. The main objectives are to improve audibility, with its hypothesized effects on social engagement and brain organization/connectivity, thus reducing the activity and participation restrictions of early ARHL. To achieve these objectives, the hearing intervention includes an auditory needs assessment, prescription hearing aid fitting (Phonak AG, Switzerland) with real-ear verification, establishing Bluetooth connectivity from hearing aids to devices such as smartphones and computers, systematic orientation and instruction in device use, and provision and discussion of hearing “toolkit” materials for self-management and communication strategies. All written materials provided as part of the hearing intervention are available in both English and Spanish. The hearing intervention is person-centered, focusing on identification of individual needs, setting of specific goals, engagement in shared-informed decision-making, and development of self-management abilities. Additional visits to troubleshoot hearing aids or address concerns are scheduled as needed.

The comparator intervention is a health education program. This program has been previously effectively implemented as a comparator in other clinical trials[36,44–46], including the recently completed ACHIEVE RCT[37,43]. It serves as an attention control to maintain the same interpersonal interaction as the hearing intervention arm[47,48]. The comparator is customized to exactly match the number and length of sessions as the hearing intervention, including compliance and phone checks. Table 3 describes components of each session. To improve recruitment, increase adherence, and alleviate ethical concerns about denying

participants treatment for hearing impairment, participants who receive the comparator intervention are placed on a waitlist to obtain the EARHLI hearing intervention without fee at the end of their 12-month participation.

The curriculum follows the protocols of the 10 Keys to Healthy Aging developed by the Center for Aging and Population Health at the University of Pittsburgh[36]. This evidence-based interactive health education program is designed for older adults and addresses chronic disease and disability prevention. Session content will be individualized for each participant based on these "keys" similar to ACHIEVE. It is available in both English and Spanish. To remove concern of improved social engagement (a trial outcome) in the comparator arm, a social contact key was replaced with a caregiving key.

Outcomes

Outcomes are divided across three main focuses (aims): cognitive performance, social engagement, and brain organization/connectivity. The primary outcome is global cognition as described below. Secondary outcomes include additional measures of cognition, social engagement, and brain organization/connectivity. Most outcome measures will be assessed at the study start (0 months), midpoint (6 months), and end (12 months). MRI measures, including brain organization/connectivity, will be recorded at 0 and 12 months in approximately half of all participants (randomized 1:1).

Before all outcome tasks, we will ensure participants understand spoken instructions according to previously developed protocols[16,49]. This will reduce the chance that participants answer wrongly because of hearing rather than, for example, their cognitive ability. Briefly, the examiner will read sentences with key words. If participants cannot read back the majority of the key words, the examiner will repeat at a louder voice. This louder voice will be used for the remainder of testing. If the participant can still not read back the words, then subsequent testing will proceed at the louder voice and written instructions will be provided to supplement verbal instructions. As an additional step, subjects will repeat instructions before a task to ensure understanding.

Aim 1: The primary outcome for which the study was powered is global cognition, measured with the Alzheimer Disease Cooperative Study-Preclinical Alzheimer Cognitive Composite (ADCS-PACC) as the primary outcome. This measure was originally designed to serve as a primary outcome for trials conducted at the asymptomatic phase of AD.[50] It includes 4 tests: (1) Free and Cued Selective Reminding Test (FC-SRT; episodic memory), (2) delayed (paragraph) recall score on the Logical Memory IIa subtest from the Wechsler Memory Scale (episodic memory), (3) Digit Symbol Substitution Test, from the Wechsler Adult Intelligence Scale-Revised[51] (processing speed), and (4) Mini-Mental State Examination 2[52] (global cognition). The composite score is determined from its components using an established normalization method. Each of the 4 component change scores is divided by the baseline sample standard deviation of that component to form standardized scores. Secondary cognitive outcomes include executive function (measured by the Trail Making Test Part B[53]), episodic memory (measured by the Free and Cued Selective Reminding Test, as well as the delayed recall score on the Logical Memory Iia subtest, both part of the ADCS-PACC), speed of processing (measured by the Digital Symbol Substitution

Test, part of the ADCS-PACC), and function (measured with the ADCS-Activities of Daily Living-Prevention Instrument, or ADCS-ADL-PI[54]).

Aim 2: The main outcome for social engagement is social activity frequency. Participants are asked on a 5-point scale how often during the past 6 months they engaged in several common activities involving socialization, and a composite score is created[18,55]. Secondary social measures include the Community Integration Measure (CIM, a 10-item measure on a 5-point scale assessing the underlying experience of community integration and participation[56,57]); Cohen's Social Network Index (a 12-item survey assessing participation in different types of social relationships[58]); and the UCLA Loneliness Scale (a 20-item measure assessing social isolation and loneliness on a 4-point scale[59]).

Aim 3: The main outcome for brain organization/connectivity is cross-modal reorganization measured on functional magnetic resonance imaging (fMRI) scans. Activity in the primary (Heschl's gyrus), secondary, and association auditory cortices is measured while subjects attend to or ignore moving dots in the visual periphery[60]. These measures will be used to examine top-down (attentional) and bottom-up (sensory) cross-modal plasticity in auditory cortex as a result of chronically untreated ARHL[15]. Additionally, we include secondary measures of resting state functional and structural connectivity. Intra-network connectivity will be measured among the brain's major functional networks. For resting-state data, we will focus on the frontoparietal control, auditory, visual, and default mode networks. Structural connectivity will be measured as mean diffusivity of white matter pathways and will focus on pathways between auditory cortex and the superior temporal sulcus, supramarginal gyrus, intraparietal sulcus, and occipital cortex[61].

Potential covariates include both demographic and medical factors. Both apolipoprotein E (*APOE*) genotype for alleles ε2, ε3, and ε4 and baseline plasma amyloid positivity using pTau-181 (which, counterintuitively, highly correlates with amyloid level) will be explored as effect moderators of the intervention.

Statistical Analysis

Extensive power calculations were performed for primary and secondary outcomes; those related to the primary outcome are described briefly below. For the primary outcome (global cognition as measured by the ADCS-PACC), with baseline and two follow ups, it is assumed that σ (standard deviation) = 2.4. The primary analyses assume intent-to-treat (ITT), α = 0.05 for a two-tailed test. However, effects assuming 10% attrition, with n = 67 per group at 1 year study end are also examined. With an n = 75 per group at baseline, it will be possible to detect an effect size of δ = 0.936 (Cohen's d = 0.390), with power of 0.80. With the correlation between baseline and follow up equal to 0.6, the Cohen's d = 0.367 (which translates to an effect size of δ = 0.881). Examining different scenarios regarding the difference between the groups and the correlation structure of compound symmetry, or autoregressive, the detectable effect sizes range from δ = 0.746 (Cohen's d = 0.311) to δ = 0.936 (Cohen's d = 0.390) with power of 0.80.

The analyses for the primary outcome will examine differences in ADCS-PACC with an ANCOVA-type model, using SAS Proc Mixed to allow for flexible modeling of

assumptions, treatment of missing data, and inclusion of all subjects with at least one wave of data. Based on prior analytic experience with the outcome variables, it is not expected that transformations will be necessary; however, distributions will be examined for confirmation. The continuous longitudinal outcomes will be modeled as functions of baseline values, randomization group, and covariates if necessary. Prior to analyses, baseline values will be examined. Variables that differ between the groups will be examined in secondary analyses.

EARHLI is an early phase II study; thus, for secondary outcomes an alpha level of 0.10 was specified as a criterion to advance to a phase III clinical trial. The analyses of secondary outcomes will examine domain-specific cognition, social engagement, and brain organization/connectivity with covariate adjustment if necessary. Model robustness will be checked with the SAS GEE procedure, a quasi-likelihood formulation useful in accounting for missing data and handling continuous covariates that may be time dependent. The shape of the change trajectory for continuous variables will be examined, and linear and mixed linear models will be checked in sensitivity analyses as appropriate.

Primary analyses will be based on the ITT population, which includes all randomized subjects. A secondary analysis of primary outcomes will be completed for the Per-protocol population, which is a subset of the ITT population who completed the 8-10-week intervention period without hearing aid intervention drop-in for the control group and major protocol deviations. Major protocol deviations include violations in inclusion and exclusion criteria at enrollment and poor compliance with hearing aids for the hearing aid intervention group. These deviations will be identified before database lock in a blinded manner.

We will advance to a phase III trial if we find an effect estimate favoring the intervention for the primary outcomes or any of the secondary outcomes with a two-sided $\alpha = 0.1$, and no effect estimates suggest harm. If only the secondary outcomes meet the benefit and significance criteria, we will consider another phase II, or a phase II/III study. If there is no evidence of benefit for any outcomes, we will not proceed to a larger trial.

Safety

Although study enrollment and participation in either intervention is expected to have a low risk of adverse events, detailed information concerning a pre-specified set of adverse events (otitis externa, cerumen impaction, or ear foreign body requiring removal by a physician) and serious adverse events (death from any cause) will be collected and evaluated throughout the trial. Participant safety will be monitored by an independent safety officer, as stipulated by the National Institute on Aging (NIA).

Data Sharing

Biospecimens, clinical data, and analytical methodology will be broadly shared. This will occur at the time of publication of the primary results or within 9 months of database lock, whichever comes first. All datasets used/generated on the project will be made accessible and reusable by qualified individuals via web-based resources with the capacity to store large and diverse datasets (such as data about audiometric configuration, clinical phenotypes, and APOE status). All analytical methodologies will be made to be fully

reproducible and transparent so that results can be vetted and existing analysis techniques applied to new application areas.

Discussion

Hearing loss has been implicated in a variety of deleterious clinical and social phenomena, such as dementia[3,4,12], depression[62,63], and social isolation[64]. Recognizing and treating ARHL has the potential to mitigate a wide variety of poor outcomes in older life, but crucial RCT-level evidence is lacking. For example, in 2021 the United States Preventative Services Task Force reported that it could not assess the balance of risks and benefits of routine hearing loss screening in older adults, citing insufficient high level evidence[65].

EARHLI builds upon the methods and design of the recently completed ACHIEVE RCT, which also examined the effect of a hearing intervention on cognition[37,43]. While ACHIEVE focused on older adults (70-84 years) with more advanced ARHL (pure tone average <70 dB HL), EARHLI focuses on adults in midlife and early older age (55-75 years) who have less hearing loss (pure tone average <55 dB HL). Additionally, EARHLI will study brain organization/connectivity as a mechanism, whereas ACHIEVE only examined brain structural changes such as regional volumes. By focusing on a population mostly unrepresented by ACHIEVE and including additional social engagement and brain organization/connectivity outcomes, EARHLI will offer unique and novel insights on the potential impact of hearing interventions on cognitive decline at a timepoint where intervention could have the greatest effect. It will also better characterize possible mechanisms underlying the relationship between hearing loss and cognitive decline. If the results meet pre-specified targets, we will plan to apply for funding a larger and longer-duration phase III RCT.

Trial enrollment will begin in February 2024. Upon its completion in 2027, EARHLI will provide evidence on the role of hearing interventions on cognitive decline in community-dwelling adults in midlife to early old age with early age-related hearing loss and amnestic mild cognitive impairment.

Conflicts of Interest and Sources of Funding:

JSG: Alcon (advisory board).

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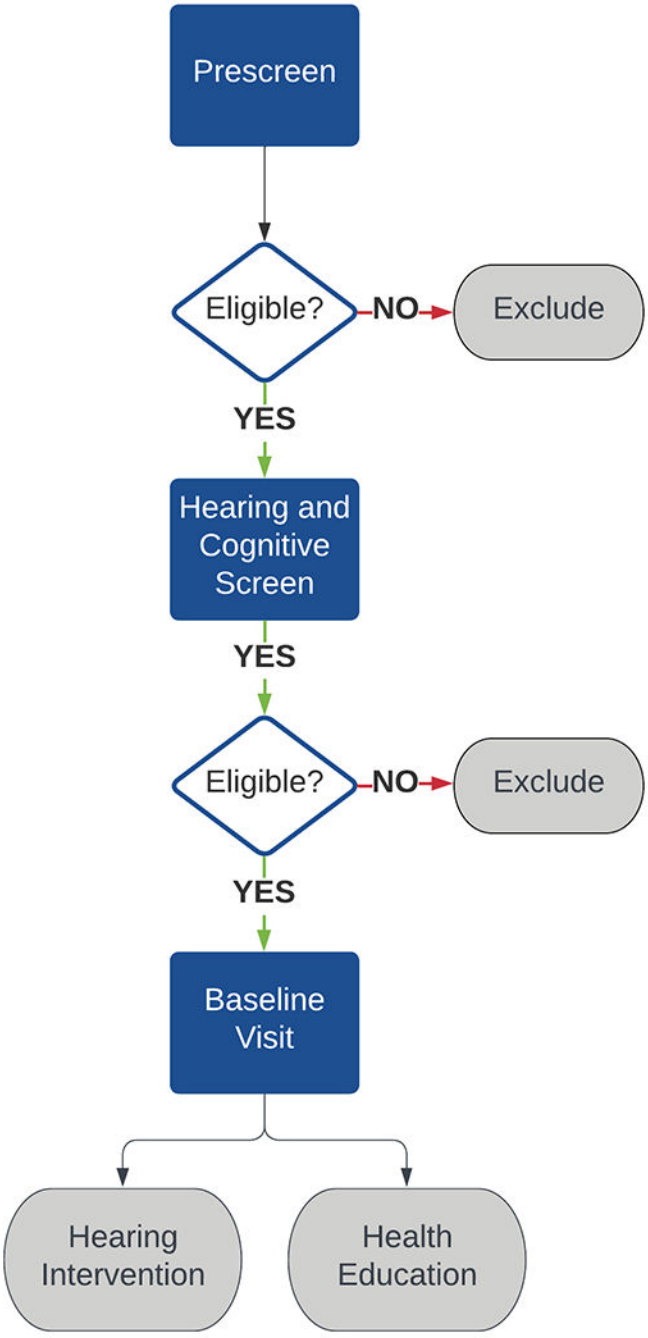

Figure 1:
Process diagram of participant screening and randomization for the Early Age-Related Hearing Loss Investigation (EARHLI) Randomized Controlled Trial

Table 1:

Study timetable per individual participant

	Weeks into Trial															
Timepoint	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Screening, Hearing Test, Randomization, Labs																
Intervention Session* *(See* Table 3*)*		A	B	C	D					E						
Intervention Compliance Assessment*																
Phone Check*																
Assessments																
Cognitive Tests																
Social Inventory																
MRI Scan**																
Adverse Events Check																

* Visit content will depend on whether participant is in the hearing intervention or comparator intervention group.

** Approximately half of participants will be scanned using MRI.

Table 2:

Inclusion and exclusion criteria: the Early Age-Related Hearing Loss Investigation (EARHLI) randomized controlled trial

Criteria	Description
Inclusion	• Age 55-75 years of age • Adult-onset hearing loss of approximately borderline to moderate in severity (4-frequency 0.5, 1, 2, 4 kHz pure tone average 20 dB to 55 dB HL in better hearing ear) • Aidable hearing loss, defined by word recognition score in quiet ≥60% in better hearing ear • Amnestic MCI defined by MMSE-2 score > 23, CDR global score equivalent = 0.5, and ADNI3 criteria of Logical Memory II score of ≤6 if 0-7 years of education, ≤9 if 8-15 years, and ≤11 if ≥16 years • Availability of a study partner (informant) for the administration of the cognitive screen and the ADCS-ADL-PI • Community-dwelling • Fluent in English or Spanish • Availability of participant in area for study duration
Exclusion	• Self-reported congenital hearing loss, known genetic mutation-related hearing loss, or hearing loss onset before middle age (< 45 years old) • Prior dementia diagnosis • Current or previous consistent hearing aid user (such as utilization of hearing aids within the past 6 months beyond brief trials) • Unwillingness to wear hearing aids regularly (≥8 hours/day) • Medical contraindications to the use of hearing aids (e.g., actively draining ear) • Reported disability in ≥2 ADLs • Corrected vision impairment (worse than 20/63 on MNRead acuity chart in worse eye) • Untreatable conductive hearing loss with air-bone gap > 15 dB in two or more contiguous octave frequencies in both ears

Abbreviations: HL, hearing level; MCI, mild cognitive impairment; MMSE-2, Mini-Mental State Exam 2; CDR, Clinical Dementia Rating; ADNI3, Alzheimer's Disease Neuroimaging Initiative 3; ADCS-ADLPI, Alzheimer's Disease Cooperative Study-Activities of Daily Living-Prevention Instrument; ADLs, activities of daily living

Table 3:

Overview of Intervention Session Components

Session	Hearing Intervention (Hearing Aid)*		Comparator Intervention (Health Education Program)*
A (Week 1)	• Hearing-related goal setting • Hearing aid fitting, verification, orientation, instructions for use/care	Education and counseling: • Written and multimedia-based hearing loss self-management materials related to participant's individual loss and hearing-related goals • Discuss specific strategies e.g., for background noise, communication, assistive listening technologies	• Build rapport and trust • Choose healthy aging "keys" to focus on, goal setting with Prevention in Practice report • Initial education
B (Week 2)	• Hearing aid verification, programming, adjustment, listening/visual check, usage recorded (data logging)		• Continued education • Discussion of healthy aging keys selected/matched to goals • Check-in on progress with prior discussed keys, goals
C (Week 4)			
D (Week 8)			
E (Week 28)			

*Number and duration of sessions, as well as social contact, is the same for both interventions.