Research Protocol *(9 pages)*
Hearing Aids to Support Cognitive Functions of Older Adults at Risk of Dementia: the HearCog trial

Study Summary

Dementia is the leading cause of disability among Australians aged 65 or older and also the second leading cause of mortality.[1] Nearly 400,000 Australians are currently living with dementia and, without a cure, this number is projected to reach 1.1 million over the next 30 years, with an estimated cost to the Australian community of more than $36.8 billion.[2] Developing effective strategies to prevent dementia has become a global health priority, with projections suggesting that the total number of people living with dementia could be reduced by 13% (or about 400,000 people) if the onset of symptoms could be delayed by 2 years or more.[3] The Lancet Dementia Taskforce, co-authored by one of our team members (AI Ames), concluded that hearing loss could account for 9% of all cases of dementia.[4] Age-related hearing loss (ARHL) is a highly prevalent form of sensory impairment in later life, affecting 40% to 45% of people aged 65 years and 83% of those aged 70 years or above.[5] At present, it is unclear if the reported association between hearing loss and dementia is causal and if the clinical remediation of sensory impairment could reduce the rate of cognitive decline among older adults at risk of dementia. We have assembled a group of accomplished hearing and dementia experts to address this question. The study will also explore the cost- effectiveness of the intervention compared to the control arm.

Primary aim

This study will determine whether correction of hearing loss through the use of hearing aids (HA) decreases the 12-month rate of cognitive decline among older adults at risk of dementia.

Secondary aims

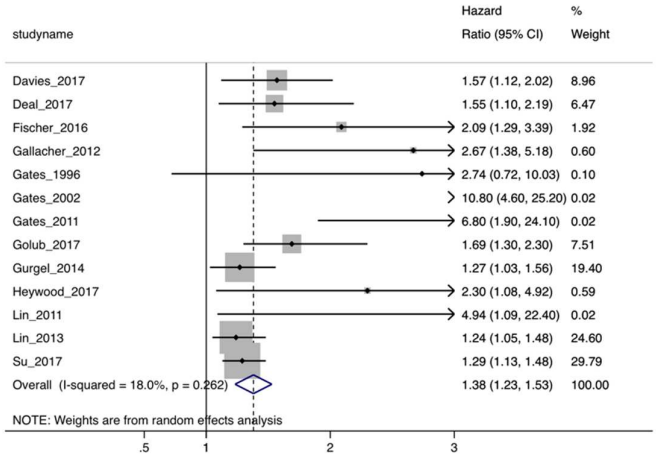
We will also investigate whether the correction of hearing loss has a beneficial impact on memory and executive functions, anxiety and depressive symptoms, quality of life, physical health, and health-related costs over 12 months. In addition, we will seek to clarify if the expected clinical gains achieved through the correction of hearing loss by 12 months can be sustained over an additional period of 12 months, and if losses experienced through the non-correction of hearing loss can be reversed with the fitting of HAs after 12 months (i.e., HAs fitting for controls at 12 months with follow up of 12 months).

Background

Hearing loss is the second highest cause of disability in the world, affecting 1.33 billion people,[6] with 90% of cases being due to age-related hearing loss (ARHL).[6] One in six Australian adults suffer from a hearing loss > 25dBHL and this number is projected to increase up to one in four by 2050.[7] Moreover, 88% of Australians aged 70 years or above have > 25 dBHL hearing loss in their worse ear.[7] There are two key components of the auditory system involved in processing incoming auditory stimuli: the peripheral and the central hearing systems.[8] The peripheral hearing system consists of the peripheral components of hearing, namely the cochlea, middle ear and outer ear.[8] The central hearing system encompasses the central auditory pathways and influences the way incoming auditory stimuli are perceived and understood, namely central auditory processing.[8] Peripheral hearing loss affects both the auditory processing of speech sounds and the higher-level cognitive functions required to process linguistically demanding sentences.[9] Evidence from both cross sectional[10] and longitudinal[11,12] studies confirmed the existence of an association between peripheral hearing impairment and cognitive impairment in older adults. Several recent studies have also reported an increase in the risk of incident dementia among older adults with ARHL,[11,12] as well as among those with central auditory dysfunction.[13]

Hearing loss and the prevention of dementia

We have completed a meta-analysis of available longitudinal studies investigating the association between hearing loss and dementia and found that, on average, hearing impairment was associated with 38% increase in the hazard of dementia (right side panel). Australian data from the Health In Men Study (APP1128083) indicate that the hazard of dementia associated with hearing impairment was 1.69 (95%CI=1.54,1.85) – Ford et al., 2018 (in press).



According to currently available evidence, the incidence of all cases of dementia can be reduced by 9% if ARHL was eliminated, perhaps through hearing loss correction.[4] As an example of potential changes in outcome measures following hearing loss correction, we have recently reported that cochlear implant recipients performed substantially better on general measures of cognitive function compared with implant candidates on a waiting list.[14]

Whether the correction of ARHL can delay the onset of dementia remains to be determined. However, treatment of ARHL is an extremely low risk procedure that is associated with significant health, social and safety benefits. Hence, our study aims to investigate whether the correction of hearing loss through the use of HAs could decrease the 12-month rate of cognitive decline among older adults at risk of dementia. This project will allow us to investigate the effect of severity of impairment on cognitive outcomes.

Pilot data: We recruited 19 normal hearing (NH) older adults, [better ear four frequency average .5, 1, 2 & 4 kHz (BE 4PTA) =13.06 dB, better ear high frequency average of 6 & 8 kHz (BE HF 2PTA) = 14.93 dB], 35 hearing impaired (HI) older adults who did not wish to use a HA, [M = 70.2 $\pm$ 6.7 years, BE 4PTA= 31.92dB, BE HF2PA = 54.07 dB] and 13 HA users (HA), [M = 71.8 $\pm$ 7.4 years, BE 4PTA 33.46 dB, BE 2HFPTA = 55.57 dB] older adults. All participants completed hearing and a non-verbal cognitive assessment using the CANTAB test battery (details below), and repeated assessments after 6 and 12 months (HA fitted after the baseline assessment). Analysis of variance revealed that the HA group performed significantly better than the HI group on delayed matching-to-sample (DMS) ($p = .02$) (Figure 2), spatial working memory (SWM) between errors ($p = .02$) and strategy ($p = .006$), and Rapid Visual Processing (RVP) mean latency ($p = .03$).

Further analysis revealed that of 7/35 HI and 5 /35 HA participants could be classified as having mild cognitive impairment (MCI) according to the Montreal Cognitive Assessment for the Hearing Impaired (MOCA-H) (see details about the instrument below). Those with normal cognitive scores (MOCA-H) are reported as NL. The figure on the right panel summarises the results on the DMS task. Participants with MCI treated with HAs showed improved memory performance compared with untreated group, although the power of the analysis was limited by the small number of participants (Figure 3).

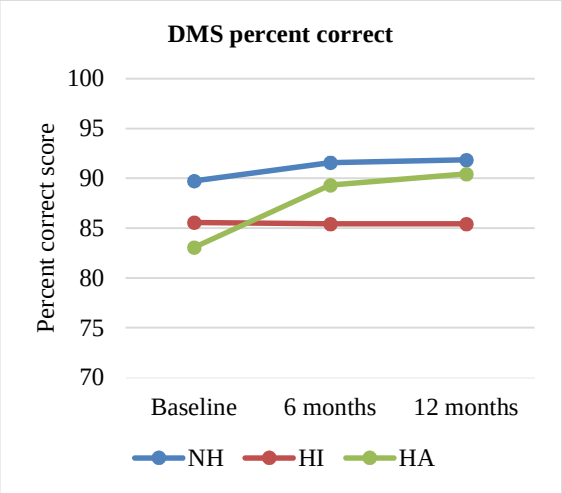


Figure 2. DMS scores for all participant groups.

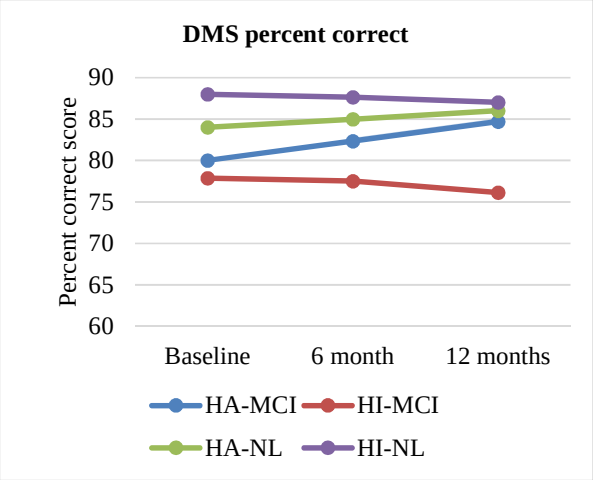


Figure 3. DMS scores for participants with and without MCI

Taken together, these results offer strong support for the rationale of this study: hearing loss is associated with an increased risk of dementia (as confirmed by our meta-analysis), and the use of HAs is associated with improved memory performance over 12 months, including among those at risk of dementia because of the presence of MCI.

Methods

Study design: Two-arm parallel randomised controlled trial.

Setting: Ear Science Institute Australia (ESIA) based in the Perth and Bunbury metropolitan regions, Western Australia.

Eligibility criteria:

- Participants will be older adults aged 70 years or older (cognitive decline is more pronounced later in life).
- Montreal Cognitive Assessment for the Hearing Impaired (MOCA-H)[15]≥ 18 and < 26 (mild impairment).
- Better ear average hearing loss at 0.5, 1 & 2 kHz (3FAHL) ≤ 23 dB or high frequency average hearing loss (2, 3 & 4 kHz) (HFAHL) ≥ 40dB as measured using air conduction pure-tone audiometry.[16] We have followed the HA fitting criteria recommended by OHS for older adults with ARHL.[16]
- Fluent English speakers

Exclusion criteria:

- Impaired instrumental activities of daily living (IADL)[17] due to cognitive deficits (requires assistance or is dependent in the use of telephone, shopping, housekeeping, laundry, transport, management of medications and finances) – i.e. has dementia or major neurocognitive disorder
- Meets clinical criteria for cochlear implantation (unaided bilateral sensorineural hearing loss ≥70 dBHL, and open-set sentence scores in quiet in the worse ear < 65% and in the better ear < 85% or open set phoneme scores in quiet in the worse ear < 45% and in the better ear < 65% with optimized HA fitting[18]
- Visual impairment that limits participant's ability to read Times New Roman font size 16 (a requirement for 2 sentences of MOCA-H)[15]

- Severe medical illness that limits the ability of the participant to attend appointments or sustain participation in the study for 24 months
- Plans to move away from the study area during the subsequent 24 months
- Unable or unwilling to provide written informed consent to participate
- Inability to complete the motor screening task (MOT) module of the Cambridge Neuropsychological Test Battery (CANTAB) due to visual impairment, inability to comprehend test instructions or inability to attend to the task due to dexterity problems.[19]

Recruitment: We will use established networks of the researchers and their respective clinical services to recruit participants (memory clinics and audiology centres). In addition, we will place advertisements in the local media and primary care networks inviting interested participants for screening. If the recruitment of participants is lower than predicted after 12 months, we will use the electoral roll list to select a random list of people aged ≥ 70 years living the study areas: they will receive information about the study and an invitation to contact the research office for screening if they believe they may potentially eligible (mail out is de-identified – i.e., investigators will not have access to the list). We have used this approach successfully in other studies (e.g., APP572594). The research assistant will contact those who have expressed interest in taking part in the study and volunteers will complete a hearing and cognitive screening at the nearest ESIA Hearing Clinic. The participants will not receive any payment for participating in the study; however, they will be reimbursed for cost of travelling.

Sample size: Based on DMS percent correct pilot test data, a total of 140 participants will be required (70 in each group; effect size d = 0.28, α = .05, power .90). To account for 25% of attrition over time, a total of 180 participants will be recruited.

Study measures:

1. Global cognitive abilities: Due to hearing impairment, the elderly may experience difficulty in following verbal instructions or completing tasks that heavily rely on hearing during cognitive assessments. This may result in overestimation of cognitive impairment in such individuals.[10] Hence, we have used a non-verbal global cognitive measure that has been validated to use with the hearing impaired older adults.[15] The global cognitive abilities will be measured using Montreal Cognitive Assessment for the Hearing Impaired (MoCA-H).[15] No significant difference was observed for MOCA and MOCA-H scores in cognitively intact normal hearing participants and the test–retest reliability coefficient was 0.66.[15]

2. Nonverbal cognition assessment using Cambridge Neuropsychological Test Battery (CANTAB)[19] - This assessment does NOT rely on verbal communication:

- *Attention Switching task (AST):* is a test of executive functioning and provides a measure of cued attentional set shifting.[19] AST is based on the Stroop test and relies heavily on the functions of the anterior right hemisphere and medial frontal structures.
- *Delayed Matching Sample (DMS):* assesses participants' ability to recognize complex visual patterns at different time intervals.[19] It is primarily sensitive to medial temporal lobe dysfunction.
- *Paired Associates Learning (PAL):* PAL is a recall test of memory which assesses episodic visuospatial memory, learning and association ability.[19] PAL is primarily sensitive to the changes in medial temporal lobe functioning.
- *Spatial Working Memory (SWM):* measures the retention and manipulation of visuospatial information in areas such as non-verbal working memory, working visuospatial memory and strategy use.[19]

3. General physical & mental health: Participants will be asked to complete the following widely used and validated assessments:

- Cognitive reserve questionnaire to obtain information on participant age, gender, education, work history and leisure activities[20]
- Health status and Quality of life: Short form survey (SF-12)[21]
- Physical function: Functional Comorbidity Index (FCI)[22]
- Depressive symptoms: Patient Health Questionnaire (PHQ-9)[23]
- Anxiety symptoms: Geriatric Anxiety Inventory (GAI)[24]
- Function: Lawton & Brody Instrumental Activities of Daily Living (IADL)[25]
- Social Support and interaction: de Jon Gierveld social support questionnaire[26]
- Frailty: hand grip strength will be measured using a Jamar Analogue Hand Dynamometer [27]
- Psychological and social adjustment problems resulting from hearing loss: Hearing Handicap Inventory of the Elderly (HHIE)[28]
- Effectiveness of the HAs application: International Outcome Inventory for HAs (IOI-HA)[29].

4. Hearing Assessment: The assessment of hearing will consist of two parts:

- Peripheral hearing assessment will be based on tympanometry, which provides information about middle ear pathologies; pure-tone audiometry, which generates information on hearing thresholds across .25-8 kHz frequency range; and speech perception in quiet environment: CNC word [30] and City University of New York (CUNY) sentence test[31]
- Central hearing assessment will comprise of the following tests: Dichotic Digits Test (DDT),[32] Synthetic Sentence Identification with Ipsilateral Competing Message (SSI-ICM),[33] and Quick Speech in Noise (Quick-SIN).[34]

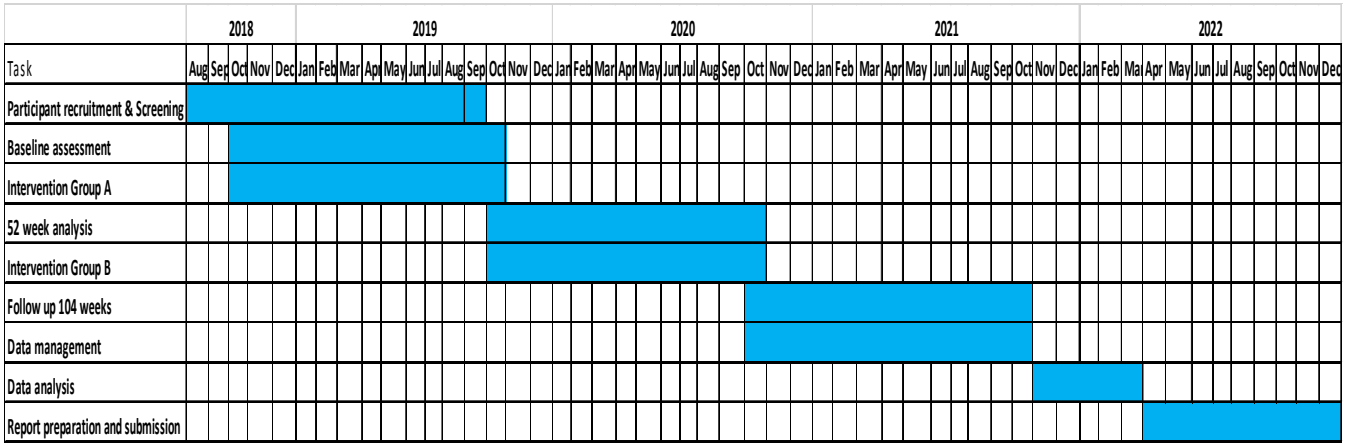
Procedures for the collection of study measures:

The procedure for the data collection will follow CONSORT guidelines. Participants who meet criteria for inclusion in the study will be randomly assigned to either the experimental (A) or control (B) group. Group A participants will receive intervention immediately after the baseline assessment, whereas group B participants will receive intervention 12 months later (Figure 5). All participants will be informed that if they get randomly allocated to group B, they will have to wait 12 months to receive the treatment. Those who prefer to receive HA immediately without having to wait 12 months will be given the option to opt out from the study. Cognition, mental health and QoL assessments will be carried out separately to the hearing assessments and HA fitting.

Group A will complete hearing assessment, cognition, mental health and QoL assessment at the baseline, 12 and 24 months.

Group B will complete hearing assessment, cognition, mental health and QoL assessment at the baseline and 12 months. (Figure 5).

Timeline for the collection of study measures:



Intervention:

The intervention consist of three parts: (i) hearing assessment and HA discussion, (ii) HA fitting, verification and validation and (iii) HA review following daily use of HAs.

The intervention will be carried out by a qualified audiologist according to the Australian Audiological Society Standards in a standardised sound proof booth.

Part I: Hearing assessment and HA discussion

Duration 1.15 hours.

During the first appointment, the participant will complete (1) a comprehensive case history that contains information on medical and hearing history, ear infections, ear surgeries, head trauma, noise exposure, ototoxic drug exposure, visual and dexterity problems, tinnitus, vertigo, and cognition. (2) Client Oriented Scale of Improvement (COSI) goals[35] for everyday listening situations and a standard hearing assessment. Finally, we will discuss with participants currently available technology of HAs that include suitable type and style of HAs and their cost, as well as participant's daily listening expectations. The choice of hearing aid will be based on hearing loss, subject preference and ease of management. An explanation on what are hearing aids and how they work, what they are used for, how to use them, and questions and answers will be provided. Study participants receiving the intervention will also be given an educational booklet summarizing the topics presented.

A HA is a device designed to improve hearing by amplifying and acoustically modifying the sound to suit a person's hearing loss. Current HA technology uses digital signal processing techniques to improve speech intelligibility and provide comfort for the user.

Part II: HA fitting, real-ear verification and validation -immediately following appointment part I.

Duration: 1 hour.

The audiologist will program the HA and carry out the real-ear verification using real ear insertion gain (REIG) to ensure that appropriate amplification is provided to a person with hearing loss.[36] The HA program will be fine-tuned to fit the participants' every day listening demands using NAL-NL2 formula[36]. Following, HA out-put verification, validation tasks will be carried out to determine that the participant is benefitting from the HAs. Validation includes asking the patient about sound quality, ear balance, comfort of the devices and finally a speech in quiet assessment using AB word list[37] will also be carried out to determine that the participants is benefitting from the HAs. Adjustments can be made to the devices so that the patient is comfortable with the devices.

Part III: HA review: 2 weeks after the HA fitting.

Duration: 30 minutes.
HA data logging information recorded in the software of the HA is analysed to ensure that the HA program provides the best solutions to the listening demands of the participant. Based on COSI goals, data logging information and feedback received from the participants, changes are made to the HA program.

HA review appointments at 12 and 24 months after HA fitting:
Duration: 1 hour.
These appointments are similar to Part II and III of the HA fitting appointments. During these appointments, a standard pure-tone audiometric assessment to obtain hearing thresholds, reprogramming of the HA according to the current hearing loss and finally REIG to ensure that the HA is programmed according to the current hearing loss of the participant will be carried out.

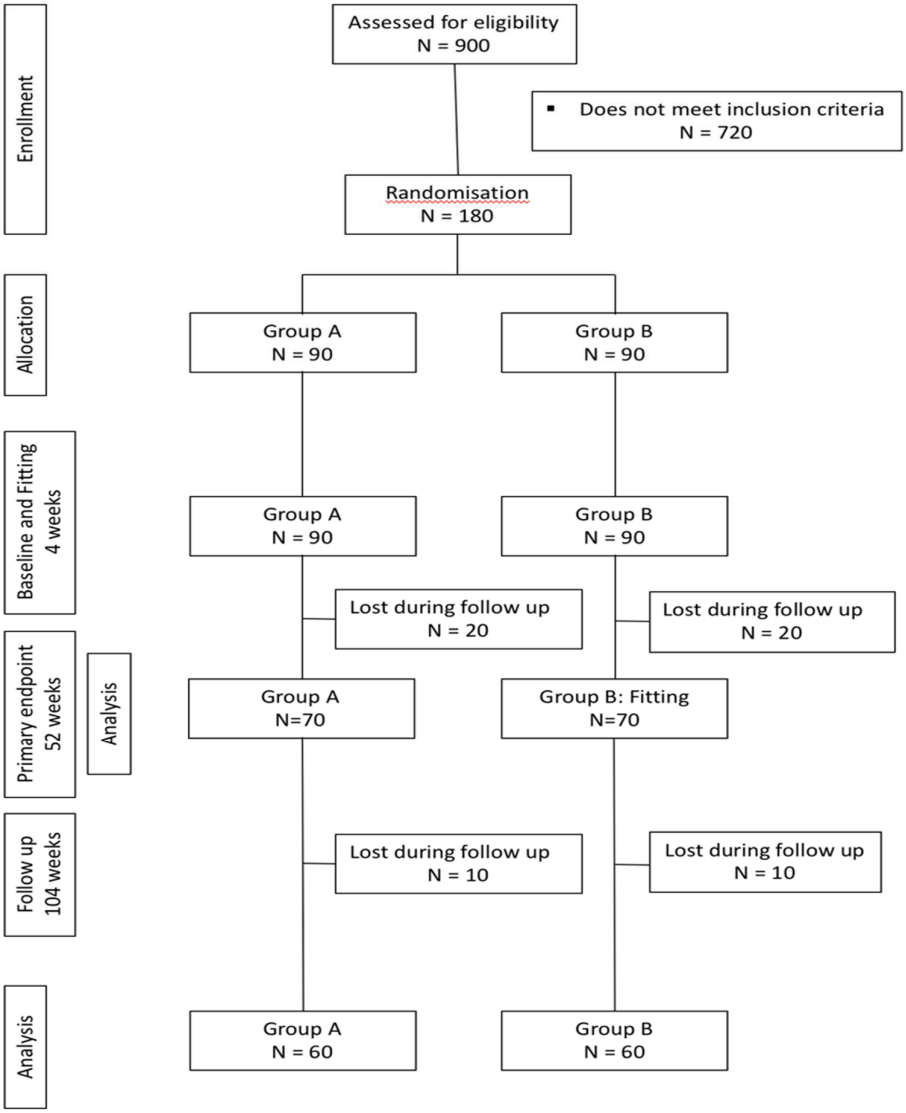


Figure 5: Flow of participants from the time of recruitment to the final collection of endpoints.

Measuring adherence with treatment: Current HAs have a "log in" feature that records both the average number of hours and different listening environments in which the participant has used the HA. These data can be retrieved when the HA is connected to the program software, which will be done at all assessments. In addition, the participant will be asked to maintain a daily listening diary in which s/he records the number of hours the HA worn.

Randomisation, concealment and blinding: This trial will be registered with the Australian and New Zealand Clinical Trials Registry before recruitment commences (http://www.anzctr.org.au). The computer generated randomisation sequence will be stratified by the severity of the hearing loss (mild to moderate vs severe) based on the results of the hearing assessment. Each stratification block will be associated with a random sequence of numbers assigned to the intervention and control groups in random permuted blocks of 6, 8 or 10. This sequence will be stored in a password-protected server housed at the University of Western Australia and will be managed by a biostatistician not involved in this project (A/Prof Kieran McCaul). Once a participant consents and is enrolled, s/he will be automatically ascribed a number and group membership (intervention or control).

Due to the nature of the intervention, participants will know their group assignment, but research staff involved in the assessment of cognitive function, quality of life, mood and physical function will remain blind to treatment allocation. This will be achieved by directing participants to **NOT**: (i) discuss any aspects of the intervention during the assessments, (ii) wear their HAs during assessment. Binaural hearing amplifiers will be used to facilitate the communication between participants and research staff during all assessment visits (including the 12 and 24-month visits).

Health Economic Analysis: This will involve the development of a model to estimate the incremental cost-effectiveness of the intervention compared to the control. The analyses will be from the perspective of the health service and will be expressed as Quality-Adjusted Life Years gained. A particular focus of the economic evaluation will be a full assessment of the cost of delivering the intervention compared to that of the control group (including the costs of intervention material, costs of procedures, visits to health service provides and medications). Given the feasibility of obtaining health administrative data within the study time frame, we will use a validated patient cost questionnaire to obtain self-reported health care utilisation data.[38] Whilst we recognise the potential for recall bias, there is evidence to suggest that this is a valid method of collecting data on healthcare resource utilization for use in economic evaluations, especially when administrative data is not easily available.[39] Costings information will be applied based on established economic costing methodologies drawing on primary research and secondary national tariffs.[40] The second aspect will include assessment of the effectiveness of the intervention – effectiveness of the intervention and control will be measured using the SF-12 which is widely used in economic evaluations.

Incremental cost-effectiveness ratios will be calculated in terms of the incremental cost per sustained remission and the incremental cost per Quality Adjusted Life Year (QALY) gained by the intervention. The QALY is a widely-used approach for estimating quality of life benefits in economic evaluations. The values obtained from the SF 12 will be transformed into utility weights using the Short Form 6D algorithm [41] to formulate the cost per QALY. Sensitivity analysis will be undertaken to test the robustness of results.

Statistical methods: All analyses will follow CONSORT guidelines. We will use standard descriptive statistics to compare basic sociodemographic and clinical data across treatment arms. We will use multilevel mixed models to investigate changes in cognitive and other scale scores over time. Mixed models provide estimates that are 'intention-to-treat' and allow for the investigation of interactions between group and time effects, as well as for the adjustment of possible imbalances between the groups following the randomisation. We will use imputed chain equations if loss to follow up exceeds 25%. All probability tests will be two-tailed.

Ethics: The trials will comply with the principles of the Declaration of Helsinki for Human Rights and will be overseen by the UWA Human Research Ethics Committees. Written informed structured consent will be required from all participants. None of the assessments or procedures are expected, or known, to cause significant harm, and participants will be free to discontinue involvement if they wish. As we are dealing with a population with, or at increased risk of dementia, treating GPs will receive clinically relevant data. We will also ensure referral to the relevant services to anyone identified to be a significant risk of self-harm. Hearing aids will be available to all study participants, albeit not at the same time.

Strengths and limitations of the study design: This trial follows CONSORT guidelines for the design of randomised controlled trials. The recruitment of participants with mild cognitive deficits was guided by our desire to test a population at risk of dementia (when prevention may be possible) and by the difficulties associated with the consenting of older adults with moderate to severe cognitive impairment. In addition, those with severe to profound hearing loss who meet criteria for a cochlear implant will not benefit from HA amplification, hence, including them would potentially undermine the impact of HA amplification on cognitive functions, mental health and QoL. We acknowledge, however, that our study will focus on cognitive decline rather than conversion to dementia. At this stage, this is a 'proof of concept' investigation, as a dementia prevention trial would require a substantially larger sample and follow up.

Outcomes and sustainability: The results of this study will be published in peer reviewed high impact journals and the results will be presented at national and international conferences. The projected outcomes of the current study can immediately be translated to practice through audiology clinics and will be applicable across practices around the world. Findings can also be used to inform the audiologists, general practitioners and other health-care providers through ESIA Education and Community Care Service Program. This will provide important information for older people about the use of hearing aids to prevent worsening cognitive impairment. In addition, consumer support will be requested in disseminating lay summaries/information to the community.

Significance, innovation and feasibility: Globally, about 47 million people were living with dementia in 2015 with this number projected to triple by 2050[4]. With no cure or effective treatment currently in sight, it is vital that factors are identified which will help prevent or delay both age-related and pathological cognitive decline and dementia. Hearing loss has been suggested as a potentially modifiable risk factor but no conclusive evidence from randomised controlled trials is currently available. The proposed randomised control trial addresses whether hearing loss intervention could delay or arrest the cognitive decline. If cognitive decline can be delayed or arrested, not only that would improve the quality of life of older adults who are at risk of developing dementia but may also lower costs to the healthcare and social support systems, by decreasing the needs for services and residential care placement. It would also significantly reduce the overall burden borne by the community.

This innovative and clinically relevant trial brings together investigators and clinicians with expertise in hearing loss, audiology, dementia and randomised controlled trials. The results of this trial will be clinically meaningful and can be translated into practice. This study will be conducted in collaboration between the Western Australian Centre for Health & Ageing and ESIA Hearing Clinics.

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