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Slowing the progression of age-related hearing loss: Rationale and study design of the ASPIRIN in HEARING, retinal vessels imaging and neurocognition in older generations (ASPREE-HEARING) trial

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Abstract

Background—Age-related hearing loss (ARHL) is a leading cause of disability in the elderly. Low-grade inflammation and microvessel pathology may be responsible for initiating or exacerbating some of the hearing loss associated with aging. A growing body of evidence demonstrates an association of hearing loss with cognitive decline. A shared etiological pathway may include a role of inflammation, alongside vascular determinants. The ASPREE-HEARING study aims to determine whether low-dose aspirin decreases the progression of ARHL, and if so, whether this decrease in progression is also associated with retinal microvascular changes and/or greater preservation of cognitive function.

Design and methods—A three year double-blind, randomized controlled trial of oral 100 mg enteric-coated aspirin or matching placebo, enrolling 1262 Australians aged 70 years with normal cognitive function and no overt cardiovascular disease. The primary outcome is the change in mean pure tone average hearing threshold (decibels) in the better ear, over a 3-year period. Secondary outcomes consist of changes in retinal microvascular indicators, and changes in cognitive function. Participants are recruited from a larger trial, ASPIRIN in Reducing Events in the Elderly (ASPREE), which is designed to assess whether daily low dose aspirin will extend disability-free life.

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Discussion—ASPREE-HEARING will determine whether aspirin slows development or progression of ARHL, and will interrogate the relationship between inflammatory and microvascular mechanisms that may underlie the effects of aspirin on ARHL. This study will improve understanding of the patterns of comorbidity with, and the relationships between, aging and ARHL, alongside modeling the impacts of ARHL.

Keywords

Age-related hearing loss; Presbycusis; Randomized controlled trial; Aspirin; Retinal vessels; Cognitive function

1. Introduction

Hearing impairment is a leading cause of disease burden in older age, with an estimated financial burden at 1.4% of Gross Domestic Product (GDP) in Australia [1]. Mild hearing impairment is defined as an inability to detect low-level sounds (>25 decibel (dB) Hearing Level (HL)) in the better ear after averaging across the sound-frequencies of 0.5, 1, 2, and 4 kHz, while >40 dB HL is considered moderate, causing significant handicap [2]. Prevalence of all hearing loss rises with age, affecting 50% to 75% of people aged 70 years in the US and Australia [1,3–6]. Presbycusis or age-related hearing loss (ARHL) is typified by elevated sound detection thresholds, primarily due to peripheral insults affecting the structure and/or function of the cochlea. In addition, the central auditory system is subject to age-related decline (central presbycusis). The major functional consequences of auditory neural changes are impaired speech perception in background noise and disrupted localization ability [7].

Hearing impairment has far-reaching effects on quality of life in older age [8], resulting in communication difficulties, social withdrawal, embarrassment, reduced self-esteem and depression [9,10]. It is also associated with functional decline, impaired activities of daily living [11], falls [12], hospitalizations [13] and all-cause mortality [14], and has recently been linked to cognitive impairment after adjustment for confounding factors [15,16].

Public health approaches to prevention of ARHL are lacking and treatment is currently limited to modifying disability and handicap through rehabilitation and hearing aids. ARHL will become a more pervasive public health issue as a corollary of population aging. Although some progress has been made to understand the mechanisms of ARHL [17], with established risk factors of age, male gender, race, noise exposure, smoking, and diabetes [18], uncertainty remains about etiology, with no single predominant or potentially modifiable cause yet identified.

2. Rationale for the ASPREE-HEARING study

Low-grade inflammation and microvessel pathology may be responsible for hearing loss associated with aging.

2.1. Aspirin and hearing loss

Aspirin is a key therapy in vascular disease and its use for secondary prevention is widely accepted [19]. Aspirin's action as an anti-inflammatory agent is also well established, with reduction in inflammatory biomarkers evident [20–23]. Animal studies provide evidence of protective effects after ototoxic noise exposure, but to our knowledge there are no studies specifically designed to evaluate the effect of low-dose aspirin on ARHL [24,25], although high-dose aspirin has been found to attenuate gentamicin-related ototoxicity in *humans* [26,27]. It is possible that low-dose aspirin may reduce ARHL through inflammatory and/or vascular mechanisms.

2.2. Inflammation and microvascular disease as potential contributing factors

Changes in the microcirculation of the cochlea have been considered an etiological factor in many forms of hearing loss. Strial atrophy, secondary to strial microvascular degeneration [28] and strial capillary loss are each strongly associated with presbycusis [29], with thickening of basement membranes and strial vascular deposits of laminin and immunoglobulin seen in animal studies [30]. In addition, TNF- α affects microvascular tone and reduces cochlear blood flow by reducing capillary diameter in the stria vascularis in vivo, potentially leading to ischemic intracochlear injury [31].

In older people, white blood cell (WBC) count, neutrophil count and inflammatory biomarkers IL-6 and CRP are significantly associated with elevated average hearing threshold, after adjustment for the effects of gender, smoking status and noise exposure [32]. A recent study from the UK Medical Research Council's national study of hearing supports a link between inflammatory status according to WBC count, and the degree of presbycusis [33]. A cohort of older people with consistently high or increasing levels of CRP were nearly twice as likely to develop hearing impairment over a 10 year period as those with normal CRP levels [34]. Moreover plasma levels of inflammatory markers TNF- α , IL-6, and CRP and WBC counts rise with age in healthy individuals [35,36]. Although functional data is scarce, TNF- α receptor single nucleotide polymorphisms have been identified to be associated with increased risk of hearing impairment in the elderly [37]. TNF- α , IL-6, and IL-1 β are all significantly induced in the cochleae of noise-exposed rodents [38]; and histological findings suggest lateral wall fibrocytes as the main source of the local inflammatory response to cochlear stress [38]. Animal models of presbycusis demonstrate high cochlear oxidative stress and concomitant increase in TNF- α , suggesting chronic inflammation as a causal factor for premature ARHL [39].

An association has also been established between ARHL and retinal vascular changes including arteriolar narrowing, and retinopathy such as retinal hemorrhages and microaneurysms [40], raising the possibility of common vascular pathways of disease. In addition, diabetes is associated with increased odds of hearing impairment after controlling for age, sex, race, education, smoking and noise exposure [41], suggesting potential microvascular commonality. However, adjusting for CRP attenuates the association of diabetes with high frequency hearing loss [42], highlighting a mediating role of inflammation. This presents a compelling case for investigation of inflammatory effects on the microvascular frameworks affecting human hearing.

2.3. Hearing and cognition

ARHL is associated with incident cognitive impairment and accelerated cognitive decline independently of other risk factors [15]. Indeed hearing loss has been associated with incident all-cause dementia after adjusting for age, sex, race, education, diabetes, smoking and hypertension [43]. Not only are elevated hearing thresholds associated with cognitive impairment [16], but cognitive impairment has also been demonstrated to independently predict faster rates of decline in hearing [16]. These relationships warrant further investigation.

2.4. Aspirin effects on microvascular disease, inflammation and hearing

Aspirin (acetylsalicylic acid) is well established as an important secondary prevention tool in cardiovascular and neurovascular diseases. A meta-analysis of aspirin in primary and secondary prevention trials [19] demonstrated an absolute reduction in vascular events for secondary prevention, especially in those who already have occlusive vascular diseases, and the net benefit in the primary prevention setting was a 12% proportional reduction in serious vascular events [19]. Some evidence suggests aspirin also has a direct vascular effect. In an observational study, regular aspirin users who also take an antihypertensive agent, have been shown to have wider retinal arterioles, after adjusting for age, blood pressure, smoking, diabetes, and non-steroidal anti-inflammatory medication use [44]. Low/intermediate doses of aspirin have also been reported to selectively prevent experimental diabetic microangiopathy [45].

Aspirin exerts the majority of its anti-inflammatory effects by disrupting prostanoid synthesis, and beneficial effects on adverse cardiovascular events are directly related to the inhibition of platelet aggregation. Growing appreciation of the dynamic role of platelet-derived inflammatory mediators firmly implicates platelets as inflammatory effector cells which bridge the thrombotic and inflammatory pathways [46]. Aspirin inhibits the platelet enzyme cyclo-oxygenase (COX), a key enzyme in the synthetic pathway for prostaglandins. During the biosynthesis of prostaglandins, expressions of genes coding for IL-1 β , IL-6, TNF- α , and COX-2 are increased [47], and this increase is attenuated by aspirin. Aspirin also stimulates the biosynthesis of other anti-inflammatory compounds referred to as 'aspirin-triggered 15-epi-lipoxins'. Production of these compounds is believed to underpin, at least in part, the drug's anti-inflammatory effect at low doses [48]. Some studies have demonstrated that aspirin suppresses systemic inflammatory biomarkers, which are the hallmarks of chronic inflammation implicated in the aging process [49]. An RCT of 100 mg aspirin in acute coronary syndrome showed that both CRP and TNF- α were significantly decreased [22]. Reports of aspirin's effect on circulating biomarkers is mixed, however the most positive effect is noted when baseline CRP is >9 mg/L, as in metabolic syndrome or acute coronary syndrome [21,22].

There is conflicting evidence about aspirin's effect on hearing. Ototoxicity is well recognized from high doses (>1.5 g/day) of aspirin, leading to reversible hearing loss and tinnitus [50]. However, a large prospective observational study of 62,261 women found self-reported hearing loss *did not* increase with reported aspirin use [51]. In contrast, a cross-sectional study of 26,917 men suggested an increase in self-reported hearing impairment

was associated with aspirin use [52]; however, dose and indication were unspecified. High doses of aspirin have been shown to be protective against aminoglycoside-induced or cisplatin-induced hearing loss through anti-inflammatory and/or oxidative stress reduction mechanisms [26]. A second small double-blind RCT suggested that half this dose, 1.5 g aspirin also attenuated gentamicin-related ototoxicity [27]. These results are encouraging, but examining the effect of low dose aspirin on ARHL is a priority.

Small mammal experimental models have appraised us of some of the plausible direct effects of aspirin on cochleae. Coleman et al. concluded that aspirin protects against noise-induced cochlear damage, particularly outer hair cell loss, but the effect is restricted by a relatively narrow therapeutic dosing window [53]. Treating small mammals with salicylate after toxic noise exposure reduces hair cell damage and provides immunohistological evidence of aspirin-mediated reduction of free radicals in the cochlea [25]. If cumulative noise exposure and aging are synergistic [54], then aspirin's effect on noise toxicity may translate into an even greater effect on ARHL.

ASPREE-HEARING aims to determine if low-dose aspirin slows the progression of ARHL. The primary hypothesis is that low-dose aspirin compared to placebo will reduce the rate of progression of ARHL. We also hypothesize that impaired/worsening hearing thresholds will correlate with retinal microvascular changes and cognitive impairment.

Specifically, the objectives are to determine whether:

- i. daily, low dose aspirin reduces the age-related hearing threshold shift per year;
- ii. daily, low dose aspirin attenuates the cognitive decline associated with ARHL;
- iii. daily low dose aspirin attenuates the change in speech reception threshold; and
- iv. microvascular changes, such as retinal arteriolar and venular caliber, and retinopathy correlate with changes in ARHL.

3. Methods

ASPREE-HEARING is a sub-study of the ASPirin in Reducing Events in the Elderly (ASPREE) clinical trial [55]. ASPREE-HEARING is being conducted in a subset of ASPREE participants in Australia.

The ASPREE principal trial

ASPREE is a multi-center, randomized, double-blinded, placebo-controlled trial of daily 100 mg enteric-coated aspirin in 19,000 healthy community dwelling older adults in Australia and the US. Age eligibility is 65 years and over (African Americans and Hispanics in the USA) and all others aged 70 years and over. ASPREE will determine whether 100 mg aspirin daily extends disability- and dementia- free survival in the elderly, and is a primary prevention study. The ASPREE study methods have been described in detail elsewhere [55]. In brief, the majority of ASPREE participants have been recruited through partnerships with general practitioner co-investigators. A minority has been recruited directly from the community.

Inclusion criteria include men and women who are able to give informed consent and able to attend a study visit. Exclusion criteria include a past history of cardiovascular event or established cardiovascular disease (including stroke, transient ischemic attack, myocardial infarction, unstable angina, coronary artery reperfusion procedures and bypass grafting, abdominal aortic aneurysm, cardiac failure), atrial fibrillation, dementia or score of <78 on Modified Mini-Mental State (3MS) examination [56], disability as defined by severe difficulty or inability to perform any of the 6 Katz activities of daily living (ADLs), a condition with a high current or recurrent risk of bleeding, anemia, a condition likely to cause death within 5 years, current use of other antiplatelet or antithrombotic medication, current use of aspirin for secondary prevention, and uncontrolled hypertension.

Participants meeting initial ASPREE eligibility at a screening study visit are given a four week placebo run in. A compliance check is performed at the second baseline study visit four weeks later. Randomization of study drug follows a block randomization procedure and is stratified by site and age (65–79 and >80 years). An independent statistician using the Stata ‘ralloc’ procedure generates the randomization list. Participants are randomized to receive either 100 mg of enteric coated aspirin or an enteric coated placebo, which are identical in appearance, in a ratio of 1:1. A 12 month supply of study medication is dispensed to participants upon randomization and thereafter at each annual visit. Study participants, investigators and general practitioner co-investigators remain blinded to allocation.

All ASPREE participants have face-to-face study visits annually. Contact is made via telephone at 3 monthly intervals in between. The 6 month phone call ascertains additional information relevant to study endpoints. The ASPREE study began in 2010, completed recruitment in December 2014 (16,703 in Australia and 2411 in the USA) and will conclude in 2017/2018.

The primary endpoint is a composite of death or dementia (adjudicated according to the DSM-IV criteria) or persistent loss of the same Katz ADL. Pre-specified secondary endpoints include death, cardiovascular and cerebrovascular disease, cancer, cognitive impairment, depression, physical disability and clinically significant bleeding. All clinical endpoints are adjudicated by independent committees provided with de-identified clinical information about the event.

ASPREE-HEARING

3.1. Setting and participants—ASPREE-HEARING is conducted in the Australian states of Victoria, South Australia, southern New South Wales, Tasmania and the Australian Capital Territory, with representation of people from urban and rural areas.

3.1.1. Inclusion criteria: At the time of their enrolment to the ASPREE trial, between April and December 2014, participants were also offered the opportunity to join ASPREE-HEARING. Consent to participate in ASPREE-HEARING was received generally before or at randomization in ASPREE although some participants were recruited to ASPREE-HEARING upon receipt of consent within up to one month of randomization.

3.1.2. Exclusion criteria: People fitted with bilateral cochlear implants or bilateral deeply inserted per-tympanic or implanted hearing aids were excluded from ASPREE-HEARING. The presence of hearing impairment and/or the use of other hearing aids did not constitute an exclusion criterion.

3.2. Outcomes—The primary outcome is the change in mean pure tone average (PTA) hearing threshold (decibels) in the better ear, over a 3-year period. Secondary outcomes consist of changes in retinal microvascular indicators, changes in cognitive function assessed by the 3MS, and changes in speech reception thresholds and noise.

3.3. Data collection, baseline and follow-up measures—Hearing measures are conducted at baseline, 18 months and at 3-years. For pragmatic reasons, testing will be conducted in a combination of medical clinic rooms, community centers and purpose-built mobile vans. As a sound-proof booth is not feasible across this broad range of environments, sound-attenuating ear muffs are used to guard against ambient noise, following the precedent of other studies [57].

Hearing measures performed at baseline, and after 18 months and at 3 years are as follows:

- *Otoscopy* will be performed at the outset and at each subsequent assessment. If the ear canal is occluded or if the tympanic membrane cannot be visualized, the participant will be requested to attend their GP for management of any obstruction. If this is initiated within one month of randomization, hearing reassessment will proceed. Occlusion discovered at a follow up assessment will also prompt GP management and a reassessment.
- *Air and Bone Conduction Audiometry* will be conducted using portable Interacoustics AD226 audiometers with ER3A inserts and sound-attenuating ear muffs. All thresholds are measured in decibels hearing level (dB HL). Air-conduction thresholds will be obtained for both ears at 0.25, 0.5, 1, 2, 4, and 8 kHz. A pure tone average of air conduction thresholds at 0.5, 1, 2, and 4 kHz in the better ear will be calculated as the summary measure of hearing for our analyses, as per hearing deficit definitions used by the World Health Organization [58]. Bone conduction testing will be performed using two frequencies, 1 kHz and 4 kHz, compared against air conduction in the better ear, and adjusted to allow for both central forehead positioning and presence of the insert earphones during bone-conduction testing. The combined correction figures for bone conduction thresholds, for the octave frequencies from 250 Hz to 8000 Hz, are: 10, 2, 1, -9, -9, and -9 dB [59]. This will enable distinction of age-associated sensorineural hearing loss from conductive loss. Over the 3-year study period, even subtle changes in hearing threshold will be measureable in all participants, including any deterioration that is imposed on hearing impairment at baseline.
- *Open-set speech perception ability* will be tested with the Listening in Spatialized Noise-Sentences Test (LiSN-S) [60], which assesses ability to understand speech in the presence of spatially-separated competing talkers,

representing a test of functional hearing. The result is expressed as the speech reception threshold (SRTn), the signal-to-noise ratio at which the listener can identify and repeat 50% of the words in target sentences. Speech discrimination is affected both by cochlear loss and by certain central auditory processing disorders [61], so the SRTn is sensitive to deficits other than threshold elevation. To minimize the impact of hearing threshold elevation on SRTn, the LiSN-S test pre-amplifies the stimuli according to a prescription based on each participant's hearing thresholds.

- *Hearing Handicap and Noise Exposure Questionnaires.* The 10-item Hearing Handicap Inventory for the Elderly (HHIE-S) [62] and 11-item Baltimore Longitudinal Study of Aging Self-Reported Hearing and Noise Exposure Questionnaire [63] will be administered to provide information on hearing history, noise exposure, use of hearing aids and perceived hearing handicap. This will also assist in determining the extent to which previous noise exposure contributes to baseline hearing thresholds.
- *Retinal Vascular Imaging (RVI)* with undilated retinal photography will be used to measure retinal vascular caliber, focal arteriolar narrowing, and parameters of retinal microvascular geometry (e.g. branching, and tortuosity) [64]. Retinal vascular caliber will be scored in an annulus between $\frac{1}{2}$ and 1 disc diameter from the optic disc [65]. This provides ASPREE-HEARING with a convenient and accessible indicator of *microvascular* changes, a potential causal factor in presbycusis. Retinal images will be collected at baseline, 18 months and at 3 years.
- *Cognitive function and Quality of Life* will be measured annually with the 3MS and Short Form-12 [66] by the principal ASPREE trial. Results from the *cognitive function* tests, particularly the 3MS, will enable determination of association and causal relationship through comparison of changes over time in cognition and the key factors of hearing (defined by the PTA of hearing thresholds at 0.5–4 kHz in the better hearing ear) and retinal vasculature. Cognitive assessment is conducted at baseline and years 1 and 3 after randomization to aspirin or placebo.

All hearing measures will be conducted without hearing aids after testing instructions have been heard and understood. Any hearing impairment previously unknown to participants will be advised to their GP.

3.4. Sample size—To address the primary hypothesis, 1200 participants provide 90% power to detect a difference in average hearing threshold level (HL) change from a mean annual dB HL increase of +0.86 in the placebo group to a mean annual dB HL increase of +0.64 in the aspirin group (assuming standard deviation of 1.64 dB HL for changes in HL over 3 years). This calculation is based on the background increase per annum of HL in Australians aged 75 years, with an average PTA 0.5, 1, 2, 4 kHz trajectory of +0.86 dB [6].

This difference between the two groups is not clinically relevant over a 3 year period but, considering the current life expectancy of 70 year olds, this rate of deceleration of HL loss

per year will be clinically relevant across the remaining lifespan, particularly in those who already have some loss at entry. Moreover, 0.22 dB is the average 4-frequency difference in loss; this typically equates to greater losses at 2 kHz and 4 kHz. Even subtle 0.66–1 dB shifts in the pure tone average over 3 years may represent a 5 dB shift in one of the important voice-recognition frequencies. As such, this effect size could mean the difference between complete access to the speech spectrum and a reduced ability to detect high frequency consonants that facilitate communication, especially in noisy situations in later life.

3.5. Statistical analysis—A linear mixed model; with hearing defined by the PTA in the better ear, measured at baseline, 18 months and at 3-year study-end as the primary outcome, will be used for all analyses. This is equivalent to a model for outcomes at follow-up time points that adjusts for baseline hearing [67]. For the primary hypothesis, the model will include an interaction term between treatment group (placebo/aspirin) and time since randomization; the estimated interaction effect at 3 years will summarize the evidence for/against this hypothesis as a population-averaged effect. In a secondary analysis, a patient-specific effect of treatment will be estimated, potentially with improved precision, from the same model structure with adjustment for covariates: age, gender, smoking and diabetes. The linear mixed model assumes a missing at random (MAR) mechanism for any unobserved hearing values. Secondary analyses will include a sensitivity analysis of findings to the MAR assumption with use of pattern mixture and imputation approaches, enabling exploration of whether differential drop-out between groups during the follow-up period affects the estimates of treatment effect.

Aspirin's effect on cognitive function will be assessed in the principal ASPREE trial with $n = 19,000$ and its effect on retinal vasculature will be assessed by a joint analysis of data from other ASPREE sub-studies that also perform RVI. For ASPREE-HEARING's other hypotheses, there is 80% power (two-sided $\alpha = 0.05$) to detect correlations of value $\rho < 0.1$ between HL and cognitive function (3MS score) at baseline; likewise between HL and retinal vasculature measures (central retinal arteriolar and venular equivalent measures [CRAE and CRVE]). Similarly, correlations can be detected between changes in HL and changes in the cognitive function and retinal vasculature measures. The analysis for the baseline associations will be performed with HL as the continuous scale outcome in a linear regression model and cognitive or retinal vasculature measure as the explanatory variable. Adjustment will be made for factors known to relate to hearing or likely to be confounders of the association of interest, e.g. age, sex, hypertensive status.

To relate changes in cognitive function or retinal vasculature to change in hearing loss, bivariate mixed models will be used for HL and either 3MS, CRAE, or CRVE, with correlated random effects encapsulating the association between evolution of HL and one of these other measures. To estimate the causal relationships, including aspirin's mechanism of action, a marginal structural modeling approach will be adopted.

If objectives (i) and/or (ii) are correct, subsequent analysis of the inflammatory biomarkers TNF- α , IL-6 and CRP can be conducted to assess modification of inflammation on the effect of aspirin on each relevant outcome: hearing loss, retinal microvascular change

indicators and cognitive impairment (3MS). For example, for TNF- α , the model will be extended to include the baseline TNF- α values, and the parameters of this model relating the biomarker to hearing at baseline enable assessment of cross-sectional association at baseline. For assessing association of biomarker changes with progression of hearing loss, the model will be further extended to include the time-dependent TNF- α change from baseline as an explanatory variable. For assessing whether TNF- α mediates an aspirin-induced slowing of hearing loss, the model will be extended again to include an interaction between treatment group (placebo/aspirin) and the time-dependent TNF- α change from baseline.

In addition, a structural equation model approach will be applied, based on the model conveying causal assumptions outlined in Fig. 1, to further elucidate the inter-relationships among the set of variables.

3.6. Consent and ethics approval—Written informed consent has been obtained separately from all ASPREE participants for ASPREE-HEARING. The study protocol has been approved by the Human Research Ethics Committee of Monash University (CF14/920–2,014,000,376). This includes consent to access to data collected annually by the principal ASPREE trial as detailed above.

4. Discussion

Progressive hearing loss is a common, distressing and expensive reality of older age, reported by nearly two-thirds of adults aged 70 years or more [1]. Hearing loss is associated with multiple co-morbidities; of particular interest is the association with cognitive decline [15]. Hearing loss is a significant barrier to the enjoyment of healthy, fulfilling and interactive senior years. Social ramifications include embarrassment and withdrawal, leading to isolation and functional decline. This randomized controlled trial, ASPREE-HEARING, provides a unique opportunity to investigate whether low-dose aspirin reduces progression of ARHL in community-dwelling older Australians over a 3-year period, and whether any beneficial effect is mediated by amelioration of inflammatory or vascular damage to peripheral hearing mechanisms. In addition, the study will examine whether any slowing that may be demonstrable in the rate of hearing loss is associated with retinal microvascular changes, and potentially in the future with a reduction of inflammatory biomarkers TNF- α , IL-6 or CRP, and/or with greater preservation of cognitive function.

Age-related changes in the cochlear microvasculature, the stria vascularis, may be a primary cause of ARHL. This link has been inadequately studied to date. The retina enables quantitative imaging of the microvasculature. Abnormalities are thought to reflect vascular changes in other sites such as the cochlea. Of note, there is a correlation between retinal vascular changes and deafness in women [40]; and there is also increased risk of sudden sensorineural deafness with diabetic retinopathy [68]. Supporting the role of RVI as a general marker of other vessel pathology, a link has recently been established between retinal microvascular changes and brain microvascular disease [69].

Old age is regularly accompanied by an increase in plasma inflammatory biomarkers, which is likely to reflect low-grade inflammation [35]. With increasing age, the stria vascularis of

the inner ear undergoes changes compatible with damage from an inflammatory and/or vascular degenerative process. The inflammatory biomarkers CRP, IL-6 and TNF α are the most commonly measured inflammatory markers in previous studies of older populations [49]. In addition, CRP and IL-6 are routinely measured in clinical pathology laboratories. IL-6 and TNF α are also direct mediators of inflammation. If aspirin is found to have an effect on ARHL, ASPREE-HEARING will measure these biomarkers to determine the mechanism of action.

Hearing loss may be one of the strongest late-life risk factors for cognitive impairment and dementia in older adults. It is likely that age-related decreases in hearing and cognition share a common pathogenesis, due to low-grade inflammation and/or microvascular change, leading to a parallel decline in hearing and cognition. If hearing loss also contributes to cognitive decline via a reduction of stimuli from social interaction, a yet stronger association might be expected. The contribution of peripheral hearing impairment to poorer cognitive functioning is currently hypothesized to be related to the effects of hearing loss on cognitive load, brain structure, and/or social engagement, all of which could mediate effects on impaired cognition [70]. These pathways are not mutually exclusive, and multiple pathways could and likely do coexist and synergistically contribute to impaired cognitive function, as shown in Fig. 1. We will explore whether low-dose aspirin protects cognition through direct effects on brain microvasculature or inflammation, or indirect effects through its possible beneficial role in hearing preservation, or both.

This study design is supported by extensive ASPREE standard operating procedures [55], complemented by tailored standard operating procedures for standardized audiometry assessment at multiple locations. Study internal validity is strengthened by inclusion of competency checks for staff, adherence to operating procedures and regular auditing of data collection practices. Non-compliance and loss to follow-up are features of prospective longitudinal studies in older people that have the potential to threaten interpretation of study results; however, the ASPREE trial has well established methods to maximize compliance and retention through regular telephone contact and newsletter correspondence with all participants. Current loss-to-follow up in the principal ASPREE trial is less than 5% per annum over the 4 years to date.

Low-dose aspirin has potential as an inexpensive and simple primary care intervention to slow the development or progression of ARHL. In addition to testing this hypothesis, ASPREE-HEARING affords a unique opportunity to explore the underlying mechanisms of ARHL through the use of low-dose aspirin intervention. Discoveries through ASPREE-HEARING will also enable a better understanding of the patterns of comorbidity associated with hearing loss and the relationship between aging and hearing loss. ASPREE-HEARING will help inform the evidence-base of a significant and debilitating health issue in the fastest growing age group of the Australian population.

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Legend: ovals, latent variables; rectangles, indicators; →, hypothesized connections between variables; IL-6, Interleukin-6; CRP, C-Reactive Protein; TNF-α, Tumor Necrosis Factor-α; SRHNEQ, Self-Reported Hearing and Noise Questionnaire; LiSN-S, Listening in Spatialized Noise-Sentences; HHIE-S, Hearing Handicap Inventory for the Elderly; PTA, Pure Tone Average; HVLRT-R, Hopkins Verbal Learning Test-Revised; 3MS, Modified Mini-Mental State Examination; SF-12, Short Form-12; RVI, Retinal Vascular Imaging

Fig. 1.
Hypothesized relationships in age-related hearing loss.