The impact of hearing impairment and hearing aid use on progression to mild cognitive impairment in cognitively healthy adults: a longitudinal study of 5721 participants

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Abstract

The increasing prevalence of dementia in older adults warrants attention to the identification of practices that can delay or reduce likelihood of progression to early forms of cognitive impairment, in particular, to mild cognitive impairment (MCI) which is often considered a transitional stage between healthy aging and dementia. In this study, we investigated the effect of hearing impairment and hearing aid usage on cognitive decline and progression to MCI in cognitively healthy individuals. We used data from a large referral-based cohort obtained from the National Alzheimer's Coordinating Center. The baseline sample included 5721 cognitively normal subjects aged ≥ 40. We found that hearing impairment was associated with increased risk of progression to MCI (hazard ratio [HR] = 1.40, 95%CI, 1.16-1.68, false discovery rate [FDR] $P < 0.001$) and an accelerated rate of cognitive decline ($P < 0.001$). Among hearing-impaired participants, hearing aid users were less likely to develop MCI (HR, 0.33; 95% CI, 0.23-0.47; FDR $P < 0.001$) and experienced slower cognitive decline ($P = 0.004$) when compared to those not using hearing aids. We found no statistically significant differences in risk of conversion to MCI between individuals with normal hearing and hearing-impaired adults using hearing aids (HR, 1.23; 95% CI, 0.99-1.50; FDR $P = 0.08$). Our findings highlight the need for a randomized clinical trial that will allow us to investigate whether there is a causal relationship between hearing loss, hearing aid use, and conversion to MCI. Such knowledge could provide new and novel insights into prevention of cognitive impairment and dementia.

Introduction

Mild cognitive impairment (MCI) describes individuals with demonstrable decline in cognitive abilities greater than normal age-related changes but not severe enough to meet diagnostic criteria for dementia [1]. MCI is common among older adults, with the prevalence estimates for those aged 65 or over ranging between 16% and 23% [1] and the annual conversion rate to dementia and Alzheimer's disease (AD) of 9.6% and 8.1% respectively [2].

While numerous studies have investigated the impact of different potential risk factors on progression from MCI to dementia and the effects of interventions aimed at preventing the onset of dementia, including the optimal control of vascular risk factors [3], B-vitamin treatment [4], exercise [5], stress reduction [6], antidepressant treatment [7], and non-invasive brain stimulation [8], there is a paucity of research on predictors and preventive measures for conversion from normal cognition to MCI. Such research is vital not only due to its contribution to the overall mechanism of the disease, but also because it could provide novel insights into the prevention of cognitive decline. Growing evidence indicates that the pathophysiological processes underlying AD, the most common form of dementia, begin a decade or more before the emergence of cognitive impairment [9]. Thereby, it is important to improve our ability to identify which early detection measures, or combination of measures, obtained among individuals increase the likelihood of progression from normal cognition to onset of clinical symptoms associated with MCI diagnosis.

Hearing impairment is the third most common chronic health condition, affecting about one-third of the population aged 65 years and older [10]. Several observational studies demonstrated that hearing impairment can result in accelerated cognitive decline [11,12] and a higher risk of incident dementia [12,13,14,15] and AD [16]. Furthermore, a strong connection between the severity of hearing loss and dementia risk was observed in [14]. Although the impact of hearing impairment on cognition has been studied in patients with dementia, to date, the association in those with normal cognition has not been given much attention. Most importantly, no studies have evaluated the effect of hearing aid usage on the risk of incident MCI. Previous work showed that the use of hearing aids may reduce hearing handicap [17, 18] and is associated with better cognition [19]. Furthermore, Bucholc et al. [20] found that individuals with MCI that used hearing aids were at significantly lower risk of developing all-cause dementia compared to those not using hearing aids. More research is now needed to better understand the role of hearing aids in preventing milder forms of cognitive impairment.

The aim of the present study was twofold: (1) to examine the effect of hearing impairment on cognitive function and progression to MCI in cognitively healthy individuals; and (2) to investigate the relationship between the use of hearing aids, risk of incident MCI, and cognitive decline.

Methods

Study population

We examined participant data submitted to the National Alzheimer's Coordinating Center (NACC) in the period 2005-2019 [21]. The NACC maintains a database of standardized clinical and neuropathological information collected longitudinally from the Alzheimer's Disease Research Centers (ADRCs), supported by the National Institute on Aging (NIA) grant U01AG016976 [21]. The data used in our study was the NACC Uniform Data Set (UDS) [22]. Details about design, implementation and rationale for the UDS have been published elsewhere [22].

Data from 5721 healthy individuals (i.e. not diagnosed with cognitive impairment), 40 years of age or older, having more than one ADRC visit served as the sample for our study. Data from individuals with incomplete or inconsistent clinical information were disregarded. Accordingly, individuals with inconsistent records relating to the absence/presence of hearing loss, the use/non-use of hearing aids or lack of functionally normal hearing when wearing a hearing aid were excluded. Fig. 1 shows a flowchart for the inclusion of participants and research scenarios considered in our study.

The MCI incidence was determined based on the clinical diagnosis made by a single clinician or through a consensus process. Diagnoses of MCI were established using the modified Petersen criteria [23]. Eligibility criteria for the MCI group included all MCI subtypes (amnestic, non-amnestic, single domain, and multiple domain). In addition, the longitudinally measured CDR® Sum of Boxes (CDRSB) score was used to examine changes in cognitive function [24]. Although it was not reported to NACC whether participants with hearing impairment were wearing their hearing aids during cognitive testing, ADRCs

were expected to use missing codes if there was indication that hearing loss affected test performance. Records with missing codes were excluded from the analysis.

Self-reported hearing loss was evaluated through the response to the question, "Without a hearing aid(s), is the subject's hearing functionally normal?" [25]. All individuals that responded "yes" were classified as being hearing impaired and those that responded "no" were defined as having normal hearing. No information on the degree of hearing loss was provided in the NACC-UDS.

Self-reported hearing aid use was established by asking hearing-impaired participants if they "wear a hearing aid" [25]. The participants were considered to use hearing aids if they answered "yes". Subjects that responded "no" were labelled as non-users of hearing aids. Hearing aid users were subsequently asked if the hearing aid provided them with 'functionally normal hearing'. The positive response to this question implied that a participant did not demonstrate a reduced ability to carry out everyday activities, such as listening or talking, when wearing a hearing aid. Data on daily hours of aid use and the type (analog/digital) or style (canal/in-the-ear/behind-the-ear) of hearing aids were not collected as a part of the NACC clinical assessment process.

Statistical analysis

Given that incident MCI could only be determined at the defined times of follow-up visits, time to MCI conversion was measured from the baseline visit until the date when a patient was diagnosed with MCI or until the last registered visit for those who were lost to follow-up (censored observations). Multivariable Cox proportional hazards regression models were developed to estimate the *hazard ratios* (HRs) and 95% *confidence intervals* (CIs) of primary outcomes including: 1) the impact of hearing impairment on the progression from healthy to MCI (Scenario 1); 2) the effect of hearing aid use on the progression from healthy to MCI (Scenario 2). In addition, we examined the significance of the potential impact of hearing aid use by comparing the risk of incident MCI diagnosis in participants experiencing no hearing loss and hearing-impaired subjects that used hearing aids (Scenario 3). When constructing multivariable Cox proportional hazards regression models, multiple factors, including age, gender, years of education, and the CDRSB score were treated as covariates to minimize the effects of confounding. The age variable was dichotomised using a distributional approach. The proportionality of hazards assumptions was assessed using the Schoenfeld residuals [26]. To avoid the inflation of false-positive findings, the Benjamini-Hochberg false discovery rate (FDR) procedure was applied to adjust for multiple hypothesis-testing [27]. Differences with FDR $P < 0.05$ were considered to be statistically significant.

Longitudinal changes in cognitive test performance were assessed using linear mixed-effects models, with the CDRSB test score as a dependent variable [28]. Suitability for using a multilevel modelling approach was assessed by testing an "unconditional model" ("intercept only" model) in the first instance. In the unconditional model, only the dependent variable (CDRSB score) and the grouping variable (subject ID) were entered, and other predictors were not included; thus, the model was not conditioned upon any predictor variables. Since the model showed significant between-participant variation ($P < 0.001$), the use of multilevel modelling was supported. The implementation of linear mixed-effects models allowed us to

compare changes in the dependent variable over time, incorporate a combination of fixed and random effects as predictor variables, and handle a different number of measurements per subject. The effect of time, group specification (i.e., hearing impairment or hearing aid status), and time by group interaction were included as fixed effects. The inclusion of age, gender, and years of education as fixed effects was judged against the model fit. Fitting of models was based on the maximum likelihood estimation using the Nelder-Mead approach [29]. Random intercepts were modelled for each subject. We confirmed that all models including a random intercept fitted the data significantly better than models incorporating only fixed effects ($P < 0.001$). The Akaike information criterion (AIC) was applied to evaluate the most plausible model in the set of models being tested [29].

Sensitivity analysis

We implemented measures to account for the potential impact of confounding and selection bias on the estimate of the association between the exposure status, i.e. hearing status or hearing aid use status and conversion to MCI. Specifically, propensity score matching was applied to control for measured confounding while sensitivity analysis for unmeasured confounding was used to evaluate the sensitivity of our main findings with respect to confounders not included in our study.

Propensity scores were estimated using logistic regression and represented the probability of a participant being assigned to a particular subgroup in Scenarios 1-3 given a set of observed covariates including age, gender, education, and the CDRSB score. We applied the nearest neighbour matching method to form matched samples by minimizing the average absolute within-pair distance in propensity scores [30]. The standardized mean difference was used to examine the balance of covariate distribution between patient subgroups in propensity score–matched samples. A standardized mean difference < 0.1 denoted negligible imbalance in the prevalence of a covariate between patient subgroups.

Sensitivity analysis for unmeasured confounding was performed to study the effect of potential unmeasured covariates on the estimated HRs in Scenarios 1-3 [31]. We varied the assumed prevalence rates for the confounder among the exposed (5%, 10%, and 15% of the population) and unexposed groups (10%, 20%, and 30% of the population), and used three different values of HR (0.5,2.0,3.0) for the association between the confounder and the outcome. This allowed us to assess how the inferences on the effects of exposures can be altered through an unknown variable under different simulations.

Results

Participant characteristics

We analysed a total of 5721 participants with no cognitive impairment at baseline. This includes 816 (14.3%) subjects with hearing impairment and 4905 (85.7%) subjects without hearing impairment. Among 816 participants with hearing impairment, 562 were classified as hearing aid users while 138 were not using hearing aids. Note that we considered only participants who reported hearing aid usage at

every consecutive visit. Out of 5721 participants, 689 converted to MCI during follow-up. The baseline characteristics of participants are shown in Table 1.

While evaluating the impact of hearing impairment on the progression from healthy to MCI (Scenario 1), 21.8% of individuals aged 70 and older were diagnosed with hearing impairment while among participants aged < 70, only 5.7% had hearing loss ($P < 0.001$). There was an equal proportion of males and females in the group of participants with hearing impairment whereas most of the subjects without hearing loss were women (70.2%). Those with hearing impairment had significantly higher CDRSB scores ($P < 0.001$). In Scenario 2, investigating the effect of the use of hearing aids on the healthy-to-MCI conversion, we observed significant differences in usage of hearing aids between age groups ($P < 0.001$). In Scenario 3, we found significant age ($P < 0.001$) and gender ($P < 0.001$) differences. Furthermore, hearing aid users had significantly more years of education ($P = 0.03$) than those with no hearing impairment.

Hearing Impairment and Risk of Incident MCI

The mean normal-to-MCI conversion period (standard deviation) was 2.6 (1.9) years for patients with hearing impairment and 3.4 (2.7) for those with normal hearing ($P < 0.001$). Hearing-impaired individuals were at substantially higher risk of developing MCI (HR 1.4, 95%CI, 1.16-1.68, FDR $P < 0.001$; Fig. 2A). In addition, the overall incidence rates for MCI diagnosis in Scenario 1 were significantly lower for women (HR 0.79, 95%CI, 0.67-0.92, FDR $P = 0.004$) and higher for participants aged 70 and older (HR 2.88, 95%CI, 2.41-3.45, FDR $P < 0.001$) and those with higher CDRSB score at baseline (HR 1.71, 95%CI, 1.56-1.87, FDR P < 0.001).

Hearing Aid Status and Risk of Incident MCI

The mean time of healthy-to-MCI progression (SD) for hearing aid users was 2.7 (1.9) years. The mean time to incident MCI diagnosis for non-users of hearing aids was significantly shorter, i.e., 1.8 (1.2) years ($P < 0.001$). In the multivariable Cox proportional hazards regression model, the use of hearing aids was associated with a lower risk of progression from healthy to MCI (HR, 0.33; 95% CI, 0.23-0.47; FDR $P < 0.001$; Fig. 2B). Participants at increased risk for normal-to-MCI conversion were 70 years of age and older (HR 4.05, 95%CI, 2.12-7.75, FDR P < 0.001) and with a higher CDRSB score at baseline (HR 1.92, 95%CI, 1.46-2.53, FDR P < 0.001).

Normal hearing versus corrected hearing loss

Since the use of hearing aids was negatively associated with the incidence of MCI diagnosis, we compared survival time for participants without hearing impairment and hearing-impaired adults that reported use of hearing aids (Scenario 3). We found no statistically significant differences in risk of progression from healthy to MCI between these two groups (HR, 1.23; 95% CI, 0.99-1.5; FDR $P = 0.08$; Fig. 2C). Finally, we compared the incidence rate for MCI diagnosis in group of participants with normal hearing and those with hearing loss that did no use hearing aid. We found that hearing-impaired

individuals without hearing aids were at significantly higher risk of conversion from healthy to MCI (HR, 3.94; 95% CI, 2.90-5.36; FDR $P < 0.001$).

Sensitivity Analysis

The baseline characteristics of participants in propensity score matched groups are shown in Table 2. The results from propensity score analyses revealed similar results to the findings of the primary analyses (Fig. 4). First, we reported a higher risk of conversion from healthy to MCI for patients with hearing impairment (HR, 1.38; 95% CI, 1.08-1.75; FDR $P = 0.015$; Fig. 3A). Second, the use of hearing aids was associated with reduced risk of progression to MCI when compared to non-use of hearing aids (HR, 0.29; 95% CI, 0.17-0.49; FDR $P < 0.001$; Fig. 3B). Finally, we found no statistically significant differences in time to incident MCI diagnosis between patients without hearing impairment and hearing-impaired individuals that reported use of hearing aids (HR, 1.03; 95% CI, 0.77-1.38; FDR $P = 0.95$; Fig. 3C).

Given that our project is a non-randomized study on causal associations, we also assessed the robustness of our results with respect to unmeasured confounding (Table 3). Sensitivity analysis for unmeasured confounding performed for Scenario 1 showed that hearing-impaired individuals were at substantially higher risk of developing MCI compared to participants with normal hearing for all considered values of the strength of the confounder-outcome association, and the prevalence of potential confounder in the population. The results of sensitivity analyses obtained for Scenario 2 were also consistent with those from the primary analysis i.e., the use of hearing aids was associated with lower risk of incident MCI in Scenario 2. In Scenario 3, only when larger proportion of patients with normal hearing have the unmeasured predictor and when the unmeasured predictor has effect 2-fold larger than the existing predictor i.e., 'normal hearing/hearing aid used', the unmeasured confounder may have impact on the effect of 'normal hearing/hearing aid used' predictor on the outcome.

Longitudinal Changes in Cognitive Function

To assess the effect of hearing impairment and hearing aid usage on cognitive function, we performed the longitudinal analyses for Scenarios 1-3 using linear mixed effects regression models with individual CDRSB test scores as dependent variables. We examined the impact of hearing impairment on cognitive decline in Model 1, the impact of hearing aid usage on cognitive decline in Model 2; and in Model 3, we compared the cognitive function in participants without hearing loss and hearing-impaired adults using hearing aids.

Model 1 showed a considerable variation in estimated individual intercepts, with the variance of 0.12 units change in the CDRSB score. We found that for every one-year increase, CDRSB was expected to increase by 0.14 ($P < 0.001$). On average, individuals with hearing impairment tended to have 0.13 points higher CDRSB score compared to those without hearing loss ($P = 0.005$). Cognitive decline was also positively associated with the time and hearing impairment interaction ($P < 0.001$) meaning that participants without hearing impairment showed less time-related decline than hearing-impaired subjects (Fig. 4A).

Within Model 2, we found a significant effect of longitudinal follow-up time ($P < 0.001$) and hearing aid status ($P < 0.001$) on the CDRSB score. For every one-year increase, CDRSB was shown to increase on average by 0.55. The CDRSB score reported for hearing-impaired participants using hearing aids was, on average, 0.4 points lower than for non-users of hearing aids. Most importantly, the interaction between follow-up time and hearing aid status was statistically significant ($P = 0.004$), with the time-related increase in cognitive scores steeper for participants not using hearing aids (Fig. 4B).

In Model 3, we observed a significant effect of follow-up time on the CDRSB score ($P < 0.001$), with the average annual rate of change in CDRSB of 0.14 points. However, neither the average CDRSB score for individuals without hearing loss and hearing-impaired adults using hearing aids nor temporal changes in the CDRSB score for these two groups of participants were found statistically significant ($P = 0.33$ and $P = 0.06$ respectively).

Discussion

Our study reveals that hearing impairment is independently associated with accelerated cognitive decline and incident MCI. The magnitude of the association of hearing loss with normal-to-MCI conversion is clinically significant, with hearing-impaired individuals having a 40% higher risk of MCI compared to participants with normal hearing. Furthermore, hearing loss is associated with an accelerated rate of cognitive decline as indicated by the annual *rate of change in CDR*SB scores, that is more than *twice* as *fast* for participants with hearing loss than those without. On average (standard deviation), hearing-impaired subjects experienced a 0.08 (0.39)/year increase in CDRSB score while participants with normal hearing reported a mean CDRSB increase of 0.03 (0.26)/year. Seventy five percent of participants with normal hearing did not progress to MCI for 10 years compared to 5 years in the group of hearing-impaired adults.

We also found that hearing aid use was associated with significantly lower rates of cognitive decline and risk of incident MCI. Participants using hearing aids were 67% *less likely to progress to MCI than hearing-impaired participants not using hearing aids.* On average, hearing aid users experienced a 0.06 (0.32)/year increase in CDRSB score while participants not using hearing aids reported a mean increase of 0.14 (0.63)/year. Most importantly, we demonstrated that there are no significant differences in risk of incident MCI diagnosis and cognitive decline in participants experiencing no hearing loss and those diagnosed with hearing impairment that reported the use of hearing aids. We also found that hearing-impaired individuals not using hearing aids were at significantly higher risk of conversion from healthy to MCI when compared to those with normal hearing (HR, 3.94; 95% CI, 2.90-5.36; FDR $P < 0.001$). This implies that use of hearing aids may help mitigate cognitive decline associated with hearing loss, offering an actionable strategy to reduce the incidence of MCI.

While the precise mechanism underling the association between hearing loss and cognitive decline remains to be determined, several potential mechanisms have been proposed [11,32]. Some authors suggest that hearing impairment and cognitive decline may coincide due to common neurodegenerative

processes, resulting in both hearing impairment and MCI or dementia [33]. This would however imply that cognition could only be improved through a neuroregenerative process. The results presented here demonstrate that hearing aid usage may help mitigate cognitive decline and reduce the risk of progression to MCI. Other studies have come to similar conclusions [20,34,35,36]. In a prospective interventional study involving 34 elderly participants with hearing loss, cognitive function was significantly improved after 3 months of hearing aid use [34]. The recent study by Sarant et al. [35] showed that treatment of hearing loss led to improvements in cognition and self-reported listening disability after 18 months of hearing aid use, with over 97% of participants reporting significant improvements in executive function. In addition, Bucholc et al. [20] reported that hearing aids use was associated with lower risk of incident dementia in individuals with MCI. The percentage of participants who had not developed dementia five years after the baseline MCI diagnosis was 19% for non-users of hearing aids and 33% for those using hearing aids. Furthermore, the median time of MCI-to-dementia conversion for non-users of hearing aids was 2 years and 4 years for hearing aid users.

Other potential mechanisms that may be implicated in the observed association between hearing loss and cognition are sensory deprivation [37] and cognitive resource allocation [38]. It is well known that hearing impairment results in degradation and loss of brain signalling mechanisms. This sensory deprivation may subsequently lead to changes in cortical reorganization and brain morphometry, adversely affecting cognitive performance [39]. For instance, Lin et al [37] found evidence of accelerated whole brain atrophy and volume decline in the right superior, middle and inferior temporal gyri in subjects with hearing loss when compared to individuals with normal hearing across a mean 6.4 years of evaluation. Alternatively, it has been suggested that in the presence of hearing impairment, cognitive resources are diverted from cognitive processes such as working memory into auditory perceptual processing [40].

This study has several limitations worth noting. First, our findings may not generalize to patients examined in routine clinical practice as ADRC cohort participants are not representative community samples, their education level and income is likely higher than the national average and they are predominantly Caucasian. Furthermore, even though standard criteria and procedures are applied across all ADRCs, there may be some differences in diagnostic definitions and variability in recruitment strategies implemented by each ADRC. In addition, bias may arise from the degree of precision in classifying participants with respect to their hearing loss and hearing aid use status. To reduce this bias, we included only subjects with consistent labelling of hearing deficits and use/non-use of hearing aids as indicated by the records from each follow-up visit. We also implemented a suite of complementary analytical approaches, namely, covariate-adjusted analysis, propensity score matching, and sensitivity analysis for unmeasured confounding to better account for the possible impact of bias on the observed results. Consistency between the results of primary analysis and the results of different sensitivity analyses strengthen the credibility of our findings.

Identification of risk factors for developing MCI is of paramount importance as it may lead to the development of prevention strategies to reduce the risk of AD in high-risk populations. So far, most

studies have focused on preventing dementia, the most severe stage of cognitive impairment, rather than on preventing milder forms of cognitive impairment. More research is therefore needed to better understand the relationship between hearing impairment and changes in *cognitive* ability and the role of hearing rehabilitative strategies in mitigating these effects. Future studies should investigate whether there is a causal relationship between hearing loss and cognitive function, or if they are simply dependent measures of age-related neurodegeneration. If there is a true causal relationship between hearing impairment and increased risk of progression to MCI and between hearing aid usage and reduced incident MCI in healthy, hearing-impaired adults, such knowledge would provide new and novel insights into prevention of cognitive impairment and AD. This would help researchers plan large, multisite, international clinical trials that could provide evidence for AD prevention. Since a cure for AD is not yet available, finding effective preventive strategies is essential to improve the quality of life of individuals, families, and wider society and to reduce the costs to healthcare systems.

Declarations

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Conflicts of interest: Not applicable

Ethics approval: The National Alzheimer's Coordinating Center Uniform Data Set (NACC-UDS) is approved by the University of Washington Institutional Review Board and participants provided informed consent at the Alzheimer's Disease Center where they completed their study visits.

Consent to participate: Informed consent was obtained from all study participants.

Consent for publication: Not applicable

Availability of data and material: The data sets generated and analysed during the current study are available through the publicly available National Alzheimer's Coordinating Center UDS database. The current set includes data from the June 2019 NACC data freeze (proposal nr: 1026).

Code availability: The statistical analyses were performed with R, version 3.51.

Author contributions: MB, PLM were responsible for the study design. MB, SB were involved in the acquisition of data. The data were analysed by MB. All authors were involved in the interpretation of data. MB drafted the article. All authors revised the work critically. All authors approved the final version of the manuscript for publication and agree to be accountable for all aspects of the work.

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Tables

Table 1. Demographic characteristics of participants.

	Scenario 1			Scenario 2			Scenario 3		
	Hearing impairment	No hearing impairment	*P*-value	Hearing aid used	Hearing aid not used	*P*-value	No hearing impairment	Hearing impairment, hearing aid used	*P*-value
Sex, No. (%)									
Male	408 (50.0)	1460 (29.8)	< 0.001	292 (52.0)	56 (40.6)	0.02	1460 (29.8)	292 (52.0)	< 0.001
Female	408 (50.0)	3445 (70.2)		270 (48.0)	82 (49.4)		3445 (70.2)	270 (48.0)	
Age, No. (%)									
≥ 70	663 (81.3)	2378 (48.5)	< 0.001	478 (85.0)	98 (71.0)	< 0.001	2378 (48.5)	478 (85.0)	< 0.001
< 70	153 (18.7)	2527 (51.5)		84 (15.0)	40 (29.0)		2527 (51.5)	84 (15.0)	
Education, mean (SD), years[a]	16.5 (7.1)	16.1 (6.0)	0.11	16.6 (5.7)	16.3 (10.6)	0.71	16.1 (6.0)	16.6 (5.7)	0.03
CDRSB	0.12 (0.39)	0.08 (0.32)	< 0.001	0.11 (0.35)	0.17 (0.50)	0.13	0.08 (0.32)	0.11 (0.35)	0.06

Abbreviation: SD, standard deviation; CDRSB, CDR® Sum of Boxes

[a] measured as the number of years of education completed

Table 2. The baseline characteristics of participants in propensity score matched groups

	Scenario 1			Scenario 2			Scenario 3		
	Hearing impairment	No hearing impairment	*P*-value	Hearing aid used	Hearing aid not used	*P*-value	No hearing impairment	Hearing impairment, hearing aid used	*P*-value
Sex, No. (%)									
Male	408 (50.0)	409 (50.1)	1	54 (39.1)	56 (40.6)	0.90	293 (52.1)	292 (52.0)	1
Female	408 (50.0)	407 (49.9)		84 (60.9)	82 (49.4)		269 (47.9)	270 (48.0)	
Age, No. (%)									
≥ 70	663 (81.3)	663 (81.3)	1	98 (71.0)	98 (71.0)	1	477 (84.9)	478 (85.0)	1
< 70	153 (18.7)	153 (18.7)		40 (29.0)	40 (29.0)		85 (15.1)	84 (15.0)	
Education, mean (SD), years[a]	16.5 (7.1)	16.4 (6.5)	0.93	15.5 (3.0)	16.3 (10.6)	0.43	16.8 (6.7)	16.6 (5.7)	0.64
CDRSB	0.12 (0.39)	0.11 (0.38)	0.67	0.12 (0.43)	0.17 (0.50)	0.40	0.09 (0.31)	0.11 (0.35)	0.52

Abbreviation: SD, standard deviation; CDRSB, CDR® Sum of Boxes

[a] measured as the number of years of education completed

Table 3. Sensitivity analysis for unmeasured confounding

Prevalence of unmeasured confounder (%)		HR adjusted for unmeasured confounder (95% CI)[a]		
		Unmeasured confounder HR 0.5	Unmeasured confounder HR 1.5	Unmeasured confounder HR 2.0
Scenario 1				
Normal hearing	Hearing impairment			
10	10	1.40 (1.16,1.68)	1.40 (1.16,1.68)	1.40 (1.16,1.68)
	15	1.44 (1.19,1.73)	1.37 (1.14,1.64)	1.34 (1.11,1.61)
	20	1.48 (1.23,1.78)	1.34 (1.11,1.61)	1.28 (1.07,1.54)
15	10	1.36 (1.13,1.64)	1.43 (1.19,1.72)	1.46 (1.22,1.76)
	15	1.40 (1.16,1.68)	1.40 (1.16,1.68)	1.40 (1.16,1.68)
	20	1.44 (1.19,1.73)	1.37 (1.14,1.65)	1.34 (1.11,1.61)
20	10	1.33 (1.10,1.59)	1.47 (1.22,1.76)	1.53 (1.27,1.84)
	15	1.36 (1.13,1.64)	1.43 (1.19,1.72)	1.46 (1.21,1.76)
	20	1.40 (1.16,1.68)	1.40 (1.16,1.68)	1.40 (1.16,1.68)
Scenario 2				
Hearing aid used	Hearing aid not used			
10	10	0.32 (0.23,0.47)	0.33 (0.23,0.47)	0.33 (0.23,0.47)
	15	0.33 (0.23,0.48)	0.32 (0.22,0.46)	0.31 (0.22,0.45)
	20	0.34 (0.24,0.50)	0.31 (0.22,0.45)	0.29 (0.21,0.43)
15	10	0.32 (0.22,0.46)	0.33 (0.23,0.48)	0.34 (0.24,0.49)
	15	0.33 (0.23,0.47)	0.33 (0.23,0.47)	0.33 (0.23,0.47)
	20	0.33 (0.23,0.48)	0.32 (0.22,0.46)	0.31 (0.22,0.45)
20	10	0.31 (0.21,0.44)	0.34 (0.27,0.49)	0.36 (0.25,0.51)
	15	0.32 (0.22,0.46)	0.33 (0.23,0.48)	0.34 (0.24,0.49)
	20	0.33 (0.23,0.47)	0.33 (0.23,0.47)	0.34 (0.23,0.47)
Scenario 3				
Normal hearing	Hearing aid used			
10	10	1.23 (0.99,1.54)	1.23 (0.99,1.54)	1.23 (0.99,1.54)
	15	1.26 (1.00,1.58)	1.20 (0.96,1.50)	1.18 (0.94,1.47)
	20	1.30 (1.04,1.62)	1.18 (0.94,1.47)	1.13 (0.90,1.41)
15	10	1.20 (0.96,1.50)	1.26 (1.00,1.58)	1.29 (1.03,1.61)
	15	1.23 (0.98,1.54)	1.23 (0.99,1.54)	1.23 (0.99,1.54)
	20	1.27 (1.01,1.58)	1.20 (0.96,1.50)	1.18 (0.94,1.48)
20	10	1.17 (0.93,1.46)	1.29 (1.03,1.61)	1.34 (1.08,1.68)

	15	1.20 (0.96,1.50)	1.26 (1.01,1.58)	1.28 (1.03,1.61)
	20	1.23 (0.99,1.54)	1.23 (0.99,1.54)	1.23 (0.99,1.54)

[a] All models were adjusted for sex, age, education, and CDRSB score; Abbreviation: HR, hazard ratio;

Figures

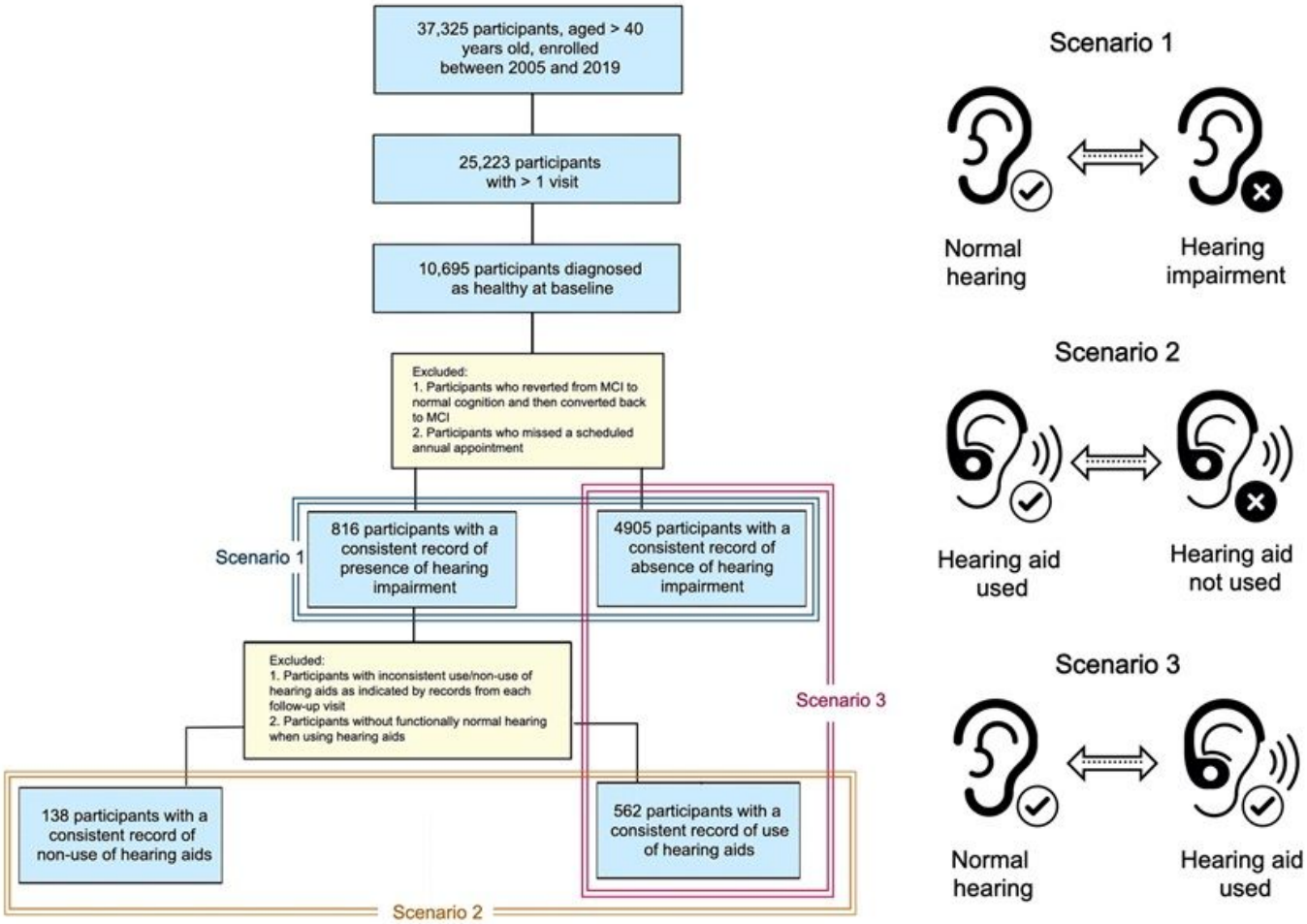

Figure 1

Selection process for study inclusion and research scenarios considered.

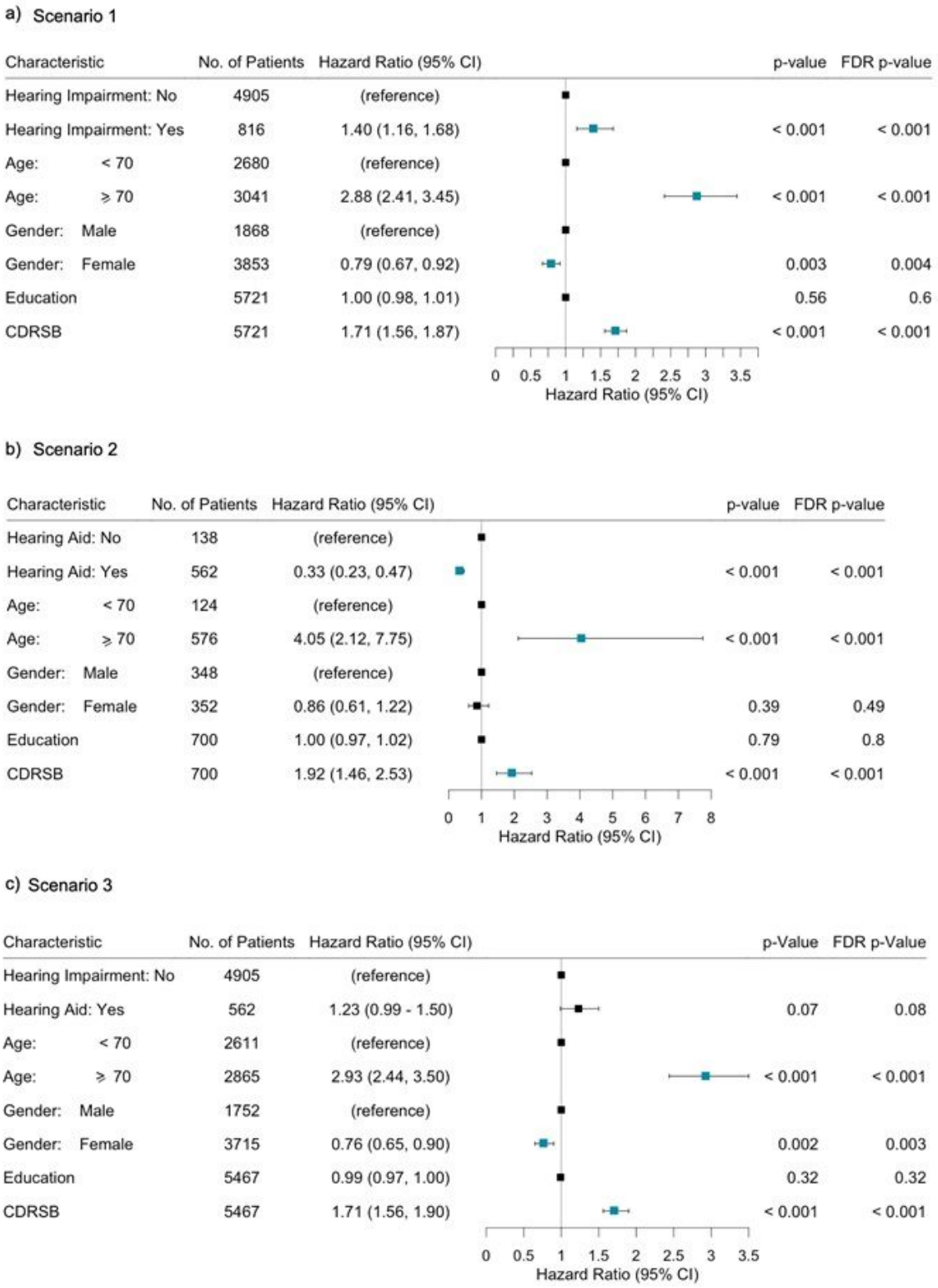

Figure 2

Multivariable Cox proportional hazards regression models estimating: A) the impact of hearing impairment on the progression from healthy to MCI (Scenario 1); B) the impact of hearing aid usage on the progression from healthy to MCI (Scenario 2); C) the risk of incident MCI diagnosis for participants experiencing no hearing loss and those diagnosed with hearing impairment that reported use of hearing aids (Scenario 3). All models were adjusted for gender, age, CDRSB score, and education measured as the

number of years of education completed. (CI: confidence interval; FDR: Benjamini-Hochberg false discovery rate).

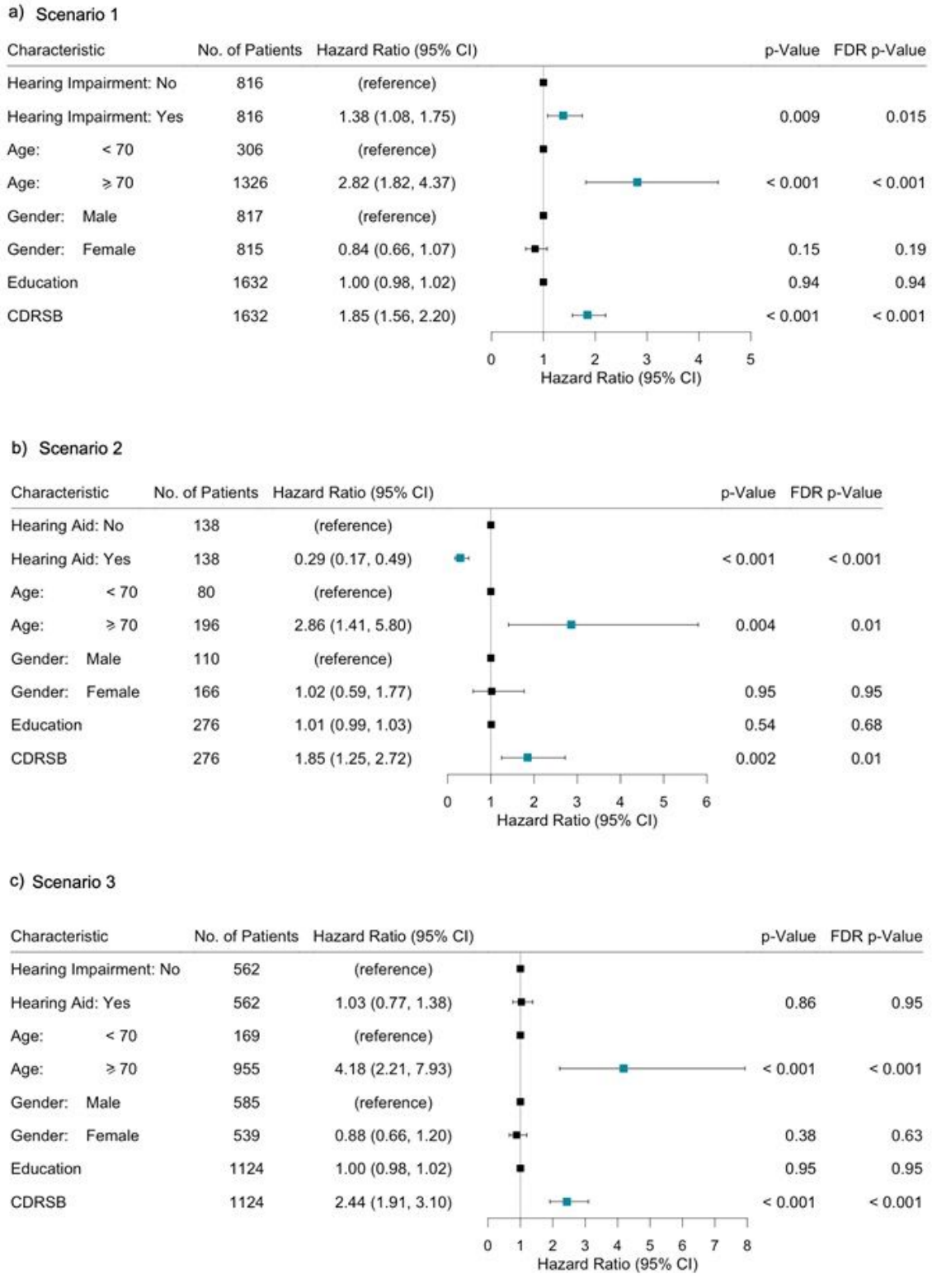

Figure 3

Prosperity score-based sensitivity analysis for risk of conversion from healthy to MCI. Participants were matched according to the group variable: A) participants with hearing impairment to participants without hearing impairment in Scenario 1; B) participants with hearing aids to participants without hearing aids in

Scenario 2; and C) participants without hearing impairment to participants with hearing impairment that use hearing aids in Scenario 3. All models were adjusted for gender, age, CDRSB score, and education measured as the number of years of education completed. (CI: confidence interval; FDR: Benjamini-Hochberg false discovery rate).

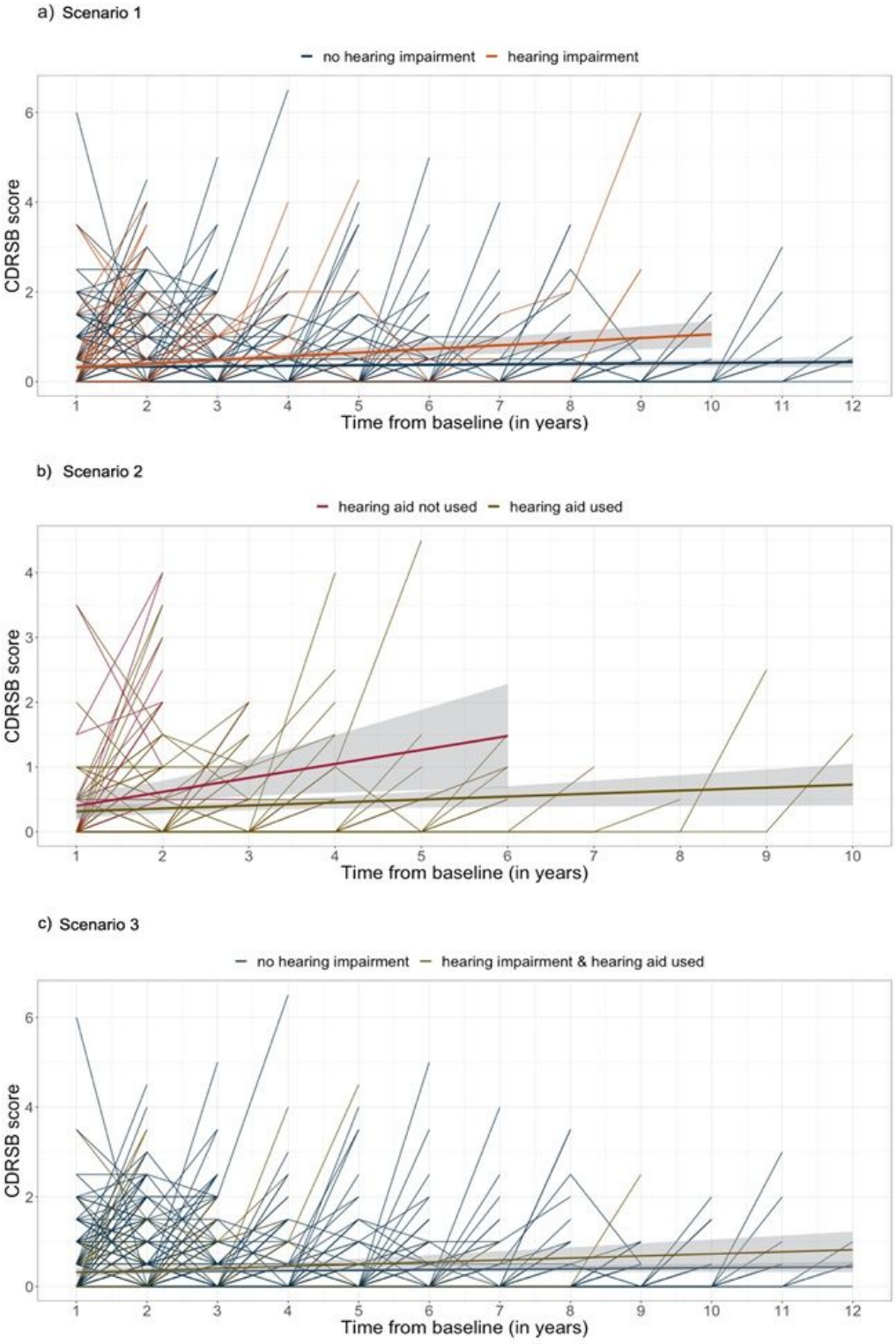

Figure 4

Longitudinal changes in cognitive test performance estimated using linear mixed-effects models for a) participants with and without hearing impairment (Model 1); b) users and non-users of hearing aids (Model 2); c) participants without hearing loss and hearing-impaired adults using hearing aids (Model 3). Individual test scores of CDRSB were used as dependent variables.