

RESEARCH ARTICLE

Exploring the genetic relationship between hearing impairment and Alzheimer's disease

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Abstract

Introduction: Hearing loss has been identified as the potentially largest modifiable risk factor for Alzheimer's disease (AD), estimated to account for a similar increase in AD risk as the apolipoprotein E (APOE) gene.

Methods: We investigated the genetic relationship between hearing loss and AD, and sought evidence for a causal relationship.

Results: We found a significant genetic overlap between hearing impairment and AD and a polygenic risk score for AD was able to significantly predict hearing loss in an independent cohort. Additionally, regions of the genome involved in inflammation were identified to be shared between hearing difficulty and AD. However, causality tests found no significant evidence of a causal relationship between these traits in either direction.

Discussion: Overall, these results show that the relationship between hearing difficulty and AD may, in part, be due to shared genes and immune response pathways between the traits. However, currently available data do not support a causal relationship.

KEYWORDS

Alzheimer's disease, cognitive decline, dementia, genetic risk score, hearing aid, hearing loss, risk factor

1 | BACKGROUND

According to the World Health Organization, the total number of individuals estimated to have Alzheimer's disease (AD) worldwide is currently more than 50 million; this is projected to triple over the course of the next 30 years. As no new drugs for the treatment of AD have been approved since 2003,¹ emphasis on identifying modifiable risk factors that could be targeted in intervention studies to reduce the risk of AD is paramount.

Hearing loss has recently been identified as the potentially largest modifiable risk factor for AD (odds ratio [OR] = 1.94, 95% confi-

dence interval [CI; 1.38–2.73]) and is highly prevalent, occurring in 32% of individuals over the age of 55 years.² This is supported by a growing body of literature reporting a robust association between hearing impairment and late-life cognitive disorders, even when controlling for other confounding variables.^{3,4} Indeed, several prospective studies have shown that cognitively normal individuals with mild to severe hearing impairment are more likely to experience cognitive decline and dementia (OR range 1.04–2.89).^{2,5–24} We have summarized studies published in the past 10 years that reported a risk ratio for cognitive impairment as a result of hearing difficulty in Table 1.

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Though the association between hearing loss and dementia has been well documented epidemiologically, a causal relationship has not been clearly established. Several theories have been proposed to explain the association between hearing loss and dementia (for thorough reviews see Amieva and Ouvrard²⁵ and Panza et al.²⁶). First, the “deprivation hypothesis” postulates that hearing loss may result in accelerated brain atrophy, which may in turn lead to dementia. Alternatively, hearing loss has been associated with social isolation, cognitive disengagement, and depression; these factors have also been associated with dementia.^{2,27,28} Last, the “common cause” hypothesis assumes that a common factor is responsible for both traits and that hearing impairment may be a prodromal symptom of dementia.

These preliminary findings underscore the importance of further research aimed at investigating the relationship between hearing impairment and AD. The identification of causal mechanisms underlying this association may allow early detection of people with a predisposition to AD and possibly prevent the progression of the disease through the treatment of the hearing impairment (eg, hearing aids).

This study aims to investigate whether the relationship between hearing loss and AD is due to a shared genetic etiology, to identify regions of the genome shared between these traits, and seek evidence for a causal relationship.

2 | METHODS

2.1 | Data

2.1.1 | Hearing

We used the genome-wide association study (GWAS) summary statistics of a recently published study examining self-reported hearing difficulty and the use of hearing aids in the UK Biobank.²⁹ Hearing difficulty cases were defined as participants that answered yes to both “Do you have any difficulty with your hearing?” and “Do you find it difficult to follow a conversation if there is background noise (such as TV, radio, children playing)?” while controls were participants who answered no to both questions. Controls <50 years of age were excluded to ensure age was consistent between case and control groups. For the hearing aid analysis, cases were defined as individuals who reported “yes” to “Do you use a hearing aid most of the time?” while controls reported “no.” Final sample sizes used for association analyses were $n = 250,389$ (87,056 cases and 163,333 control subjects) for hearing difficulty, and $n = 253,918$ (13,178 cases and 240,740 control subjects) for hearing aid.

2.1.2 | Alzheimer's disease

We used summary statistics from the Jansen et al. meta-analysis of clinically diagnosed and “AD-by-proxy” cases (71,880 cases, 383,378 controls) due to its substantial sample size and thus increased statistical power to detect small genetic effects.³⁰ Clinically diagnosed cases

RESEARCH IN CONTEXT

- 1. Systematic review:** Several recent publications have reported an association between hearing impairment and Alzheimer's disease (AD). In fact, hearing impairment was identified as the largest modifiable risk factor for AD in a *Lancet Commission* paper (odds ratio 1.94 [1.38–2.73]), estimated to account for a similar increase in AD risk as APOE.
- 2. Interpretation:** We show that the observed relationship between hearing loss and AD may be due to a shared genetic etiology, independent of APOE. Our findings support mounting evidence of the importance of inflammatory pathways in AD but current genetic data do not support the hypothesis that hearing difficulty is a modifiable risk factor for AD.
- 3. Future directions:** We propose that future investigations target clinically diagnosed forms of hearing loss rather than broad phenotypes and that further clinical investigation of the role of the human leukocyte antigen region and immune response in this relationship is needed.

came from three case-control cohorts ($n = 79,145$) while the “AD-by-proxy” phenotype was defined by UK Biobank participants reporting whether their biological parent ever suffered from AD along with each parent's current age (or age at death, if applicable). The genetic correlation between the Jansen et al. summary statistics and the Lambert et al. GWAS of clinically diagnosed AD patients is 0.81, standard error (SE) = 0.18.³¹

Due to the large effect on AD risk and far-reaching linkage disequilibrium (LD) of the apolipoprotein E (APOE) region, the inclusion of this region in post-GWAS analyses can erroneously affect results. Thus, summary statistics excluding the APOE gene and flanking 500 kb (hg19, 19:44,909,039–45,912,650) were also generated for analyses.

2.2 | Genetic correlations between hearing difficulty, use of hearing aid and AD

Genetic correlations between all traits of interest were assessed using LD score regression (LDSC).³² Significance levels were corrected for multiple testing using Bonferroni correction (0.05/2 tests; $\alpha = 0.025$). Due to limited number of significantly associated single nucleotide polymorphisms (SNPs) for hearing aid use, all further analysis was conducted using the hearing difficulty GWAS.

2.3 | Target samples and prediction of hearing difficulty

To test whether a polygenic risk score (PRS) for AD is able to predict hearing impairment we used an independent cohort that was not

TABLE 1 Summary of studies published in previous 10 years that report a valid outcome measure of risk of cognitive impairment from hearing difficulty

Reference and study type	Sample size	Auditory measure	Cognitive measure	Mean follow-up	OR (95% CI or P-value)
Amieva et al. (2015) ⁶ Prospective	3670	Self-reported hearing loss	MMSE score decline	25 years	1.04 ($P < .01$)
Bushet al. (2015) ⁵ Prospective	894	PTA >25 dB	MMSE score decline and other cognitive tests	<3 weeks	1.11 ($P < .001$)
Davies et al. (2017) ⁷ Prospective	8780	Self-reported hearing loss	Self-reported diagnosis of dementia or relevant medication	11 years	1.57 (1.12-2.02)
Deal et al. (2017) ⁸ Prospective	1889	PTA >25 dB	Decline in 3MS or self-reported diagnosis of dementia or relevant medication	9 years	1.55 (1.10-2.19)
Fischer et al. (2016) ⁹ Prospective	1884	PTA >25 dB	MMSE <24 or self-reported diagnosis of dementia or AD	10 years	1.96 (1.16-3.29)
Ford et al. (2018) ¹⁰ Prospective	37,898	ICD Coding for hearing loss	ICD Coding for dementia	11.1 years	1.69 (1.54-1.85)
Ford et al. (2018) ¹⁰ Meta-analysis (14 studies)	72,831	Peripheral ARHL and CAPD	Incident dementia	NA	1.49 (1.30-1.67)
Fritze et al. (2016) ¹¹ Prospective	154,783	ICD Coding for hearing loss	ICD Coding for dementia	4 years	1.43 ($P < .001$)
Gallacher et al. (2012) ¹² Prospective	1612	Audiometry (PTA)	Clinical diagnosis	16.8 years	2.67 (1.38-5.18)
Gates et al (2011) ¹³ Prospective	274	Behavioral central auditory test	Clinical diagnosis	2.2 years	6.8 (1.9-24.1)
Golub et al (2017) ¹⁴ Prospective	1881	Examiner determined hearing loss	Neurological assessment and consensus diagnosis of dementia	7.4 years	1.69 (1.3-2.3)
Gurgel et al (2014) ¹⁵ Prospective	4463	Self-report or examiner determined	Neurological assessment and consensus diagnosis of dementia	4.2 years	1.27 (1.03-1.56)
Heywood et al (2017) ¹⁶ Prospective	1515	Whispered voice test	Neurological assessment and consensus diagnosis of dementia	3.8 years	2.3 (1.08-4.92)
Kiely et al (2012) ¹⁷ Prospective	4221	Audiometry (PTA)	<24 MMSE	11 years	1.49 ($P < .01$)
Lin et al (2014) ¹⁸ Prospective	1984	PTA >25 dB	3MS Score <80 or decline >5 points from baseline score	6 years	1.24 (1.05-1.48)
Lin et al (2011) ¹⁹ Prospective	639	Audiometry (PTA)	Neurological assessment and consensus diagnosis of dementia	11.9 years	1.27 (1.06-1.50) per 10 dB loss
Livingston et al (2017) ² Meta-analysis (3 studies)	3585	Peripheral ARHL	Incident dementia	NA	1.94 (1.38-2.73)
Loughrey et al (2018) ²⁰ Meta-Analysis (5 cross-sectional studies)	6582	PTA	Diagnosis or cognitive test	NA	2.0 (1.24-4.72)

(Continues)

TABLE 1 (Continued)

Reference and study type	Sample size	Auditory measure	Cognitive measure	Mean follow-up	OR (95% CI or P-value)
Loughrey et al (2018) ²⁰ Meta-analysis (3 prospective studies)	7817	PTA	Incident dementia		1.28 (1.02-1.59)
Quaranta et al (2014) ²¹ Cross-sectional	488	PTA >35 dB	MMSE score and clinical assessment for dementia	NA	1.6 (P = .03)
Su et al (2017) ²² Prospective	4108	ICD coding for hearing loss	ICD coding for dementia	2 years	1.29 (1.13-1.48)
Tomioka et al (2015) ²³ Prospective	4427	Self-reported hearing loss	MMSE <24	5 years	1.39 (1.02-1.76)
Wei et al (2017) ²⁴ Meta-analysis (10 studies)	15,521	Peripheral ARHL	Dementia		2.39 (1.58-3.61)
Yuan et al ³ Meta-analysis (11 studies)	176,893	Peripheral ARHL	Cognitive impairment	>6 years	1.57 (1.13-2.20)
Zheng et al (2017) ⁴ Meta-analysis (four studies)	7461	Peripheral ARHL and CAPD	Incident dementia		2.82 (1.47-5.42)

Abbreviations: 3MS, Modified Mini-Mental State Examination; ARHL, age-related hearing loss; CAPD, central auditory processing dysfunction; CI, confidence intervals; dB, decibel; ICD, international classification of disease; MMSE, Mini-Mental State Examination; OR, odds ratio; PTA, pure-tone audiometry.

^aWhen a study reported >1 hearing impairment threshold, only most severe is reported.

included in the AD GWAS. The Prospective Imaging Study of Aging (PISA) currently consists of approximately 3000 genotyped individuals that have completed extensive behavioral, psychological, and medical questionnaires, as well as cognitive testing and brain imaging.³³ Of these, 2548 individuals completed a disease checklist which included an item regarding hearing loss: Please indicate whether you have currently or have had any of the following conditions in the past: Hearing Loss (yes/no), with 448 individuals reporting “yes.”

The Jansen et al.³⁰ (without APOE) summary statistics were used to calculate the AD PRS for individuals in the PISA cohort (n = 2548). AD PRS were calculated using PLINK 1.9. SNPs were clumped according to Purcell et al. guidelines to account for LD.³⁴ Eight AD PRSs were calculated using different SNP *P*-value significance thresholds: $P < 5 \times 10^{-8}$, $P < 1 \times 10^{-5}$, $P < .001$, $P < .01$, $P < .05$, $P < .1$, $P < .5$, $P < 1$. For each individual, at each threshold, an AD PRS was calculated by multiplying the dosage score and effect size for each SNP, and then these values were summed across all loci. APOE genotype (derived from rs429358 and rs7412) was either obtained from imputed SNP data (where either the APOE SNPs were directly genotyped on the array or imputed with a high degree of certainty) or directly genotyped using TaqMan SNP genotyping assays, as described in Lupton et al.³⁵

The AD PRS were then used to predict an association with hearing difficulty. This was done in GCTA 1.91.7 using a logistic regression while accounting for APOE $\epsilon 4$ presence, sex, age, and the first 10 genetic ancestry PCs as fixed effects; relatedness among individuals was accounted for as a random effect with a genetic relatedness matrix.³⁶ Additionally, the presence of APOE $\epsilon 4$ was also used as a predictor (independent of the PRS) with the same covariates in a separate analysis. A Nagelkerke's R^2 was used to estimate the variance

explained by the PRS or APOE status. Significance values were calculated using a two-tailed Student's *t* test and the threshold adjusted for the number of tests using Bonferroni correction ($\alpha = 0.007$).

2.4 | Pairwise GWAS

The pairwise GWAS (GWAS-PW) method³⁷ was used to further fine-tune the genetic overlap between hearing difficulty²⁹ and AD (including APOE)³⁰ by identifying specific shared regions in the genome.

First, the genome is split into 1703 approximately independent regions. For each region, GWAS-PW was used to calculate the posterior probability of four different models: the region is unique to hearing difficulty, unique to AD, shared by both traits, and associated with both traits but via separate variants. To account for potential confounding due to sample overlap between traits, GWAS-PW requires the correlation between effect sizes in non-associated regions of the genome. To do this, fGWAS³⁷ was used to calculate the posterior probability of association (PPA) for each region separately for both traits. Regions with a PPA < 0.2 in both traits were selected and the correlation in SNP effect sizes between the two traits determined. The model with the highest posterior probability (given the posterior probability is >0.5) was selected.

2.5 | Gene mapping of shared region

SNPs in the shared region identified from the GWAS-PW analysis were uploaded to the FUMA platform v1.3.5³⁸ for functional annotation.

SNPs in this shared region were mapped to genes using either positional mapping (SNPs are mapped to genes based on proximity as being within a 10 kb window), eQTL mapping (significant association with the expression level of that gene), or chromatin interaction mapping (significant chromatin interaction between a risk and promoter regions of genes 250 bp upstream and 500 bp downstream of the transcription start site). As a secondary analysis, MAGMA v1.07³⁹ was used to conduct gene-based and gene-set tests to map protein-coding genes to the region of interest. A Bonferroni corrected significance threshold was applied ($P < 7.6 \times 10^{-4}$).

2.6 | Causality tests

Mendelian randomization (MR) is a statistical genetic method used to identify causal relationships between traits using genetic variants as instrumental variables.⁴⁰ SNPs that are robustly associated with a trait of interest are used as instruments to estimate the causal effect of that variable on other phenotypes of interest. For a SNP to be considered a valid instrument for MR, three assumptions must be fulfilled: that the SNP is associated with the exposure trait of interest, it is only associated with the outcome through that exposure, and that the SNP is not associated with a third factor has a *shared* effect on both our exposure and outcome that drives the observed association (horizontal pleiotropy).⁴⁰ When using results from studies that have overlapping participants (such as the UK Biobank), SNPs may be weak instruments from “winners curse” and their effects biased toward the observation.^{41,42} Thus, for this analysis we used the summary statistics from Lambert et al.’s International Genomics Alzheimer’s Project meta-analysis³¹ (which predominantly formed the non-UKB component of the Jansen et al.³⁰ meta-analysis) to select AD instruments (Table S2 in supporting information). Independent SNPs that reached genome-wide significance in the hearing difficulty GWAS were filtered for minor-allele frequency (MAF < 0.005) and harmonized with the AD summary statistics.

The causal relationship between hearing impairment and AD was tested in both directions using two-sample MR with the MRBase package.⁴³ Sensitivity analyses were conducted using five MR methods: inverse variance weighted (IVW)-MR, MR Egger, penalized weighted median, weighted median, and weighted mode.

A caveat of traditional MR methods is that the assumptions for instrument selection are often violated, leading to false positives through correlated horizontal pleiotropy. Therefore, we tested a new MR method, causal analysis using summary effect estimates (CAUSE),⁴⁴ which claims to accurately differentiate correlated pleiotropy from causal effects. CAUSE assumes that the relationship between SNP effect on exposure and SNP effect on outcome is a mixture of both causal and correlated pleiotropy and estimates posterior distributions of the causal effect, the shared effect, and the proportion of correlated pleiotropic SNPs from two models, one with a causal effect and one without (aka the sharing model). If the sharing model is not a significantly worse fit than the causal model, then the causal effect is not considered to be significant.

3 | RESULTS

3.1 | Genetic correlations

Genetic correlations among AD, hearing difficulty, and use of hearing aid summary statistics were examined using LDSC. The use of a hearing aid had the highest genetic correlation with AD ($r_g = 0.29$, SE = 0.11, $P = .01$) while hearing difficulty had a correlation of 0.13 (SE = 0.04, $P = .02$). The strong, long-reaching LD of the APOE locus can overly represent the APOE signal. Thus, we also tested the genetic correlations between AD (without APOE), hearing difficulty, and use of hearing aid. Both genetic correlations remained significant despite the exclusion of APOE; use of a hearing aid ($r_g = 0.24$, SE = 0.08, $P = .004$) and hearing difficulty ($r_g = 0.10$, SE = 0.03, $P = .02$).

3.2 | Prediction of hearing impairment

AD PRS were calculated using the Jansen et al.³⁰ summary statistics excluding the APOE region for 2458 individuals in the PISA cohort. PRSs for AD were significantly associated with hearing difficulty at all but one P -value threshold ($P < 1$), explaining up to 0.35% of variance (Figure 1A). Additionally, individuals with higher PRS for AD were more likely to experience hearing difficulty than those with lower PRS (Figure 1B). APOE $\epsilon 4$ status did not significantly predict hearing difficulty in this cohort ($R^2 = 0.0002$, $P = .48$).

3.3 | Pairwise GWAS

We used GWAS-PW to identify which regions of the genome were shared between AD and hearing difficulty. Out of model 3 and 4 (shared genomic regions), only one region had a posterior probability higher than 0.5. This region is located in the MHC region on chromosome 6 (hg19 chr 6:31,571,971–32,682,443) and is predominantly associated with human leukocyte antigen (HLA) immune response. A noted caveat of GWAS-PW is the inability to reliably distinguish model 3 and model 4 in the presence of strong LD between variants in the region.³⁷ As the identified region has a known complex LD structure, we visually inspected the variants in that region. Initially, this region was classified as best fitting in model 4, where the region is shared but each trait has separate causal variants. However, upon visual inspection, it appeared that the lead variants in this region are indeed shared between both traits (Figure 2).

3.4 | Gene mapping and annotation of shared region

Two SNPs, rs9469112 and rs6931277, from the AD GWAS were identified as lead SNPs in this region while three SNPs (rs644045,

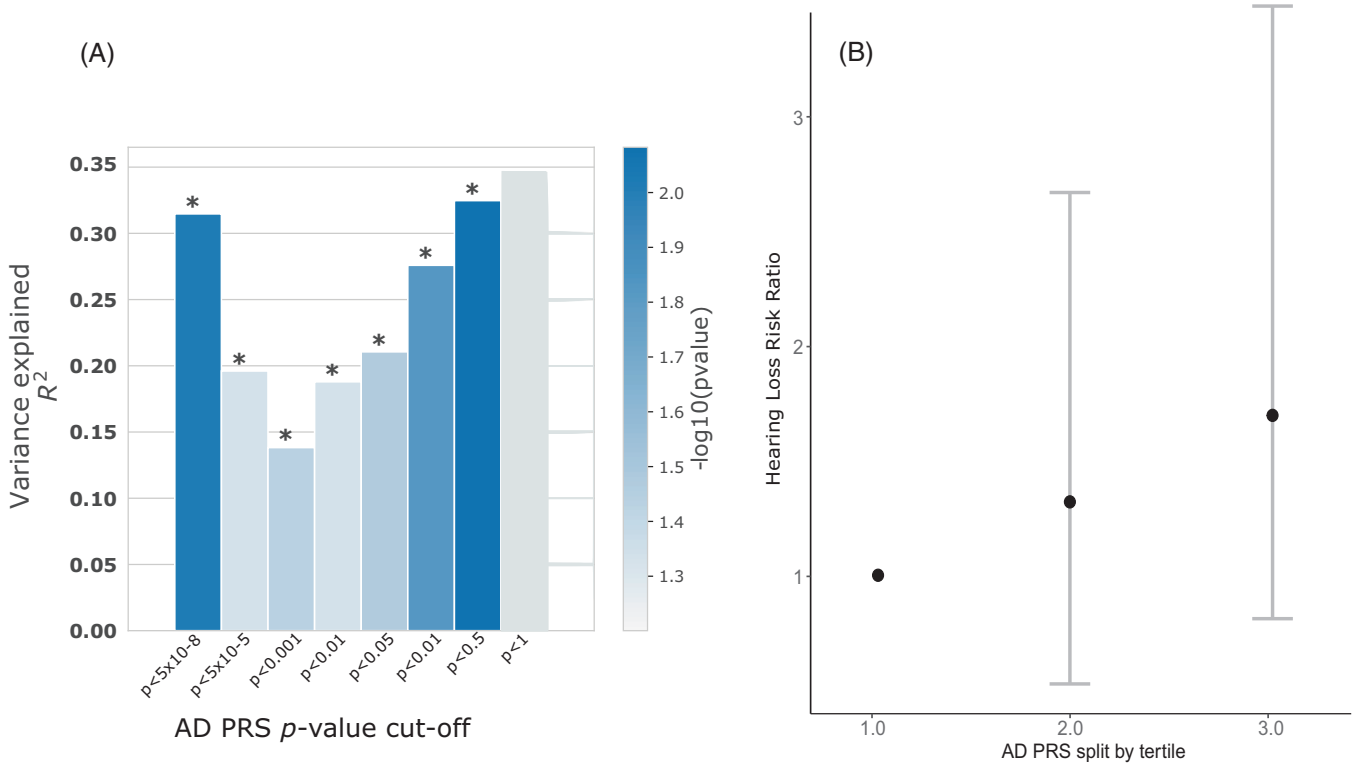


FIGURE 1 A, Polygenic risk scores (PRS) for Alzheimer's disease (AD) significantly predict hearing difficulty in the PISA sample ($n = 2548$) at all P -value thresholds except $P < 1$. * $P < .01$. B, Risk of self-reported hearing loss is positively associated with AD PRS. Error bars indicate 95% confidence intervals

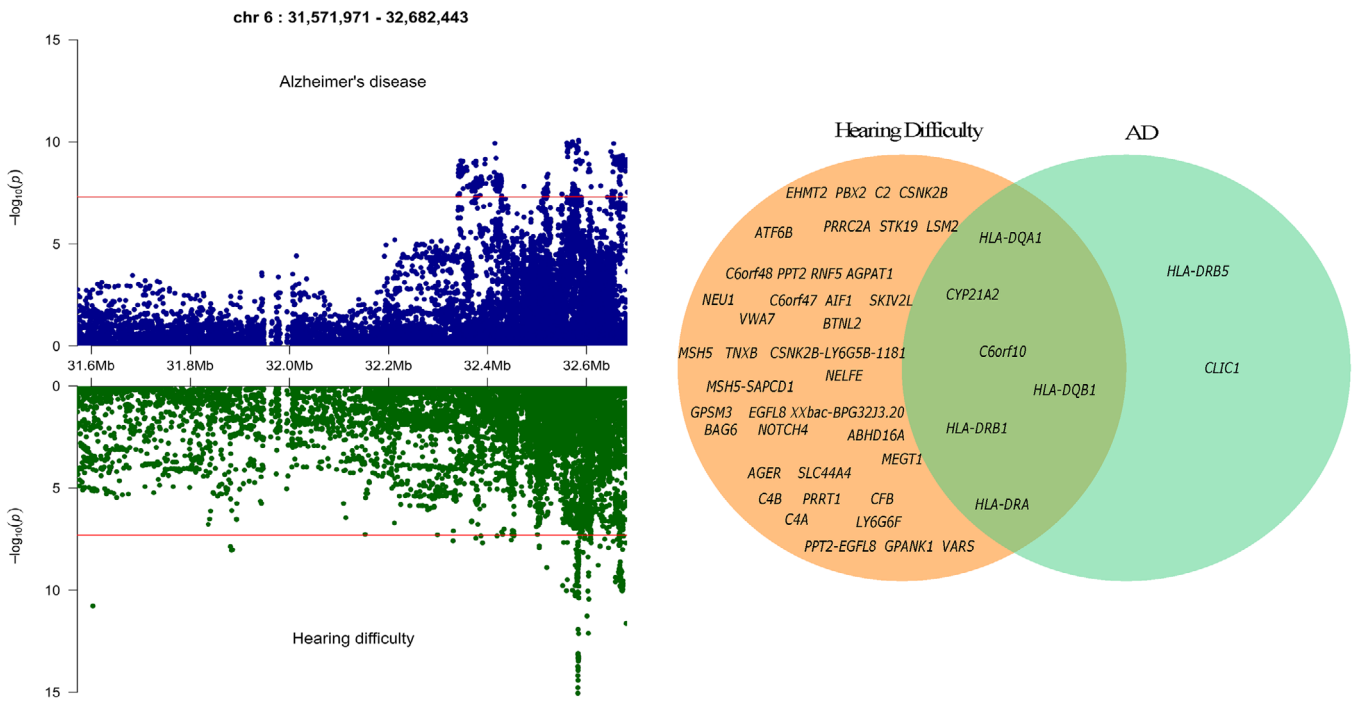


FIGURE 2 Left, Miami plot of single nucleotide polymorphisms in the shared MHC region (as pre-defined by pairwise genome-wide association study) on chromosome 6 between hearing difficulty and Alzheimer's disease (AD) indicates that the region shares causal variants. Right, Overview of genes mapped to this shared region using MAGMA; orange depicts 47 genes in this region that are significantly associated with hearing difficulty and green depicts 8 genes associated with AD. Six genes are significantly associated with both traits

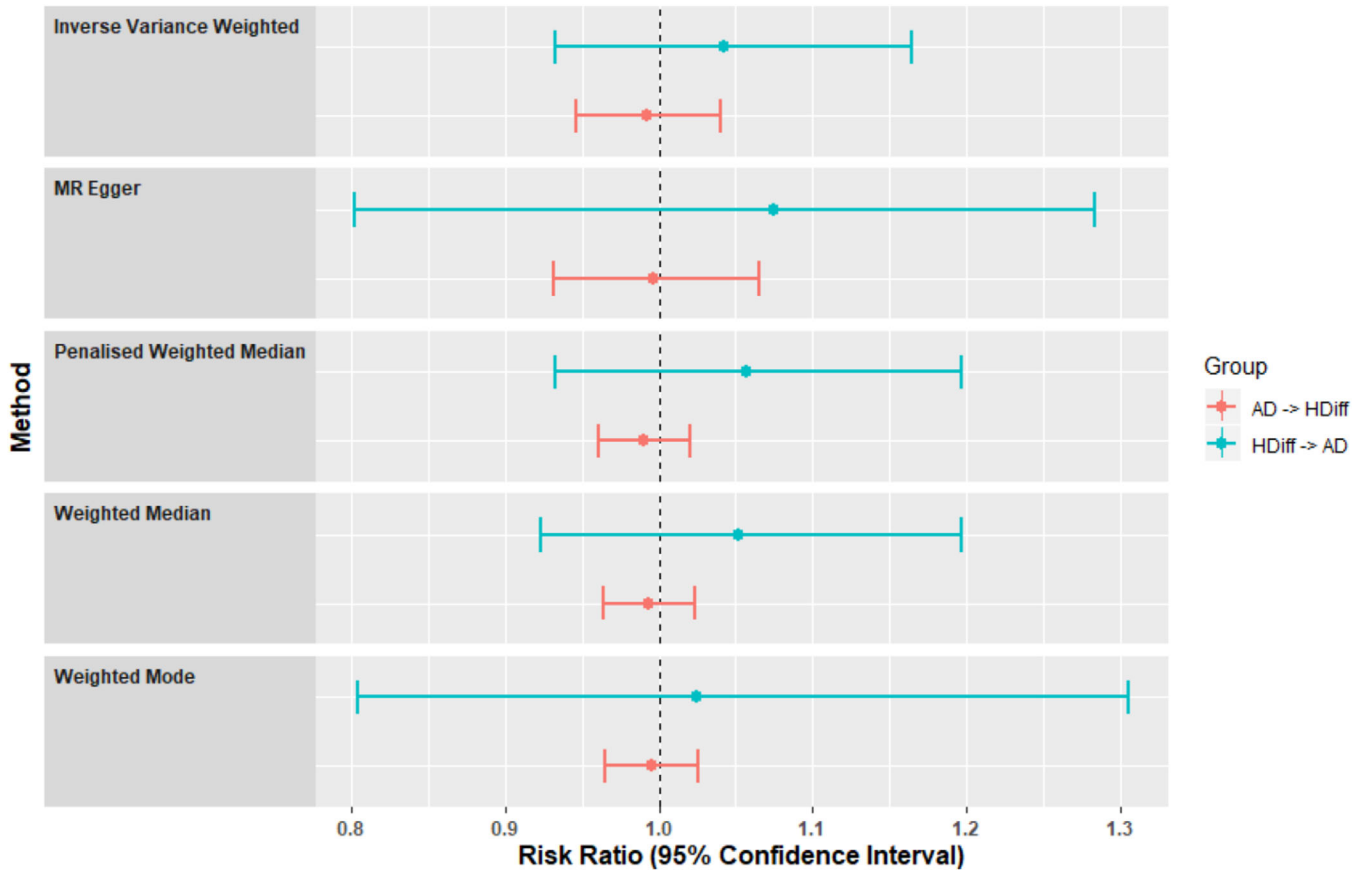


FIGURE 3 No evidence for a significant causal effect between hearing difficulty and Alzheimer's disease was observed in either direction using five Mendelian randomization methods. Error bars indicate 95% confidence intervals

rs13204736, and rs28445646) were identified from the hearing difficulty GWAS (Table 1). Genes were then mapped to this region using positional, eQTL, and chromatin interaction mapping, resulting in 55 genes in common between both AD and hearing difficulty (Table S3 in supporting information). Using MAGMA, 65 genes were mapped to the shared region of interest, of which, 47 were significantly associated with hearing difficulty (Table S4 in supporting information) and 8 with AD (Table S5 in supporting information) after Bonferroni correction ($\alpha = 0.0008$). Six of the overlapping genes were significant in both MAGMA tests: *HLA-DRA*, *C6orf10*, *HLA-DRB1*, *HLA-DQA1*, *CYP21A2*, and *HLA-DQB1* (Figure 2).

Gene set enrichment analysis of the mapped genes in the region of interest was conducted and 41 gene sets were significantly enriched for Gene Ontology (GO) biological processes (Tables S6 and S7 in supporting information). For both traits, the most significant biological processes were "antigen processing and presentation of peptide antigen," "interferon GAMMA-mediated signaling pathway," and "positive regulation of immune response." These gene sets are robustly shared with those from several disorders reported in the GWAS catalog,⁴⁵ the most significant of which are autism spectrum disorder or schizophrenia, ulcerative colitis and inflammatory bowel disease (Tables S8 and S9 in supporting information).

3.5 | Causality tests

We used MR to test for a causal relationship between AD and hearing difficulty. First, we tested for a bidirectional causal relationship using five traditional MR methods. None of these methods supported a causal relationship between AD and hearing difficulty in either direction (Figure 3). While the point estimates for AD causing hearing impairment are close to zero, for hearing impairment causing AD, the point estimates are all in the supportive direction, albeit non-significant, indicating that the instruments for hearing difficulty may be insufficiently powered. Next, to ensure that our analysis did not violate any MR assumptions we tested for horizontal pleiotropy using the MR Egger intercept test and examining heterogeneity between Wald ratio estimates from the IVW-MR analysis. Neither analysis reached significance, indicating that the SNPs used in our analysis did not violate any pleiotropy assumptions.

However, to add confidence to these results, we decided to do the same analysis using a newer MR method, CAUSE, which has shown superior ability to account for correlated horizontal pleiotropy. Using CAUSE, the model fit for both the sharing and causal models was not significantly different from the null model (no causal or shared effect; Table 2). Though the causal model trended toward having a better fit

TABLE 2 Results from CAUSE MR show that the sharing model is not a significantly worse fit than the causal model and thus does not support a significant causal relationship between hearing difficulty and AD

Model 1 ^a	Model 2 ^a	Δ ELPD ^b	s.e. Δ ELPD	z-Score	P-value
Null	Sharing	0.03	0.54	0.059	.52
Null	Causal	-0.97	1.90	-0.52	.30
Sharing	Causal	-1.00	1.40	-0.74	.23

^aModel 1 and Model 2 refer to the models being compared (null, sharing, or causal).

^bModel fit is measured by Δ Expected Log Pointwise Posterior Density (ELPD); Negative values indicate that model 2 is a better fit.

Abbreviations: AD, Alzheimer's disease; CAUSE, causal analysis using summary effect; ELPD, expected log pointwise posterior density; MR, Mendelian randomization.

than the sharing model, ultimately neither fit was statistically better than the other.

4 | DISCUSSION

In this study we examined the genetic relationship between hearing loss and AD using post-GWAS statistical methods. We found significant genetic correlations between self-reported hearing difficulty and the use of a hearing aid with AD. The use of a hearing aid had the largest genetic correlation with AD, despite being far less powered than hearing difficulty, likely indicating increased heterogeneity in self-reported hearing difficulty. We also show that a polygenic risk score of genetic variants associated with AD is able to significantly predict self-reported hearing loss in an independent sample after controlling for the effect of sex, age, and presence of *APOE* ϵ 4 allele. Interestingly, *APOE* alone was not significantly associated with hearing difficulty. Though the question used to define hearing loss in the PISA sample lacks clinical verification, these results are in line with a recent study that examined the same relationship in the UK Biobank and found *APOE* was not significantly associated with objectively measured hearing difficulty ($P = .2$).⁴⁶

Over the past 10 years, epidemiological studies have consistently reported a positive association between hearing impairment and dementia risk as summarized in Table 1. Such studies have shown that the risk of dementia increases (OR 1.3 [1.0–1.6]) per 10 dB of worsening of hearing loss²⁰ and that the use of hearing aids significantly delays the onset of late-life cognitive disorders (OR 0.82 [0.76–0.89]).^{25,47,48} In fact, it has recently been shown that the increased risk of dementia as a result of hearing impairment continues even below the clinical threshold for hearing impairment.⁴⁹ This may indicate that subtle hearing impairment may erode cognitive reserve that may in turn lead to AD.

Several other theories have been proposed to explain the association between hearing impairment and AD. Hearing impairment has been proposed as a risk factor for AD through mediating pathways such as sensory deprivation and social isolation leading to decreased cognitive function^{15,50,51} and an increased cognitive load through auditory processing rather than other cognitive processes.^{52,53} This decreased auditory stimulation may lead to micro-changes in the brain that increase risk of AD brain pathology, such as amyloid decomposition.¹⁸

An alternative hypothesis is that the relationship between these two traits may be due to a common cause, such as shared genes or age-related changes in the brain, and that hearing impairment may be an early symptom of cognitive decline.^{2,53}

To further examine the genetic relationship between AD and hearing difficulty, we used GWAS-PW to identify which regions of the genome were most likely to be shared between hearing difficulty and AD. The implicated region on chromosome 6 is predominantly associated with genes linked to immune response and has been associated with disorders such as schizophrenia and inflammatory bowel disease. Immune system response and the *HLA* gene region have been robustly associated with AD,^{54–56} as well as hearing impairment.^{57,58} Though shared genes in this region may be partially responsible for the epidemiological observations between hearing difficulty and AD, this region of the genome has a complex linkage disequilibrium structure, therefore it is difficult to distinguish whether the same or different genes in this region are responsible for correlation between the two phenotypes.⁵⁹

We tested for evidence of a causal association between hearing difficulty and AD using several genetic causality methods but found no significant evidence of a causal relationship in either direction. Therefore, although there is mounting epidemiological evidence that hearing impairment may be a risk factor for AD, we find no support for a causal relationship using only genetic variants associated with both traits. Notably, a limitation of such causality methodologies is that the results are highly dependent on how well the chosen instrument (SNPs) represents the phenotypes that are being tested. The SNPs used to represent hearing difficulty are from a GWAS based on the self-reported occurrence of a relatively common disorder²⁹ that may not meet clinical classification of hearing loss, nor adjusts for timing of the hearing impairment. Although the hearing aid GWAS showed a promising genetic correlation with AD, the low number of significant SNPs limits its applicability in such studies.⁶⁰ Similarly, the AD meta-analysis included participants that were “AD-by-proxy” as cases based on self-reported diagnoses of their parents. These individuals may or may not have AD themselves and the phrasing of the question from the UK Biobank does not differentiate between AD and other forms of dementia. Future studies may benefit from results of more statistically powered GWAS results and/or GWAS conducted on more clinically or objectively defined samples (and therefore stronger instruments for MR).

5 | CONCLUSION

This study identified a significant genetic correlation between hearing impairment and AD and supports mounting evidence of the importance of inflammatory pathways in AD. However, currently available data are insufficiently powered to resolve the presence or direction of causation between these traits, or potential pleiotropy of the implicated shared genes. While we cannot discount the possibility that future larger and less heterogeneous samples may find evidence of causality, for the present, our results currently do not support the hypothesis that hearing difficulty is a modifiable risk factor for AD and that the simple management of hearing loss will likely not mitigate the risk of AD. Further investigation into this relationship may benefit from targeting specific, diagnosed types of hearing loss, such as peripheral versus central hearing loss.

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AUTHOR CONTRIBUTIONS

BLM, JGT, and MKL designed this study and wrote the first version of the manuscript. BLM performed the analyses with input from JGT, DME, and DRN. NGM and MKL led the PISA study data collection efforts. All authors contributed to the interpretation of the results and provided feedback on the preliminary versions of the manuscript.

CONFLICTS OF INTEREST

All authors report no conflicts of interest in relation with this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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