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ARTICLE

Association of genetic risk for Alzheimer disease and hearing impairment

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Abstract

Objective

To test the hypothesis that incipient Alzheimer disease (AD) may adversely affect hearing and that hearing loss may adversely affect cognition, we evaluated whether genetic variants that increase AD risk also increase problem hearing and genetic variants that increase hearing impairment risk do not influence cognition.

Methods

UK Biobank participants without dementia ≥56 years of age with Caucasian genetic ancestry completed a Digit Triplets Test of speech-in-noise hearing (n = 80,074), self-reported problem hearing and hearing with background noise (n = 244,915), and completed brief cognitive assessments. A genetic risk score for AD (AD-GRS) was calculated as a weighted sum of 23 previously identified AD-related polymorphisms. A genetic risk score for hearing (hearing-GRS) was calculated using 3 previously identified polymorphisms related to hearing impairment. Using age-, sex-, and genetic ancestry–adjusted logistic and linear regression models, we evaluated whether the AD-GRS predicted poor hearing and whether the hearing-GRS predicted worse cognition.

Results

Poor speech-in-noise hearing (>-5.5-dB speech reception threshold; prevalence 14%) was associated with lower cognitive scores (ß = −1.28; 95% confidence interval [CI] −1.54 to −1.03). Higher AD-GRS was significantly associated with poor speech-in-noise hearing (odds ratio [OR] 1.06; 95% CI 1.01–1.11) and self-reported problems hearing with background noise (OR 1.03; 95% CI 1.00–1.05). Hearing-GRS was not significantly associated with cognitive scores (ß = −0.05; 95% CI −0.17 to 0.07).

Conclusions

Genetic risk for AD also influences speech-in-noise hearing. We failed to find evidence that genetic risk for hearing impairment affects cognition. AD disease processes or a that shared etiology may cause speech-in-noise difficulty before dementia onset.

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Glossary

AD = Alzheimer disease; **CI** = confidence interval; **DTT** = Digit Triplet Test; **GERA** = Genetic Epidemiology Research on Adult Health and Aging; **GRS** = genetic risk score; **ICD-9** = *International Classification of Diseases, 9th revision*; **IGAP** = International Genomics of Alzheimer's Project; **MR** = mendelian randomization; **OR** = odds ratio; **PC** = principal component; **SE** = standard error; **SNP** = single nucleotide polymorphism; **SRT** = speech reception threshold.

Age-related hearing impairment is among the most important potentially modifiable determinants of Alzheimer disease (AD).[1] Many observational studies have found that hearing impairment is associated with cognitive decline.[2–7] However, given the long, insidious development of hearing loss and dementia, it is difficult to establish temporal order or to rule out shared etiologies.

Age-related hearing impairment is caused by loss of peripheral hearing (involving the ear) or loss of central hearing (brain processing abilities). Hearing loss, especially peripheral, is thought to cause dementia through effects on social isolation or cognitive capacity,[8] but the evidence is not conclusive. Underlying AD-related neurodegeneration may affect central hearing loss even in prodromal stages.[9–11] In addition, other diseases, including vascular or metabolic disease, may affect hearing[12,13] and promote cognitive decline.[14,15] Prior observational studies cannot evaluate these different hypothesized mechanisms; novel study designs are needed to test these alternatives.

To begin to evaluate these hypotheses; we used an approach paralleling a bidirectional mendelian randomization (MR) study, which uses genetic variants to evaluate the causal effect of a risk factor on a health outcome.[16–18] First, we took advantage of known genetic variation in AD risk,[19] which is established at birth, to test the hypothesis that shared genetics or incipient AD may influence hearing in older adults without dementia (figure 1A), focusing on a speech-in-noise test, which may be sensitive to central hearing loss. Second, we took advantage of known genetic variation in hearing-impairment risk[20] to test the hypothesis that hearing impairment may influence cognition (figure 1B).

Methods

Study setting and participants

UK Biobank is an ongoing study of >500,000 adults. Participants 40 to 69 years of age were recruited from 2006 to 2010 from across the United Kingdom to provide detailed information about themselves via computerized questionnaires, provide biological samples, undergo clinical measurements, and have their health followed up prospectively.[21] Participants are generally healthy volunteers compared to the general UK population and do not have dementia at enrollment.[22]

The current analysis was restricted to UK Biobank participants ≥56 years of age (n = 291,516) to focus on older adults in whom hearing loss was likely to be common. We excluded those with missing genetic information (n = 8,560) or who were flagged as recommended for genetic analysis exclusion (n = 226) and those without any hearing assessments (n = 693). We also excluded participants classified as of non-European genetic ancestry (n = 37,122) on the basis of a combination of self-report and genetic ancestry principal components (PCs) because genetic predictors of AD may differ by race/population stratification.[23] This left an analytic sample of 244,915 with at least 1 hearing measure. A speech-in-noise hearing test was available for 80,074 of these participants.

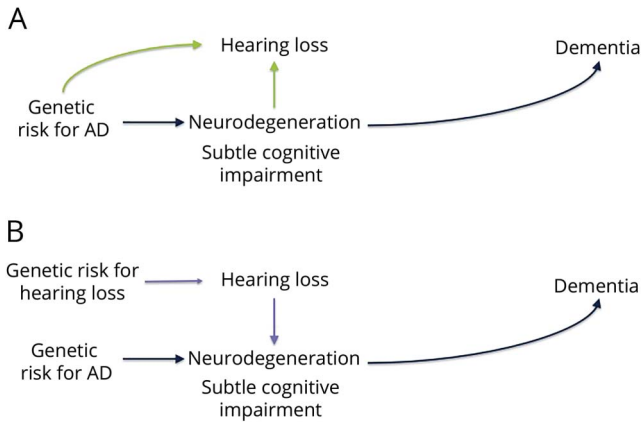
Standard protocol approvals, registrations, and patient consents

Ethics approval was obtained from the National Health Service National Research Ethics Service, and all participants provided written informed consent.

Hearing

A Digit Triplet Test (DTT), a measure of speech-in-noise hearing ability, was incorporated into visits during 2009 and was completed by 80,136 eligible participants. Participants with hearing aids were asked to remove hearing aids before

Figure 1 Conceptual models of AD genetic risk, dementia, and hearing loss motivating analysis



Genetic variants known to increase Alzheimer disease (AD) risk can be used to distinguish between mechanisms that may explain the previously documented association between hearing loss and dementia risk. If incipient neurodegeneration or other shared etiologies influence hearing loss, it implies that genetic variants that increase the risk of dementia will also be associated with increased risk of hearing loss (A). If hearing loss has effects on biological or social processes that increase risk of dementia, it implies that genetic risk for AD will be independent of (not associated with) hearing loss (B) but that genetic risk for hearing impairment will be associated with risk of dementia.

testing, and those with cochlear implants were asked not to attempt the test. Participants were guided by a video demonstration, performed the test via touchscreen, and wore circumaural headphones (Sennheiser HD-25, Wedemark, Germany). The English speech materials for the UK Biobank DTT were developed at the University of Southampton and are described elsewhere.[24,25] Digit triplets (e.g., group of 3 monosyllabic digits such as 2-8-5) were presented in a total of 15 sets. A background noise matched to the spectrum of speech stimuli played simultaneously while digit triplets were presented. In initial triplets, both noise and speech levels were adjusted together to a comfortable level. The speech level was then fixed, and noise levels were increased or decreased adaptively after each triplet to estimate the signal-to-noise ratio at which a participant had 50% correct recognition of 3 digits. A speech reception threshold (SRT) was used as the primary measure of speech-in-noise hearing. SRT was calculated as the mean signal-to-noise ratio for triplets 8 to 15. Higher scores correspond to worse performance. In analyses, we used the SRT of the better-hearing ear, following the approach of other studies.[3,26] Due to outliers and skewed distribution, we log-transformed the SRT (calculated as log [SRT + 13] to account for negative SRT values) when analyzing it as a continuous measure of speech-in-noise hearing. We also created a dichotomous indicator for poor speech-in-noise hearing, defined as an SRT >−5.5 dB, corresponding to cutoffs used in previous research.[3,26] The DTT test requires both peripheral and central hearing processing.[27]

All participants were also asked about problems hearing ("Do you have any difficulty with your hearing?") and problems hearing in noise (e.g., "Do you find it difficult to follow a conversation if there is background noise [such as television, radio, children playing]?"). Possible answers were "yes," "no," "do not know," and "prefer not to answer." We considered the answers "do not know" or "prefer not to answer" as missing data. Self-reports of hearing difficulty are complementary to audiometric measurements and have been validated against audiometric measures of hearing impairment for use in large epidemiologic studies,[28] and prior work has found that the measures of hearing with background noise are highly correlated with the UK Biobank DTT.[3]

Genotyping and genetic risk scores for AD

Genotyping of UK Biobank samples was conducted with 2 closely related arrays (Affymetrix using a bespoke BiLEVE Axiom array and Affymetrix UK Biobank Axiom array; Santa Clara, CA) and is described in detail elsewhere.[29,30] Briefly, all genetic data were quality controlled and imputed by UK Biobank (downloaded on December 1, 2017) to a reference panel that merged the 1,000 Genomes phase 3 and UK10K reference panels. A secondary imputation was completed with the Haplotype Reference Consortium reference panel, and results from the Haplotype Reference Consortium imputation were preferentially used at single nucleotide polymorphisms (SNPs) present in both panels. Before the release of the UK Biobank genetic data, a stringent quality control protocol was applied, which was performed at the Welcome Trust Centre for Human Genetics and is described elsewhere.[31] We additionally excluded participants from the present study if they had non-European ancestry (as described above), were missing genetic information, or were recommended for genetic exclusion by UK Biobank due to a high heterozygosity rate (after correction for ancestry) or high missing rate.[32]

We used summary results from the 2013 International Genomics of Alzheimer's Project (IGAP) meta-analyzed genome-wide association study on late-onset AD in White populations[19] to calculate an AD genetic risk score (GRS) for each participant. The IGAP study identified 23 loci associated with AD, including 2 SNPs used to characterize *APOE* ε4 allele status. The GRS was based on the meta-analyzed β coefficients obtained in the IGAP stage 1 study, which included genotyped and imputed data (7,055,881 SNPs, 1000 G phase 1α imputation, build 37, assembly Hg19) of 17,008 AD cases and 37,154 controls. We calculated the AD-GRS by multiplying each individual's risk allele count for each locus by the β coefficient (expressed as the log odds ratio [OR]) for that polymorphism (table 1) and summing the products for all 23 loci. This step weights each SNP in proportion to its anticipated effect (either positive or negative) on AD risk. The scores can be interpreted as the log OR for AD conferred by that individual's profile on the 23 SNPs compared to a person who had the major allele at each locus. With this construction, a 1-unit increase in the AD-GRS connotes a 2.7 times higher risk of AD. To assess the association with the AD-GRS beyond the effects of *APOE* ε4 (AD-GRS without *APOE*), we also calculated an alternative AD-GRS after removing the 2 SNPs associated with *APOE*. In a sensitivity analysis of the effects of *APOE* genotype alone, we created a score based on the 2 SNPs associated with *APOE*. From the *APOE*-only scores, we derived a dichotomous variable noting the presence of at least 1 *APOE* ε4 allele.

Using similar methods, we also calculated a GRS for age-related hearing impairment (hearing-GRS). This score was based on 3 SNPs that have previously been identified to be significantly associated with age-related hearing impairment in the Kaiser Permanente Northern California Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort with replication in the UK Biobank.[20] Age-related hearing impairment in GERA was defined by ICD-9 codes 388.01 (presbycusis), 389.12 (bilateral neural hearing loss), and 389.19 (bilateral sensorineural hearing loss). We used effect estimates from GERA to calculate the hearing-GRS (table 1).[20]

Cognition

The verbal reasoning assessment (also called fluid intelligence in some UK Biobank reports) was a visual touchscreen-based test that required participants to solve problems based on logic and reasoning. A summary score was calculated from the number of correct responses to 13 questions within a 2-minute time limit. Although other cognitive measures were

Table 1 SNPs and their log OR estimates for the AD-GRS and the hearing-GRS

Marker name	Chromosome	Closest gene	Effect allele	Effect estimate
AD-GRS				
rs6656401	1	*CR1*	A	0.1567
rs35349669	2	*INPP5D*	T	0.0663
rs6733839	2	*BIN1*	T	0.188
rs190982	5	*MEF2C*	G	−0.0799
rs10948363	6	*CD2AP*	G	0.0978
rs11771145	7	*EPHA1*	A	−0.1024
rs1476679	7	*ZCWPW1*	C	−0.0783
rs2718058	7	*NME8*	G	−0.0697
rs28834970	8	*PTK2B*	C	0.0959
rs9331896	8	*CLU*	C	−0.1457
rs10792832	11	*PICALM*	A	−0.1297
rs10838725	11	*CELF1*	C	0.0753
rs11218343	11	*SORL1*	C	−0.2697
rs670139	11	*MS4A4E*	T	0.0803
rs983392	11	*MS4A6A*	G	−0.1084
rs10498633	14	*SLC24A4-RIN3*	T	−0.1044
rs17125944	14	*FERMT2*	C	0.1223
rs8093731	18	*DSG2*	T	−0.6136
rs3865444	19	*CD33*	A	−0.0954
rs4147929	19	*ABCA7*	A	0.1348
rs429358	19	*APOE*	C	1.3503
rs7412	19	*APOE*	T	−0.3871
rs7274581	20	*CASS4*	C	−0.1390
Hearing-GRS				
rs2877561	3	*ILDR1*	A	0.0862
rs9493627	6	*EYA4*	A	0.0797
rs4932196	15	*ISG20*	T	0.1697

Abbreviations: AD = Alzheimer disease; GRS = genetic risk score; OR = odds ratio; SNP = single nucleotide polymorphism.

assessed for some UK Biobank participants, we used these 2 measure for several reasons: the test was completed on a large fraction of the eligible sample; it declines with age; and it is correlated with all other cognitive measures.[33] Associations between poor hearing and cognition using other cognitive tests have been reported previously.[3]

Other covariates

Age and sex were reported during baseline assessment via touchscreen questionnaires. The UK Biobank provides PCs related to genetic population stratification, we used the first 5 PCs in our analyses to adjust for confounding by population stratification.

Statistical analysis

Following the general approach of a bidirectional MR study, we evaluated bidirectional relationships between hearing impairment and cognition using genetic risk as an analytic tool.[16–18] First, we estimated whether genetic variants known to increase risk for AD were associated with problem hearing by DDT or self-report. Next, we evaluated whether genetic variants known to increase risk for age-related hearing impairment were also

Table 2 Characteristics of UK Biobank participants included in the analyses

Participant characteristics	No. nonmissing	Mean (SD) or n (%)
Age	244,915	62.5 (3.8)
Female	244,915	130,092 (53.1)
AD-GRS with *APOE* (1 unit = log OR AD)	244,915	0.1 (0.4)
AD-GRS without *APOE* (1 unit = log OR AD)	244,915	−0.1 (0.2)
Hearing-GRS	239,868	0.4 (0.1)
Verbal reasoning score	80,542	6.1 (2.1)
SRT for speech-in-noise test	80,074	−7.1 (1.8)
At least 1 *APOE* ε4 allele	244,915	70,122 (28.6)
Poor speech-in-noise (SRT >−0.5.5 dB)	80,074	11,865 (14.8)
Self-reported problem hearing	235,971	72,876 (30.9)
Self-reported problem hearing in noise	240,842	100,870 (41.9)
Reported hearing aid use	244,915	10,934 (4.5)

Abbreviations: AD = Alzheimer disease; GRS = genetic risk score; OR = odds ratio; SRT = speech reception threshold.

associated with poor cognition. This approach takes advantage of the fact that genetic variants have an established temporal order (i.e., determined at conception, before disease onset) before the exposure (e.g., AD or hearing loss). Furthermore, one's genotypes are not as susceptible to traditional confounders in observational studies such as an one's socioeconomic status, health behaviors, or health conditions. This established temporal order helps improve causal inference in observational data.[16] If AD-related genetic variants influence hearing impairment, this provides evidence that either AD influences hearing impairment or the variants share a genetic etiology (figure 1A). In contrast, if hearing impairment–related genetic variants influence cognition, this provides evidence that hearing loss influences cognition (figure 1B).

First, we confirmed that, consistent with previous literature, (1) AD-GRS was associated with cognition (verbal reasoning), (2) hearing-GRS was associated with hearing impairment, and (3) hearing impairment was associated with cognition in our sample. We tested our primary hypotheses by evaluating the association between (1) AD-GRS and speech-in-noise hearing impairment and (2) hearing-GRS and cognition. We evaluated associations between AD-GRS (with and without *APOE*) and self-reported hearing measures as secondary analyses to evaluate the consistency of results because self-reported measures were available on a larger sample of participants. We estimated separate logistic regressions with each AD-GRS as the predictor and each hearing impairment measure as the outcome (poor speech-in-noise hearing, self-reported hearing problems, and self-reported problems with hearing in noise). We conducted a sensitivity analysis to attempt to isolate the effects of AD-GRS on peripheral hearing because the available hearing measures represent both central and peripheral hearing. We therefore adjusted for cognition (verbal reasoning) to evaluate the association between AD-GRS and speech-in-noise hearing loss, which may suggest an effect of the AD-GRS on peripheral hearing. SRT is a continuous measure, so we also ran a linear regression model between the AD-GRS and continuous log SRT.

We used linear regressions to test the association between hearing-GRS and cognitive test scores. We also estimated a traditional 2-stage least-squares instrumental variable model using the hearing-GRS as an instrument for hearing problems to further test whether findings were consistent with a causal effect of worse hearing on cognition.[34] The coefficients can be interpreted as the cognitive effects of differences in hearing resulting from the genetic variants and can be directly compared to the observational estimate of poor hearing on cognitive scores. All regression models included adjustment for age, sex, and 5 PCs to account for ancestry differences. We ran MR-Egger regression as a sensitivity analyses to test for any horizontal pleiotropy (e.g., independent effect of genetic variants on both hearing and cognition).[35] We report intercept terms and the intercept test from MR-Egger analysis for primary models; a nonzero intercept suggests horizontal pleiotropy. Analyses were conducted in R (version 3.3.2, R Foundation for Statistical Computing, Vienna, Austria). All tests were 2 sided with $\alpha = 0.05$, and we report 95% confidence intervals (CIs) to represent uncertainty in our effect estimates.

Data availability

Researchers can apply to UK Biobank to access the data used in this study (ukbiobank.ac.uk/).

Results

Average age of participants was 62.5 years (SD 3.8 years; table 2). The SRT was on average −7.1 dB (SD 1.8 dB); 14% had poor speech-in-noise hearing (SRT >−5.5 dB). Self-report of hearing problems was common (30%–40%). Of those who reported any hearing problems, 85% also reported problems hearing in noise; of those who reported any hearing problems in noise, 64.5% also reported problems hearing in general. Speech-in-noise hearing was significantly worse (higher value) in those with self-reported hearing problems (mean [SD] SRT −6.7 dB [2.1 dB] compared to −7.4 dB [1.5 dB]) and those with self-reported hearing problems in noise (mean [SD] SRT −6.8 dB [2.1 dB] compared to −7.4 dB [1.5 dB]) (both $p < 0.001$, Kruskal-Wallis test). Among those with poor speech-in-noise hearing (SRT >−5.5 dB), 52% had self-reported problems hearing, and 57% had self-reported problems hearing in noise.

Table 3 Linear regression coefficients predicting verbal reasoning scores as a function of self-reported and speech-in-noise measures of hearing and AD-GRS

Predictors	Verbal reasoning score β Value (95% CI)
Speech-in-noise test, n[a]	78,010
Poor SRT	−1.28 (−1.54 to −1.03)
SRT (continuous)	−0.13 (−0.14 to −0.12)
Self-reported hearing measures[a]	
Problem hearing (n = 76,156)	−0.08 (−0.12 to −0.05)
Problem hearing in noise (n = 78,642)	−0.08 (−0.11 to −0.05)
AD-GRS, n[b]	80,542
AD-GRS with *APOE*	−0.04 (−0.07 to −0.0002)
AD-GRS without *APOE*	0.02 (−0.07 to 0.10)

Abbreviations: AD-GRS = Alzheimer disease genetic risk score; CI = confidence interval; OR = odds ratio; SRT = speech reception threshold.
[a] Adjusted for age, sex.
[b] Additionally adjusted for 5 principal components to account for confounding by population stratification.

Confirming associations of hearing and AD-GRS with cognition

Every measure of poor hearing was associated with worse verbal reasoning (table 3). Higher AD-GRS with *APOE* was also associated with worse verbal reasoning (table 3), although the AD-GRS without *APOE* was not.

AD-GRS and hearing associations

AD-GRS was associated with poor speech in-noise hearing (SRT) ($p < 0.02$ for AD-GRS with *APOE* and $p < 0.02$ for AD-GRS without *APOE*). AD-GRS also predicted self-reported problems hearing in noise (table 4). The association of the AD-GRS and self-reported problems hearing was in the same direction but not statistically significantly. Effect sizes across all hearing outcomes ranged from a 2% to 13% increased odds of poor hearing per 1-unit increase in AD-GRS; to put this into more interpretable terms, an increase in the AD-GRS that would roughly triple the odds of AD would also increase risk of hearing impairment by 2% to 13%. There was a trend toward slightly higher effect sizes in analyses using poor speech-in-noise hearing.

Results were relatively similar with adjustment for cognition (verbal reasoning) as a covariate (table 4). The point estimate for poor speech-in-noise hearing was slightly reduced and CIs were slightly wider; however, fewer participants were included in these analyses due to missing cognitive data. *APOE* alone was not significantly associated with poor SRT (OR 1.04; 95% CI 0.98–1.10). Tests for horizontal pleiotropy of AD-GRS SNPs with MR-Egger regression were not significant, and intercepts were close to 0 for each hearing outcome (self-reported problem hearing:β = 0.000, standard error [SE] 0.000, $p = 0.97$; self-reported problem hearing in noise: β = 0.004, SE 0.002, $p = 0.11$; poor SRT: β = 0.006, SE 0.004, $p = 0.18$).

When SRT was used as a continuous measure of hearing, the AD-GRS with *APOE* (but not AD-GRS without *APOE*) was associated with worse average speech-noise hearing (SRT) (figure 2 shows effects by sample quartiles of AD-GRS with *APOE*).

Hearing-GRS and associations with hearing and cognition

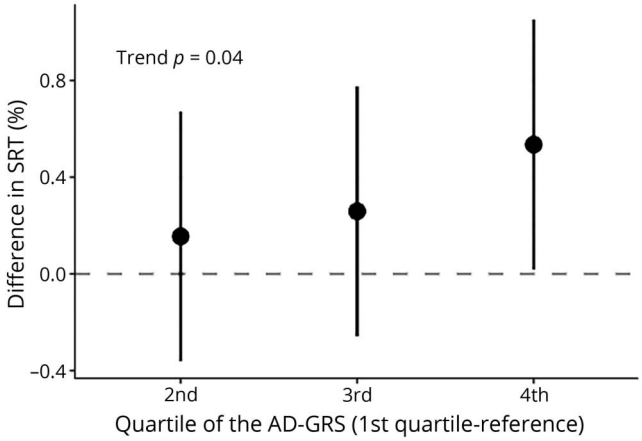
The hearing-GRS was significantly associated with worse speech-in-noise hearing (table 5) as expected: a 1-log-unit higher GRS was associated with 35% higher odds of poor speech-in-noise hearing (*F* statistic 9.62%) and 43% higher odds of self-rated problem hearing (*F* statistic 29.7). However, there was no significant association between the hearing-GRS and verbal reasoning scores (table 6). Conducted as an instrumental variable analysis in which the hearing-GRS was used as an instrument for SRT values, the point estimates for the effect of poor speech-in-noise hearing (SRT) on cognition (−1.89 points) were similar to the observational point estimate (−1.28 points); however, the instrumental variables–based effect estimate was lacking precision (table 6).

Table 4 ORs for the association between AD-GRS calculated with and without *APOE* variants and 3 measures of hearing[a]

AD-GRS	Poor speech-in-noise SRT OR (95% CI)	Self-reported problems hearing OR (95% CI)	Self-reported problems hearing in noise OR (95% CI)
No.	80,074	235,971	240,842
AD-GRS with *APOE*	1.06 (1.01–1.11)	1.02 (1.00–1.05)	1.03 (1.01–1.05)
AD-GRS without *APOE*	1.13 (1.01–1.27)	1.05 (0.99–1.10)	1.07 (1.02–1.13)
No.	78,010	78,641	76,156
AD-GRS with *APOE* adjusted for cognition	1.04 (0.99–1.10)	1.03 (1.00–1.07)	1.03 (0.99–1.07)

Abbreviations: AD-GRS = Alzheimer disease genetic risk score; CI = confidence interval; OR = odds ratio; SRT = speech reception threshold.
[a] Adjusted for age, sex, and 5 principal components to account for population stratification.

Figure 2 Association between speech-in-noise SRT and quartiles of AD-GRS (n = 80,074)



There was a significant trend ($p = 0.04$) for increasing quartile of Alzheimer disease genetic risk score (AD-GRS) and worse speech reception threshold(SRT) (positive change) on a continuous scale. However, only the fourth quartile had a significantly worse SRT than the first quartile of AD-GRS (reference group). Based on a linear regression of log SRT adjusted for age, sex, and 5 principal components to account for confounding by population stratification.

Discussion

In this study, we found that higher AD-GRS was associated with worse speech-in-noise hearing in a large sample of middle-aged and older adults without dementia. Findings were consistent across self-reported hearing problems and poor speech-in-noise hearing measurements. Effect estimates were generally small; the largest effect estimates were for the association of AD-GRS and speech-in-noise hearing assessment. Results were similar but slightly stronger for the AD-GRS without *APOE* compared to the AD-GRS with *APOE*. Participants did not have dementia at baseline, and these associations were independent of cognitive abilities at baseline; in addition, we did not find evidence for pleiotropic effects. We did not find evidence for an association between hearing-GRS and cognition, although estimates were in the expected direction. Future work will be necessary to fully tease apart the interplay of neurodegeneration, cognitive decline, and hearing loss.

Table 5 Regression coefficients predicting hearing as a function of hearing-GRS[a]

Predictor	Poor speech-in-noise SRT OR (95% CI)	Self-reported problems hearing OR (95% CI)
No.	78,398	231,107
Hearing-GRS	1.35 (1.14–1.59)	1.43 (1.32–1.53)

Abbreviations: CI = confidence interval; GRS = genetic risk score; OR = odds ratio; SRT = speech reception threshold.
[a] Adjusted for age, sex, and 5 PCs to account for confounding by population stratification.

Table 6 Regression coefficients predicting verbal reasoning score as a function of hearing-GRS

Model	Verbal reasoning score β Value (95% CI)
No.	78,865
Hearing-GRS[a]	−0.05 (−0.17 to 0.07)
Hearing-GRS as instrument for poor SRT[b]	−1.89 (−5.67 to 1.88)
Hearing-GRS as instrument for self-rated poor hearing[b]	−0.63 (−2.22 to 0.96)

Abbreviations: CI = confidence interval; GRS = genetic risk score; SRT = speech reception threshold.
[a] Adjusted for age, sex, and principal components to account for confounding by population stratification.
[b] Estimate for the predicted effect of poor hearing on verbal reasoning based on hearing-GRS.

However, our current findings are consistent with the hypothesis that the underlying AD process influences speech-in-noise hearing ability before the onset of cognitive impairment.

Sensory impairments are emerging as a potential marker of preclinical AD.[36] Amyloid plaque and neurofibrillary tangle deposition occurs in auditory pathways in patients with dementia.[10,37] Several studies have found that central auditory processing is significantly worse in those with AD dementia or even mild cognitive impairment[11,38–40]; 1 longitudinal study suggests that this auditory dysfunction may predict dementia onset.[11] Speech-in-noise hearing is correlated with cognitive tests, including attention and memory, beyond correlations with pure tone audiometry.[27] In addition, children with auditory processing disorders often can present with comorbid cognitive, reading, and language deficits[41] and have white matter structural abnormalities on brain MRI.[42] Participants with high AD-GRS in this study are disproportionately likely to be experiencing early effects of AD but do not have severe cognitive impairments at baseline; in fact, only a small fraction have developed dementia over follow-up.[43] Because neurodegeneration and even very subtle cognitive impairments may occur many years before the development of dementia symptoms,[44] these changes may in turn lead to worse hearing, consistent with our finding that higher genetic AD risk is associated with worse speech-in-noise hearing.

We used GRSs to begin to evaluate alternative causal hypotheses linking poor hearing and dementia. The majority of studies on hearing and dementia focus on peripheral hearing loss as a risk factor for developing dementia.[2–7] However, detecting speech in noise requires both peripheral and central hearing processing, as well as general cognitive abilities to discriminate digits.[3] As an important caveat, it is unclear from our findings whether genetic risk for AD is associated with peripheral hearing loss or purely central hearing. In prior studies, the *APOE* ε4 allele was both inversely[45] and positively[46] associated with peripheral hearing loss. However, in this study, the AD-GRS without *APOE* tended to have slightly stronger

associations with hearing impairment. Our findings suggest the AD-GRS is associated with hearing abilities independently of cognition and that further research with pure tone audiometric testing on a large sample of older adults is warranted.

Genetic variants related to AD may have pleiotropic pathways via which they influence hearing such as by affecting non-neurodegenerative factors such as vascular disease that may act as shared risk factors for hearing loss and cognitive decline. Variation in several AD genes, including *APOE*, affect lipid metabolism[47] and cardiovascular risk factors.[48] Our sensitivity analyses using MR-Egger regression, however, did not find strong evidence for pleiotropic effects. Furthermore, a genome-wide association study of neuropathologic contributors to dementia found that AD genetic loci are associated with AD neuropathology but not with vascular brain injury.[49] This lends further evidence to the hypothesis that the AD disease process may contribute to impairment in hearing but does not exclude the possibility of pleiotropic effects. Our analyses cannot distinguish whether these findings are the result of neurodegeneration in auditory or other brain regions or very early symptoms of cognitive impairment, although effects were independent of overall cognition. Regardless of this ambiguity in interpretation, our results suggest that problem hearing in noise may be an early marker for AD.

We did not find an association between the GRS for hearing impairment and cognition. Given the imprecision of our estimates, however, our findings do not conclusively exclude the possibility that hearing loss causes cognitive decline. Point estimates were similar between our observational and instrumental variable analyses; thus, it is possible that this analysis was underpowered. Age-related hearing impairment is likely highly polygenic, and few SNPs have shown significant associations in genome-wide association studies.[20] In future studies, it may be worth investigating the use of whole-genome information or combining samples to enhance analytic power.

The Lancet commission on dementia prevention calculated a relative risk of impaired peripheral hearing on dementia of 1.9,[1] equating to an OR of 2.0 to 2.5, depending on the prevalence of dementia. This estimated association between hearing and dementia is much higher than could be attributed to the effects of known AD genetic risk on impaired hearing in this study (OR 1.05–1.13). This suggests other mechanisms link hearing and dementia but does not establish that those other mechanisms are necessarily a causal effect of hearing on dementia. If peripheral hearing loss does cause dementia, then auditory interventions maybe be an effective a way to reduce dementia burden.[1] However, such an intervention would not be as effective if the association between peripheral hearing and dementia is partly explained by underlying AD or dementia processes, shared etiologies, or noncausal links. Although interventions to improve hearing and communication for older adults likely have broad benefits for social engagement and quality of life,[50] future studies are still needed to show that prevention of hearing loss slows cognitive decline.

There are several important caveats and limitations to our analysis. Effect sizes are small, and it is unclear how well speech-in-noise hearing impairment predicts future development of dementia. Our results are potentially influenced by selection bias due to selective survival because the AD-GRS is associated with mortality.[43] However, this effect is likely limited because the sample is relatively young and healthy with a low mortality rate, especially due to dementia. There is substantial variation in risk for AD that is not captured by our risk score. This limitation would likely reduce our ability to detect associations, and estimates may be underestimated. This analysis focused on genetic variants for AD, so we may not have captured associations specific to other dementia subtypes. However, these findings likely broadly apply to dementia because AD is the most common form of dementia and often co-occurs with other pathologies.[1] There may have been misclassification in the self-reported hearing measures, and directions for answering questions were unclear for participants with hearing aids. However, this also likely would bias results toward the null. This sample did not include participants of non-European ancestry, which may limit generalizability. There are also considerable strengths to this study, particularly the size of sample, the use of several measures of hearing abilities, and an innovative analytic approach.

We used variation in genetic risk for AD as an approach to examine whether the AD disease process or a shared etiology influences hearing. In support of this hypothesis, we found that higher genetic risk for AD was positively associated with worse hearing ratings and worse speech-in-noise testing. We also used variation in genetic risk for hearing impairment to examine whether hearing loss influences cognition. Although we did not find evidence to support this effect of hearing loss on cognition, our estimates were imprecise. Our findings suggest that poor speech-in-noise hearing may be an early marker of underlying dementia processes. However, additional research will be needed to replicate findings in other samples, to investigate measures of peripheral hearing loss, and to determine whether loss of speech-in-noise testing can be useful as a tool to identify preclinical AD.

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Disclosures

W. Brenowitz reports no disclosures relevant to the manuscript. T. Filshtein works at 23andMe but conducted the work while at the University of California, San Francisco. K. Yaffe, S. Walter, S. Ackley, T. Hoffmann, E. Jorgenson, R. Whitmer. and M. Glymour reports no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Appendix Authors

Name	Location	Contribution
Willa D. Brenowitz, PhD, MPH	University of California, San Francisco	Design and conceptualized study; analyzed the data; performed statistical analysis; drafted the manuscript for intellectual content
Teresa J. Filshtein, PhD	23andMe, Mountain View, CA	Analyzed and interpreted the data; revised the manuscript for intellectual content
Kristine Yaffe, MD	University of California, San Francisco	Interpreted the data; revised the manuscript for intellectual content
Stefan Walter, PhD	Rey Juan Carlos University, Madrid, Spain	Analyzed and interpreted the data; revised the manuscript for intellectual content
Sarah F. Ackley, PhD	University of California, San Francisco	Analyzed the data; revised the manuscript for intellectual content
Thomas J. Hoffmann, PhD	University of California, San Francisco	Interpreted the data; revised the manuscript for intellectual content
Eric Jorgenson, PhD	Kaiser Permanente Northern California Division of Research, Oakland	Interpreted the data; revised the manuscript for intellectual content
Rachel A. Whitmer, PhD	UC Davis School of Medicine, CA	Interpreted the data; revised the manuscript for intellectual content
M. Maria Glymour, ScD	University of California, San Francisco	Design and conceptualized study; interpreted the data; revised the manuscript for intellectual content

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