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RESEARCH ARTICLE

Women with hearing loss show increased dementia risk and brain atrophy

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Abstract

Hearing loss is a modifiable risk factor for dementia. However, it is unknown whether risk differs by sex.

Study 1 used Cox proportional hazard models to examine sex differences in the association between hearing loss (measured by speech-reception thresholds) and dementia risk. Study 2 examined how 2-year changes in hearing is associated with changes in brain volume in auditory–limbic regions. Both studies used UK Biobank data.

Women with poor hearing had the greatest risk of dementia, whereas women and men with insufficient hearing were at similar risk. Men with poor hearing did not have increased risk. Presence of social isolation/depressed mood minimally contributed to dementia risk in men and women. Women, but not men, with hearing loss had greater atrophy in auditory and limbic regions compared to normal hearing women and men.

Women with hearing loss show greater risk of dementia and brain atrophy, highlighting the need to examine sex-specific mechanisms.

KEYWORDS
brain volume, dementia risk factor, hearing loss, sex differences, UK Biobank

1 | INTRODUCTION

Hearing loss in mid- to late life is highly prevalent[1–3] and is associated with increased dementia risk and cognitive decline.[1,4–6] Similar to studies that measured hearing loss with pure-tone audiometry, Stevenson et al. report that poorer hearing as measured by a speech-in-noise task is also associated with increased dementia risk.[7] However, potential mechanisms linking hearing loss and dementia are poorly understood. One theory, the sensory deprivation hypothesis, suggests that reduced sensory input due to hearing loss negatively affects brain structure and cognition, thereby increasing dementia risk.[8,9] There is a growing body of literature showing that hearing loss is associated with lower brain volume and altered functional connectivity, in part, between auditory and medial temporal lobe regions.[10–14] These regions are proposed to be indirectly connected via an auditory–limbic pathway[15] and provide a potential mechanism linking hearing loss to dementia risk. A second theory suggests that the relationship between hearing loss and dementia is mediated by reduced socialization and mood.[8]

Large-scale efforts worldwide have highlighted the need to examine sex as a biological variable to better understand etiologies of complex diseases,[16] including hearing loss[17] and dementia.[18,19] For example, hearing loss is more prevalent and severe in men compared to women, particularly at higher frequencies.[2,3,20] Conversely, women have a greater prevalence of dementia and increased risk at older ages compared to men.[21] Yet, few studies have examined the relationship between hearing and cognition stratified by sex and those that have report equivocal results.[22] Therefore, there is a strong need to

determine whether there are sex differences in the association between hearing loss and dementia risk.

The purpose of this study was to investigate sex differences in the association between hearing loss and dementia risk and examine possible mechanisms explaining observed associations. Two studies were conducted using a large dataset of adults from the UK Biobank. In Study 1, we replicate the findings by Stevenson et al.[7] on the association between hearing loss and incident of dementia and its relationship with psychosocial mechanisms of social isolation/depressed mood. However, unique to our study, we disaggregate these associations separately by sex. In Study 2, we examined neural mechanisms by comparing sex differences in the association between hearing loss and brain atrophy within the auditory–limbic pathway. Given that men are more likely to have a hearing loss and with an earlier age of onset than women, we hypothesized that (1) dementia risk would be greater in men with hearing loss compared to women with hearing loss and (2) that change in brain volume in auditory–limbic regions would be more extensive in men with hearing loss compared to women with hearing loss.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature on associations among hearing loss, dementia risk, and magnetic resonance imaging measures of brain structure. A study which also used UK Biobank data, referenced in the text, investigated the association between dementia risk with increasing levels of hearing loss. Novel to our study is an interaction between hearing loss and sex on dementia risk (Study 1) and a longitudinal analysis of brain atrophy with the development of hearing loss by sex (Study 2).
2. **Interpretation**: Our findings suggest that women with hearing loss may have increased dementia risk compared to men and greater atrophy in auditory and limbic regions.
3. **Future directions**: Future studies should investigate sex-specific mechanisms that may explain why women with hearing loss may have increased dementia risk. One potential mechanism of interest is the relationship between hearing and estrogen, given the presence of estrogen receptors in the cochlea and estrogen's role in maintaining auditory function.

2 | METHODS

2.1 | Data source

The participants were obtained from the UK Biobank, which is a population-based, prospective cohort study of 500,000 participants who were aged 39 to 69 at recruitment. Recruitment occurred between 2006 and 2010 (i.e., study baseline). The dataset contains assessments of health, lifestyle, physical and cognitive abilities, and biological samples. Beginning in 2014, a subset of participants was invited to obtain a second assessment. At this second visit, magnetic resonance imaging (MRI) was added to the protocol (i.e., first imaging visit), though most of the participants in this study obtained their first MRI between 2017 and 2018. Beginning in 2019, participants were invited to a third assessment and a second MRI (i.e., second imaging visit).

2.2 | Participants

Participants in Study 1 were selected based on having non-missing hearing data in at least one ear and the absence of a dementia diagnosis at baseline. Participants in Study 2 were selected based on having non-missing hearing data in at least one ear, neuroimaging at both the first and second imaging visits, and the absence of a dementia diagnosis at either visit. Exclusionary criteria for both studies included a history of cancers of the brain or auditory pathway (e.g., brain, ear) throughout the study. Participants were further excluded for missing demographic variables that were used in statistical analyses. These demographic variables included, participants' self-reported age, sex, educational attainment, handedness, history of heart conditions or smoking, frequency of social visits, number of leisure activities, feelings of depressed mood, and the Townsend Deprivation Index (a measure of socioeconomic status based on postcode,[23] with a mean of zero and negative values reflecting higher socioeconomic status).

2.3 | Consent statement

All participants provided informed consent,[24,25] and all procedures were overseen by the Ethics and Guidance Council that has developed an Ethics and Governance Framework with the UK Biobank. Approval was also obtained from the North West Multi-center Research Ethics Committee.

2.4 | Hearing measures

Hearing was quantified using speech reception threshold (SRT) scores from the Digit Triplet Test.[26,27] This was the only objective assessment of hearing ability performed by the UK Biobank. In this task, 15 triplets of digits were presented in white noise shaped to the average spectrum of the triplets. Participants entered the triplet into a keypad. The background noise remained constant while the triplet increased or decreased by 2 dB for incorrect and correct responses, respectively. The SRT score was computed as the average signal-to-noise ratio from the last eight sets and could range from −12 to +8 dB, with more positive values reflecting poorer hearing. Each ear was tested separately.

Hearing was categorized into "SRT groups" based on SRT scores from the better ear (i.e., lowest score from either ear, < 2% data

missing) using previously published criteria and nomenclature:[26] normal hearing < 5.5 dB; insufficient hearing −5.5 to −3.5 dB; and poor hearing > 3.5 dB. SRT scores in either the insufficient or poor groups were considered a hearing loss;[26] however, we recognize that this phrase is typically associated with pure-tone audiometry, which was not conducted by the UK Biobank.

For Study 2, SRT scores were obtained at both the first and second imaging visits and categorized into SRT groups at both visits. A dummy variable was then created based on change in SRT group over time, forming three new groups: normal hearing at both visits (stable normal hearing); normal hearing at the first visit and insufficient or poor hearing at the second visit (hearing loss converters); and insufficient or poor hearing at both visits (stable hearing loss).[13] This grouping variable is referred to as "hearing change group."

While hearing aid use was collected, these data were not analyzed due to the low number of participants with the combination of hearing loss, hearing aids, and dementia ($n = 18$). If the participant wore hearing aids, the aids were removed for hearing testing and the SRT scores were obtained unaided.

2.5 | Dementia diagnosis

Presence of dementia and diagnosis date was determined by the UK Biobank through algorithmic combinations of coded health outcomes. These algorithms use self-reported health information, linked hospital admissions data, and death register data that are regularly updated to diagnose health conditions for each participant. Our study used the outcome for all-cause dementia. Possible etiologies for all-cause dementia included Alzheimer's disease (AD), vascular dementia, frontotemporal dementia, Parkinson's disease, and others.[28] A validation study comparing the algorithms to electronic medical records review by clinicians with dementia expertise reported a 82.5% agreement between dementia codes and clinician diagnosis.[29] A review of other studies using dementia diagnosis algorithms found agreements > 75%.[30] This suggests that the diagnosis for all-cause dementia obtained from algorithms in the UK Biobank has high accuracy, similar to other population-based studies that used algorithmic combinations of diagnostic coding.

2.6 | Apolipoprotein E genotyping

Genotyping for UK Biobank participants was conducted for ≈50,000 participants using the Applied Biosystems UK BiLEVE Axiom Array by Affymetrix and, for the remaining ≈450,000, using the Applied Biosystems UK Biobank Axiom Array. Both arrays were designed for the UK Biobank and are extremely similar in marker content.[31] The apolipoprotein E (*APOE*) genotype is directly genotyped from two single nucleotide polymorphisms (SNPs), rs429358 and rs7412. Quality control and processing applied to the data are described elsewhere.[31] Participants with at least one copy of the ε4 allele were considered *APOE* ε4 carriers.

2.7 | Social isolation and depressed mood composite score

A composite score similar to one used by Stevenson et al. and others[7,32] was generated from three responses on the computerized questionnaire: (1) frequency of social visits in a month; (2) number of leisure or social activities engaged in at least once a week; and (3) frequency of feeling down, depressed, or hopeless in the last 2 weeks. A point was given for social visits less than or equal to once a month, for reporting no leisure or social activities in a week, or for experiencing low mood more than half the time over the previous 2 weeks. A binary variable for the presence of social isolation/depressed mood was created from this composite score, with a 1 (yes) given to a composite score ≥ 2, and a 0 (no) given to scores < 2.

2.8 | MRI acquisition and processing

Details about the T1-weighted structural MRI acquisition and data processing pipelines are described in detail elsewhere.[33] Our study used measures of brain volume within regions of interest (ROIs), which were generated by an imaging processing pipeline conducted by the UK Biobank using FSL software and derived from the Harvard–Oxford cortical and subcortical atlases. Brain ROIs analyzed in this study included 16 regions within the auditory and limbic pathways that are associated with reduced volumes with hearing loss,[9–13,34] including bilateral Heschl's gyrus, posterior superior and middle temporal gyri, thalamus, amygdala, anterior and posterior parahippocampal gyri, and hippocampus. To test for regional specificity of the association between hearing loss and volume, the left postcentral gyrus was also examined as a control region, as it is not hypothesized to be affected by hearing loss.

2.9 | Statistical analysis

In Study 1, multivariable Cox proportional hazard regression was used to investigate the association between SRT group (normal, insufficient, and poor) and incident dementia. Time to follow-up was calculated as years from participant baseline visit to the date of dementia diagnosis, date of death, date of loss to follow-up, or date of last assessment. Less than 5% of right-censored participants experienced death before the last assessment date; therefore, we did not evaluate death as a competing risk. Models were adjusted for age, sex (in non-stratified models), education, socioeconomic status, history of heart conditions, history of ever smoking, handedness, and *APOE* ε4 status. To test the main hypothesis of sex differences in the association between hearing and dementia risk, the model included a sex-by-SRT group interaction term. The models were then stratified by sex. Results were reported with hazard ratios (HRs) compared to the normal hearing group (the reference group) and with 95% confidence intervals (CIs). The proportional hazard assumption was tested by evaluating the significance of time-dependent covariates in the model. Significance for the sex-by-SRT group interaction and the main effect of SRT group in sex-stratified

TABLE 1 Study 1 participant characteristics.

		Women ($n = 73,196$)			Men ($n = 60,641$)			Sex differences
Total sample ($N = 133,387$)		Normal ($n = 64,023$)	Insufficient ($n = 7991$)	Poor ($n = 1,182$)	Normal ($n = 52,721$)	Insufficient ($n = 6580$)	Poor ($n = 1,240$)	*P* value (effect size)
Age, mean (SD), years	56.7 (8.2)	56.0 (8.1)	59.6 (7.4)	60.0 (7.5)	56.3 (8.3)	60.4 (7.4)	61.2 (7.3)	<.001 (0.05)
Education (%, college/university degree)	34.9	34.3	28.2	22.6	37.8	29.8	21.9	<.001 (0.03)
Handedness (%, right)	89.0	90.2	90.3	91.4	87.6	87.9	87.4	<.001 (0.04)
History of heart conditions (%, yes)	29.2	23.9	32.0	36.5	33.0	42.7	46.3	<.001 (0.10)
History of smoking (%, yes)	44.3	39.5	37.5	37.4	50.0	53.7	54.7	<.001 (0.11)
Townsend deprivation index, mean (SD)	−1.2 (2.9)	−1.3 (2.8)	−0.8 (3.1)	−0.2 (3.3)	−1.2 (2.9)	−0.7 (3.2)	0.0 (3.3)	.002 (0.02)
APOE ε4 status (%, carrier)	28.2	28.2	28.1	29.1	28.1	28.5	26.7	.704 (<.01)
Social isolation/depressed mood composite (%, yes)	5.4	4.6	6.1	7.8	5.8	7.6	9.6	<.001 (0.03)

Note. Demographics at study baseline, shown for the entire sample and stratified by sex and SRT group. Differences in demographic variables between men and women, collapsed across SRT groups, were tested using independent samples *t* tests for continuous variables and using chi-square tests for categorical variables. Cohen *d* and Phi or Cramer V effect sizes were computed for continuous and categorical variables, respectively.
Abbreviations: *APOE*, apolipoprotein E; SD, standard deviation; SRT, speech reception threshold.

models was defined as $P < 0.05$. Sensitivity analyses were also performed that included (1) SRT as a continuous variable, (2) participants that were ≥ 60 years in age, and (3) a diagnosis of AD dementia.

Secondary analyses were performed in Study 1 to examine whether social isolation/depressed mood mediated the association between hearing loss and dementia risk, similar to Stevenson et al.[7] However, in our study, this mediation was conducted within each sex. The effect of the composite score on the association between SRT group and dementia risk was evaluated by calculating the percentage of excess risk mediated (PERM, see equation below).[7] This approach, which quantifies the degree of mediation by comparing the covariate-adjusted HRs to the covariate-unadjusted HRs, is commonly used in epidemiologic research.[35]

$$\text{PERM} = \frac{\text{HR}_{\text{covariates}} - \text{HR}_{\text{covariates+mediator}}}{\text{HR}_{\text{covariates}} - 1} \times 100$$

In Study 2, linear mixed models stratified by sex were used to investigate whether change in brain volume between imaging visits differed by hearing change group (stable normal hearing, hearing loss converters, stable hearing loss). ROI volume was the dependent variable, with each ROI run in parallel models. Hearing change group, time (i.e., first and second imaging visits), and a hearing change group-by-time interaction term were included as independent variables. Covariates mirrored Study 1 and also included SRT scores at first imaging visit, time between visits in years, and total brain volume at first imaging visit. All variables were entered as fixed factors except participant, which was entered as a random factor with random intercepts and an identity covariance matrix. Restricted maximum likelihood was used as the estimation method in these models. Significant hearing change group-by-time interactions were followed by pairwise comparisons to determine which hearing change groups significantly differed in change in ROI volume over time. Significance for the hearing change group-by-time interactions and follow-up pairwise comparisons was defined as $P < 0.05$.

Demographics were compared between sexes in each study using independent samples *t* tests for continuous variables and chi-squared tests for categorical variables. Statistical analyses were performed using SPSS (IBM Corp., release 2020, IBM SPSS Statistics for Macintosh, version 28.0.1).

3 | RESULTS

The sample size for Study 1 was 133,837 participants (mean [standard deviation (SD)] age = 56.7 [8.2] years, ranging from 39 to 72, 55% female; Table 1) followed for 9 years (mean [SD] = 9.0 [1.0] years). There were more men with a history of heart conditions and smoking, while sex differences in the remaining demographic variables had very small effect sizes (e.g., Cohen $d < 0.10$). Of this sample, 487 participants developed all-cause dementia (mean [SD] age = 63.8 [5.3] years, ranging from 42 to 70, 57% female at baseline), in which 338 participants had normal hearing, 119 had insufficient hearing, and 30 had poor hearing.

In the whole sample, insufficient hearing (HR = 1.8, 95% CI 1.3–2.3) was associated with increased risk of dementia compared to normal hearing, but not poor hearing (HR = 1.6, 95% CI 0.9–2.7) compared to normal hearing. The interaction between sex and insufficient hearing (HR = 1.0, 95% CI 0.7–1.5) compared to normal hearing was not significant, nor was the interaction between sex and poor hearing (HR = 2.0, 95% CI 0.9–4.1) compared to normal hearing (full model reported in Table SA.1 in supporting information). However, both the main effect of poor hearing and the interaction of poor hearing and sex were

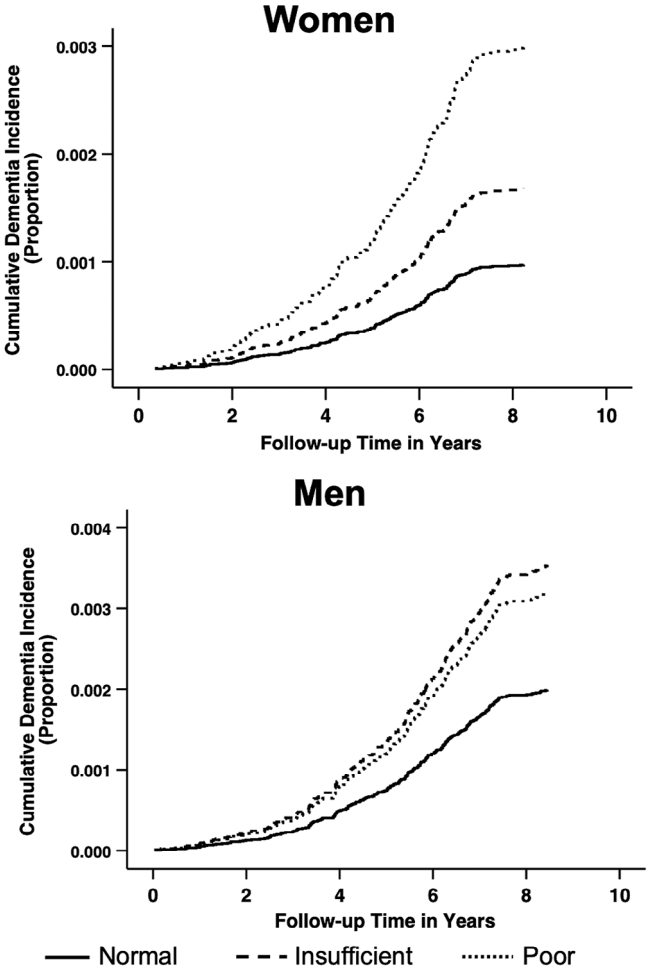

FIGURE 1 Hazard curves depicting the cumulative incidence of dementia risk over time for each speech reception threshold group (normal, insufficient, and poor hearing) separated by sex. Women are shown in the top plot. These curves show that there is a stepwise increase in dementia risk with increasing levels of hearing loss in women. Men are shown in the bottom plot and the curves show that men with insufficient and poor hearing have a similar increased risk of dementia compared to men with normal hearing. Models are adjusted for age, education, socioeconomic status, history of heart conditions, history of smoking, handedness, and apolipoprotein E ε4 status

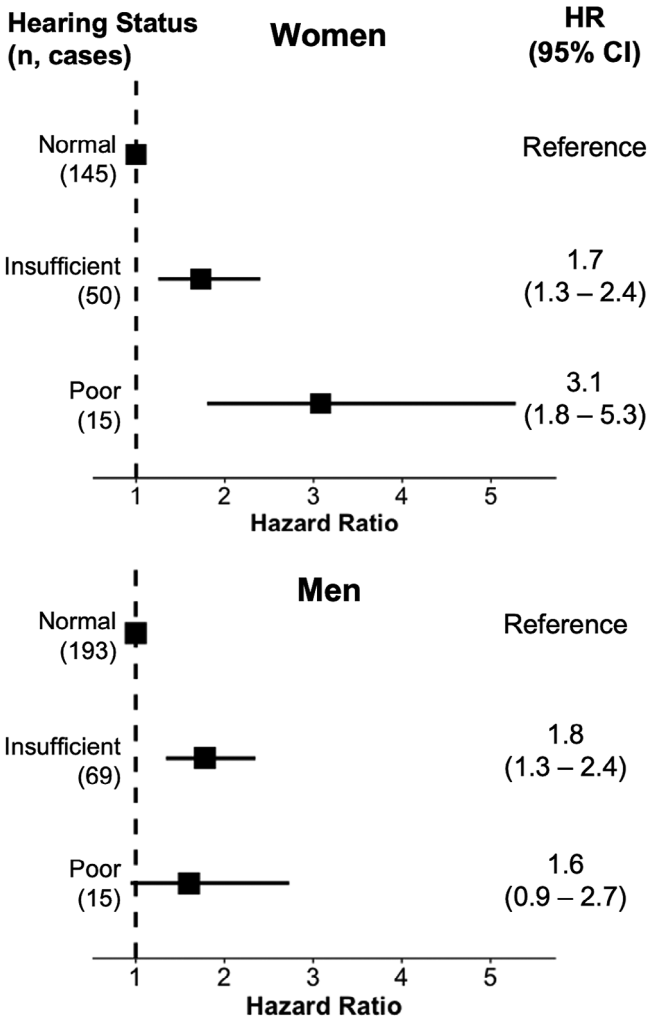

FIGURE 2 Forest plots depicting Cox proportional hazard ratios for the association between hearing loss and incidence of dementia for women (top) and men (bottom). Plots show that women with poor hearing are at greatest risk for dementia. Models are adjusted for age, education, socioeconomic status, history of heart conditions, history of smoking, handedness, and apolipoprotein E ε4 status. CI, confidence interval; HR, hazard ratio

trending toward significant, indicating a potential sex difference for those with poor hearing. Furthermore, in a sensitivity analysis, there was a significant interaction between sex and SRT scores when used as a continuous variable (Table SA.2 in supporting information), which also suggests a sex difference in the association between hearing and dementia and supports stratified analyses (see Figure 1 for hazard curve plots by SRT groups and sex).

When analyzed separately by sex, women with insufficient hearing (HR = 1.7, 95% CI 1.3–2.4) and poor hearing (HR = 3.1, 95% CI 1.8–5.3) had greater risk of dementia compared to women with normal hearing (Figure 2). In contrast, only men with insufficient hearing (HR = 1.8, 95% CI 1.3–2.4), but not men with poor hearing (HR = 1.6, 95% CI 0.9–2.7), had increased risk of dementia compared to men with normal hearing (Figure 2). Sensitivity analyses restricted to participants ≥ 60 years (Table SA.3 in supporting information) and using dementia due to AD (Table SA.4 in supporting information) align with these results, though caution should be used when interpreting these findings due to lower numbers of dementia cases in stratified groups.

Secondary analyses revealed only a small contribution of social isolation/depressed mood on the association between hearing loss and dementia risk in women or men. In women, the composite score accounted for 1.2% of the risk of dementia associated with insufficient hearing and 4.3% of the risk associated with poor hearing. In men, the composite score accounted for 1.7% of the risk of dementia associated with insufficient hearing and 3.8% of dementia risk associated with poor hearing.

The sample size for Study 2 was 1892 participants (mean [SD] age = 62.2 [7.3] years, ranging from 46 to 80, 52% female; Table 2). There were more men with a history of heart conditions, more men

TABLE 2 Study 2 participant characteristics.

		Women ($n = 977$)			Men ($n = 915$)			Sex differences
Total sample ($N = 1,892$)		Stable normal hearing ($n = 450$)	Hearing loss converters ($n = 246$)	Stable hearing loss ($n = 281$)	Stable normal hearing ($n = 430$)	Hearing loss converters ($n = 224$)	Stable hearing loss ($n = 261$)	*P* value (effect size)
Age, mean (SD), years	62.2 (7.3)	60.0 (7.1)	62.3 (6.8)	64.6 (6.8)	60.3 (7.1)	62.9 (7.1)	66.1 (6.7)	.023 (.11)
Education, no. (%, college/university degree)	919 (48.6)	213 (47.3)	114 (46.3)	137 (48.8)	203 (47.2)	116 (51.8)	136 (52.1)	.331 (.02)
Handedness, no. (%, right)	1,703 (90.0)	415 (92.2)	224 (91.1)	258 (91.8)	379 (88.1)	196 (87.5)	231 (88.5)	.007 (.06)
History of heart conditions, no. (%, yes)	326 (17.2)	59 (13.1)	36 (14.6)	42 (14.9)	81 (18.8)	25 (20.1)	63 (24.1)	<.001 (.09)
History of smoking, no. (%, yes)	612 (32.3)	137 (30.4)	77 (31.3)	90 (32.0)	126 (29.3)	90 (40.2)	92 (35.2)	.237 (.03)
Townsend deprivation index, mean (SD)	−2.1 (2.5)	−2.2 (2.4)	−2.0 (2.4)	−2.0 (2.7)	−2.3 (2.5)	−2.0 (2.7)	−2.1 (2.6)	.461 (.03)
APOE ε4 status, No. (%, carrier)	465 (24.6)	117 (26.0)	53 (21.5)	76 (27.0)	101 (23.5)	56 (25.0)	62 (23.8)	.530 (.01)
Baseline SRT, mean (SD), dB	−6.1 (1.6)	−6.9 (0.8)	−6.8 (0.8)	−4.3 (1.3)	−7.1 (0.9)	−6.8 (0.8)	−4.2 (1.6)	.683 (.02)
Time between visits, mean (SD), years	2.3 (0.5)	2.3 (0.5)	2.3 (0.6)	2.3 (0.4)	2.3 (0.6)	2.3 (0.5)	2.3 (0.4)	.905 (<.01)

Note. Demographics at imaging baseline shown for the entire sample and stratified by sex and hearing change group. Differences in demographic variables between men and women, collapsed across hearing change groups, were tested using independent samples *t* tests for continuous variables and using chi-square tests for categorical variables. Cohen *d* and Phi or Cramer V effect sizes were computed for continuous and categorical variables, respectively.
Abbreviations: *APOE*, apolipoprotein E; SRT, speech reception threshold; SD, standard deviation.

were left-handed, and men were slightly older than women, though the effect sizes for these differences were small (e.g., Cohen $d \leq 0.11$). From this sample, 644 participants overlapped with Study 1. The mean (SD) duration between the first and second imaging visits was 2.3 (0.5) years. Significant interactions of hearing change group by time on brain volume were observed in 3 of the 16 regions in the auditory and limbic pathways (see Table SB.1 in supporting information for statistics for all ROIs).

In women only, there were significant interactions on change in brain volume over time in the left posterior middle temporal gyrus ($R^2 = 0.33$, $F[2,974] = 4.50$, $P = 0.01$), left anterior parahippocampal gyrus ($R^2 = .26$, $F[2,974] = 04.41$, $P = 0.01$), and left posterior parahippocampal gyrus ($R^2 = .16$, $F[2,974] = 3.41$, $P = 0.03$). Follow-up pairwise comparisons revealed that, for the posterior middle temporal gyrus, those with stable normal hearing ($t[974] = 2.31$, $P = 0.02$) and hearing loss converters ($t[974] = 2.85$, $P < 0.01$) exhibited greater volume loss over time compared to those with stable hearing loss. Last, for both the left anterior and posterior parahippocampal gyri, hearing loss converters had greater volume loss over time than those with stable normal hearing (anterior: $t[974] = -2.96$, $P < 0.01$, posterior: $t[974] = -2.61$, $P < 0.01$). For ease of interpretation, percent annual atrophy was calculated and plotted between hearing change groups in Figure 3 to visualize these differences (see Figure SB.1 in supporting information for added variable plots of interactions).

There were no significant interactions of hearing change group by time on brain volume in men. Finally, there was no significant interaction of hearing change group by time on volume in the left postcentral gyrus (i.e., the control region) in either women or men.

4 | DISCUSSION

We examined sex differences in the association between hearing loss and dementia risk, and in the psychosocial and neural mechanisms that may underlie this association. In Study 1, we replicate previous work by Stevenson et al.[7] and show that hearing loss (defined as insufficient and poor speech-reception thresholds) is associated with increased dementia risk. Unique to our study, hearing status and sex interacted, such that women with the greatest levels of hearing loss showed increased dementia risk while men did not, contrary to our hypothesis. In considering possible explanatory mechanisms, differences in social isolation/depressed mood minimally mediated the association between hearing loss and dementia risk. In Study 2, we showed that women who converted to hearing loss exhibited greater rates of atrophy in auditory and limbic brain regions compared to women with stable normal hearing or stable hearing loss. Together, these findings reveal that women with hearing loss have increased dementia risk, which may be related to greater atrophy in regions associated with auditory and memory processing.

We hypothesized that men with hearing loss would show increased dementia risk compared to women due to the greater prevalence and earlier age of onset of hearing loss in men. However, this hypothesis

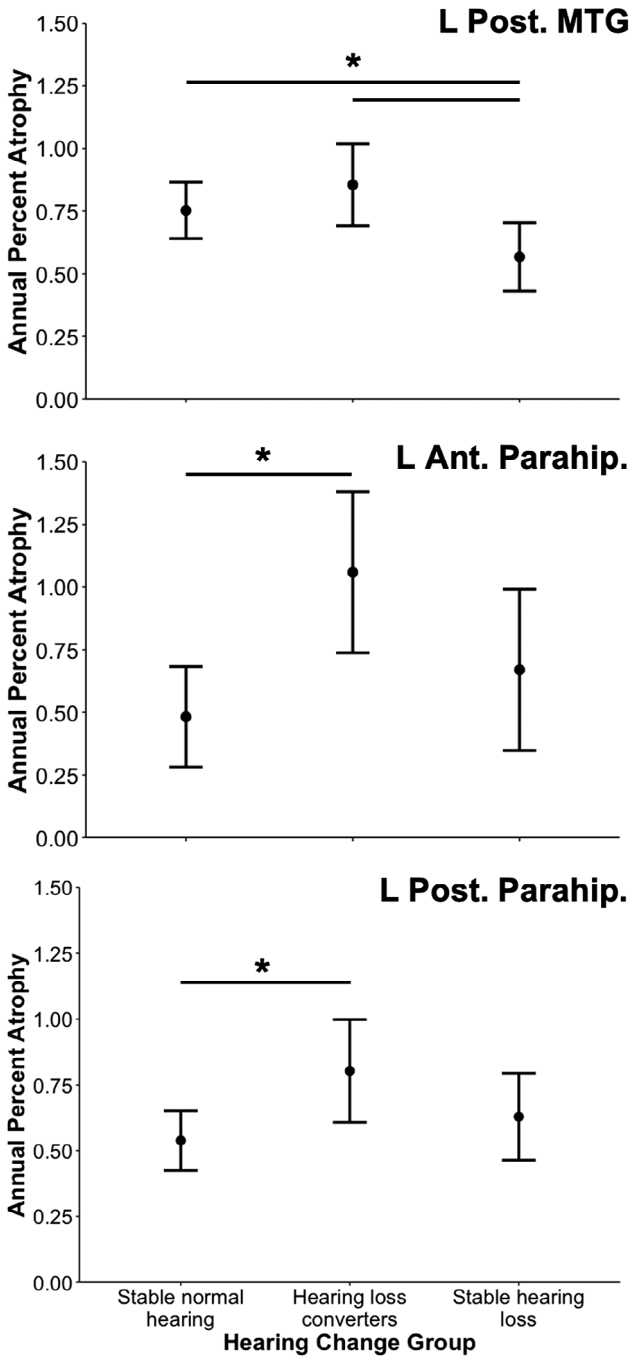

FIGURE 3 Annual percent atrophy in brain volume separated by hearing change groups. Brain regions shown are those with a significant hearing change group-by-time interaction on brain volume in women. Men showed no significant interactions of hearing change group by time on volume. Asterisk denotes which groups had significantly different rates of atrophy at $P < 0.05$. Error bars reflect 95% confidence intervals. Ant, anterior; L, left; Post, posterior; MTG, middle temporal gyrus, Parahip, parahippocampal gyrus

was informed by literature that defined hearing loss using pure-tone audiometry. An examination of SRT scores in the UK Biobank[36] and another longitudinal cohort[37] found no sex differences in scores. However, speech-in-noise tasks, like the Digit Triplet Test, measure auditory processing within both the cochlea and the brain and may more strongly predict dementia risk and AD pathology compared to pure-tone audiometry.[38] Thus, it may be that declines in SRT scores with age are equivalent between sexes but have a stronger effect on dementia risk in women compared to men, similar to other risk factors of dementia (e.g., *APOE* ε4 genotype).[18]

One possible explanation for why women may experience stronger, detrimental effects of hearing loss is related to hormonal changes in mid-life. In early life, women perform better on other types of hearing measures related to speech-in-noise, possibly due to the protective effects that estrogen serves in maintaining auditory function pre-menopause.[17,39] However, around the time of menopause, women experience accelerated declines in hearing ability.[40] It is possible that decreased estrogen levels around menopause may impact the protective role (e.g., anti-inflammatory) that estrogen receptors serve within the cochlea.[41] More research is needed to examine whether the onset of menopause and/or levels of circulating estrogen may mediate the relationship between dementia risk and hearing loss in women.

This study further compared changes in brain volume over a 2-year period among three groups of participants (hearing loss converters, stable normal hearing, and stable hearing loss) within each sex. The results showed that women who converted to hearing loss had greater atrophy in left auditory and parahippocampal brain regions, while men showed no differences in atrophy between hearing groups. To understand these findings, we compared the rate of atrophy among the three hearing change groups in women. Studies of brain volume changes in normal aging report decreases in temporal lobe volume between 0.5% and 0.6% and in hippocampal volume between 0.4% and 0.7% for adults aged 60 to 80,[42] with men typically exhibiting greater rates of decline compared to women.[43] As shown in Figure 3, the rate of atrophy per year in the left anterior parahippocampal gyrus in hearing loss converters was ≈1.0%, which was two times larger than the rate of atrophy in those with stable normal hearing (≈0.5%) and larger than the average age-related atrophy in the hippocampus reported in the literature.

The medial temporal lobe is a key region to consider for the association between hearing loss and dementia. The hippocampus is indirectly connected to the auditory cortex via the parahippocampal and perirhinal cortices, as well as through the thalamus and amygdala.[15] Importantly, it serves as a mediator between perception and memory recall processes.[44] Animal models of hearing loss report synaptic degradation and impairments in neuronal function and neurogenesis within the hippocampus.[45–48] Similarly, human studies indicate that hearing loss is associated with reduced hippocampal volume, both cross-sectionally[10] and longitudinally.[11–13] It is plausible that hearing loss causes neuronal dysfunction and subsequent atrophy in auditory cortex which then, due to direct and indirect connections and its role in perceptual processing, leads to similar declines in regions within the medial temporal lobe. Our study suggests that women with hearing loss may be particularly vulnerable to this process, though more research on sex-specific effects is needed.

A potential limitation in this study is the use of a coarse composite score of social isolation/depressed mood, which resulted in a limited number of participants available to examine psychosocial factors that mediate the association between hearing loss and dementia. Though

similar composite scores have been derived from UK Biobank data,[7,32] more comprehensive measures that assess social isolation and depression are needed to capture the range of depressive symptoms that may contribute to dementia risk. Second, the dementia diagnosis variable provided by the UK Biobank relies, in part, on participant self-report. Thus, it is possible that some participants with memory impairments went undiagnosed. Last, a relatively small number of participants with dementia were in the poor hearing group in Study 1. Additional studies are needed that use dementia diagnoses derived from comprehensive cognitive assessments and health histories and with a more equal distribution of dementia status across hearing groups.

This investigation showed that women with greater levels of hearing loss have increased dementia risk, possibly due to increased atrophy within auditory and medial temporal regions, compared to men. Our findings suggest that social isolation/depressed mood had a minimal effect on the association between hearing loss and dementia risk, though the effect was slightly larger for those with poor hearing. Future studies with comprehensive assessments of socialization and mood are needed to interrogate this association further. With the recent positive clinical trial showing that hearing aids reduced cognitive decline in those at increased risk for dementia,[49] our studies highlight the need to examine sex-specific mechanisms for dementia risk and risk reduction via hearing interventions.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

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

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