Association between hearing loss and development of dementia using formal behavioural audiometric testing within the Mayo Clinic Study of Aging (MCSA): a prospective population-based study

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Summary

Background Hearing loss has been identified as a potential major modifiable risk factor for developing dementia. This study examined associations between formal behavioural pure-tone and speech audiometry assessed by an audiologist with development of dementia in the Mayo Clinic Study of Aging (MCSA).

Methods The MCSA is a prospective population-based study examining the incidence, prevalence, and risk factors of mild cognitive impairment and dementia in Olmsted County, Minnesota, USA. Participants undergo clinical examinations with neuropsychological testing at enrolment and every 15 months. Participants were 50 years or older at enrolment between Nov 29, 2004, and Dec 23, 2019, who underwent formal behavioural audiometric evaluation by an audiologist due to concerns about hearing loss or as a part of annual comprehensive health assessments. Associations of pure-tone average (PTA) and word recognition scores (WRS) with the development of dementia were evaluated using Cox proportional hazards regression with age as the timescale, and associations with changes in cognitive testing scores over time were evaluated using linear mixed-effects models.

Findings Among 1200 eligible participants, the mean age at enrolment was 79 years (SD 9) , 593 (49%) were men, and 207 developed dementia during a mean of 7·0 years (SD 3·7) of follow-up. After adjusting for sex, years of education, smoking status, diabetes, hypertension, apolipoprotein E ε4 carriership, and hearing rehabilitation (defined as hearing aid or cochlear implant use), neither PTA (hazard ratio [HR] per 10-decibels hearing level increase of 0·99 (95% CI 0·89–1·12; p=0·91) nor WRS (HR per 10% decrease of 0·98, 95% CI 0·89–1 ·07; p=0·65) was significantly associated with the development of dementia. However, both PTA and WRS were significantly associated with poorer performance in cognitive testing over time: participants with a PTA higher than 25 decibels hearing level or a WRS lower than 100% had significantly worse declines in cognitive testing scores. Informant-based hearing difficulties assessed by the participant's study partner were significantly associated with the development of dementia (HR 1·95, 95% CI 1·45–2·62; p<0·0001).

Interpretation In this prospective population-based study, subjective informant-based hearing difficulties were associated with development of dementia, whereas objective measures on formal behavioural audiometry were predictive of poorer performance on cognitive testing over time but not the development of dementia. Other factors related to central processing might potentiate the effects of peripheral hearing loss detected on behavioural audiometric testing.

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Introduction

Although historically regarded simply as an inevitable sequela of senescence, adult-onset hearing loss is increasingly being recognised as a chronic disease with important health consequences. Decreased communication capabilities and increased listening effort carry pragmatic safety concerns while also placing patients at increased risk of social isolation, loneliness, depression, and cognitive decline.[1–5] The association between hearing loss and dementia has received particular attention within the past decade and was identified as the largest potentially modifiable risk factor for the development of dementia in both the 2017 and 2020 *Lancet* Commission reports.[6,7] With the projection that nearly 2·5 billion people globally will suffer from hearing loss by the year 2050, delineation of adult-onset hearing loss as a true

Research in context

Evidence before this study

We did not do a formal systematic review before starting this study. In both the 2017 and 2020 *Lancet* Commission reports on dementia, hearing loss was identified as the largest potentially modifiable risk factor for the development of dementia. However, only three studies provide the foundation for this estimate. In 2011, Lin and colleagues reported on 58 incident cases of dementia in a cohort of 639 individuals, demonstrating an increased risk of dementia with increasing degree of hearing loss assessed with an automated testing device (hazard ratio [HR] per 10-decibels hearing level [dB HL] increase in pure-tone average [PTA] of 1·27 [95% CI 1·06–1·50). Gallacher and colleagues subsequently reported on 79 incident cases of dementia from a cohort of 1057 men, showing an increased odds of dementia with increasing PTA measured in a community clinic environment with background noise between 1983 and 1988 (odds ratio per 10-dB HL increase of 2·67, 95% CI 1·38–5·18). Third, the Health ABC study followed 1889 individuals over 9 years with 229 incident cases of dementia, showing an increased risk of dementia with increasing degree of hearing loss (HR per 10-dB HL increase in PTA of 1·14, 95% CI 1·03–1·26).

Added value of this study

The current investigation followed 1200 participants over a mean of 7·0 years (SD 3·7), with hearing thresholds assessed exclusively through formal behavioural audiometry performed by audiologists in sound-attenuating booths within a prospective population-based cohort specifically designed to examine incident dementia over time. Among 207 incident cases of dementia, hearing loss assessed by PTA was not predictive of the development of dementia (HR per 10-dB HL increase of 0·99, 95% CI 0·89–1·12). Uniquely assessing speech discrimination, word recognition scores were also not predictive of dementia (HR per 10% decrease of 0·98, 95% CI 0·89–1·07). However, both PTA and word recognition scores were significantly associated with poorer performance on cognitive testing over time. Informant-based hearing difficulties assessed by the participant's study partner were significantly associated with the development of dementia (HR 1·95, 95% CI 1·45–2·62).

Implications of all the available evidence

In aggregate with existing data, the current study suggests that the link between objective measures of hearing loss and dementia might not be as strong as previously considered. These data support previous work that implicates degradation in central processing as contributing to both the perceived hearing difficulty and dementia. Because faster cognitive decline is observed in people with worse hearing loss, additional research delineating causal pathways between hearing loss and cognitive decline is needed.

disease state and its attendant consequences is becoming increasingly relevant,[8] especially in light of scarce existing published literature on hearing loss among providers and the general populace.[9,10]

To date, only three studies provide the foundation from which the *Lancet* Commission established hearing loss as the largest potentially modifiable risk factor for the development of dementia.[11–13] In 2011, Lin and colleagues reported on 58 incident cases of dementia among a cohort of 639 individuals, demonstrating an increased risk of dementia with increasing degree of hearing loss assessed with an automated testing device (hazard ratio [HR] per 10-decibels hearing level [dB HL] increase in pure-tone average [PTA] of 1·27, 95% CI 1·06–1·50).[11] Gallacher and colleagues subsequently reported on 79 incident cases of dementia from a cohort of 1057 men, showing an increased odds of dementia with increasing PTA measured in a community clinic environment with background noise between 1983 and 1988 (odds ratio [OR] per 10-dB HL increase of 2·67, 95% CI 1·38–5·18), although this association was attenuated when omitting those with evidence of early-onset cognitive decline (OR 1·32, 95% CI 0·57–3·12).[13] Most recently, in 2017, the Health ABC study followed 1889 individuals over 9 years with 229 incident cases of dementia, showing an increased risk of dementia with increasing degree of hearing loss (HR per 10-dB HL increase in PTA of 1·14, 95% CI 1·03–1·26).[12] A recent meta-analysis pooled the time-dependent HRs and time-independent ORs among these studies, reporting a combined OR of 1·28 (95% CI 1·02–1·59) connecting age-related hearing loss and dementia.[4]

The small number of prospective studies, along with the substantial variability in audiometric and dementia assessments across studies, underscores the need for additional prospective longitudinal epidemiologic data. Using formal behavioural pure-tone and speech audiometry exclusively performed by audiologists with the Mayo Clinic Study of Aging (MCSA), in the current study we examined hearing loss and its potential connection to the development of mild cognitive impairment and dementia.

Methods

Participant selection

The MCSA is a prospective population-based study examining incidence, prevalence, and risk factors of mild cognitive impairment and dementia in Olmsted County, Minnesota, USA. Participants in the MCSA undergo clinical examinations with neuropsychological testing at enrolment and every 15 months. Exhaustive descriptions of the MCSA design, enrolment, and longitudinal assessments of cognitive function, mild cognitive impairment, and dementia have been described previously.[14,15] Generalisability of the population of Olmsted County to the general population of the USA has also been described.[16]

There were 5766 participants in the MCSA who were 50 years or older at enrolment between Nov 29, 2004, and Dec 23, 2019, including 5497 with a status of cognitively unimpaired or mild cognitive impairment at enrolment who were eligible for the study. Cognitive status at each MCSA visit was determined by an expert panel that included a physician and neuropsychologist.[12] Of these, 1200 underwent formal pure-tone and speech audiometry assessed by board-certified audiologists using American National Standards Institute-calibrated audiometers in a sound-attenuating booth within 5 years of the enrolment visit, with a median duration between the audiogram and enrolment visit of 1·3 years (IQR 0·6–2·5). The 1200 participants who underwent formal audiometric testing were usually referred for audiometric assessment due to hearing complaints or as a part of annual comprehensive health assessments. For participants with multiple audiograms, the audiogram closest to enrolment was chosen to represent the baseline audiogram. Institutional review board approval was obtained before data retrieval and analysis. All participants provided written, informed consent.

Exposures

Air-conduction and bone-conduction PTAs were calculated using preferentially masked frequencies at 0·5, 1, 2, and 3 kilohertz (kHz) in accordance with reporting standards.[17] If 3 kHz was not available, the average of 2 and 4 kHz was used.[18] The lowest (best) air-conduction PTA from the left and right ears and the corresponding bone-conduction PTA from that ear were selected for analysis. Air-conduction PTA was categorised as normal hearing (≤25 dB HL), or mild (26–39 dB HL), moderate (40–69 dB HL), severe (70–89 dB HL), or profound (≥90 dB HL) hearing loss.[19] The highest (best) standard speech audiometry (including Isophonemes,[20] W-22,[21] and NU-6[22]) word recognition score (WRS) from the left and right ears was selected for analysis. All audiometric tests were performed in the non-aided condition.

Lastly, subjective hearing difficulties that interfere with daily activities were assessed during the enrolment interview with the participants' study partners (so-called informants, selected by the participant). The informants were asked "Does [the participant] have significant hearing difficulties that interfere with daily activities?" Analyses using informant-based data have been previously reported for the MCSA cohort overall.[23]

Demographic and clinical features

Demographic and clinical features assessed at enrolment included age; sex; race and ethnicity; years of education (≤12 *vs* 13–16 *vs* >16 years); smoking status, the comorbidities of diabetes, hypertension, stroke, and heart disease (defined as atrial fibrillation, coronary artery disease, or congestive heart failure); the Beck Depression Inventory (score of <13 *vs* ≥13), apolipoprotein E (APOE) ε4 carriership (yes *vs* no), and hearing rehabilitation defined as hearing aid or cochlear implant use (yes *vs* no).

Except for hearing rehabilitation, demographic and clinical features were ascertained during the enrolment interview or by medical record review. To augment the prospective data collection conducted as part of the MCSA, hearing rehabilitation (yes *vs* no) was ascertained by electronic retrieval of participant-provided information from surveys completed during Mayo Clinic visits and searches of diagnosis and procedure codes for hearing aids and cochlear implants. For hearing aid use, surveys were searched for answers to the question "Do you have hearing aid(s)?"; diagnosis codes included internal Mayo Clinic codes 09999190 and 34175110,[24] International Classification of Diseases (ICD)-9 V53.2, and ICD-10 Z46.1 and Z97.4; procedure codes included Current Procedural Terminology codes 92590 through 92595. An exhaustive list of relevant diagnosis and procedure codes used to identify individuals with cochlear implants is included in the appendix (pp 2–3).

See Online for appendix

Outcomes

Time-to-event outcomes assessed through follow-up MCSA visits or medical record review were development of dementia among all participants and development of mild cognitive impairment among participants who were cognitively unimpaired at enrolment. Longitudinal outcomes assessed at follow-up MCSA visits included changes in four psychometric domains (memory, attention/executive function, language, and visuospatial skills), z-scores, and global cognition z-scores over time. Cross-sectional outcomes at enrolment included cognitive status (unimpaired *vs* mild cognitive impairment), domain z-scores, and global cognition z-scores. The four aforementioned psychometric domains were derived from a mixture of nine auditory and visual neuropsychological tests administered during each MCSA visit.[14] Scores from these tests were converted to z-scores using means and SDs from the subset of participants classified as cognitively unimpaired. Test-specific z-scores within each domain were averaged to obtain domain-specific scores that were converted to z-scores. Similarly, domain-specific z-scores were averaged to obtain a global cognition score that was converted to a z-score. As such, the domain and global cognition z-scores had a mean of 0 and a SD of 1 among the subset of participants classified as cognitively unimpaired. Z-scores were calculated using the same process for the subset of participants with a baseline audiogram available for study.

Statistical analysis

Comparisons of demographic and clinical features between participants with and without a baseline audiogram available for study were evaluated using two-sample *t*, Wilcoxon rank sum, and χ^2 tests. Among participants with a baseline audiogram, associations of

	Underwent formal audiometric testing		p value
	No (N=4297)	Yes (N=1200; study cohort)	
Demographic and clinical features			
Age, years	72 (10)	76 (9)	<0·0001
Sex	..	..	0·31
Female	2102 (49%)	607 (51%)	..
Male	2195 (51%)	593 (49%)	..
White race (N=4277; N=1196)	4206 (98%)	1177 (98%)	0·86
Non-Hispanic or Latino ethnicity (N=4273; N=1194)	4254 (>99%)	1193 (>99%)	0·10
Years of education (N=4292; N=1198)	..	..	<0·0001
≤12	1506 (35%)	342 (29%)	..
13–16	1976 (46%)	544 (45%)	..
>16	810 (19%)	312 (26%)	..
Smoking status (N=4295; N=1200)	..	..	0·18
Never	2310 (54%)	619 (52%)	..
Current or former	1985 (46%)	581 (48%)	..
Comorbidities (N=4275; N=1199)			
Diabetes	748 (18%)	220 (18%)	0·49
Hypertension	2850 (67%)	868 (72%)	0·0002
Stroke	180 (4%)	63 (5%)	0·12
Heart disease	1458 (34%)	504 (42%)	<0·0001
Beck Depression Inventory II score ≥13 (N=4218; N=1169)	316 (7%)	100 (9%)	0·23
APOE ε4 carriership (N=3974; N=1148)	1110 (28%)	285 (25%)	0·04
Hearing rehabilitation	399 (9%)	492 (41%)	<0·0001
Exposures			
PTA in dB HL	..	32 (16)	..
Hearing severity classification			
Normal hearing	..	437 (36%)	..
Mild hearing loss	..	383 (32%)	..
Moderate hearing loss	..	363 (30%)	..
Severe or profound hearing loss	..	17 (1%)	..
WRS in % (N=1173)	..	91 (14)	..
WRS <90% (N=1173)	..	271 (23%)	..
WRS <100% (N=1173)	..	545 (46%)	..
Informant-based hearing difficulties (N=1177)	..	388 (33%)	..
Cognitive status at enrolment			
Unimpaired	..	1041 (87%)	..
Mild cognitive impairment	..	159 (13%)	..
Z-scores at enrolment			
Memory (N=1177)	..	−0·22 (1·13)	..
Attention/executive function (N=1145)	..	−0·16 (1·11)	..
Language (N=1150)	..	−0·18 (1·13)	..
Visuospatial skills (N=1141)	..	−0·12 (1·06)	..
Global cognition (N=1111)	..	−0·20 (1·13)	..

Data are mean (SD) or n (%). Sample sizes for features with missing data are indicated in parentheses. dB HL=decibels hearing level. APOE=apolipoprotein E. PTA=pure-tone average. WRS=word recognition score.

***Table 1*: Demographic and clinical features of the cohort, with comparison of features between participants within the Mayo Clinic Study of Aging who underwent formal behavioural audiometric testing versus those who did not**

PTA, WRS, and hearing difficulties interfering with daily activities with demographic and clinical features were evaluated using Pearson and Spearman rank correlation coefficients and two-sample *t*, Wilcoxon rank sum, and χ^2 tests. Associations with time-to-event outcomes during follow-up were evaluated after multivariable adjustment for sex, years of education, smoking status, diabetes, hypertension, APOE ε4 carriership, and hearing rehabilitation using Cox proportional hazards regression models with age as the timescale (ie, the start age was age at enrolment and the end age was age at the development of dementia or last follow-up). In a sensitivity analysis, associations of PTA and WRS with time to dementia were also evaluated without adjustment for hearing rehabilitation and with further adjustment for the duration between the audiogram and enrolment visit. Changes in domain and global cognition z-scores over time were evaluated using linear mixed-effects models with random participant-specific intercepts and slopes using an unstructured covariance structure. Associations with cross-sectional outcomes at enrolment were evaluated using logistic regression models for mild cognitive impairment and linear regression models for domain and global cognition z-scores. Multivariable models were assessed using a complete case approach.

Statistical analyses were done using SAS version 9.4 and R version 4.0.3. All tests were two-sided and p values less than 0·05 were considered statistically significant.

Results

The mean age at enrolment in the MCSA for the 1200 participants in the study cohort was 76 years (SD 9), and 593 (49%) of participants were men. Participants in the current study were on average 4 years older than the larger MCSA cohort, with a greater prevalence of hypertension, heart disease, education exceeding 16 years, and hearing rehabilitation (table 1). A total of 1041 (87%) participants were cognitively unimpaired at enrolment and 159 (13%) had a diagnosis of mild cognitive impairment. 437 (36%) participants had normal hearing, 383 (32%) had mild hearing loss, 363 (30%) had moderate hearing loss, and 17 (1%) had severe-to-profound hearing loss. Of the 763 participants with hearing loss, 741 (97%) had sensorineural hearing loss, 17 (2%) had mixed hearing loss, and five (1%) had conductive hearing loss. The 388 participants (33%) who displayed informant-based hearing difficulties were significantly more likely to use hearing rehabilitation and have significantly worse PTAs and WRSs than those without informant-based hearing difficulties (appendix p 4). The continuous assessments of PTA and WRS were significantly associated with several of the demographic and clinical features studied (appendix pp 5–6).

Among all 1200 participants, 1159 (97%) were followed up for development of dementia, including 207 who developed dementia at a mean age of 87 years (SD 6) at a mean of 5·6 years (SD 3·5) from enrolment. The mean

duration of follow-up for the 952 participants who did not develop dementia and were censored was 7·0 (SD 3·7) years; of these individuals, 316 died and 636 were still alive without a diagnosis of dementia as of their last follow-up visit. Associations of PTA and WRS with development of dementia were adjusted for sex, years of education, smoking status, diabetes, hypertension, APOE ε4 carriership, and hearing rehabilitation in Cox models using age as the timescale. Neither PTA as a continuous variable (HR per 10-dB HL increase of 0·99, 95% CI 0·89–1·12; p=0·91) nor WRS as a continuous variable (HR per 10% decrease of 0·98, 95% CI 0·89–1·07; p=0·65) were significantly associated with the development of dementia, although informant-based hearing difficulties were significantly associated with development of dementia (HR 1·95, 95% CI 1·45–2·62; p<0·0001; table 2). Sensitivity analysis without adjusting for hearing rehabilitation showed similar results, with HRs for PTA as a continuous variable of 0·95 (95% CI 0·85–1·05; p=0·29) and WRS as a continuous variable of 0·96 (0·88–1·05; p= 0·36). Furthermore, adjusting for the duration between the audiogram and enrolment visit did not substantially change the results presented in table 2 (appendix p 7). Among the 1041 participants who were cognitively unimpaired at enrolment, 1005 (97%) were followed for the development of mild cognitive impairment. Of these, 283 participants developed mild cognitive impairment at a mean age of 85 years (SD 7). The mean duration of follow-up for the 722 participants who did not develop mild cognitive impairment was 6·9 years (SD 3·7). No significant associations of PTA or WRS with the development of mild cognitive impairment were found (appendix p 8).

Of the 1200 participants studied, 989 (82%) were followed up for changes in domain and global cognition z-scores, with a mean duration of follow-up of 5·5 years (SD 3·4) from a mean of 5·0 (SD 2·5) follow-up MCSA visits (range 2–12). Participants with poorer PTAs and WRSs demonstrated a steeper rate of decline in cognitive testing performance than those with better PTAs and WRSs (appendix pp 9–11), with participants with a PTA higher than 25 dB HL or a WRS lower than 100% having significantly worse declines in z-scores across all cognitive testing domains and the global score.

Cross-sectional associations of PTA and WRS with mild cognitive impairment and cognitive testing at enrolment are included in the appendix (pp 12–13). In summary, neither PTA as a continuous variable (OR per 10-dB HL increase of 0·96, 95% CI 0·83–1·11) nor as a categorical variable (OR for PTA >25 *vs* ≤25 dB HL of 0·80, 95% CI 0·50–1·29) was significantly associated with the cross-sectional outcome of mild cognitive impairment at enrolment, and similar non-statistically significant findings were observed with cross-sectional cognitive testing outcomes at enrolment (appendix p 12). The cross-sectional assessment of WRS was not significantly associated with mild cognitive impairment, either as a continuous variable (OR per 10% decrease of 0·91, 95% CI 0·79–1·04) or as a categorical variable (OR for WRS of <100% *vs* 100% of 1·00, 95% CI 0·67–1·50). By contrast, informant-based assessments of hearing difficulties were significantly associated with both the cross-sectional outcome of mild cognitive impairment (OR 1·49, 95% CI 1·02–2·19) and nearly all cognitive tests at enrolment (appendix p 14).

	HR (95% CI)	p value
PTA as a continuous variable (10-dB HL increase)	0·99 (0·89–1·12)	0·91
PTA ≥40 *vs* <40 dB HL	1·11 (0·79–1·57)	0·55
PTA >25 *vs* ≤25 dB HL	0·81 (0·56–1·16)	0·24
WRS as a continuous variable (10% decrease)	0·98 (0·89–1·07)	0·65
WRS <90 *vs* ≥90%	0·97 (0·69–1·35)	0·85
WRS <100 *vs* 100%	1·13 (0·83–1·54)	0·43
Informant-based hearing difficulties (yes *vs* no)	1·95 (1·45–2·62)	<0·0001

HR, 95% CI, and p value were calculated from multivariable Cox proportional hazards regression models with age as the timescale adjusted for sex, years of education, smoking status, diabetes, hypertension, APOE ε4 carriership, and hearing rehabilitation. APOE=apolipoprotein E. dB HL=decibels hearing level. HR=hazard ratio. PTA=pure-tone average. WRS=word recognition score.

Table 2: **Associations of exposures with development of dementia**

Discussion

In contrast with previous work, this prospective population-based study did not show a significant association between hearing loss assessed by PTA and the development of dementia after adjustment for selected demographic and clinical features.[11–13] Speech discrimination testing (ie, WRS) was also not predictive of the development of dementia. Despite the absence of significant associations with incident dementia, both PTA and WRS were significantly associated with declines in scores on cognitive tests over time. Nonetheless, this poorer performance on cognitive testing did not sufficiently manifest clinically as a diagnosis of dementia in this cohort. Notwithstanding these weak associations with objective measures, informant-based assessments of hearing difficulties were significantly associated with the development of dementia, similar to previous studies examining so-called observed hearing loss.[23,25] The absence of association between PTA or WRS and dementia suggests that the informant-based assessments of hearing difficulties might have captured an element of central auditory processing dysfunction beyond the difficulties created by decreased peripheral auditory input alone. To this end, although participants with informant-based hearing difficulties were significantly more likely to have objective hearing loss than those without informant-based hearing difficulties, about half of those with objective hearing loss did not exhibit informant-based hearing difficulties. This observation suggests that other factors

	Cohort size, N	Incident dementia, n	Mean age, years	Method of hearing testing	Median or mean follow-up, years	Adjusted HR or OR (95% CI)*
Lin et al (2011)†[11]	639	58	64	Automated audiometer in sound-attenuating booth	12	1·27 (1·06–1·50)
Gallacher et al (2012)[13]	1057	79	56	Behavioural audiometry in community clinic with background noise	17	2·67 (1·38–5·18)
Deal et al (2017)[12]	1889	229	76	Behavioural audiometry in sound-attenuating booth	9	1·14 (1·03–1·26)
Current study	1200	207	76	Comprehensive behavioural audiometry with audiologist in sound-attenuating booth	7	0·99 (0·89–1·12)

HR=hazard ratio. OR=odds ratio. *The study by Gallacher et al reported an OR to assess the odds of having hearing loss and dementia; the remaining studies listed in the table reported HRs. All HRs or ORs represent the association of a 10 decibels hearing level increase in PTA with development of dementia. All HRs or ORs were adjusted for age but studies differed in the number of additional adjusting features. †The study by Lin et al did not directly report mean age for the entire cohort; the summary included in this table was derived from published mean ages for the subsets of the 639 patients with and without dementia. Moreover, the reported follow-up of 12 years represents a median, not a mean.

***Table 3*: Comparison of prospective studies meeting 2017 and 2020 *Lancet* Commission inclusion criteria examining associations with pure-tone threshold and development of dementia[6,7]**

related to central processing might potentiate the impact of peripheral hearing loss detected on behavioural audiometric testing.

When attempting to reconcile the results of the current study with the three previous studies that met *Lancet* Commission inclusion criteria (table 3),[11–13] several considerations deserve mention. First, mean participant age and sex distribution in the current study are similar to the Health ABC study, but the studies by Lin and colleagues[11] and Gallacher and colleagues[13] report younger mean age, with the latter study only including men at a mean age of 56 years. The differences in age are notable because, although the mean follow-up of the current study was shorter, it involves follow-up of the age group at highest risk for development of dementia. This fact helps to explain the higher rate of incident dementia in the current study and the Health ABC study[12] than in the the studies by Lin and colleagues[11] and Gallacher and colleagues.[13] Related to the differences in participant age, the prevalence and severity of hearing loss also differed across all four studies. In the study by Lin and colleagues, more than 70% of participants demonstrated thresholds within the normal hearing range whereas only 9% displayed moderate or worse hearing loss. In the Health ABC cohort, 42% of participants had normal hearing thresholds whereas 20% had moderate or worse hearing loss. The study by Gallacher and colleagues reported a mean PTA of 25·8 dB HL but did not report data further delineating severity of hearing loss. In the present study cohort, hearing loss severity was relatively balanced, with 36% of participants having normal hearing thresholds and 32% having moderate or worse hearing loss. The greater prevalence of hearing loss speaks to the inherent selection bias of the current study in which many participants underwent formal audiometric testing due to clinical concerns about hearing loss. This selection bias results in a prevalence of hearing loss that probably exceeds that in the general population—other population-based studies have shown that the prevalence of moderate or worse hearing loss is approximately 16% among those aged 70–79 years and approaches 40% for those aged 80 years and older.[26] In this way, the current study cohort might have been at elevated risk of incident dementia from the study onset. However, because previous studies have suggested a relationship between incident dementia per 10-dB HL across the continuum of PTA, it still would have been expected that the current study would have shown a similar finding despite the selection bias towards a population with a greater prevalence of hearing loss. Therefore, the absence of this relationship within the present study suggests that the selection bias of the current study does not substantially undermine the overarching message of the current work: that other factors related to central processing might potentiate the impact of peripheral, objective measures of hearing loss on the development of dementia.

A notable methodological difference between the current study and previous work pertains to the audiological measurements. Whereas previous prospective studies used automated testing devices or performed testing in a clinic with background noise,[11,13] the present study exclusively used formal behavioural audiometric testing with board-certified audiologists in a sound-attenuating booth. Formal audiometric assessments with an audiologist allow for otoscopic examination (which can avoid observing artificially decreased thresholds, for example, from cerumen impaction), patient instruction throughout the test, and differentiation between intentionally correct versus unintentionally correct responses. For these reasons, formal audiometric testing with an audiologist can result in different observed thresholds to those thresholds obtained by other methods—a reality illustrated in the study by Gallacher and colleagues in which 70 participants subsequently underwent formal audiometric testing with correlations to the in-clinic readings in background noise ranging from r=0·69 at 0·5 kHz to r=0·93 at 4 kHz.[13]

Notwithstanding the study by Gallacher and colleagues that reported the odds of dementia in men based on PTA,[13] both previous time-to-event analyses examining associations of PTA with development of dementia had lower bounds of the 95% CIs that approached 1·0 (table 3).[11,12] The present study found HRs centred around 1·0 with precise CIs for both PTA and WRS. Other previous studies with various designs have failed to demonstrate statistically significant associations between hearing loss and dementia.[27,28] In the Cognitive Vitality

subset analysis of the Health ABC study, no significant associations between hearing loss and cognitive performance over time were recorded.[12] When restricted to incident Alzheimer's dementia in the study by Lin and colleagues, the association between hearing loss and dementia was attenuated (HR per 10-dB HL increase of 1·20, 95% CI 0·94–1·53).[11] Gallacher and colleagues' study showed a correlation between hearing loss and vascular dementia and did not identify a significant association with cognitive impairment without dementia.[13] Because cognitive impairment is heterogeneous with presumably multiple causes, previous work and the current study together suggest that hearing loss might be a risk factor for some types of cognitive decline but not others. Furthermore, the observations from the current work attenuate the association between hearing loss and dementia suggested by the recent *Lancet* Commissions.[6,7]

Despite the absence of significant associations with objective measures of hearing loss, informant-based assessments of hearing difficulties were significantly associated with the development of dementia in the current study, similar to previous investigations of so-called observed hearing loss.[25] This finding suggests that individuals at the highest risk of developing dementia not only had hearing loss but probably also had additional sensory processing dysfunction—presumably central in origin—that could not be measured on audiometry. Alternatively, individuals with cognitive deficits might be misattributing cognitive dysfunction to hearing loss. The current work uniquely included WRSs, and the absence of statistically significant associations surrounding these speech discrimination scores with dementia are noteworthy because speech discrimination is traditionally thought to be more representative of functional hearing capacity than pure-tone audiometry. Nonetheless, the current study supports previous work that implicates degradation in central processing as contributing to both perceived hearing difficulty and dementia.[5] In this way, the decline in auditory function could be a harbinger of impending cognitive decline with a common underlying cause.[29] Because faster cognitive decline is observed in those with worse hearing loss (as seen in the present study), further research delineating the causal pathways between hearing loss and cognitive decline is necessary.

There are several limitations of the current work. First, the Olmsted County population has an elevated life expectancy, higher socioeconomic status, and good access to health care relative to the general population of the USA.[16] The latter two factors might contribute to patients' access to hearing rehabilitation devices. If hearing loss increases the risk of developing dementia, hearing rehabilitation use could attenuate an association. For this reason, an adjustment for hearing rehabilitation use was included in the present analysis. Next, as previously discussed, there is an inherent selection bias in the present cohort who underwent formal audiometric testing compared with the larger MCSA cohort. Although not everyone who underwent audiometric testing had subjective hearing complaints and 36% had hearing within normal thresholds on testing, most participants underwent audiometric testing due to clinical concerns for hearing loss. Relatedly, the assessment of hearing rehabilitation was binary (yes *vs* no); however, in practice, hearing loss that is rehabilitated is not akin to hearing loss that is not adequately rehabilitated. Conclusions surrounding the utility of hearing rehabilitation must therefore be interpreted within this limited context. Additionally, adjustment for potential confounders that were not collected in the MCSA or misclassification of demographic or clinical features that were collected during enrolment interviews could affect our reported associations. Finally, because the current study analysed participants enrolled up to December, 2019, the mean duration of follow-up in the current work of 7 years is shorter than that in prior work, which ranged from 9 to 17 years, although this limitation is attenuated by the mean age of the cohort, as discussed previously.

To conclude, in this study, subjective informant-based hearing difficulties were associated with development of dementia, whereas objective measures on formal behavioural audiometry were predictive of poorer performance on cognitive testing over time but not the clinical diagnosis of dementia. These findings suggest that other central processing deficits could potentiate the effects of hearing loss; however, the association between peripheral hearing loss alone, detected on formal behavioural audiometric testing, and the development of dementia might be less robust.

Contributors

JPM, CML, MV, and MLC conceived and designed the project. JPM and CML were responsible for drafting the manuscript. Data analysis was performed by CML. JPM, CML, and MLC verified the data. All authors have access to the underlying data. All authors contributed to the interpretation of findings, provided revisions to the manuscript, and approved the final manuscript.

Declaration of interests

RCP has been a consultant for Roche, Biogen, Merck, Eisai, Genentech, and Nestle; receives publishing royalties from Mild Cognitive Impairment (Oxford University Press, 2003) and UpToDate; and receives research support from the US National Institutes of Health. NSR is on the advisory board of Neosensory and receives funding from the National Institute of Health and the National Institute on Aging. MV has received research funding from F. Hoffmann-La Roche and Biogen in the past, consults for F. Hoffmann-La Roche, receives research funding from the National Institutes of Health, and has equity ownership in Abbott Laboratories, Johnson and Johnson, Medtronic, AbbVie, and Amgen. All other authors declare no competing interests.

Data sharing

De-identified patient data, including a data dictionary defining each field in the set, will be made available with the publication for the purposes of systematic reviews and meta-analyses or verification of study findings following request approval by the study team and establishment of a data-sharing agreement with the originating institution. Data sharing requests should be sent via email to the corresponding author.

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References

1 Anstey KJ, Wood J, Lord S, Walker JG. Cognitive, sensory and physical factors enabling driving safety in older adults. *Clin Psychol Rev* 2005; **25:** 45–65.

2 Shukla A, Harper M, Pedersen E, et al. Hearing loss, loneliness, and social isolation: a systematic review. *Otolaryngol Head Neck Surg* 2020; **162:** 622–33.

3 Lawrence BJ, Jayakody DMP, Bennett RJ, Eikelboom RH, Gasson N, Friedland PL. Hearing loss and depression in older adults: a systematic review and meta-analysis. *Gerontologist* 2020; **60:** e137–54.

4 Loughrey DG, Kelly ME, Kelley GA, Brennan S, Lawlor BA. Association of age-related hearing loss with cognitive function, cognitive impairment, and dementia: a systematic review and meta-analysis. *JAMA Otolaryngol Head Neck Surg* 2018; **144:** 115–26.

5 Powell DS, Oh ES, Reed NS, Lin FR, Deal JA. Hearing loss and cognition: what we know and where we need to go. *Front Aging Neurosci* 2021; **13:** 769405.

6 Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission. *Lancet* 2020; **396:** 413–46.

7 Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet* 2017; **390:** 2673–734.

8 WHO. World report on hearing. Geneva: World Health Organization, 2021.

9 Carlson ML, Nassiri AM, Marinelli JP, Lohse CM, Sydlowski SA, Hearing Health Collaborative. Awareness, perceptions, and literacy surrounding hearing loss and hearing rehabilitation among the adult population in the United States. *Otol Neurotol* 2022; **43:** e323–30.

10 Sydlowski SA, Marinelli JP, Lohse CM, Carlson ML, Hearing Health Collaborative. Hearing health perceptions and literacy among primary healthcare providers in the United States: a national cross-sectional survey. *Otol Neurotol* 2022; **43:** 894–99.

11 Lin FR, Metter EJ, O'Brien RJ, Resnick SM, Zonderman AB, Ferrucci L. Hearing loss and incident dementia. *Arch Neurol* 2011; **68:** 214–20.

12 Deal JA, Betz J, Yaffe Ket al. Hearing impairment and incident dementia and cognitive decline in older adults: the Health ABC Study. *J Gerontol A Biol Sci Med Sci* 2017; **72:** 703–09.

13 Gallacher J, Ilubaera V, Ben-Shlomo Y, et al. Auditory threshold, phonologic demand, and incident dementia. *Neurology* 2012; **79:** 1583–90.

14 Roberts RO, Geda YE, Knopman DS, et al. The Mayo Clinic Study of Aging: design and sampling, participation, baseline measures and sample characteristics. *Neuroepidemiology* 2008; **30:** 58–69.

15 Pankratz VS, Roberts RO, Mielke MM, et al. Predicting the risk of mild cognitive impairment in the Mayo Clinic Study of Aging. *Neurology* 2015; **84:** 1433–42.

16 St Sauver JL, Grossardt BR, Leibson CL, Yawn BP, Melton LJ 3rd, Rocca WA. Generalizability of epidemiological findings and public health decisions: an illustration from the Rochester Epidemiology Project. *Mayo Clin Proc* 2012; **87:** 151–60.

17 Gurgel RK, Jackler RK, Dobie RA, Popelka GR. A new standardized format for reporting hearing outcome in clinical trials. *Otolaryngol Head Neck Surg* 2012; **147:** 803–07.

18 Gurgel RK, Popelka GR, Oghalai JS, Blevins NH, Chang KW, Jackler RK. Is it valid to calculate the 3-kilohertz threshold by averaging 2 and 4 kilohertz? *Otolaryngol Head Neck Surg* 2012; **147:** 102–04.

19 Clark JG. Uses and abuses of hearing loss classification. *ASHA* 1981; **23:** 493–500.

20 Olsen WO, Van Tasell DJ, Speaks CE. Phoneme and word recognition for words in isolation and in sentences. *Ear Hearing* 1997; **18:** 175–88.

21 Hirsh IJ, Davis H, Silverman SR, Reynolds EG, Eldert E, Benson RW. Development of materials for speech audiometry. *J Speech and Hear Disord* 1952; 17: 321–37.

22 Tillman TW, Carhart R. An expanded test for speech discrimination utilizing CNC monosyllabic words. Northwestern University Auditory Test No. 6. *Tech Rep SAM-TR* 1966; 1–12.

23 Vassilaki M, Aakre JA, Knopman DS, et al. Informant-based hearing difficulties and the risk for mild cognitive impairment and dementia. *Age Ageing* 2019; **48:** 888–94.

24 Pakhomov SV, Buntrock JD, Chute CG. Automating the assignment of diagnosis codes to patient encounters using example-based and machine learning techniques. *J Am Med Inform Assoc* 2006; **13:** 516–25.

25 Golub JS, Luchsinger JA, Manly JJ, Stern Y, Mayeux R, Schupf N. Observed hearing loss and incident dementia in a multiethnic cohort. *J Am Geriatr Soc* 2017; **65:** 1691–97.

26 Goman AM, Lin FR. Prevalence of hearing loss by severity in the United States. *Am J Public Health* 2016; **106:** 1820–22.

27 Anstey KJ, Luszcz MA, Sanchez L. Two-year decline in vision but not hearing is associated with memory decline in very old adults in a population-based sample. *Gerontology* 2001; **47:** 289–93.

28 Gennis V, Garry PJ, Haaland KY, Yeo RA, Goodwin JS. Hearing and cognition in the elderly. New findings and a review of the literature. *Arch Intern Med* 1991; **151:** 2259–64.

29 Kurniawan C, Westendorp RG, de Craen AJ, Gussekloo J, de Laat J, van Exel E. Gene dose of apolipoprotein E and age-related hearing loss. *Neurobiol Aging* 2012; **33:** 2230.7–2230.e12.