



Published in final edited form as:

Arch Neurol. 2011 February ; 68(2): 214–220. doi:10.1001/archneurol.2010.362.

Hearing Loss and Incident Dementia

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Abstract

Context—Earlier studies have suggested that hearing loss, which is prevalent in more than 30% of adults >60 years, may be a risk factor for dementia, but this hypothesis has never been investigated prospectively.

Objective—To determine if hearing loss is associated with incident all-cause dementia and Alzheimer's disease (AD).

Design, Setting, and Participants—Prospective study of 639 participants (age 36–90 y) of the Baltimore Longitudinal Study of Aging who had audiometric testing and who were dementia-free in 1990–1994. Hearing loss was defined by a pure-tone average of hearing thresholds at 0.5, 1, 2, and 4 kHz in the better-hearing ear (normal <25 dB [n = 455], mild loss 25–40 dB [n = 125], moderate loss 41–70 dB [n = 53], severe loss >70 dB [n = 6]). Diagnosis of incident dementia was made by consensus diagnostic conference. Cox proportional hazard models were used to model time to incident dementia according to severity of hearing loss and were adjusted for age, sex, race, education, diabetes, smoking, and hypertension.

Main Outcome Measure—Incidence of all-cause dementia and AD until May 31, 2008.

Results—During a median follow-up of 11.9 years, 58 cases of incident all-cause dementia were diagnosed of which 37 cases were AD. The risk of incident all-cause dementia increased logarithmically with the severity of baseline hearing loss (1.27 per 10 db loss, 95% CI: 1.06–1.50). Compared to normal hearing, the hazard ratio for incident all-cause dementia was 1.89 for mild hearing loss (95% CI: 1.00–3.58), 3.00 for moderate hearing loss (95% CI: 1.43–6.30), and 4.94

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Analysis and interpretation of data: Lin, Metter, O'Brien, Resnick, Zonderman, Ferrucci

Drafting of the manuscript: Lin, Ferrucci

Critical revision of the manuscript for important intellectual content: Lin, Metter, O'Brien, Resnick, Zonderman, Ferrucci

Statistical analysis: Lin, Metter, Ferrucci

Obtained funding: Ferrucci

Study supervision: Ferrucci

Financial disclosures: None

for severe hearing loss (95% CI: 1.09 – 22.4). The risk of incident AD also increased with baseline hearing loss but with a wider confidence interval (1.20 per 10 dB of hearing loss, 95% CI: 0.94 – 1.53).

Conclusions—Hearing loss is independently associated with incident all-cause dementia. Whether hearing loss is a marker for early stage dementia or is actually a modifiable risk factor for dementia deserves further study.

Introduction

The prevalence of dementia is projected to double every twenty years such that by 2050 over 100 million people or nearly 1 in 85 persons will be affected worldwide^{1,2}. The devastating impact of dementia on affected individuals and the burden imposed on their families and society has made the prevention and treatment of dementia a public health priority. Interventions that could merely delay the onset of dementia by one year would lead to a more than 10% decrease in the global prevalence of dementia in 2050³. Unfortunately, there are no known interventions that currently have such effectiveness.

Epidemiologic approaches have focused on the identification of putative risk factors that could be targeted for prevention based on the assumption that dementia is easier to prevent than to reverse. Candidate factors include low involvement in leisure activities and social interactions, sedentary state, diabetes, and hypertension⁴. Some researchers have also suggested that hearing loss, by reducing stimulatory input and hampering social interaction, may be associated with dementia^{5,6}, but this hypothesis has never been prospectively studied. Given the growing number of people with hearing loss⁷ and the array of technologic interventions currently available for aural rehabilitation, understanding whether hearing loss is a risk factor for dementia is important. We performed the current study to investigate the prospective association of hearing loss with incident dementia within the cohort of the Baltimore Longitudinal Study of Aging (BLSA).

Methods

Subjects

Subjects were participants in the BLSA, an ongoing prospective study of the effects of aging that was initiated in 1958 by the National Institute on Aging⁸. The BLSA cohort is comprised of community-dwelling volunteers who travel to the National Institute on Aging in Baltimore biennially for 2.5 days of intensive testing. From 1990-1994, 1305 subjects participated in at least one study visit of which 976 of the participants had audiometry testing, and 749 had both audiometry and cognitive testing. Some subjects had missing audiometry or cognitive testing data because of inadequate time for testing or tester unavailability during study visits. After excluding subjects with prevalent dementia (n = 58), >3 errors on the Blessed test (n = 39), and suspected dementia (n = 13), our baseline cohort was comprised of 639 subjects who were followed until May 31, 2008 (Figure 1). For subjects with more than 1 visit during this time period, data from the first assessment were used. All participants provided written informed consent, and the BLSA study protocol was approved by the Institutional Review Board.

Cognitive testing and diagnosis of dementia

The protocol for adjudication of dementia in the BLSA has been used continuously since 1986 and has been described previously⁹. Participants ≥65 years old underwent a complete neurological and neuropsychological examination using a standard battery of tests. Participants <65 were first screened with the Blessed-Information-Memory-Concentration test and underwent further examination if they made three or more errors. Dementia

diagnosis was established during a multidisciplinary consensus diagnostic conference using Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised for diagnosis of dementia¹⁰, and National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer’s Disease and Related Disorders Association criteria for diagnosis of Alzheimer’s disease¹¹. If subjects were determined to have clinically-significant cognitive decline (typically memory) but did not meet criteria for dementia, they were classified as suspected dementia which corresponds to the current diagnosis of mild cognitive impairment¹². Subjects were initially evaluated for dementia every 2 years during their routine BLSA follow-up visits. In 1997, follow-up was shifted to a sliding-scale schedule to reduce subject burden and improve data collection. Subjects >80 years were seen annually, subjects 60-80 years were seen biennially, and subjects <60 years were seen every 4 years.

Audiometry

Audiometry was performed in the BLSA study from 1958 to 1994. Over the entire period from 1990-1994 when the baseline evaluation for this analysis was performed, hearing thresholds were measured using an automated testing device (Virtual Equipment Co., Audiometer Model 320) in a soundproof chamber under unaided conditions. A pure tone average (PTA) of air-conduction thresholds at 0.5, 1, 2, and 4 kHz was calculated for each ear, and the PTA in the better-hearing ear was used for subsequent analyses since this ear would be the principal determinant of hearing and speech perception ability on an everyday basis. PTA in dB was used as both a continuous variable and as a categorical variable defined by commonly-used levels of hearing loss: normal (PTA <25 dB), mild loss (25-40 dB), moderate loss (41-70 dB), and severe loss (>70 dB). Prior to 1990, audiometric testing was performed using a Bekesy audiometer (GSI(1701)) and these data were used in analyses of pre-baseline hearing trajectories.

Other covariates

A diagnosis of diabetes was established based on a fasting glucose >125 mg/dL, a pathologic oral glucose tolerance test, or a positive history of a physician diagnosis plus treatment with oral anti-diabetic drugs or insulin. The diagnosis of hypertension was established based on a systolic blood pressure >140 and/or diastolic blood pressure ≥90 mmHg or treatment with antihypertensive medications. Race (white/black/other), education (in years), smoking status (current/former/never), and hearing aid use were based on self-report.

Statistical analyses

Baseline characteristics of cohort subjects were compared using one-way analysis of variance for continuous variables and chi-square or Fisher exact test for categorical variables. Cox proportional hazard models were used to study time to incident all-cause dementia or Alzheimer’s disease. Subjects not diagnosed with dementia were censored at the time of their last negative cognitive evaluation. Time-on-study (i.e. time of entry into the baseline study cohort) was used as the time scale with the exception of one model that utilized age as the time scale.

All Cox models included covariates of sex, age, race, education, diabetes, smoking, and hypertension. Diabetes and hypertension were included as covariates in the analysis because they have been found to be risk factors for dementia⁴. Additional models included baseline Blessed scores (residual variability in cognition after definition of the baseline cohort) and hearing aid use. All covariates were treated as time-constant variables. Cox model proportionality assumptions and the linear association between hearing loss and dementia were tested using the Schoenfeld residuals method. To examine the graphical association between hearing threshold and dementia, we utilized a smoothing spline for the hearing

threshold and age in the proportional hazard model¹³. A loess smoother was then applied to the exponential of the partial residuals derived from the hazard model against the hearing threshold. A bootstrap procedure was utilized to generate 10000 datasets that were then used to estimate the 95% confidence interval for the loess smoother. Analysis of hearing loss trajectories pre-baseline was performed using a random effects analysis and adjusted for age. Population attributable risk (PAR) was calculated by¹⁴: $PAR = P_{\text{exposed}}(RR - 1) / [1 + P_{\text{exposed}}(RR - 1)]$ where P_{exposed} was the prevalence of baseline hearing loss ≥ 25 dB and RR was the rate ratio (hazard ratio) of dementia risk associated with hearing loss. Subjects with missing data were excluded from analyses, and this represented $< 0.2\%$ of the study sample (1 subject) for all analyses except for analyses incorporating hearing aid use where there was more extensive missing data (typically among normal hearing subjects who did not respond). Significance testing for all analyses was 2-sided with a type I error of 0.05. The statistical software used was R version 2.9.1 (www.r-project.org).

Results

Baseline demographic characteristics of participants by hearing loss category are presented in Table 1. In general, subjects with greater hearing loss were more likely to be older, male, and hypertensive. Blessed scores did not differ by hearing loss category ($p = .08$), although the range of errors was narrow (0-3) because subjects with >3 errors were excluded from the study cohort at baseline.

Baseline covariates associated with an increased risk of incident all-cause dementia are hearing loss, age, hypertension, hearing aid use, and Blessed score (Table II). Independent of age, in the 15 years prior to baseline assessment ($n = 520$ with 2678 observations), participants who later developed incident dementia lost on average 0.52 dB PTA/year (95% CI: 0.34 – 0.70) compared to 0.27 dB PTA/year (95% CI: 0.21 – 0.33) in those who remained non-demented.

In Cox proportional hazard models adjusted for sex, age, race, education, diabetes, smoking, and hypertension (base model), the excess risk of incident dementia per 10 dB of hearing loss was 1.27 (95% confidence interval [CI]: 1.06 – 1.50) (Table III). The risk of incident dementia becomes evident for hearing loss > 25 dB and thereafter increases log-linearly with more severe loss (Figure 2). This association remained significant after censoring individuals who developed dementia within a 2, 4, or 6 year washout period from baseline ($p = 0.008, 0.003, \text{ and } 0.04$, respectively).

Confirmatory analyses from models including baseline Blessed error score (to account for baseline cognitive function) or using age as the time-scale rather than time-on-study (to account for residual confounding between age and hearing loss) produced virtually unchanged findings (Table III). Restricting the analytical cohort to participants ≥ 65 y at baseline ($n = 315$) or excluding participants at baseline with a prior history of stroke or transient ischemic attack ($n = 19$) also did not substantially change the main findings (cf. Table III). There was no evidence to suggest that self-reported hearing aid use was associated with a reduction in dementia risk (HR = 0.97, $p = .92$).

In subsequent analyses we categorized hearing loss according to commonly-accepted levels of hearing loss severity. Compared to normal hearing, participants with mild hearing loss had a hazard ratio [HR] for incident dementia of 1.89 [95% CI: 1.00 – 3.58, $p = 0.049$], those with moderate hearing loss had a HR of 3.00, [95% CI: 1.43 – 6.30, $p = 0.004$], and those with severe hearing loss ($n=6$) had a HR of 4.94 [95% CI: 1.09 – 22.4, $p = 0.04$].

When the outcome of the analysis was restricted to incident Alzheimer's disease (37 of the 58 dementia cases), hearing loss was associated with an excess risk of 1.20 per 10 dB of

hearing loss (95% CI: 0.94 – 1.53). This result is comparable to the risk seen for all-cause dementia (cf. Table III) but with a wider confidence interval, possibly due to the smaller sample size.

We estimated the proportion of incident all-cause dementia risk that was attributable to hearing loss for participants >60 years in our cohort assuming that hearing loss could be causally associated with dementia. Hearing loss ≥ 25 dB in the better-hearing ear was present in 43% of this sub-cohort, and the relative risk (hazard ratio) of dementia associated with hearing loss was 2.32 (95% CI: 1.32- 4.07). Thus, the attributable risk of dementia associated with hearing loss in this sub-cohort was 36.4% (95% CI: 12.8 – 58.6).

Comment

In this study we found that hearing loss was independently associated with incident all-cause dementia after adjustment for sex, age, race, education, diabetes, smoking, and hypertension, and our findings were robust to multiple sensitivity analyses. The risk of all-cause dementia increased log-linearly with hearing loss severity, and for individuals >60 years in our cohort, over one-third of the risk of incident all-cause dementia was associated with hearing loss.

Our findings contribute significantly to the discussion in the literature on whether hearing loss is a risk factor for dementia. Previous studies suggested that individuals with hearing loss are more likely to have a diagnosis of dementia^{5,6} and poorer cognitive function¹⁵. Supporting this hypothesis, smaller prospective studies have observed that hearing loss is associated with accelerated cognitive decline in individuals with prevalent dementia^{16,17}. Although, a prospective study of cognitively-normal elderly volunteers failed to find any meaningful association between hearing loss at study entry and later cognitive function, the results of this study are questionable because of the short (5-year) follow-up and a 50% dropout rate¹⁸. In our study, hearing loss, a condition that is highly prevalent in older adults and often remains untreated¹⁹, was strongly and prospectively associated with incident dementia.

A number of mechanisms may be theoretically implicated in the observed association between hearing loss and incident dementia. There may be an over-diagnosis of dementia in individuals affected by hearing loss, or vice versa an over-diagnosis of hearing loss in individuals with cognitive impairment at baseline. An over-diagnosis of dementia in our study is unlikely because the diagnostic protocol for incident dementia relied on a consensus conference that examined information from multiple sources. We also conducted sensitivity analyses censoring individuals diagnosed with dementia during a 6-year washout period from baseline that did not affect our results. In such an analysis, individuals would already have had several “normal” cognitive exams with hearing loss before being diagnosed with dementia, likely making the dementia diagnosis not confounded by poor communication. Hearing loss (short of profound deafness) also minimally impairs face-to-face communication in quiet environments (i.e. during cognitive testing) particularly in the setting of testing by experienced examiners who are accustomed to working with older adults²⁰.

An over-diagnosis of hearing loss is also unlikely since there is no evidence that mild cognitive impairment would affect the reliability of audiometric testing. Behaviorally, pure-tone audiometry has been performed even in children as young as 5 years. We also excluded any individuals with recognized cognitive impairment at baseline (mild cognitive impairment or Blessed > 3), and our results were robust to models controlling for baseline Blessed scores.

Another possibility is that both hearing loss and progressive cognitive impairment are caused by a common neuropathologic process, possibly the same that leads to Alzheimer's disease. However, pure tone audiometry is typically considered a measure of the auditory periphery because detection of pure tones relies solely on cochlear transduction and neuronal afferents to brainstem nuclei and the primary auditory cortex. Perception of pure tones do not require higher levels of auditory cortical processing²¹, and auditory brainstem response testing of these pathways is usually normal in AD patients²². In contrast, central auditory nuclei required for higher order auditory processing can be affected by AD neuropathology²³⁻²⁵, and tests of central auditory function have been found to be associated with Alzheimer's disease²⁶.

The likelihood of another neurobiological process such as vascular disease or factors related to family history (e.g. ApoE status) causing both hearing loss and dementia also cannot be fully excluded. However, risk factors for vascular disease such as diabetes, smoking, and hypertension were adjusted for in our models, and a preliminary study has not found a positive association between ApoE status and hearing loss²⁷. Other variables such as mental and leisure activities were not included as covariates in our models since these variables would not be expected to cause hearing loss and act as meaningful confounders in our models. Our results were also robust to excluding individuals at baseline who had a prior history of stroke or TIA.

Finally, hearing loss may be causally related to dementia, possibly through exhaustion of cognitive reserve, social isolation, environmental deafferentation, or a combination of these pathways. Cognitive reserve reflects inter-individual differences in neurocognitive processing that allow some individuals to cope better with neuropathology than others²⁸. Functional MRI studies showing inter-individual variation in efficiency of task-related neural processing provide some evidence for this concept^{29;30}. Cognitive reserve has also been used to explain discrepancies between the extent of neuropathology seen at autopsy and clinical expression of dementia³¹. The potential effect of hearing loss on cognitive reserve is suggested by studies demonstrating that under conditions where auditory perception is difficult (i.e. hearing loss), greater cognitive resources are dedicated to auditory perceptual processing to the detriment of other cognitive processes such as working memory^{32;33}. This reallocation of neural resources to auditory processing could deplete the cognitive reserve available to other cognitive processes and possibly lead to the earlier clinical expression of dementia neuropathology³⁴.

Communication impairments caused by hearing loss can also lead to social isolation in older adults^{35;36}, and epidemiologic^{37;38} and neuroanatomic studies³⁹ have demonstrated associations between poor social networks and dementia. Our results would also seem to support this possible pathway because the risk of dementia associated with hearing loss only appeared to increase at hearing thresholds >25 dB which is considered the threshold at which hearing loss begins to impair verbal communication⁴⁰. Finally, a hypothetical mechanism by which hearing loss could directly affect Alzheimer's neuropathology is suggested by animal studies demonstrating that environmental enrichment (possibly analogous in humans to having access to auditory and environmental stimuli) can reduce β -amyloid levels in transgenic mouse models⁴¹. This hypothesis is also supported by studies showing that individuals who remain engaged in leisure activities have a lower risk of dementia⁴².

In the current study, self-reported hearing aid use was not associated with a significant reduction in dementia risk, but data on other key variables (e.g. type of hearing aid used, hours worn per day, number of years used, characteristics of subjects choosing to use hearing aids, use of other communicative strategies, adequacy of rehabilitation, etc) that

would affect the success of aural rehabilitation and affect any observed association were not gathered. Consequently, whether hearing aids and aural rehabilitative strategies could have an effect on cognitive decline and dementia remains unknown and will require further study.

Our study has limitations. First, only the severity of hearing loss at baseline was considered in the analysis, and information was not available on the trajectory of hearing loss after baseline assessment or the possible etiology of the hearing loss. However, it is unlikely that this limitation substantially biased our findings given that reversible hearing loss is rare, and hearing loss tends to only worsen with time. Residual confounding by other environmental, genetic, or neuropathologic processes is also plausible but speculative based on our current knowledge of established risk factors for hearing loss and dementia. Given the very close association between age and both hearing loss and dementia, there is a possibility of unaccounted residual confounding. This is unlikely, however, because we also confirmed our findings in a statistical model using age rather than time-on-study as the time-scale to account for non-linear effects of age on hearing and cognition⁴³. Our findings were also unchanged after restricting our cohort to participants ≥ 65 years at baseline.

Finally, caution must be applied when generalizing the results of our current study because the BLSA is a volunteer cohort of subjects of high socioeconomic status. Further confirmation of our results will need to be performed in larger studies using more representative, community-based samples. This potential limitation to broad generalizability, however, could strengthen the internal validity of our findings given the relative homogeneity of the study cohort in both observed and likely unobservable characteristics.

If confirmed in other independent cohorts the findings of our study could potentially have substantial implications for individuals and public health. Hearing loss in older adults may be preventable⁴⁴ and can be practically addressed with current technology (digital hearing aids, cochlear implants) and with other rehabilitative interventions focused on optimizing social and environmental conditions for hearing. With the increasing number of people with hearing loss, research into the mechanistic pathways linking hearing loss with dementia and the potential of rehabilitative strategies to moderate this association are critically needed.

Acknowledgments

Funding/Support: This work was supported by the intramural research program of the National Institute on Aging

Role of the Sponsor: The National Institute on Aging funded the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation and review of the manuscript, but was not involved in manuscript approval.

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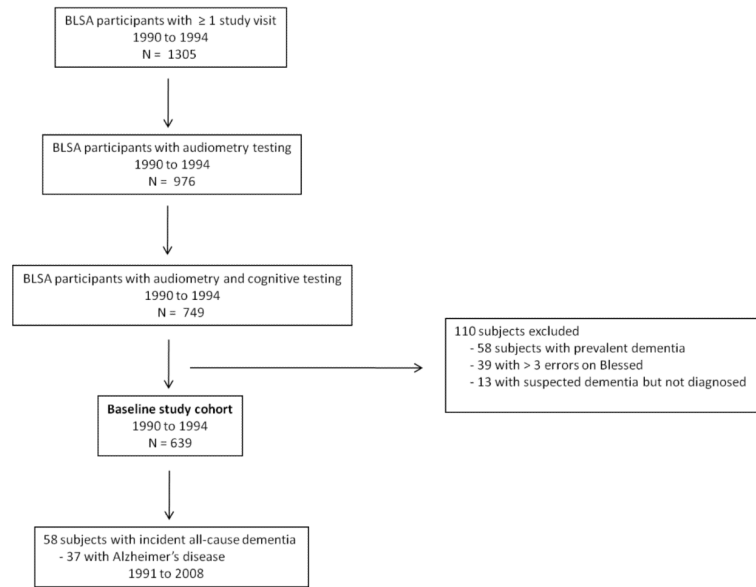


Figure 1.
Selection of subjects for study inclusion

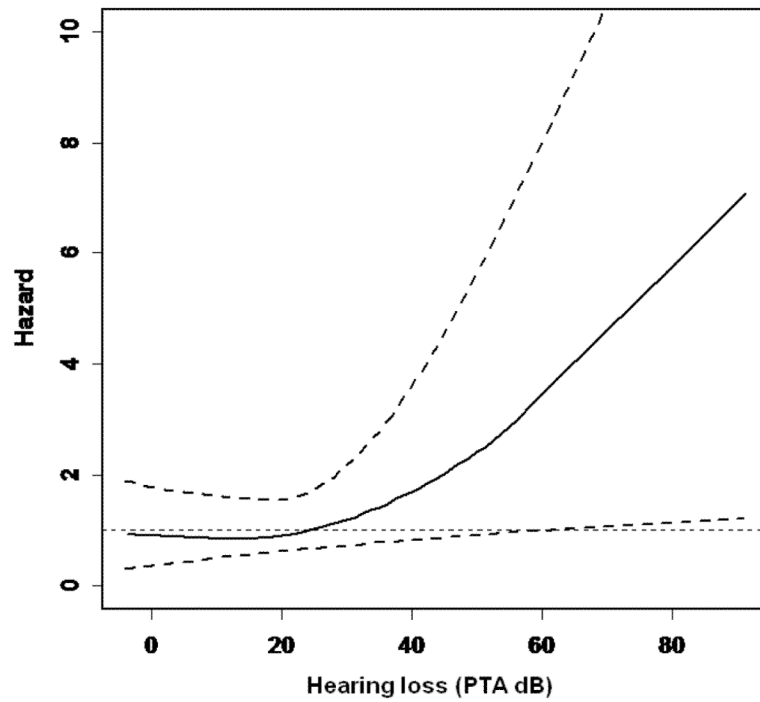


Figure 2. Risk of incident all-cause dementia by baseline hearing loss after adjustment for age, sex, race, education, diabetes, smoking, and hypertension. Hearing loss is defined by the pure tone average (PTA) of 0.5, 1, 2, and 4 kHz tones presented by air-conduction in the better hearing ear. Upper and lower dashed lines correspond to the 95% confidence interval.

Table 1
Demographic and clinical characteristics of baseline study cohort by hearing loss status

	Hearing loss status ^a				P value
	Normal (n = 455)	Mild (n = 125)	Moderate (n = 53)	Severe (n = 6)	
Male sex	225 (50)	94 (75)	36 (68)	5 (83)	<.001
Age, mean (SD), y	59.9 (12.2)	71.1 (8.6)	77.0 (8.4)	77.7 (4.8)	<.001
Race					.17
White	404 (89)	121 (97)	49 (92)	6 (100)	
Black	44 (10)	4 (3)	4 (8)	0 (0)	
Other	7 (2)	0 (0)	0 (0)	0 (0)	
Education, mean (SD), y	16.6 (2.8)	16.2 (3.0)	16.7 (3.6)	16.2 (4.0)	.74
Diabetes	62 (14)	20 (16)	12 (23)	1 (17)	.27
Smoking					.05
Current	19 (4)	1 (1)	1 (2)	0 (0)	
Former	244 (54)	85 (68)	35 (66)	3 (50)	
Never	192 (42)	39 (31)	17 (32)	3 (50)	
Hypertension	204 (45)	79 (63)	38 (72)	6 (100)	<.001
Hearing aid use ^b	6 (2)	14 (12)	39 (78)	4 (67)	<.001
Blessed Information-Memory-Concentration test					.08
0	265 (58)	65 (52)	31 (58)	0 (0)	
1	112 (25)	32 (26)	13 (25)	2 (33)	
2	49 (11)	19 (15)	6 (11)	3 (50)	
3	29 (6)	9 (7)	3 (6)	1 (17)	
Subjects developing all-cause dementia during follow-up	20 (4.4)	21 (16.8)	15 (28.3)	2 (33.3)	<.001

^a Values are expressed as number (percentage) unless otherwise indicated. Hearing loss categories are defined by the pure tone average (PTA) of hearing thresholds at 500, 1000, 2000, and 4000hz with tones presented by air-conduction to the better hearing ear: Normal (PTA < 25dB), Mild (25-40 dB), Moderate (41-70 dB), and Severe (>70 dB).

^b Data on hearing aid use were missing for 72 subjects. Subjects with hearing aid use data per hearing loss category were normal (n=393), mild (n=118), moderate (n=50), severe (n=6).

Table II

Demographic and clinical characteristics of baseline study cohort by incident dementia

	No Dementia ^a n = 581	Dementia ^a n = 58	Univariate Hazard (95% CI)
Hearing loss, mean (SD), PTA ^b	18.8 (13.9)	32.6 (17.0)	1.06 (1.04, 1.07) ^c
Hearing loss ^d			
Normal	435 (75)	20 (34)	1
Mild	104 (18)	21 (36)	4.9 (2.6, 8.8)
Moderate	38 (7)	15 (26)	12.1 (6.2, 23.9)
Severe	4 (1)	2 (3)	21.9 (5.1, 94.2)
Male sex	327 (56)	33 (57)	1.09 (0.65, 1.82)
Age, mean (SD), y	62.2 (12.3)	78.3 (6.4)	1.20 (1.15, 1.24)
Race			
White	523 (90)	57 (98)	1
Black	51 (9)	1 (2)	0.17 (.02, 1.25)
Other	7 (1)	0 (0)	--
Education, mean (SD), y	16.5 (3.0)	16.6 (3.0)	1.01 (0.92, 1.10)
Diabetes	84 (14)	11 (19)	1.57 (0.87, 3.01)
Smoking			
Current	20 (3)	1 (2)	1
Former	333 (57)	34 (59)	2.33 (0.32, 17.0)
Never	228 (39)	23 (40)	2.07 (0.28, 15.3)
Hypertension	286 (49)	41 (71)	2.92 (1.66, 5.15)
Hearing aid use ^e	47 (9)	16 (30)	5.3 (2.9, 9.6)
Blessed Information-Memory Concentration test			
0	338 (58)	23 (40)	1
1	140 (24)	19 (33)	2.12 (1.15, 3.89)
2	64 (11)	13 (22)	2.84 (1.44, 5.61)
3	39 (7)	3 (5)	1.23 (0.37, 4.08)

^a Values are expressed as number (percentage) unless otherwise indicated.

^b Pure tone average (PTA) of hearing thresholds at 0.5, 1, 2, and 4 kHz with tones presented by air-conduction to the better hearing ear

^c Hazard per 1 dB of PTA.

^d Normal (PTA < 25dB), Mild (25-40 dB), Moderate (41-70 dB), and Severe (>70 dB).

^e Data on hearing aid use were missing for 72 subjects. Subjects with hearing aid use data per dementia category were no dementia (n = 514) and dementia (n = 53).

Table III

Cox proportional hazard models for incident all-cause dementia per 10 decibel (dB) of hearing loss

	N	Hazard per 10 dB of Hearing Loss ^a (95% CI)	P value
Base Model ^b	638	1.27 (1.06 – 1.50)	.008
Base + Blessed Score	638	1.24 (1.04 – 1.48)	.01
Base with age as time scale	638	1.29 (1.08 – 1.53)	.005
Base + hearing aid use	566	1.33 (1.07 – 1.64)	.008

^aHearing loss defined by the pure tone average (PTA) of air-conduction hearing thresholds at 0.5, 1, 2, and 4 kHz in the better-hearing ear.

^bBase model covariates include sex, age, race, education, diabetes, smoking, and hypertension