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### Title

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### Permalink

<https://escholarship.org/uc/item/4bf4k26g>

### Journal

The Journals of Gerontology Series A, 75(3)

### ISSN

1079-5006

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### Publication Date

2020-02-14

### DOI

10.1093/gerona/glz035

Peer reviewed

Research Article

# Hearing Impairment and Cognitive Decline in Older, Community-Dwelling Adults

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Received: July 27, 2018; Editorial Decision Date: January 24, 2019

**Decision Editor:** Anne Newman, MD, MPH

## Abstract

**Background:** Hearing impairment is prevalent among older adults and has been identified as a risk factor for cognitive impairment and dementia. We evaluated the association of hearing impairment with long-term cognitive decline among community-dwelling older adults.

**Methods:** A population-based longitudinal study of adults not using hearing aids who had hearing acuity and cognitive function assessed in 1992–1996, and were followed for a maximum of 24 years with up to five additional cognitive assessments. Hearing acuity was categorized based on pure-tone average (PTA) thresholds: normal (PTA ≤ 25 dB), mild impairment (PTA > 25–40 dB), moderate/severe impairment (PTA > 40 dB).

**Results:** Of 1,164 participants (mean age 73.5 years, 64% women), 580 (49.8%) had mild hearing impairment and 196 (16.8%) had moderate/severe hearing impairment. In fully adjusted models, hearing impairment was associated with steeper decline on the Mini-Mental State Examination (MMSE) (mild impairment  $\beta = -0.04$ ,  $p = .01$ ; moderate/severe impairment  $\beta = -0.08$ ,  $p = .002$ ) and Trails B (mild impairment  $\beta = 1.21$ ,  $p = .003$ ; moderate/severe impairment  $\beta = 2.16$ ,  $p = .003$ ). Associations did not differ by sex or apolipoprotein E (APOE)  $\epsilon 4$  status and were not influenced by social engagement. The MMSE-hearing association was modified by education: mild hearing impairment was associated with steeper decline on the MMSE among participants without college education but not among those with college education. Moderate/severe hearing impairment was associated with steeper MMSE decline regardless of education level.

**Conclusions:** Hearing impairment is associated with accelerated cognitive decline with age, and should be screened for routinely. Higher education may provide sufficient cognitive reserve to counter effects of mild, but not more severe, hearing impairment.

**Keywords:** Hearing loss, Cognitive reserve, Cognitive aging, Education

With the aging of the population and high costs associated with caring for cognitively impaired older adults, identification of risk factors for cognitive decline in aging is becoming increasingly important. Hearing impairment, which affects 60%–68% of U.S. adults older than 70 years (1), is recognized as a risk factor for age-related cognitive impairment, disability, and dementia (2–5). A recent systematic review and meta-analysis indicated that age-related hearing loss was associated with twofold or greater pooled odds of cognitive impairment and dementia in cross-sectional studies (6). A smaller,

but still significant, increase in the pooled odds of cognitive decline was observed in the much smaller number of available longitudinal cohort studies (6). These studies suggest that the magnitude of hearing-loss-related cognitive decline varies by cognitive domain (7–14).

A recent report from the American Geriatrics Society/National Institute on Aging Bench-to-Bedside Conference called for further research on the association of hearing loss with cognitive function in aging (5). It is not known whether the association between hearing loss and cognitive function is mediated by social isolation or

depression, nor is it known whether associations differ by sex, genetic risk for Alzheimer's disease, or cognitive reserve. Additionally, prior longitudinal studies have not accounted for the potential influence of survival bias, an important consideration given that hearing impairment has been associated with higher risk of mortality (15) and cognitive decline accelerates prior to death (16).

To further understand the association of hearing impairment with age-related cognitive decline, we examined the association between severity of hearing impairment at baseline and change in cognitive performance over a 24-year follow-up period in a large, well-characterized cohort of community-dwelling older adults. We investigated whether associations of hearing impairment and cognitive decline varied by sex, education, or apolipoprotein E (APOE) status, and whether hearing-related differences in social engagement or mortality may have contributed to any observed associations between hearing impairment and cognitive function.

## Methods

### Participants

Participants were from the Rancho Bernardo Study (RBS) of Healthy Aging (17). In 1992–1996, 1,781 members of this observational cohort participated in a research clinic visit at which cognitive function and hearing were assessed. After excluding 73 participants with missing cognitive data, 313 with missing hearing data, and 231 who wore a hearing aid, there remained 1,164 participants in the analytic sample. Participants were followed through 2014–2016, with cognitive testing approximately every 4 years for a maximum of six assessments over 24 years. Each visit was approved by the University of California San Diego (UCSD) institutional review board. All participants provided written informed consent prior to each visit.

### Hearing Assessment

Hearing measurements were performed with a Welch Allyn portable audiometer in a quiet room. Pure-tone auditory thresholds were measured at frequencies of 500, 1,000, 2,000, and 4,000 Hz in each ear. If a participant was unable to hear the tone at 40 dB, measurement was stopped at that frequency and a value of 50 dB was assigned.

The pure-tone average (PTA) threshold was calculated as the average threshold across the four frequencies for each ear. The PTA of the better-hearing ear was used to define hearing categories according to guidelines from the World Health Organization as normal (PTA  $\leq$  25 dB), mild impairment (PTA > 25–40 dB), and moderate/severe impairment (PTA > 40 dB).

### Cognitive Assessment

The Mini-Mental State Examination (MMSE) (18), a test of global function, the Trail-Making Test Part B (Trails B) (19), a test of executive function, and category naming (animals) (20), a verbal fluency test (VFT), were administered at each visit.

### Covariate Assessment

A standardized questionnaire was used to assess health-related behaviors including smoking status (never/former/current), alcohol intake (nondrinker/moderate drinker/heavy drinker, the latter defined as more than one drink per day for women or more than two drinks per day for men), and physical activity (three or more times per week, yes/no). Participants were asked about

number and frequency of contact with close friends and family, and about their involvement in several types of social groups (categorized according to highest level of activity in any social group as not active/somewhat active/very active). Marital status was coded as currently married versus unmarried. Education was categorized as high school or less versus at least some college. Depression was assessed using the self-administered Beck Depression Inventory (21).

Clinical measures and health history were obtained as described previously (22). Briefly, fasting lipid levels were measured in a Lipids Research Clinic laboratory at UCSD. Total cholesterol and triglyceride levels were measured by enzymatic techniques and high-density lipoprotein (HDL) cholesterol after manganese chloride precipitation; low-density lipoprotein (LDL) cholesterol was estimated using the Friedewald formula (23). Prevalent vascular disease was defined as physician-diagnosed myocardial infarction, coronary artery revascularization, congestive heart failure, stroke or transient ischemic attack, carotid surgery, peripheral artery surgery, or intermittent claudication. APOE genotype data were available for a subset of the cohort ( $n = 707$ ).

### Statistical Analysis

Differences in demographic and clinical variables across hearing groups were assessed using  $\chi^2$  tests for categorical variables and analyses of variance for continuous variables. Differences between hearing groups on cognitive test performance over time were assessed using linear mixed effects regression models, with separate models for each test (17). Models included fixed effect terms, which model the mean trajectory of participants as a function of covariates: baseline age, sex, education, and time (years since baseline). Models also included random effect terms that allow individual participants' baseline performance (intercept) and rate of change (slope) to vary randomly about the mean trajectory defined by the fixed effect terms. A retest term was included and defined as zero for a participant's first cognitive assessment and one for all subsequent assessments (17). Time was modeled as a linear variable and a quadratic variable (time<sup>2</sup>) to assess nonlinear trends. Interaction terms of hearing group and time indicated group differences in performance trajectories. The interaction of hearing group with time<sup>2</sup> was not significant for any test, and was not included in the final models.

Base models adjusted for age, sex, education, and retest. Adjusted models included baseline levels of covariates that have a known or suspected association with hearing and cognition including LDL and HDL cholesterol (24), physical activity (25), smoking (26), alcohol use (27), depression (28), prevalent cardiovascular disease, hypertension, and diabetes (29).

Possible mediation by social engagement was examined by adding variables for social group involvement, number and frequency of contact with close friends or family, and marital status to the adjusted models. Sex, education, and APOE status were individually examined as potential effect modifiers by including interaction terms of these covariates in the base models. The effect of informative drop-out due to death was assessed for each cognitive test using a longitudinal joint shared random effect model adjusted for base model variables (30).

All statistical tests were two-sided;  $p < .05$  was regarded as significant. Data were analyzed using open-source statistical analysis software (R version 3.4.2). The package "lme4" was used for linear mixed models and the package "JM" was used for joint models.

## Results

### Participant Characteristics

The sample was 64% women and 98% white non-Hispanic adults. Mean age was 73.5 ± 9.3 years (range 31–92 years; only 1% of the sample was below age 50); 69% attended some college. One third of the sample (33.3%) had normal hearing, 49.8% had mild hearing impairment, and 16.8% had moderate/severe impairment. Relative to those included in the analytic sample, excluded participants were younger (mean 67.3 vs 73.5), more likely to be men (41% of men excluded vs 31% of women), and to have college education (79% vs 69%) (all *ps* < .001).

Table 1 shows select participant characteristics at baseline by hearing category (Supplementary Table S1 shows additional characteristics). Participants with hearing impairment were older and more likely to be men. After adjustment for age and sex, those with moderate/severe hearing impairment were also more likely to be non-drinkers and had lower LDL cholesterol levels. Groups did not differ in education, smoking status, APOE genotype, social engagement, or physical activity. The percentage of participants with three or more cognitive assessments declined from 70% to 35% with increasing hearing impairment (Supplementary Table S1). Mean follow-up time was 10 ± 7 years for those with normal hearing, 7 ± 6 years for those with mild hearing impairment, and 4 ± 5 years for those with moderate/severe hearing impairment. The main reason for non-participation in follow-up visits was death.

### Hearing Impairment and Cognitive Function

Figure 1 shows modeled trajectories of performance on each test by hearing group. Selected parameter estimates are shown in Table 2; parameter estimates for all variables in the base and fully adjusted models are included in Supplementary Tables S2 and S3, respectively. As evident in the figure (and from the significant time<sup>2</sup> term in the models), performance decline on all tests accelerated with advancing age, as previously reported for this cohort (17). In base models,

performance on all tests was worse for those with moderate/severe hearing impairment relative to those with normal hearing. For the MMSE and Trails B, both hearing-impaired groups showed steeper decrease in performance over time relative to normal hearing adults. For the VFT, only those with mild hearing impairment showed steeper decline over time than normal hearing adults. These associations were consistent in joint models that accounted for increased risk of mortality among those with moderate/severe hearing impairment (Supplementary Table S4).

With adjustment for health-related variables, associations of hearing impairment with performance on MMSE and Trails B remained significant. Associations were unaffected by inclusion of social engagement variables in the models (Table 2). The performance deficit at baseline for the MMSE was equivalent to an additional 7 years of age for individuals with moderate/severe hearing impairment compared to those with normal hearing. The yearly effect of mild hearing impairment on the rate of decline in MMSE performance was equivalent to an additional 0.5 years of age, while the effect of moderate/severe hearing impairment was equivalent to an additional 1.1 years of age.

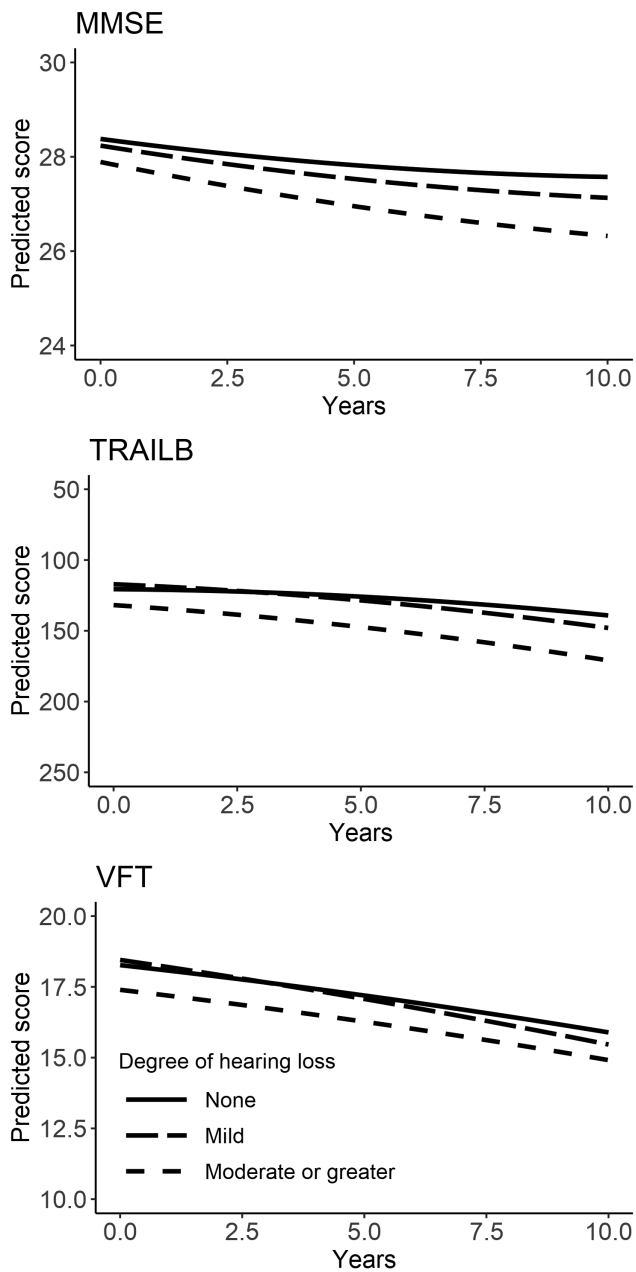
Associations of hearing impairment with rates of cognitive decline did not differ between men and women (three-way interaction of sex by hearing group by time, all *ps* > .15; Supplementary Table S5), nor did they differ by APOE ε4 status (three-way interaction, all *ps* > .05; Supplementary Table S6). Education modified the association of hearing impairment with decline on the MMSE (three-way interaction *p* = .037) for those with mild, but not more severe hearing impairment. Mild hearing impairment was associated with steeper MMSE decline among participants without college education but not among those with at least some college (education by time by mild hearing impairment β = 0.06; SE = 0.03; *p* = .034). Moderate/severe hearing impairment was associated with steeper MMSE decline relative to normal hearing adults regardless of education level (education by time by moderate/severe impairment β = -0.04; SE = 0.05; *p* = .42). There was a trend (three-way interaction

**Table 1.** Characteristics of Rancho Bernardo Study Participants by Hearing Acuity Group

Variable	None ( <i>n</i> = 388)	Mild ( <i>n</i> = 580)	Moderate+ ( <i>n</i> = 196)	<i>p</i> -Value	<i>p</i> -Value <sup>a</sup>
Age (years)	67.2 (8.6)	75.1 (8.0)	81.0 (6.4)	<.001	
Male	103 (26.7)	248 (42.9)	63 (32.3)	<.001	
College education	262 (68.6)	417 (73.0)	126 (65.3)	.087	.062
Alcohol consumption				.009	.048
None	114 (29.6)	182 (31.7)	84 (43.1)		
Moderate	171 (44.4)	262 (45.6)	66 (33.9)		
Heavy	100 (26.0)	130 (22.7)	45 (23.1)		
Married	301 (77.8)	402 (69.3)	128 (65.3)	.002	.17
Social group activity				.31	.108
Not active	109 (28.2)	144 (25.1)	62 (31.8)		
Somewhat active	131 (33.9)	217 (37.9)	70 (35.9)		
Very active	146 (37.8)	212 (37.0)	63 (32.3)		
Contact with friends/family				.13	.84
>Once a week	278 (72.6)	370 (65.4)	124 (66.3)		
Once a week	55 (14.4)	115 (20.3)	33 (17.7)		
<Once a week	50 (13.1)	81 (14.3)	30 (16.0)		
Beck Depression Inventory	4.6 (4.0)	5.4 (4.2)	6.8 (5.4)	<.001	.06
LDL cholesterol (mg/dL)	127.8 (32.2)	128.5(33.4)	120.4 (32.0)	.010	.009
HDL cholesterol (mg/dL)	60.7 (16.8)	57.1 (16.9)	59.7 (18.6)	.003	.093
APOE ε4+ ( <i>n</i> = 707)	43 (18.1)	78 (22.7)	31 (24.6)	.46	.36

Note. APOE ε4+ = one or more ε4 alleles; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Moderate+ = moderate/severe hearing impairment. Values are mean (SD) for continuous variables and N (%) for categorical variables..

<sup>a</sup>Adjusted for age and sex.



**Figure 1.** Modeled trajectories of cognitive function test performance over time as a function of hearing status. Plots are based on base model coefficients using hearing group-specific mean values for covariates: age, sex, education, and practice effect. The axis for Trails B is reversed so that for all tests, downward sloping lines represent declining performance. Trajectories are plotted to 10 years follow-up time, the 90th percentile of follow-up time for the moderate/severe hearing impairment group.

$p = .13$ ) for higher education to be associated with slower decline on the Trails B test in those with mild ( $\beta = -1.74$ ;  $SE = 0.87$ ;  $p = .05$ ) but not more severe hearing impairment ( $\beta = -0.66$ ;  $SE = 1.53$ ;  $p = .67$ ; [Supplementary Table S7](#)). Education did not interact with hearing impairment-related decline for VFT (three-way interaction of education by hearing group by time  $p = .55$ ; [Supplementary Table S7](#)).

## Discussion

We quantified the association between hearing impairment and longitudinal cognitive function in a large community-dwelling cohort of

older adults followed for up to 24 years. The prevalence of hearing impairment was high and comparable with age-matched national averages (1). Severity of hearing impairment was associated with reduced performance and steeper decline for tests of global function (MMSE) and executive function (Trails B). These associations were independent of many potential confounders, including vascular disease and cardiovascular disease risk factors, and were unaffected by differential survival. Associations did not differ by sex or genetic risk for Alzheimer's disease. We found some evidence that education may modify the association of mild, but not more severe hearing impairment with cognitive decline. We found no evidence that the association of hearing impairment with cognitive decline was mediated by hearing-related differences in social engagement.

In assessing associations of hearing impairment with cognitive test performance it is critical to consider the possibility that hearing impairment may lead to lower performance due to difficulty in hearing and understanding test instructions or questions. Most participants had prior experience with the tests, and our trained test administrators ensured participants understood study instructions before each test was begun. While it is possible that an inability to hear specific test questions may have contributed to lower scores on the orally administered MMSE, performance was also lower as a function of hearing status on Trails B and VFT, which do not rely on auditory comprehension during test performance.

Our findings that hearing impairment is associated with poorer performance and accelerated decline on measures of global cognitive function and executive function, but not verbal fluency, are consistent with those in a Health ABC study, in which hearing impairment among 1,984 participants was associated with worse baseline performance and steeper 6-year decline on the Modified MMSE and a test of executive function (11); and with findings in the Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study ( $n = 253$ ), in which individuals with moderate/severe hearing impairment showed steeper 20-year decline on a word recall task and on a global composite score, but not on a test of verbal fluency (12). Similarly, hearing impairment was associated with greater 6-year decline on tests of executive function but not verbal fluency among 418 older adults in the Maastricht Aging Study (9). Hearing impairment was also associated with poorer baseline performance and greater decline over 17 years on orally administered tests, but not on computer-administered tests of reaction time and fluid intelligence, among 1,057 men in the Caerphilly cohort (10).

Several prior studies did not observe significant associations between hearing impairment and cognitive decline (7,13,14,31). No association between hearing impairment and rate of decline on tests of memory or perceptual or psychomotor processing speed was observed among 721 participants of the Health ABC Cognitive Vitality Substudy (14). Since individuals with exceptional functional ability were over-represented in that cohort, rates of cognitive decline were smaller than those observed in more representative populations, potentially limiting power to detect associations with subtle cognitive change (14). In the Framingham ( $n = 1,334$ ), and Blue Mountains Eye Study ( $n = 1,382$ ), hearing impairment was not associated with risk of categorical MMSE decline (7,13). In the Study of Osteoporotic Fractures ( $n = 4,754$ ), older women with hearing impairment showed a nonsignificant trend for greater decline on the 3MS over 2 years (31). A longer follow-up period may have revealed a significant association. Taken together, our findings and those of prior studies suggest that hearing impairment is associated with greater cognitive decline, but that associations differ by cognitive domain, may be more apparent in studies with longer follow-up and with continuous rather than categorical measures of cognitive

**Table 2.** Longitudinal Change in Cognitive Test Performance for Mild and Moderate/Severe Hearing Impairment Relative to Normal Hearing Participants of the Rancho Bernardo Study

	MMSE		Trails B		VFT	
	$\beta$ (SE)	<i>p</i> -Value	$\beta$ (SE)	<i>p</i> -Value	$\beta$ (SE)	<i>p</i> -Value
<b>Base model</b>						
Time	-0.14 (0.02)	<b>&lt;.001</b>	0.25 (0.46)	.58	-0.19 (0.04)	<b>&lt;.001</b>
Time <sup>2</sup>	0.006 (0.001)	<b>&lt;.001</b>	0.16 (0.03)	<b>&lt;.001</b>	-0.005 (0.002)	<b>.035</b>
Mild hearing impairment	-0.14 (0.13)	.29	-3.51 (3.68)	.34	0.18 (0.31)	.55
Moderate/severe impairment	-0.49 (0.19)	<b>.009</b>	11.23 (5.12)	<b>.031</b>	-0.87 (0.43)	<b>.043</b>
Time × hearing impairment		<b>.005</b>		<b>.001</b>		<b>.09</b>
Time × mild	-0.03 (0.01)	<b>.032</b>	1.23 (0.40)	<b>.002</b>	-0.06 (0.03)	<b>.033</b>
Time × moderate/severe	-0.08 (0.03)	<b>.003</b>	2.05 (0.71)	<b>.004</b>	-0.01 (0.05)	.84
<b>Fully adjusted model</b>						
Time	-0.14 (0.02)	<b>&lt;.001</b>	0.21 (0.47)	.66	-0.19 (0.04)	<b>&lt;.001</b>
Time <sup>2</sup>	0.006 (0.001)	<b>&lt;.001</b>	0.17 (0.03)	<b>&lt;.001</b>	-0.004 (0.002)	.06
Mild hearing impairment	-0.19 (0.13)	.15	-2.17 (3.80)	.57	0.23 (0.32)	.47
Moderate/severe impairment	-0.54 (0.19)	<b>.004</b>	11.41 (5.40)	<b>.035</b>	-0.70 (0.45)	.12
Time × hearing impairment		<b>.003</b>		<b>.002</b>		<b>.039</b>
Time × mild	-0.03 (0.01)	<b>.015</b>	1.25 (0.40)	<b>.002</b>	-0.07 (0.03)	<b>.012</b>
Time × moderate/severe	-0.08 (0.03)	<b>.003</b>	1.91 (0.72)	<b>.008</b>	-0.02 (0.05)	.74

*Note.* MMSE = Mini-Mental State Examination; VFT = verbal fluency test. Based on linear mixed effects regressions. Base model: age, sex, education, retest, time, and time<sup>2</sup>. Fully adjusted model: base model plus depression, physical activity, smoking, alcohol use, high-density lipoprotein and low-density lipoprotein cholesterol, prevalent cardiovascular disease, hypertension, diabetes, marital status, social group activity, frequency of contacts with friends/family, and number of close friends/family. For parameter estimates, for all variables see [Supplementary Tables S2 and S3](#). Bold values represent significance level *p* < 0.05.

decline, and that associations may be less apparent in those with exceptional ability.

We found some support for the hypothesis that cognitive reserve modifies the association between hearing impairment and cognitive decline. It has been suggested that associations between hearing impairment and cognitive impairment arise, at least partly, from competition for limited cognitive resources (12,32). Individuals with hearing impairment need to devote greater resources to understanding poor-quality auditory signals, leaving insufficient resources available for other cognitive activities (11,12,32). Those with greater resources may be better able to compensate for hearing impairment. We found a significant interaction between education level, a proxy for cognitive reserve (33), and mild hearing impairment on MMSE decline, and a trend-level effect on Trails B decline. For both tests, mild hearing impairment was associated with greater decline in those without college education, but not among those with college education. This may suggest that higher education provides sufficient reserve to compensate for mild, but not more severe hearing impairment. However, it is also possible that these tests, particularly the MMSE, are not adequately sensitive to subtle decline among highly educated adults.

Hearing-related social isolation has also been proposed to contribute to the association between hearing loss and poorer cognitive function (34). Hearing impairment can lead to social withdrawal, and reduced social engagement can lead to cognitive impairment (35,36). In our cohort, there were no differences in measures of social engagement between those with and without hearing impairment, and inclusion of social engagement measures in our models did not attenuate associations. Thus, accelerated cognitive decline can be observed even among hearing-impaired individuals who remain socially active.

The link between hearing impairment and cognitive impairment may be due to a common underlying cause such as vascular disease (3,34) or neurodegenerative diseases such as Alzheimer's disease. However, control for prevalent cardiovascular disease,

cardiovascular risk factors, and genetic risk for Alzheimer's disease did not change the observed associations. There were no differences in APOE genotypes across hearing groups, and associations did not significantly differ by genetic risk for Alzheimer's disease.

The association between hearing impairment and cognitive impairment may arise from structural changes in the brain secondary to disuse of circuits responsible for encoding and interpreting auditory signals among individuals with hearing impairment (32). Although our study does not address this potential explanation, our finding that a greater degree of hearing impairment predicts greater cognitive decline over time is consistent with progressive brain changes due to reduced auditory input.

Limitations of our study include homogeneity of the sample, which is almost entirely white, educated, and middle class, limiting generalizability. Also, we examined hearing at baseline only, so we are unable to comment on the effect of time-varying hearing impairment. Men, and participants who were older at baseline, may have been more likely to develop hearing loss over the follow-up period. Thus, some of the cognitive decline over time observed among our normal hearing adults may be attributable to the development of hearing impairment over the follow-up period (37), which would have biased our findings towards the null. We also did not have information on pure-tone thresholds >40 dB, which likely served to underestimate the degree of hearing impairment in those with moderate/severe hearing impairment. Finally, survival bias may have affected our results as participants with greater hearing impairment were less likely to return for subsequent visits. However, associations remained significant in joint models including survival analyses, suggesting that observed associations were not due to differences in survival.

This study has several strengths. The cohort was large and well characterized, which allowed control for numerous potential confounders and examination of potential effect moderators and mediators. The analysis was based on more than 20 years of longitudinal data, which strengthened our ability to detect the association

between hearing impairment and change in cognition over time. We were also able to assess associations of hearing impairment with different domains of cognitive function.

## Conclusions

Hearing impairment is associated with poorer performance and steeper decline over time on tests of global function and executive function among community-dwelling older adults. Although the basis of these associations is not fully understood, they do not appear to arise from hearing-related differences in social engagement, nor from common effects of vascular disease. Instead, they may stem, partly, from increased cognitive load and competition for limited cognitive resources imposed by hearing impairment, or from progressive brain changes due to reduced auditory input. Physicians should be aware that older patients with hearing impairment are at increased risk for cognitive decline and consider including hearing assessments in routine health screening. While the magnitude of the associations of mild hearing impairment with cognitive decline were small, with the aging of our society and high prevalence of hearing loss with age, these associations could have large societal impact. Greater emphasis should be placed on minimizing loud noise exposure, the largest modifiable risk factor for hearing impairment, and care should be taken when prescribing potentially ototoxic medications.

## Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

## Funding

This work was supported by a Clinical Research Fellowship from UC San Diego School of Medicine (to A.A.A) and grants from the National Institutes of Health (NIH; grant numbers R01 AA021187 and R01 AG054067). Data collection for the Rancho Bernardo Study was supported by grants from the NIH (grant numbers R01 AG028507, R37 AG007181, R01 DK31801). Some study data were collected and managed using REDCap electronic data capture tools hosted at University of California San Diego and supported by a grant from the NIH (grant number UL1TR001442).

## Acknowledgments

*Authors' contributions:* A.A.A.: study concept and design, data analysis and interpretation, and manuscript preparation; J.B.: data analysis and interpretation, and manuscript preparation; G.A.L.: data collection, data interpretation, and manuscript preparation; D.K.-S.: data collection, data interpretation, and manuscript preparation; E.L.R.: data interpretation and manuscript preparation; E.T.R.: data interpretation and manuscript preparation; J.P.H.: study concept, data interpretation, and manuscript preparation; E.B.-C.: study design, data collection, data interpretation, and manuscript preparation; L.K.M.: study design, data collection, data interpretation, and manuscript preparation.

## Conflict of Interest

None reported.

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