Title

Examining the Combined Estimated Effects of Hearing Loss and Depressive Symptoms on Risk of Cognitive Decline and Incident Dementia

Journal

The Journals of Gerontology Series B, 77(5)

ISSN

1079-5014

Authors

Powell, Danielle S
Brenowitz, Willa D
Yaffe, Kristine
et al.

Publication Date

2022-05-05

DOI

10.1093/geronb/gbab194

Peer reviewed

THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Psychological Sciences
cite as: *J Gerontol B Psychol Sci Soc Sci*, 2022, Vol. 77, No. 5, 839–849
https://doi.org/10.1093/geronb/gbab194
Advance Access publication October 16, 2021

OXFORD

Editor's choice

Research Article

Examining the Combined Estimated Effects of Hearing Loss and Depressive Symptoms on Risk of Cognitive Decline and Incident Dementia

Danielle S. Powell, AuD, PhD,[1,2,*] Willa D. Brenowitz, PhD, MPH,[3,4] Kristine Yaffe, MD,[3,4,5] Nicole M. Armstrong, PhD,[6] Nicholas S. Reed, AuD,[2,7] Frank R. Lin, MD, PhD,[2,8] Alden L. Gross, PhD,[1,7] and Jennifer A. Deal, PhD[2,7]

[1]Center on Aging and Health, Johns Hopkins University, Baltimore, Maryland, USA. [2]Cochlear Center for Hearing and Public Health, Baltimore, Maryland, USA. [3]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California, USA. [4]Department of Psychiatry, Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, California, USA. [5]Department of Neurology, University of California, San Francisco, San Francisco, California, USA. [6]Department of Psychiatry and Human Behavior, Warren Alpert Medical School, Brown University, Providence, Rhode Island, USA. [7]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA. [8]Department of Otolaryngology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

*Address correspondence to: Danielle S. Powell, AuD, PhD, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, Baltimore, MD 21295, USA. E-mail: dpowel33@jhu.edu

Received: May 19, 2021; Editorial Decision Date: October 11, 2021

Decision Editor: Vanessa Taler, PhD

Abstract

Objectives: Late-life depression is a comorbidity that may co-occur in older adults with hearing loss—each has prevalent and independent modifiable risk factors for dementia.

Methods: Using data from 1,820 Health, Aging and Body Composition study participants (74 ± 2.8 years, 38% Black race), we compared the hearing loss–dementia/cognitive decline relationship between those with normal hearing/mild hearing loss and those with moderate or greater hearing loss. Using linear mixed-effects and Cox proportional hazard models, we investigated if the associations between hearing loss and cognitive decline or dementia (Modified Mini-Mental State [3MS] Examination and Digit Symbol Substitution Test [DSST]) differed by the presence or absence of depressive symptoms. Depressive symptoms were defined as Center for Epidemiologic Study—Depression scale 10 ≥10 at one or more visits from Years 1–5. Algorithmic incident dementia was defined using medication use, hospitalizations, and cognitive test scores. Audiometric hearing loss was measured at Year 5 and categorized as normal/mild versus moderate or greater hearing loss.

Results: Having both hearing loss and depressive symptoms (vs. having neither) was associated with faster rates of decline in 3MS Examination (β = −0.30; 95% confidence interval [CI]: −0.78, −0.19) and DSST (β = −0.35; 95% CI: −0.67, −0.03) over 10 years of follow-up. Having both hearing loss and depressive symptoms (vs. neither) was associated with increased risk (hazard ratio [HR]: 2.91; 95% CI: 1.59, 5.33 vs. HR: 1.54; 95% CI: 1.10, 2.15 hearing loss only and HR: 2.35; 95% CI: 1.56, 3.53 depressive symptoms only) of incident dementia in multivariable-adjusted Cox proportional hazards models.

Discussion: Comorbid conditions among hearing-impaired older adults should be considered and may aid in dementia prevention and management strategies.

Keywords: Cognition, Depression, Hearing loss, Mental health

With the growing prevalence of dementia worldwide, there is a pressing need to identify potential avenues for prevention of dementia and cognitive decline. Globally, an estimated 43.8 million individuals were living with dementia in 2016, more than double that estimated in 1990 at 20.2 million (GBD 2016 Dementia Collaborators, 2019). Hearing loss (HL) is an independent and potentially modifiable risk factor for dementia (Livingston et al., 2020). Approximately two thirds of adults aged 70 years and older have an HL (Goman & Lin, 2016). Moreover, around 67% of older adults 65 years of age and older have multimorbidity (Salive, 2013); therefore, HL is likely present in older adults along with other health conditions. Given the high prevalence of HL in older adults, identification of differences in dementia risk by subgroups of older adults with concurrent modifiable risk factors for cognitive decline could have a meaningful public health benefit.

Diagnosed late-life depression is a potential comorbidity that may co-occur in older adults with HL. Previous work suggests the prevalence of even depressive symptomatology is approximately 15% in a community sample of older adults (Fiske et al., 2009). Depressive symptomatology in older adults may present as a heterogeneous course, susceptible to variation over time or acute instances from life events (Fiske et al., 2009). Furthermore, depressive symptomatology itself has been identified as another potentially independent modifiable risk factor for dementia (Livingston et al., 2020).

While the independent effect of HL, clinical depression, and increased depressive symptomatology on cognitive decline and dementia in older adults has been reported (Rutherford et al., 2018; Livingston et al., 2020; Wiels et al., 2020), the estimated effect from the presence of each condition as either a mediator or moderator in the relationship has received little study. A prior study of 8,529 participants aged 60 years or older from the National Alzheimer's Coordinating Center Uniform Data Set, one of the few studies to consider both HL and depression, investigated the potential mediating effect of depression and found no evidence of suggested change in the HL–dementia association (Brewster et al., 2021). While mediation analyses have benefits for understanding mechanisms, analyses of modification (i.e., interaction) have important public health relevance for the identification of high-risk groups. As HL and depression are both potentially modifiable, understanding if the risk presented by each condition in isolation differs from the risk in the presence of both conditions may allow for more targeted dementia intervention efforts in older adults.

Our study objectives, using data from the Health, Aging and Body Composition (Health ABC) study, are to test if (a) rates of cognitive decline and (b) risk of incident dementia differ for participants with both HL and depressive symptoms, compared to what would be expected given their independent effects. We hypothesized that the additional presence of depressive symptomatology among hearing-impaired older adults demonstrates faster rates of cognitive decline and greater risk of incident dementia.

Method

Study Population

Participants were enrolled in the Health ABC study, a biracial prospective study of 3,075 community-dwelling older adults, aged 70–79 years at study initiation in 1997–1998 (Visit 1), recruited from Pittsburgh, Pennsylvania or Memphis, Tennessee (Simonsick et al., 2001). As the Health ABC Study was designed to assess differences in function, disability, and longevity across race (Black vs. White) and gender, participants enrolled in the study were free of difficulty walking ¼ mile or difficulty climbing up 10 steps at study initiation. This study was approved by the Institutional Review Boards of all participating institutions. Audiometric hearing was assessed at study Year 5 (2001–2002).

Analytic sample: rates of cognitive decline

From an initial sample of 3,075, a total of 2,198 participants had completed audiologic measures (872 excluded), completed the baseline Center for Epidemiologic Study—Depression (CES-D) scale, and self-reported depression medication use measured at baseline (five excluded). We excluded 137 participants who were missing baseline covariates or had less than 2 measures of the Modified Mini-Mental State (3MS) Examination or the Digit Symbol Substitution Test (DSST) during the 10 years of follow-up. Our final analytic sample was 2,061.

Analytic sample: incident dementia

Of the 2,034 study participants who had completed audiologic measures in 2001–2002 (872 excluded), were dementia-free at Visit 1 (1997–1998; 159 excluded), and had completed baseline CES-D scores (10 excluded), an additional 214 participants were missing covariate data leading to an analytic sample in our secondary analysis of 1,820 participants.

Cognitive Decline

Two neurocognitive tests, the 3MS Examination (Teng & Chui, 1987) and the DSST (Weschler, 1981), were collected 6 times during the study: Year 1 (1997–1998), Year 3 (1999–2000), Year 5 (2001–2002), Year 8 (2004–2005), Year 10 (2006–2007), and Year 11 (2007–2008).

As a test of global cognitive function, the 3MS Examination (Teng & Chui, 1987) provides an assessment of an individual's orientation, registration, attention, calculation, recall, and visual–spatial skills similar to the 30-item Mini-Mental State Examination (MMSE; Folstein et al., 1975) it was adapted from. Expanded from the 30-item MMSE and scored from 0 to 100, this modification from

the 30-item scale is designed for enhanced reliability and validity.

The DSST (Weschler, 1981) tests attention, processing speed, and executive function requiring the participant to use a key of symbols and matched numbers to translate the corresponding number and symbol as fast as possible. Scoring is completed as the total number of symbols correctly matched within 90 seconds time—higher scores indicate better performance.

Incident Dementia

As has been implemented in prior work (Deal et al., 2017; Yaffe et al., 2013), incident dementia was defined in one or more of the following ways: (a) as initiating use of a prescribed dementia medication (galantamine, rivastigmine, memantine, donepezil, or tacrine) determined via medication inventory at annual visits; (b) a dementia diagnosis from adjudicated hospital records reviewed every 6 months at interim follow-ups for dementia-related hospital event or a primary or secondary diagnosis of dementia; or (c) decline on the 3MS Examination of 1.5 *SD* or more, based on race-specific SDs at baseline. Within our sample, the majority of participants diagnosed with incident dementia were done so via more than one of the described ways. Only 32% of participants were noted for incident dementia by a change in 3MS Examination score alone, with a mean change in 3MS Examination score for this group of a decrease of 25.4 points and *SD* of 12.4.

Hearing Loss

Hearing acuity measures were performed via audiometry in a sound-proof booth at Year 5 (2001–2002). Air conduction thresholds, as measured in decibels hearing level (dB HL), were completed in each ear from 250 Hz to 8,000 Hz with TDH 39 headphones using an MA40 audiometer (Maico Diagnostics, Eden Prairie, MN) calibrated to the American National Standards Institute standards (ANSI S3.6-1996).

For comparison of hearing levels, we calculated a commonly used metric of the speech frequency pure tone average (PTA) using thresholds at 500, 1,000, 2,000, and 4,000 Hz in the better hearing ear in agreement with the World Health Organization's definition of HL (World Report on Hearing, 2021). We created a binary variable of HL according to common clinical cutpoints (normal hearing or mild HL, PTA <40 dB HL; moderate or greater HL, ≥40 dB HL). Moderate or greater HL is recognized as a level at which HL begins to adversely affect communication ability, thereby may be referred to here as a significant HL (Olusanya et al., 2019), whereas a mild HL or those with normal hearing are commonly minimally affected by their hearing ability in specific situations.

Depressive Symptoms

Depressive symptoms were assessed using the CES-D scale (Lewinsohn et al., 1997), including both the full 20-item scale (Year 1) and abbreviated 10-item scale (Years 3–11). All scores were converted to the CES-D 10 scale. For our analysis, we utilized CES-D 10 scores from the start of follow-up until when hearing was assessed (Years 1, 3, 4, and 5) and defined significant depressive symptoms as a CES-D 10 score ≥10 (Andresen et al., 1994; Irwin et al., 1999). A history of having ever been treated for depression was ascertained at Year 1. Baseline depressive symptoms were therefore defined as a CES-D 10 score ≥10 at Year 1 or the presence of medication intended for depression. To better understand how the potential variability in depressive symptom presentation over time might modify the hearing–dementia relationship, we modeled repeated depressive symptoms as any repeated instance (consecutive or not) of clinically significant depressive symptoms (>1 elevated CES-D 10 score at Years 1, 3, 4, or 5).

Additional Covariates

We included age, gender (determined from sex identified at birth; women/men), race (Black/White), study center (Memphis or Pittsburgh), and education (less than postsecondary vs. postsecondary or greater) at Year 1 (1997–1998). We include the term gender as we intend for this to represent the social construct of gender rather than the biological influences of sex; however, our measure collected within the data set was sex as reported at birth. We also included a number of health-related factors. Diabetes was considered present if prevalent at Year 1, defined as physician-diagnosed diabetes (reported by the participant), use of diabetes drug, or a fasting glucose ≥126 mg/dL. Hypertension was considered present if prevalent at baseline (systolic blood pressure ≥140 mmHg, or diastolic blood pressure >90 mmHg, or by participant self-report of a diagnosis by a physician with or without antihypertensive medication use). History of stroke was assessed at baseline by the question, "Has a doctor ever told you that you had a stroke, mini-stroke, or TIA?" Smoking status (ever vs. never) was assessed at baseline by the questions: "Do you smoke cigarettes now?" and "Have you smoked at least 100 cigarettes in your life?" Body mass index (BMI, continuous kg/m) was evaluated at baseline. Marital status (never married, married, widowed/divorced/separated) was evaluated with the question: "What is your marital status?" Living alone (yes/no) was defined as reported presence of living with one or more individuals versus none. As it is possible hearing aid use for the management of HL may influence the estimated risk presented by HL alone or in the presence of other conditions, in a sensitivity analysis, we additionally adjusted for self-reported hearing aid use at baseline. All covariates were measured at baseline, except for hearing aid use, which was measured at Year 5.

Statistical Analysis

Descriptive analysis compared demographic information and clinical characteristics across levels of hearing status. Baseline characteristics were compared using means and standard deviations and analysis of variance tests for continuous measures. Categorical variables were described using frequencies with differences tested using chi-square tests.

We used linear mixed-effects models with person-specific slopes and intercepts to assess differences in rates of cognitive decline by hearing and depressive symptom status. Cognitive decline on the DSST and 3MS Examination was modeled separately. The linear mixed-effects model accounts for the correlation between repeated measures over time within an individual (Laird & Ware, 1982). We assumed an unstructured correlation matrix. We used Cox proportional hazard models to investigate risk of incident dementia by depressive symptom status and category of hearing acuity over 9 years of follow-up. We confirmed the proportionality assumption via Schoenfield's residuals (Grambsch & Therneau, 1994) and included an interaction between our exposure and time. As most participants were not at risk for incident dementia until the second administration of the 3MS Examination at Year 3, our time origin was modeled as Year 3 (1999–2000) and time on study was used as the time scale. For our analysis, follow-up for incident dementia continued until Year 11 (2007–2008) at the last time the 3MS Examination was administered to our study sample.

We described differences in the association of hearing and cognition by depressive symptom status in two ways, as has been recommended for observational studies (Knol & VanderWeele, 2012; von Elm et al., 2007): (a) modeling the joint risk of dementia using four exposure categories—(i) normal hearing or mild HL and no depressive symptoms (reference group), (ii) depressive symptoms only, (iii) HL only, and (iv) both HL and depressive symptoms and (b) inclusion of an interaction term between HL and depressive symptoms in the regression model. In our analysis of incident dementia, we also stratified results of the hazard of incident dementia from HL by depressive symptoms status, as well as the hazard from depressive symptoms by hearing status. This framework enabled us to assess the presence of both joint effects (i.e., four exposure categories) and heterogeneity of effects (i.e., interaction term) of depressive symptoms and HL on cognitive outcomes.

Model fit for both analyses was assessed using residual plots and through statistical methods including the Bayesian Information Criterion, Akaike Information Criterion, and likelihood ratio tests. As the additive scale has important public health implications (Knol et al., 2011) for our analysis of incident dementia, we present the independent and combined estimated effect of exposures on the additive scale using the relative excess risk of interaction (RERI) and the synergy index (ratio between the combined effect of an exposure and the individual effects; Assmann et al., 1996; de Mutsert et al., 2009; Richardson & Kaufman, 2009) and include a 95% confidence interval (CI) calculated via the delta method (Knol & VanderWeele, 2012; de Mutsert et al., 2009).

We adjusted for gender, education (postsecondary vs less than postsecondary), age, race (Black vs. White), smoking (ever vs. never), the presence or absence of hypertension or diabetes, BMI, marital status (never married, married, widowed/divorced/separated), and living alone. All analyses were completed using Stata 15.0 (StataCorp., 2017).

In a secondary analysis, we additionally adjusted for self-reported hearing aid use at baseline to understand if the management of HL may alter the effect estimates observed. We further completed a sensitivity analysis evaluating the combined estimated effects of HL and depressive symptoms on cognitive decline and incident dementia using Year 5 as the study baseline, at the time when hearing was measured. Additionally, to consider the influence of any HL on rates of cognitive change, in a sensitivity analysis, we defined the presence of HL as mild or greater HL (n = 1,295) compared to those clinically considered to have normal hearing (PTA <25 dB HL; n = 913).

Results

Descriptive Analysis

In our analytic sample of 2,061 participants, 20.7% had a moderate or greater HL, and 7.1% had clinically significant depressive symptoms at baseline, while 220 (10.7%) had repeated depressive symptoms over the first 4 years of follow-up. Categorizing participants based on both hearing status and baseline depressive symptoms, 1,529 (74.2%) had normal hearing or mild HL and no baseline depressive symptoms, 385 (18.7%) had a moderate or greater HL only, 104 (5.0%) had clinically meaningful depressive symptoms at baseline only, and 43 (2.1%) had both significant HL and depressive symptoms. Those without significant HL or depressive symptoms were generally younger and female compared to those with HL and/or depressive symptoms (Table 1). Participants not included in our sample due to exclusion criteria or missing data were more likely to be slightly older (mean age 74.5 years), Black, be widowed/divorced/separated, live alone, have greater prevalence of health conditions, have higher CES-D 10 scores (median 3.0), and lower 3MS Examination (median 90.0) or DSST (mean 31.1) scores.

Baseline Cognitive Test Performance and Rates of Cognitive Decline

Compared to participants with neither significant HL nor baseline depressive symptoms, participants with a moderate or greater HL (without depressive symptoms) on average had lower baseline test scores (β = −0.86; 95% CI: −1.53, −0.18 on 3MS Examination; β = −0.81; 95% CI: −2.08, 0.47 on DSST) and faster rates of decline on both

Table 1. Baseline Characteristic of the Analytic Sample in the Health ABC Study (*N* = 2,061)

Characteristic	Overall	Normal or mild hearing loss or depressive symptoms *N* (%)	Moderate+ hearing loss only *N* (%)	Depressive symptoms only *N* (%)	Moderate+ hearing loss and depressive symptoms *N* (%)	*p*
N	2,061	1,529	385	104	43	
Baseline age, mean (*SD*)	74.0 (2.8)	73.7 (2.8)	74.9 (2.9)	73.8 (2.8)	74.7 (2.8)	<.001
PTA, mean (*SD*)	30.3 (13.5)	25.0 (8.6)	50.7 (9.1)	26.7 (7.7)	47.5 (8.5)	<.001
BMI, kg/m^2, mean (*SD*)	27.4 (4.7)	27.4 (4.8)	27.1 (4.1)	27.8 (4.4)	26.9 (4.2)	.52
Black	776 (37.7)	630 (41.2)	95 (24.7)	39 (37.5)	12 (27.9)	<.001
Women	1072 (52.0)	849 (55.5)	131 (34.0)	74 (71.2)	18 (41.9)	<.001
Postsecondary education	1136 (55.1)	828 (54.2)	218 (56.6)	59 (56.7)	31 (72.1)	.11
Memphis	1009 (49.0)	731 (47.8)	214 (55.6)	46 (44.2)	18 (41.9)	.025
Marital status						.11
Never married	103 (5.0)	79 (5.2)	18 (4.7)	3 (2.9)	3 (7.0)	
Married	1201 (58.3)	882 (57.7)	242 (62.9)	51 (49.0)	26 (60.5)	
Widowed/divorced/separated	757 (36.7)	568 (37.1)	125 (32.5)	50 (48.1)	14 (32.6)	
Live alone	594 (28.8)	437 (28.6)	104 (27.0)	40 (38.5)	13 (30.2)	.14
Diabetes	714 (34.6)	531 (34.7)	144 (37.4)	22 (21.2)	17 (39.5)	.018
Smoking	1119 (54.3)	799 (52.3)	238 (61.8)	51 (49.0)	31 (72.1)	<.001
Hypertension	1018 (49.4)	763 (49.9)	173 (44.9)	60 (57.7)	22 (51.2)	.11
Stroke	158 (7.7)	121 (7.9)	25 (6.5)	9 (8.7)	3 (7.0)	.79
Baseline CES-D 10, median (IQR)	2.0 (0.0–4.0)	2.0 (0.0–4.0)	2.0 (0.0–4.0)	10.0 (10.0–13.0)	11.0 (2.0–12.0)	<.001
Repeated depressive symptoms	220 (10.5)	0 (0.0)	0 (0.0)	167 (8.1)	53 (2.6)	
Antidepressant use	50 (2.4)	0 (0.0)	0 (0.0)	31 (29.8)	19 (44.2)	<.001
DSST, mean (*SD*)	37.5 (14.1)	37.9 (14.1)	36.3 (13.7)	37.8 (15.7)	32.3 (14.7)	.018
3MS, median (IQR)	93.0 (88.0–96.0)	93.0 (88.0–97.0)	92.0 (87.0–96.0)	94.0 (88.0–97.0)	93.0 (84.0–96.0)	.013

Note: Health ABC = Health, Aging and Body Composition study; PTA = pure tone average; BMI = body mass index; CES-D 10 = Center for Epidemiologic Study—Depression scale short form; repeated depressive symptoms = more than one CES-D 10 score ≥10 during the first 4 years of follow-up; DSST = Digit Symbol Substitution Test; 3MS = Modified Mini-Mental State Examination; IQR = interquartile range; Moderate+ hearing loss = moderate or greater hearing loss.

the 3MS Examination (β = −0.14; 95% CI: −0.26, −0.02) and DSST (β = −0.17; 95% CI: −0.29, −0.05). Results were consistent across both ways of measuring depressive symptoms (Table 2).

The association between depressive symptoms alone, without HL, varied by how depressive symptoms were measured. We found no evidence of an association between baseline depressive symptoms and baseline test performance or rates of cognitive decline. Depressive symptoms at repeated visits (depressive symptoms at more than one time point between Year 1 and Year 5) was consistently associated with poorer baseline scores (β = −1.34; 95% CI: −2.30, −0.38 on 3MS Examination; β = −1.94; 95% CI: −3.77, −0.11 on DSST) and faster rates of cognitive decline for both tests (β = −0.21; 95% CI: −0.37, −0.05 on 3MS Examination; β = −0.21; 95% CI: −0.40, −0.03 on DSST; Figure 1).

When considering the estimated joint effect for both HL and depressive symptoms, moderate or greater HL and repeated depressive symptoms (i.e., >1 elevated CES-D 10 score at Years 1, 3, 4, or 5), compared to no HL or mild loss and no depressive symptoms, were associated with lower average baseline test scores on the 3MS Examination (β = −1.91; 95% CI: −3.74, −0.09) but not the DSST at baseline (β = −0.26; 95% CI: −3.29, 2.77). We found no associations for HL plus measures of depressive symptoms (baseline, repeated) on baseline 3MS Examination or DSST scores. However, faster rates of cognitive decline were observed across all measures and tests, significantly faster with repeated depressive symptoms on the DSST (β = −0.35; 95% CI: −0.67, −0.03.) No interactions between HL and depressive symptoms at baseline or for rate of cognitive decline were significant.

Incident Dementia

Over 9 years, 223 (12.2%) participants developed incident dementia, those with dementia demonstrated significantly lower scores on the DSST (mean 34.7 no dementia/mean 20.5 dementia) and 3MS Examination (mean 91.9 no dementia/mean 76.7 dementia) as expected. Relative to those without significant HL (i.e., normal hearing or mild HL) or clinically meaningful depressive symptoms, those with moderate or greater HL alone demonstrated a significantly

Table 2. Independent and Joint Effects of Hearing and Depressive Symptom Status on Difference in Baseline Cognitive Test Score and Rate of Cognitive Decline Across Measures of Depressive Symptoms Over 11 Years of Follow-Up

			Modified Mini-Mental State Examination		Digit Symbol Substitution Test	
Hearing loss	Depressive symptoms	*N*	Difference in baseline score	Difference in change per year (95% CI)	Difference in baseline score	Difference in change per year (95% CI)
Normal hearing or mild HL	No baseline depressive symptoms	1,529	Reference	Reference	Reference	Reference
	Baseline depressive symptoms	103	0.17 (–0.60, 0.94)	0.01 (–0.13, 0.15)	0.80 (–1.06, 2.66)	–0.11 (–0.31, 0.10)
Moderate+ HL	No baseline depressive symptoms	385	–0.86 (–1.53, –0.18)	–0.14 (–0.26, –0.02)	–0.81 (–2.08, 0.47)	–0.17 (–0.29, –0.05)
	Baseline depressive symptoms	43	–0.78 (–2.35, 0.78)	–0.35 (–0.74, 0.04)	–2.44 (–5.21, 0.34)	–0.16 (–0.46, 0.15)
Interaction (*p* value)			0.91	0.31	0.15	0.54
Normal hearing or mild HL	No repeated depressive symptoms	1,322	Reference	Reference	Reference	Reference
	Repeated depressive symptoms	311	–1.34 (–2.30, –0.38)	–0.21 (–0.37, –0.05)	–1.94 (–3.77, –0.11)	–0.21 (–0.40, –0.03)
Moderate+ HL	No repeated depressive symptoms	343	–0.87 (–1.57, –0.16)	–0.18 (–0.30, –0.07)	–1.39 (–2.70, –0.08)	–0.16 (–0.28, –0.05)
	Repeated depressive symptoms	85	–1.91 (–3.74, –0.09)	–0.30 (–0.78, –0.19)	–0.26 (–3.29, 2.77)	–0.35 (–0.67, –0.03)
Interaction (*p* value)			0.79	0.72	0.09	0.89

Notes: HL = hearing loss; CES-D = Center for Epidemiologic Study—Depression scale. *N* = 2,061. Depressive symptoms = CES-D 10 score ≥10 at baseline of Visit 1; repeated depressive symptoms = CES-D 10 score ≥10 on more than one evaluation of CES-D during first 4 years of follow-up (Visits 1, 3, 4, 5); Moderate+ = moderate or greater hearing loss.

greater risk of incident dementia across both ways of measuring depressive symptoms (hazard ratio [HR]: 1.42; 95% CI: 1.03, 1.95 baseline symptoms, and 1.54; 95% CI: 1.10, 2.15 repeated symptoms; Table 3).

The association in those with high depressive symptoms alone without HL is suggestive of greater risk for baseline depressive symptoms (HR: 1.70; 95% CI: 0.92, 3.15) and indicates a greater risk for incident dementia with repeated depressive symptoms over the first 4 years of follow-up (HR: 2.35; 95% CI: 1.56, 3.53; Figure 2).

The strongest estimated risk for incident dementia was observed for the presence of both HL and depressive symptoms across both measures of depressive symptoms used (HR: 3.81; 95% CI: 1.90, 7.62 baseline; HR: 2.91; 95% CI: 1.59, 5.33 repeated).

To present results on an additive scale, the RERI for baseline depressive symptoms is suggestive of an interaction (RERI: 1.69; 95% CI: –1.10, 4.47), though not significant, but not for repeated depressive symptoms (RERI: 0.02; 95% CI: –1.93, 1.97). A measure of the excess risk from exposure to both exposures relative to the risk from no exposure interaction (Richardson, 2009) (Synergy Index) again suggests a departure from additivity (*S*: 2.51; 95% CI: –0.87, 5.88) for baseline depressive symptoms but not repeated (*S*: 1.01; 95% CI: 0.03, 2.04). Our investigation of the heterogeneity of the effects of each exposure on incident dementia, while not statistically significant, suggests heterogeneity in the degree of risk, with the greater risk presented by the presence of both comorbid conditions (Figure 2).

Sensitivity and Secondary Analysis

In a sensitivity analysis using Year 5 as the analytic baseline, the estimated effects were slightly attenuated, but inferences were unchanged. In the investigation of cognitive decline by exposure group, we continued to observe the fastest rate of cognitive change in DSST score among those with both conditions (β = –0.39; 95% CI: –0.74, –0.03 baseline depressive symptoms; β = –0.44; 95% CI: –0.78, –0.10 repeated depressive symptoms). However, no significant difference in the rate of cognitive changes was observed on the 3MS Examination. Poorest baseline test scores were observed in those with both HL and baseline depressive symptoms on either DSST or 3MS Examination, or for HL and repeated depressive symptoms on the 3MS Examination compared to each condition independently (Supplementary Table 1). Our investigation of incident dementia using Year 5 as baseline (Supplementary Table 2) suggests smaller samples for those with depressive symptoms (with or without HL) compared to Year 1 as baseline and fewer cases of incident dementia given the shorter follow-up period, leading to smaller samples within our exposure group, particularly those with combined HL and depressive symptoms. The greatest hazard for incident dementia when considering baseline depressive symptoms at Year 5 continued to be among those with both conditions (HR: 2.30; 95% CI: 1.21,

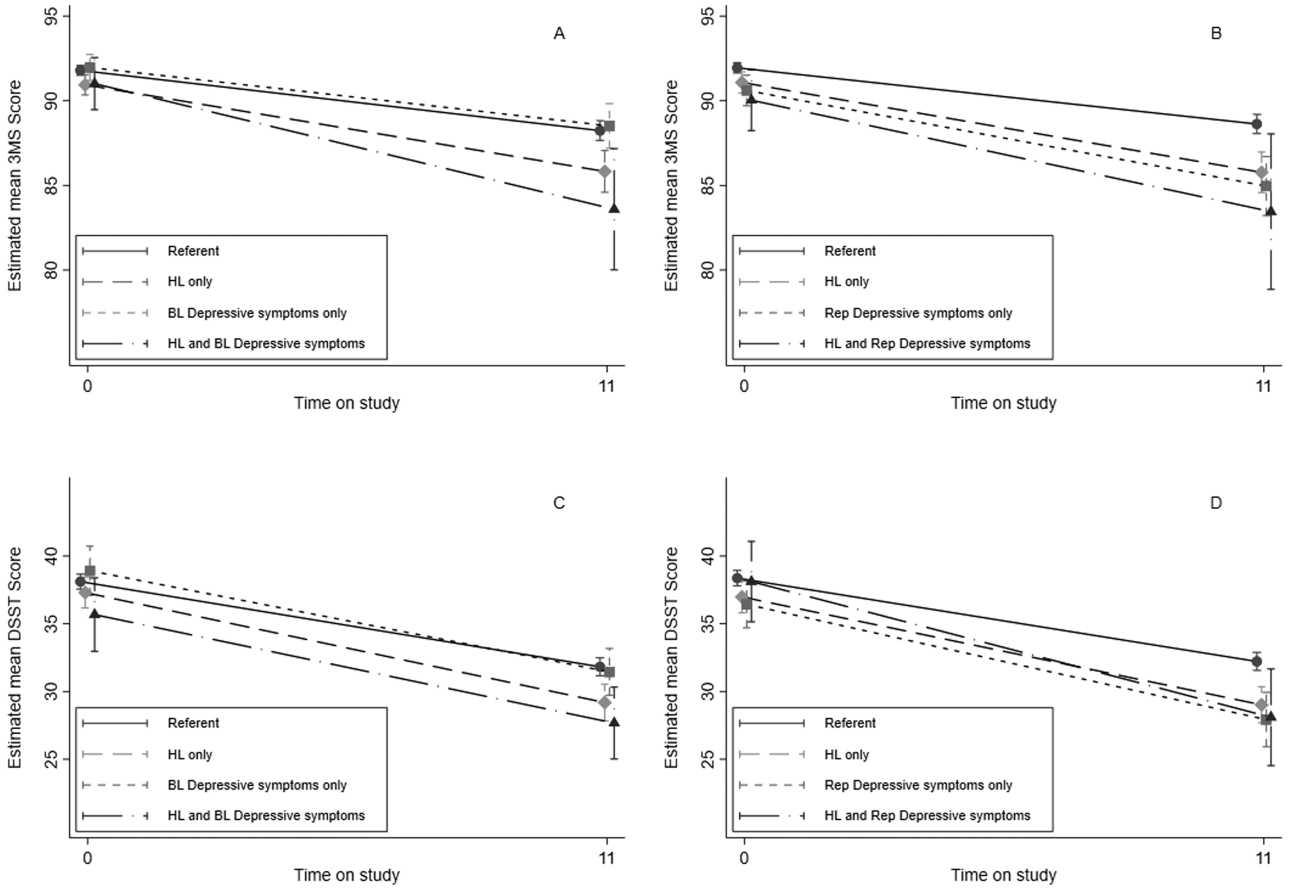

Figure 1. Estimated mean scores on cognitive test by exposure and measure of depressive symptom in the Health ABC Study over 11 years of follow-up (N = 2,061). (A) Estimated mean 3MS score over follow-up by hearing loss and baseline depressive symptoms status. (B) Estimated mean 3MS score over follow-up by hearing loss and repeated depressive symptoms status. (C) Estimated mean DSST score over follow-up by hearing loss and baseline depressive symptoms status. (D) Estimated mean DSST score over follow-up by hearing loss and repeated depressive symptoms status. *Notes:* BL depressive symptoms = CES-D 10 score ≥10 at baseline of Visit 1; Rep Depressive Symptoms = repeated depressive symptoms, CES-D 10 ≥10 at more than one visit between Visits 1–5; HL = moderate or greater hearing loss; Referent = normal or mild hearing loss and no depressive symptoms (CES-D 10 score <10); 3MS = Modified Mini-Mental State Examination; DSST = Digit Symbol Substitution Test.

4.34) compared to each in isolation or neither condition. When evaluating repeated depressive symptoms, the hazard for incident dementia was not significantly greater among those with both HL and repeated depressive symptoms. However, the small sample in the combined exposure groups when using Year 5 as baseline limits inferences.

In a sensitivity analysis considering the influence of the independent or combined effect of depressive symptoms with the presence of any HL, results are similar, suggesting overall significantly poorer baseline performance on the 3MS Examination and DSST for those with repeated depressive symptoms and any HL at baseline. Results suggest overall significantly faster rates of cognitive change on both the 3MS Examination (rate of change = –0.32; 95% CI: –0.55, –0.08) and DSST (rate of change = –0.27; 95% CI: –0.46, –0.08) for the combined presence of each risk factor, and a marginally faster rate of change on the 3MS Examination (–0.18; 95% CI: –0.39, 0.02) for the presence of both baseline depressive symptoms and any HL compared to those with neither condition. In the investigation of incident dementia, while all estimates were slightly attenuated when considering the presence of any HL and/or depressive symptoms, the greatest risk for incident dementia continued to be observed among those with the presence of both a mild or greater HL and baseline depressive symptoms (HR: 2.77; 95% CI: 1.60, 4.79) or repeated depressive symptoms (HR: 2.65; 95% CI: 1.69, 4.17).

In our secondary analyses, models adjusted for self-reported hearing aid use demonstrated results similar in magnitude and inferences overall did not change for analysis of cognitive decline over time. For incident dementia, results suggest similar inferences for baseline (HR: 4.37; 95% CI: 2.15, 8.90 HL and depressive symptoms; HR: 1.57; 95% CI: 1.12, 2.21 HL alone) and repeated depressive symptoms (HR: 3.22; 95% CI: 1.73, 5.99 HL and depressive symptoms; HR: 1.70; 95% CI: 1.19, 2.42 HL alone).

Discussion

In a longitudinal investigation of 2,061 older adults over 11 years of follow-up, moderate or greater HL (vs. normal or mild loss) was associated with faster rates of cognitive

Table 3. Multivariable-Adjusted Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) of the Joint Association Between Hearing Impairment and Incident Dementia by Depressive Symptom Status, Health ABC Study

	No depressive symptoms		Depressive symptoms	
Level of hearing loss	*N* with/without dementia	HR (95% CI)[a]	*N* with/without dementia	HR (95% CI)[a]
Normal or mild	145/1,233	1.00 [Ref]	11/57	1.70 (0.92–3.15)
Moderate or greater	58/293	1.42 (1.03–1.95)	9/14	3.81 (1.90–7.62)
	No Depressive Symptoms		Repeated Depressive Symptoms	
Level of hearing loss	*N* with/without dementia	HR (95% CI)[a]	*N* with/without dementia	HR (95% CI)[a]
Normal or mild	127/1,184	1.00 [Ref]	29/106	2.35 (1.56–3.53)
Moderate or greater	55/275	1.54 (1.10–2.15)	13/32	2.91 (1.59–5.33)

Notes: *N* = 1,820. CES-D = Center for Epidemiologic Study—Depression scale; RERI = relative excess risk of interaction. Depressive symptoms = CES-D 10 score ≥10 at baseline of Visit 1; repeated depressive symptoms = CES-D 10 score ≥10 on more than one evaluation of CES-D during first 4 years of follow-up (Visits 1, 3, 4, 5). RERI (95% CI) = 1.69; 95% CI (−1.10, 4.47) depressive symptoms; 0.02; 95% CI (−1.93, 1.97) repeated depressive symptoms. Synergy Index (95% CI) = 2.51; 95% CI (−0.87, 5.88) depressive symptoms; 1.01; 95% CI (−0.03, 2.04) repeated depressive symptoms.
[a]Adjusted for age, gender, race, education, study center, marital status, living alone, BMI, hypertension, stroke history, and diabetes.

Figure 2. Stratified hazard ratio of incident dementia for heterogeneity of effect between hearing loss and measure of depressive symptom. A: Hazard ratio of incident dementia among strata of hearing loss. B: Hazard of incident dementia among strata of depressive symptoms. *Note:* Depressive symptoms = CES-D 10 score ≥10 at baseline of Visit 1; Repeated Depressive Symptoms = CES-D; Hearing loss = moderate or greater hearing loss. CES-D = Center for Epidemiologic Study—Depression.

decline and greater risk of incident dementia independent of depressive symptoms. The presence of elevated depressive symptoms alone was associated with faster rates of cognitive change and incident dementia, particularly when symptomatology was repeated at more than 1 year of follow-up. While each independent condition demonstrates elevated risk for cognitive impairment, individuals with HL who also had depressive symptoms overall presented the greatest estimated risk for both rates of cognitive decline and risk of incident dementia—highlighting potential dementia prevention opportunities. Findings suggest depressive symptomatology among hearing-impaired older adults may play a modifying role in the hearing–dementia relationship. Intervention on both HL and depressive symptoms may have the potential to improve quality of life for a significant number of older adults in our population.

While many other studies have looked at the hearing–dementia or depression–dementia link in isolation (Abrams et al., 2006; Brewster et al., 2018; Gopinath et al., 2009; Rutherford et al., 2018), few have considered the risk presented by the joint presence of these two independent risk factors for dementia (Brewster et al., 2021). Our results uniquely consider both the individual estimated effects of hearing and depressive symptoms as well as the combined presence of depressive symptoms among those with HL. As significant variability in the length of depressive symptoms exists, our study investigated differences in risk by the longevity of depressive symptom status. Findings suggest that those with clinically meaningful HL at levels that may impair communication ability are at risk for significantly faster rates of cognitive change as well as increased risk of incident dementia, especially among those who additionally develop clinically meaningful depressive symptomatology. The study of potential biological interaction or a

biological versus behavioral/social mechanism behind this relationship may further inform our dementia intervention efforts.

The findings presented complement prior research that performed a mediation analysis of HL, late-life depression, and dementia (Brewster et al., 2018). While this study did not find that depression mediated the hearing–dementia relationship, results indicated treated HL (defined as participants who wore hearing aids resulting in perceived functionally normal hearing) was associated both with depression and conversion to dementia. In contrast, our analysis quantified how the combined presence of clinically meaningful depressive symptoms among those with significant HL presents a differing risk for cognitive change or dementia than the presence of each condition in isolation, highlighting a potential interrelated link between HL, depression, and dementia, which has notable clinical relevance.

Our study uniquely estimated effects among hearing-impaired adults with the additional presence of depressive symptomatology using a variety of means to measure depression. Across ways to measure depressive symptoms, the estimated effect on rates of cognitive decline was more consistent with DSST measures than with 3MS Examination measures. However, our test scores were not standardized; therefore, we exercise caution in comparison of rates of change across cognitive tests. It is possible that the observed estimated combined effect failed to reach significance in our analysis due to our overall small sample size (i.e., 43 with baseline depressive symptoms and HL). These small sample sizes may have limited the power and width of confidence intervals obtained, therefore placing constraints on available inferences. However, the greater estimated observed effect among those with both conditions presents public health and clinical opportunity. As the ability to hear and communicate effectively has a significant influence on quality of life and behaviors, it is possible that the additional development of depressive symptomatology—particularly that lasting longer than an acute event—among those with HL exacerbates psychosocial or neuropsychological buffers, leading to accelerated cognitive decline. Thus, consideration of low-risk strategies that could minimize the adverse effects of each condition, such as the use of hearing aids to manage HL and cognitive behavioral therapy for depressive symptoms, could have downstream beneficial impacts for older adults. Given the importance of social isolation and loneliness as associated outcomes of HL as well as risk factors for depressive symptomatology and dementia, further investigation of how these aspects of social connectedness may modify or mediate the hearing–depression–dementia association presented here. Furthermore, it is possible that those with significant HL who then develop depression may be less likely to seek or adhere to clinical or public health recommendations (Abrams et al., 2006; Brewster et al., 2018; Gopinath et al., 2009). However, the use of hearing aids and management of HL have the potential to alter this risk landscape. We observed that those with repeated depressive symptoms who developed incident dementia had nearly 10% lower prevalence (27% vs. 16%) of self-reported hearing aid use compared to those who remained free of dementia at the end of follow-up. In exploratory models for those eligible for a hearing aid, those with depressive symptoms who reported hearing aid use showed a suggestion of, but not statistically significant, qualitatively protective effect of incident dementia and cognitive decline, although small sample size limited inference. However, differences in equitable access to hearing services, care, and assistive listening devices (i.e., hearing aids) must be acknowledged when investigating modification of outcomes by hearing aid use. Further study is required regarding personal, social, and societal factors that may influence how these individuals seek and obtain hearing care. Such factors should include investigation of potential differences by sex given prior work has demonstrated differential risk of each risk factor and cognitive performance, an investigation not completed in our study due to sample size concerns and a focus on determining simply differences between combined and individual effects of each risk factor.

Our dementia definition is based on an algorithm and not a clinical diagnosis and therefore may lead to some misclassification of dementia status. Our study was limited in the ascertainment of the presentation of depressive symptoms via one evaluative scale, the CES-D 10. While the CES-D is not a comprehensive medical evaluation and is subject to episodic depression or may miss certain aspects of late-life depression in older adults, the CES-D has widespread use and has demonstrated good reliability and validity of symptoms (Andresen et al., 1994; Irwin et al., 1999). The number of repeat measures of CES-D 10 over time is a strength of our study. Additionally, hearing was not measured until Year 5 of the study. However, hearing generally changes very gradually at 1–2 dB per year in adults (Echt et al., 2010; Wiley et al., 2008). We therefore would expect minimal misclassification of hearing status for our analysis. In our analysis, we can reclassify those (n = 180) with a PTA measured at Year 5 between 40 and 48 dB and who then, on average, might be misclassified as with HL due to the later time point of measurement. Results using baseline depressive symptoms suggest reduced magnitude for the estimated effect of the joint effects of hearing and depression on incident dementia (HR = 2.22; 95% CI: 0.69, 7.11) and a similar magnitude of estimated effect for repeated depressive symptoms (HR = 3.05; 95% CI: 1.41, 6.60). We opted to consider Year 1 as our study baseline to capitalize on a longer follow-up period and more detailed measures. As we are interested in both HL status as well as depressive symptom status, we carefully decided to capitalize on the more comprehensive depressive symptom definition during the early years of follow-up that more accurately accounts for use of depression medication and more frequent depressive symptom measures. Additionally, results from our

sensitivity analysis using Year 5 as baseline, while reduced in magnitude, continued to suggest that the greatest risk for cognitive change and incident dementia was among those with both conditions. Our study sample overall demonstrates a lower prevalence of depressive symptoms than the overall population. Therefore, our results are within a group of older adults with minimal symptomatology and overall good health and may not be generalizable to the overall population with a high prevalence of depressive symptoms. However, even in our sample with minimal depressive symptoms, we continue to see an estimated effect of both depressive symptoms and increased effect of both depressive symptoms and HL; therefore, our estimates may be conservative compared to the broader population.

Our results highlight that how consideration of comorbid conditions, each independent risk factor for dementia, could potentially present pivotal intervention options for cognitive trajectory for older adults with modifiable risk factors. Management and consideration of HL in conjunction with other conditions may have beneficial effects beyond just communication ability. With the high prevalence of HL among older adults and underutilization of treatment strategies such as hearing aids, a significant room for intervention and potential interruption of the hearing–depression–dementia relationship exists. While we completed sensitivity analyses with models adjusted for reported hearing aid use at baseline, our measure of hearing aid use was via self-report, leaving a potential room for misclassification as many adults overreport on their hearing aid use (Taubman et al., 1999). Continued investigation of how the management of HL may influence downstream psychosocial outcomes using a more specific and valid assessment of hearing aid use may greatly improve our understanding of how intervention on these measures may reduce dementia risk. Current clinical trials of hearing aid use among older adults are underway and may further aid in our understanding and quantification of the broad benefits of hearing management.

In conclusion, in a longitudinal cohort study of 2,061 older adults, the combined presence of moderate or greater HL and depressive symptoms demonstrated the highest estimated effect on the rates of cognitive decline and risk of incident dementia. While our results warrant further investigation, clinical providers of older adults, particularly those with HL, may consider coexisting psychosocial conditions such as depression when considering recommendations for dementia intervention and monitoring. Identification of low-risk intervention options for dementia among subgroups of older adults at a particularly greater risk for cognitive decline or dementia could vastly improve public health strategies as well as quality of life for older adults with improved intervention utilization.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences* online.

Funding

This research was supported by the National Institute on Aging (NIA) contracts #N01-AG-6-2101, N01-AG-6-2103, N01-AG-6-2106; NIA grant R01-AG028050; National Institute of Nursing Research grant R01-NR012459. D. S. Powell was supported by fellowship funding through the Cochlear Center for Hearing and Public Health and by the National Institutes of Health (NIH)/NIA (T32AG000247 and T32AG066576). N. S. Reed was supported by the NIH/NIA (K23AG065443). J. A. Deal was supported by the NIH/NIA grant K01AG054693. A. L. Gross was supported by NIH/NIA grant K01AG050699. W. D. Brenowitz is supported by the NIH/NIA grant K01AG062722 and Alzheimer's Association (AARF-18-565846).

Conflict of Interest

N. S. Reed reports being a scientific advisory board member (no financial relationship) of Shoebox Inc. and Good Machine Studio. F. R. Lin reports being a consultant to Frequency Therapeutics, speaker honoraria from Caption Call, and being the director of a public health research center funded in part by a philanthropic gift from Cochlear Ltd to the Johns Hopkins Bloomberg School of Public Health. All other authors have no conflicts of interest declared.

Acknowledgments

We must thank the Health, Aging and Body Composition study participants, staff, clinicians, and others involved who made this research possible.

References

Abrams, T. E., Barnett, M. J., Hoth, A., Schultz, S., Kaboli, P. J. (2006). The relationship between hearing loss and depression in older veterans. *Journal of the American Geriatric Society*, **54**(9), 1475–1477. doi:10.1111/j.1532-5415.2006.00875.x

Andresen, E. M., Malmgren, J. A., Carter, W. B., & Patrick, D. L. (1994). Screening for depression in well older adults: Evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *American Journal of Preventive Medicine*, **10**(2), 77–84. doi:10.1016/s0749-3797(18)30622-6

Assmann, S. F., Hosmer, D. W., Lemeshow, S., & Mundt, K. A. (1996). Confidence intervals for measures of interaction. *Epidemiology (Cambridge, Mass.)*, **7**(3), 286–290. doi:10.1097/00001648-199605000-00012

Brewster, K. K., Ciarleglio, A., Brown, P. J., Chen, C., Kim, H., Roose, S., Golub, J., Rutherford, B. (2018). Age-related hearing loss and its association with depression in later life. *The American Journal of Geriatric Psychiatry*, **27**(7), 788–796. doi:10.1016/j.jagp.2018.04.003

Brewster, K. K., Hu, M. C., Zilcha-Mano, S., Stein, A., Brown, P., Wall, M., Roose, S., Golub, J., Rutherford, B. (2021). Age-related hearing loss, late-life depression, and risk for incident dementia in older adults. *The Journals of Gerontology, Series*

A: Biological Sciences and Medical Sciences, **76**(5), 827–834. doi:10.1093/gerona/glaa242

Deal, J. A., Betz, J., Yaffe, K., Harris, T., Purchase-Helzner, E., Satterfield, S., Pratt, S., Govil, N., Simonsick, E., Lin, F. (2017). Hearing impairment and incident dementia and cognitive decline in older adults: The Health ABC study. *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences*, **72**(5), 703–709. doi:10.1093/gerona/glw069

Echt, K. V., Smith, S. L., Burridge, A. B., & Spiro, A. 3rd. (2010). Longitudinal changes in hearing sensitivity among men: The Veterans Affairs Normative Aging Study. *The Journal of the Acoustical Society of America*, **128**(4), 1992–2002. doi:10.1121/1.3466878

von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., & Vandenbroucke, J. P.; STROBE Initiative. (2007). The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Lancet (London, England)*, **370**(9596), 1453–1457. doi:10.1016/S0140-6736(07)61602-X

Fiske, A., Wetherell, J. L., & Gatz, M. (2009). Depression in older adults. *Annual Review of Clinical Psychology*, **5**, 363–389. doi:10.1146/annurev.clinpsy.032408.153621

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, **12**(3), 189–198. doi:10.1016/0022-3956(75)90026-6

GBD 2016 Dementia Collaborators. (2019). Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*, **18**(1), 88–106. doi:10.1016/S1474-4422(18)30403-4

Goman, A. M., & Lin, F. R. (2016). Prevalence of hearing loss by severity in the United States. *American Journal of Public Health*, **106**(10), 1820–1822. doi:10.2105/AJPH.2016.303299

Gopinath, B., Wang, J. J., Schneider, J., Burlutsky, G., Snowdon, J., McMahon, C. M., Leeder, S. R., Mitchell, P. (2009). Depressive symptoms in older adults with hearing loss: The blue mountains study. *Journal of the American Geriatric Society*, **57**(7), 1306–1308. doi:10.1111/j.1532-5415.2009.02317.x

Grambsch, P., Therneau, T. (1994). Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*, **81**, 515–526. doi:10.1093/biomet/81.3.515

Irwin, M., Artin, K. H., & Oxman, M. N. (1999). Screening for depression in the older adult: Criterion validity of the 10-item Center for Epidemiological Studies Depression Scale (CES-D). *Archives of Internal Medicine*, **159**(15), 1701–1704. doi:10.1001/archinte.159.15.1701

Knol, M. J., & VanderWeele, T. J. (2012). Recommendations for presenting analyses of effect modification and interaction. *International Journal of Epidemiology*, **41**(2), 514–520. doi:10.1093/ije/dyr218

Knol, M. J., VanderWeele, T. J., Groenwold, R. H., Klungel, O. H., Rovers, M. M., & Grobbee, D. E. (2011). Estimating measures of interaction on an additive scale for preventive exposures. *European Journal of Epidemiology*, **26**(6), 433–438. doi:10.1007/s10654-011-9554-9

Laird, N. M., & Ware, J. H. (1982). Random-effects models for longitudinal data. *Biometrics*, **38**(4), 963–974. doi:10.2307/2529876

Lewinsohn, P. M., Seeley, J. R., Roberts, R. E., & Allen, N. B. (1997). Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychology and Aging*, **12**(2), 277–287. doi:10.1037//0882-7974.12.2.277

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., Cooper, C., Costafreda, S., Dias, A., Fox, N., Gitlin, L., Howard, R., Kales, H., Kivimäki, M., Larson, E., Ogunniyi, A., et al. (2020). Dementia prevention, intervention, and care: 2020 Report of the Lancet Commission. *The Lancet*, **6736**(20), 413–446. doi:10.1016/S0140-6736(20)30367-6

de Mutsert, R., Jager, K. J., Zoccali, C., & Dekker, F. W. (2009). The effect of joint exposures: Examining the presence of interaction. *Kidney International*, **75**(7), 677–681. doi:10.1038/ki.2008.645

Olusanya, B. O., Davis, A. C., & Hoffman, H. J. (2019). Hearing loss grades and the international classification of functioning, disability and health. *Bulletin of the World Health Organization*, **97**(10), 725–728. doi:10.2471/BLT.19.230367

Richardson, D. B., & Kaufman, J. S. (2009). Estimation of the relative excess risk due to interaction and associated confidence bounds. *American Journal of Epidemiology*, **169**(6), 756–760. doi:10.1093/aje/kwn411

Rutherford, B. R., Brewster, K., Golub, J. S., Kim, A. H., & Roose, S. P. (2018). Sensation and psychiatry: Linking age-related hearing loss to late-life depression and cognitive decline. *The American Journal of Psychiatry*, **175**(3), 215–224. doi:10.1176/appi.ajp.2017.17040423

Salive, M. E. (2013). Multimorbidity in older adults. *Epidemiologic Reviews*, **35**, 75–83. doi:10.1093/epirev/mxs009

Simonsick, E. M., Newman, A. B., Nevitt, M. C., Kritchevsky, S. B., Ferrucci, L., Guralnik, J. M., & Harris, T.; Health ABC Study Group. (2001). Measuring higher level physical function in well-functioning older adults: Expanding familiar approaches in the Health ABC study. *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences*, **56**(10), 644–649. doi:10.1093/gerona/56.10.m644

StataCorp. (2017). Stata Statistical Software: Release 15. College Station, TX: StataCorp LP.

Taubman, L. B., Palmer, C. V., Durrant, J. D., & Pratt, S. (1999). Accuracy of hearing aid use time as reported by experienced hearing aid wearers. *Ear and Hearing*, **20**(4), 299–305. doi:10.1097/00003446-199908000-00003

Teng, E. L., & Chui, H. C. (1987). The Modified Mini-Mental State (3MS) examination. *The Journal of Clinical Psychiatry*, **48**(8), 314–318.

Weschler, D. (1981). *Weschler Adult Intelligence Scale—Revised*. Psychological Corporation.

Wiels, W., Baeken, C., Engelborghs, S. (2020). Depressive symptoms in the elderly—An early symptom of dementia? A systematic review. *Frontiers in Pharmacy*, **11**, 34. doi:10.3389/fphar.2020.00034

Wiley, T. L., Chappell, R., Carmichael, L., Nondahl, D. M., & Cruickshanks, K. J. (2008). Changes in hearing thresholds over 10 years in older adults. *Journal of the American Academy of Audiology*, **19**(4), 281–92; quiz 371. doi:10.3766/jaaa.19.4.2

World Report on Hearing. (2021). World Report on Hearing. Geneva: World Health Organization. doi:10.2307/j.ctvndv9bj

Yaffe, K., Falvey, C., Harris, T. B., Newman, A., Satterfield, S., Koster, A., Ayonayon, H., & Simonsick, E.; Health ABC Study. (2013). Effect of socioeconomic disparities on incidence of dementia among biracial older adults: Prospective study. *BMJ (Clinical Research ed.)*, **347**, f7051. doi:10.1136/bmj.f7051