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Association of Age-Related Hearing Loss With Cognitive Function, Cognitive Impairment, and Dementia
A Systematic Review and Meta-analysis

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IMPORTANCE Epidemiologic research on the possible link between age-related hearing loss (ARHL) and cognitive decline and dementia has produced inconsistent results. Clarifying this association is of interest because ARHL may be a risk factor for outcomes of clinical dementia.

OBJECTIVES To examine and estimate the association between ARHL and cognitive function, cognitive impairment, and dementia through a systematic review and meta-analysis.

DATA SOURCES AND STUDY SELECTION A search of PubMed, the Cochrane Library, EMBASE, and SCOPUS from inception to April 15, 2016, with cross-referencing of retrieved studies and personal files for potentially eligible studies was performed. Keywords included *hearing*, *cognition*, *dementia*, and *Alzheimer disease*. Cohort and cross-sectional studies published in peer-reviewed literature and using objective outcome measures were included. Case-control studies were excluded.

DATA EXTRACTION AND SYNTHESIS One reviewer extracted and another verified data. Both reviewers independently assessed study quality. Estimates were pooled using random-effects meta-analysis. Subgroup and meta-regression analyses of study-level characteristics were performed.

MAIN OUTCOMES AND MEASURES Hearing loss measured by pure-tone audiometry only and objective assessment measures of cognitive function, cognitive impairment, and dementia. Cognitive function outcomes were converted to correlation coefficients (*r* value); cognitive impairment and dementia outcomes, to odds ratios (ORs).

RESULTS Forty studies from 12 countries met our inclusion criteria. Of these, 36 unique studies with an estimated 20 264 unique participants were included in the meta-analyses. Based on the pooled maximally adjusted effect sizes using random-effects models, a small but significant association was found for ARHL within all domains of cognitive function. Among cross-sectional studies, a significant association was found for cognitive impairment (OR, 2.00; 95% CI, 1.39-2.89) and dementia (OR, 2.42; 95% CI, 1.24-4.72). Among prospective cohort studies, a significant association was found for cognitive impairment (OR, 1.22; 95% CI, 1.09-1.36) and dementia (OR, 1.28; 95% CI, 1.02-1.59) but not for Alzheimer disease (OR, 1.69; 95% CI, 0.72-4.00). In further analyses, study, demographic, audiometric, and analyses factors were associated with cognitive function. Vascular dysfunction and impaired verbal communication may contribute to the association between hearing loss and cognitive decline.

CONCLUSIONS AND RELEVANCE Age-related hearing loss is a possible biomarker and modifiable risk factor for cognitive decline, cognitive impairment, and dementia. Additional research and randomized clinical trials are warranted to examine implications of treatment for cognition and to explore possible causal mechanisms underlying this relationship.

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Invited Commentary
Supplemental content

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Dementia affects an estimated 46.8 million persons worldwide and is projected to affect approximately 131.5 million in 2050 with an estimated cost of US $818 billion in 2015 and US $2 trillion by 2050.[1] Current pharmaceutical approaches targeting neuropathologic processes such as Alzheimer disease (AD) offer limited benefit with symptom-modifying effects at best.[2] Switching to a preventive strategy through reduction of risk factors may be more beneficial than pharmacologic therapy after clinical expression of neuropathologic changes[3] and may lead to significant reductions in medical costs.[4]

Approximately one-third of adults older than 65 years experiences a disabling hearing loss.[5] Cohort studies indicate that age-related hearing loss (ARHL) precedes the onset of clinical dementia by 5 to 10 years, is a possible noninvasive biomarker, and may offer a pathway to modify clinical outcomes.[6] As an emerging risk factor, a limited number of studies have examined ARHL and cognitive decline. Epidemiologic findings have been inconsistent possibly owing to suboptimal methods (eg, self-reported hearing loss or cognitive tests with auditory stimuli).[7] Prior reviews[8-10] have not included a meta-analysis or have included different measures of hearing impairment and studies of different designs.

We conducted a systematic review and meta-analysis to investigate and quantify the association between ARHL and cognitive function, cognitive impairment, and dementia. We reduced conceptual heterogeneity by including only observational cross-sectional and cohort studies that assessed hearing loss using pure-tone audiometry (the criterion standard). We conducted exploratory subgroup and meta-regression analyses to examine possible explanations for heterogeneity owing to demographic, study, health, and analysis factors.

Key Points

Question Is age-related hearing loss associated with an increased risk for cognitive decline, cognitive impairment, and dementia?

Findings In this systematic review and meta-analysis of 36 epidemiologic studies and 20 264 unique participants, age-related hearing loss was significantly associated with decline in all main cognitive domains and with increased risk for cognitive impairment and incident dementia. Increased risks for Alzheimer disease and vascular dementia were nonsignificant.

Meaning Age-related hearing loss is a possible biomarker and modifiable risk factor for cognitive decline, cognitive impairment, and dementia.

Methods

This systematic review was performed according to an a priori established protocol. It adhered to the Primary Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement[11] and met the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[12] All analyses were conducted using Comprehensive Meta-Analysis software (version 3; Biostat). Institutional review board approval and informed consent were not required for this systematic review and meta-analysis.

Search Strategy and Selection Criteria

Six a priori meta-analyses were planned across 2 levels of study design (cross-sectional and cohort) and 3 levels of outcome (cognitive function, cognitive impairment, and dementia). The inclusion criteria consisted of (1) cross-sectional and cohort studies, excluding case-control studies because of greater concern about sampling and retrospective analysis bias[13] (all study designs have selected types of bias); (2) published studies (any language); (3) study sample 18 years or older; (4) baseline sample including the general, community-dwelling population rather than special risk groups (eg, patients with coronary heart disease); (5) individual's peripheral hearing status (as assessed by pure-tone audiometric assessment) as the main exposure variable; (6) full inclusion of hearing loss sample (ie, no pure-tone audiometric cutoff); (7) assessment of cognitive function, cognitive impairment,[14] and/or dementia as outcome(s); and (8) exposure and outcome measurements obtained by health care professionals or trained investigators (ie, not based on self-reported data).

Studies published on or before August 26, 2015, were retrieved from the following 4 electronic databases by one of us (D.G.L.): (1) PubMed, (2) the Cochrane Library, (3) EMBASE, and (4) SCOPUS. Keywords included *hearing*, *cognition*, *dementia*, and *Alzheimer disease* (eTable 1 in the Supplement). Results were updated on April 15, 2016. Cross-referencing for potentially eligible studies was conducted using retrieved studies and personal files belonging to one of us (D.G.L.).

Data Extraction and Quality Assessment

Two of us (D.G.L. and M.E.K.) independently screened for eligible studies and conducted data extraction. If consensus could not be reached, another of us (B.A.L.) acted as arbitrator for study inclusion, and another (G.E.K.) was consulted regarding data extraction. Cognitive function was subdivided into 10 domains, including episodic memory (delayed recall and immediate recall), executive functions (attention, fluency, reasoning, and working memory), global cognition, processing speed, semantic memory, and visuospatial ability.[15] Among dementia studies, a secondary outcome of interest was any data that examined subgroups (eg, AD).

Data from the most recently published study were selected. Data from different studies that examined the same cohort were included if they were for different cognitive outcomes and were treated as separate studies in analysis. Priority was given to outcomes that were maximally adjusted for covariates. Two of us (D.G.L. and M.E.K.) independently assessed the quality of reporting for each study using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) instrument.[16] With use of the Cohen κ coefficient,[17] agreement was excellent (κ = 0.91) before correcting discrepant items.

Statistical Analysis

We chose the Pearson *r* correlation coefficient as the effect size of the linear association between hearing loss and cognitive

function (continuous variables). Negative scores indicated that greater hearing loss was associated with poorer cognition. Odds ratios (ORs) were chosen for cognitive impairment and dementia (categorical variables). Influence of various audiometric criteria (eg, worse vs better ear) and cognitive tests (visual vs auditory stimuli) on outcome were examined in subgroup analyses. If the required outcome metric was not reported in the study, values were calculated using available data. Random-effects, method-of-moments models that incorporate heterogeneity into the overall estimate were used to pool effect sizes from each study.[18] All outcomes were converted to Fisher *z* values or logarithm ORs for analysis purposes and then converted back to the original metric (ie, *r* correlation coefficient and OR, respectively). For both meta-analyses of cognitive function, multiple tests of the same cognitive domain from the same study were collapsed into a single effect size and within-study subgroups were analyzed independently as separate effect sizes.

Heterogeneity was examined using the *Q* test, and $P \leq .10$ was considered to be statistically significant.[19] Inconsistency was examined using the I^2 statistic, and the following grades were applied: less than 25% indicated very low; 25% to less than 50%, low; 50% to less than 75%, moderate; and 75% or greater, large.[19] Small-study effects were examined using funnel plots, and the regression-intercept approach of Egger and colleagues[20] provided at least 10 effect sizes were present. To examine the influence of each result on the overall findings, outcomes were analyzed by deleting each study from the model once. Cumulative meta-analysis ranked by year was used to examine the accumulation of evidence over time.[21]

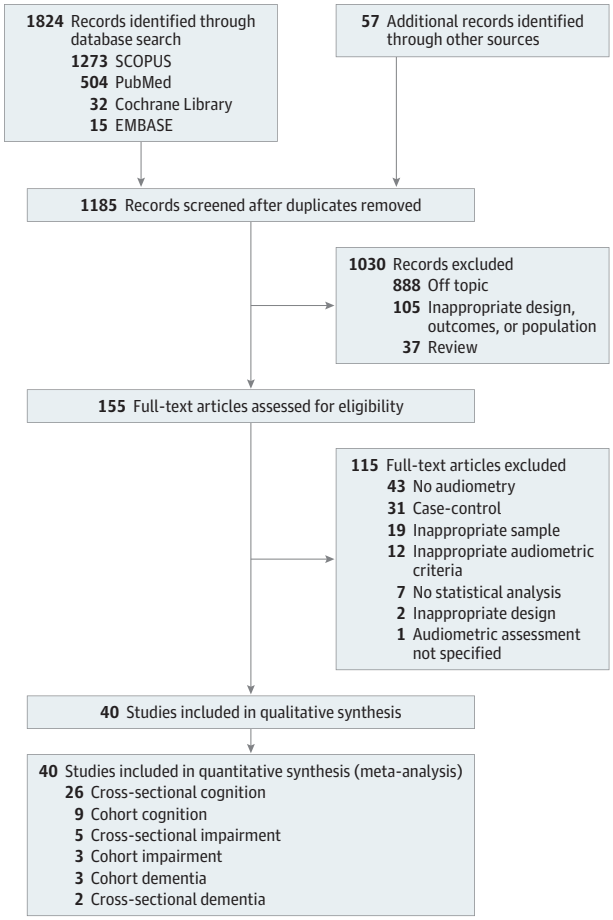
We conducted subgroup and meta-regression analyses to examine heterogeneity between studies. Planned variables included (1) study characteristics, (2) participant characteristics, (3) audiometric factors, (4) cognitive measures, and (5) statistical analysis (eTable 2 in the Supplement provides a list of each planned variable). For continuous variables, we used random-effects meta-regression[22] where at least 4 effect sizes were found. For categorical variables, we examined between-group differences (between-group *Q* value) in effect sizes using mixed effects analysis of variance–like models for meta-analysis[22] if at least 3 effect sizes were available for each category. These analyses were considered to be exploratory.

Results

Characteristics and Quality of Included Studies

The characteristics of included studies are shown in eTable 3 in the Supplement. Of the 1185 citations reviewed, 40 studies[7,23-61] met the inclusion criteria, representing 34 471 participants from 12 countries (**Figure 1**). Of these, 36 unique studies with an estimated 20 264 unique participants were included in the meta-analyses. Study quality results are shown in **Table 1** and **Table 2** and eFigure 1 in the Supplement. Further details on the main analyses are found in eFigures 2 to 27 and eTables 3 to 9 in the Supplement; and further details on the small-study, influence, and cumulative analyses, in the eResults and eFigures 28 to 74 in the Supplement. Thirty-five of the 40 included studies (88%) met the criteria for at least 16 of 22 STROBE items. Further details on the main analyses and descriptions of the small-study, influence, and cumulative analyses are found in eFigures 2 to 27 and eTables 3 to 9 in the Supplement. Diagnostic criteria for each clinical outcome are shown in the Table 1 and Table 2.

Figure 1. PRISMA Flow Diagram



Study selection for the meta-analysis. Some studies were allocated to more than 1 category.

Twenty-six studies with 15 620 participants were included in the cross-sectional cognitive function analysis.[23-48] Two studies were omitted because of duplicate data.[49,50] Nine studies with 8233 participants[7,29,36,40,46,48,51-53] were included in the cohort cognitive function analysis with a follow-up ranging from 2 to 23 years (mean [SD], 10.4 [6.7] years).

Five studies with 6582 participants (797 cases of 6553 included participants [12.2%])[30,55-58] were included in the cross-sectional cognitive impairment analysis. Two studies were omitted because of duplicate data.[54,59] Three studies with 7817 participants (1395 cases of 6825 included participants [20.4%]) were included in the cohort cognitive impairment analysis with a follow-up ranging from 6 to 18 years (mean [SD], 11.7 [6.0] years).[7,40,55]

Two studies with 741 participants (59 cases of 679 included participants [8.7%])[58,60] were included in the cross-sectional dementia analysis. One study assessed dementia (39

Table 1. Characteristics of Cross-sectional Studies

Source	Country	Study Name	No. of Participants	Age, Mean (SD) or Range, y	Female, %	Audiometric Assessment[a]	Cognitive Domains Assessed	Clinical Outcomes (Criteria)	Covariates	STROBE Score[b]
Anstey,[23] 1999	Australia	NA	180	70.56 (7.13)	100	2, 4, and 8 kHz/both ears	Attention, processing speed	None	Age, grip strength, forced expiratory volume, vibration sense, and vision	14
Anstey and Smith,[24] 1999	Australia	NA	180	70.56 (7.13)	100	2, 4, and 8 kHz/both ears	Processing speed, reasoning, semantic memory, visuospatial ability, working memory	None	Age	17
Anstey et al,[25] 2001	Australia	ALSA	894	77.7 (5.6)	49	0.5, 1, 2, 3, and 4 kHz/both ears	Immediate recall, processing speed, semantic memory	None	None	17
Baltes and Lindenberger,[26] 1997	Germany	BASE and young adult sample	315	64.9 (22)	NA	0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz/both ears	Fluency, global cognition, immediate recall, processing speed, reasoning, semantic memory	None	Age	17
Bucks et al,[27] 2016	Australia	BHAS	1969	56.2 (5.5)	53.8	0.5, 1, 2, and 4 kHz/better ear	Attention, delayed recall, fluency, processing speed, working memory	None	Age, sex, educational attainment, depression, and premorbid IQ	21
Clark[28] 1960	United States	NA	102	20-70	Approximately 50	3 kHz/both ears	Attention, immediate recall, processing speed, reasoning, visuospatial ability	None	None	11
Deal et al,[48] 2015	United States	ARIC	253	56.6 (5.3)	60.9	>25 dB, >40 dB; 0.5, 1, 2, and 4 kHz/better ear	Attention, delayed recall, fluency, global cognition, processing speed, semantic memory	None	Age, sex, educational attainment, smoking, hypertension, diabetes, premorbid IQ, and depression	22
Deal et al,[29] 2017	United States	HABC	1889	75.5 (3)	52.73	0.5, 1, 2, and 4 kHz/better ear	Immediate recall, processing speed	Dementia (diagnosis, medication use or race-stratified 3MS decline more than 1.5 SDs from the baseline mean)	Age, sex, race, educational attainment, study site, smoking, hypertension, diabetes, and stroke	22
Dupuis et al,[30] 2015	Canada	NA	301	71.13 (7.4)	64	>25 dB; 0.5, 1, and 2 kHz/worse ear	Global cognition	Cognitive impairment (MoCA)	None	20
Era et al,[31] 1986	Finland	NA	547	31-35, 51-55, 71-75	0	0.5, 1, and 2 kHz; PTT 4 kHz/better ear	Fluency, reasoning, visuospatial ability, working memory	None	None	17
Gussekloo et al,[32] 2005	The Netherlands	Leiden 85+ study	459	85 (0)	66	1, 2, and 4 kHz/both ears	Attention, delayed recall, global cognition, immediate recall, processing speed	None	Sex and educational attainment	17
Harrison Bush et al,[33] 2015	United States	SKILL	894	73.47 (6)	57.8	0.5, 1, and 2 kHz/better ear	Attention, global cognition, immediate recall, processing speed, working memory	None	Age, sex, educational attainment, race, diabetes, heart disease, hypertension, stroke, and depression	21

(*continued*)

Table 1. Characteristics of Cross-sectional Studies (continued)

Source	Country	Study Name	No. of Participants	Age, Mean (SD) or Range, y	Female, %	Audiometric Assessment[a]	Cognitive Domains Assessed	Clinical Outcomes (Criteria)	Covariates	STROBE Score[b]
Helzner et al,[49] 2005	United States	HABC	2052	77.5 (2.8)	52.7	>25 dB; 0.5, 1, and 2 kHz/worse ear	Global cognition	None	Age, sex, educational attainment, household income, study site, blood pressure, diabetes, CVD, cerebrovascular disease, hip bone mineral density, history of ear surgery, alcohol use, smoking, walking calorie expenditure, ototoxic medication use, and occupational noise exposure	19
Herbst and Humphrey,[60] 1980	United Kingdom	NA	253	≥70	64	≥35 dB; 1, 2, and 4 kHz/better ear	None	Dementia (CARE)	None	14
Heron and Chown,[34] 1967	United Kingdom	NA	540	20-79	44.44	1 kHz/both ears	Attention, immediate recall, processing speed, reasoning, semantic memory	None	None	22
Hofer et al,[35] 2003	Denmark, Finland, and Sweden	NORA	1041	75 (0)	57.26	0.25 kHz, 0.5, 1, and 2kHz; 4 and 8 kHz/both ears	Fluency, immediate recall, processing speed, reasoning, working memory	None	None	18
Hong et al,[36] 2016	Australia	BMES	2334	>49	NA	>40 dB; 0.5, 1, 2, and 4 kHz /worse and better ear	Global cognition	None	None	20
Karpa et al,[54] 2010	Australia	BMHS	2815	66.6 (9.3)	56.7	>25 dB; 0.5, 1, 2, and 4 kHz/better ear	None	Cognitive impairment (MMSE)	None	20
Kiely et al,[55] 2012	Australia	ALSA and BMES	4221	73.6 (8.9)	53.7	0.5, 1, 2, and 4 kHz/better ear	None	Cognitive impairment (MMSE)	Age, years in study, sex, educational attainment, diabetes, stroke, hypertension, workplace noise exposure, and high-frequency audiometric noise notches	20
Kurniawan et al,[56] 2012	The Netherlands	Leiden 85+ study	435	85 (0)	66.7	>35 dB; 1, 2, and 4 kHz/better ear	None	Cognitive impairment (MMSE)	None	19
Li et al,[37] 1998	Germany	NA	179	30-51	51.96	0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz/both ears	Fluency, immediate recall, global cognition, processing speed, reasoning, semantic memory	None	Age	17
Lin,[38] 2011	United States	NHANES	605	64.1 (2.9)	52.9	0.5, 1, and 2, 4 kHz/better ear	Processing speed	None	Age, sex, hearing aid, income, educational attainment, race, and CVD risk factors (diabetes, hypertension, smoking, and stroke)	20
Lin et al,[39] 2011	United States	BLSA	347	71 (7.2)	35.2	0.5, 1, 2, and 4 kHz/better ear	Attention, fluency, global cognition, immediate recall, processing speed, semantic memory	None	Age, sex, race, educational attainment, diabetes, smoking, and hypertension	19

(continued)

Table 1. Characteristics of Cross-sectional Studies (continued)

Source	Country	Study Name	No. of Partici-pants	Age, Mean (SD) or Range, y	Female, %	Audiometric Assessment[a]	Cognitive Domains Assessed	Clinical Outcomes (Criteria)	Covariates	STROBE Score[b]
Lin et al,[40] 2013	United States	HABC	1984	77.4 (2.76)	52.1	>25 dB; 0.5, 1, 2, and 4 kHz/better ear	Global cognition, processing speed	Cognitive impairment (3MS score <80 or decline >5 from baseline)	Age, sex, educational attainment, race/ethnicity, study site, hypertension, diabetes, smoking, and stroke	20
Lindenberger and Baltes,[41] 1994	Germany	BASE	156	84.9 (9)	50	0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz/both ears	Global cognition	None	Age and vision	18
Lindenberger and Baltes,[50] 1997	Germany	BASE	516	84.9 (8.7)	50	0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz/both ears	Global cognition	None	Age	17
López-Torres Hidalgo et al,[57] 2009	Spain	NA	1161	73.3 (5.9)	55.9	≥40 dB; 1 and 2 kHz/either ear; ≥40 dB; 1 or 2 kHz/both ears	None	Cognitive impairment (SPMSQ)	None	20
MacDonald et al,[42] 2004	Australia	VLS	125	78.9 (3.12)	61.6	0.5, 1, and 2 kHz/both ears	Immediate recall, processing speed, reasoning, semantic memory, working memory	None	None	18
Quaranta et al,[58] 2014	Italy	GA	488	72.8 (6.2)	39.3	>35 dB; 0.5, 1, and 2 kHz/both ears	None	Cognitive impairment (Neuropsycho-logical assessment[14] Dementia (*DSM-5*)	Age, sex, and educational attainment	17
Schaie et al,[43] 1964	United States	NA	47	76.4 (NA)	48.9	0.128, 0.256, 0.512, 1.024, 2.048, 4.096, and 8.192 kHz/both ears	Global cognition	None	Age	15
Sugawara et al,[44] 2011	Japan	NA	846	63.9 (8.3)	63.4	>25 dB; 0.5, 1, and 2 kHz/better ear	Global cognition	None	Age, sex, and educational attainment	18
Tay et al,[59] 2006	Australia	BMES	3509	66.7 (NA)	57	>40 dB; 0.5, 1, 2, and 4 kHz/better ear	None	Cognitive impairment (MMSE)	Age, sex, educational attainment, and history of stroke	22
Thomas et al,[45] 1983	United States	NA	259	72 (NA)	54	0.5, 1, and 2 kHz/better ear	Delayed recall, global cognition, reasoning, working memory	None	None	13
Valentijn et al,[46] 2005	The Netherlands	MAAS	391	65.1 (6.6)	48.6	1, 2, and 4 kHz/better ear	Attention, delayed recall, fluency, immediate recall, processing speed	None	None (cross-sectional) Age, sex, educational attainment, and baseline hearing and cognitive function	20
van Boxtel et al,[47] 2000	The Netherlands	MAAS	453	51.4 (16.5)	50.8	1, 2, and 4 KHz/better ear	Delayed recall, immediate recall, processing speed	None	Age, sex, and educational attainment; processing speed (delayed and immediate recall only)	18

Abbreviations: ALSA, Australian Longitudinal Study of Aging; ARIC, Atherosclerosis Risk in Communities neurocognitive study; BASE, Berlin Aging Study; BHAS, Busselton Healthy Aging Study; BLSA, Baltimore Longitudinal Study of Aging; BMES, Blue Mountains Eye Study; BMHS, Blue Mountains Hearing Study; CARE, Comprehensive Assessment and Referral Evaluation; CVD, cardiovascular disease; *DSM-5, Diagnostic and Statistical Manual of Health* (Fifth Edition); GA, Great Age study; HABC, Health, Aging and Body Composition study; MAAS, Maastricht Aging Study; MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; NA, not applicable; NHANES, National Health and Nutritional Examination Survey; NORA, Nordic Research on Aging study; PTT, pure-tone threshold; SKILL, Staying Keen in Later Life study; SPMSQ, Short Portable Mental Status Questionnaire; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; VLS, Victoria Longitudinal Study; 3MS, Modified Mini-Mental State Examination.

[a] Expressed as frequencies and ears assessed in pure-tone audiometry. Cutoff decibel level is included where applied to determine case of hearing loss.

[b] Scores range from 0 to 22, with higher scores indicating better study quality.

Table 2. Characteristics of Cohort Studies

Source (Length of Study, y)	Country	Study Name	No. of Participants	Age, Mean (SD) or Range, y	Female, %	Audiometric Assessment[a]	Cognitive Domains Assessed	Clinical Outcomes (Criteria)	Covariates	STROBE Score[b]
Anstey et al,[51] 2001 (2)	Australia	ALSA	2087	≥65	49.4	0.5, 1, and 2 kHz or 3 and 4 kHz or 6 and 8 kHz/both ears	Immediate recall, processing speed, semantic memory	None	Age	15
Anstey et al,[52] 2003 (8)	Australia	ALSA	1823	77.77 (6.56)	48.8	PTA of lesser PTT at 2, 3, and 4 kHz in either ear	Immediate recall, processing speed, semantic memory	None	Age, sex, educational attainment, depression, self-rated health, and number of medical conditions	20
Deal et al,[48] 2015 (23)	United States	ARIC	253	56.6 (5.3)	60.9	>25 dB, >40 dB; 0.5, 1, 2, and 4 kHz/better ear	Attention, delayed recall, fluency, global cognition, processing speed, semantic memory	None	Age, sex, educational attainment, smoking, hypertension, diabetes, premorbid IQ, and depression	22
Deal et al,[29] 2017 (9)	United States	HABC	1889	75.5 (3)	52.73	0.5, 1, 2, and 4 kHz/better ear	Immediate recall, processing speed	Dementia (diagnosis, medication use or race-stratified 3MS decline more than 1.5 SDs from the baseline mean)	Age, sex, race, educational attainment, study site, smoking, hypertension, diabetes, and stroke	22
Gallacher et al,[7] 2012 (17)	United Kingdom	CaPS	1057	56.1 (4.4)	0	0.5, 1, 2, and 4 kHz/both ears	Delayed recall, global cognition, immediate recall, processing speed, reasoning	Cognitive impairment (NINCDS-AIREN, *DSM-IV*, and no functional impairment); dementia (*DSM-IV* or NINCDS-AIREN); AD (*DSM-IV*, most met criteria for NINCDS-ADRDA); vascular dementia (NINCDS-AIREN)	Age, social class, anxiety, baseline cognitive function (cognitive function only), and premorbid IQ (clinical outcomes only)	21
Hong et al,[36] 2016 (10)	Australia	BMES	2334	>49	NA	>40 dB; 0.5, 1, 2, and 4 kHz /worse and better ear	Global cognition	None	Age and sex	20
Kiely et al,[55] 2012 (11)	Australia	ALSA and BMES	4221	73.6 (8.9)	53.7	0.5, 1, 2, and 4 kHz/better ear	None	Cognitive impairment (MMSE)	Age, years in study, sex, educational attainment, diabetes, stroke, hypertension, workplace noise exposure, and high-frequency audiometric noise notches	20
Lin et al,[61] 2011 (18)	United States	BLSA	639	36-90	43.7	0.5, 1, 2, and 4 kHz/better ear	None	Dementia (*DSM-III*), AD (NINCDS-ADRDA)	Age, sex, race, educational attainment, diabetes, smoking, hypertension, and baseline cognitive function	21
Lin et al,[40] 2013 (6)	United States	HABC	1984	77.4 (2.76)	52.1	>25 dB; 0.5, 1, 2, and 4 kHz/better ear	Global cognition, processing speed	Cognitive impairment (3MS score <80 or decline >5 from baseline)	Age, sex, educational attainment, race/ethnicity, study site, hypertension, diabetes, smoking, and stroke	20
Lindenberger and Ghisletta,[53] 2009 (13)	Germany	BASE	516	84.9 (8.7)	50	2, 3, 4, and 6 kHz/ both ears	Fluency, immediate recall, processing speed	None	Age, time to death, and risk for dementia	18
Valentijn et al,[46] 2005 (6)	The Netherlands	MAAS	391	65.1 (6.6)	48.6	1, 2, and 4 kHz/ better ear	Attention, delayed recall, fluency, immediate recall, processing speed	None	Age, sex, educational attainment, and baseline hearing and cognitive function	20

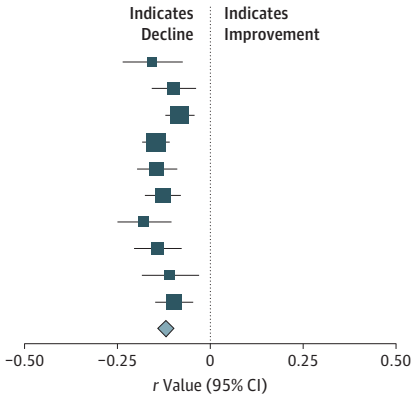
Abbreviations: ALSA, Australian Longitudinal Study of Aging; ARIC, Atherosclerosis Risk in Communities neurocognitive study; BASE, Berlin Aging Study; BLSA, Baltimore Longitudinal Study of Aging; BMES, Blue Mountains Eye Study; CaPS, Caerphilly Prospective Study; *DSM-III*, *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition); *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); HABC, Health, Aging and Body Composition study; MAAS, Maastricht Aging Study; MMSE, Mini-Mental State Examination; NA, not applicable; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association; NINCDS-AIREN, NINCDS–Association Internationale pour la Recherché et l'Enseignement en Neurosciences; PTA, pure-tone average; PTT, pure-tone threshold; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; 3MS, Modified Mini-Mental State Examination.

[a] Expressed as frequencies and ears assessed in pure-tone audiometry. Cutoff decibel level is included where applied to determine case of hearing loss.

[b] Scores range from 0 to 22, with higher scores indicating better study quality.

Figure 2. Forest Plot of Correlations for Cognition Cross-sectional Outcomes

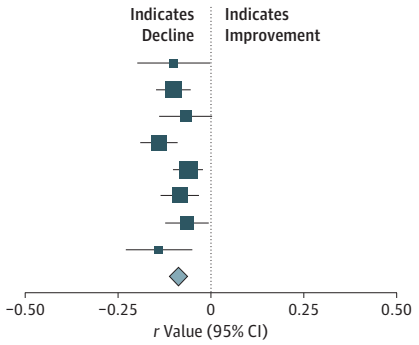
Outcome	No. of Participants/Events	r Value (95% CI)
Attention	5159/11	−0.16 (−0.24 to −0.07)
Delayed recall	3808/7	−0.10 (−0.16 to −0.04)
Fluency	4629/9	−0.08 (−0.12 to −0.04)
Global cognition	7702/15	−0.15 (−0.18 to −0.11)
Immediate recall	6747/15	−0.14 (−0.20 to −0.09)
Processing speed	10 660/20	−0.13 (−0.18 to −0.08)
Reasoning	3128/12	−0.17 (−0.25 to −0.10)
Semantic memory	2906/10	−0.14 (−0.20 to −0.08)
Visuospatial ability	669/5	−0.11 (−0.19 to −0.03)
Working memory	4855/9	−0.10 (−0.15 to −0.05)
Summary	15 620/113	−0.12 (−0.14 to −0.10)



Twenty-six studies were included in the analysis.[23-48] Squares represent correlation (*r* value); different sizes of markers, weight; diamond, overall correlation; and error bars, 95% CIs.

Figure 3. Forest Plot of Correlations for Cognition Cohort Outcomes

Outcome	No. of Participants/Events	r Value (95% CI)
Attention	5159/11	−0.10 (−0.20 to 0.00)
Delayed recall	3808/7	−0.10 (−0.15 to −0.05)
Fluency	4629/9	−0.07 (−0.14 to 0.01)
Global cognition	7702/15	−0.14 (−0.19 to −0.09)
Immediate recall	6747/15	−0.06 (−0.10 to −0.02)
Processing speed	10 660/20	−0.08 (−0.14 to −0.03)
Reasoning	3128/12	−0.06 (−0.12 to 0.00)
Semantic memory	2906/10	−0.14 (−0.23 to −0.05)
Summary	15 620/113	−0.09 (−0.11 to −0.07)



Nine studies were included in the analysis.[7,29,36,40,46,48,51-53] Squares represent correlation (*r* value); different sizes of markers, weight; diamond, overall correlation; and error bars, 95% CIs.

cases of 245 included participants [15.9%]),[60] and the other assessed AD (20 cases of 434 included participants [4.6%]).[58] Three studies with 3585 participants[7,29,61] (10.4%) were included in the cohort dementia analysis with a follow-up length ranging from 9 to 18 years (mean [SD], 15.0 [5.2] years). All 3 studies reported incident dementia outcomes (366 cases of 3439 included participants [10.6%]), 2 examined an AD subset (78 cases of 1491 included participants [5.2%]),[7,61] and 1 examined a vascular dementia subset (38 cases of 870 included participants [4.4%]).[7]

Hearing Loss and Cognitive Function

We found a small but statistically significant association between ARHL and all 10 cognitive domains of interest in cross-sectional studies, including global cognition (*r* = −0.15; 95% CI, −0.18 to −0.11), executive functions (range, *r* = −0.08 [95% CI, −0.12 to −0.04] to *r* = −0.18 [95% CI, −0.25 to −0.10), episodic memory (range, *r* = −0.10 [95% CI, −0.16 to −0.04] to *r* = −0.14 [95% CI, -0.20 to -0.09]), processing speed (*r* = −0.13; 95% CI, -0.18 to 0.08), semantic memory (*r* = −0.14; 95% CI, -0.20 to -0.08), and visuospatial ability (*r* = −0.11; 95% CI, -0.19 to -0.03). Similar results were observed in 7 of 8 domains in cohort studies, excluding fluency, which was not significant (*r* = −0.07; 95% CI, -0.14 to 0.01). These results included global cognition (*r* = −0.14; 95% CI, -0.19 to -0.09), executive functions (range, *r* = −0.06 [95% CI, -0.12 to -0.004] to *r* = −0.10 [95% CI, -0.20 to -0.001]), episodic memory (range, *r* = −0.06 [95% CI, -0.10 to -0.02] to *r* = −0.10 [95% CI, -0.15 to -0.05), processing speed (*r* = −0.08; 95% CI, -0.14 to -0.03), and semantic memory (*r* = −0.14; 95% CI, -0.23 to -0.05) (**Figure 2**, **Figure 3**, and eFigures 10-27 and eTables 1-9 in the Supplement). No cohort data were available for visuospatial ability or working memory. Heterogeneity was significant in most domains (*Q* range, 0.0-79.9). Inconsistency ranged from very low to high.

Hearing Loss and Cognitive Impairment

We found a statistically significant association between ARHL and cognitive impairment across cross-sectional (OR, 2.00; 95% CI, 1.39-2.89) and cohort studies (OR, 1.22; 95% CI, 1.09-1.36) (eFigures 2 and 3 and eTable 7 in the Supplement). Statistically significant heterogeneity (*Q* range, 0.1-23.7) and a large amount of inconsistency were observed in cross-sectional but not in cohort studies.

Hearing Loss and Dementia

We found a significant association between ARHL and dementia in cross-sectional (OR, 2.42; 95% CI, 1.24-4.72) and cohort (OR, 1.28; 95% CI, 1.02-1.59) studies (eFigures 4-9 and eTable 7 in the Supplement). Statistically significant heterogeneity (*Q* range, 0.4-6.6) and a moderate amount of inconsistency were observed in cohort but not cross-sectional studies. No statistically significant association was found between ARHL and AD for cross-sectional (OR, 1.80; 95% CI, 0.58-5.60) or cohort

(OR, 1.69; 95% CI, 0.72-4.00) studies. In addition, the association between ARHL and vascular dementia was not significant (OR, 2.40; 95% CI, 0.99-5.82).

Subgroup Analyses and Meta-regression

The results of the subgroup and meta-regression analyses for cognitive outcomes are summarized below (eTables 8 and 9 in the Supplement). The respective Fisher *z* values (moderator analysis), slope (meta-regression), SEs, and 95% CIs for each variable are available in eTables 10 to 36 in the Supplement.

Study Characteristics

Studies conducted in the United States reported weaker associations between ARHL and cognition compared with Australian and European studies, possibly owing to differences in prevalence of ARHL or cognitive decline and dementia. Associations generally became weaker with later publication dates (possibly owing to increased adjustment for covariates) and, in some cases, with higher STROBE score. Results for journal impact factor were mixed. Among cohort studies, results for length of follow-up were mostly insignificant.

Participant Characteristics

Cross-sectional associations were weaker when studies excluded participants with cognitive impairment and dementia and included participants with cardiovascular risk. Associations with cohort processing speed were mixed with regard to whether participants with cognitive impairment were removed at baseline or in analysis. The age and sex of the sample generally had mixed results. Associations were weaker for studies with mixed-race participants compared with studies in which the breakdown by race was not declared. Associations were typically stronger with an increased proportion of white participants but weaker with black participants and nonsignificant for those of other races, possibly owing to selective survival. Associations were also typically stronger with an increased proportion of primary educational attainment, weaker with tertiary educational attainment, and mixed with secondary educational attainment and mean years of education. Smoking (current and previous) had a significant association.

Audiometric Factors

Stronger associations were usually found for lower-frequency hearing loss (<4 kHz) and when auditory function was assessed with both ears (compared with only the better ear). No significant difference was found for hearing loss examined as a categorical (>25 dB) vs a continuous variable. Weaker associations were generally found when studies used a sound-treated room or booth or followed the World Health Organization criteria.[62] Declared inclusion of hearing aid users weakened the association for immediate recall and semantic memory. However, the proportion of hearing aid users included in the study had no significant result. The sample degree of hearing loss significantly weakened the association with cross-sectional attention and immediate recall. The proportion of individuals diagnosed with hearing loss by study authors weakened the association with immediate recall. Results were otherwise mixed and nonsignificant.

Cognitive Measures

Results were mostly minor and inconsistent with respect to whether the cognitive test was accessible to a sample with hearing loss. The only significant result found a stronger association for nonbiased tests.

Statistical Analysis

A stronger association was generally found for studies that used correlation as the statistical model (compared with linear regression or linear mixed models) and those that reported results as significant. Studies that used age, sex, race, educational attainment, and vascular factors as covariates in their analysis typically reported weaker (sometimes significantly weaker) associations. This same trend was observed for studies that controlled for stroke, hypertension, diabetes, and current or previous smoking. Controlling for depression significantly weakened the association with cross-sectional attention. Results for premorbid IQ were mixed and nonsignificant except for cohort global cognition.

Because of a lack of data, no other a priori variables were examined. Other variables were reviewed ad hoc. A significantly weaker association was generally found for analyses that controlled for study site. These analyses were not conducted for cognitive impairment and dementia outcomes owing to lack of studies, with the exception of cross-sectional cognitive impairment studies. Year of publication, age (mean and minimum), sex, sample degree of hearing loss, proportion with hearing loss and cognitive impairment, impact factor, and STROBE were assessed (eTable 37 in the Supplement). No association was statistically significant.

Discussion

In this meta-analysis, ARHL had significant associations with accelerated multidomain cognitive decline, cognitive impairment, and dementia, thus supporting further consideration of ARHL as a risk factor for these outcomes.[3,6] The associations, although small, were comparable in size and significance with other more commonly researched risk factors using meta-analysis.[3]

The result for AD indicated increased risk with ARHL but was nonsignificant, most likely owing to small sample sizes or to causal factors other than AD etiology underpinning the association.[6] Age-related hearing loss has been associated with increased global and regional gray matter atrophy and white matter hyperintensities, whereas AD substrate has been found in the auditory neural regions but not in the peripheral auditory structures.[63]

Study quality assessment showed that reporting was generally of very good quality. Poor reporting of attrition rates may conceal a greater decline in cognition and risk for dementia in older cohorts owing to higher numbers of dropouts among those with poorer health. Subgroup analysis found no bias for verbal or audio cognitive tests. However, some potential bias may have existed because a stronger effect size was found with substandard audiometric assessment.

Causal Mechanisms for ARHL and Cognitive Decline

The association between ARHL and cognitive decline remains unclear.[61] One hypothesis is a common etiology, such as decline in the vascular system or a broader physiological decline. Age-related hearing loss has been linked with multiple indicators of functional decline and is a biomarker for frailty syndrome, which has been causally linked to dementia.[64] Other hypotheses suggest that the association may be mechanistic, for example, ARHL causing cognitive decline through impaired speech perception.[61]

Vascular risk factors contributed significantly to decline in global cognition and processing speed. However, the pooled effect size of studies controlling for vascular risk factors in these outcomes remained significant, suggesting other contributing factors, for example, depression, which significantly moderated the association with attention.

Of interest, the pattern of decline observed in this study was consistent with estimated cognitive outcomes based on behavioral and neuroimaging research.[65] This research reports increased recruitment of short-term memory and executive functions to aid speech perception after acquired hearing loss and concomitant decline in auditory cortex regions.[66] This situation is estimated to lead to less decline in these functions but greater decline in episodic and semantic long-term memory owing to reallocation of cognitive resources.[65] Consistent with this research, we observed that hearing loss was less associated with decline in executive functions and immediate recall compared with delayed and semantic memory and was increasingly less predictive of decline in attention and immediate recall among those with greater hearing loss. In addition, semantic memory, usually maintained in older age compared with episodic memory,[67] demonstrated a decline similar to that of episodic memory. Furthermore, the results indicated that hearing aids may benefit short-term and semantic memory.

The stronger association for low- to middle-frequency hearing loss with immediate recall and processing speed may be attributable to advanced aging as ARHL progresses from high to low frequencies.[64] Of interest, vascular dysfunction has been associated with lower-frequency hearing loss and white matter hyperintensities.[68] Alternatively, reallocation of executive functions to support accuracy in speech perception may be associated with decline in performance speed, as also observed in older adults with visual processing deficits.[69]

Future Directions

Cognitive decline is influenced by multiple modifiable health factors.[3] Hearing loss may be another serviceable risk factor, because it is easily diagnosed and can be treated.[70] Although associations were small, treatment may cumulatively benefit cognition as observed in intervention studies in older adults without cognitive impairment.[71-73] This benefit was not observed in patients with dementia, but treatment may still reduce disability.[74] Decline in lexical or semantic, episodic memory, and executive functions is used by clinicians as a marker for probable AD and vascular dementia.[75] In patients with ARHL, these domains may benefit from improved verbal communication through use of hearing aids. Additional randomized clinical trials exploring the cognitive benefits of hearing loss treatment are required, as is more research as to whether treatment, alone or as part of a wider approach to risk factors, modifies dementia outcomes. Neuroimaging studies could examine modification of cortical changes and neurocognitive compensation with hearing aid use in speech tasks. Future epidemiologic research might assess whether ARHL is associated with cognitive decline independently of neuropathologic hallmarks of dementia and whether a mediator of this association exists (eg, loneliness). Also of interest would be whether cognitive reserve moderates cognitive decline in the population with ARHL. Our results indicated a moderator effect of educational attainment, which is often used as a proxy for cognitive reserve.[76]

Increasing evidence suggests that ARHL is associated with a wide range of health issues, higher disease burden, and increased risk for hospitalization,[64,77] leading to greater awareness of this condition as a critical public health concern.[70,77] In the United States, only 1 in 5 adults with hearing loss wears hearing aids, possibly owing to cost, lack of insurance coverage, or lack of knowledge of health care options, particularly for milder loss.[70] The National Academies of Sciences, Engineering, and Medicine recently outlined several recommendations to address this issue, with implications for public health services and policy.[70,78] Initiatives to expand access to treatment through screening programs, expand delivery of hearing services, and provide coverage for assistive hearing devices would be beneficial.[70] In addition, primary health care clinicians would benefit from standard guidelines for screening and referring patients with hearing loss.[70]

Strengths and Limitations

To the our knowledge, this study is the first systematic review and meta-analysis of ARHL and cognitive decline that used only pure-tone thresholds as the audiometric criteria. Our strict inclusion criteria in study design and measurement allowed us to reduce conceptual heterogeneity and thus provide the most accurate quantitative measure of this association. Considerable heterogeneity remained across most outcomes. However, in any adjusted estimate of effect size for risk factors derived from aging studies, residual confounding will exist. Extensive subgroup and meta-regression analyses investigating this heterogeneity provided insight into how future studies may reduce bias and explore the potential basis of this association in experimental and clinical trials.

This study has several limitations. We could not examine whether studies controlled for etiology of hearing loss (eg, congenital or prelingual deafness). However, because of the low prevalence (<2%) of hearing loss in patients younger than 40 years, this prevalence was considered to be insignificant.[77] Some of the meta-analyses had a low number of effect sizes. We could not examine other planned moderators and covariates, such as attrition, owing to lack of data. For meta-analyses of dementia subgroups, the number of cases was small. Furthermore, because the meta-analyses were of observational studies, support for any inferences regarding the causal nature of the association is limited and cannot

provide direct evidence for policy recommendations. However, our analyses of prospective studies give an indication of the temporal order of the association consistent with a causal effect. Further research is required to determine whether a causal relationship exists. Owing to the large number of statistical tests conducted, some of our findings could have been the result of chance. However, we did not want to risk missing potentially important findings that could be tested in future original studies. Finally, as is the case with any aggregate data meta-analysis, the potential for ecological fallacy exists.

Conclusions

Age-related hearing loss is a potential risk factor for cognitive decline, cognitive impairment, and dementia. The effect sizes for all 3 main outcomes were small, but they compared with meta-analytic estimates for other risk factors more commonly investigated in this population. Additional research, particularly randomized clinical trials, is warranted to examine cognitive implications of treatment and to explore the possible causal mechanisms underlying this relationship.

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