ASSOCIATION OF AGE-RELATED HEARING LOSS WITH COGNITIVE FUNCTION, COGNITIVE IMPAIRMENT, AND DEMENTIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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IMPORTANT: 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 analysis 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.
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. Current pharmaceutical approaches targeting neuropathologic processes such as Alzheimer disease (AD) offer limited benefit with symptommodifying effects at best. Switching to a preventive strategy through reduction of risk factors may be more beneficial than pharmacologic therapy after clinical expression of neuropathologic changes and may lead to significant reductions in medical costs.

Approximately one-third of adults older than 65 years experience a disabling hearing loss. 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. 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). Prior reviews 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 and met the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. 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 (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, 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. 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. With use of the Cohen κ coefficient, 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. 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 ≤ .10 was considered to be statistically significant. Inconsistency was examined using the I² 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. Small-study effects were examined using funnel plots, and the regression-intercept approach of Egger and colleagues 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.

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 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 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 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 eRe-

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*Figure 1. PRISMA Flow Diagram*

- **1834** Records identified through database search
- **1273** SCOPUS
- **504** PubMed
- **32** Cochrane Library
- **15** EMBASE
- **1185** Records screened after duplicates removed
- **1010** Records excluded
- **888** Off topic
- **105** Inappropriate design, outcomes, or population
- **37** Review
- **155** Full-text articles assessed for eligibility
- **115** Full-text articles excluded
- **43** No audiology
- **31** Case-control
- **19** Inappropriate sample
- **12** Inappropriate audiometric criteria
- **7** No statistical analysis
- **2** Inappropriate design
- **1** Audiometric assessment not specified
- **40** Studies included in qualitative synthesis
- **36** Studies included in quantitative synthesis (meta-analysis)
- **26** Cross-sectional cognition
- **9** Cohort cognition
- **5** Cross-sectional impairment
- **3** Cohort impairment
- **3** Cohort dementia
- **2** Cross-sectional dementia

Study selection for the meta-analysis. Some studies were allocated to more than one category.
Table I. Characteristics of Cross-sectional Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Country</th>
<th>Study Name</th>
<th>No. of Participants</th>
<th>Age, Mean (SD) or Range, y</th>
<th>Female, %</th>
<th>Audiometric Assessmenta</th>
<th>Cognitive Domains Assessed</th>
<th>Clinical Outcomes (Criteria)</th>
<th>Covariates</th>
<th>STROBE Scoreb</th>
</tr>
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<tbody>
<tr>
<td>Anstey,23 1999</td>
<td>Australia</td>
<td>NA</td>
<td>180</td>
<td>70.56 (7.13)</td>
<td>100</td>
<td>2, 4, and 8 kHz/both ears</td>
<td>Attention, processing speed</td>
<td>None</td>
<td>Age, grip strength, forced expiratory volume, vibration sense, and vision</td>
<td>14</td>
</tr>
<tr>
<td>Anstey and Smith,24 1999</td>
<td>Australia</td>
<td>NA</td>
<td>180</td>
<td>70.56 (7.13)</td>
<td>100</td>
<td>2, 4, and 8 kHz/both ears</td>
<td>Processing speed, reasoning, semantic memory, visuospatial ability, working memory</td>
<td>None</td>
<td>Age</td>
<td>17</td>
</tr>
<tr>
<td>Anstey et al,25 2001</td>
<td>Australia</td>
<td>ALSA</td>
<td>894</td>
<td>77.7 (5.6)</td>
<td>49</td>
<td>0.5, 1, 2, 3, and 4 kHz/both ears</td>
<td>Immediate recall, processing speed, semantic memory</td>
<td>None</td>
<td>None</td>
<td>17</td>
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<tr>
<td>Baltes and Lindenberger,26 1997</td>
<td>Germany</td>
<td>BASE and young adult sample</td>
<td>315</td>
<td>64.9 (22)</td>
<td>NA</td>
<td>0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz/both ears</td>
<td>Fluency, global cognition, immediate recall, processing speed, reasoning, semantic memory</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Bucks et al,27 2016</td>
<td>Australia</td>
<td>BHAS</td>
<td>1969</td>
<td>56.2 (5.5)</td>
<td>53.8</td>
<td>0.5, 1, 2, and 4 kHz/better ear</td>
<td>Attention, delayed recall, fluency, processing speed, working memory</td>
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<td>Age, sex, educational attainment, depression, and premorbid IQ</td>
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<td>Clark28 1960</td>
<td>United States</td>
<td>NA</td>
<td>102</td>
<td>20-70</td>
<td>Approximately 50</td>
<td>3 kHz/both ears</td>
<td>Attention, immediate recall, processing speed, reasoning, visuospatial ability</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Deal et al,48 2015</td>
<td>United States</td>
<td>ARIC</td>
<td>253</td>
<td>56.6 (5.3)</td>
<td>60.9</td>
<td>&gt;25 dB; &gt;40 dB; 0.5, 1, 2, and 4 kHz/better ear</td>
<td>Attention, delayed recall, fluency, global cognition, processing speed, semantic memory</td>
<td>None</td>
<td>Age, sex, educational attainment, smoking, hypertension, diabetes, premorbid IQ, and depression</td>
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<td>United States</td>
<td>HABC</td>
<td>1889</td>
<td>75.5 (3)</td>
<td>52.73</td>
<td>0.5, 1, 2, and 4 kHz/better ear</td>
<td>Immediate recall, processing speed</td>
<td>Dementia (diagnosis, medication use or race-stratified 3MS decline more than 1.5 SDs from the baseline mean)</td>
<td>Age, sex, race, educational attainment, study site, smoking, hypertension, diabetes, and stroke</td>
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<tr>
<td>Dupuis et al,30 2015</td>
<td>Canada</td>
<td>NA</td>
<td>301</td>
<td>71.13 (7.4)</td>
<td>64</td>
<td>&gt;25 dB; 0.5, 1, and 2 kHz/worse ear</td>
<td>Global cognition</td>
<td>Cognitive impairment (MoCA)</td>
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<td>Era et al,31 1986</td>
<td>Finland</td>
<td>NA</td>
<td>547</td>
<td>31-35, 51-55, 71-75</td>
<td>0</td>
<td>0.5, 1, and 2 kHz; PTT 4 kHz/better ear</td>
<td>Fluency, reasoning, visuospatial ability, working memory</td>
<td>None</td>
<td>None</td>
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<td>Gusseldoo et al,32 2005</td>
<td>The Netherlands</td>
<td>Leiden 85+ study</td>
<td>459</td>
<td>85 (0)</td>
<td>66</td>
<td>1, 2, and 4 kHz/both ears</td>
<td>Attention, delayed recall, global cognition, immediate recall, processing speed</td>
<td>None</td>
<td>Sex and educational attainment</td>
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<tr>
<td>Harrison Bush et al,33 2015</td>
<td>United States</td>
<td>SKILL</td>
<td>894</td>
<td>73.47 (6)</td>
<td>57.8</td>
<td>0.5, 1, and 2 kHz/better ear</td>
<td>Attention, global cognition, immediate recall, processing speed, working memory</td>
<td>None</td>
<td>Age, sex, educational attainment, race, diabetes, heart disease, hypertension, stroke, and depression</td>
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<tr>
<th>Source</th>
<th>Country</th>
<th>Study Name</th>
<th>No. of Participants</th>
<th>Age, Mean (SD) or Range, y</th>
<th>Female, %</th>
<th>Audiometric Assessment</th>
<th>Cognitive Domains Assessed</th>
<th>Clinical Outcomes (Criteria)</th>
<th>Covariates</th>
<th>STROBE Score</th>
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<tr>
<td>Hetzner et al., 1992</td>
<td>United States</td>
<td>HABC</td>
<td>2052</td>
<td>77.5 (2.8)</td>
<td>52.7</td>
<td>&gt;25 dB; 0.5, 1, and 2 kHz/worse ear</td>
<td>Global cognition</td>
<td>None</td>
<td>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</td>
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<td>Herbst and Humphrey, 1980</td>
<td>United Kingdom</td>
<td>NA</td>
<td>253</td>
<td>≥70</td>
<td>64</td>
<td>≥35 dB; 1, 2, and 4 kHz/better ear</td>
<td>None</td>
<td>Dementia (CARE)</td>
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<td>Heron and Chown, 1967</td>
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<td>540</td>
<td>20-79</td>
<td>44.44</td>
<td>1 kHz/both ears</td>
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<td>Hofer et al., 2003</td>
<td>Denmark, Finland, and Sweden</td>
<td>NORA</td>
<td>1041</td>
<td>75 (0)</td>
<td>57.26</td>
<td>0.25 kHz; 0.5, 1, and 2 kHz; 4 and 8 kHz/both ears</td>
<td>Fluency, immediate recall, processing speed, reasoning, working memory</td>
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<td>BMES</td>
<td>2334</td>
<td>&gt;49</td>
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<td>&gt;40 dB; 0.5, 1, 2, and 4 kHz/worse and better ear</td>
<td>Global cognition</td>
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<td>Karp et al., 2010</td>
<td>Australia</td>
<td>BMHS</td>
<td>2815</td>
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<td>Kiely et al., 2012</td>
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<td>ALSA and BMES</td>
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<td>53.7</td>
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<td>None</td>
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<td>Kurskawęski et al., 2012</td>
<td>The Netherlands</td>
<td>Leiden 85+ study</td>
<td>435</td>
<td>85 (0)</td>
<td>66.7</td>
<td>&gt;35 dB; 1, 2, and 4 kHz/better ear</td>
<td>None</td>
<td>Cognitive impairment (MMSE)</td>
<td>None</td>
<td>19</td>
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<td>Li et al., 1998</td>
<td>Germany</td>
<td>NA</td>
<td>179</td>
<td>30-51</td>
<td>51.96</td>
<td>0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz/both ears</td>
<td>Fluency, immediate recall, global cognition, processing speed, reasoning, semantic memory</td>
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<td>Age</td>
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<td>Lin, 2011</td>
<td>United States</td>
<td>NHANES</td>
<td>605</td>
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<td>52.9</td>
<td>0.5, 1, and 2, 4 kHz/better ear</td>
<td>Processing speed</td>
<td>None</td>
<td>Age, sex, hearing aid, income, educational attainment, race, and CVD risk factors (diabetes, hypertension, smoking, and stroke)</td>
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<tr>
<th>Source</th>
<th>Country</th>
<th>Study Name</th>
<th>No. of Participants</th>
<th>Age, Mean (SD) or Range, y</th>
<th>Female, %</th>
<th>Audiometric Assessmenta</th>
<th>Cognitive Domains Assessed</th>
<th>Clinical Outcomes (Criteria)</th>
<th>Covariates</th>
<th>STROBE Scoreb</th>
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<tr>
<td>Lin et al., 2011</td>
<td>United States</td>
<td>BLSA</td>
<td>347</td>
<td>71 (7.2)</td>
<td>35.2</td>
<td>0.5, 1, 2, and 4 kHz/better ear</td>
<td>Attention, fluency, global cognition, immediate recall, processing speed, semantic memory</td>
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<td>Age, sex, race, educational attainment, diabetes, smoking, and hypertension</td>
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<td>Lin et al., 2013</td>
<td>United States</td>
<td>HABC</td>
<td>1984</td>
<td>77.4 (2.76)</td>
<td>52.1</td>
<td>&gt;25 dB; 0.5, 1, 2, and 4 kHz/better ear</td>
<td>Global cognition, processing speed</td>
<td>Cognitive impairment (3MS score &lt;80 or decline &gt;5 from baseline)</td>
<td>Age, sex, educational attainment, race/ethnicity, study site, hypertension, diabetes, smoking, and stroke</td>
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<tr>
<td>Lindenberger and Baltes, 1994</td>
<td>Germany</td>
<td>BASE</td>
<td>156</td>
<td>84.9 (9)</td>
<td>50</td>
<td>0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz/better ears</td>
<td>Global cognition</td>
<td>None</td>
<td>Age and vision</td>
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<td>Lindenberger and Baltes, 1997</td>
<td>Germany</td>
<td>BASE</td>
<td>516</td>
<td>84.9 (8.7)</td>
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<td>0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz/better ears</td>
<td>Global cognition</td>
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<td>Age</td>
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<td>López-Torres Hidalgo et al., 2009</td>
<td>Spain</td>
<td>NA</td>
<td>1161</td>
<td>73.3 (5.9)</td>
<td>55.9</td>
<td>≥40 dB; 1 and 2 kHz/either ear; ≥40 dB; 1 or 2 kHz/better ears</td>
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<td>Cognitive impairment (SPMSQ)</td>
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<td>MacDonald et al., 2004</td>
<td>Australia</td>
<td>VLS</td>
<td>125</td>
<td>78.9 (3.12)</td>
<td>61.6</td>
<td>0.5, 1, and 2 kHz/better ears</td>
<td>Immediate recall, processing speed, reasoning, semantic memory, working memory</td>
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<tr>
<td>Quaranta et al., 2014</td>
<td>Italy</td>
<td>GA</td>
<td>488</td>
<td>72.8 (6.2)</td>
<td>39.3</td>
<td>&gt;35 dB; 0.5, 1, and 2 kHz/better ears</td>
<td>None</td>
<td>Cognitive impairment (Neuropsychological assessment)</td>
<td>Age, sex, and educational attainment</td>
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<td>United States</td>
<td>NA</td>
<td>47</td>
<td>76.4 (NA)</td>
<td>48.9</td>
<td>0.128, 0.256, 0.512, 1.024, 2.048, 4.096, and 8.192 kHz/better ears</td>
<td>Global cognition</td>
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<td>Sugawara et al., 2011</td>
<td>Japan</td>
<td>NA</td>
<td>846</td>
<td>63.9 (8.3)</td>
<td>63.4</td>
<td>&gt;25 dB; 0.5, 1, and 2 kHz/better ear</td>
<td>Global cognition</td>
<td>None</td>
<td>Age, sex, and educational attainment</td>
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<tr>
<td>Tay et al., 2006</td>
<td>Australia</td>
<td>BMES</td>
<td>3509</td>
<td>66.7 (NA)</td>
<td>57</td>
<td>&gt;40 dB; 0.5, 1, 2, and 4 kHz/better ear</td>
<td>None</td>
<td>Cognitive impairment (MMSE)</td>
<td>Age, sex, educational attainment, and history of stroke</td>
<td>22</td>
</tr>
<tr>
<td>Thomas et al., 1983</td>
<td>United States</td>
<td>NA</td>
<td>259</td>
<td>72 (NA)</td>
<td>54</td>
<td>0.5, 1, and 2 kHz/better ear</td>
<td>Delayed recall, global cognition, reasoning, working memory</td>
<td>None</td>
<td>None</td>
<td>13</td>
</tr>
<tr>
<td>Valentijn et al., 2005</td>
<td>The Netherlands</td>
<td>MAAS</td>
<td>391</td>
<td>65.1 (6.6)</td>
<td>48.6</td>
<td>1, 2, and 4 kHz/better ear</td>
<td>Attention, delayed recall, fluency, immediate recall, processing speed</td>
<td>None</td>
<td>None (cross-sectional)</td>
<td>20</td>
</tr>
<tr>
<td>van Rostel et al., 2000</td>
<td>The Netherlands</td>
<td>MAAS</td>
<td>453</td>
<td>51.4 (16.5)</td>
<td>50.8</td>
<td>1, 2, and 4 kHz/better ear</td>
<td>Delayed recall, immediate recall, processing speed</td>
<td>None</td>
<td>Age, sex, educational attainment; processing speed (delayed and immediate recall only)</td>
<td>18</td>
</tr>
</tbody>
</table>

Abbreviations: ALSA, Australian Longitudinal Study of Aging; ARIC, Atherosclerosis Risk in Communities neurocognitive study; BASE, Berlin Aging Study; BHAS, Bispeullet 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 Mental Disorders (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 Nutrition 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 Scores range from 0 to 22, with higher scores indicating better study quality.

b Expressed as frequencies and ears assessed in pure-tone audiometry. Cutoff decibel level is included where applied to determine case of hearing loss.
### Table 2. Characteristics of Cohort Studies

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

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

*Scores range from 0 to 22, with higher scores indicating better study quality.

**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; CoPS, 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-ADRA, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association; NINCDS-ADARE, NINCDS-Association Internationale pour la Recherche 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.
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 (36 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 \(^{29,61}\) (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 \((r = -0.15; 95\% \text{CI}, -0.18 \text{ to } -0.11)\), executive functions \((r = -0.08; 95\% \text{CI}, -0.12 \text{ to } -0.04)\), episodic memory \((r = -0.10; 95\% \text{CI}, -0.16 \text{ to } -0.04)\), processing speed \((r = -0.13; 95\% \text{CI}, -0.18 \text{ to } 0.08)\), semantic memory \((r = -0.14; 95\% \text{CI}, -0.20 \text{ to } -0.08)\), and visuospatial ability \((r = -0.11; 95\% \text{CI}, -0.19 \text{ to } -0.03)\). Similar results were observed in 7 of 8 domains in cohort studies, excluding fluency, which was not significant \((r = -0.07; 95\% \text{CI}, -0.14 \text{ to } 0.01)\). These results included global cognition \((r = -0.14; 95\% \text{CI}, -0.19 \text{ to } -0.09)\), executive functions \((r = -0.06; 95\% \text{CI}, -0.12 \text{ to } -0.004)\), episodic memory \((r = -0.06; 95\% \text{CI}, -0.10 \text{ to } -0.02)\), processing speed \((r = -0.10; 95\% \text{CI}, -0.15 \text{ to } -0.05)\), and semantic memory \((r = -0.14; 95\% \text{CI}, -0.23 \text{ to } -0.05)\) (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, 0.1-23.7) and a large amount of inconsistency were observed in cross-sectional but not in cohort studies.
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. 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. The associations, although small, were comparable in size and significance with other more commonly researched risk factors using meta-analysis.

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. 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.

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. 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. Other hypotheses suggest that the association may be mechanistic, for example, ARHL causing cognitive decline through impaired speech perception.

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. 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. 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. 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, 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. Of interest, vascular dysfunction has been associated with lower-frequency hearing loss and white matter hyperintensities. 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.

Future Directions
Cognitive decline is influenced by multiple modifiable health factors. Hearing loss may be another serviceable risk factor, because it is easily diagnosed and can be treated. Although associations were small, treatment may cumulatively benefit cognition as observed in intervention studies in older adults without cognitive impairment. This benefit was not observed in patients with dementia, but treatment may still reduce disability. Decline in lexical or semantic, episodic memory, and executive functions is used by clinicians as a marker for probable AD and vascular dementia. 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 (e.g., 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.

Increasing evidence suggests that ARHL is associated with a wide range of health issues, higher disease burden, and increased risk for hospitalization, leading to greater awareness of this condition as a critical public health concern. 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. The National Academies of Sciences, Engineering, and Medicine recently outlined several recommendations to address this issue, with implications for public health services and policy. Initiatives to expand access to treatment through screening programs, expand delivery of hearing services, and provide coverage for assistive hearing devices would be beneficial. In addition, primary health care clinicians would benefit from standard guidelines for screening and referring patients with hearing loss.

Strengths and Limitations
To 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 (e.g., 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. 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.