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Adult-onset hearing loss and incident cognitive impairment and dementia – A systematic review and meta-analysis of cohort studies

Ruan-Ching Yu, PhD[1](ruan-ching.yu.18@ucl.ac.uk), Danielle Proctor, MSc[2] (d.proctor@ucl.ac.uk), Janvi Soni, MSc[3] (159069226@aston.ac.uk), Liam Pikett, MSc[1] (l.pikett@herts.ac.uk), Gill Livingston, MD[1] (g.livingston@ucl.ac.uk), Glyn Lewis, MD[1] (glyn.lewis@ucl.ac.uk), Anne Schilder, MD[4] (a.schilder@ucl.ac.uk), Doris Bamiou, PhD[4] (d.bamiou@ucl.ac.uk), Rishi Mandavia, PhD[4] (rishimandavia@gmail.com), Rumana Omar, PhD[4] (r.omar@ucl.ac.uk), Menelaos Pavlou, PhD[5] (m.pavlou@ucl.ac.uk), Frank Lin, MD[6] (flin1@jhmi.edu), Adele M. Goman, PhD[7] (a.goman@napier.ac.uk), Sergi Costafreda Gonzalez, MD[1] (s.costafreda@ucl.ac.uk)

[1]Division of Psychiatry, University College London, 6th Floor, Maple House, 149 Tottenham Court Road, London W1T 7NF

[2]Department of Clinical, Educational and Health Psychology, University College London, Gower Street, London WC1E 6BT

[3]Royal Free London NHS Foundation Trust, Pond Street, Rosslyn Hill, London NW3 2QG

[4]The Ear Institute, University College London, 332 Grays Inn Rd, London WC1X 8EE

[5]Department of Statistical Science, University College London, Gower Street, London, WC1E 6BT

[6]Center on Aging and Health, Johns Hopkins Medical Institutions, 2024 E Monument St suite 2-700, Baltimore, MD 21205

[7]School of Health and Social Care, Edinburgh Napier University, 9 Sighthill Ct, Edinburgh EH11 4BN

Corresponding Author: Sergi Costafreda Gonzalez, s.costafreda@ucl.ac.uk, Division of Psychiatry, University College London, 6th Floor, Maple House, 149 Tottenham Court Road, London W1T 7NF

ABSTRACT

Background: We comprehensively summarized the cohort evidence to date on adult-onset hearing loss as risk factor for incident cognitive impairment and dementia, and examined the evidence for dose-response, risk for various dementia subtypes, and other moderators. Previous meta-analyses were less comprehensive.

Methods: We included cohort studies with participants without dementia and with hearing assessments at baseline, minimum 2 years follow-up and incident cognitive outcomes. We used random-effect models and subgroup and meta-regression on moderator analyses.

Results: We identified fifty studies (N=1,548,754). Hearing loss (yes/no) was associated with incident dementia risk (HR=1.35 [95% CI = 1.26 – 1.45), mild cognitive impairment (MCI HR=1.29 [95% CI = 1.11 – 1.50]), cognitive decline not specified as MCI or dementia (HR=1.29 [95% CI = 1.17 – 1.42]), and Alzheimer's disease dementia (ADD, HR=1.56 [95% CI = 1.30 – 1.87]), but not with vascular dementia (HR, 1.30 [95% CI = 0.83 – 2.05]). Each 10-decibel worsening of hearing was associated with a 16% increase in dementia risk (95% CI = 1.07 – 1.27). The effect of hearing loss did not vary across potential moderators.

Conclusions: Cohort studies consistently support that adult-onset hearing loss increases the risk of incident cognitive decline, dementia, MCI, and ADD.

Keywords: hearing loss, dementia, cognitive impairment, meta-analysis, moderators

INTRODUCTION

The World Health Organization estimates that 1.5 billion people worldwide are affected by hearing loss (Haile et al., 2021; McDaid et al., 2021), a number set to rise as the global population ages. The Lancet Commission on Dementia identified that hearing loss could be a modifiable risk factor for dementia (Livingston et al., 2017; Livingston et al., 2020) as it is associated with increased risk of cognitive impairment (MCI) and accelerated cognitive decline (Bucholc et al., 2022). This raises the possibility that treatments like hearing aids could potentially prevent or delay dementia (Yeo et al., 2023). The causal pathways might involve reduced social interaction or accelerated brain pathology (Ray et al., 2019). However, it is also possible that the observed association is not causal, but due to residual confounding from inadequately controlled factors like age or cardiovascular health.

Experimental evidence from randomized controlled trials is essential to establish causality, but the evidence to date has been limited and inconclusive. The ACHIEVE trial is the only large scale RCT with a cognitive outcome to date (Lin et al., 2023). ACHIEVE did not find evidence of benefit of hearing aid treatment on cognitive outcomes at three years in the whole sample, but a sub-sample of participants with higher baseline dementia risk did experience substantially reduced cognitive decline compared to those who received an educational intervention but no hearing aids.

Previous systematic reviews and meta-analyses of epidemiological studies on this topic (Supplementary Table 1) have shown varied results, partly due to differences in methodology. These systematic review also included cross-sectional studies, which do not address the sequence in which hearing loss and cognitive decline happen (Lau et al., 2022; Loughrey et al., 2018), not setting a minimal follow-up duration for cohort studies (Ford et al., 2018; Lau et al., 2022; Wei et al., 2018; Yuan et al., 2018), and combining studies reporting varying effect size measures (hazard ratios (HR), odds ratios (OR), risk ratio (RR))

despite their methodological differences (Ford et al., 2018; Liang et al., 2021; Livingston et al., 2017; Loughrey et al., 2018; Wei et al., 2018; Yuan et al., 2018; Zheng et al., 2017). Dementia is an umbrella term for several diseases affecting cognition (WHO, 2018). The most common is Alzheimer's disease (ADD), a brain degenerative disease caused by amyloid plaques and tau tangles. The second most common is vascular dementia, resulting from decreased brain blood flow (Livingston et al., 2020). So far, few have investigated whether hearing loss is associated with specific dementia subtypes (Ford et al., 2018; Liang et al., 2021; Loughrey et al., 2018; Zheng et al., 2017). Moreover, recent interest and research has expanded the available literature in this area, which earlier meta-analyses may not have included.

In light of these uncertainties, our systematic review aims to provide a comprehensive analysis of the existing epidemiological evidence to date, guided by the Bradford Hill criteria (Bradford et al., 1965; Fedak et al., 2015). This is a set of nine principles to help assess whether an observed association may be due to a causal relationship. We focused on the following four principles: the strength of the association (strength criterion) and the presence of a dose-response relationship (dose/response criterion), where greater hearing loss potentially leads to a higher risk of dementia. We also assessed the consistency of the evidence across different methods, populations, and outcomes between studies (consistency criterion). We incorporated an extensive analysis on different variables from cognitive impairment to dementia subtypes, methods of hearing assessments from self-report to the gold standard of pure tone audiometry (PTA) (Ramkissoon, 2011; Santana et al., 2011); and other variables like follow-up duration, use of hearing aids in the sample, baseline age, and cardiovascular risk factors. Moreover, to establish a clear sequence of events where hearing loss precedes dementia (temporality criterion), we only included cohort studies if they

excluded people who had dementia at baseline and followed them up for at least two years before cognitive outcome assessment.

METHODS

The protocol of this is systematic review was pre-registered on the international prospective register of systematic reviews PROSPERO (registration number: CRD42016048835) and followed standard guidelines for conducting and reporting systematic reviews, including Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Page et al., 2021).

Data sources and search strategy

We searched the following electronic databases starting from their inception up to March 20th, 2023: PubMed, Ovid Embase, PsycINFO, Web of Science, The Cochrane Library, and The Centre for Reviews and Dissemination (CRD). We used the search terms: "dementia" or "cognitive decline" or "Alzheimer's disease" or "mild cognitive impairment" AND "hearing" or auditory or aural or "presbycusis".

Inclusion criteria

We applied the following inclusion criteria:

- Prospective or retrospective cohort studies with a minimum follow-up period of 2 years.
- At baseline:
    - No diagnosis of dementia (except for studies that included dementia at baseline for other research purposes, such as dementia prevalence, and removed these participants from the dementia risk analysis).

  - Determination of hearing loss conducted at baseline by clinical diagnosis, PTA, a speech-based hearing tests (speech in noise testing, whisper test), or a self-report hearing questionnaire.
- During follow-up:
  - Diagnosis of incident dementia or incident cognitive decline based on operationalized criteria or clinical diagnosis based on internationally recognized criteria, such as Diagnostic and Statistical Manual of Mental Disorders (DSM) or ICD.
  - The studies reported a measure of risk association between adult-onset hearing and incident cognitive outcomes, adjusted at least by age.

Study selection

We exported the searches to Endnote and eliminated duplicates. Five authors - DP, LP, JS, R-CY, and SCG, independently screened the titles and abstract of retrieved articles, and evaluated the full text, to determine their eligibility for inclusion. Disagreements were resolved through discussion. We contacted the authors of five publications to obtain further details regarding eligibility criteria. Of these, four provided further information so their studies were included in the meta-analysis. One author did not respond, this study was not included.

Data extraction and quality assessment

Four authors (DP, LP, JS, and R-CY) extracted data from each included paper using a data extraction excel form. Data were extracted on: number of participants at baseline, demographics (age, sex, education, country), methods of hearing assessment, proportion of population with hearing loss and hearing aid users, number of follow-up years, cognitive

outcomes (dementia and its subtypes, MCI, or cognitive decline not specified as MCI or dementia), and adjustment variables in the models (age, sex, education, cardiovascular factors, and other factors). Disagreements were resolved through discussion.

Five authors (DP, LP, JS, R-CY, and SCG) independently assessed the quality of studies using the Mixed Methods Appraisal Tool (MMAT) diagnostics criteria (Nha Hong et al., 2018) (see Supplementary Table 3 for MMAT details for this study).

Data selection and synthesis

We selected only one effect measure per study in each subgroup, thereby avoiding the potential bias introduced by "double counting" study findings. When a study reported several effect measures, we prioritized outcomes that were maximally adjusted for co-variates, those with the longest follow-up period, and those based on PTA (rather than self-report or other methods). For studies presenting effect measures across different subgroups (e.g., participants with or without depression (Powell et al., 2022)), we combined these effect measures into an overall pooled estimate using random effects meta-analysis, and then this pooled estimate was integrated into the overall meta-analyses. Finally, the goal of our study was to assess the link between hearing loss and dementia, but there is evidence that treated hearing loss may not confer such risk; we therefore excluded from the main analysis studies with more than 50% hearing aid users (Yeo et al., 2023).

Statistical analysis

We used random-effects meta-analyses to calculate pooled estimates of association between hearing loss and incident cognitive outcomes and corresponding 95% confidence intervals. We used the I^2 statistic to describe heterogeneity between studies (Lin et al., 2020). We computed separate pooled estimates for the following effect measures: (1) HR, (2) OR,

(3) RR because these measures are different in definition, computation, and interpretation (George et al., 2020). We computed separate pooled estimates for studies where hearing was categorized as normal hearing versus different degrees of hearing impairment, and those that categorized it per 10-decibels of hearing level [10-dB HL]. We meta-analyzed according to cognitive outcomes: (1) incident dementia, (2) incident MCI, (3) incident cognitive decline not specified as MCI or dementia (4) incident ADD, (5) incident VaD.

We conducted subgroup and moderator analyses comprising: mean age of the cohort participants at baseline (≥ 65 and < 65 years, with the total age range among studies being 40 to 83 years), length of follow-up (2 to 6 years, > 6 to 10 years, and > 10 years), whether the findings were adjusted by (a) cardiovascular risk factors, (b) a measure of education or premorbid cognitive function, PTA vs non-PTA studies, and severity of hearing loss (mild and moderate-severe, as defined by each study). We conducted meta-regressions for continuous variables: average age at baseline, sex, and the length of follow-up in years.

We used visual inspection of funnel plots of study effect measures versus precision to assess evidence for publication bias on subgroups with at least 10 studies based on Cochrane Library's guidelines (Page et al., 2023). We reported Egger's test, with $p < 0.05$ for the slope coefficient indicating significant asymmetry. We used R software (version 4.3.1), and applied the function 'metagen' (package 'metafor' (Viechtbauer, 2010)) for meta-analyses and function 'metareg'(package 'meta' (Schwarzer, 2023)) for univariable meta-regression.

RESULTS

Study characteristics

We identified 50 studies in the systematic review (Table 1, Figure 1 for PRISMA diagram and Supplementary Table 5 for PRISMA checklist). Most studies were prospective (37 out of 50, or 74%), and 24 studies were conducted in the US (48%), 10 in Europe, 5 in

Australia, 11 in East Asia (Supplementary Table 2). Regarding determination of hearing, 24 (48%) studies used self-reported questionnaires, 15 (30%) studies used PTA and one used a screening audiometer (Lin et al., 2004), 9 used clinical diagnoses, and other less frequently used methods included the whispered voice test (2 studies, Heywood et al., 2017; Rolandi et al., 2020), and dichotic digits test (1 study, Stevenson et al., 2022).

Quality assessment using the MMAT (Nha Hong et al., 2018), was based on 5 indicators: (i) representativeness of the sample, (ii) appropriateness of outcome and exposure measurements, (iii) completeness of outcome data, (iv) accounting of confounding and (v) exposure occurrence during the study (details in Supplementary Table 3); 23 studies (46%) met at least four out of these quality criteria, while 12 studies (24%) met only two of the five criteria, and no study met less than two criteria (Supplementary Table 4).

Among the included studies, 39 studies reported the effect measures using HR, nine used OR, four used RR, four used HR in per 10-dB HL, one used OR and RR in per 10-dB HL, respectively. Incident dementia was reported as an outcome in 33 studies, cognitive decline in 16 studies, MCI in 3 (Heywood et al., 2017; Strutt et al., 2022; Vassilaki et al., 2019) , Alzheimer's disease dementia (ADD) in 5 and Vascular dementia (VaD) in 3 (Golub et al., 2017; Hwang et al., 2020, 2022), with some studies reporting more than one outcome. We conducted separate meta-analyses for each combination of effect measure and cognitive outcome, with moderator analyses restricted to the 37 studies (excluding two studies with more than 50% hearing aids users; Bucholc et al., 2022; Marinelli et al., 2022) that reported HR as the effect measure for the association between hearing loss as a yes/no variable and any incident cognitive impairment.

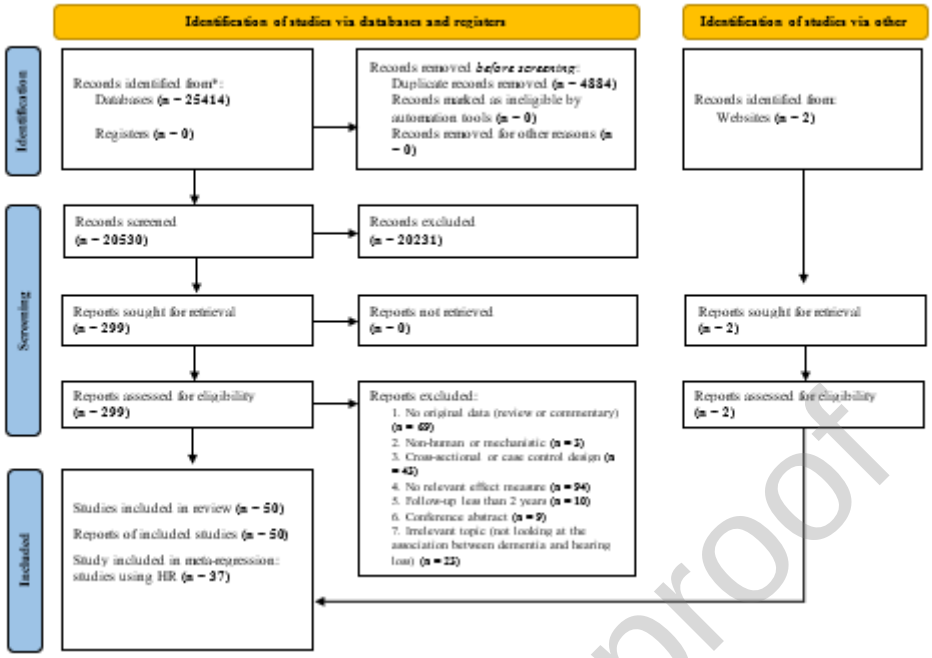

Figure 1: PRISMA diagram

Table 1. Characteristics of the studies included (in alphabetical order by first author)

First author & year	Number of people at baseline	Drop-out rate (%)	Mean age	Sex (number of females)	Education (level or mean years)	Hearing assessment	Number with baseline HL	HA users at baseline	Follow-up years	Outcome subtypes	Number who develops CI (%)	Adjusted factors				
												A	S	E	C	O
Amieva et al (2018)	3588	NR	75	2075 (58%)	2344 school certificate	self-report	1289 (36%)	176 (14%)	up to 25 years	Dementia	876 (24%)	✓	✓	✓	✓	✓

Beason-Held et al., (2022)	1234	NR	82	463 (38%)	NR	ICD-9	NR	NR	5 years	ADD, VaD	357 (29%)	✓	✓			✓
Brenowitz et al., (2019)	1810	NR	77	938 (52%)	1438 high school	PTA	1344 (75%)	237 (18%)	> 10 years	Dementia	336 (19%)	✓	✓	✓	✓	✓
Brewster et al., (2021a,b)	8529	NR	74	5412 (64%)	16 years	self-report	2051 (24%)	1102 (54%)	6 years (mean)	Dementia, CD	498 (6%)	✓	✓	✓		✓
Bucholc et al., (2022)	4358	NR	69	2994 (69%)	16 years	self-report	450 (10%)	313 (70%)	4 years	MCI	416 (10%)	✓	✓	✓	✓	✓
Byeon et al., (2021)	6520	around 49%	70	3709 (57%)	1158 university	self-report	NR	NR	6 years	Dementia	245 (4%)	✓	✓	✓	✓	✓
Chen et al., (2019)	6309	NR	83	3112 (49%)	3179 >1 year education)	self-report	2562 (41%)	NR	6 years	CD	1936 (31%)	✓	✓	✓	✓	✓
Chen (2021)	10341	NR	79	5093 (49%)	5041 literate	self-report	995 (10%)	NR	6 years (median)	CD	2614 (25%)	✓	✓	✓	✓	✓
Chern et al., (2022)	206 801	NR	69	117 407 (57%)	NR	ICD-9 and ICD-10	56523 (57%)	1265 (2%)	6 years (mean)	Dementia	8269 (4%)	✓	✓		✓	✓
Deal et al., (2019)	154 414	NR	64	74464 (48%)	124749 some college	ICD 9-CM	77207 (50%)	NR	up to 10 years	Dementia	2499 (2%)	✓	✓		✓	✓
Deal et al., (2017)	1889	NR	76	996 (53%)	920 post-secondary	PTA	1103 (58%)	240 (22%)	6 years	Dementia	229 (12%)	✓	✓	✓	✓	✓
Fischer et al., (2016)	1884	NR	67	1113 (59%)	697 post-secondary	PTA	826 (44%)	NR	10 years	CD	187 (10%)	✓	✓	✓	✓	✓

Ford et al., (2018)	37898	NR	73	0	NR	ICD 8 - 10	1420 (4%)	NR	11 years (mean)	Dementia	6948 (18%)	✓			✓	✓
Fritze et al., (2016)	154783	NR	NR	92161 (60%)	NR	ICD-10	70294 (45%)	NR	2-6 years	Dementia	14602 (9%)	✓	✓		✓	✓
Gates et al., (1996)	1509	NR	72	NR	NR	PTA	NR	NR	6 years	Dementia	41 (3%)	✓				
Amin Gharbi-Meliani et al., (2023)	15278	NR	65	8323 (55%)	2943 tertiary education	self-reported	NR	NR	13 years	Dementia	535 (4%)	✓	✓			
Golub et al., (2017)	1881	NR	76	1308 (70%)	10 years	self-reported	204 (11%)	75 (37%)	7 years (mean)	ADD, VaD	377 (20%)	✓	✓	✓	✓	✓
Gurgel et al., (2014)	4463	2%	75	2543 (57%)	13 years	self-reported	836 (19%)	NR	5.8 years (mean)	Dementia	575 (13%)	✓	✓	✓	✓	✓
Heywood et al., (2017)	1515	around 26%	>55	988 (65%)	658, <6 years education	whispered voice test	32 (2%)	NR	3.8 years (median)	CD, MCI	155 (MCI), 11 (1%, dementia)	✓	✓	✓	✓	✓
Hong et al., (2016)	1352	NR	NR	NR	NR	PTA	303 (17%)	NR	10 years	CD	167 (12%)	✓	✓		✓	
Hwang et al., (2020)	2051	6%	79	905 (44%)	14 years	self-reported	161 (8%)	NR	8 years	Dementia,ADD, VaD	321 (16%)	✓	✓	✓	✓	✓
Hwang et al., (2022)	2254	NR	75	1704 (58%)	703 college graduate	self-reported	311 (11%)	NR	8 years	Dementia	307 (11%)	✓	✓	✓	✓	✓
Karpa et al., (2010)	2815	25%	67	1597 (57%)	NR	PTA	929 (33%)	NR	5 years	CD	79 (3%)	✓	✓			

Kim et al., (2018)	26950	NR	> 40	12180 (45%)	NR	ICD 10	5390 (20%)	NR	7.9 years (mean)	Dementia	1789 (7%)	✓	✓		✓	✓
Kojima et al., (2022)	53549	NR	74	29015 (54%)	261330, >10 years education	self-reported	4039 (8%)	NR	6 years	Dementia	6013 (11%)	✓	✓			
Kuo et al., (2021)	7562	NR	41% > 80 years old	4411 (58%)	1671, < high school	self-reported	1664 (22%)	NR	4 years (median)	Dementia	1572 (21%)	✓	✓	✓	✓	✓
Lavrencic et al., (2022)	155	37%	66	96 (62%)	10 years (no CD), 8 years (CD)	previous medical history	32 (21%)	NR	6.2 years (mean)	CD	36 (23%)	✓				
Lin et al., (2011)	639	NR	NR	279 (44%)	NR	PTA	184 (3%)	58 (32%)	12 years (median)	Dementia	58 (9%)	✓	✓	✓	✓	✓
Lin et al., (2013)	1626	NR	NR	NR	967, ≥ some college	PTA	1162 (72%)	257 (22%)	6 years	CD	609 (38%)	✓	✓	✓	✓	✓
Lin et al., (2004)	1333	NR	76	1333 (100%)	NR	PTA Screening audiometer	NR	NR	4 years	CD	960 (72%)	✓		✓	✓	✓
Luck et al., (2020)	3027	NR	80	1970 (65%)	329, higher education	self-reported	924 (31%)	NR	13 years	Dementia	704 (23%)	✓				
Maharani et al., (2020)	19618	NR	58	10871 (55%)	9675, > some college	self-reported	2532 (13%)	NR	18 years	Dementia, CD	951 (5%)	✓	✓	✓	✓	✓
Marinelli et al., (2022)	1159	3%	76	607 (52%)	886, <16 years	PTA	763 (64%)	492 (65%)	7 years	Dementia	207 (18%)	✓	✓	✓	✓	✓
Maruta et al.,	2190	NR	79	1738	NR	self-reported	961 (21%)	NR	8 years	Dementia	1153 (53%)	✓	✓			✓

(2020)				(79%)											
Mohammed et al., (2022)	280	5%	80	177 (63%)	144, < 16 years	PTA	121 (43%)	NR	8 years (mean)	Dementia, ADD	89 (32%)	✓		✓	
Myrstad et al., (2023)	7135	NR	57	3943 (55%)	1447, primary school only	PTA	1058 (15%)	NR	22 years (mean)	Dementia, ADD	1089 (15%)	✓	✓	✓	✓	✓
Osler et al., (2019)	658465	NR	59	0 (0%)	NR	PTA	59834 (9%)	NR	7 years (mean)	Dementia	9114 (1%)	✓		✓	✓	✓
Pabst et al., (2021)	3497	NR	80	2349 (67%)	1207, ≥10 years	self-reported	1061 (30%)	NR	7 years (mean)	Dementia	902 (26%)	✓	✓	✓	✓	✓
Powell et al., (2022)	2408	7%	74	1072 (45%)	1136, > secondary edu	PTA	1495 (62%)	NR	8 years	Dementia	223 (9%)	✓	✓	✓	✓	✓
Rolandi et al., (2020)	1100	NR	70 - 74	589 (54%)	617, <5 years	whispered voice test	139 (13%)	NR	7 years	Dementia	111 (10%)	✓				✓
Schubert et al., (2019)	2556	NR	49	1401 (55%)	918, > 16 years	PTA	332 (13%)	NR	10 years	CD	89 (4%)	✓	✓	✓		✓
Stevenson et al., (2022)	82039	NR	64	42772 (52%)	18160, no secondary edu	digit triplets test	14394 (18%)	1844 (13%)	10 years (median)	Dementia	1285 (2%)	✓	✓	✓	✓	✓
Strutt et al., (2022)	529	5%	79	NR	12 years (mean)	self-reported	397 (40%)	111 (28%)	6 years	Dementia, MCI, CD	216 (40.8%)	✓	✓	✓	✓	✓
Su et al., (2017)	8121	NR	69	3171 (39%)	NR	Clinical diagnosis	4108 (51%)	NR	up to 10 years	Dementia	869 (11%)	✓	✓		✓	✓
Sugiura et al., (2022)	1193	NR	72	533 (45%)	494, ≤9 years	PTA	582 (49%)	6%	up to 10 years	CD	525 (44%)	✓	✓	✓	✓	✓

Tai CJ et al., (2021)	1418	NR	74	558 (39 %)	34, > college	self-reported	709 (50 %)	83 (12 %)	9 years	CD	1018 (72 %)	✓	✓		✓ ✓
Tai SY et al., (2021)	14900	NR	52	6933 (46.5%)	NR	ICD-9	3725 (25 %)	NR	5 years (mean)	Dementia	442 (3%)	✓	✓		✓ ✓
Tomata et al., (2020)	9017	NR	72	4968 (55 %)	4743, low education	self-reported	748 (8%)	NR	<16 years	Dementia	1950 (22 %)	✓	✓	✓	
Vassilaki et al., (2019)	4812	7%	74	2333 (49 %)	14 years (mean)	self-reported	981 (20 %)	NR	5 years (mean)	MCI and Dementia	1032 (21 %)	✓	✓	✓	

Adjusted factors: A, age; S, Sex; E, education; C, cardiovascular factors; O, other factors not included in the four categories; ADD, Alzheimer's disease dementia; CD, cognitive decline; HA, Hearing aids; ICD, International Classification of Diseases; VaD, Vascular dementia; PTA, Pure-tone assessment; MCI, mild cognitive impairment; NR = Not reported. P, prospective design; R, retrospective design.

Meta-analyses of incident cognitive outcomes

Presence of hearing loss as a dichotomic yes/no variable was associated with a range of incident cognitive outcomes (Table 2, Figure 2) including increased hazard ratio of incident dementia (Table 2, HR = 1.35 [1.26-1.45], based on k = 30 studies), MCI (1.29 [1.11-1.50], k = 3, Heywood et al., 2017; Strutt et al., 2022; Vassilaki et al., 2019), cognitive decline not specified as MCI or dementia (1.29 [1.17-1.42], k = 9), and Alzheimer's disease (HR = 1.56 [1.30-1.87], k = 4), whilst the association with vascular dementia was not statistically significant (HR = 1.30 [0.83 – 2.05], k = 3, Golub et al., 2017; Hwang et al., 2020, 2022).

For studies that reported their findings as odds ratios (OR, Table 2) presence of hearing loss was associated with increased risk of MCI or dementia (OR = 1.42 [1.05 – 1.91], k = 5), whilst the association with dementia only was not statistically significant (OR = 1.52 [0.86-2.70], k = 3, Beason-Held et al., 2022; Brewster et al., 2021; Byeon et al., 2021). Pooling of two studies that reported risk ratios for dementia did not reveal a statistically

significant association (RR = 1.20 [0.67-2.16], k = 2, Table 2, Deal et al., 2019; Gates et al., 1996), and another isolated study did not find a statistically significant association for cognitive decline not specified as MCI or dementia (RR = 0.93 [0.63-1.37], k = 1, Schubert et al., 2019).

Two studies investigated how dementia risk changes with every 10 dB decrease in hearing ability, and found increased hazard ratios for dementia (HR = 1.16 [1.07-1.27], k = 2, Table 2, Figure 3, Deal et al., 2017; Lin et al., 2011). Additionally, individual studies reported increased risk of incident cognitive impairment when using hazard ratios (HR = 1.07 [1.01-1.14], k = 1, Lin et al., 2013) and odds ratios (OR = 1.36 [1.21-1.53], k = 1, Sugiura et al., 2022) and dementia when using risk ratios (RR = 1.04 [1.00-1.09], k = 1, Myrstad et al., 2023). We found varying degrees of residual heterogeneity in these meta-analyses, ranging from 0% to 93% for different meta-analyses (Figures 2 and 3).

Figure 2. Meta-analysis of the association between hearing loss as a yes/no variable and dementia, MCI, cognitive decline not specified as dementia or MCI, Alzheimer's disease dementia, and vascular dementia

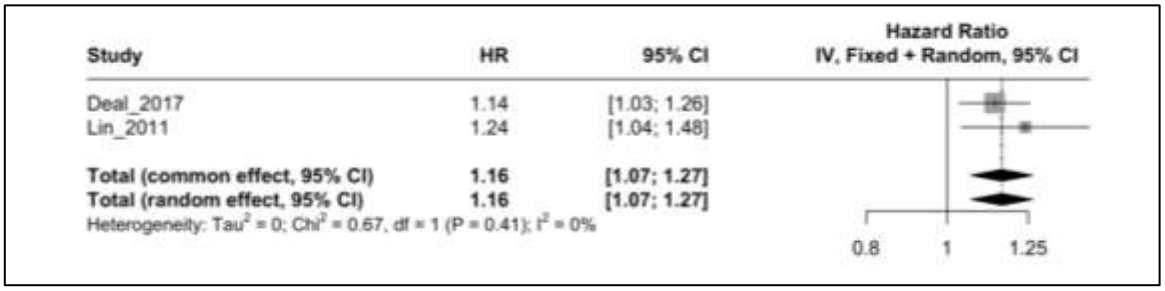

Figure 3. Meta-analysis of the association between change per 10 dB (HR) of hearing loss and dementia

Table 2. Summary of effect sizes across cognitive outcomes

Outcome	HL vs non-HL			Per 10 dB
	HR	OR	RR	HR
Dementia	1.35 [1.26-1.45] k = 30	1.52 [0.86-2.70] k=3	1.20 [0.67-2.16] k=2	1.16 [1.07-1.27] k = 2
Cognitive decline (not specified as MCI or dementia)	1.29 [1.17-1.42] k = 9	1.42 [1.05-1.91] k = 5	-	-
MCI	1.29 [1.11-1.50] k=3	-	-	-
ADD	1.56 [1.30-1.87] k=4	-	-	-
VaD	1.30 [0.83-2.05] k=3	-	-	-

* Numbers in bold indicate a significant outcome; ADD; Alzheimer's disease dementia; HL, hearing loss; HR, hazard ratio; MCI, mild cognitive impairment; OR, odds ratio; RR; risk ratio; VaD, vascular dementia. For clarity, cells with only 1 study have been omitted.

Moderator analyses

We conducted moderator analyses on 37 studies that reported HR. None of the factors investigated moderated the relationship between hearing loss and any type of incident cognitive impairment, including the age at baseline of the study participants, the type of hearing assessment, the length of follow-up or whether the analysis was adjusted by a

measure of baseline cognitive state or vascular factors (Figure 4, Supplementary Figures 1 - 6).

Regarding hearing severity, both mild (HR = 1.27 [95% CI: 1.05-1.53]) and moderate to severe hearing loss (HR =1.69 [95% CI: 1.29-2.22]) were associated with increased dementia risk, but the degree of hearing loss did not moderate the relationship between hearing loss and dementia risk (p = 0.09, Figure 4, Supplementary Figure 6).

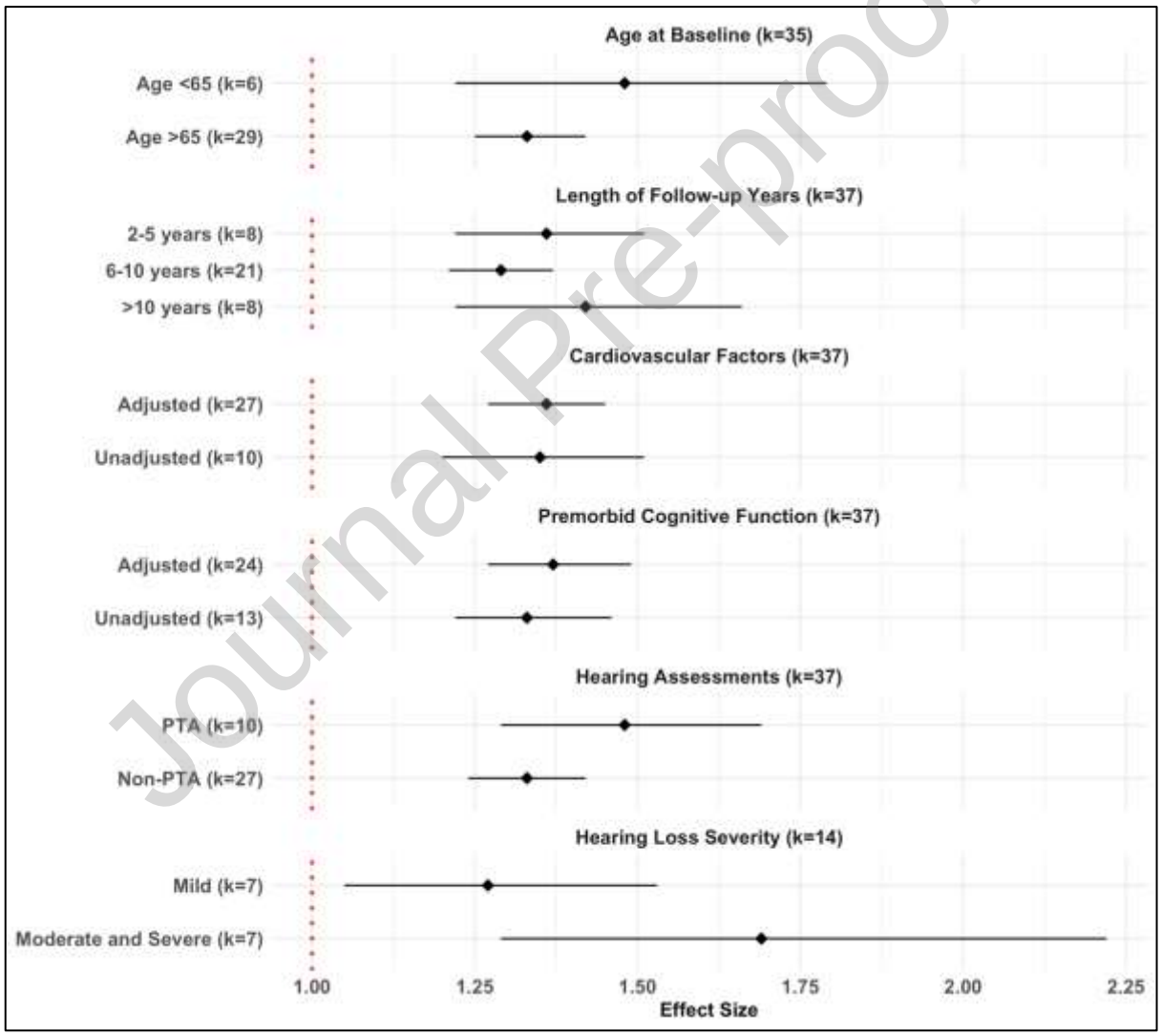

Figure 4 Moderator analyses of the association between adult-onset hearing loss and any incident cognitive outcome (studies reporting HR, k=37)

Meta-regression analyses did not reveal any statistically significant effect of the number of follow-up years, the proportion of the sample who were female, or the average age of the sample at baseline (Table 3).

Table 3. Meta-regression analyses of the association between adult-onset hearing loss and any incident cognitive outcomes (studies reporting HR, k=37) results

Moderator	Number Studies	Estimate [95% CI]	p-value	I^2
Proportion of Sample Female	37	-0.333 [-0.675,0.008]	0.0558	63%
Age at baseline	33	-0.007 [-0.014, 0.002]	0.1114	68%
Follow-up years	37	-0.004 [-0.017, 0.009]	0.5520	70%

Publication bias

We examined the publication bias by graphical analyses through funnel plots, which revealed dispersion of study findings but no evidence of systematic asymmetry on examination (Supplementary Figure 7); Egger's test for publication bias was also not statistically significant for HR in the studies of dementia (p = 0.77, k = 30) and cognitive decline not specified as dementia or MCI (p = 0.12, k = 9), the remaining subgroups were excluded from the analysis of publication bias due to a small number of studies included.

DISCUSSION

This meta-analysis is the most extensive to date with fifty cohorts reporting on a total sample of 1,548,754 participants. We found that hearing loss as a yes-no variable was consistently associated to increase risk for a range of clinically relevant cognitive outcomes, including dementia, MCI and Alzheimer's disease, whilst the association with vascular dementia was not statistically significant. Only three studies (Beason-Held et al., 2022;

Golub et al., 2017; Hwang et al., 2020) specifically looked at the association between hearing loss and vascular dementia, thus resulting in limited statistical power. Two of the three studies also adjusted for cardiovascular factors, which may have diluted the association (Golub et al., 2017; Hwang et al., 2020).

The magnitude of the increased risk for dementia that we report for hearing loss as a yes-no variable (1.35 [1.26-1.45], k = 30) is in line with previous meta-analyses (OR, 1.28 [1.02-1.59], k = 3) (Loughrey et al., 2018) and overlapping but on the lower end of the confidence interval of the effect reported by the 2017 Lancet commission (1.9 [1.4-2.7]; k = 3) (Livingston et al., 2017). These previous meta-analyses relied on a substantially smaller sample of studies, so the findings from our updated meta-analysis should be more robust.

Our findings provide support to the possibility of a causal relationship between adult-onset hearing loss and dementia. First, our results are overall consistent in that despite heterogeneity between studies in population, methodology, and type of incident cognitive outcome, most of the meta-analyses we conducted identified a statistically significant increase in risk across effect measures and cognitive outcomes, and even for those that were not significant, the magnitude of the effect consistently pointed towards risk increase (Figures 2 and 3, Table 2).

Second, we found evidence of a dose-response relationship. Both mild hearing loss and moderate-severe hearing loss were associated with increasing dementia risk, although the difference in risk increase by degree of hearing loss was not statistically significant. We found a statistically significant association between every 10 dB decrease in hearing ability and increased dementia risks. Taken together, these findings are consistent with a dose response between degree of hearing loss and dementia risk.

Third, our meta-analysis supported an appropriate temporal sequence between hearing loss and dementia by excluding studies with participants who already had dementia at

baseline, and excluding studies with less than two-year follow-up between hearing loss and subsequent dementia. However, dementia has a long prodrome of several years so reverse causality cannot be completely excluded. To further investigate this issue, we tested whether length of study follow-up was associated with the magnitude of the association between hearing loss and dementia, but found no statistically significant effect.

Additionally, there is separate evidence that treating hearing loss with hearing aids may mitigate this association. A meta-analysis on the effects of hearing aids and cochlear implants on the risk of future dementia found that hearing aid use was associated with 19% reduction in long-term incidence of cognitive decline relatively to uncorrected hearing (Yeo et al., 2023). There is one large-scale randomized trial, ACHIEVE, which has investigated the effect of hearing intervention on reducing cognitive decline in older adults. ACHIEVE randomized 977 people aged 70 to 84 years to hearing aids or an educational health intervention. No effect of hearing intervention on reducing cognitive decline was seen in the total cohort, but a substantial 48% reduction in cognitive decline was observed in a cohort of participants who had been recruited from a long-running population-based cohort and who had more baseline risk factors for cognitive decline and dementia (Lin et al., 2023; Livingston & Costafreda, 2023). This was a pre-planned but secondary analysis, and we therefore need to see if further RCTs to replicate this effect in people at higher risk for dementia.

In terms of limitations, our systematic literature search identified a large number of studies, but these were heterogeneous in samples, methods of assessment of hearing and cognitive outcomes, duration of follow-up and methods of analysis. We addressed this heterogeneity by conducting separate meta-analyses depending on cognitive outcomes and effect measures, and by conducting extensive moderator analyses. We identified moderate to substantial residual heterogeneity in the meta-analyses (Figures 2 and 3), but found no

evidence that any of the potential moderating factors (the type of hearing assessments, the length of follow-up year, adjustment on cardiovascular risk factors, premorbid cognitive function, the severity of hearing loss, the age group of participants at baseline, and when age and gender proportion at baseline) had a statistically significant effect on the magnitude of the association or explained a significant amount of the heterogeneity. It is possible that this residual heterogeneity could be explained through other moderating or confounding factors that were not included in our analyses or adequately reported by the primary studies.

In conclusion, this meta-analysis of cohort studies provided compelling evidence across diverse study settings and designs of adult-onset hearing loss being a robust and consistent independent risk factor for dementia. Adult-onset hearing loss is also potentially treatable, most often with hearing aids. Our findings suggest that this treatment may also reduce dementia risk.

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DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available within the article and its supplementary material.

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AUTHORS' CONTRIBUTIONS

Sergi Costafreda Gonzalez, Gill Livingston, Anne Schilder conceptualized and designed the study. Rumana Omar and Menelaos Pavlou wrote the statistical analysis plan and checked the main results. Ruan-Ching Yu, Danielle Proctor, Janvi Soni, Liam Pikett, and Sergi Costafreda Gonzalez prepared (searching, screening, retrieving, and maintaining the research data) and scored the included articles. Ruan-Ching Yu analysed the data, visualised the results, interpreted the results and wrote up the original draft. Sergi Costafreda Gonzalez, Gill Livingston, Anne Schilder, Danielle Proctor, Janvi Soni, Liam Pikett, Glyn Lewis, Doris Bamiou, Rishi Mandavia, Rumana Omar, Menelaos Pavlou, Frank Lin, and Adele Goman reviewed, and edited the manuscript.

CONFLICT OF INTEREST AND DISCLOSURE STATEMENT

None of the authors have any financial or other conflicts of interest to disclose.

Highlights:

- We summarize evidence on adult-onset hearing loss as a risk factor for dementia
- Hearing loss increases risk of incident cognitive impairment, dementia, and Alzheimer's disease
- Risk of dementia increases by 16% for each 10-decibel worsening of hearing.
- The impact of hearing loss on dementia does not vary across dementia subtypes or other moderators.