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Title Page

Title: Age Related Hearing Loss and Mild Cognitive Impairment: A Meta- analysis and systematic review of Population Based Studies

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Abstract

Background: The aim of this study is to identify any relationship between hearing loss(HL) and mild cognitive impairment(MCI).

Methods:

- *Design:* Systematic review and meta-analysis of randomised control trials.
- *Data:* MEDLINE and the Cochrane Library up to 24/6/2020.
- *Study Selection:* Prospective, cohort and cross-sectional, observational studies that reported on the relationship between MCI and HL.

Findings: A total of 34 studies reporting data on 48,017 participants were included. Twenty-three studies observed a significant association between HL and MCI. The pooled RR across all studies of *prevalence* of MCI in people with HL was 1.44(random-effects, 95%CI 1.27-1.64, p<0.00001, I^2=0%). Significantly more people with MCI had peripheral HL compared with those without(RR=1.40 random-effects, 95%CI 1.10-1.77, p=0.005, I^2=0%). When the *incidence* was studied, significantly more people with peripheral HL had MCI compared with those without(RR=2.06, random-effects, 95%CI 1.35-3.15, p=0.0008, I^2=97%); however; a high level of statistical heterogeneity was evident.

Interpretation: Most of the studies included in this systematic review observed a significant association between HL and MCI.

Keywords

Hearing loss, Mild cognitive impairment, Dementia, Presbycusis

Introduction

Age-Related Hearing Loss (ARHL) is a decrease in hearing ability that happens with age and is a common sensory abnormality of the elderly. According to the World Health Organisation, 466 million adults globally, amongst whom nearly one in three people aged over 65 years, live with disabling hearing loss (HL)(1). Hearing impairment not only affects interpersonal communication but also health, independence, wellbeing, quality of life and daily function and can lead to social isolation, depression and early mortality(2–5). In recent years there has been a growing speculation about the association between cognitive decline and ARHL(6). Uhlmann et al. (1989) were amongst the first to find that HL was a strong, independent risk factor for cognitive decline(7). However, other studies have contested this association(8,9).

A recent Commission document by Lancet postulated that HL in mid- and later life is associated with increased risk of dementia(10). Dementia is the loss of cognitive functioning and behavioral abilities to such an extent that it interferes with a person's daily life and activities. The aim of the present study is to identify any relationship between HL and a prodromal state of dementia, or mild cognitive impairment (MCI). Establishing such an association would strengthen the case for a relationship between hearing impairment and dementia, and focus intervention development to an earlier stage. Mild Cognitive Impairment is an intermediate state between normal cognitive functioning and development of dementia(11,12). Individuals with MCI have slight impairment in cognitive function with otherwise normal function in the performance of activities of daily living(13). They are at a significantly elevated risk of developing

dementia during their lifetime, which is estimated to be around 80%(14).

Hearing impairment can be either peripheral or central(3). The peripheral hearing system consists of the peripheral components of hearing (including the cochlea) whereas the central hearing system encompasses the central auditory pathways and influences the way incoming auditory stimuli are perceived and understood (central auditory processing). The key symptom of central HL is an inability of the individual to understand speech in a noisy environment(15), particularly if peripheral hearing (the ability to hear in quiet) remains relatively normal. In the present review article, we include studies that have assessed the link between both types of HL with early dementia.

Methods

The systematic review was undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)(16).

A systematic computer-based literature search was performed on the biomedical bibliographic databases: MEDLINE and Cochrane library. The search was done on the 24/06/2020 and run from database inception. A copy of the search strategy is presented in Appendix 1. The protocol for this systematic review has been deposited in the PROSPERO international prospective register of systematic reviews (ID: CRD42017076183) and can be accessed at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=76183

Inclusion and exclusion criteria

The inclusion and exclusion criteria for the population of interest, outcomes and study design are presented in Table 1.

Data analysis

Three authors (KL, PD and CM) independently selected studies, extracted data and assessed the quality of included studies. Data were extracted from each study and included information on the article identification, year of publication, population (continent), matching for covariates between groups, evaluation period (for longitudinal studies), number of patients per group, hearing and cognition assessment methods, number of male subjects and mean age of subjects. Where data were missing, the corresponding authors of the articles were approached by emails.

The quality assessment of the cohort studies included in the meta-analysis was done using the Newcastle–Ottawa scale(17).

Statistical Analyses

The meta-analysis was undertaken using Cochrane RevMan software (version 5.3). Outcomes reported as dichotomous were estimated as risk ratios (RRs) with associated 95% CI. Where studies did not report participant numbers, but an effect size with 95% CI, these were pooled in RevMan using the generic inverse variance (IV) method. Random-effects models were applied. Effect estimates (estimated in RevMan as Z-scores) were considered significant at $p<0.05$. Statistical heterogeneity was assessed using the I-squared (I2) statistic. Where data were not suitable for pooling in a meta-analysis, a narrative synthesis using tables and text was reported.

Results

The electronic searches identified 521 unique citations. One additional citation was provided by a clinical expert. Of these, 465 were excluded based on their title and abstract. Of 56 citations obtained as full-text, 22 were excluded(18,19,28–37,20,38,39,21–27). Details of the studies excluded at full-text are presented in Table 2.

Thirty-four studies, reporting on 48,017 participants, fulfilled the inclusion criteria and were included in the systematic review. Eighteen of these studies were eligible for and were included in the meta-analysis. A PRISMA flowchart of the study selection process is shown in Figure 1.

(Figure 1)

The characteristics of the included studies are shown in Table 3.

These studies were published between 1986 and 2019 and conducted in America, Asia, Australia, Africa and Europe. Ten of them were cohort(40–49) and twenty-three were cross-sectional studies(7,50,59–68,51,69–71,52–58), and one study was both a cross-sectional and cohort study(72). Recruited participant numbers ranged from 20(70) to 13,731(46). The results of the quality assessment are presented in Table 4. All of the cohort studies scored more than 6 stars (out of a total of 9 stars).

Hearing Assessment

Most of the studies used Pure Tone Audiometry (PTA) as the main auditory assessment method which measures hearing sensitivity. Self-reported or assessor-reported HL was used by 10 studies(41–44,46,48,51,64,71,72) and in one paper the assessment method was not reported(50). Some studies used central auditory function tests, such as dichotic

digits test, speech audiometry, synthetic sentence identification with ipsilateral competing message etc(7,49,56,59,61–63,65,68,70). The definition of HL from the World Health Organisation(73) was used by most studies, but the frequencies tested ranged: 500 to 4000Hz(45,47,54,55,57,60,66), 1000 to 4000 Hz(67), 250 to 2000 Hz(58), 500 to 3000Hz(7). One study used the hearing threshold at 4kHz only to separate the different groups of HL(68).

Cognitive Assessment

The cognitive assessment tool that was used by most researchers was the Mini Mental State Examination (MMSE)(7,40,59,60,62,64,66,71,72,42,46,47,49,50,53,54,58) or its modified version, the Modified Mini Mental State (3MS)(45,48,70). A score below 24 on MMSE(74) was considered abnormal by most studies(7,40,46,47,53,58,66). The cut-off score was 27 in two studies(71,72). In another study MMSE score thresholds were adjusted for education level(50). Other cognitive assessment tests used included the Montreal Cognitive Assessment (MoCA)(53,56), Cognitive Drug Research Computerised Assessment System(55), verbal fluency(42,55,57,64), National Adult Reading Test(55), Delayed Word Recall Test(57), Digit Symbol Substitution Test(57), Wechsler Adult Intelligence Test(58), Clinical Dementia Rating Scale(44,59,72), Frontal Assessment Battery(59), Free and Cued Selective Reminding Test(60), Trail making A&B(40,42,60,63,64), Rey Osterrieth Complex Figure - Recall test(42), Stroop, Letter and category fluency(60,63), American Version of the Nelson Adult Reading Test(60), Abbreviated Memory Inventory for the Chinese(41), Cambridge Cognitive Examination(61), Clock drawing(42,63), Cognitive Abilities Screening Instrument(63,65), Letter-digit Symbol test(67), Auditory Verbal Learning Test(67), Clinical Dementia Rating Scale(69) and Storandt battery(70).

Results of quantitative analysis (Meta-analysis)

1. **Prevalence of MCI amongst hearing impaired subjects**

Across four cross-sectional studies comparing MCI between people with peripheral hearing loss (n=1292) and without peripheral hearing loss (n=1041), the risk ratio (RR) was 1.39 (random-effects, 95%CI 1.18 to 1.64, p=0.0001, I^2=0%) – *significantly more people with peripheral hearing loss had MCI compared with those without.*

The RR for one study comparing MCI between people with central hearing loss (n=113) and without central hearing loss (n=86) was 1.54 (random-effects, 95%CI 1.24 to 1.90, p<0.0001, I^2not applicable) – *significantly more people with central hearing loss had MCI compared with those without.*

The pooled RR across all studies was 1.44 (random-effects, 95%CI 1.27 to 1.64, p<0.00001, I^2=0%).

(Figure 2. Prevalence of MCI amongst hearing impaired subjects)

2. **Prevalence of hearing impairment amongst patients with MCI**

Across three cross-sectional studies comparing peripheral hearing loss between people with MCI (n=82) and without MCI (n=108), the risk ratio (RR) was 1.40 (random-effects, 95%CI 1.10 to 1.77, p=0.005, I^2=0%) – *significantly more people with MCI had peripheral hearing loss compared with those without.*

(Figure 3. Prevalence of hearing impairment amongst patients with MCI (risk ratio))

Across two cross-sectional studies reporting the between-group difference as an odds ratio (i.e., no raw data were available) comparing peripheral hearing loss between people with MCI and without MCI , the odds ratio (OR) was 1.41 (random-effects, 95%CI 1.02 to 1.96, p=0.04, I^2=59%) – *statistical heterogeneity was evident and the between-group difference was not statistically significant*.

(Figure 4. Prevalence of hearing impairment amongst patients with MCI (odds ratio))

3. Hearing loss in people with MCI

Peripheral hearing loss

Across six cohort studies comparing MCI between people with peripheral hearing loss (n=8235) and without peripheral hearing loss (n=17891), the risk ratio (RR) was 2.06 (random-effects, 95%CI 1.35 to 3.15, p=0.0008, I^2=97%) – *significantly more people with peripheral hearing loss had MCI compared with those without; however; a high level of statistical heterogeneity was evident*.

(Figure 5. Incidence of MCI with and without peripheral hearing loss (risk ratio))

Across two cohort studies reporting the between-group difference as a hazard ratio (i.e., no raw data were available) comparing MCI between people with and without peripheral hearing loss, the hazard ratio was 1.40 (random-effects, 95%CI 1.64 to 1.95, p<0.00001, I^2=0%) – *significantly more people with peripheral hearing loss had MCI compared with those without.*

(Figure 6. Incidence of MCI with and without peripheral hearing loss (hazard ratio))

The between-group difference for one cohort study reporting the outcome as an odds ratio (i.e., no raw data were available) comparing MCI between people with and without peripheral hearing loss, was 1.70 (random-effects, 95%CI 1.30 to 2.22, p=0.0001) – *significantly more people with peripheral hearing loss had MCI compared with those without.*

(Figure 7. Odds ratio outcomes in between-group difference (with and without peripheral hearing loss))

The between-group differences for one cohort study reporting the outcome as risk ratio (i.e., no raw data were available) comparing MCI between people with and without mild, moderate or severe peripheral hearing loss, were: mild 1.26 (random-effects, 95%CI 1.15 to 1.38, p<0.0001), moderate 1.29 (random-effects, 95%CI 1.13 to 1.47, p=0.0002), severe 1.37 (random-effects, 95%CI 1.06 to 1.77, p=0.02) – *significantly more people with peripheral hearing loss had MCI compared with those without in all categories.*

(Figure 8. Risk ratio outcomes in between-group difference (with and without peripheral hearing loss)

Results of narrative synthesis

Studies of Prevalence of early dementia amongst hearing-impaired subjects

The outcomes from these studies are presented in Table 5.

Out of 9 studies included in this category, 4(54,55,58,66) did not identify a significant association between HL and early dementia. The demographics of the participants (age, gender, race, comorbidities) and the outcome measures used differed between the studies and a direct comparison of the results is not possible. The number of participants ranged from 21(58) to 1,969(55). Bucks et al. (2016) assessed the participants' premorbid IQ using the National Adult Reading Test, as an index of cognitive reserve(55). They concluded that HL is not an important factor of contemporaneous attention, memory or executive function in middle-aged adults once several covariates, including cognitive reserve, education, age, sex and depression are accounted for. During the 23-year follow up and after adjusting for demographics and disease covariates, Deal et al. (2015) found that patients with moderate/severe HL had a 0.29SD (95% CI: 0.05-0.54) decline for the global composite score (sum of the three neuropsychological tests administered – Word Fluency Test, Delayed Word Recall Test and Digit Symbol Substitution Test)(57). A hearing assessment was completed at baseline only. There was no strong association observed on the global composite score between patients with mild HL and those with normal hearing at baseline (p=0.570). Interestingly, it was observed that hearing aid users had a slower rate of cognitive decline compared to non-users. Lin et al. (2011) commented "the magnitude of the reduction in cognitive performance associated with HL is clinically significant with the reduction associated with a 25 dB HL being equivalent to an age difference of 6.8 years on tests of executive function``(60).

Studies of Prevalence of hearing impairment amongst patients with early dementia

The outcomes of these studies are presented in Table 6.

Similarly, to the studies described above, the results in this category vary considerably. Four studies out of fifteen, failed to find any strong association between MCI and HL(51,52,64,72). Some studies found a strong association between MCI and central HL(50,56,61–63,65,69,70). Peripheral HL was found to be significantly associated with MCI in 2 studies(32,71) but no such association was observed in 2 other studies(62,69). There was considerable variance in the number of recruited participants per study from 20(70) to 2,146(64). There was no consistency in the outcome measures used (e.g in DeVore's study (1992), the participants did not undergo any formal audiometry(71) whereas in Gates' study (1995) they underwent several tests including PTA, speech audiometry, SSI-ICM, DP-OAEs, ABR)(69). Lister et al. (2016) sought to identify an association between cortical auditory evoked potentials, by means of changes to the P1-N1-P2 complex, and MCI(56). Their findings might be consistent with further changes of inhibition, in the presence of MCI, with fewer overall resources being available to devote to the task. The P1-N1-P2 latencies were similar in both groups. Gates et al. (2010) recruited 313 subjects from the longitudinal Adult Changes in Thought study and grouped them according to their cognitive function as normal (n=232), memory-impaired (n=60) or demented (n=21)(63). One SD poorer executive function was associated with -9.2% point difference in SSI-ICM, -15% point difference in DSI and -8.4% point difference in DDT. Finally, Uhlmann et al. (1989) postulated that the risk of dementia was increased for mild and moderate HL, and reached statistical significance for HL>40dB HL ($p<0.05$)(7).

Studies of incidence of early dementia or cognitive decline amongst subjects with hearing impairment

The outcomes of these studies are presented in Table 7.

A significant correlation between HL and incidence of early dementia or cognitive decline was reported in seven out of eleven studies included in this category(41–47). The number of recruited participants ranged from 1,662(49) to 13,731(46). The means of assessing hearing varied between the studies (PTA(40,45) vs self-reported(41–44,46)). Majority of studies used the MMSE or 3MS to assess cognition, but in a few studies Clinical Dementia Rating Scale(44), abbreviated Memory Inventory for the Chinese(41) and subjective cognitive decline(43) were used.

In Gurgel et al. (2014) study, all-cause dementia was observed in 16.3% of patients with HL (at baseline), but only in 12.1% of those without HL ($p<0.001$)(48). Following multivariate analysis, HL was found to be an independent factor for dementia. When evaluating the subgroup of patients who were cognitively intact at baseline, and taking into account all covariates, HL was not found to be a strong independent risk factor for developing dementia ($p=0.09$). Gates et al. (1996) postulated that central hearing dysfunction precedes the emergence of cognitive decline and dementia and recommended that both peripheral and central hearing tests be obtained as part of the general health evaluation of the elderly(49).

Discussion

We present a quantitative and qualitative analysis of cross-sectional and longitudinal, observational studies looking at the relationship between hearing impairment and mild cognitive impairment. Most of the included studies, except eleven(40,46,72,51,52,54,55,58,64,66,71) have observed a significant association between HL and early dementia or cognitive decline.

The pooled RR across all studies of prevalence of MCI in people with HL(54,57,59) was 1.44 (random-effects, 95%CI 1.27 to 1.64, p<0.00001, I^2=0%). When analysed separately, significantly more people with either peripheral or central hearing loss had MCI compared with those without. When analysing the prevalence of HL amongst patients with MCI, the RR was 1.40 (random-effects, 95%CI 1.10 to 1.77, p=0.005, I2=0%), showing significantly more people with MCI had peripheral hearing loss compared with those without. However, on analysis of the papers that presented their data as an odds ratio, statistical heterogeneity was evident and the between-group difference was not statistically significant.

The meta-analysis of incidence of HL in patients with MCI showed that there was a correlation between HL and incidence of early dementia or cognitive decline. Across 6 cohort studies where data was provided, the RR was 2.06 (random-effects, 95%CI 1.35 to 3.15, p=0.0008, I2=97%); across 2 cohort studies, the hazard ratio was 1.40 (random-effects, 95%CI 1.64 to 1.95, p<0.00001, I2=0%). Even in two separate cohort studies where the raw data was not available, the report outcomes that were reported as OR and RR did show that significantly more people with peripheral hearing loss had MCI compared with those without.

The included studies varied significantly in terms of the outcome measures used, the number of participants, the length of follow-up and the use of covariates when analyzing their results. Therefore, a direct comparison of the studies was not always possible. Most studies present cross-sectional data rather than on longitudinal trajectories of cognitive function and HL over time. Therefore, our estimates of the expected change in cognitive scores associated with HL and age may be subject to bias by cohort effects or obscured by inter-individual heterogeneity in participant characteristics. Most studies have included homogeneous populations e.g white people, well-educated, heath-aware etc.(60) Therefore, we should be cautious when generalizing the outcomes of these studies. One key limitation across multiple studies is the variability in how HL was measured and how audiometric data were analysed (e.g. choice of pure tone thresholds used to define HL). The effect of biased or imprecise assessments of hearing thresholds would likely decrease sensitivity to detect associations due to increased variance. Some studies relied on subjective reporting of HL(41–43,46,48,51,64). This represents a crude method identifying hard of hearing people but studies have shown that subjective hearing assessments have been valid and reliable when compared against standard audiometry(75,76). Similarly, the cognitive assessment tools used, varied between the studies, therefore making a direct comparison of the outcomes difficult. Finally, the use of covariates during regression analysis varied between the studies included in this meta-analysis, from none(71) to many(64). Using the NOS scale, all of the cohort studies scored 7 or more stars out of 9, indicating generally good quality of the individual studies.

Strengths and Limitations of study

This study was undertaken according to PRISMA, two electronic sources were searched and there was contact with experts. Study selection and data extraction were undertaken independently, a quality assessment was undertaken and data were pooled in a meta-analysis. The limitations are that grey literature and conference abstracts were not searched. We also acknowledge the limitations of pooling data from observational studies in a meta-analysis, and the potential for spurious results, included the I-squared statistic. Finally, a formal assessment of publication bias was not undertaken.

A recent commissioning document postulated that HL is an independent risk factor for developing dementia(10). This is consistent with our findings that there might be a link between HL and MCI, a prodromal stage of dementia. Finally, HL may be causally related to MCI and dementia, possibly through exhaustion of cognitive reserve, social isolation, environmental de-afferentation, or a combination of these pathways(60). Studies have shown that in cases where auditory perception is difficult (i.e. HL), greater cognitive resources are dedicated to auditory processing mechanisms rather than other cognitive processes, such as memory(77,78). In a continually increasing aging population, this has obvious implications for health policy and social care services, aiming towards prevention, early diagnosis and treatment. Brief cognitive assessments (such as MoCA and MMSE) can successfully detect MCI in primary care, although their sensitivity is not as high as for established dementia(79). There might be a role for routine cognitive assessment for people who present with HL in an Audiology clinic. Similarly, a referral for hearing assessment might be in the patient's best interest when they are diagnosed with MCI in the primary care. Early intervention to address both issues might prove crucial in improving quality of life and reducing morbidity associated with HL and dementia. Prospective cohort studies need to investigate

whether early diagnosis of cognitive impairment improves important patient or caregiver outcomes(79). Moreover, it is not yet known whether prompt hearing rehabilitation prevents cognitive decline. Future research should focus on identifying the underlying mechanisms linking HL with dementia and developing rehabilitation strategies to delay or prevent its occurrence.

Conclusions

Most of the studies included in this systematic review observed a significant association between HL and incident mild cognitive impairment. It is important for clinicians to be aware of this association and allow for early detection and intervention to try and delay onset of dementia. Further research investigating the mechanisms of this observed association and whether prompt hearing rehabilitation alters the natural course of this relationship should be the focus of future research.

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Summary

- This is the first meta-analysis and systematic review article of all cross-sectional and cohort studies evaluating the relationship between age-related hearing loss and mild cognitive impairment.
- Most of the studies included in this systematic review observed a significant association between hearing loss and incident MCI.
- Further, well-designed, large scale, prospective studies are needed to verify this association.

Tables

Table 1: Inclusion and Exclusion Criteria for the population of interest, outcomes and study design.

	Inclusion criteria	Exclusion Criteria
Population	Cohort studies: adults with early dementia who were cognitively intact at baseline and were followed up for any period of time. Hearing and cognition assessment were available at baseline and end-point. Cross-sectional studies: adults who had HL or mild cognitive impairment at the point of assessment	Paediatric populations and participants with a diagnosis of established dementia (instead of early dementia or mild cognitive impairment)
Outcomes	The proportion of patients with the condition (peripheral or central hearing loss, cognitive impairment) in the case group compared to the control group	None
Study Design	Prospective cohort, case- control and cross-sectional Full-text was available Published in English language	Book chapters, reviews, editorials and commentaries Interventional studies

Table 2: Articles excluded at full-text

Reason for exclusion	Studies excluded
Outcomes were reported for patients with both visual and hearing impairments (could not distinguish results from patients with just hearing impairment)	Davidson 2019(38), Maharani 2018(39)
Absence of control group	Ray 2018(36), Murphy 2018(37), Villeneuve 2017(18), Wong 2014(22), Daggett 2014(33), Pronk 2013(24), Gurina 2011(27), Srinivasan 2010(28), Munshi 2006(29), Riello 2004(30), Allen 2003(31), Uhlmann 1986(32)
Relevant outcomes on cognition or hearing not available	Yu 2017(35), Schnitker 2016(19), Moradi 2014(23), Lin FR 2014(6), No authors listed 2013(25), Helvik 2012(26)
No report on association between mild cognitive hearing impairment and hearing loss	Dotchin 2015(21)
Article replaced by Fischer 2016 that reported outcomes of interest on the same population, after communication with senior author	Schubert 2017(20)

Table 3: Characteristics of included studies

Reference	**Design**	**Matching[a]**	**Population**	**Cognition assessment**	**Auditory assessment**	**Patients (n)**	**Control (n)**	**Follow-up (years)**
Schubert 2019 (40)	Cohort	1,2, visual impairment	America	MMSE, Trail Making Tests A and B	PTA	331	2126	10
Yu 2019 (41)	Cohort	1,2,3,4,,marital status, diabetes, baseline cognitive status	Asia	Abbreviated Memory Inventory for the Chinese	Self-reported	858	1089	1
Vaccaro 2019 (42)	Cohort	1	Europe	MMSE, Semantic Verbal Fluency Test, Rey Osterrieth Complex Figure - Recall (ROCF-R) test, Clock Drawing Test, Trail Making Test part A	Self-reported, Whispered Voice Test	159	1012	5
Curhan 2019 (43)	Cohort	1,4, Race, Occupation, BMI, Smoking, Cholesterol, Diabetes	America	Subjective Cognitive Decline	Self-reported	1181	1208	8
Han 2019 (50)	Cross-sectional	None	Asia	MMSE	Not reported	274	1743	NA
Gallagher 2018 (44)	Cohort	None	America	CDRS	Observed by assessor	505	2150	3.5
Heward 2018 (51)	Cross-sectional	3	Africa	IDEA cognitive screen	Self-reported	50	255	NA
MacDonald 2018 (52)	Cross-sectional	1	America	word recall task, Letter Series test, WAIS-R Digit Symbol Substitution task, Controlled Associations test, recognition vocabulary test	PTA	211	197	NA
Iliadou 2017 (53)	Cross-sectional	1,2 pure tone thresholds	Europe	MMSE, MoCA, CDRS, Geriatric Depression Scale	PTA, speech in quiet, central auditory processing test	18	11	NA

					(Random Gap Detection Test, speech in bubble, Gaps-in-noise)			
Heywood 2017 (72)	Cross-sectional	1,2,3,4, ethnicity, central obesity, diabetes, dyslipidemia, smoking, alcohol, leisure time activity, cardiac diseases, depressive symptoms	Asia	MMSE, CDRS	Whispered Voice Test	507	2052	NA
	Cohort					144	1360	3.8
Deal 2017(45)	Cohort	1,2,3	America	3MS	PTA	1,103	786	9
Bruckmann 2016 (54)	Cross-sectional	3	America	MMSE	PTA	17	13	NA
Yang 2016 (46)	Cohort	1,2,3,occupation, wealth	Asia	MMSE	Self-reported	4,820	8,911	3
Fischer 2016 (47)	Cohort	1,2,3,4, smoking, exercise, alcohol consumption, hypertension, diabetes, non-HDL-C, frailty score, IMT	America	MMSE	PTA	1,209	1,209	17
Bucks 2016 (55)	Cross-sectional	1,2,3, depression, cognitive reserve (premorbid IQ)	Australia	Cognitive Drug Research System, verbal fluency, National Adult Reading Test	PTA	112	1,857	NA

Lister 2016 (56)	Cross-sectional	1,3,race,PTA	America	MoCA	Cortical Auditory Evoked Potential, PTA, tympanometry, SRT, speech in noise	13	17	NA
Deal 2015 (57)	Cross-sectional	1,2,3,4	America	DWRT, word fluency test, DSST	PTA	180	73	23
Zhang 2015 (58)	Cross-sectional	1,3	Asia	MMSE, Wechsler Adult Intelligence Test	PTA	21	11	NA
Gurgel 2014 (48)	Cohort	1,2,3,4, APOE-ε4 allele, diabetes, smoking, high cholesterol	America	3MS-Revised, Interview, Neuropsychological testing	Observed by assessor, self-reported	836	3,627	Mean follow-up: 4.32 (HL group), 6.08 (control group)
Quaranta 2014 (59)	Cross-sectional	1,2,3	Europe	MMSE, CDRS, FAB	PTA, Speech audiometry, SSI-ICM, HHIE-S	207	245	NA
Lin 2011 (60)	Cross-sectional	1,2,3,5, race,depression, smoking	America	MMSE, FCSRT, Trail making A&B, Stroop, Letter& category fluency, AMNART	PTA	142	205	NA
Rahman 2011(61)	Cross-sectional	1,2,3,5,PTA	Africa	Cambridge Cognitive Examination	Speech audiometry, CAP, PTA, Tympanometry	150	150	NA
Idrizbegovic 2011(62)	Cross-sectional	1	Europe	MMSE	PTA, speech audiometry,	59	34	NA

					dichotic digit test			
Gates 2010 (63)	Cross-sectional	1,3,PTA	America	Trail Making; Clock,Drawing, Stroop Color and Word, and subtests from the Cognitive Abilities Screening Instrument	PTA, DP-OAEs, SSI-ICM, Dichotic Sentence Identification, Dichotic Digits	60	232	NA
Benito-Leon 2010 (64)	Cross-sectional	1,2,3, premorbid intelligence, cognition altering medications, depression	Europe	Expanded version of MMSE, Trail making test A, verbal fluency, memory, premorbid intelligence	Self-reported	1,073	1,073	NA
Gates 2008 (65)	Cross-sectional	1,2, hearing threshold, word recognitions score, frequency of exercise, depressive symptoms	America	Cognitive Ability Screening Instrument	Identification Test, Dichotic Digits Test, Pitch Pattern Sequence	64	232	NA
Tay 2006 (66)	Cross-sectional	1,2 cerebrovascular disease	Australia	MMSE	PTA	89	75	NA
Van Boxtel 2000 (67)	Cross-sectional	1,2,3, information processing speed	Europe	Letter-Digit Symbol Test, Auditory Verbal Learning Test	PTA	56	397	NA
Frisina 1997 (68)	Cross-sectional	5, cardiovascular disorders	America	Extent of benefit gained from supportive context during speech audiometry	PTA, speech audiometry	30	20	NA
Gates 1996 (49)	Cohort	stroke	America	MMSE	PTA, speech audiometry, SSI-ICM,	452	364	6

					staggered spondaic word, PIPBW			
Gates 1995 (69)	Cross-sectional	1,2,3	America	CDRS	PTA, speech audiometry, SSI-ICM, DP-OAEs, ABR	40	42	NA
Strouse 1995(70)	Cross-sectional	1,2, hearing loss	America	3MS, Storandt battery	PTA, speech and immitance audiometry, SSI-ICM, OAEs, dichotic digits, dichotic sentence identification, pitch and duration patterns	10	10	NA
DeVore 1992 (71)	Cross-sectional	none	America	MMSE	Self-reported	5	45	NA
Uhlmann 1989 (7)	Cross-sectional	1,2,3	America	MMSE	PTA, speech audiometry	100	100	NA

3MS: Modified Mini-Mental State Examination,

ABR: Auditory Brainstem Repsonses, AMNART: American Version of the Nelson Adult Reading Test, CAP: selective auditory attention test,dichotic digits test, auditory fusion test, pitch pattern sequences test and auditory memory battery of Goldman–Fristoe–Woodcock, CDRS: Clinical Dementia Rating Scale, DP-AOEs: Distotion products- Otoacoustic Emissions, DWRT: Delayed Word Recall Test, DSST: Digit Symbol Substitution Test, FAB: Frontal Assessment Battery, HL: Hearing loss, HHIE-S: Hearing Handicap Inventory for the Elderly Screening Version questionnaire, IMT:

mean intima media thickness, MMSE: Mini Mental State Exam, PIPBW: Performance Intensity function of Phonetically Balanced Words, PTA: Pure Tone Audiometry, SSI-ICM: synthetic sentence identification with ipsilateral competing,

[a] Matching: 1 = age; 2 = gender; 3 = education; 4 = hypertension

Table 4: Quality assessment of the included cohort studies using the Newcastle Ottawa Scale

	Selection				Comparability	Outcome		
Reference	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascetainment of exposure	Demonstration that outcome of interest was not present at start of study	Of cohorts on the basis of the design or analysis	Assessment	Follow-up long-enough	Adequacy of follow up of cohorts
Schubert 2019 (40)	★	★	★	★	★★	★	★	★
Yu 2019 (41)	★	★	★	★	★★	★		★
Vaccaro 2019 (42)	★	★	★	★	★★	★	★	★
Curhan 2019 (43)		★	★	★	★★	★	★	★
Gallagher 2018 (44)	★	★	★	★	★★	★		★
Heywood 2017 (72)	★	★	★	★	★★	★	★	★
Deal 2017(45)	★	★	★	★	★★	★	★	★
Yang 2016(46)	★	★	★	★	★★		★	
Fischer 2016(47)	★	★	★	★	★★	★	★	★
Gurgel 2014(48)	★	★	★	★	★★		★	★
Gates 1996(49)	★	★	★	★		★	★	★

Table 5: Outcomes from the studies of prevalence of early dementia amongst hearing- impaired subjects

Study	Participants Number (mean age)	Outcomes from cognitive assessment
Bruckmann 2016(54)	30 (68.5)	No difference in MMSE scores (p=0.880)
Bucks 2016(55)	1,969 (56.2)	No difference in contemporaneous attention, memory or executive function
Zhang 2015(58)	21 (51.7)	No difference in the neurophsychological tests between a group of patients with unilateral HL and normal hearing
Deal 2015(57)	253 (76.9)	Participants with mild HI showed poorer concurrent memory domain performance (− 0.35 SDs, 95% CI − 0.62, − 0.07; P = 0.01)
Quaranta 2014(59)	488 (72.8)	Strong association between MCI and HL (OR: 1.6, p:0.05).
Lin 2011(60)	347 (71)	Significant deterioration on scores of MMSE (p<0.05), CSR Free recall (p<0.01), and Stroop Mixed (p<0.05) was observed with greater HL. There was some association between HL and Trail Making Test part A & B (p<0.10), but no association between Stroop colours and words or Verbal function and language tests.
Tay 2006(66)	164 (NR)	No significant differences in the cognitive function between people with none-to-mild and moderate-to-severe HL (p=0.571).
Van Boxtel 2000(67)	453 (NR)	The predictive value of a 10dB loss in hearing acuity was comparable in size to that of being up to 7.1 years cognitively older
Frisina 1997(68)	50 (43.2)	Patients with HL took significantly better advantage of supportive context during speech audiometry than subjects without HL (p<0.05)

CSR: Cued Selective Reminding, HL: Hearing Loss, MCI: Mild Cognitive Impairment, MMSE: Mini Mental State Exam, NR: Not reported

Table 6: Outcomes from the studies of prevalence of hearing loss amongst subjects with mild cognitive impairment

Study	Participants Number (mean age)	Outcomes from Hearing assessment
Han 2019(50)	2017 (73.2)	Significant association between HL and MCI (p=0.001).
Heward 2018(51)	305 (77.6)	No strong association between the two groups (p = 0.109)
MacDonald 2018(52)	408 (74.2)	No significant association between HL and cognitive impairment (p>0.05)
Iliadou 2017(53)	29 (66.1)	The MCI group had significantly poorer scores for Speech in Bubble and temporal resolution abilities of MCIs versus normal controls for both ears.
Heywood 2017(72)	2,559 (NR)	There was no significant association of HL with prevalent MCI at baseline.
Lister 2016(56)	30 (74.5)	Comparable P1 and N1 amplitudes of Cortical Auditory Evoked Potentials between the two groups, but significantly lower P2 amplitudes for subjects with MCI (p<0.05). The P1-N1-P2 latencies were similar in both groups
Rahman 2011(61)	300 (66.5)	The MCI group scored significantly lower than the control group in Selective Auditory Attention Test, dichotic digit test left ear, pitch pattern sequence test, recognition memory, auditory memory for content and auditory memory for sequence. There were no significant differences between the two groups in the dichotic digit test right ear and auditory fusion tests.
Idrizbegovic 2011(62)	136 (64.3)	No significant differences in PTA, speech in quiet or speech in noise. MCI group performed worse at the Dichotic Digit Test
Gates 2010(63)	313 (NR)	Strong association between executive function score and central auditory processing disorder, as measured by SSI-ICM
Benito-Leon 2010(64)	2,146 (75.7)	No strong association between the two groups (p=0.114).
Gates 2008(65)	313 (80)	Strong negative association between mild memory impairment and central auditory processing disorders
Gates 1995(69)	82 (NR)	No significant difference in PTA. However, a significant association was observed between central auditory dysfunction and mild cognitive impairment (SSI, ICM, p<0.001).
Strouse 1995(70)	20 (71.2)	Significant association between central auditory dysfunction and cognitive impairment (p<0.05)

DeVore 1992(71)	50 (75.9)	MCI present in 60% of those with HL but only 24.4% of those with normal hearing
Uhlmann 1989(7)	200 (77)	Significant association between HL and MCI (p=0.03).

MCI: Mild Cognitive Impairment, PTA: Pure Tone Audiomtery, SSI-ICM: Synthetic Sentence Identification with Ipsilateral Competing Message

Table 7: Studies of incidence of early dementia or cognitive decline amongst subjects with hearing impairment

Study	Participants Number	Outcomes from cognitive assessment
Schubert 2019(40)	2,457	There is no association between HL and cognition when visual impairment was included in the model.
Yu 2019(41)	2,258	Poor hearing is significantly associated with an increased risk of subjective memory complaints. OR 1.7 (95% CI:1.3–2.1)
Curhan 2019(43)	2,389	There is significant association with HL and risk of cognitive impairment with risk (p<0.001)
Vaccaro 2019(42)	1,171	Significant relationship between HL and cognitive impairment (p=0.001)
Gallagher 2018(44)	2,655	HL associated with increased risk of MCI (p<0.001).
Heywood 2017(72)	1,504	HL is not associated with an increase of MCI (HR 1.85, 95% CI: 0.78 – 4.40, p=0.161)
Deal 2017(45)	1,889	Strong association between HL and increased risk of developing dementia. Moderate/ severe HL to normal hearing: HR: 1.64 (95% CI: 1.16-2.30). Mild HL to normal hearing: HR:1.03 (95% CI: 0.75-1.42).
Yang 2016(46)	13,731	Abnormal cognition was found in 96.7% of those with HL but only in 36.8% of those with normal hearing
Fischer 2016(47)	1,884	Significant relationship between HL and cognitive impairment (HR: 2.09, 95% CI: 1.29-3.39).
Gurgel 2014(48)	4,463	No significant association between HL and risk for developing dementia (p=0.09).
Gates 1996(49)	1,662	No significant association between PTA and cognitive decline. Significant association between central auditory disorder and incident dementia (p<0.05)

CI: Confidence Interval, HL: Hearing Loss, HR: Hazard Ratio, PTA: Pure Tone Audiometry

Appendix 1: Search Strategy, performed on the 24/06/2020

Search Terms:

(Deafness OR Hearing Or Presbycusis) AND (Mild Cognitive Impairment OR MCI)

Filters:

Text Availability: Full Text

Species: Humans

Languages: English

Figures

Figure 1

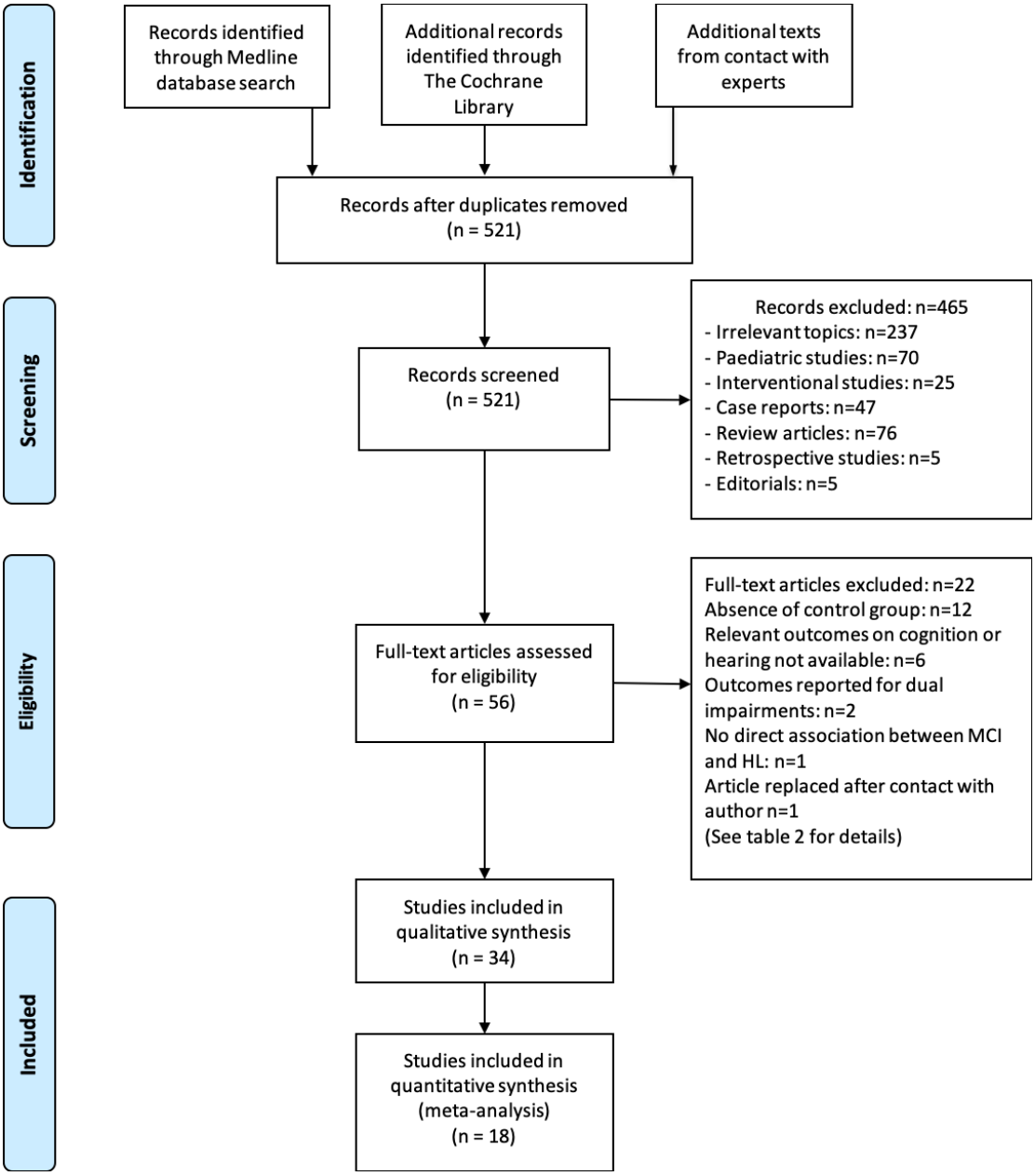

Figure 2

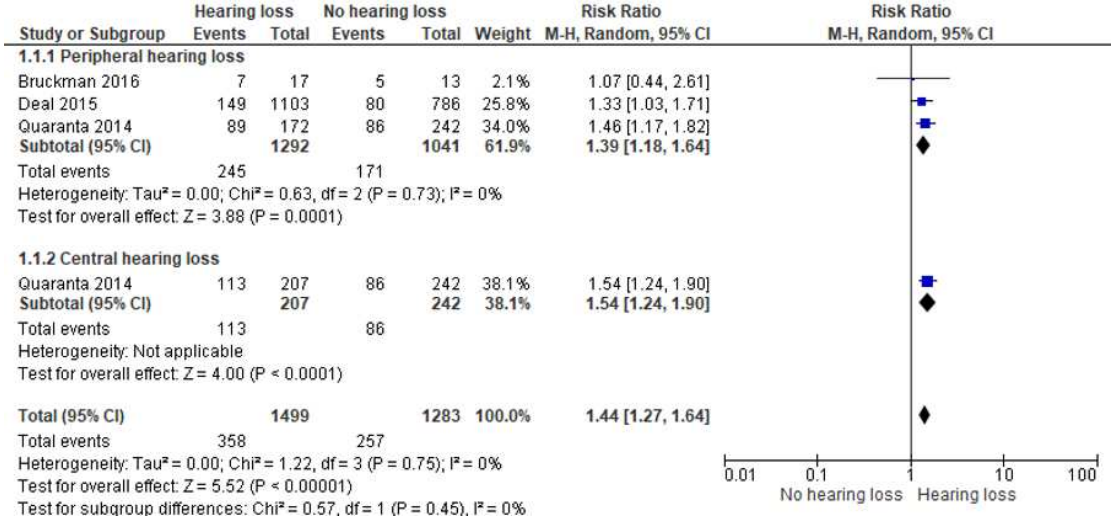

Figure 3

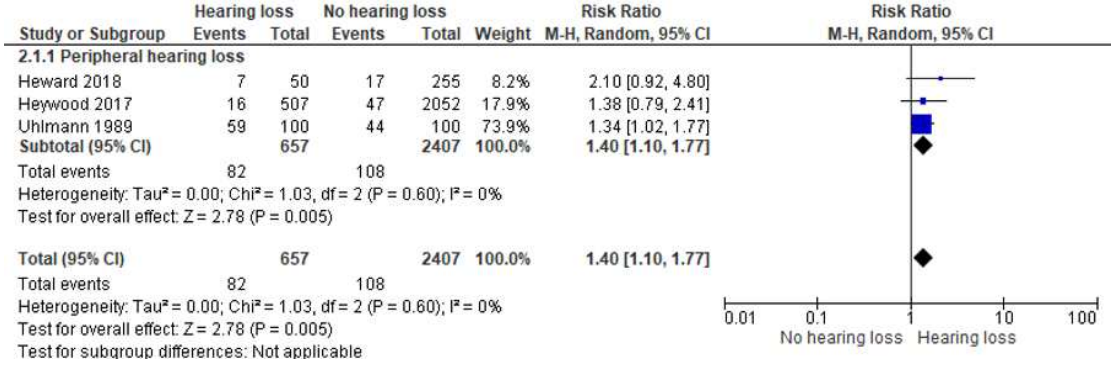

Figure 4

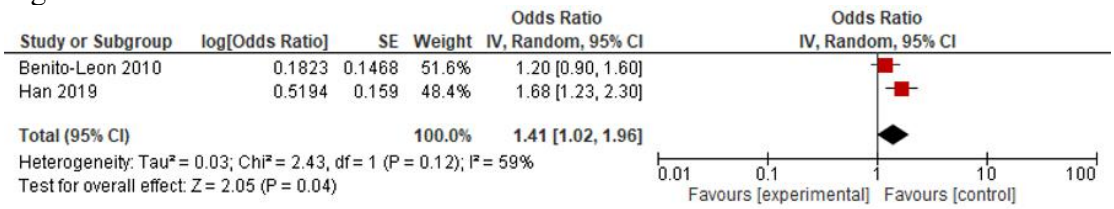

Figure 5

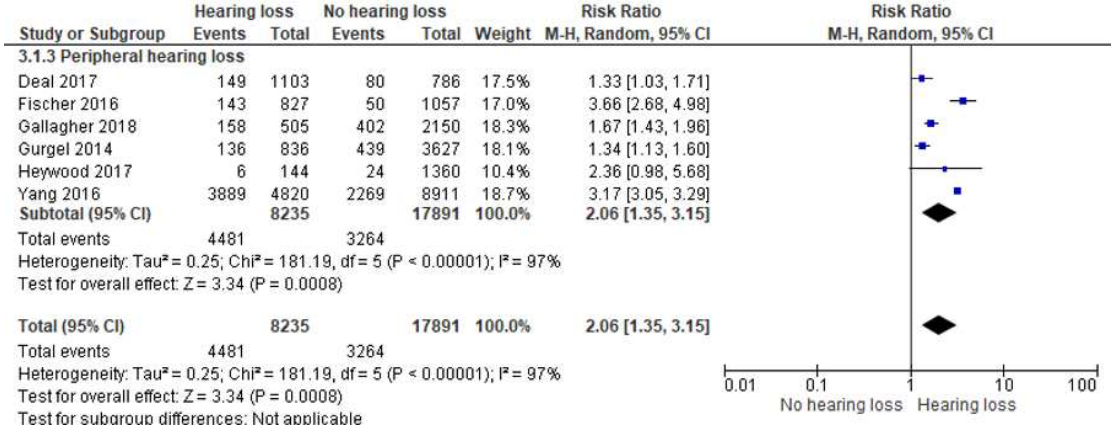

Figure 6

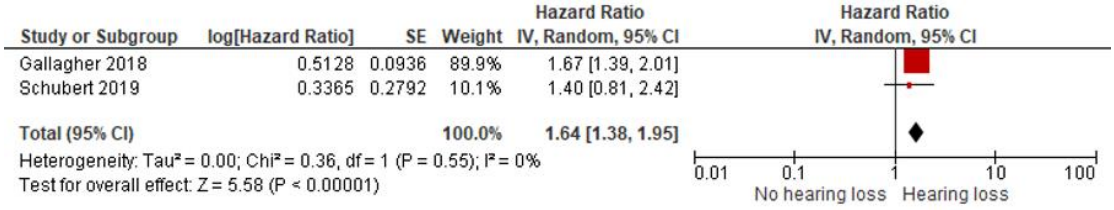

Figure 7

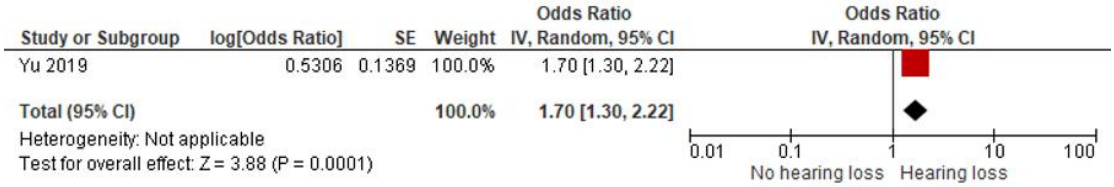

Figure 8