Hearing Impairment and Diverse Health Outcomes: An Umbrella Review of Meta-analyses of Observational Studies

Mike Trott[1,2], Lee Smith[2*], Tao Xiao[3], Nicola Veronese[4], Ai Koyanagi[5,6], Louis Jacob[6,7], Guillermo F Lopez-Sanchez[1], Yvonne Barnett[8], Shahina Pardhan[1]

1. Vision and Eye Research Institute (VERI), School of Medicine, Anglia Ruskin University, East Road, Cambridge, CB1 1PT
2. The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge UK, CB1 1PT
3. College of Mathematics and Statistics, Shenzhen University, China
4. Geriatric Unit, Department of Internal Medicine and Geriatrics, University of Palermo, Palermo, Italy
5. ICREA, Pg. Lluis Companys 23, Barcelona, Spain
6. Research and Development Unit, Parc Sanitari Sant Joan de Déu, CIBERSAM, Barcelona, Spain
7. Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux 78180, France
8. Anglia Ruskin University, Cambridge, UK

*Corresponding Author

Dr Lee Smith; The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge UK, CB1 1PT, lee.smith@aru.ac.uk

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Abstract (271)

Background: Globally, it is estimated that approximately 1.3 billion people live with some form of hearing impairment. Major causes of hearing loss include infection/disease, age-related factors, and occupational factors. Numerous systematic reviews and meta-analyses have attempted to synthesise literature on these topics. To date there has not been a systematic evaluation of the relationships between hearing impairment and diverse physical, mental, and social outcomes.

Objective: We performed an umbrella review of systematic reviews of observational studies with meta analyses for any physical disease, biomarkers of disease, mental health or cognitive outcomes, and/or modifiable risk factors associated with hearing impairment.

Methods: For each meta-analytic association, random-effects summary effect size, 95% confidence intervals, heterogeneity, evidence for small-study effect, excess significance bias and 95% prediction intervals were calculated, and risk of bias was assessed via the AMSTAR2 tool. These were used to grade significant evidence ($p<0.05$) from I to IV, using the recommendations from the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria.

Results: From 3,747 studies, 21 were included covering 54 outcomes. Overall, 44/54 outcomes (82%) yielded significant results. Of the highest quality evidence, age related hearing loss and non-specific hearing impairment was negatively associated with several types of cognitive impairments; paediatric bilateral hearing loss was negatively associated with quality of life; sensorineural hearing loss was

positively associated with rheumatoid arthritis; and tinnitus was positively associated with temporomandibular disorders.

Conclusions and Relevance: Results show moderate quality evidence for associations between several types of hearing impairments and cognitive difficulties, quality of life and systemic diseases such as rheumatoid arthritis. Practitioners and public health policies should note these findings when developing relevant healthcare policies.

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Transparency Statement

The lead author confirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted.

Ethics Statement

Because this was a systematic review, ethical approval was not required.

1. Introduction

Globally, it is estimated that approximately 1.3 billion people live with some form of hearing impairment [1], defined as having hearing thresholds of <20 dB in one or both ears [2]. Hearing loss impacts a substantial portion of the world, and is commonly measured as Years Lived with Disability (YLD) [3] and Disability Adjusted Life Years (DALY) [4]. For example, hearing loss has been reported to have a global YLD of 41 years/100,000 years [3], and a global DALY of 10,875,000 years [4]. The economic impact of hearing loss in adults has been estimated to be very large. Indeed, a 2017 systematic review in the USA estimated the economic cost of lost productivity due to hearing impairment to be as high as 194 billion dollars [5]. A large body of literature reports that those who have hearing impairment may be at a higher risk of physical and mental health complications when compared to those with normal hearing (e.g. diabetes [6], dyslipidaemia [7], hypertension [8], cognitive function [9],[10], and depression [11]).

Given the incidence, morbidity, and mortality rates associated with hearing impairment, numerous systematic reviews and meta-analyses have published to quantify this disparate literature. From these reviews, several significant associations between hearing impairment and several physical, mental and psychosocial co-variates have been reported, including emotional difficulties, depression and quality of life [12,13]. To date, most of the systematic reviews have focused on a single health-related end point, and there have been few studies that have systematically evaluated the relationships between hearing impairment and diverse physical, mental, and/or psychosocial health outcomes. To a certain extent, the Global Burden of Disease project has carried this out for different levels of hearing impairment although various parameters such as quality of life and mental states have yet to be examined. In order

to address the breadth of the literature of complex conditions and comorbid outcomes, an increasing number of studies have used an 'umbrella review' approach, a novel method of synthesising existing systematic reviews with meta-analyses to capture the breadth of outcomes associated with a given exposure [14,15].

Therefore, the aim of the present study was to assess the strength and credibility of the evidence on any type of hearing impairment and associated mental, physical, or social outcomes, derived from published meta-analyses of existing observational studies using an umbrella review approach, aiming to answer the following questions:

1. What physical, mental, and social outcomes are associated with hearing impairment?
2. What is the epidemiological credibility of the relationships between hearing impairment and comorbid outcomes?

The results of these questions has the potential to inform practitioners working with people with hearing impairment, related public health policy, and inform further research, especially regarding systemic review reporting.

2. Methods

An umbrella review was carried out following established, pre-published procedures (see Ioannidis 2009[14] and Aromataris 2015 [16]). The protocol for the present umbrella review was preregistered with PROSPERO (registration number CRD42018093358).

2.1 Search strategy and selection criteria

We searched PsycINFO, Medline, CINAHL, and Embase databases (from inception to 04/06/2020) to identify systematic reviews with meta-analyses, pooling observational (cross-sectional, case-control, cohort) studies to examine any association between hearing impairment and any physical, mental, or social outcome. The following search key was used: "(meta-analysis or meta-anal* or systematic review) AND (hearing OR hearing impair* OR deaf OR deafness)". Two independent reviewers (MT, DP) searched titles/abstracts for eligibility, and then evaluated the full text of those articles surviving the initial title/abstract screening. A third reviewer resolved any potential conflict (LS). When more than one meta-analysis assessed the same risk factor or the same outcome, we only included the one with the greatest number of included studies [17–19]. Exclusion criteria were: 1) meta-analyses of randomized controlled trials (RCTs); 2) studies published in languages other than English, 3) meta-analyses reporting only one study for the outcome of interest, since no meta-analysis was possible.

2.2 Data extraction

Data was independently extracted by two investigators (MT, DP) into a pre-prepared spreadsheet. For each meta-analysis, we extracted PMID/DOI, first author, publication

year, population included in the study, study design, number of included studies, the total sample size and number of cases, i.e. people having the outcome of interest. risk of bias of each included meta-analysis was assessed with the Assessment of Multiple Systematic Reviews (AMSTAR) 2 tool (available at https://amstar.ca/Amstar-2.php), which is a recent update of AMSTAR [20], by two independent investigators (MT, DP).

2.3 Data analysis

For each association of meta-analyses providing individual study data, we extracted effect sizes (ESs) of individual studies and re-performed the meta-analysis calculating the pooled effect size and the 95% confidence intervals (CIs), with random-effects models[21]. Heterogeneity was assessed with the I^2 statistic [22]. Additionally, we calculated the 95% prediction intervals (PIs) for the summary random ESs providing the possible range in which the ESs of future studies is expected to fall [23].

We also tested the presence of small-study effect bias [17,24–26], which is deemed to be present when both pooled estimates are larger than the individual largest study, and in the presence of publication bias (Egger's regression asymmetry test ($p<0.10$)). We then assessed the existence of excess significance bias by evaluating whether the observed number (O) of studies with nominally statistically significant results ($p<0.05$) was different from the expected number of studies with statistically significant results (significance threshold set at $p<0.10$) [26,27], a test designed to assess whether the published meta-analyses comprise an over-representation of false positive findings [26].

2.4 Assessment of the credibility of the evidence

Credibility of meta-analyses providing individual study data was assessed according to stringent criteria based on previously published umbrella reviews [19,24,25,28–30]. In brief, associations that presented nominally significant random-effects summary effect sizes (p<0.05) were ranked as Grade I, II, III, and IV (see Table 1), based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria [31].

3. Results

3.1 Search

The initial search yielded 3,747 results, of which 1,936 were duplicates and removed, leaving 1,811 articles for title and abstract review. Of these 1,811 articles, 68 articles were selected for full-text review against the inclusion and exclusion criteria, which yielded 21 articles [6–12,32–45] (with 54 outcomes) to be used in the final analysis. The full PRIMSA flowchart can be found in Figure 1 and full descriptive information on included studies can be found in Table 2.

3.2 Findings from studies examining hearing impairment and mental health and/or cognition.

Of the reviews that examined associations between hearing impairment and mental health and/or cognition, 34 associations were assessed (16 from case-control or cross-sectional studies and 16 from prospective and retrospective studies). The median number of studies was 7 and the median number of participants was 6,109. Full details of all types of hearing impairment and outcomes are shown in **Table 3**.

The *p*-value for effect-size, under a random effects model, was <0.05 in 32/34 outcomes and, among them, eight reported a *p*-value $<1*10^{-6}$. Among the 34 outcomes, 14 reported low heterogeneity (I^2<50%), eight moderate heterogeneity (I^2 between 50 and 75%) and 12 high heterogeneity. Small study effect affected 10/34 outcomes, whilst seven outcomes had excess significance bias (see **Table 3**). The largest study for each outcome was significant in 21/34 outcomes.

Using the GRADE criteria, eight outcomes yielded Grade II evidence, 16 yielded Grade III, and eight outcomes yielded Grade IV quality of evidence , while two had no significance. Regarding the highest quality evidence (Grade II), age-related hearing loss was negatively associated with cognition: processing fluency (Fisher's Z = -0.08 95% CI -0.12; -0.04), cognition: delayed recall (Fisher's Z= -0.10; 95%CI: -0.15; -0.05), non-specific hearing impairment was negatively associated with delusion, delusion like symptoms, or paranoid symptoms (OR=1.55 95% CI 1.36-1.78), non-specific hearing impairment was associated with hallucinations (OR=1.40 95% CI 1.18-1.65) and mild cognitive impairment (RR=1.30 95% CI=1.12-1.52). Furthermore, significant associations were also found between hearing impairment and quality of life measures, including paediatric bilateral hearing loss being negatively associated with quality of life in both the school and social domains (school: SMD=-0.39 95%CI -0.59; -0.19; social: SMD= -0.25 95% CI= -0.48; -0.03).

3.3 Findings from studies examining hearing impairment and disease or disease biomarkers

Of the reviews that examined associations between hearing impairment and disease/disease biomarkers, 13 associations were assessed (10 from case-control or cross-sectional studies and 3 from prospective and retrospective studies). The median number of studies was 6 and the median number of participants was 1,560. Full details of all types of hearing impairment and outcomes are shown in **Table 4**.

The *p*-value for effect-size, under a random effects model, was <0.05 in 9/13 outcomes and, among them, three reported a *p*-value $<1*10^{-6}$. Among the 13 outcomes, five reported low heterogeneity (I^2<50%), three moderate heterogeneity (I^2 between 50

and 75%) and four high heterogeneity. Small study effect affected 6/13 outcomes, whilst one outcomes had excess significance bias (see **Table 4**). The largest study for each outcome was significant in 10/13 outcomes.

Using the GRADE criteria, three outcomes yielded Grade II evidence, two yielded Grade III, and four outcomes yielded Grade IV quality of evidence , while four had no significance. Regarding the highest quality evidence (Grade II), sensorineural hearing loss was negatively associated with rheumatoid arthritis in both case control/cross-sectional and prospective and retrospective studies (case-control or cross-sectional OR=3.42 95% CI 2.50-4.69; prospective and retrospective OR=2.28 95% CI 1.88-2.75), and tinnitus was negatively associated with temporomandibular disorders (OR=1.80 95% CI 1.64-1.99).

3.4 Findings from studies examining hearing impairment and modifiable risk factors.

Of the reviews that examined associations between hearing impairment and modifiable risk factors, seven associations were assessed (four from case-control or cross-sectional studies and three from prospective and retrospective studies). The median number of studies was 4 and the median number of participants was 5,892. Full details of all types of hearing impairment and outcomes are shown in **Table 5**.

The *p*-value for effect-size, under a random effects model, was <0.05 in 3/7 outcomes and none of them reported a *p*-value $<1*10^{-6}$. Among the seven outcomes, one reported low heterogeneity (I^2<50%), two moderate heterogeneity (I^2 between 50 and 75%) and four high heterogeneity. Small study effect affected 3/7 outcomes, whilst

two outcomes had excess significance bias (see **Table 5**). The largest study for each outcome was significant in 6/7 outcomes. Using the GRADE criteria, one outcome yielded Grade III evidence, two outcomes yielded Grade IV quality of evidence , while four had no significance.

3.5 Risk of Bias

The majority of meta-analyses scored 'critically low' (*n*=20/21) on AMSTAR2, and one scored 'low' (see Supplementary Table 1). The main reasons for the low scoring was that all included studies failed to provide a list of excluded studies and justify their exclusions (AMSTAR2 question 7), and the majority studies failed to report an explicit statement that the review methods were established prior to the conduct of the review (AMSTAR2 question 2; 5/21 studies satisfied this criteria). According to Shea and colleagues [20], these constitute a major risk of bias in all included studies, and as a result the credibility of evidence for all studies were downgraded by one (see Tables 1, 3, and 4).

4. Discussion

The present umbrella review, including 21 studies and 54 health outcomes, provides a broad overview of the existing evidence of associations between hearing impairment and diverse health outcomes, including diseases and/or disease biomarkers, mental health or cognition, and modifiable risk factors. Furthermore, this review provides a systematic evaluation of the methodological quality of available meta-analyses. According to the GRADE assessment, there were 11 outcomes that yielded Grade II evidence, 19 outcomes yielded Grade III evidence, and 14 outcomes yielded Grade IV evidence.

4.1 Mental health/cognition

4.1.1 Grade II Evidence

Of the Grade II evidence that examines hearing impairment and mental health or cognition, several outcomes were related to cognitive functioning, including cognitive processing fluency being negatively associated with ARHL in cross-sectional studies only (prospective studies showed no significance), delayed recall being negatively associated with ARHL in prospective studies (and in cross-sectional studies with a lower grade of evidence), and mild cognitive impairment being positively associated with having hearing impairment in prospective studies, which broadly agrees with primary studies that explores cognitive function using neuroimaging [46]. The underpinning mechanisms for these cognitive declines remain unclear, however one proposed mechanism that cognitive function could be reduced as a result of the impaired speech perception that comes with age related hearing loss [36]. Given the disparity between cross-sectional and prospective studies, the differing strengths of

evidence in different types of cognitive decline, and cognitive decline's effect on quality of life, further research to confirm or refute these associations are warranted. Another mental health outcome that yielded high levels of evidence were related to psychosis. In cross-sectional and case-control studies having a hearing impairment was positively associated with the incidence of delusions, delusion like symptoms, or paranoid symptoms, and in cohort studies having hearing impairment was positively associated with the incidence of hallucinations, and general psychotic symptoms. Although there is no clear consensus on the mechanisms underlying hearing impairment and incidence psychotic symptoms/episodes, two models have been proposed by Linszen et al [10]. In brief, one model describes how hearing impairment and psychosis could independently share a common precursor: mainly genetic defects, preterm and early-life central nervous system infections, and disease [47,48], all of which could lead to hearing impairment, psychosis, or both. Linszen et al also suggests several possible direct causal relationships. For example, hearing impairment has been linked to disturbances in the ability to attribute mental states to oneself and to others, which further has been linked to delusions. Furthermore, hearing impairment related disturbances in source monitoring and top-down processing have been linked to hallucinations [10]. To confirm or refute these models/relationships between hearing impairment and psychoses, longitudinal studies are warranted. Regarding quality of life outcomes, this study found Grade II evidence that paediatric bilateral hearing loss was negatively associated with quality of life (in the 'school' and 'social' domains) - both being related to social relationships. These results highlight the need to both monitor mental health and social outcomes in children with bilateral hearing loss and highlights the need for targeted interventions to be created and implemented in this population.

4.1.2 Grade III and IV evidence

Of the Grade III evidence, hearing impairment was negatively associated with several mental health or cognitive outcomes. This review found negative associations between ARHL and several types of cognitive processes, including attention, delayed and immediate recall, processing speed, reasoning, visuospatial ability and global cognition, as well as negative associations between non-specific hearing impairment and types of psychoses including delirium and schizophrenia, as well as depression and IQ scores. Furthermore, unilateral hearing loss was negatively associated with quality of life. Of the Grade IV evidence, several outcomes were associated with mental health or cognitive outcomes, including negative associations between ARHL and working memory, semantic memory, and immediate recall, autism spectrum disorder, Alzheimer's disease, dementia, and psychotic disorders. Furthermore, paediatric tinnitus was negatively associated with depression. Due to the lack of quality in these associations, further studies need to be carried out to add credibility to these associations.

4.2 Diseases and/or disease biomarkers

4.2.1 Grade II evidence

One type of association that yielded Grade II evidence in both cross-sectional, case-control and prospective studies was sensorineural hearing loss (SNHL) and rheumatoid arthritis. Whilst the mechanisms underlying the association are open to debate, one mechanism that has been frequently used in the literature is linked to one of the main causes of SNHL: damage to the cochlear via the different types of

antibodies caused by rheumatoid arthritis either directly or indirectly (via autoantibody-antigen reactions or cytotoxic reactions) damaging the cochlear [44,49,50]. Furthermore, a common complication of rheumatoid arthritis is rheumatoid vasculitis, which could affect the (already limited) vascular supply to the cochlear [44]. Given the both the strength of evidence and large effect sizes yielded (OR=3.42 and 2.28 for cross-sectional and case control and retrospective studies, respectively), it is recommended that practitioners working with rheumatoid arthritis patients routinely monitor for possible hearing impairment. Furthermore, to assist with treatment and possible prevention, researchers should focus their studies on longitudinal studies to establish causality , and the underlying mechanisms. There was also Grade II evidence that tinnitus is positively associated with temporomandibular disorders. One mechanism for this that is common in the literature is the anatomical link between the tensor veli palatini, the eustachian tube, or one of the several ligaments and the middle ear, a disorder of which could cause middle ear tension of ventilation that leads to tinnitus symptoms [43]. It is recommended that practitioners who are working with patients with either tinnitus or temporomandibular disorders should screen for respective temporomandibular disorders and tinnitus. Furthermore, longitudinal research is required to establish causal directions.

4.2.2 Grade III and IV evidence

Of the associations of Grade III evidence, non-specific hearing loss was negatively associated with type 1 diabetes, and sensorineural hearing loss was negatively associated with vertigo. Of the Grade IV quality, age-related hearing loss (ARHL) was negatively associated with diabetes, and pure tone audiometry differences were found with COPD patients. Moreover, non-specific hearing loss was negatively associated

with low bone mineral density or osteoporosis. Due to the lack of quality in these associations, further studies need to be carried out to add credibility to these associations.

4.3 Modifiable risk factors

Of the modifiable risk factors, paediatric tinnitus was negatively associated with noise exposure, noise induced hearing loss was negatively associated with smoking; and sensorineural hearing loss with negatively associated with iron deficiency anaemia. Because all of these associations were of low quality of evidence, it is difficult to conclude if modifiable risk factors are truly associated with any type of hearing impairment. Further homogeneous studies are required to confirm or refute these findings.

Despite the lower quality of evidence regarding hearing loss and modifiable risk factors, it is still recommended that people minimise the risk of damaging the ear wherever possible. These include (a) avoiding loud noises; including (b) taking care when listening to loud music; (c) protecting hearing during loud events and activities; including (d) taking hearing-related precautions at places of work; and (e) having regular hearing tests [51]. Taking these precautions can prevent several hearing related problems and also identify hearing problems at an early stage, which increases the chances of favourable treatment in many cases [51].

4.4 Limitations

Umbrella reviews provide top-tier evidence and important insights, however there are a number of limitations. Although we measured for heterogeneity, the meta-analyses included in this study included differing study designs, methods of measuring different types of hearing impairment and populations, especially regarding age. Furthermore, meta-analyses have inherent limitations [52]: their findings are dependent on estimates that are selected from each primary study and how they are applied in the meta-analysis. Finally, almost all of the studies included scored 'critically low' in the AMSTAR2 tool, indicating high risk of bias [20], and therefore a lower GRADE rating. Some studies were scored low as they had missed critical quality indicators such as confirming review methods or details about excluded studies. It is important that all the quality indicators are included in order to assure confidence in the data presented.

5. Conclusion

Our results show Grade II evidence for associations between ARHL and delayed recall and processing fluency; paediatric bilateral hearing loss with quality of life in both the school and social domains; non-specific hearing impairment with hallucinations, mild cognitive impairment, delusion, delusion like symptoms, or paranoid symptoms; sensorineural hearing loss with rheumatoid arthritis; and tinnitus was associated with temporomandibular disorders. Clinicians should take note of these and consider these associations in the delivery of care. Furthermore, public health policies should reflect and accommodate these associations in healthcare policies, practices and guidelines.

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551

Figure 1: PRIMSA flowchart of included studies

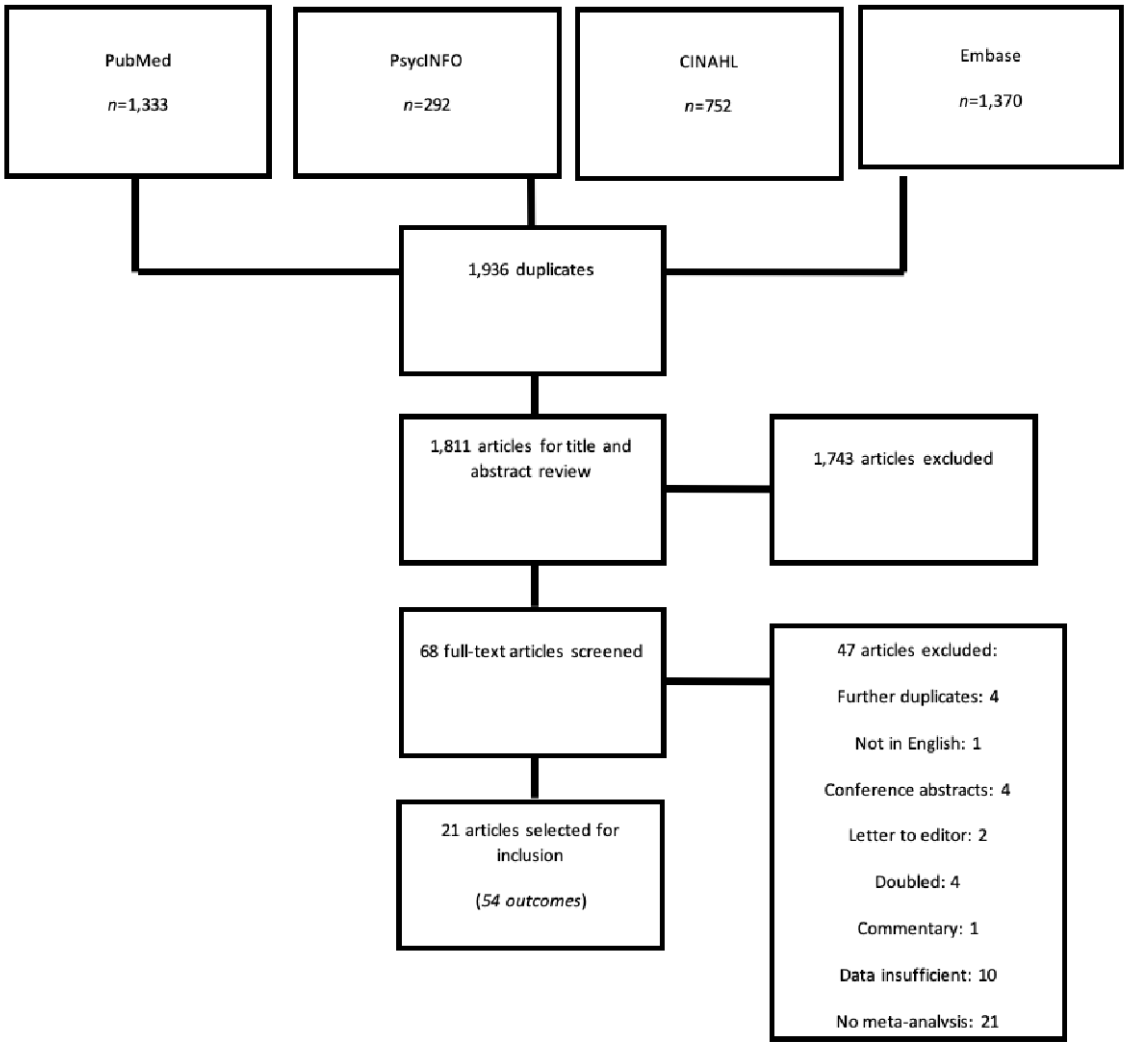

Table 1: Credibility assessment criteria and grading

Grading of evidence	Criteria
Grade I*	- Statistical significance of $p<1*10^{-6}$, including more than 1, 000 cases (or more than 20, 000 participants for continuous outcomes) - Have the largest component study reporting a significant result ($p<0.05$), have a 95% prediction interval that excluded the null, - Did not have large heterogeneity (I^2 <50%) - Showed no evidence of small study effects ($p>0.10$) and excess significance bias ($p>0.10$)
Grade II*	- Significance of $p<0.001$, including more than 1,000 cases (or more than 20, 000 participants for continuous outcomes) - Have the largest component study reporting a statistically significant result ($p<0.05$)
Grade III*	- Significance of $p<0.01$ with more than 1,000 cases (or more than 20, 000 participants for continuous outcomes)
Grade IV	- Remaining significant associations with $p<0.05$

*If studies showed a high risk of bias (defined as an AMSTAR2 score of 'low' or 'critically low'), the studies were downgraded by one level.

Table 2: Descriptive Characteristics of included studies

Author (year)	Hearing impairment type	Author(s) definition concerning respective hearing impairment	Type of Outcome	Outcome	Total included studies	Total participants	Age range	Conflict of Interest
Lin et al (2012)	Sudden sensorineural hearing loss	'sudden hearing impairment of more than 30 dB across three contiguous frequencies in <3 days.'	Modifiable disease risk factor	Smoking	11	5,892	NR	Reported: none declared.
				Heavy alcohol consumption	2	5,193		
			Disease/ disease biomarkers	Hypertension	4	243		
				Diabetes	4	83		
Horikawa et al (2013)	Hearing impairment	Bilateral or unilateral threshold for hearing loss >15dB	Disease/ disease biomarkers	Diabetes	15	25,086	15-86	Reported: none declared.
Chang et al (2015)	Sudden sensorineural hearing loss	'rapid hearing loss of at least 30 dB in 3 contiguous audiometric frequencies within 3 days'	Disease/ disease biomarkers	Total cholesterol	6	1,241	NR	Reported: none declared.
				Low density lipoprotein	4	829		
Roland et al (2015)	Bilateral hearing loss	NR	Mental health/cognition	Quality of life - school domain	4	1,395	6-18	Reported: none declared.
				Quality of life - social domain	4	1,395		
	Unilateral hearing loss			Quality of life - school domain	3	417		
				Quality of life - social domain	3	417		
Linszen et al (2016)	Hearing impairment	'the entire scope of hearing impairment'	Mental health/cognition	Hallucinations	5	227,406	18+	Not reported.
				Delusions	11	250,470	16+	
				General psychotic symptoms	7	229,647	14+	
				Schizophrenia	3	50,490	NR	
				Psychotic disorders	9	8794	30+	
				Delirium	16	12,432	23+	
Purcell et al (2016)	Unilateral hearing loss	NR	Mental health/cognition	Full scale IQ score	4	375	6-18	Reported: one author declares financial support.
				Verbal IQ	3	331		
				Performance IQ	2	250		
Do et al (2017)	Hearing impairment	Mild hearing loss (minimum aided hearing threshold of ≥ 30 dB)	Mental health/cognition	Autism spectrum disorder	7	NR	1-18	Reported: none declared.
Wei et al (2017)	Hearing impairment	NR	Mental health/cognition	Mild cognitive impairment	4	7,524	NR	Reported: none declared
Teng et al (2017)	Hearing loss	Pure-tone threshold over 25 dB at any frequency without specific causes, such	Disease/ disease biomarkers	Type I diabetes	4	505	NR	Reported: none declared

		as presbycusis, noise, and hereditary disorders						
Upala et al (2017)	Hearing loss	'clear diagnostic criteria for hearing loss were reported - conductive, sensorineural, or mixed'	Disease/ disease biomarkers e	Low bone mineral density or osteoporosis	12	NR	NR	Reported: none declared
Loughrey (2018)	Age related hearing loss	NR	Mental health/cognition	Attention	11	5,928	NR	Reported: none declared
				Delayed recall	11	5,991		
				Fluency	13	7,296		
				Immediate recall	21	11,079		
				Processing speed	30	23,743		
				Reasoning	12	4,922		
				Semantic memory	10	3,626		
				Visuospatial ability	5	1,923		
				Working memory	9	6,109		
				Global cognition	21	16,899		
Lee et al (2018)	Hearing loss	NR	Disease/ disease biomarkers	Paediatric tinnitus	9	26,487	5-19	Reported: one author declares financial support.
	Paediatric tinnitus	NR	Modifiable risk factor	Noise exposure	3	7,073		
Ford et al (2018)	Hearing impairment	'ICD-8 and ICD-9 codes 388.12 (hearing loss induced by noise), 388.2 (unspecified sudden hearing loss), 389 (hearing loss, conductive or sensorineural); ICD-10 codes H90 (conductive and sensorineural hearing loss) and H91 (hearing loss due to other causes)'	Mental health/cognition	Dementia	14	68,818	NR	Reported: none declared
				Alzheimer's Disease	5	7,642		
Ji et al (2018)	Sudden sensorineural hearing loss	'hearing loss of at least 30 decibels occurring over at least three consecutive frequencies and lasting at least 3 days'	Disease/ disease biomarkers	Mean platelet volume	12	1,560	NR	Reported: none declared
Yu et al (2018)	Sudden sensorineural hearing loss	'rapid-onset sensorineural hearing loss of more than 30 dB in at least 3 contiguous audiometric frequencies within 3 days.'	Disease/ disease biomarkers	Vertigo	10	4,365	NR	Reported: none declared
Bayat et al (2019)	Pure tone audiometry differences	'hearing assessment in adult COPD patients using conventional PTA, ABR, or auditory P300'	Disease/ disease biomarkers	Chronic obstructive pulmonary disease	4	436	NR	Reported: none declared
Mohammed et al (2019)	Sensorineural hearing loss	NR	Disease/ disease biomarkers	Iron deficiency anaemia	4	344,080	NR	Reported: none declared

Omidvar et al (2019)	Tinnitus	NR	Disease/ disease biomarkers	Temporomandibular disorders	2	21,245	NR	Reported: none declared
Lawrence et al (2020)	Hearing loss	'measures of hearing loss (objective or subjective)'	Mental health/cognition	Depression	42	147,148	NR	Reported: five authors declare financial support.
Chaitidis et al (2020)	Sensorineural hearing loss	'sensorineural, conductive and/or mixed hearing loss'	Disease/ disease biomarkers	Rheumatoid arthritis	12	99,266	NR	Reported: none declared
	Conductive Hearing loss		Disease/ disease biomarkers		6	620		
Li et al (2020)	Noise induced hearing loss	'chronic and irreversible sensorineural hearing loss resulting from long-term exposure to noise'	Modifiable risk factor	Smoking	29	33,269	NR	Reported: none declared

Table 3. Main findings of studies examining hearing impairment and mental health and/or cognition

Hearing impairment type	Outcome	Type of metric	N of studies	Cases	Sample size	Effect size (95% CI)	P	I^2	Small study effect	Excess significance bias	Largest study significant	PI	Level of evidence before RoB assessment	Level of evidence after RoB assessment
Case-control and cross-sectional studies														
Age-related hearing loss	Cognition: processing fluency	Fisher's Z	9	NA	5883	-0.08 (-0.12; -0.04)	<0.001	30.4	No	No	Yes	-0.17; 0.01	Grade I	Grade II
	Cognition: attention	Fisher's Z	11	NA	5928	-0.16 (-0.24; -0.07)	<0.001	87.5	No	No	No	-0.47; 0.15	Grade II	Grade III
	Cognition: delayed recall	Fisher's Z	7	NA	4037	-0.10 (-0.16; -0.04)	0.002	65.0	No	No	No	-0.28; 0.09	Grade II	Grade III
	Cognition: visuospatial ability	Fisher's Z	5	NA	1923	-0.11 (-0.19; -0.03)	0.009	7.7	Yes	No	No	-0.26; 0.05	Grade II	Grade III
	Cognition: immediate recall	Fisher's Z	15	NA	6786	-0.14 (-0.2; -0.09)	<0.001	80.6	No	No	Yes	-0.36; 0.07	Grade II	Grade III
	Cognition: processing speed	Fisher's Z	20	NA	11704	-0.13 (-0.18; -0.08)	<0.001	85.1	No	No	No	-0.35; 0.09	Grade II	Grade III
	Cognition: reasoning	Fisher's Z	12	NA	4922	-0.18 (-0.26; -0.10)	<0.001	75.9	No	No	Yes	-0.45; 0.09	Grade II	Grade III
	Global cognition	Fisher's Z	15	NA	9034	-0.15 (-0.19; -0.11)	<0.001	55.0	No	No	Yes	-0.27; -0.03	Grade II	Grade III
	Cognition: semantic memory	Fisher's Z	10	NA	3626	-0.14 (-0.21; -0.08)	<0.001	65.8	Yes	No	Yes	-0.35; 0.07	Grade III	Grade IV
	Cognition: working memory	Fisher's Z	9	NA	6109	-0.10 (-0.15; -0.05)	<0.001	56.0	Yes	No	No	-0.24; 0.04	Grade III	Grade IV
Non-specific hearing impairment	Delusions, delusion like symptoms, or paranoid symptoms	OR	11	NA	250470	1.55 (1.36; 1.78)	<0.001	24.2	No	No	Yes	1.18; 2.05	Grade I	Grade II
	Schizophrenia	OR	3	NA	50490	3.15 (1.25; 7.95)	0.015	53.7	No	No	Yes	0.00; 56761.98	Grade II	Grade III
Non-specific hearing loss	Depression	OR	27	NA	123728	1.53 (1.34; 1.74)	<0.001	72.6	No	No	Yes	0.90; 2.59	Grade II	Grade III
Unilateral hearing loss	Full-scale IQ score	WMD	4	173	375	-6.88 (-10.67;-3.1)	<0.001	38.9	No	No	No	-20.15; 6.38	Grade II	Grade III

	Performance IQ	WMD	2	131	250	-3.76 (-7.27; -0.25)	0.036	0.0	No	No	No	NA	Grade II	Grade III
	Verbal IQ Scores	WMD	3	152	331	-9.07 (-18.73; 0.58)	0.066	86.2	No	NA	Yes	-127.02; 108.88	NS	NS
Prospective and/or retrospective studies														
Age-related hearing loss	Cognition: delayed recall	Fisher's Z	4	NA	1954	-0.10 (-0.15; -0.05)	<0.001	0.0	No	No	Yes	-0.20; 0.00	Grade I	Grade II
	Cognition: processing fluency	Fisher's Z	4	NA	1413	-0.07 (-0.14; 0.01)	0.074	57.7	No	NA	Yes	-0.36; 0.23	NS	NS
	Cognition: processing speed	Fisher's Z	10	NA	12039	-0.08 (-0.14; -0.03)	0.002	96.9	No	No	Yes	-0.27; 0.11	Grade II	Grade III
	Global cognition	Fisher's Z	6	NA	7865	-0.14 (-0.19; -0.09)	<0.001	73.3	No	No	No	-0.29; 0.01	Grade II	Grade III
	Cognition: immediate recall	Fisher's Z	6	NA	4293	-0.06 (-0.10; -0.02)	0.004	87.7	Yes	Yes	Yes	-0.19; 0.07	Grade III	Grade IV
Non-specific hearing impairment	Hallucinations	OR	5	NA	227406	1.40 (1.18; 1.65)	<0.001	0.0	No	No	Yes	1.07; 1.83	Grade I	Grade II
	Mild cognitive impairment	RR	4	NA	7524	1.30 (1.12; 1.52)	0.001	0.0	No	No	No	0.93; 1.82	Grade I	Grade II
	Psychotic symptoms in general	OR	7	NA	229647	2.23 (1.83; 2.72)	<0.001	0.0	No	No	Yes	1.72; 2.90	Grade I	Grade II
	Delirium	OR	16	NA	12432	2.67 (2.05; 3.48)	<0.001	47.8	Yes	Yes	Yes	1.25; 5.71	Grade II	Grade III
	Dementia	HR	14	NA	68818	1.73 (1.46; 2.04)	<0.001	76.0	Yes	Yes	Yes	1.01; 2.94	Grade III	Grade IV
	Alzheimer's Disease	HR	5	NA	7642	2.15 (1.37; 3.36)	0.001	88.1	Yes	Yes	Yes	0.45; 10.20	Grade III	Grade IV
	Psychotic disorders	OR	9	NA	8794	2.79 (1.25; 6.22)	0.012	86.3	Yes	Yes	No	0.18; 43.59	Grade III	Grade IV
	Autism Spectrum Disorder	RR	7	48541	NR	0.10 (0.03; 0.26)	<0.001	98.2	Yes	Yes	Yes	0.00; 3.00	Grade III	Grade IV
No-specific hearing loss	Depression	OR	15	NA	23420	1.39 (1.11; 1.73)	0.004	90.7	Yes	Yes	Yes	0.57; 3.39	Grade III	Grade IV
Paediatric bilateral hearing loss	QoL - school domain	SMD	4	NA	1395	-0.39 (-0.59; -0.19)	<0.001	0.0	No	No	No	-0.82; 0.04	Grade I	Grade II
	QoL - social domain	SMD	4	NA	1395	-0.25 (-0.48; -0.03)	0.027	22.2	No	No	No	-0.94; 0.43	Grade I	Grade II
	QoL - school domain	SMD	3	NA	417	-0.47	<0.001	0.0	No	No	Yes	-2.13; 1.20	Grade II	Grade III

						(-0.72; -0.21)								
	QoL - social domain	SMD	3	NA	417	-0.27 (-0.52; -0.01)	0.041	0.0	No	No	No	-1.92; 1.39	Grade II	Grade III

Abbreviations: PI=prediction interval; OR= Odds ratio; HR=hazard ratio; RR=risk ratio; SMD=Standard mean difference; WMD=weighted mean difference; QoL = Quality of life; NS= Non-significant; NA = not applicable

Table 4. Main findings of studies examining hearing impairment and disease or disease biomarkers

Hearing impairment type	Outcome	Type of metric	N of studies	Cases	Sample size	Effect size (95% CI)	P	I^2	Small study effect	Excess significance bias	Largest study significant	PI	Level of evidence before RoB assessment	Level of evidence after RoB assessment
Case-control and cross-sectional studies														
Sensorineural hearing loss	Rheumatoid arthritis	OR	10	633	1249	3.42 (2.50; 4.69)	<0.001	13.0	No	No	Yes	1.96; 6.00	Grade I	Grade II
Sudden sensorineural hearing loss	Diabetes	OR	4	41	83	1.44 (0.63; 3.28)	0.389	55.8	No	NA	Yes	0.06; 36.08	NS	NS
	Hypertension	OR	4	100	243	0.99 (0.60; 1.66)	0.977	58.0	No	NA	No	0.13; 7.54	NS	NS
	Mean platelet volume	SMD	12	847	1560	0.16 (-0.07; 0.39)	0.179	80.7	Yes	NA	No	-0.69; 1.00	NS	NS
Conductive Hearing loss	Rheumatoid arthritis	OR	6	371	620	1.37 (0.54; 3.5)	0.511	18.6	Yes	NA	No	0.20; 9.47	NS	NS
Hearing impairment	Diabetes	OR	15	NA	25086	2.15 (1.72; 2.68)	<0.001	76.1	Yes	No	Yes	0.97; 4.75	Grade III	Grade IV
Non-specific hearing loss	Type 1 diabetes	OR	4	252	505	41.69 (9.94; 174.94)	<0.001	0.0	Yes	No	Yes	1.79; 971.27	Grade II	Grade III
	Low bone mineral density or osteoporosis	OR	12	NA	43134	1.20 (1.01; 1.43)	0.041	84.1	Yes	No	Yes	0.64; 2.26	Grade III	Grade IV
Pure tone audiometry differences	COPD	SMD	4	272	436	1.77 (0.29; 3.24)	0.019	96.9	No	No	Yes	-5.34; 8.87	Grade III	Grade IV
Tinnitus	Temporomandibular disorders	OR	2	NA	21245	1.80 (1.64; 1.99)	<0.001	0.0	No	No	Yes	NA	Grade I	Grade II
Prospective and/or retrospective studies														
Sensorineural hearing loss	Rheumatoid arthritis	OR	2	19389	98017	2.28 (1.88; 2.75)	<0.001	0.0	No	No	Yes	NA	Grade I	Grade II
Sudden sensorineural hearing loss improvements	Vertigo	OR	10	NA	4365	2.22 (1.54; 3.20)	<0.001	74.1	No	No	Yes	0.73; 6.74	Grade II	Grade III
Non-specific hearing loss	Paediatric tinnitus	OR	9	NA	26487	2.40 (1.48; 3.88)	<0.001	90.4	Yes	Yes	Yes	0.44; 13.07	Grade III	Grade IV

Abbreviations: PI=prediction interval; COPD= Chronic obstructive pulmonary disease; CHL= total cholesterol; LDL = low-density lipoprotein; OR= Odds ratio; SMD=Standard mean difference; NS= Non-significant

Table 5. Main findings of studies examining hearing impairment and modifiable risk factors

Hearing impairment type	Outcome	Type of metric	N of studies	Cases	Sample size	Effect size (95% CI)	P	I^2	Small study effect	Excess significance bias	Largest study significant	PI	Level of evidence before RoB assessment	Level of evidence after RoB assessment
Case-control and cross-sectional studies														
Sudden sensorineural hearing loss	Heavy alcohol consumption	OR	2	114	5193	1.81 (0.72; 4.56)	0.210	87.6	No	NA	Yes	NA	NS	NS
	Total CHL	OR	5	NA	1241	1.79 (0.98; 3.27)	0.057	76.5	No	NA	Yes	0.27; 11.94	NS	NS
	LDL	OR	4	NA	829	1.18 (0.67; 2.07)	0.568	48.1	No	NA	Yes	0.16; 8.76	NS	NS
	Smoking	OR	11	339	5892	1.39 (0.96; 2.01)	0.078	69.0	Yes	NA	No	0.43; 4.51	NS	NS
Prospective and/or retrospective studies														
Paediatric tinnitus	Noise exposure	OR	3	NA	7073	11.34 (1.87; 68.89)	0.008	97.9	No	No	Yes	0.00; 1302672998 40	Grade II	Grade III
Noise induced hearing loss	Smoking	OR	29	286	33269	2.05 (1.71; 2.46)	<0.001	87.4	Yes	Yes	Yes	0.88; 4.74	Grade III	Grade IV
Sensorineural hearing loss	Iron deficiency anaemia	OR	4	NA	344080	1.55 (1.17; 2.06)	0.002	66.9	Yes	Yes	Yes	0.49; 4.88	Grade III	Grade IV

Abbreviations: PI=prediction interval;; CHL= total cholesterol; LDL = low-density lipoprotein; OR= Odds ratio; NS= Non-significant

Supplementary Table 1: Full details of AMSTAR2 results

Author of Meta-Analysis	Year of Meta-Analysis	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	AMSTAR 2 Rating
Lin et al	2012	Yes	No	Yes	Partial Yes	Yes	Yes	No	No	No	No	Yes	Yes	No	No	No	Yes	Critically low
Horikawa et al	2013	Yes	No	Yes	Partial Yes	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Chang et al	2015	Yes	No	Yes	Partial Yes	Yes	Yes	No	Partial Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Critically low
Roland et al	2015	Yes	No	No	Partial Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	No	No	No	Yes	Critically low
Linszen et al	2016	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Partial Yes	No	Yes	Yes	No	No	Yes	Yes	Critically low
Purcell et al	2016	Yes	No	Yes	Partial Yes	Yes	Yes	No	Yes	Partial Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Do et al	2017	Yes	No	Yes	No	Yes	Yes	No	Partial Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Wei et al	2017	Yes	No	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Critically low
Teng et al	2017	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Critically low
Upala et al	2017	Yes	Yes	Yes	Partial Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Loughrey	2018	Yes	Yes	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	No	No	No	Critically low
Lee et al	2018	Yes	No	Yes	Partial Yes	Yes	Yes	No	Partial Yes	No	No	Yes	No	No	No	Yes	Yes	Critically low
Ford et al	2018	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	No	No	Yes	Critically low
Ji et al	2018	Yes	No	Yes	Partial Yes	Yes	Yes	No	Partial Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Yu et al	2018	Yes	No	Yes	Partial Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	No	No	Critically low
Bayat et al	2019	Yes	No	Yes	Partial Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Critically low
Mohammed et al	2019	Yes	Yes	Yes	Partial Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	No	No	No	Yes	Critically low
Omidvar et al	2019	Yes	No	Yes	Partial Yes	Yes	Yes	No	Partial Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Critically low
Lawrence et al	2020	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Critically low
Chaitidis et al	2020	Yes	Yes	Yes	Partial Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Critically low
Li et al	2020	Yes	No	Yes	Partial Yes	Yes	Yes	No	Partial Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Critically low

AMSTAR@ Questions: Q1: Did the research questions and inclusion criteria for the review include the components of PICO?; Q2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?; Q3: Did the review authors explain their selection of the study designs for inclusion in the review?; Q4: Did the review authors use a comprehensive literature search strategy?; Q5: Did the review authors perform study selection in duplicate?; Q6: Did the review authors perform data extraction in duplicate?; Q7: Did the review authors provide a list of excluded studies and justify the exclusions?; Q8: Did the review authors describe the included studies in

adequate detail?; Q9: Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?; Q10: Did the review authors report on the sources of funding for the studies included in the review?; Q11: If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?; Q12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?; Q13: Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?; Q14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?; Q15: If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?; Q16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?