

# BMJ Open Relation between otitis media and sensorineural hearing loss: a systematic review

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## ABSTRACT

**Objectives** This systematic review summarises the evidence on the correlation between recurrent acute otitis media (rAOM) or chronic suppurative otitis media (CSOM) and sensorineural hearing loss (SNHL).

**Research methods** PubMed, Embase and Cochrane Library databases were searched from inception to 15 January 2021. Two authors independently identified articles, extracted data and performed quality assessment for included studies. Studies comparing the sensorineural hearing levels of patients with a history of rAOM/CSOM for >3 months to a control group were included.

**Results** Screening of 4168 articles lead to inclusion of two case-control studies (control-group: patients non-OM) and seven cohort-studies (control group: contralateral ear). Quality assessment indicated considerable risk of bias in all studies. Reported populations varied (sample size 13–607, mean age 22–41.5 years, mean duration of disease 6.1–12.4 years). The OR for SNHL in the OM-group was 3.30–7.86 (95% CI 1.16 to 9.40,  $p < 0.05$ ) in cohort studies ( $n = 2$ ), and 0.05 (95% CI 0 to 0.78,  $p < 0.05$ ) in a case-control study. Mean/median bone conduction thresholds were respectively 1.19–32.21/0–10 dB higher on all frequencies (0.5–4 kHz) for the OM-group in four cohort studies ( $p < 0.05$ ). Two other studies reported no statistical test outcomes.

**Conclusion** Due to the high risk of bias of included studies, effect estimates heterogeneity and suboptimal research designs, no conclusion on the correlation between OM and SNHL can be made. It emphasises the need for future prognostic studies.

## INTRODUCTION

Otitis media (OM) has a great variety in presentation; it can occur transient as acute otitis media (AOM) and OM with effusion, or persistent as recurrent AOM (rAOM) and chronic suppurative otitis media (CSOM).<sup>1</sup> It impacts lives worldwide, with global incidence rates estimated at 11% for AOM and 5% for CSOM, of which respectively 51% and 23% are children.<sup>2</sup> The exact incidences of the OM-subtypes vary between populations, depending on social, demographic and genetic factors for instance.<sup>1</sup>

## Strengths and limitations of this study

- A minimal otitis exposure of 3 months was adhered to safeguard presence of inner-ear toxin-exposure before outcome assessment.
- A lack of prognostic studies complicates interpretation of effect estimates.
- Heterogeneity of definitions for otitis media and sensorineural hearing loss among studies complicate comparability.
- Recruitment of patients in an otolaryngology setting with audiogram data introduces selection bias.
- Deficits in longitudinal design and methodology limit the quality of our results.

During the acute inflammatory process, OM can lead to conductive hearing loss (HL).<sup>3</sup> In children, this transient loss during the acute phase has not been related to a significant risk of delayed speech development or impaired school performance later on.<sup>4,5</sup> Though, the inflammatory process of the middle ear can be detrimental to the inner ear as shown in histological and animal studies.<sup>6–8</sup> During the inflammatory process, toxins can initiate damage to the round window membrane. This leads to diffusion of toxins to the inner ear and leakage of inner ear fluids, resulting in cochlear function loss; a permanent loss.<sup>6–8</sup> Until, it remains unknown how many episodes of OM, and what duration of disease lead to inner ear HL.

Given the age-related deterioration of inner-ear function, additional OM-related cochlear damage may become more prominent in later life. In observational studies, a statistical significant higher risk of developing permanent conductive and/or sensorineural hearing loss (SNHL) in adulthood has been demonstrated after experiencing CSOM at childhood age.<sup>9–11</sup> Several studies reported incidence numbers of SNHL up to 23%–24% in patients with CSOM.<sup>12,13</sup> In contrast to other risk factors for SNHL, OM

is considered treatable by antibiotic or surgical interventions, which are available treatment options in most countries.<sup>7</sup> Though, up to this day, consensus on the long-term hearing effects of OM has not been met, which complicates drawing conclusions and making recommendation for clinical care.<sup>13</sup>

Considering the above, we recognise a need for evidence on the effect of OM on sensorineural hearing levels in time. This knowledge could contribute to establish the best treatment guideline for this common condition, avoiding possible adverse long-term effects. We therefore conducted a systematic review to summarise the evidence on the correlation between rAOM or CSOM and SNHL in time.

## METHODS

### Patient and public involvement

No patients were involved.

### Reporting

We applied the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline for this systematic review.<sup>14</sup>

### Search strategy

On 15 January 2021, a systematic search was performed in Embase, PubMed and Cochrane Library databases. No filters were applied. We used search terms and synonyms for the domain (CSOM, rAOM) and outcome (SNHL), including Emtree, and medical subject headings (MeSH) term fields. Used synonyms for the domain were otitis media, (middle) ear infection/inflammation and abbreviations. Used synonyms for the outcome were hearing loss/impairment, deafness, cochlear dysfunction, hypacusis and inner ear impairment (Search syntax in online supplemental appendix 1). Although SOM did not apply to the study domain, it was included as a synonym to prevent exclusion of relevant articles during the initial search.

### Study selection

Two authors blindly screened studies for inclusion (HBEE, HDvO), and disagreements were resolved by discussion. Where disagreements could not be resolved, a third reviewer (IS or ALS) made the final decision. Prognostic, cohort and cross-sectional studies were included. Cohort studies were categorised in retrospective or prospective study designs. Where this was methodologically unclear, the study was labelled as cohort study. Conference abstracts, or case reports were excluded. In case of an unavailable full text or abstract, the author was contacted to request full text. Reference screening and backwards citation tracking were performed to identify any missed literature. Rayyan was used as screening tool.<sup>15</sup> Full text screening and data extraction were independently performed by two authors (HBEE, HDvO).

Original studies reporting on hearing outcome of patients of all ages with rAOM or CSOM and a control-group were included. Studies including participants with SNHL-related syndromes, cholesteatoma or a history of ear surgery were excluded, as these factors independently cause SNHL. Articles that reported outcomes for several subgroups, of which only a selection met the inclusion criteria, data of that section were extracted and included in the analysis. CSOM was defined as a minimal presence of OM for three consecutive months or longer. Studies that included patients with OM of more than 3 months or had a minimal follow-up of 3 months were included. These criteria were set to safeguard a minimum period of 3 months in which inner-ear toxin exposure was present, before outcomes were assessed. Studies reporting effect estimates on hearing outcome for both the exposed and control-group were selected. To establish the relation between OM and SNHL, a shift of >5 dB in hearing level between tone audiometric test results was found relevant considering the search range of 5 dB during these test procedures.<sup>16</sup>

### Data collection and analysis

#### Quality assessment of the studies

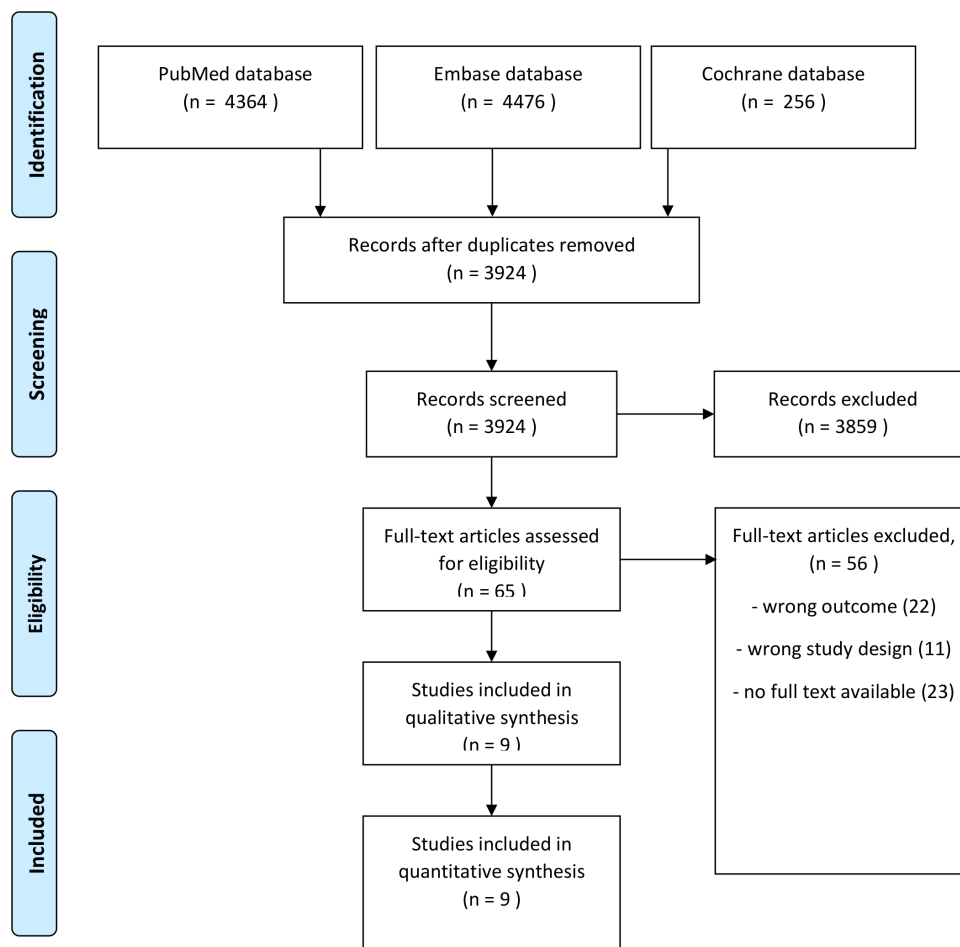
Critical appraisal of included studies was independently performed by two reviewers (HBEE, HDvO) for validity and relevance. The Quality In Prognosis Studies (QUIPS) tool was used to assess risk of bias for prognostic study designs, and the Newcastle-Ottawa Scale (NOS) was used for cohort and case-control studies.<sup>17 18</sup> To score risk of bias consistently, criteria were predefined for both tools by the authors (online supplemental appendix 2). (HBEE, HDvO) Using these tools, studies could be scored to contain low, moderate or high risk of bias (QUIPS), or to be of good, fair or poor quality (NOS). Differences in the appraisal of studies between the two reviewers in either tool were resolved through discussion.

#### Data and outcome extraction

Data on study and patient characteristics, follow-up and bone conduction (BC) hearing outcome of the included patients were independently extracted by two reviewers (HBEE, HDvO). The primary outcome measure of cases and controls was reported in BC thresholds (dB) per frequency (0.5–4 kHz) and/or average hearing levels. Age, duration of disease and the use of ototoxic ear drops were considered as confounding factors for outcomes of SNHL in groups.

#### Outcome measures and analyses

ORs were either extracted directly or calculated by the authors (HBEE, HDvO) if data were sufficient. If an OR could not be extracted or calculated, means and medians were extracted. A p value of <0.05 was considered statistically significant. A meta-analysis was performed in case of methodologically homogenous studies.



**Figure 1** Flow chart for included studies. Last date of search 15 January 2021 Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 flow diagram.<sup>14</sup>

## RESULTS

### Search strategy and study collection

The search identified 4168 articles (figure 1). After removal of duplicates, 3725 (89.4%) studies were screened based on title and abstract, as a result of which 3662 (98.3%) studies were excluded. After full-text analysis, 54 articles were excluded based on the outcome (n=22), study design (n=9) or by unavailability of the full text (n=23). No articles were received after correspondence with authors for full text. This resulted in a total of nine articles meeting all inclusion criteria.<sup>19–27</sup> Seven studies were cohort studies with a retrospective or prospective study design, or not further specified design.<sup>19 20 22 24–26 28</sup> Two studies were case-control studies.<sup>23 27</sup> No prognostic studies were found. Due to the methodological heterogeneity in included studies, no meta-analysis could be performed.

### Quality of the included articles

Critical appraisal of all studies was performed with the NOS (table 1). The quality of included studies ranged from good (n=5),<sup>19 20 26–28</sup> to fair (n=2),<sup>23 25</sup> and poor (n=2).<sup>22 24</sup>

### Selection

Selection bias was present in all studies, as patients were visiting an otolaryngology department before inclusion, none of the studies included a longitudinal cohort of the general population. Also, there was no objective demonstration that SNHL was not present before inclusion.<sup>19–27</sup> One study included self-reported diagnosis of OM instead of a doctor diagnosis.<sup>23</sup> Another study did not document information on recruitment of the cohort.<sup>25</sup>

### Comparability

Most studies excluded patients with a history of ototoxic drug use.<sup>19 22 24–27</sup> Case-control studies matched cases and controls according to age and gender,<sup>23 27</sup> cohort studies used the contralateral ear as control-group.<sup>19–22 24–26</sup> Hearing outcomes were not corrected for known or unknown confounding factors in the included studies.<sup>19–27</sup>

### Outcome

Rana *et al*'s study was the only study scoring low risk of bias for the outcome domain.<sup>26</sup> All other studies did not report information on missing data or loss to follow-up.<sup>19 20 23 25 27 28</sup> Two studies could not guarantee a minimum duration of disease of 3 months for all

**Table 1** Risk of bias assessment of included studies according to the Newcastle-Ottawa Quality Assessment Scale

Author (year)	Amali (2017)	de Azevedo (2007)	da Costa (2009)	Kolo (2011)	Krakau (2017)	Paparella (1984)	Papp (2003)	Rana (2019)	Subramaniam (2020)
Domain									
Selection Max: 4★	3★	3★	3★	3★	2★	3★	2★	3★	3★
Comparability Max: 2★	1★	1★	1★	1★	1★	1★	1★	1★	1★
Outcome Max: 3★	2★	2★	2★	1★	2★	1★	2★	3★	2★
Quality assessment	G	G	G	P	F	P	F	G	G

Risk of bias assessment of included studies according to the Newcastle-Ottawa Quality Assessment Scale.<sup>17</sup>

F, fair quality; G, good quality; Max, maximum; P, poor quality.

their included patients.<sup>22–24</sup> Demographic information of included patients was retrieved from chart reviews. Otoscopy and audiometry were performed by trained personnel using conventional equipment.<sup>19–27</sup> Only the study of de Azevedo *et al* reported that audiometry exams were carried out blinded in double by two independent professionals.<sup>20</sup>

### Data extraction and study characteristics

#### Trial design and study sample

Included studies were published between 1984 and 2019 and pertained to patients from Africa, Asia, Europe, North America and South America (table 2). The sample sizes for the OM-group in cohort and case-control studies ranged from 70 to 607 (controls 70–534) and 13–137 (controls 13–137), respectively. Cohort studies used the contralateral ear as control-group.<sup>19–22 24–26</sup> Case-control studies used adults with <2AOM episodes until 30 years of age<sup>23</sup> and volunteers of same age and gender<sup>27</sup> as control group. Mean duration of disease varied between 6.1 and 12.4 years (range 0.2–42 years) in the four studies reporting it.<sup>19 20 22 25</sup> The mean age of patients was 22–41.5 years (range 0.25–73 years). Most study populations included both adults and children, except for two studies.<sup>23 25</sup> Paparella *et al* did not describe the age of included patients, but excluded patients older than 60 years.<sup>24</sup>

#### Definitions for OM and SNHL

The included studies handled different inclusion criteria for the OM-group, namely: unilateral otorrhea >2 or >3 months with a tympanic membrane perforation (TMP),<sup>19 22 26</sup> chronic unilateral otorrhea,<sup>20</sup> inflammation of the middle ear compartment (MEC) of >3 months,<sup>21</sup> rAOM defined as ≥3 episodes of AOM during 6 months or ≥4 episodes during 12 months,<sup>23</sup> a history of recurrent otorrhea within 3 years before data assembly,<sup>24</sup> and chronic inflammation of the MEC with recurrent episodes

of otorrhea through a TMP.<sup>27</sup> For Krakau *et al*, no criteria for inclusion in the OM-group were reported.<sup>23</sup>

Four studies defined their outcome as difference in BC threshold (dB) for cases and controls.<sup>19 21 22 25</sup> Four other studies defined a specific BC threshold level to establish cases with SNHL, namely: ≥30 dB,<sup>20</sup> ≥15 dB/≥30 dB/any loss at 4 kHz,<sup>24</sup> ≥25 dB,<sup>26</sup> and ≥20 dB.<sup>27</sup> Papp *et al*<sup>25</sup> did not report a hearing outcome definition to be considered as SNHL.

### Results—outcomes

Three studies (2 cohort studies, 1 case-control study) reported ORs for the presence of SNHL after 3 months or longer exposure to OM (tables 3 and 4).<sup>20 24 27</sup> The other six studies (5 cohort studies, 1 case-control studies) reported their outcome as a mean and/or median BC threshold for the OM-group and the control-group (tables 5 and 6).<sup>19 21–23 25 26</sup>

#### Outcomes in cohort studies

The OR for having SNHL could be extracted or calculated in two cohort studies comparing the contralateral to the diseased ear (table 3).<sup>20 24</sup> Both reported higher ORs for the presence of SNHL after 3 months or longer exposure to OM. Paparella *et al* reported an OR of 7.86 for a BC loss of ≥15 dB at ≥2 frequencies, 6.49 for BC loss of ≥30 dB at ≥2 frequencies, and 4.41 for any BC loss at 4 kHz (95% CI not reported).<sup>24</sup> For de Azevedo *et al*, the OR was 3.30 (95% CI 1.16 to 9.40, p=0.03).<sup>20</sup>

Five cohort studies reported a mean,<sup>19 22 26</sup> or both mean and median<sup>21 25</sup> for the BC hearing levels per frequency, stratified per study group (table 5). Of those, four studies had a higher mean and/or median BC threshold in the OM-group compared with the control-group for all individually tested frequencies (0.5–4 kHz).<sup>19 21 22 26</sup> Mean and/or median differences between both groups per frequency ranged from 1.19 to 32.21 dB (p<0.05) for means and 0–10 dB (p<0.05) for medians.<sup>19 21 22 26</sup> Papp

**Table 2** Characteristics of studies included in systematic review

Author (country, year of publication)	Study design	Sample size OM group (control group)	Control group	Mean duration of disease in years:±SD (min-max)	Mean age in years ±SD (min-max)	OM-group definition	SNHL outcome definition
Amali (Iran, 2017)	RCS	70 (70)	CE	6.5±7.1 (0.25-30)	37.9±15 (0.25-30)	Unilateral otorrhea >3 months and TMP	Difference in BC threshold for cases and controls BC loss of ≥30 dB
de Azevedo (Brazil, 2007)	RCS	115 (115)	CE	12.4±10.9 (1-42)	26.3±15.7 (4-59)	Chronic unilateral otorrhea	
da Costa (Brazil, 2009)	RCS	150 (150)*	CE	NR	22±13 (3-55)	Inflammation of MEC >3 months	Difference in BC threshold for cases and controls
Kolo (Nigeria, 2011)	RCS	69 (69)	CE	6.1±6.4 (0.2-20)	28.9±18.6 (4-73)	Unilateral otorrhea >2 months and TMP	Difference in BC threshold for cases and controls
Krakau (Sweden, 2017)	Case-control	13 (15)	<2 AOM episodes until 30 years of age	±	30.1-31.8†	rAOM: ≥3 episodes of AOM during 6 months or ≥4 episodes during 12 months	NR
Paparella (Multicenter†, 1984)	CS	607 (534)	CE	NR	NR	History of recurrent otorrhea <3 years of selection date	BC loss of ≥15 dB, ≥30 dB or any loss at 4 kHz
Papp (Hungary, 2003)	RCS	121 (121)	CE‡	10.0±9.6	36.9±14.3	NR	Difference in BC threshold for cases and controls
Rana (India, 2019)	PCS	146 (146)	CE	NR	41.5±8.9 (10-60)	(Unilateral) otorrhea >3 months and TMP	BC threshold of ≥25 dB
Subramaniam (Iran, 2020)	Case-control	137 (137)	Volunteers of same age and gender	NR	(11-45)	Chronic inflammation of MEC with recurrent episodes of otorrhea through a TMP	BC loss of ≥20 dB at 0.25-4 kHz¶

The characteristics of the included studies are presented.

\*Including 31% patients with cholesteatoma.

†Multicentre study reporting on subjects from Minnesota, Italy, Finland, Sweden, Korea and New York.<sup>24</sup>

‡Research population ±30 years of age with a history of recurrent acute otitis media (rAOM) during childhood.<sup>23</sup>

§Averages in bone conduction (BC) threshold of the contralateral (normal) ear were subtracted from that of the chronic suppurative otitis media (OM) side.<sup>25</sup>

¶The obtained thresholds were used to quantitatively assess the degree of hearing loss using Clark's (1981) modification of Goodman classification of severity of hearing loss (1965).<sup>27</sup>

CE, contralateral ear; CS, cohort study; MEC, middle ear compartment; NR, not reported; PCS, prospective cohort study; RCS, retrospective cohort study; SNHL, sensorineural hearing loss; ; TMP, tympanic membrane perforation.

**Table 3** Results of studies included in systematic review: OR of having sensorineural hearing loss (SNHL) when exposed to otitis media (OM) in cohort studies

Author (year)	Control group	SNHL outcome description	OR (95% CI)	P value
de Azevedo* (2007)	CE	BC loss of $\geq 30$ dB	3.30 (1.16 to 9.40)	0.03
Paparella (1984)	CE	BC loss $\geq 15$ dB at $\geq 2$ frequencies	7.86 (NR)	<0.05
		BC loss $\geq 30$ dB at $\geq 2$ frequencies	6.49 (NR)	<0.05
		BC loss a 4 kHz only	4.41 (NR)	<0.05

Relevant results reported in OR for having SNHL when exposed to OM compared with controls (contralateral ear (CE))<sup>20 24</sup> in cohort studies.

\*OR was calculated manually using the reported data of the study by authors (HBEE, HDvO).

BC, bone conduction.;

*et al* reported the mean and median BC threshold for low (0.5–2 kHz) and high (4 kHz) frequencies. The mean differences were higher for the OM-group compared with the control-group, though no statistical significance was determined.<sup>25</sup>

#### Outcomes in case-control studies

Subramaniam *et al* reported data that were sufficient to calculate the OR (table 4: 0.05 (95% CI 0.00 to 0.78,  $p=0.03$ ) for SNHL when comparing the patients with OM to healthy volunteers, with SNHL defined as a BC loss of  $\geq 20$  dB at 0.25–4 Hz (table 4).<sup>27</sup>

In one case-control study by Krakau *et al*, the authors reported median BC thresholds for the OM and control-group, stratified for the left and right ear (table 6). The right ear showed a higher BC threshold (difference 10 dB, no  $p$  value) for the OM-group compared with the control-group at 3 kHz. For all other frequencies, of both the right and left ear, the BC threshold difference between the groups was 5 dB or less.<sup>23</sup>

## DISCUSSION

In this study, we described the results of a systematic search on the relation between rAOM or CSOM and the occurrence of SNHL in time. Two case-control studies (control-group: patients with non-OM) and seven cohort-studies (control-group: contralateral ear) reported hearing outcomes for both the exposed and control-group.<sup>19–26</sup> The OR for the presence of SNHL after a minimal exposure to OM of 3 months was statistically significantly higher in two cohort studies,<sup>20 24</sup> but lower in one case-control study.<sup>27</sup> Studies in which no OR was provided or could be calculated, mean and/or median BC thresholds were statistically significantly higher in the OM-group in four out of six studies. Mean or

median differences between both groups ranged between 1.19–32.21 dB and 0–10 dB, respectively.<sup>19 21 22 26</sup> The other two studies reported differences of 0–5 dB in mean or median between OM-group and the contralateral ear<sup>25</sup> or controls,<sup>23</sup> though did not provide outcomes of statistical testing between groups. Outcomes of included studies should be interpreted cautiously by the small shift in hearing thresholds observed. Besides this, the heterogeneity between studies, the limited quality of included studies and the lack of prognostic studies are all major limitations to draw conclusions about the effect of OM on SNHL.

None of the included articles assessed the effect of duration of the OM on SNHL. A longer period of exposure of the inner ear to inflammation, and therefore to toxins, could increase the portion of patients with SNHL.<sup>29</sup> Previous population studies analysed the effect of the duration of the OM on hearing levels. Thakur *et al* studied 100 cases (15–50 years of age) presenting with unilateral mucosal COM. They found an SNHL incidence of 23% (hearing level  $>20$  dB), with a statistically significant positive correlation between duration of disease and SNHL.<sup>12</sup> A comparable SNHL incidence of 24% in 100 unilateral CSOM cases (aged 11–50 years) was published by Kaur *et al*, where the SNHL incidence (defined as hearing level  $>20$  dB) increased with the duration of disease (up to  $>30$  years).<sup>13</sup>

Besides exposure-time, one should take the following into consideration. Included studies were heterogenous due to varying sample sizes, age of study populations, definitions used for the OM-group, criteria for SNHL and method of reporting of outcome. Recruitment of patients was mostly done in an ENT-setting, and some studies handled absence of an audiogram as exclusion criterion which introduces selection or information bias. For example, Kolo *et al* excluded patients if they had

**Table 4** Results of studies included in systematic review: OR of having sensorineural hearing loss (SNHL) when exposed to otitis media (OM) in case-control studies

Author (year)	Control group	SNHL outcome description	OR (95% CI)	P value
Subramaniam* (2020)	Volunteers of same age and gender	BC loss of $\geq 20$ dB at 0.25–4 kHz	0.05 (0.00 to 0.78)	0.03

Relevant results reported in OR for having SNHL when exposed to OM compared with controls (healthy 'volunteers' of same age and gender)<sup>27</sup> in case-control studies.

\*OR was calculated manually using the reported data of the study by authors (HBEE, HDvO).

BC, bone conduction.;

**Table 5** Results of studies included in systematic review: mean and median bone conduction (BC) thresholds of the otitis media (OM)-group and the contralateral ear

Author (year)	Effect estimate reported in dB: Mean±SD Median (min/max)		Frequency						
			0.25 kHz	0.5 kHz	1 kHz	1.5 kHz	2 kHz	3 kHz	4 kHz
Amali (2017)	Mean	OM-group	–	17.57±13.93	18.36±16.30	–	21.71±16.92	–	21.71±16.92
		Control-group	–	10.57±9.07	10.81±9.96	–	13.21±12.10	–	18.29±14.77
	P value	–	<0.001	<0.001	–	<0.001	–	<0.001	
da Costa (2009)	Mean	OM-group	–	6.63±9.06	6.88±9.01	–	8.81±8.28	12.44±9.41	12.56±10.40
		Controlgroup	–	5.44±5.69	4.69±4.80	–	5.25±4.96	6.00±4.73	5.69±5.20
		P value	–	0.001	0.001	–	<0.0001	<0.0001	<0.0001
	Median	OM-group	–	5 (0/50)	10 (0/50)	–	10 (0/40)	15 (0/40)	15 (0/50)
	Control-group	–	5 (0/20)	5 (0/15)	–	5 (0/20)	5 (0/20)	5 (0/20)	
Kolo (2011)	Mean	OM-group	–	32.46±14.587	36.06±14.140	–	42.18±15.183	–	45.511±15.384
		Control-group	–	10.14±4.470	10.14±5.208	–	9.97±4.585	–	10.99±3.930
	P value	–	<0.05	<0.05	–	<0.05	–	<0.05	
Papp (2003)	Mean	OM-group	–	10.4 ±4.89				–	11.9±6.78
		Control-group	–	4.49 ±3.947				–	3.10±4.510
		P value	–	NR				–	NR
	Median	OM-group	–	10 (3.3/30)				–	3.34 (0/21.67)
	Control-group	–	10 (2.5/35)				–	2.5 (0/30)	
Rana (2019)	Mean	OM-group	–	23.50±4.5	24.06±2.4	–	36.18±5.6	–	40.50±6.4
		Control-group	–	18.40 (SD 4.2)	16.6±2.1	–	9.90±4.1	–	11.00±5.2
	P value	–	<0.001	<0.001	–	<0.001	–	<0.001	

Relevant results of BC thresholds reported in mean and/or median of cohort studies included in systematic review are presented.

**Table 6** Results of studies included in systematic review: median bone conduction (BC) thresholds of the otitis media (OM)-group and the control-group

Author (year)	Effect estimate reported in dB: Mean±SD Median (min/max)		Frequency						
			0.25 kHz	0.5 kHz	1 kHz	1.5 kHz	2 kHz	3 kHz	4 kHz
Krakau (2017)	Median	OM-group	5	5	0	0	10	10	0
		Right ear	(0/20)	(0/15)	(–5/10)	(–10/25)	(0/20)	(–5/25)	(–5/25)
		Control-group	0	5	0	0	10	0	5
		Right ear	(–5/10)	(–5/10)	(–10/10)	(–10/15)	(–10/40)	(–5/10)	(–10/20)
		OM-group	5	5	0	0	10	5	5
		Left ear	(0/20)	(0/20)	(–10/10)	(–10/10)	(–5/45)	(–5/25)	(–5/25)
		Control-group	5	5	0	5	10	0	0
		Left ear	(–5/10)	(0/15)	(–5/10)	(–5/20)	(0/45)	(–5/10)	(–10/15)
	P value		NR						

Relevant results of BC thresholds reported in mean and/or median of case-control studies included in systematic review are presented.

'incomplete' clinical records or no audiograms.<sup>22</sup> Age was accounted for by matching cases and controls or by using the contralateral ear. The use of the contralateral ear as non-affected control-group in cohort studies had the advantage of limiting the effect of inter-subject variations. On the other hand, if this ear suffered from infection prior to the study start, but was free of disease during the inclusion process, this could influence outcomes. However, in case-control studies, it could not be guaranteed that their control-group was free of previous OM-exposure.<sup>22-24</sup> For instance, Krakau *et al* included a patient with 10 self-reported episodes of AOM in the control-group.<sup>23</sup> As stated above, no prognostic studies were included, and a meta-analysis could not be performed due to heterogeneity of reported results. A limitation of the present study is the considerable number of studies of which the full text could not be retrieved.

One could hypothesise that when inflammatory toxins are detrimental to the inner ear, the higher frequencies could be most affected considering their location at the base of the cochlea and in proximity of the inflammatory process in the middle ear. Four out of seven of our included studies reporting mean and/or median BC thresholds show a larger difference in HL in the higher frequencies (up to 4kHz). This is of interest for further studies as it could make people prone for HL in the middle frequency by progression of a high frequency HL by ageing.

The lack of longitudinal study designs and the selected sample of population studied so far hinder strong conclusions. In order to overcome this methodological flaw, studies with a longitudinal design, assessing a random sample of children and adults with and without OM for several decades is necessary.<sup>30</sup>

## CONCLUSION

Considering the high risk of bias and the suboptimal research design of current evidence, no conclusions could be made about the relation between OM and SNHL in time. The high impact of SNHL on daily life, the high prevalence of OM in children and adults, and its potential effect on hearing, underpin the need for longitudinal studies assessing the effect of OM on HL in time.

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## APPENDIX 1: Search syntax

<b>PUBMED SEARCH</b>
"Otitis Media"[Mesh] OR otitis media[Title/Abstract] OR ear infection*[Title/Abstract] OR ear inflammation*[Title/Abstract] OR otiti* media[Title/Abstract] OR middle ear inf*[Title/Abstract] OR OME[Title/Abstract] OR OMA[Title/Abstract] OR CSOM[Title/Abstract] OR otitides[Title/Abstract] OR ACSOM[Title/Abstract]
AND
"Hearing Loss"[Mesh] OR hearing loss*[Title/Abstract] OR deafness[Title/Abstract] OR cochlear dysfunction*[Title/Abstract] OR hypoacusis[Title/Abstract] OR hearing impairment[Title/Abstract] OR inner ear impairment[Title/Abstract]
<b>EMBASE SEARCH</b>
'otitis media'/exp OR 'otitis media':ti,ab,kw OR 'ear infection*':ti,ab,kw OR 'ear inflammation*':ti,ab,kw OR 'otiti* media':ti,ab,kw OR 'middle ear inf*':ti,ab,kw OR 'OME':ti,ab,kw OR 'OMA':ti,ab,kw OR 'CSOM':ti,ab,kw OR 'otitides':ti,ab,kw OR 'ACSOM':ti,ab,kw
AND
'inner ear hearing loss'/exp OR 'hearing loss*':ti,ab,kw OR 'deafness':ti,ab,kw OR 'cochlear dysfunction*':ti,ab,kw OR 'hypoacusis':ti,ab,kw OR 'hearing impairment':ti,ab,kw OR 'inner ear impairment':ti,ab,kw
<b>COCHRANE SEARCH</b>
"otitis media":ti,ab,kw OR "ear infection*":ti,ab,kw OR "ear inflammation*":ti,ab,kw OR "otiti* media":ti,ab,kw OR "middle ear inf*":ti,ab,kw OR "OME":ti,ab,kw OR "OMA":ti,ab,kw OR "CSOM":ti,ab,kw OR "otitides":ti,ab,kw OR "ACSOM":ti,ab,kw
AND
"hearing loss*":ti,ab,kw OR "deafness":ti,ab,kw OR "cochlear dysfunction*":ti,ab,kw OR "hypoacusis":ti,ab,kw OR "hearing impairment":ti,ab,kw OR "inner ear impairment":ti,ab,kw

**APPENDIX 2: predefined risk of bias consistently criteria****The Quality In Prognosis Studies tool (QUIPS)**

Domain	Criteria
Study Participation	- In-/exclusion criteria: if only including patients with audiograms, choose no (selection bias). - Baseline characteristics: when most important factors are described but no table is given, choose yes.
Study attrition	No additional criteria
Prognostic factor measurement	- Definition of the prognostic factor: must contain >3 months.
Outcome measurement	No additional criteria
Study confounding	- Confounders: age, duration of disease, (prior) use of ototoxic ear drugs.
Statistical analysis and reporting	No additional criteria

**Newcastle-Ottawa Score (NOS)**

Category	Criteria
• Selection	No additional criteria
• Comparability	- Total of 1 star when accounting for age (cohort: contralateral ear; case-control: matching). - Total of 2 stars when also accounting for duration of disease and prior use of ear drugs.
• Outcome	- Choose record linkage when outcome information was derived from chart reviews. - Follow up was long enough when duration of disease was >3 months.