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Association between auditory system pathology and sudden infant death syndrome (SIDS): a systematic review

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ABSTRACT

Objective A theory has emerged, suggesting that abnormalities in the auditory system may be associated with sudden infant death syndrome (SIDS). However, current clinical evidence has never been systematically reviewed.

Design A systematic review was conducted according to the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Data sources PubMed, Embase and Web of Science were systematically searched through 7 September 2020.

Eligibility criteria for selecting studies Only human studies with a reference group were included. Studies were eligible for inclusion if they examined infants exposed to otoacoustic emissions (OAEs), auditory brainstem response (ABR) or had autopsies with brainstem histology of the auditory system. SIDS was the primary outcome, while the secondary outcome was near-miss sudden infant death syndrome episodes.

Data extraction and synthesis Two independent reviewers extracted data and assessed risk of bias, and the quality of evidence. Due to high heterogeneity, a narrative synthesis was conducted. Risk of bias and quality of evidence was assessed using the Newcastle-Ottawa Scale and Grading of Recommendations Assessment, Development and Evaluation.

Results Twelve case–control studies were included. Seven studies on OAEs or ABR had a high degree of inconsistency. Contrarily, four out of five studies reporting on brainstem histology found that auditory brainstem abnormalities were more prevalent in SIDS cases than in controls. However, the quality of evidence across all studies was very low.

Conclusion This systematic review found no clear association between auditory system pathology and SIDS. The higher prevalence of histological abnormalities in the auditory system of SIDS may indicate an association. However, further studies of higher quality and larger study populations are needed to determine whether these findings are valid.

PROSPERO registration number CRD42020208045.

Strengths and limitations of this study

- ► This is the first systematic review based on human studies that investigates the association between the auditory system pathology and sudden infant death syndrome.
- ► The systematic review was reported according to the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
- ► Risk of bias was assessed systematically with the validated Newcastle-Ottawa Scale for case–control studies.
- ► Due to the heterogeneity of the included studies, this is a narrative systematic review without meta-analysis.

INTRODUCTION

Sudden infant death syndrome (SIDS) is defined as the sudden death of an infant under the age of 1 year occurring unexpectedly, with no other potential explanation of death and absence of any other pathological diagnosis at autopsy.[1] The recommendation for infants to sleep in a supine position has significantly decreased the incidence of SIDS.[2] In the UK, SIDS incidence decreased from 2.3 per 1000 live births in 1988 to 0.77 per 1000 live births in 1992 after the 'back to sleep' campaign, with similar trends being observed in other Western countries.[3 4] However, SIDS is still one of the leading causes of death in infancy (0.30 per 1000 live births) and a scientific mystery.[4] A near-miss sudden infant death syndrome (NMSIDS) episode may be considered as a precursor before an actual SIDS event. However, evidence for this association is limited.[5–7] NMSIDS is also known as an apparent life-threatening event (ALTE), which to some degree has replaced the term NMSIDS.[7] Previous studies have examined infants surviving NMSIDS episodes anticipating to improve the understanding of SIDS.[8 9]

Even though SIDS is a diagnosis of exclusion, deficiencies in the cardiorespiratory system and arousal response are believed to play an important role in SIDS.[10–12] Human and animal studies have indicated that the inner ear is connected to the respiratory system and may be essential for the arousal response.[13–18] Furthermore, the anatomical

proximity between the respiratory system and the auditory pathway in the brainstem imply that there may be synaptic connections.[19 20] If abnormalities in the auditory system are associated with SIDS and may be captured by newborn hearing screening, we would be able to follow infants at risk and potentially reduce the number of SIDS cases further. Two methods are used for newborn hearing screenings: otoacoustic emission (OAE)[21 22] and auditory brainstem response (ABR).[23 24] OAE examines hearing from the external ear to the cochlea, while ABR tests the entire auditory pathway reaching the auditory cortex. Furthermore, if abnormalities of the auditory pathway can be shown histologically, we would get one step closer to a biological understanding of the cause of SIDS.

Several studies have investigated this association. However, current human evidence has never been compiled. This systematic review aims to provide a comprehensive overview of the literature on the association between auditory system pathology measured by newborn hearing screening or autopsy with histology of the brainstem and SIDS. Additionally, NMSIDS and ALTE are included as secondary outcomes to investigate the possible association.

METHODS

This systematic review was conducted according to the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[25] A protocol with predefined methods, search strategy and inclusion criteria was registered at the International Prospective Register of Systematic Reviews on 7 September 2020 (registration number: CRD42020208045).

Study selection and eligibility criteria

Studies, languages and population

Case–control and cohort studies of infants below 1 year of age were eligible for inclusion. Experimental studies and studies without a reference group were excluded. We included studies in English, Danish and other languages with adequate translation by Google Translate. No limitations regarding publication date or location were implemented.

Exposure

Auditory system pathology was defined by abnormal OAE, ABR or autopsy of the auditory system with histology of the brainstem, including the cochlear nuclei, the superior olivary complex and the inferior colliculus (IC).[26]

Comparators

In case–control studies, SIDS cases were compared with survivors (ABR or OAE studies) or infants dying from other well-defined causes (autopsy studies). In cohort studies, infants with normal OAE or ABR served as the reference.

Types of outcome

The primary outcome was SIDS defined as the sudden death of a child under the age of 1 year that occurred unexpectedly and with an autopsy showing no other potential explanation of death.[1] Studies with no definition or other definitions were still included but rated accordingly by the Newcastle-Ottawa Scale (NOS) for case–control and cohort studies. We included NMSIDS and ALTE as secondary outcomes. NMSIDS and ALTE were defined as severe life-threatening apnoea with marked changes in muscle tone, colour change, choking or gasping, and an apparent need for resuscitation by vigorous stimulation or ventilation.[9 27]

Search strategy

The literature search was conducted in PubMed, Embase and Web of Science. A search strategy was developed for each database using words related to the auditory system and SIDS. Medical Subject Headings in PubMed and the Explode function in Embase was used. References of included studies were scrutinised as well as citations identified in Scopus. The search strategy was developed by the reviewers and peer-reviewed by a scientific librarian. The search was performed on 8 September 2020. The complete search strategy is available in online supplemental additional file 1. Additionally, we hand-searched grey literature at Open Grey, Ovid and The National Technical Information Service without any additional results.[28]

Study selection

The search results were transferred to EndNote V.X9[29] and duplicates were removed. The search results were then uploaded to Covidence[30] to manage the study selection process. Titles and abstracts were screened and any articles that seemingly met the inclusion criteria were extracted for full-text analysis. This process was conducted independently by two reviewers (KD and MA) with any disagreements resolved by discussion or by a third reviewer (TBH).

Data extraction

Data extraction was performed by two reviewers (KD and MA). The data were extracted using a predefined template, which was tested before use to identify any missing data plots. Authors of eligible studies were not contacted regarding missing information. The following data were extracted from the included studies: (1) title, authors, year of publication, country, study design, and aim of the study; (2) characteristics of the study population, including age, sex, gestational age at birth, birth weight, sleeping position and condition, maternal smoking, and socioeconomic status; (3) methods of hearing assessment and autopsy; (4) definition of SIDS, NMSIDS and/or ALTE; (5) point estimates and statistics; and (6) information for assessment of risk of bias and quality of evidence by the NOS and the Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Risk of bias

A modified version of the NOS for case–control studies and cohort studies was used to assess the risk of bias.[31] The

assessment was performed independently by two reviewers (KD and MA), and any disagreements were resolved by discussion or by a third reviewer (TBH). Each study was evaluated within three categories: the selection process, the comparability between groups and the exposure. A maximum of nine points (*) could be awarded to each study by NOS. 'Low' risk of bias required 3–4 points in selection, 1–2 points in comparability and 2–3 points in exposure; 'fair' risk required two points in selection, 1–2 points in comparability and 2–3 points in exposure; and 'high' risk was given 0–1 point in selection or 0 points for comparability or 0–1 point in exposure. Regarding comparability, 1 point was awarded if the study adjusted or matched for sleeping position or condition, while an additional point was awarded if they adjusted for either maternal smoking, sex, gestational age at birth or birth weight.

Synthesis

The heterogeneity between included studies was too high to allow for a meta-analysis. A narrative synthesis was therefore performed, comparing differences and similarities of the studies according to Ryan *et al*.[32] Any missing estimates from the studies were calculated by use of GraphPad Prism V.8.00 for MacOS.[33] Statistical significance was defined as a two-sided p value of less than 0.05 and a 95% CI was used.

Quality of evidence

The quality of evidence by GRADE was assessed independently by two reviewers (KD and MA).[34] Five factors could lower the quality: risk of bias, inconsistency, indirectness, imprecision and publication bias. Serious limitations in any of these five factors resulted in a downgrading of the overall rating. The limitations could either be serious or very serious and downgraded one or two points. Regarding risk of bias, the studies were downgraded if they achieved 1 or 0 points in comparability. Furthermore, they were downgraded 1 point if they missed a point in the selection process and exposure, or downgraded 2 points if they miss 2 points or more in these categories. The overall quality was rated as high, moderate, low or very low.[33]

Risk of bias across studies

Due to high heterogeneity, a formal test of asymmetry could not be performed. Therefore, a qualitative analysis of publication bias was conducted with consideration of variability in study sample sizes. Furthermore, selective outcome reporting was assessed by comparing outcomes reported in the Methods and Results sections of the included studies.

Patient and public involvement

No patient was involved.

RESULTS

Study selection

A total of 461 studies were identified by the search strategy. After the removal of duplicates, 302 studies were screened by title and abstract. Subsequently, 33 studies were screened by full text and a total of 12 case–control studies were included.[35–46] No cohort studies were identified. No studies in other languages than English were included and no additional studies were identified by snowball search or search for grey literature. The selection process is documented in a PRISMA flowchart in figure 1.[25] Online supplemental additional file 2 contains an overview of excluded studies with reasons for exclusion.

Study characteristics

Table 1 shows the main characteristics of each study including study period, country, population, outcome definition (SIDS and NMSIDS), methods for the examination of the auditory system and the provided estimations. The studies included a total of 335 cases and 392 controls. A total of 209 SIDS cases[35–41] and 126 infants with an NMSIDS episode[42–46] were included. OAE or ABR were assessed in 193 cases and 327 controls.[35 36 42–46] Histological examination of the brainstem was evaluated in 142 cases and 65 controls.[37–41] Three Italian studies of Lavezzi *et al*[37–39] may have overlapping populations. These studies examined auditory system pathology of the brainstem in infants who died of SIDS.

SIDS, NMSIDS and controls

Seven studies[35–41] evaluated SIDS cases. All SIDS diagnoses were given following the absence of any other pathological diagnosis at autopsy. However, SIDS diagnoses were described differently across studies. Two studies[35 36] included controls with infants who survived the first year of life, while five studies[37–41] included infants dying of well-defined causes. These well-defined causes were described further in four studies.[37 38 40 41] Five studies[42–46] investigated infants under the age of 1 year with an NMSIDS episode. Similarly, the NMSIDS episodes were described in varying detail; however, all studies defined it as an apnoeic episode that required resuscitation. The majority of NMSIDS studies found no clear predisposing or explainable cause for the NMSIDS episode.[42–44 46] Stockard[46] restricted the age criteria from 3 weeks to 6 months of life. Orlowski *et al*[44] used the term infant apnoea syndrome for NMSIDS. All NMSIDS cases were age-matched with healthy control infants.

Study results

Otoacoustic emission

OAE was applied as the exposure in two studies.[35 36] The studies used various measures of OAE and different cut-offs for a failed test. Rubens *et al*[36] examined the signal to noise ratio (SNR) on both ears and discovered that SIDS cases had lower SNRs on the right ear compared with the left ear, which was reverse for controls. SNRs on the right ear were approximately 4 dB lower at 2–4 kHz. An abnormal transient evoked OAE on the right ear was more prevalent in SIDS cases compared with controls. Due to the result of Rubens *et al*,[36] Blair *et al*[35] assessed the association between an abnormal OAE on the right ear and SIDS. They found no association between abnormal OAE and SIDS. SNRs were marginally higher rather than

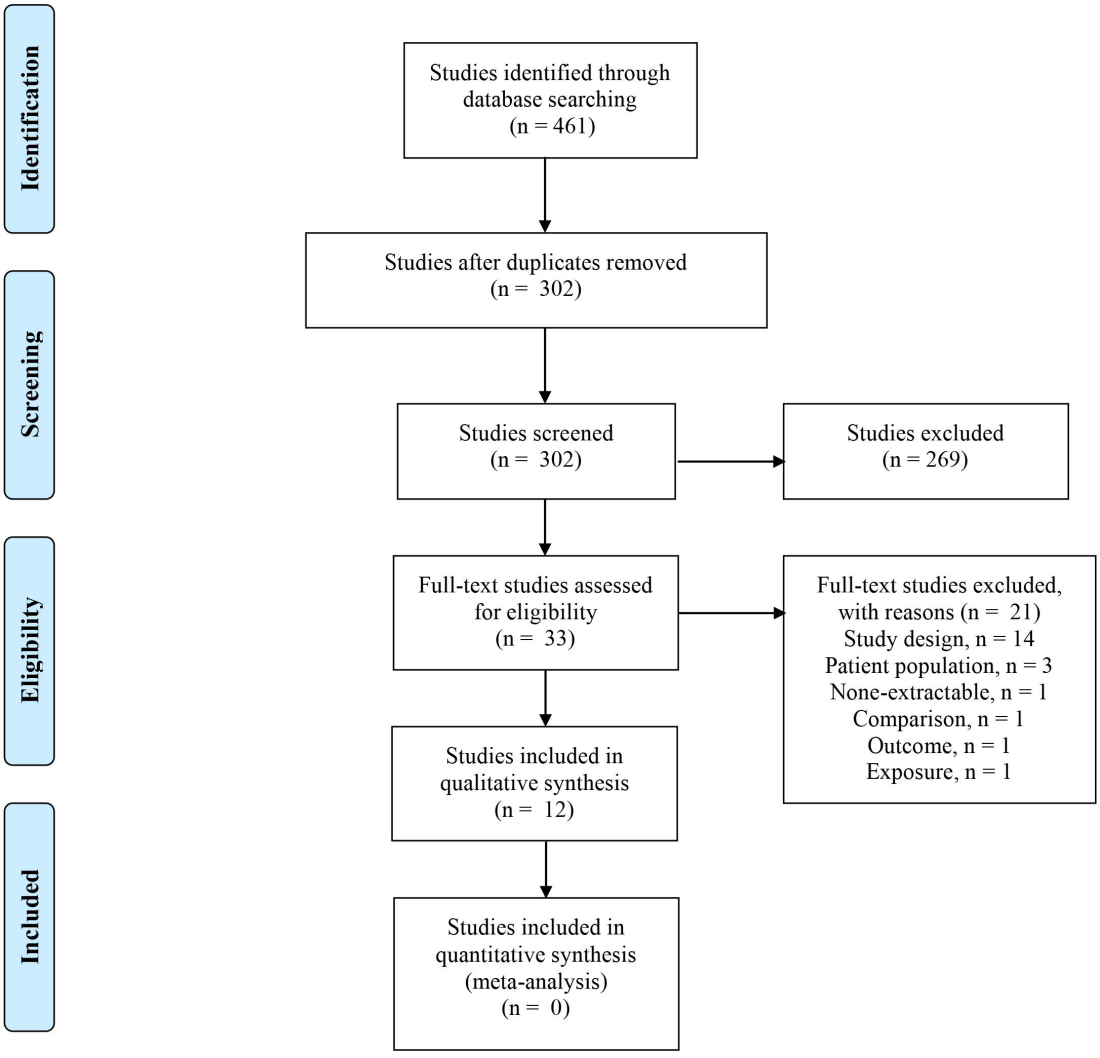

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart showing the selection process of the systematic review. Source: Moher *et al*.[62]

lower on the right ear among SIDS cases compared with controls, but not significantly.[35]

Histology

Histological and histochemical examination of the brainstem nuclei was performed in five studies.[37–41] Four studies[37–39 41] found that abnormalities in the auditory structures of the brainstem occurred more frequently in infants with SIDS compared with infants with a well-defined cause of death. All studies used H&E staining. The three studies of Lavezzi *et al*[37–39] performed a histological examination, which was carried out independently by two blinded pathologists. Lavezzi *et al*[37] discovered hypoplasia of the cochlear nuclei, decreased number of neurons in the medial superior olivary nucleus (MSO) and cytoarchitectural abnormalities of the IC in SIDS cases. Overall, 47% of SIDS cases and 10% of controls had two or more abnormalities in the auditory structures. According to this study,[37] the odds of SIDS were 8.0 (CI 1.7 to 38.1) times as high in infants with abnormal brainstem nuclei compared with infants with normal brainstem nuclei. Lavezzi *et al*[38] and Lavezzi and Matturri[39] found similar abnormalities of the IC and MSO in SIDS cases compared with infants dying of well-defined causes. Furthermore, immunohistochemistry showed absent or very reduced markers of serotonin in the IC in infants with SIDS.[38] Rickert *et al*[41] investigated the expression of c-jun, an immediate–early gene, which is part of the response to neuronal injury.[41 47] The study discovered an increased expression of c-jun in the IC by immunohistochemistry in SIDS cases indicating neuronal injury in the IC.[41 47] Contrarily, the study of Oehmichen *et al*[40] found no IC abnormalities in infants with SIDS when semiqualitative evaluation of gliosis was performed.

Auditory brainstem response

Five studies[42–46] assessed the auditory pathway by ABR. Most infants were tested while asleep, but Orlowski *et al*[44] and Pettigrew *et al*[45] also allowed for chloral hydrate sedation and quiet rest. Various details of the ABR method were provided in the different studies. Similar ABR tests were mostly performed; however, tests differed by intensity (from 55 to 90 dB HL), use of masking[46] and electrode placement. However, all infants within the

Table 1 Overview of study characteristics from 12 included case–control studies on auditory system pathology and SIDS and NMSIDS

Study	Inclusion period	Country of study population	Study population—how cases and controls are matched	SIDS and NMSIDS definition	Method	Cases (n) Controls (n)	Results and effect estimates
SIDS studies							
Blair *et al*[35]	2007–2017	UK	Cases: Request was sent to families to contact The Lullaby Trust.[63] Controls: St. Michael's Hospital, Bristol and Birmingham Women's Hospital Controls that survived the first year of life Controls matched on sex[63]	SIDS: Each case was categorised according to the Avon clinicopathological system[64] as an unexplained death.	OAE	SIDS cases: 36 Controls: 177	Non-statistically significant difference between cases and controls, p values >0.05
Rubens *et al*[36]	1993–2005	USA	Cases: infants born in the State of Rhode Island who died of SIDS Controls: individually matched controls that survived the first year of life Controls matched by sex, full term vs preterm and NICU versus routine nursery admission	SIDS confirmed by autopsy reports	OAE	SIDS cases: 31 Controls: 31	Statistically significant difference between cases and controls at 2, 3 and 4 kHz on the right ear; p values <0.05
Lavezzi *et al*[37]	N/R	Italy	Cases and controls: 69 infants were sent to the research centre and diagnosed according to the application of the guidelines stipulated to the Italian law. Controls: death due to well-defined causes Controls matched on sex.	SIDS: the sudden unexpected death of an infant <1 year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation including performance of a complete autopsy and review of the circumstances of death and the clinical history.[1]	Histology of cochlear nuclei, MSO and IC	SIDS cases: 49 Controls: 20	Abnormal auditory brainstem nuclei: 47% SIDS cases and 10% controls (p=0.003) OR=8.0 (CI 1.7 to 38.1) Cochlear nuclei abnormalities: 39% cases, 0 controls MSO abnormalities: 24% cases, 10% controls IC abnormalities: 41% cases, 0 controls
Lavezzi *et al*[38]	N/R	Italy	Cases and controls: 44 infants were sent to the research centre and diagnosed according to the application of the guidelines stipulated by Italian law. Controls: death due to well-defined causes Controls matched on sex	SIDS: no precise definition However, the Italian law decrees that all infants suspected of SIDS who died suddenly in Italian regions within the first year of age must undergo an in-depth anatomopathological examination.	Histology of IC and SOC, and immunohistochemistry for serotonergic fibres	SIDS cases: 29 Controls: 15	IC abnormalities: 59% cases, 0 controls; p<0.05 SOC abnormalities: 38% cases, 7% controls; p<0.01 OR=8.6 (CI 1.0 to 74.4) Serotonergic immunoreactivity: reduced or absent in 66% of cases and none of controls; p<0.01
Lavezzi and Matturri[39]	N/R	Italy	Cases: no information Controls: death due to well-defined causes	No definition	Histology of MSO	SIDS cases: 30 Controls: 12	MSO abnormalities: 40% cases, 17% controls OR=3.3 (CI 0.6 to 18.0)
Oehmichen *et al*[40]	N/R	Germany	Cases: no information Controls: death due to well-defined causes Controls matched on sex and sleeping position	SIDS: sudden and unexpected death with failure of autopsy, histological evaluation and chemical–toxicological analysis to demonstrate a definitive cause of death	Histological examination with immunohistochemistry of IC	SIDS cases: 11 Controls: 11	IC: no statistically significant difference concerning gliosis, neither astrocyte morphology or density; microglia and lysozyme-positive cells were not observed.
Rickert *et al*[41]	N/R	Germany	Cases: recruited through the German Study on Sudden Infant Death Controls: death due to well-defined causes Controls matched on sex	SIDS: The postmortem examination, including histology, is by definition, negative with no anatomical or toxicological cause for the death ascertained.	Histological examination with immunohistochemistry of IC	SIDS cases: 23 Controls: 7	IC: increased c-jun expression compared with controls, p=0.008
NMSIDS studies							

Continued

Table 1 Continued

Study	Inclusion period	Country of study population	Study population—how cases and controls are matched	SIDS and NMSIDS definition	Method	Cases (n) Controls (n)	Results and effect estimates
Gupta *et al*[42]	March–August 1980	USA	Cases: all infants suspected of NMSIDS were hospitalised on Stanford University Hospital. Controls: recruited in the Palo Alto community and from infants delivered at Stanford University Hospital Controls matched on sex	NMSIDS defined by strict criteria[65]; episodes during sleep, in which parents believe that infants almost died Cyanosis, apnoea and loss of consciousness was observed.	ABR	NMSIDS cases: 9 Controls: 9	9/9 normal ABR Interpeak latencies, wave latencies, interear latency were for all cases p>0.1.
Kileny *et al*[43]	N/R	Canada	Cases: infants found in their homes who required immediate resuscitation. Controls: normal control infants Controls matched on sex and birth weight	NMSIDS: infants who had been apnoeic, blue or pale in their homes who required immediate resuscitation and for whom no cause could be found for this episode following a detailed hospital investigation	ABR	NMSIDS cases: 11 Controls: 11	11/11 normal ABR No statistically significant difference observed in interpeak latencies, p>0.05
Orlowski *et al*[44]	N/R	USA	No information Controls with similar age distribution	NMSIDS=IAS: infants older than 42 weeks postconception and younger than 12 months of chronological age who have experienced a frightening event at home or in the hospital characterised by prolonged apnoea (>20 s) requiring vigorous stimulation or resuscitation and not explained by clinical investigation	ABR	NMSIDS cases: 36 Controls: 25	36/36 abnormal ABR Statistically significant difference for peak latencies I, III and V, and amplitude III; p<0.05 42% cases had bilateral ABR abnormalities. 47% cases had left-sided ABR abnormalities. 11% cases had right-sided ABR abnormalities.
Pettigrew and Rahilly[45]	N/R	Australia	Cases: infants admitted to the hospital following a period of prolonged apnoea during apparent sleep Controls: referred for study by verbal contact or had returned to hospital for regular postnatal check-up Controls matched on sex and prematurity	NMSIDS: a period of prolonged apnoea during apparent sleep which was associated with pallor or cyanosis and which ceased only after vigorous shaking or mouth-to-mouth resuscitation	ABR	NMSIDS cases: 63 Controls: 67	Cases: 88% normal ABR, 12% abnormal ABR Difference in distribution of V-IIn interpeak interval, p<0.05 Difference in distribution of V-I interpeak interval, p>0.05
Stockard[46]	N/R	USA	Cases: no information Controls: normal infants matched on sex	NMSIDS: episodes of prolonged apnoea during sleep in a previously thriving infant of 3 weeks–6 months old, which result in generalised cyanosis and flaccidity and required resuscitation	ABR	NMSIDS cases: 7 Controls: 7	7/7 normal ABR 71% cases had I-V interpeak latency, 1.2–2.2 SD above normal mean value

The study characteristics include study period, country, study population, outcome definition for SIDS and NMSIDS, methods for examination of the auditory system, and the provided results. Seven SIDS studies and five NMSIDS studies.
ABR, auditory brainstem response; IAS, infant apnoea syndrome; IC, inferior colliculus; MSO, medial superior olivary nucleus; NICU, neonatal intensive care unit; NMSIDS, near-miss sudden infant death syndrome; N/R, not reported; OAE, otoacoustic emission; SIDS, sudden infant death syndrome; SOC, superior olivary complex.

same study were subjected to the same method. Two studies[42 43] found no association between abnormal ABR and NMSIDS with all infants with NMSIDS having normal ABR. Contrarily, Orlowski *et al*[44] found that left-sided ABR abnormalities appeared more frequently among NMSIDS cases compared with controls. In the study of Pettigrew *et al*,[45] the majority (88%) of infants with NMSIDS had normal ABR, but approximately 12% had significant different interpeak intervals compared with controls. Stockard[46] found normal ABR in all NMSIDS but found a tendency towards a prolonged V-I interpeak interval.

Risk of bias within studies

Table 2 shows the points (*) awarded by NOS for case–control studies. The seven studies on SIDS[35–41] were classified as having *low risk of bias* with the exception of Lavezzi and Matturri,[39] who did not describe the selection process or the comparability between infants who died from SIDS and other well-defined causes. Furthermore, two studies[40 41] did not state whether their histological examination was blinded. The five studies with NMSIDS cases[42–46] had higher risk of bias. Evaluation of exposure in all studies indicated little risk of bias. However, none of the studies adjusted for all our predefined confounders, and two studies[39 44] failed to control for any of them. Table 1 shows which key variables were included in the matching for each study. In total, six studies were assessed to having *low risk of bias*,[35–38 40 41] while two studies[42 45] had a *fair risk of bias* and four studies[39 43 44 46] had a *high risk of bias*.

Quality of evidence

The included studies were initially rated as low quality due to their observational nature. The quality of evidence across all outcomes was very low. This was mainly due to serious concerns in risk of bias within studies and inconsistency between the study results. Furthermore, NMSIDS as a surrogate outcome for SIDS were downgraded for indirectness according to the GRADE assessment, as it is unclear whether NMSIDS is in fact associated with SIDS.

Risk of bias across studies

Publication bias due to small study effects appears to be unlikely as several studies reported no association between auditory pathology and SIDS or NMSIDS. Selective outcome reporting bias was not detected as all outcomes in the included studies were reported and described in the Method sections.

DISCUSSION

Statement of principal findings

We identified 12 case–control studies that were eligible for this systematic review of the association between auditory system pathology and SIDS. Seven studies[36–39 41 44 45] reported that abnormalities in the auditory system measured either by function (hearing screen) or autopsy (histology or immunohistochemistry) were more frequent in infants with SIDS/NMSIDS than in controls. Five studies[35 40 42 43 46] found no association. The results of two studies[45 46] tended towards an abnormal ABR in some NMSIDS cases with prolonged interpeak intervals indicating neuronal dysfunction. Studies based on histology showed a more pronounced and consistent association than studies of functional measures. However, the three histological studies by Lavezzi *et al*[37–39] may have overlapping populations, which makes the association less convincing.

Functional measures

Rubens *et al*[36] found a lower response on the right ear than the left ear. Studies[48–50] have shown that newborn OAE and ABR responses are greater on the right ear compared with the left ear, which is consistent with the control group in the study of Rubens *et al*.[36] Therefore, Rubens *et al*[36] hypothesised that an inner ear injury may be due to high foetal venous blood pressure during delivery. High blood pressure may damage the small auricular veins because they drain directly to the jugular veins. However, the left ear may be protected against this high pressure by a greater length and angulation of the left brachiocephalic vein compared with the right side.[51 52] A inner ear lesion may result in a vulnerable infant at risk of SIDS. Different studies, both the included study of Blair *et al*[35] and excluded studies,[53 54] have not been able to find the same association. Examination of OAEs in a larger study of SIDS cases found no abnormalities on the right ear but three had left-sided hearing loss.[53] The study of Chan *et al*[54] did neither report findings in support of the hypothesis by Rubens *et al*.[36] Unfortunately, Rubens *et al*[36] provided no SIDS definition and used a paired t-test between cases and controls only matched by gender, date of birth and neonatal intensive care unit versus routine nursery admission, which may devaluate the evidence from the study.[53 55 56]

The other functional test of the auditory system, ABR, was used in the five older NMSIDS studies.[42–46] Only Orlowski *et al*[44] found consistent signs of abnormal ABR in infants with NMSIDS, but contrary to Rubens *et al*,[36] left-sided abnormalities were most frequent in Orlowski *et al*.[44] Generally, the included studies with ABR as exposure[42–46] were inconsistent as the studies with OAE.[35 36] Additionally, Lüders *et al*[57] and the newer study of Brinsmead *et al*[58] could not demonstrate abnormal ABR results in infants with SIDS. By full-text screening, these studies[57 58] were excluded from this review due to missing information about infants with NMSIDS and missing reference groups.

Histological measures

The greatest consistency in the results was seen in the histological studies.[37–41] However, comparisons between the studies are difficult due to the examination of different cells and proteins. However, three studies all found abnormalities in the IC.[37 38 41] The histological studies support that abnormalities in the auditory system

Table 2 Newcastle-Ottawa Scale for case–control studies: points awarded to the included studies investigating the association between the auditory system and SIDS

	Is the case definition adequate?*	Representativeness of the cases†	Selection of controls‡	Definition of controls§	Comparability of cases and controls¶	Ascertainment of exposure**	Same methods of ascertainment for cases and controls ††	Non-response rate‡‡	Risk of bias§§
Blair *et al*[35]	A (✷)	B	A (✷)	A (✷)	B (✷)	A (✷)	A (✷)	C	Low
Rubens *et al*[36]	A (✷)	B	A (✷)	A (✷)	B (✷)	B (✷)	A (✷)	A (✷)	Low
Lavezzi *et al*[37]	A (✷)	A (✷)	A (✷)	A (✷)	B (✷)	A (✷)	A (✷)	A (✷)	Low
Lavezzi *et al*[38]	A (✷)	A (✷)	A (✷)	A (✷)	B (✷)	A (✷)	A (✷)	A (✷)	Low
Lavezzi and Matturri[39]	C	B	A (✷)	A (✷)	–	A (✷)	A (✷)	A (✷)	High
Oehmichen *et al*[40]	A (✷)	B	A (✷)	A (✷)	A, B (✷✷)	C	A (✷)	A (✷)	Low
Rickert *et al*[41]	A (✷)	A (✷)	A (✷)	A (✷)	B (✷)	C	A (✷)	A (✷)	Low
Gupta *et al*[42]	B	B	A (✷)	A (✷)	B (✷)	A (✷)	A (✷)	A (✷)	Fair
Kileny *et al*[43]	B	B	C	A (✷)	B (✷)	A (✷)	A (✷)	A (✷)	High
Orlowski *et al*[44]	A (✷)	B	C	B	-	A (✷)	A (✷)	A (✷)	High
Pettigrew and Rahilly[45]	B	B	A (✷)	A (✷)	B (✷)	A (✷)	A (✷)	A (✷)	Fair
Stockard [46]	A (✷)	B	C	B	B (✷)	A (✷)	A (✷)	A (✷)	High

*(A) Yes, with independent validation (✷); (B) yes, for example, record linkage or based on self-reports; (C) no description.
†(A) Consecutive or obviously representative series of cases (✷), (B) potential for selection biases or not stated.
‡(A) Community controls (✷), (B) hospital controls, (C) no description.
§(A) No history of endpoint (✷), (B) no description of source.
¶(A) sStudy controls for sleeping position and conditions (✷); (B) study controls for sex, smoking exposure, birth weight or gestational age (✷) .
**(A) Secure record (eg, surgical records) (✷); (B) structured interviews were blind to case/control status (✷); (C) written self-report or medical record only; (D) no description.
††(A) Yes (✷), (B) no.
‡‡(A) Same rate for both groups (✷), (B) non-respondents described, (C) rate different and no designation.
§§'Low risk' was given 3–4 points in selection, 1–2 points in comparability and 2–3 points in outcome; 'fair risk' was given two points in selection, 1–2 points in comparability and 2–3 points in outcome; 'high risk' was given 0–1 point in selection or 0 points in comparability or 0–1 point in outcome.

may be associated with SIDS. If the histological abnormalities in the auditory system may be captured by a newborn hearing screening, the number of SIDS cases could potentially be reduced. However, the inconsistent ABR and OAE studies do not indicate this as a possibility. Additionally, the CIs of the calculated ORs in the three studies of Lavezzi *et al*[37–39] were wide, which indicate uncertainty of the results.

Rickert *et al*[41] had no mention of whether the histological examination was blinded, which may interfere with the interpretation as many of the measures were qualitative rather than quantitative. In contrast, the three studies by Lavezzi *et al*[37–39] all stated that the examination of the different nuclei was blinded.

Overall limitations of the studies

In all studies, information was missing on potential confounding factors. Information was limited or absent on factors such as sleeping position, sleeping conditions, maternal smoking, gestational age at birth, birth weight and sex, which all are associated with SIDS. For example, maternal smoking during pregnancy increases the risk of hearing disorders and preterm birth and is also a known risk factor for SIDS.[59–61] The lack of adjustment for these factors may have caused an overestimation of the association between auditory system pathology and SIDS. However, due to the small study populations, adjustment for multiple factors were impossible. All studies had poor comparability between cases and controls, which affected the assessment of the quality of evidence. Oehmichen *et al*[40] was the only study achieving two points in comparability during the NOS assessment; however, the study adjusted only for sleeping position and sex.

Additionally, there may be some concern regarding the evidence from the NMSIDS studies. First, we assessed the studies to have a higher degree of risk of bias compared with the SIDS studies. Second, the NMSIDS studies are from the 1980s when the SIDS incidence was higher and the knowledge on SIDS risk factor was less. Therefore, generalisability to current time may be questionable due to different patient populations. Third, a NMSIDS event may not be associated with SIDS.[5–7] Actually, the objectives in the NMSIDS studies were to examine ABR as a tool to examine the brainstem generally rather than the auditory function. By these concerns, the NMSIDS studies were of especially poor quality and did not influence our overall conclusion.

SIDS is a rare outcome resulting in few SIDS cases which led to the inclusion of underpowered studies with small study sizes. Generally, the study results were inconsistent, and further studies with larger study populations are needed to investigate the association.

Strengths and weaknesses of the systematic review

According to our knowledge, this is the first systematic review about the association between auditory system pathology and SIDS. This systematic review was conducted following PRISMA guidelines with studies searched in different databases. To minimise the overall risk of bias, each step was performed independently by two reviewers. The possibility of publication bias seemed unlikely, but we were unable to assess this further by formal test of asymmetry. Our inclusion criteria were broad to ensure that all relevant studies were included. We included three different exposures: OAE, ABR and brainstem histology of the auditory system and two different outcomes: SIDS and NMSIDS, which were either rather ill-defined or prone to different definitions between studies. Only one study[37] used the San Diego definition of SIDS.[1] The differences in exposure and outcome definition comprised comparability between studies, and in case of inadequate outcome definition, the quality of the individual study was downgraded during NOS assessment.

We had no expert evaluation of the OAE and ABR measures used in the included studies. Consequently, we may have overrated the quality of these. The comparability between SIDS and NMSIDS cases and controls was limited, which may have hampered the overall conclusion. At last, the included studies were small, resulting in imprecision of estimates.

CONCLUSION

Despite many years of investigation, it is still impossible to conclude whether auditory system pathology is associated with SIDS. Four out of five histological studies indicate an association between the auditory system and SIDS, particularly abnormalities in the IC. However, studies investigating the OAE or ABR and SIDS were inconsistent. The studies included in this review were generally of poor quality, and future studies should focus on studying the association between auditory system pathology and SIDS in larger current study populations.

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