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BMJ Open

Sudden Infant Death Syndrome (SIDS) and the routine otoacoustic emission infant hearing screening test: an epidemiological retrospective case-control study.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030026
Article Type:	Research
Date Submitted by the Author:	23-Feb-2019
Complete List of Authors:	Blair, Peter; University of Bristol, Bristol Medical School Rubens, Daniel; Seattle Children's Hospital Pease, Anna; University of Bristol, Bristol Medical School Mellers, Diane; Birmingham Women's Hospital, Department of Research & Development Ingram, Jenny; University of Bristol, Bristol Medical School Ewer, Andrew; University of Birmingham, Institute of Metabolism and Systems Research Cohen, Marta; University of Sheffield, Department of Oncology and Metabolism Sidebotham, Peter; University of Warwick Warwick Medical School Ward Platt, Martin; Newcastle University, Institute of Health and Society Coombs, Robert; University of Sheffield Davis, Adrian; Imperial College London Hall, Amanda; University of Bristol, National Institute of Health Research Clinical Research Network: West of England Fleming, Peter; University of Bristol, Bristol Medical School
Keywords:	SIDS, SUDI, Epidemiology < TROPICAL MEDICINE, hearing, screening

Sudden Infant Death Syndrome (SIDS) and the routine otoacoustic emission infant hearing screening test: an epidemiological retrospective case-control study.

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Abstract word count: 300/300

Main Manuscript word count: 3397/4000

Key Words: SIDS, SUDI, epidemiology, hearing, screening

Abstract

objectives: To investigate whether decreased oto-acoustic emission (OAE) signal recordings in the right ear are associated with an increased risk of sudden infant death syndrome (SIDS) and to monitor any temporal changes in risk factors.

design: Retrospective case-control study

setting: Telephone interviews with families recruited in England between July 2016 and October 2017 who experienced the unexpected death of a child <4 years old since 2008 and control families recruited from maternity wards in Bristol and Birmingham.

participants: We recruited 91(89%) of the 102 bereaved families who made initial contact, 64 deaths were under 1 year old (Sudden Unexpected Death in Infancy) of which 60 remained unexplained (SIDS). Of the 220 control families, 194(88%) follow-up interviews were conducted. We had analysable hearing data for 24 SIDS infants (40%) and 98 controls (51%).

results: OAE signals were marginally increased rather than decreased among SIDS infants for the right ear, especially at lower frequencies, but not significantly so. The strongest predictors of SIDS were bed-sharing in hazardous (infant sleeping next to a carer who smoked, drank alcohol or slept on a sofa) circumstances (35% vs 3% controls, $p<0.0001$), infants found prone (33% vs 3% controls, $p<0.0001$) and infants whose health in the final week was 'not good' (53% vs 9% controls, $p<0.0001$). The prevalence of maternal smoking during pregnancy amongst both SIDS mothers(20%) and controls(10%) was much lower than previous studies.

conclusions: Hearing data were difficult to obtain; larger numbers would be needed to determine if asymmetrical differences between the right and left ear were a marker for SIDS. A national prospective registry for monitoring and a renewed campaign to a new generation of parents needs to be considered underlining the initial message to place infants on their backs for sleep and the more recent message to avoid bed-sharing in hazardous circumstances.

Strengths and limitations of this study

- This study uses routinely collected hearing data to test a novel hypothesis
- This study also collects valuable data from bereaved parents to monitor SIDS risk factors
- The retrospective nature of the study (collecting data from bereaved families over a 10 year period) limits the generalisability of the findings and leaves it open to recall bias
- Difficulties in collecting routine hearing data hinders interpretation of the findings

Introduction

Despite its reduced incidence, Sudden Infant Death Syndrome (SIDS) is the second leading cause of post-neonatal infant mortality in England & Wales[1], the highest among infants of younger mothers[2] and common in socially-deprived families.[3] Epidemiological markers at birth are available to identify some families at increased risk[4] but are neither sensitive nor specific enough to make targeted intervention possible.[5] A physiological marker independent of current demographic identifiers would have the potential for making targeted intervention viable.

In 2008 a study demonstrated an altered newborn oto-acoustic emission (OAE) hearing test in thirty-one infants who subsequently died of SIDS compared to thirty-one control infants.[6] The OAE is the sound signal generated by the cochlea as a response to sound and recorded in the ear canal. This observation begs the question - are altered OAEs a marker of predisposition to SIDS? If so, can the newborn OAE hearing test be used in combination with epidemiological markers to identify 'at risk' infants at birth? However maternal smoking during pregnancy was not measured in the Rhode Island Study, so it could be that exposure to tobacco smoke *in utero* resulted in developmental differences associated with infant hearing which would confound the potential of an improved screening tool but would still add to our understanding of causal mechanisms for some of these deaths. Most infants (>99%) in England have a hearing test shortly after birth and the data, stored by Public Health England since 2010, could be suitable for analysis.

In England & Wales SIDS deaths have fallen from a peak of nearly 1600 deaths in 1988[7] to just over 200 deaths in 2016.[2] Longitudinal data collected in Avon suggest not only that there has been a shift towards poorer families but that prone positioning is still a feature of these deaths[3] and bed-sharing in hazardous conditions (next to a parent who has consumed alcohol, drugs or regularly smokes or uses an unsafe sleeping surface such as a sofa) has emerged as a highly significant risk factor.[4,8]

We conducted a retrospective case-control study of SIDS infants and surviving controls primarily to investigate whether decreased OAE signal recordings in the right ear are associated with an increased risk of SIDS, and secondarily to investigate any recent changes in epidemiological characteristics.

Methodology

Ethical approval and governance

Ethical approval was sought and gained from the South West Central Bristol Research Ethics Committee; REC (reference :14/SW/1084). The date of approval was 22 March 2016. We work closely with bereaved parents who encourage us to collect detailed observational data to both further our understanding of causal mechanisms and provide evidence for risk reduction advice. We used the STROBE case-control checklist when writing our report.[9]

Recruitment of cases

Families were recruited retrospectively via *The Lullaby Trust* (The main SIDS charity in England https://www.lullabytrust.org.uk/). A request was sent for families to contact *The Lullaby Trust* if they had experienced an unexpected death of an infant or child up to and including the age of 3 years since 2008. Data on children who died from 1 to 3 years old will be reported separately.

Families who responded to this request were given a brief written and verbal explanation of what the study involved by the *Trust* as well as being asked to agree to be contacted by the research team. The subsequent telephone interview was conducted by one of the clinical members of the team using a semi-structured questionnaire format. On receipt of signed consent forms, we wrote to the relevant coroners' offices to request copies of all inquest documentation, including (but not limited to) the police report, SUDI paediatrician report and post-mortem report. We then conducted multi-professional case review meetings to categorise each case according to the Avon clinico-pathological system[10] as an explained or unexplained (SIDS) death.

Recruitment of controls

We recruited controls from St Michael's Hospital, Bristol, and Birmingham Women's Hospital from June 2016 to August 2017 inclusive. Mothers who had given birth to infants at or after 35 weeks' gestation who had no significant medical problems were approached by one of the research team within 24 hours of delivery. Participants were interviewed by telephone using the same semi-structured interview to obtain information about a reference infant sleep within 24 hours of the call, when their infants were at similar ages to the anticipated ages of death of the index infants. We tried to distribute the times and days of the week for the reference sleep to match as closely as possible those on which the deaths had occurred.

Collection of hearing data

The hearing data obtained depended on the screening equipment being used. Two different recording systems are used within the NHS to collect infant hearing data which are stored by a private company contracted to Public Health England. The systems are Otoport™ (Otodynamics Ltd, Hatfield, UK) system and Accuscreen™ (Madsen from Natus, formerly GN Otometrics, Copenhagen, Denmark]. The Otodynamics system collects signal and noise recordings (as in the early US study) for both the right and left ear at 5 frequencies (I kHz, 1.5 kHz, 2 kHz, 3 kHz and 4 kHz) with the signal generally improving the higher the frequency. The Otodynamics recordings included signal and noise measured in decibels (dB) and provided as logarithms, so the ratio is calculated as noise subtracted from the signal. A measure (%) of confidence in the reliability of the recording is also given. There is debate as to whether signal to noise ratio or just signal would be the best measure, so we have provided both. The data were extracted using the Otodynamics ILO Data Explorer. The Accuscreen™ device also provides data for both right and left ear but is more limited as the OAE result at the different frequencies are combined. The only useful measurement related to the strength of the OAE signal from these recordings appears to be the length of time it took to get a positive response (a total of 8 valid peaks in alternating direction of the OAE waveform has been achieved to formulate a 'pass' for the test). The Accuscreen™ recordings included the duration to achieve a positive response (in seconds), the artefact rate (related to noise) which should below 20% if possible, the stimulus stability (emanating from the probe stability) which should be above 80% if possible and the probe fit which is also measured as a % in terms of how successfully it was fitted. These data were extracted using the Madsen Acculink™ package.

Statistical Methodology

The univariable and multivariable analyses were calculated using logistic regression in SPSS. Medians and interquartile ranges were used to describe continuous data that were not normally distributed and comparisons tested using the Mann Whitney test. Categorical data were tested using Chi-Square. Given the expected relatively low number of SIDS cases, multivariate adjustments were limited to essential covariates and simple dichotomies were used for multi-categorical and continuous variables. Variable selection used the backward stepwise selection method and any variable with more than 10% data missing was modelled separately in a sensitivity analysis.

Results

Ascertainment

Of 102 bereaved families who contacted *the Lullaby Trust,* we completed the interviews with the families of 91 children who died suddenly and unexpectedly. There were 27 deaths between the ages of 1-3 years (SUDC) which will be reported separately and 64 were sudden unexpected deaths in infancy (SUDI). Four unexpected infant deaths were fully explained: two from previously unrecognised cardiac abnormalities, and two from acute infections. For 50/60 SIDS deaths (83%) the multiagency review process identified possible or probable contributory factors that could not in themselves fully explain the death (Table 1).

Of the 220 control families who consented to take part in the maternity hospital, 194 (88%) completed a follow-up telephone interview (79 from Bristol and 115 from Birmingham). The 26 control families lost to follow-up were more likely to have pre-term infants (<37 weeks: 7.7% vs 1.5%, p=0.08) and a greater proportion of mothers with lower educational achievements (highest qualification ≤ GCSE or equivalent: 36% vs 16.5%, p=0.02) but there were no major differences in gender, ethnicity, maternal smoking during pregnancy, maternal age, number of siblings or birthweight.

Temporal weighting

The 60 SIDS deaths occurred between 2007 and 2017 with no marked seasonal difference. The reference sleep of the controls occurred between June 2016 and August 2017 inclusive with an increased number in the coldest quarter of December, January and February (25% SIDS deaths vs 60% controls, p<0.0001). As Figure 1 shows, the median age of the SIDS infants was 85 days [iqr: 49-159 days], the median age of the control infants in this study was 77 days [iqr: 44-114 days]. The slight difference in age distribution was not statistically significantly (Mann-Whitney test: p=0.18]. Of the 60 SIDS deaths 58 occurred while the infant was thought by the parents to be asleep; 17/58 (29.3%) deaths occurred during what the parents considered to be a day-time sleep, significantly more than the day-time reference sleeps of control infants (26/194 or 13.4%, p=0.007). There was no significant variation in the number of deaths or of reference sleeps by day of the week. (Mann Whitney test: p=0.97). (Figure 2).

Demographic characteristics

Table 2 compares the background and perinatal demographics of the SIDS infants and controls. There was a slight preponderance of males and a higher proportion with white ethnicity among the SIDS infants. Lower levels of maternal educational achievement were more prevalent among the SIDS families; highest educational attainment was either below or no more than the standard expected at 16 years old for half of the SIDS mothers (three times more than control mothers). The SIDS mothers were slightly younger (median age 29 years [IQR: 26-33 years]) than the control mothers (median age 31 years [IQR: 28-34 years]) but this difference was not significant.

Hearing Data

Hearing screening tests were conducted for all but one of the SIDS cases and all the controls although analysable records were only available for 60% of the SIDS infants and 91% of the controls. For the SIDS infants lack of written consent (15%), missing records post 2010 (8%), unusable records pre-2010 (5%) and no clear OAE response (12%) explain the lack of availability. Among the controls there was no clear OAE response for 17/194 infants (9%).

We had *Accuscreen* hearing records for the right and left ear available for 12 SIDS infants and 79 controls. The median duration of the test recording that was required to achieve a pass in the right ear was slightly shorter among the SIDS infants (20 seconds) compared to the controls (23 seconds) but not significantly different (Table 3). The median duration of the test recording was shorter for both groups in the left ear but significantly so for the SIDS infants (10.5 seconds) compared to the controls (16 seconds). There were no significant differences observed between SIDS infants and controls in artefact rate, stimulus stability or probe fit.

We had *OtoDynamics* hearing records for the right and left ear available for 24 SIDS infants and 98 controls. Table 4 compares the median signal, noise, signal to noise ratio and confidence (in percentage terms) of these findings between SIDS and controls in the right and left ear. The median signal in the right ear was slightly higher among the control infants at 1 kHz and 2 kHz frequency and slightly higher among the SIDS infants at 1.5 kHz, 3 kHz and 4 kHz frequencies but none of these differences were statistically significant. The signal to noise ratio in the right ear was consistently slightly higher among the SIDS infants compared to the controls but again none of these differences were statistically significant. At 2 kHz, 3 kHz and 4 kHz this difference increased with frequency (0.15 dB, 1.45 dB and 2.55 dB). The median signal in the left ear was significantly higher among the control infants at 1 kHz ($p=0.004$), albeit within the equipment noise floor, higher (but not significantly so) at 1.5 kHz ($p=0.33$) and at 2 kHz ($p=0.63$), conversely the median signal was slightly higher among the SIDS infants at 3 kHz ($p=0.23$) and 4 kHz ($p=0.25$). The noise was also significantly higher among the control infants at 1 kHz ($p=0.023$) and almost significant at 1.5 kHz ($p=0.06$). Subtracting the signal in the right ear from the left ear to look at right/left asymmetry (Figure 3) the right ear was more dominant among the SIDS infants at all frequencies but particularly for the lower frequencies, albeit this was not significant and the confidence score at these lower frequencies was quite low.

Multivariable risk factors

Table 5 lists those factors that remained significant in the multivariable analysis when adjusted for infant age and the other factors in the model. The highest risk was associated with those infants sleeping next to a carer who had consumed alcohol, smoked tobacco or was sleeping on a sofa (35% vs 3% controls). In this study 8/60 SIDS infants were found co-sleeping on a sofa compared to 1/194 control infants. Infants being found prone exhibited a strong association; notably, for all 6 control infants found in this position this was the usual positioning and only one was younger than 3 months of age; in contrast for nearly two-thirds of the SIDS infants found prone (10 out of the 16 who responded) this was not the usual position found and 9 of these 20 infants were aged less than 3 months. Fewer Infants were put down in the prone position although this was more common among the SIDS infants and significant (11% vs 1.6% controls, p=0.004); only 3 SIDS infants (5.7%) were placed on their side and all 3 were found on their side, a similar proportion to the controls (7.3%).

In the final week before the last sleep over half the SIDS infants were described by the carer as having health that was only fair or poor (rather than good) and a third were reported to have fed less than usual compared to a smaller proportion for both these factors among the controls (11% and 6% respectively). Being a twin and having a less well-educated mother were the two strongest demographic characteristics of SIDS infants.

Maternal smoking during pregnancy was notable for its absence in the final model, mainly because of the low prevalence both among the SIDS mothers (20%) and controls (10%). More of the SIDS infants used a dummy for the last sleep but this was not significant (40% vs 35% controls, p=0.50). Only around a quarter of the SIDS carers who provided a dummy could recall what happened during the final infant sleep and 5 of the 6 carers responded that the dummy fell out or was removed soon after the infant fell asleep. Among the controls nearly all (61/65 or 94%) thought the dummy fell out or was removed soon after sleep onset. More of the control infants used an infant sleeping bag for the last sleep but this did not reach univariable significance (22% SIDS vs 36% controls, p=0.06)

Discussion

We were not able to confirm the promising findings on oto-acoustic emissions from the previous study.[6] In that study the signal to noise ratio was consistently and significantly 4dB lower at 2kHz, 3kHz and 4kHz in the right ear of infants who subsequently went on to die of SIDS compared to surviving controls. In our study the difference in signal to noise ratio was in the opposite direction; higher in the right ear of SIDS infants than controls and this difference increased (from 0.15dB to 2.55dB) the higher the frequency albeit this was not statistically significant. There were potential asymmetrical differences between the SIDS infants and controls at lower frequencies but the low confidence in these scores and small numbers requires cautious interpretation.

The right ear advantage in cochlear function has been well described in infants, with right OAEs approximately 1 dB larger than left.[11-13] This inter-aural asymmetry is hypothesised to reflect developmental differences in the activity of the medial olivoochlear efferent system between the ears;[14,15] differences in ear asymmetry between SIDS and control infants could indicate developmental differences in early auditory efferent function.

The major limitation is that both studies were underpowered. A larger study would be needed to detect any subtle differences in infant hearing should such differences genuinely exist. Accessing hearing data in the UK was difficult; we encountered delays, missing records, inability for the contracted company to read the data they store and monitoring systems that were incompatible.

As with our study conducted 10 years ago[4] just over half the SIDS infants were found next to a carer and bed-sharing in hazardous circumstances was the strongest association with SIDS in the multivariable model. Initiatives to highlight the specific hazards to parents who bed-share and clearly explain the evidence to health professionals such as the UNICEF '*Caring for your baby at night*' leaflets[16] and '*Co-sleeping and SIDS*' infographic[17] need to be encouraged. The proportion of SIDS infants found prone seems stubbornly persistent over the years; 38% in our study 20 years ago[18], 29% in our study 10 years ago[4] and 33% in our current study. Although the proportion found prone in the control population was low, our studies of high-risk families in socio-economically deprived areas in Bristol suggest that parental awareness of this risk factor was poor (only a half of the 400 mothers surveyed in 2014 identified avoiding prone sleep position as one of the top 3 risk reduction strategies for SIDS).[19]

Our three studies conducted in England show that the prevalence of maternal smoking during pregnancy has fallen from 27% 20 years ago[20] to 14% 10 years ago[5] to 10% in this study reflecting a national trend. Among the SIDS families the prevalence in these three studies has fallen from 66%, to 59% and just 20% in the current study. This may be a consequence of a reduced population prevalence but may partly be explained by the bias towards less-deprived and more articulate families who volunteered to take part in this study compared with the families in our previous prospective population-based studies.

As well as using a retrospective design and a relatively small sample, there were other limitations to this study. Most of the SIDS deaths occurred between 2010 and 2017; during this period there were over 2000 SIDS deaths in England suggesting our self-selected SIDS sample was around 3% of the SIDS population which may not be representative of the wider English population. The potential for recall bias was high especially regarding specific details of the final sleep such as response to what happened to the infant dummy which was only recollected by a quarter of the SIDS parents compared to virtually all the controls. The data from the controls were prospectively collected but recruitment was opportunistic and access to the more vulnerable infants was difficult, yielding a control population with fewer premature and low birthweight infants than the national average. We were not able to arrange control interviews that would reflect the seasonal distribution of SIDS deaths or reflect the higher than expected proportion of day-time deaths, and telephone interviews are a poor substitute for face-to-face ones.

Many of the families with whom we spoke were under the impression that the information they had already given to the healthcare staff or the police after their child's death were available to be used for research, and many expressed surprise and anger when informed this was not the case. All but one bereaved family told us that, had they been asked at the time of their child's death, they would have given permission for the data and the pathology samples to be used in future research projects aimed at preventing such deaths. This information has led us to propose the establishment of a national Registry of unexpected infant and childhood deaths, to which families could opt in soon after the death of their child, and which would thus have written informed consent to make available the routinely collected information and pathology samples.

We conclude that if routinely collected data are to be fully utilised for both national monitoring and efficiently designed research investigations, then bodies such as Public Health England need to consider single or compatible monitoring systems that can provide easy access to analysable data, as well as a routine quality control of recorded and stored data. For parents, there need to be renewed efforts to underline the need to place infants on their backs for sleep and avoid bed-sharing in hazardous circumstances.

Acknowledgements

We would like to thank Francine Bates, Lucy Lyus and Jenny Ward at the Lullaby Trust for helping with recruitment, Dr Siobhan Ryan at Public Health England for helping obtain the hearing records, Mark Cook at Northgate Public Services for his assistance with sending the data, Mr Abhilash Vora for data entry and cleaning and most of all the parents who have provided information for this study that may help future parents.

Funding

This work was supported by the *Lullaby Trust* (project number 268) with funding also received from *Teddy's Wish* and *Seattle Children's Hospital.* These sponsors had no role in the study design; in the collection, analysis and interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication.

Competing interests

None declared

Author Contributions

DR, PJF, PSB, AP & JI were responsible for developing the research question. PJF, DR, PSB, JI, AP, AH, DM, AE, AD were responsible for the study design. PJF, AP, PS, MCC, MWP & RC were responsible for data collection, death classification and quality assessment of the investigation into the death. AP was responsible for study management. PSB initially drafted the paper. All authors read, commented on and approved the final manuscript.

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Table 1: Avon Classification of Sudden Unexpected Deaths in Infancy (SUDI)*			
0	Information not collected	0/64	0%
IA	No potentially significant factors or contributory factors found (SIDS)	0/64	0%
IB	Factors present but not likely to have contributed to the death (SIDS)	10/64	15.6%
IIA	Factors present and may possibly have contributed to the death (SIDS)	29/64	45.3%
IIB	Factors present and probably contributed to the death (SIDS)	21/64	32.8%
III	Fully explained death	4/64	6.3%

* The multi-professional case review meetings included a range of relevant professionals with experience in the field (paediatrician, paediatric pathologist, health visitor, police officer, social worker). After discussion of each case, each was categorised according to the Avon clinicopathological categorisation system[8] as an explained or unexplained (SIDS) death.

Figure 1 – Age at death or reference sleep (SIDS vs Controls)

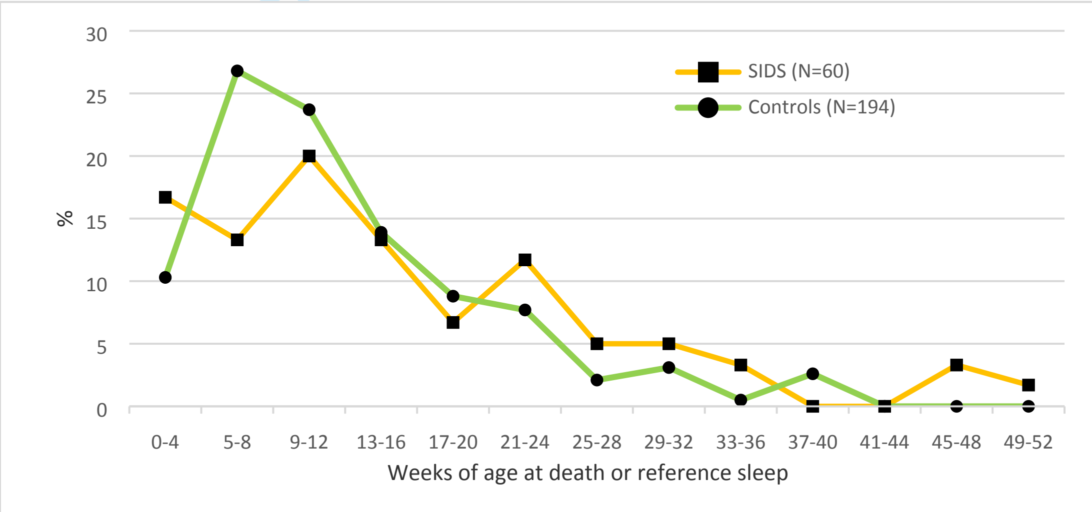

Figure 2 – Day of week of death or reference sleep (SIDS vs Controls)

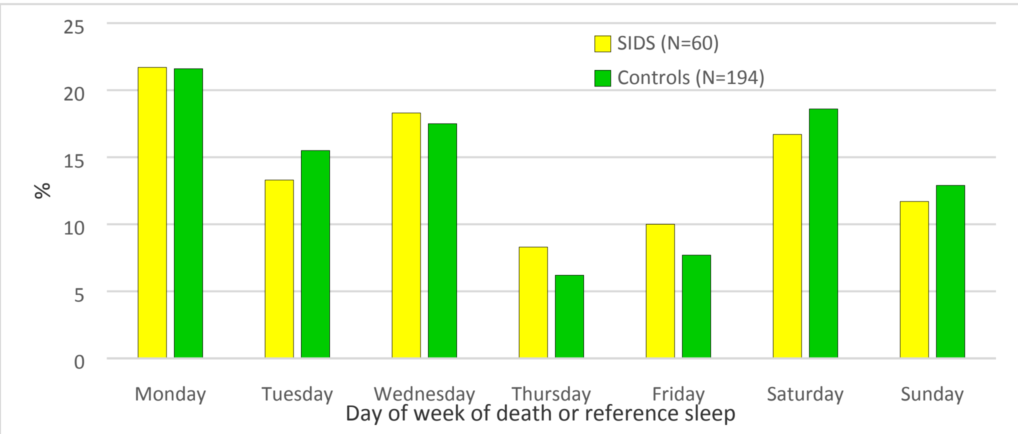

Table 2: Demographic Characteristics (SIDS vs Controls)								
Characteristic	**Category**	**SIDS**		**Controls**		**OR**	**95% CI**	**p-value**
		n/N	**%**	**n/N**	**%**			
Gender	*Male*	33/60	55.0%	90/194	46.4%	1.41	[0.79-2.53]	0.24
Ethnicity	*Non-white*[1]	6/60	10.0%	37/194	19.1%	0.47	[0.19-1.18]	0.11
Maternal Education	*≤ GCSE*[2]	30/60	50.0%	32/194	16.5%	5.06	[2.69-9.53]	<0.0001
Maternal age	*≤22 years*[3]	6/60	10.0%	16/194	8.2%	1.51	[0.50-4.54]	0.46
Paternal age	*≤25 years*[3]	4/54	7.4%	22/186	11.8%	0.60	[0.20-1.81]	0.36
Maternal smoking	*In pregnancy*	12/60	20.0%	19/193	9.8%	2.29	[1.04-5.05]	0.04
Maternal smoking	*After pregnancy*	15/60	25.0%	18/192	9.4%	3.22	[1.51-6.89]	0.003
Paternal smoking	*yes*	11/55	20.0%	20/182	11.0%	2.03	[0.90-4.54]	0.09
Parity	*4+ children*	8/60	13.3%	13/194	6.7%	2.14	[0.84-5.45]	0.10
Support status	*No partner*	5/60	8.3%	7/194	3.6%	2.43	[0.74-7.96]	0.14
Gestation	*<37 weeks*	9/60	15.0%	3/194	1.5%	11.24	[2.93-43.02]	0.0004
Birthweight	*<2500g*	11/60	18.3%	6/194	3.1%	7.03	[2.48-19.97]	0.0002
Multiple birth	*Twin or triplet*	5/60[1]	8.3%	2/194	1.0%	8.73	[1.65-46.22]	0.01
NICU[4]	*Admitted*	10/60	16.7%	9/194	4.6%	4.11	[1.59-10.66]	0.004

1 SIDS (3 Mixed race,2 Asian, 1 Black), Controls (21 Mixed Race, 10Asian, 4 Black, 2 other)
2 Highest educational qualification of mother was the General Certificate of Secondary Education (awarded at 16 years) or below
3 Cut-off based on 10% youngest of the age distribution from all the data
4 Neonatal Intensive Care Unit

Table 3: *Accuscreen* Recordings in the Right and Left Ear (SIDS vs Controls)								
	Unit	**SIDS**			**Controls**			**P-value**
Right Ear		N	Median	IQR	N	Median	IQR	
Duration	*seconds*	12	20	[18-38.5]	77	23	[11-37.5]	0.98
Artefact Rate[1]	*%*	11	2	[0-13]	75	7	[1-19]	0.36
Stimulus Stability[2]	*%*	11	100	[100-100]	75	100	[100-100]	0.62
Probe Fit	*%*	8	42	[20.5-72.25]	75	49	[28-58]	0.83
Left Ear								
Duration	*seconds*	*12*	*10.5*	*[6.75-15.5]*	77	16	[11-38]	0.03
Artefact Rate[3]	*%*	*11*	*0*	*[0-29]*	74	4	[0-17]	0.40
Stimulus Stability[4]	*%*	*11*	*100*	*[100-100]*	74	100	[100-100]	0.23
Probe Fit	*%*	*8*	*42*	*[20.5-72.25]*	74	44	[33.75-54]	0.42

1 Artefact Rate < 20% in 2/11 (18.2%) SIDS and 17/75 (22.7%) controls (p=0.74)
2 Stimulus Stability > 80% in all 11 SIDS and 72/75 (96%) controls
3 Artefact Rate < 20% in 3/11 (27.3%) SIDS and 13/74 (17.6%) controls (p=0.45)
4 Stimulus Stability > 80% in all 11 SIDS and 71/74 (95.9%) controls

Table 4: *Otodynamics* Recordings for the Right and Left Ear (SIDS vs Controls)

Freq	Measure	SIDS (N=24)		Controls (N=98)		p-value[1]
		Median	IQR	Median	IQR	
Right Ear						
1kHz	*Signal*	-2.70	[-9.65 to +6.35]	-1.40	[-6.43 to +5.23]	0.62
	Noise	+7.70	[+1.20 to +11.08]	+7.05	[+1.80 to +12.43]	0.47
	SNR	-7.75	[-12.98 to -2.60]	-8.00	[-13.63 to -1.30]	0.93
	Confidence	14.5%	[5.0% to 35.0%]	14.0%	[4.0% to 43.0%]	0.90
1.5kHz	*Signal*	+9.30	[+5.98 to +14.08]	+8.45	[+2.28 to +11.00]	0.25
	Noise	+6.80	[-0.08 to +11.05]	+6.60	[+2.38 to +12.38]	0.91
	SNR	+2.45	[-0.63 to +8.80]	+0.55	[-3.85 to +4.70]	0.16
	Confidence	63.5%	[46.5% to 88.5%]	53.5%	[29.0% to 74.25%]	0.15
2kHz	*Signal*	+11.25	[+8.75 to +15.63]	+12.10	[+7.43 to 16.50]	0.92
	Noise	+4.25	[-1.40 to +8.08]	+4.15	[-0.90 to +7.83]	0.85
	SNR	+7.25	[+4.83 to +14.73]	+7.10	[+3.85 to +11.33]	0.71
	Confidence	84.0%	[75.0% to 96.25%]	84.0%	[70.75% to 93.0%]	0.72
3kHz	*Signal*	+17.15	[+12.53 to +20.58]	+15.00	[+0.18 to +20.38]	0.26
	Noise	+6.00	[+1.73 to +8.50]	+4.20	[+1.75 to +7.90]	0.56
	SNR	+9.50	[+6.73 to +17.10]	+8.05	[+6.40 to +12.45]	0.29
	Confidence	90.0%	[82.75% to 97.75%]	86.0%	[82.0% to 94.25%]	0.27
4kHz	*Signal*	+13.00	[+7.98 to +20.43]	+11.05	[+6.40 to +16.33]	0.20
	Noise	+2.25	[-1.75 to +4.68]	+0.50	[-2.43 to +3.68]	0.35
	SNR	+12.40	[+7.78 to +17.20]	+9.85	[+6.28 to +15.00]	0.18
	Confidence	94.5%	[85.25% to 98.0%]	90.5%	[81.0% to 97.0%]	0.20
Left Ear						
1kHz	*Signal*	-6.95	[-12.20 to +0.43]	-0.10	[-5.43 to +5.40]	0.004
	Noise	+2.70	[+0.55 to +6.28]	+6.35	[+0.50 to +11.13]	0.023
	SNR	-8.55	[-12.23 to -1.90]	-4.35	[-10.70 to +0.63]	0.11
	Confidence	12.5%	[5.25% to 39.5%]	27.0%	[8.5% to 53.25%]	0.10
1.5kHz	*Signal*	+5.50	[+3.58 to +10.73]	+8.05	[+3.98 to +11.00]	0.33
	Noise	+3.40	[+0.75 to +9.00]	+6.90	[+2.93 to +10.83]	0.06
	SNR	+3.20	[-2.60 to +6.38]	+1.75	[-2.65 to +5.53]	0.54
	Confidence	67.5%	[35.25% to 81.0%]	60.0%	[34.75% to 78.5%]	0.15
2kHz	*Signal*	+9.25	[+4.93 to +16.78]	+11.10	[+7.38 to 14.80]	0.63
	Noise	+2.40	[-2.65 to +4.53]	+2.05	[-0.53 to +6.10]	0.50
	SNR	+7.90	[+4.43 to +12.28]	+7.10	[+4.55 to +13.23]	0.79
	Confidence	86.0%	[73.0% to 94.5%]	84.00	[73.75% to 95.0%]	0.80
3kHz	*Signal*	+16.35	[+10.35 to +20.33]	+13.30	[+8.95 to +18.30]	0.23
	Noise	+3.20	[+0.78 to +4.70]	+2.45	[-0.13 to +5.53]	0.53
	SNR	+11.25	[+6.89 to +17.65]	+9.55	[+6.30 to +14.50]	0.28
	Confidence	93.0%	[82.75% to 98.0%]	90.0%	[81.0% to 96.25%]	0.31
4kHz	*Signal*	+14.20	[+6.53 to +17.28]	+10.70	[+5.73 to +15.63]	0.25
	Noise	-0.70	[-2.35 to +2.80]	-0.75	[-3.00 to +2.43]	0.74
	SNR	+12.45	[+6.78 to +16.50]	+10.80	[+6.20 to +15.40]	0.38
	Confidence	94.5%	[82.75% to 98.0%]	92.5%	[81.0% to 97.0%]	0.42

1 Mann Whitney test
Signal, Noise and SNR measured in dB

Figure 3 – Comparison of individual right/left ear symmetry of signal (SIDS vs Controls)

Median difference and inter-quartile range

Table 5: Multivariable model (SIDS vs Controls)

Characteristic	Category	SIDS		Controls		OR[1]	95% CI	p-value
		n/N	%	n/N	%			
Sleeping with carer	*Hazardous*[2]	21/60	35.0%	6/194	3.1%	40.2	[10.6-152.8]	<0.0001
Sleeping position	*Found prone*	20/60	33.3%	6/194	3.1%	29.1	[7.2-118.0]	<0.0001
Health final week	*Fair or poor*	32/60	53.3%	18/194	9.3%	10.9	[3.9-31.1]	<0.0001
Multiple birth	*Twin*	5/60	8.3%	2/194	1.0%	57.4	[7.4-444.1]	0.0002
Feeding final week	*< usual*	20/60	33.3%	12/194	6.2%	5.0	[1.5-16.7]	0.009
Maternal Education	*≤ GCSE*[3]	30/60	50.0%	32/194	16.5%	3.9	[1.4-11.0]	0.01

1 Adjusted for infant age, 60 SIDS cases and 194 controls in the model
2 Includes those sleeping directly next to a parent that has consumed alcohol or smoked or where carer or infant slept on a sofa
3 Highest educational qualification of mother was the General Certificate of Secondary Education (awarded at 16 years) or below

Reporting checklist for case-control study.

Based on the STROBE case-control guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE case-control reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	#3	State specific objectives, including any prespecified hypotheses	3
Study design	#4	Present key elements of study design early in the paper	4
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case	4

	#6b	For matched studies, give matching criteria and the number of controls per case	n/a
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for cases and controls.	4,5
Bias	#9	Describe any efforts to address potential sources of bias	4,5
Study size	#10	Explain how the study size was arrived at	4,5
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	4,5
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	5
	#12b	Describe any methods used to examine subgroups and interactions	5
	#12c	Explain how missing data were addressed	5
	#12d	If applicable, explain how matching of cases and controls was addressed	n/a
	#12e	Describe any sensitivity analyses	5
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for cases and controls.	6
	#13b	Give reasons for non-participation at each stage	6
	#13c	Consider use of a flow diagram	n/a
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for cases and controls	6,7
	#14b	Indicate number of participants with missing data for each variable of interest	14-17

Outcome data	#15	Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls	14-17
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17
	#16b	Report category boundaries when continuous variables were categorized	17
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	7,8
Key results	#18	Summarise key results with reference to study objectives	9,10
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	9,10
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	9,10
Generalisability	#21	Discuss the generalisability (external validity) of the study results	9,10
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

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Sudden Infant Death Syndrome (SIDS) and the routine otoacoustic emission infant hearing screening test: an epidemiological retrospective case-control study.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030026.R1
Article Type:	Research
Date Submitted by the Author:	25-Apr-2019
Complete List of Authors:	Blair, Peter; University of Bristol, Bristol Medical School Rubens, Daniel; Seattle Children's Hospital Pease, Anna; University of Bristol, Bristol Medical School Mellers, Diane; Birmingham Women's Hospital, Department of Research & Development Ingram, Jenny; University of Bristol, Bristol Medical School Ewer, Andrew; University of Birmingham, Institute of Metabolism and Systems Research Cohen, Marta; University of Sheffield, Department of Oncology and Metabolism Sidebotham, Peter; University of Warwick Warwick Medical School Ward Platt, Martin; Newcastle University, Institute of Health and Society Coombs, Robert; University of Sheffield Davis, Adrian; Imperial College London Hall, Amanda; University of Bristol, National Institute of Health Research Clinical Research Network: West of England Fleming, Peter; University of Bristol, Bristol Medical School
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Paediatrics
Keywords:	SIDS, SUDI, Epidemiology < TROPICAL MEDICINE, hearing, screening

Sudden Infant Death Syndrome (SIDS) and the routine otoacoustic emission infant hearing screening test: an epidemiological retrospective case-control study.

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Abstract word count: 300/300

Main Manuscript word count: 3397/4000

Key Words: SIDS, SUDI, epidemiology, hearing, screening

Abstract

objectives: To investigate whether decreased oto-acoustic emission (OAE) signal recordings in the right ear are associated with an increased risk of sudden infant death syndrome (SIDS) and to monitor any temporal changes in risk factors.

design: Retrospective case-control study

setting: Telephone interviews with families recruited in England between July 2016 and October 2017 who experienced the unexpected death of a child <4 years old since 2008 and control families recruited from maternity wards in Bristol and Birmingham.

participants: We recruited 91(89%) of the 102 bereaved families who made initial contact, 64 deaths were under 1 year old (Sudden Unexpected Death in Infancy) of which 60 remained unexplained (SIDS). Of the 220 control families, 194(88%) follow-up interviews were conducted. We had analysable hearing data for 24 SIDS infants (40%) and 98 controls (51%).

results: OAE signals were marginally increased rather than decreased among SIDS infants for the right ear, especially at lower frequencies, but not significantly so. The strongest predictors of SIDS were bed-sharing in hazardous (infant sleeping next to a carer who smoked, drank alcohol or slept on a sofa) circumstances (35% vs 3% controls, $p<0.0001$), infants found prone (33% vs 3% controls, $p<0.0001$) and infants whose health in the final week was 'not good' (53% vs 9% controls, $p<0.0001$). The prevalence of maternal smoking during pregnancy amongst both SIDS mothers(20%) and controls(10%) was much lower than previous studies.

conclusions: Hearing data were difficult to obtain; larger numbers would be needed to determine if asymmetrical differences between the right and left ear were a marker for SIDS. A national prospective registry for monitoring and a renewed campaign to a new generation of parents needs to be considered underlining the initial message to place infants on their backs for sleep and the more recent message to avoid bed-sharing in hazardous circumstances.

Strengths and limitations of this study

- This study uses routinely collected hearing data to test a novel hypothesis
- This study also collects valuable data from bereaved parents to monitor SIDS risk factors
- The retrospective nature of the study (collecting data from bereaved families over a 10 year period) limits the generalisability of the findings and leaves it open to recall bias
- Difficulties in collecting routine hearing data hinders interpretation of the findings

Introduction

Despite its reduced incidence, Sudden Infant Death Syndrome (SIDS) is the second leading cause of post-neonatal infant mortality in England & Wales[1], the highest among infants of younger mothers[2] and common in socially-deprived families.[3] Epidemiological markers at birth are available to identify some families at increased risk[4] but are neither sensitive nor specific enough to make targeted intervention possible.[5] A physiological marker independent of current demographic identifiers would have the potential for making targeted intervention viable.

In 2008 a study demonstrated an altered newborn oto-acoustic emission (OAE) hearing test in thirty-one infants who subsequently died of SIDS compared to thirty-one control infants.[6] The OAE is the sound signal generated by the cochlea as a response to sound and recorded in the ear canal. This observation begs the question - are altered OAEs a marker of predisposition to SIDS? If so, can the newborn OAE hearing test be used in combination with epidemiological markers to identify 'at risk' infants at birth? However maternal smoking during pregnancy was not measured in the Rhode Island Study, so it could be that exposure to tobacco smoke *in utero* resulted in developmental differences associated with infant hearing which would confound the potential of an improved screening tool but would still add to our understanding of causal mechanisms for some of these deaths. Most infants (>99%) in England have a hearing test shortly after birth and the data, stored by Public Health England since 2010, could be suitable for analysis.

In England & Wales SIDS deaths have fallen from a peak of nearly 1600 deaths in 1988[7] to just over 200 deaths in 2016.[2] Longitudinal data collected in Avon suggest not only that there has been a shift towards poorer families but that prone positioning is still a feature of these deaths[3] and bed-sharing in hazardous conditions (next to a parent who has consumed alcohol, drugs or regularly smokes or uses an unsafe sleeping surface such as a sofa) has emerged as a highly significant risk factor.[4,8]

We conducted a retrospective case-control study of SIDS infants and surviving controls primarily to investigate whether decreased OAE signal recordings in the right ear are associated with an increased risk of SIDS, and secondarily to investigate any recent changes in epidemiological characteristics.

Methodology

Ethical approval and governance

Ethical approval was sought and gained from the South West Central Bristol Research Ethics Committee; REC (reference :14/SW/1084). The date of approval was 22 March 2016. We used the STROBE case-control checklist when writing our report.[9]

Patient and Public Involvement

We work closely with bereaved parents who encourage us to collect detailed observational data to both further our understanding of causal mechanisms and provide evidence for risk reduction advice. For this study families were recruited retrospectively via *The Lullaby Trust* (the main SIDS charity in England https://www.lullabytrust.org.uk/). As with our previous studies the bereaved families involved in this study will be the first to receive the findings before wider dissemination is made in publications and scientific conferences largely organised by bereaved parent groups.

Recruitment of cases

A request was sent for families to contact *The Lullaby Trust* if they had experienced an unexpected death of an infant or child up to and including the age of 3 years since 2008. Data on children who died from 1 to 3 years old will be reported separately.

Families who responded to this request were given a brief written and verbal explanation of what the study involved by the *Trust* as well as being asked to agree to be contacted by the research team. The subsequent telephone interview was conducted by one of the clinical members of the team using a semi-structured questionnaire format. On receipt of signed consent forms, we wrote to the relevant coroners' offices to request copies of all inquest documentation, including (but not limited to) the police report, SUDI paediatrician report and post-mortem report. We then conducted multi-professional case review meetings to categorise each case according to the Avon clinico-pathological system[10] as an explained or unexplained (SIDS) death.

Recruitment of controls

We recruited controls from St Michael's Hospital, Bristol, and Birmingham Women's Hospital from June 2016 to August 2017 inclusive. Mothers who had given birth to infants at or after 35 weeks' gestation who had no significant medical problems were approached by one of the research team within 24 hours of delivery. Participants were interviewed by telephone using the same semi-structured interview to obtain information about a reference infant sleep within 24 hours of the call, when their infants were at similar ages to the anticipated ages of death of the index infants. We tried to distribute the times and days of the week for the reference sleep to match as closely as possible those on which the deaths had occurred.

Collection of hearing data

The hearing data obtained depended on the screening equipment being used. Two different recording systems are used within the NHS to collect infant hearing data which are stored by a private company contracted to Public Health England. The systems are Otoport™ (Otodynamics Ltd, Hatfield, UK) system and Accuscreen™ (Madsen from Natus, formerly GN Otometrics, Copenhagen, Denmark]. The Otodynamics system collects signal and noise recordings (as in the early US study) for both the right and left ear at 5 frequencies (I kHz, 1.5 kHz, 2 kHz, 3 kHz and 4 kHz) with the signal generally improving the higher the frequency. The Otodynamics recordings included signal and noise measured in decibels (dB) and provided as logarithms, so the ratio is calculated as noise subtracted from the signal. A measure (%) of confidence in the reliability of the recording is also given. There is debate as to whether signal to noise ratio or just signal would be the best measure, so we have provided both. The data were extracted using the Otodynamics ILO Data Explorer. The Accuscreen™ device also provides data for both right and left ear but is more limited as the OAE result at the different frequencies are combined. The only useful measurement related to the strength of the OAE signal from these recordings appears to be the length of time it took to get a positive response (a total of 8 valid peaks in alternating direction of the OAE waveform has been achieved to formulate a 'pass' for the test). The Accuscreen™ recordings included the duration to achieve a positive response (in seconds), the artefact rate (related to noise) which should below 20% if possible, the stimulus stability (emanating from the probe stability) which should be above 80% if possible and the probe fit which is also measured as a % in terms of how successfully it was fitted. These data were extracted using the Madsen Acculink™ package.

Statistical Methodology

The univariable and multivariable analyses were calculated using logistic regression in SPSS. Medians and interquartile ranges were used to describe continuous data that were not normally distributed and comparisons tested using the Mann Whitney test. Categorical data were tested using Chi-Square. Given the expected relatively low number of SIDS cases, multivariate adjustments were limited to essential covariates and simple dichotomies were used for multi-categorical and continuous variables. Variable selection used the backward stepwise selection method and any variable with more than 10% data missing was modelled separately in a sensitivity analysis.

Results

Ascertainment

Of 102 bereaved families who contacted *the Lullaby Trust,* we completed the interviews with the families of 91 children who died suddenly and unexpectedly. There were 27 deaths between the ages of 1-3 years (SUDC) which will be reported separately and 64 were sudden unexpected deaths in infancy (SUDI). Four unexpected infant deaths were fully explained: two from previously unrecognised cardiac abnormalities, and two from acute infections. For 50/60 SIDS deaths (83%) the multiagency review process identified possible or probable contributory factors that could not in themselves fully explain the death (Table 1).

Of the 220 control families who consented to take part in the maternity hospital, 194 (88%) completed a follow-up telephone interview (79 from Bristol and 115 from Birmingham). The 26 control families lost to follow-up were more likely to have pre-term infants (<37 weeks: 7.7% vs 1.5%, p=0.08) and a greater proportion of mothers with lower educational achievements (highest qualification ≤ GCSE or equivalent: 36% vs 16.5%, p=0.02) but there were no major differences in gender, ethnicity, maternal smoking during pregnancy, maternal age, number of siblings or birthweight.

Temporal weighting

The 60 SIDS deaths occurred between 2007 and 2017 with no marked seasonal difference. The reference sleep of the controls occurred between June 2016 and August 2017 inclusive with an increased number in the coldest quarter of December, January and February (25% SIDS deaths vs 60% controls, p<0.0001). As Figure 1 shows, the median age of the SIDS infants was 85 days [iqr: 49-159 days], the median age of the control infants in this study was 77 days [iqr: 44-114 days]. The slight difference in age distribution was not statistically significantly (Mann-Whitney test: p=0.18]. Of the 60 SIDS deaths 58 occurred while the infant was thought by the parents to be asleep; 17/58 (29.3%) deaths occurred during what the parents considered to be a day-time sleep, significantly more than the day-time reference sleeps of control infants (26/194 or 13.4%, p=0.007). There was no significant variation in the number of deaths or of reference sleeps by day of the week. (Mann Whitney test: p=0.97). (Figure 2).

Demographic characteristics

Table 2 compares the background and perinatal demographics of the SIDS infants and controls. There was a slight preponderance of males and a higher proportion with white ethnicity among the SIDS infants. Lower levels of maternal educational achievement were more prevalent among the SIDS families; highest educational attainment was either below or no more than the standard expected at 16 years old for half of the SIDS mothers (three times more than control mothers). The SIDS mothers were slightly younger (median age 29 years [IQR: 26-33 years]) than the control mothers (median age 31 years [IQR: 28-34 years]) but this difference was not significant.

Hearing Data

Hearing screening tests were conducted for all but one of the SIDS cases and all the controls although analysable records were only available for 60% of the SIDS infants and 91% of the controls. For the SIDS infants lack of written consent (15%), missing records post 2010 (8%), unusable records pre-2010 (5%) and no clear OAE response (12%) explain the lack of availability. Among the controls there was no clear OAE response for 17/194 infants (9%).

We had *Accuscreen* hearing records for the right and left ear available for 12 SIDS infants and 79 controls. The median duration of the test recording that was required to achieve a pass in the right ear was slightly shorter among the SIDS infants (20 seconds) compared to the controls (23 seconds) but not significantly different (Table 3). The median duration of the test recording was shorter for both groups in the left ear but significantly so for the SIDS infants (10.5 seconds) compared to the controls (16 seconds). There were no significant differences observed between SIDS infants and controls in artefact rate, stimulus stability or probe fit.

We had *OtoDynamics* hearing records for the right and left ear available for 24 SIDS infants and 98 controls. Table 4 compares the median signal, noise, signal to noise ratio and confidence (in percentage terms) of these findings between SIDS and controls in the right and left ear. The median signal in the right ear was slightly higher among the control infants at 1 kHz and 2 kHz frequency and slightly higher among the SIDS infants at 1.5 kHz, 3 kHz and 4 kHz frequencies but none of these differences were statistically significant. The signal to noise ratio in the right ear was consistently slightly higher among the SIDS infants compared to the controls but again none of these differences were statistically significant. At 2 kHz, 3 kHz and 4 kHz this difference increased with frequency (0.15 dB, 1.45 dB and 2.55 dB). The median signal in the left ear was significantly higher among the control infants at 1 kHz ($p=0.004$), albeit within the equipment noise floor, higher (but not significantly so) at 1.5 kHz ($p=0.33$) and at 2 kHz ($p=0.63$), conversely the median signal was slightly higher among the SIDS infants at 3 kHz ($p=0.23$) and 4 kHz ($p=0.25$). The noise was also significantly higher among the control infants at 1 kHz ($p=0.023$) and almost significant at 1.5 kHz ($p=0.06$). Subtracting the signal in the right ear from the left ear to look at right/left asymmetry (Figure 3) the right ear was more dominant among the SIDS infants at all frequencies but particularly for the lower frequencies, albeit this was not significant and the confidence score at these lower frequencies was quite low.

Multivariable risk factors

Table 5 lists those factors that remained significant in the multivariable analysis when adjusted for infant age and the other factors in the model. The highest risk was associated with those infants sleeping next to a carer who had consumed alcohol, smoked tobacco or was sleeping on a sofa (35% vs 3% controls). In this study 8/60 SIDS infants were found co-sleeping on a sofa compared to 1/194 control infants. Infants being found prone exhibited a strong association; notably, for all 6 control infants found in this position this was the usual positioning and only one was younger than 3 months of age; in contrast for nearly two-thirds of the SIDS infants found prone (10 out of the 16 who responded) this was not the usual position found and 9 of these 20 infants were aged less than 3 months. Fewer Infants were put down in the prone position although this was more common among the SIDS infants and significant (11% vs 1.6% controls, p=0.004); only 3 SIDS infants (5.7%) were placed on their side and all 3 were found on their side, a similar proportion to the controls (7.3%).

In the final week before the last sleep over half the SIDS infants were described by the carer as having health that was only fair or poor (rather than good) and a third were reported to have fed less than usual compared to a smaller proportion for both these factors among the controls (11% and 6% respectively). Being a twin and having a less well-educated mother were the two strongest demographic characteristics of SIDS infants.

Maternal smoking during pregnancy was notable for its absence in the final model, mainly because of the low prevalence both among the SIDS mothers (20%) and controls (10%). More of the SIDS infants used a dummy for the last sleep but this was not significant (40% vs 35% controls, p=0.50). Only around a quarter of the SIDS carers who provided a dummy could recall what happened during the final infant sleep and 5 of the 6 carers responded that the dummy fell out or was removed soon after the infant fell asleep. Among the controls nearly all (61/65 or 94%) thought the dummy fell out or was removed soon after sleep onset. More of the control infants used an infant sleeping bag for the last sleep but this did not reach univariable significance (22% SIDS vs 36% controls, p=0.06)

Discussion

We were not able to confirm the promising findings on oto-acoustic emissions from the previous study.[6] In that study the signal to noise ratio was consistently and significantly 4dB lower at 2kHz, 3kHz and 4kHz in the right ear of infants who subsequently went on to die of SIDS compared to surviving controls. In our study the difference in signal to noise ratio was in the opposite direction; higher in the right ear of SIDS infants than controls and this difference increased (from 0.15dB to 2.55dB) the higher the frequency albeit this was not statistically significant. There were potential asymmetrical differences between the SIDS infants and controls at lower frequencies but the low confidence in these scores and small numbers requires cautious interpretation.

The right ear advantage in cochlear function has been well described in infants, with right OAEs approximately 1 dB larger than left.[11-13] This inter-aural asymmetry is hypothesised to reflect developmental differences in the activity of the medial olivoochlear efferent system between the ears;[14,15] differences in ear asymmetry between SIDS and control infants could indicate developmental differences in early auditory efferent function.

The major limitation is that both studies were underpowered. A larger study would be needed to detect any subtle differences in infant hearing should such differences genuinely exist. Accessing hearing data in the UK was difficult; we encountered delays, missing records, inability for the contracted company to read the data they store and monitoring systems that were incompatible.

As with our study conducted 10 years ago[4] just over half the SIDS infants were found next to a carer and bed-sharing in hazardous circumstances was the strongest association with SIDS in the multivariable model. Initiatives to highlight the specific hazards to parents who bed-share and clearly explain the evidence to health professionals such as the UNICEF '*Caring for your baby at night*' leaflets[16] and '*Co-sleeping and SIDS*' infographic[17] need to be encouraged. The proportion of SIDS infants found prone seems stubbornly persistent over the years; 38% in our study 20 years ago[18], 29% in our study 10 years ago[4] and 33% in our current study. Although the proportion found prone in the control population was low, our studies of high-risk families in socio-economically deprived areas in Bristol suggest that parental awareness of this risk factor was poor (only a half of the 400 mothers surveyed in 2014 identified avoiding prone sleep position as one of the top 3 risk reduction strategies for SIDS).[19]

Our three studies conducted in England show that the prevalence of maternal smoking during pregnancy has fallen from 27% 20 years ago[20] to 14% 10 years ago[5] to 10% in this study reflecting a national trend. Among the SIDS families the prevalence in these three studies has fallen from 66%, to 59% and just 20% in the current study. This may be a consequence of a reduced population prevalence but may partly be explained by the bias towards less-deprived and more articulate families who volunteered to take part in this study compared with the families in our previous prospective population-based studies.

As well as using a retrospective design and a relatively small sample, there were other limitations to this study. Most of the SIDS deaths occurred between 2010 and 2017; during this period there were over 2000 SIDS deaths in England suggesting our self-selected SIDS sample was around 3% of the SIDS population which may not be representative of the wider English population. The potential for recall bias was high especially regarding specific details of the final sleep such as response to what happened to the infant dummy which was only recollected by a quarter of the SIDS parents compared to virtually all the controls. The data from the controls were prospectively collected but recruitment was opportunistic and access to the more vulnerable infants was difficult, yielding a control population with fewer premature and low birthweight infants than the national average. We were not able to arrange control interviews that would reflect the seasonal distribution of SIDS deaths or reflect the higher than expected proportion of day-time deaths, and telephone interviews are a poor substitute for face-to-face ones.

Many of the families with whom we spoke were under the impression that the information they had already given to the healthcare staff or the police after their child's death were available to be used for research, and many expressed surprise and anger when informed this was not the case. All but one bereaved family told us that, had they been asked at the time of their child's death, they would have given permission for the data and the pathology samples to be used in future research projects aimed at preventing such deaths. This information has led us to propose the establishment of a national Registry of unexpected infant and childhood deaths, to which families could opt in soon after the death of their child, and which would thus have written informed consent to make available the routinely collected information and pathology samples.

We conclude that if routinely collected data are to be fully utilised for both national monitoring and efficiently designed research investigations, then bodies such as Public Health England need to consider single or compatible monitoring systems that can provide easy access to analysable data, as well as a routine quality control of recorded and stored data. For parents, there need to be renewed efforts to underline the need to place infants on their backs for sleep and avoid bed-sharing in hazardous circumstances.

Acknowledgements

We would like to thank Francine Bates, Lucy Lyus and Jenny Ward at the Lullaby Trust for helping with recruitment, Dr Siobhan Ryan at Public Health England for helping obtain the hearing records, Mark Cook at Northgate Public Services for his assistance with sending the data, Mr Abhilash Vora for data entry and cleaning and most of all the parents who have provided information for this study that may help future parents.

Funding

This work was supported by the *Lullaby Trust* (project number 268) with funding also received from *Teddy's Wish* and *Seattle Children's Hospital.* These sponsors had no role in the study design; in the collection, analysis and interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication.

Competing interests

None declared

Author Contributions

DR, PJF, PSB, AP & JI were responsible for developing the research question. PJF, DR, PSB, JI, AP, AH, DM, AE, AD were responsible for the study design. PJF, AP, PS, MCC, MWP & RC were responsible for data collection, death classification and quality assessment of the investigation into the death. AP was responsible for study management. PSB initially drafted the paper. All authors read, commented on and approved the final manuscript.

Data availability statement

The data we have collected is sensitive and includes information from bereaved parents and coroner's reports. We are happy to comply with University of Bristol regulations in this matter although it must be understood that ethical approval would be a prerequisite to access

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Table 1: Avon Classification of Sudden Unexpected Deaths in Infancy (SUDI)*			
0	Information not collected	0/64	0%
IA	No potentially significant factors or contributory factors found (SIDS)	0/64	0%
IB	Factors present but not likely to have contributed to the death (SIDS)	10/64	15.6%
IIA	Factors present and may possibly have contributed to the death (SIDS)	29/64	45.3%
IIB	Factors present and probably contributed to the death (SIDS)	21/64	32.8%
III	Fully explained death	4/64	6.3%

* The multi-professional case review meetings included a range of relevant professionals with experience in the field (paediatrician, paediatric pathologist, health visitor, police officer, social worker). After discussion of each case, each was categorised according to the Avon clinicopathological categorisation system[8] as an explained or unexplained (SIDS) death.

Table 2: Demographic Characteristics (SIDS vs Controls)

Characteristic	Category	SIDS		Controls		OR	95% CI	p-value
		n/N	%	n/N	%			
Gender	*Male*	33/60	55.0%	90/194	46.4%	1.41	[0.79-2.53]	0.24
Ethnicity	*Non-white[1]*	6/60	10.0%	37/194	19.1%	0.47	[0.19-1.18]	0.11
Maternal Education	*≤ GCSE[2]*	30/60	50.0%	32/194	16.5%	5.06	[2.69-9.53]	<0.0001
Maternal age	*≤22 years[3]*	6/60	10.0%	16/194	8.2%	1.51	[0.50-4.54]	0.46
Paternal age	*≤25 years[3]*	4/54	7.4%	22/186	11.8%	0.60	[0.20-1.81]	0.36
Maternal smoking	*In pregnancy*	12/60	20.0%	19/193	9.8%	2.29	[1.04-5.05]	0.04
Maternal smoking	*After pregnancy*	15/60	25.0%	18/192	9.4%	3.22	[1.51-6.89]	0.003
Paternal smoking	*yes*	11/55	20.0%	20/182	11.0%	2.03	[0.90-4.54]	0.09
Parity	*4+ children*	8/60	13.3%	13/194	6.7%	2.14	[0.84-5.45]	0.10
Support status	*No partner*	5/60	8.3%	7/194	3.6%	2.43	[0.74-7.96]	0.14
Gestation	*<37 weeks*	9/60	15.0%	3/194	1.5%	11.24	[2.93-43.02]	0.0004
Birthweight	*<2500g*	11/60	18.3%	6/194	3.1%	7.03	[2.48-19.97]	0.0002
Multiple birth	*Twin or triplet*	5/60[1]	8.3%	2/194	1.0%	8.73	[1.65-46.22]	0.01
NICU[4]	*Admitted*	10/60	16.7%	9/194	4.6%	4.11	[1.59-10.66]	0.004

1 SIDS (3 Mixed race,2 Asian, 1 Black), Controls (21 Mixed Race, 10Asian, 4 Black, 2 other)
2 Highest educational qualification of mother was the General Certificate of Secondary Education (awarded at 16 years) or below
3 Cut-off based on 10% youngest of the age distribution from all the data
4 Neonatal Intensive Care Unit

Table 3: *Accuscreen* Recordings in the Right and Left Ear (SIDS vs Controls)

	Unit	SIDS			Controls			P-value
Right Ear		N	Median	IQR	N	Median	IQR	
Duration	*seconds*	12	20	[18-38.5]	77	23	[11-37.5]	0.98
Artefact Rate[1]	*%*	11	2	[0-13]	75	7	[1-19]	0.36
Stimulus Stability[2]	*%*	11	100	[100-100]	75	100	[100-100]	0.62
Probe Fit	*%*	8	42	[20.5-72.25]	75	49	[28-58]	0.83
Left Ear								
Duration	*seconds*	*12*	*10.5*	*[6.75-15.5]*	77	16	[11-38]	0.03
Artefact Rate[3]	*%*	*11*	*0*	*[0-29]*	74	4	[0-17]	0.40
Stimulus Stability[4]	*%*	*11*	*100*	*[100-100]*	74	100	[100-100]	0.23
Probe Fit	*%*	*8*	*42*	*[20.5-72.25]*	74	44	[33.75-54]	0.42

1 Artefact Rate < 20% in 2/11 (18.2%) SIDS and 17/75 (22.7%) controls (p=0.74)
2 Stimulus Stability > 80% in all 11 SIDS and 72/75 (96%) controls
3 Artefact Rate < 20% in 3/11 (27.3%) SIDS and 13/74 (17.6%) controls (p=0.45)
4 Stimulus Stability > 80% in all 11 SIDS and 71/74 (95.9%) controls

Table 4: *Otodynamics* Recordings for the Right and Left Ear (SIDS vs Controls)						
Right Ear						
Freq	**Measure**	**SIDS (N=24)**		**Controls (N=98)**		**p-value[1]**
		Median	**IQR**	**Median**	**IQR**	
1kHz	*Signal*	-2.70	[-9.65 to +6.35]	-1.40	[-6.43 to +5.23]	0.62
	Noise	+7.70	[+1.20 to +11.08]	+7.05	[+1.80 to +12.43]	0.47
	SNR	-7.75	[-12.98 to -2.60]	-8.00	[-13.63 to -1.30]	0.93
	Confidence	14.5%	[5.0% to 35.0%]	14.0%	[4.0% to 43.0%]	0.90
1.5kHz	*Signal*	+9.30	[+5.98 to +14.08]	+8.45	[+2.28 to +11.00]	0.25
	Noise	+6.80	[-0.08 to +11.05]	+6.60	[+2.38 to +12.38]	0.91
	SNR	+2.45	[-0.63 to +8.80]	+0.55	[-3.85 to +4.70]	0.16
	Confidence	63.5%	[46.5% to 88.5%]	53.5%	[29.0% to 74.25%]	0.15
2kHz	*Signal*	+11.25	[+8.75 to +15.63]	+12.10	[+7.43 to 16.50]	0.92
	Noise	+4.25	[-1.40 to +8.08]	+4.15	[-0.90 to +7.83]	0.85
	SNR	+7.25	[+4.83 to +14.73]	+7.10	[+3.85 to +11.33]	0.71
	Confidence	84.0%	[75.0% to 96.25%]	84.0%	[70.75% to 93.0%]	0.72
3kHz	*Signal*	+17.15	[+12.53 to +20.58]	+15.00	[+0.18 to +20.38]	0.26
	Noise	+6.00	[+1.73 to +8.50]	+4.20	[+1.75 to +7.90]	0.56
	SNR	+9.50	[+6.73 to +17.10]	+8.05	[+6.40 to +12.45]	0.29
	Confidence	90.0%	[82.75% to 97.75%]	86.0%	[82.0% to 94.25%]	0.27
4kHz	*Signal*	+13.00	[+7.98 to +20.43]	+11.05	[+6.40 to +16.33]	0.20
	Noise	+2.25	[-1.75 to +4.68]	+0.50	[-2.43 to +3.68]	0.35
	SNR	+12.40	[+7.78 to +17.20]	+9.85	[+6.28 to +15.00]	0.18
	Confidence	94.5%	[85.25% to 98.0%]	90.5%	[81.0% to 97.0%]	0.20
Left Ear						
1kHz	*Signal*	-6.95	[-12.20 to +0.43]	-0.10	[-5.43 to +5.40]	0.004
	Noise	+2.70	[+0.55 to +6.28]	+6.35	[+0.50 to +11.13]	0.023
	SNR	-8.55	[-12.23 to -1.90]	-4.35	[-10.70 to +0.63]	0.11
	Confidence	12.5%	[5.25% to 39.5%]	27.0%	[8.5% to 53.25%]	0.10
1.5kHz	*Signal*	+5.50	[+3.58 to +10.73]	+8.05	[+3.98 to +11.00]	0.33
	Noise	+3.40	[+0.75 to +9.00]	+6.90	[+2.93 to +10.83]	0.06
	SNR	+3.20	[-2.60 to +6.38]	+1.75	[-2.65 to +5.53]	0.54
	Confidence	67.5%	[35.25% to 81.0%]	60.0%	[34.75% to 78.5%]	0.15
2kHz	*Signal*	+9.25	[+4.93 to +16.78]	+11.10	[+7.38 to 14.80]	0.63
	Noise	+2.40	[-2.65 to +4.53]	+2.05	[-0.53 to +6.10]	0.50
	SNR	+7.90	[+4.43 to +12.28]	+7.10	[+4.55 to +13.23]	0.79
	Confidence	86.0%	[73.0% to 94.5%]	84.00	[73.75% to 95.0%]	0.80
3kHz	*Signal*	+16.35	[+10.35 to +20.33]	+13.30	[+8.95 to +18.30]	0.23
	Noise	+3.20	[+0.78 to +4.70]	+2.45	[-0.13 to +5.53]	0.53
	SNR	+11.25	[+6.89 to +17.65]	+9.55	[+6.30 to +14.50]	0.28
	Confidence	93.0%	[82.75% to 98.0%]	90.0%	[81.0% to 96.25%]	0.31
4kHz	*Signal*	+14.20	[+6.53 to +17.28]	+10.70	[+5.73 to +15.63]	0.25
	Noise	-0.70	[-2.35 to +2.80]	-0.75	[-3.00 to +2.43]	0.74
	SNR	+12.45	[+6.78 to +16.50]	+10.80	[+6.20 to +15.40]	0.38
	Confidence	94.5%	[82.75% to 98.0%]	92.5%	[81.0% to 97.0%]	0.42

1 Mann Whitney test
Signal, Noise and SNR measured in dB

Table 5: Multivariable model (SIDS vs Controls)

Characteristic	Category	SIDS		Controls		OR[1]	95% CI	p-value
		n/N	%	n/N	%			
Sleeping with carer	*Hazardous*[2]	21/60	35.0%	6/194	3.1%	40.2	[10.6-152.8]	<0.0001
Sleeping position	*Found prone*	20/60	33.3%	6/194	3.1%	29.1	[7.2-118.0]	<0.0001
Health final week	*Fair or poor*	32/60	53.3%	18/194	9.3%	10.9	[3.9-31.1]	<0.0001
Multiple birth	*Twin*	5/60	8.3%	2/194	1.0%	57.4	[7.4-444.1]	0.0002
Feeding final week	*< usual*	20/60	33.3%	12/194	6.2%	5.0	[1.5-16.7]	0.009
Maternal Education	*≤ GCSE*[3]	30/60	50.0%	32/194	16.5%	3.9	[1.4-11.0]	0.01

1 Adjusted for infant age, 60 SIDS cases and 194 controls in the model
2 Includes those sleeping directly next to a parent that has consumed alcohol or smoked or where carer or infant slept on a sofa
3 Highest educational qualification of mother was the General Certificate of Secondary Education (awarded at 16 years) or below

Figure 1 – Age at death or reference sleep (SIDS vs Controls)

Figure 2 – Day of week of death or reference sleep (SIDS vs Controls)

Figure 3 – Comparison of individual right/left ear symmetry of signal (SIDS vs Controls)

Median difference and inter-quartile range

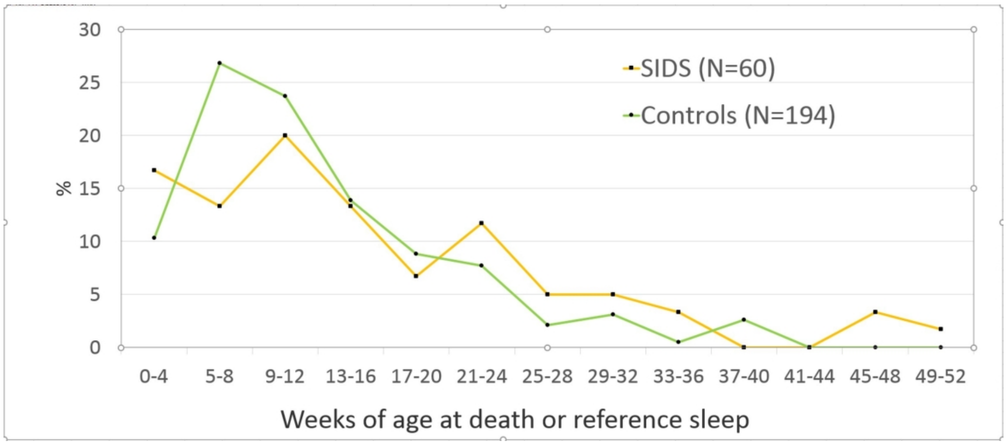

Figure 1 – Age at death or reference sleep (SIDS vs Controls)

205x90mm (300 x 300 DPI)

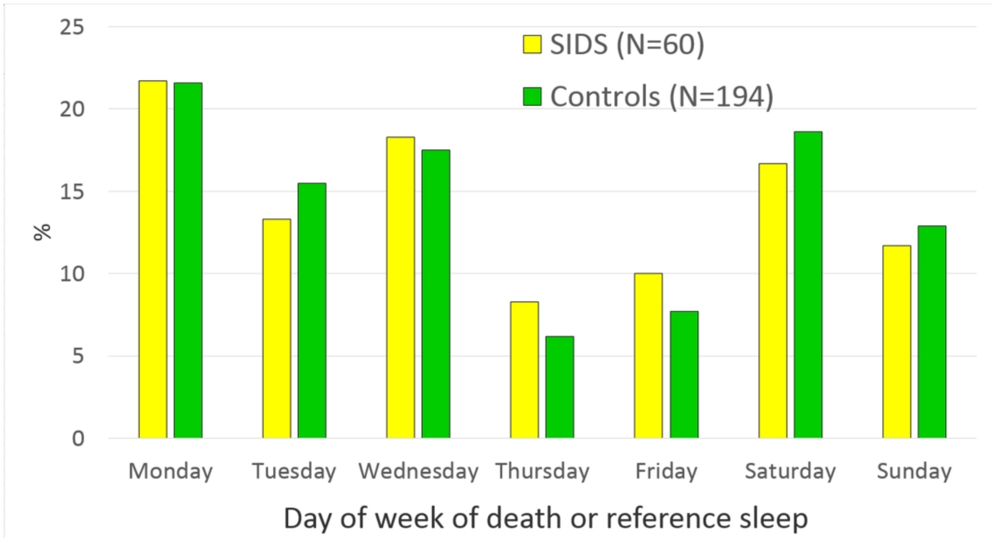

Figure 2 – Day of week of death or reference sleep (SIDS vs Controls)

390x209mm (300 x 300 DPI)

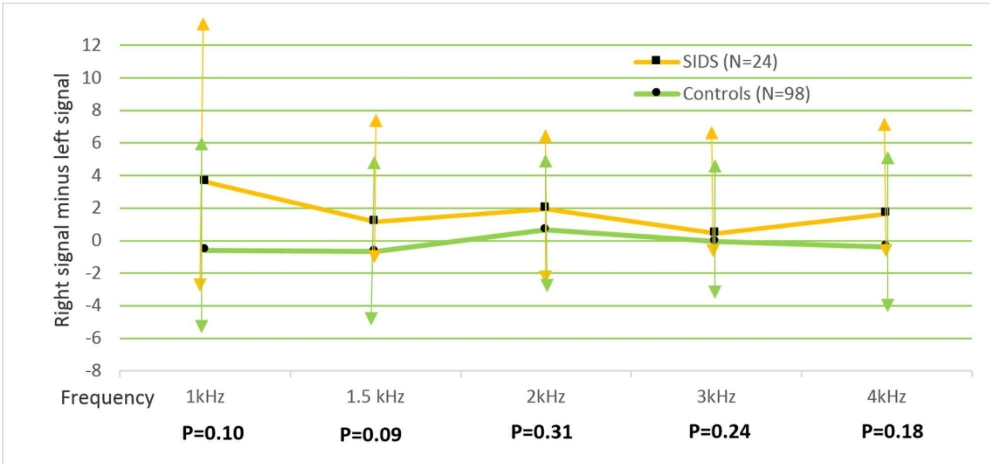

Figure 3 – Comparison of individual right/left ear symmetry of signal (SIDS vs Controls)
Median difference and inter-quartile range

192x90mm (300 x 300 DPI)

Reporting checklist for case-control study.

Based on the STROBE case-control guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE case-control reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study’s design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	#3	State specific objectives, including any prespecified hypotheses	3
Study design	#4	Present key elements of study design early in the paper	4
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case	4

	#6b	For matched studies, give matching criteria and the number of controls per case	n/a
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for cases and controls.	4,5
Bias	#9	Describe any efforts to address potential sources of bias	4,5
Study size	#10	Explain how the study size was arrived at	4,5
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	4,5
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	5
	#12b	Describe any methods used to examine subgroups and interactions	5
	#12c	Explain how missing data were addressed	5
	#12d	If applicable, explain how matching of cases and controls was addressed	n/a
	#12e	Describe any sensitivity analyses	5
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for cases and controls.	6
	#13b	Give reasons for non-participation at each stage	6
	#13c	Consider use of a flow diagram	n/a
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for cases and controls	6,7
	#14b	Indicate number of participants with missing data for each variable of interest	14-17

Outcome data	#15	Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls	14-17
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17
	#16b	Report category boundaries when continuous variables were categorized	17
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	7,8
Key results	#18	Summarise key results with reference to study objectives	9,10
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	9,10
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	9,10
Generalisability	#21	Discuss the generalisability (external validity) of the study results	9,10
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

 This checklist was completed on 22. February 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai