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Recurrence rates for sudden infant death syndrome (SIDS): the importance of risk stratification

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ABSTRACT

Objective: To investigate the importance of stratification by risk factors in computing the probability of a second death from sudden infant death syndrome (SIDS) in a family.

Design: Simulation study.

Background: The fact that a baby dies suddenly and unexpectedly means that there is a raised probability that the baby's family have risk factors associated with SIDS. Thus one cannot consider the risk of a subsequent death to be that of the general population. The Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI) identified three major social risk factors: smoking, age<27 and parity>1, and unemployed/unwaged as major risk factors. It gave estimates of risk for families with different numbers of these risk factors. We investigate whether it is reasonable to assume that, conditional on these risk factors, the risk of a second event is independent of the risk of the first and as a consequence one can square the risks to get the risk of two SIDS in a family. We have used CESDI data to estimate the probability of a second SID in a family under different plausible scenarios of the prevalence of the risk factors. We have applied the model to make predictions in the Care of Next Infant (CONI) study.

Results: The model gave plausible predictions. The CONI study observed 18 second SIDS. Our model predicted 14 dealths (95% prediction interval 7 to 21).

Conclusion: When considering the risk of a subsequent SIDS in a family one should always take into account the known risk factors. If all risks have been identified, then conditional on these risks, the risk of two events is the product of the individual risks. However, for a given family we cannot quantify the magnitude of the increased risk because of other possible risk factors not accounted for in the model.

What is already known on this topic

► Environmental influences play a major role in the pathogenesis of SIDS. The risk of a second SIDS in a family who have already suffered a SIDS will depend on these factors. It is a mistake to square the probability of a single SIDS to obtain the probability of two successive SIDS without taking into account environmental factors, since these factors will be present on both occasions and so the events will not be independent.

What this study adds

► We simulated cohorts with varying prevalences of the risk factors (smoking, unemployment and young multiparous mothers) identified in the Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI) study. We showed that it is important to consider environmental factors to investigate risk of recurrence of SIDS. In a community with high rates of risk factors most of the second SIDS cases would occur in high-risk families, and the overall recurrence rate would be high. But in a community where these factors were not common, high-risk families would account for only a minority of second SIDS. Our model gave reasonable predictions in the high risk CONI study.

Each year in England and Wales about 350 babies die suddenly and unexpectedly in the first year of life. Such cases are designated "sudden unexpected death in infancy" (SUDI). In about two thirds of cases the death is unexplained by history, autopsy or investigation, and may then be registered as sudden infant death syndrome (SIDS).[1]

The question "how common is a second SIDS death in the same family?" has attracted increased public and professional interest in recent years because of controversy about how often repeat unexplained infant deaths in the same family are due to unrecognised familial disorders or to covert homicide.[2][3]

In a recent literature review,[4] we identified eight studies that addressed the issue of recurrence of SIDS. The authors of all eight studies appeared to assume that the recurrence risk would be the same in all families, and all reported an increase in risk after one SIDS. In reality, a cohort of families with a first SIDS is not a random cross-section of the population but rather is a selected group with a higher proportion of "high-risk" families. Since the majority of subsequent children born to the families in such a cohort will be exposed to the same risk factors as in the index cases, the predicted risk of a second SIDS will also be higher than in the total population and this must be taken into account in studies of recurrence risk.

In this paper we suggest that the question should be re-formulated as follows: "what is the risk of a second SIDS in a given family if risk factors pertaining to that family at the time of the first SIDS persist subsequently?" As pointed out by Hill,[5] it is a mistake to square the probability of a single SIDS to obtain the probability of two successive SIDS since the events are not independent. However, conditional on known risk factors

Table 1 Risk of SIDS in families with 0, 1, 2 or 3 risk factors (from CESDI study)

	0 risk† factors	1 risk factor	2 risk factors	All 3 risk factors	Overall risk
Risk of SIDS‡	0.12	0.62	1.68	4.67	0.77
Incidence 1:(1000/ Risk)	1:8543	1:1616	1:596	1:214	1:1300

†Risk factors: any smokers in household; parity >1 and age<27; unemployed/unwaged. ‡per thousand births.

it may be reasonable to multiply the risks, and this is what we test here. Crucial to this calculation is the assumption that the risk factors we use are the only ones. We use data from a recent large UK study of infant deaths (the Confidential Enquiry into Stillbirths and Deaths in Infancy or ''CESDI study'')[6] to model the implications of this approach and consider the interpretation of the published data on repeat SIDS cases. We also compare our predictions with the results in the largest of the recurrence risk studies.[7]

METHOD

For the purposes of this analysis, the term ''SIDS'' implies that investigation has as far as possible excluded all specific causes of sudden unexpected death, including familial disorders or covert homicide. The risk of SIDS as thus defined is strongly related to environmental and social factors. Table 1, which is derived from the CESDI study, shows that the risk of SIDS in a family is strongly related to three risk factors: one or more smokers in the household; maternal age under 27 *and* parity greater than 1; having no earned income. Families with all three risk factors have a 40-fold increase in risk compared with families with none. In most cases, the same risks will apply to subsequent children as to the index SIDS case, although some families may stop or start smoking, or acquire or lose an income.

Assuming that the risk factors do persist, it follows that the predicted risk of a second SIDS in a family is not that of the population as a whole but is related to the risk factors that applied to the index case.

To address the question posed at the beginning of this article, we have to determine the number of second SIDS cases predicted by the risk factors of the families of the index cases – not the number predicted by the SIDS rate of the whole population.

Calculation

To calculate the predicted risk, the prevalence of the risk factors in the SIDS index cases and in the population as a whole must be known. The CESDI study generated comprehensive data on risk factors in SIDS cases and in controls. However, values derived from the CESDI controls for the prevalence of these risk factors in the population may not reflect the UK population as a whole because the controls were obtained from the same locality as the cases. This may mean that the differences between SIDS cases and the population as a whole may be greater than was shown in that study. We have therefore used a range of hypothetical values for the prevalence of the three main risk factors identified in the CESDI study and tested the sensitivity of the findings to changes in these values. Appendix 1 describes the methods used.

The essential assumption is that, given the known risk factors, the risks of a subsequent SIDS case are independent of the fact that an earlier SIDS has occurred. This would imply that the risk of two SIDS cases is the square of the risk of one.

Table 2 shows the prevalence of the individual risk factors and the prevalence of the combination of risk factors. In a hypothetical population of 100 million babies we calculated the expected number of births to mothers with zero, one, two or three risk factors. The CESDI risk estimate for each of these groups in table 1 was then used to calculate the number of first cases of SIDS that would be expected, and from this the predicted total number of SIDS cases was determined. We then applied the same risk estimate to each group of SIDS to determine the predicted number of second SIDS. We assumed that the net effect of changes in the risk factors over time would be zero. Finally we calculated the total number of second SIDS cases and related this to the number of index cases. The result is presented as the risk of a second SIDS for a cohort of families who have already had one SIDS death.

In our study calculation we used the prevalences for risk factors found in the CESDI study, then notional prevalences found by either increasing or decreasing the odds of the prevalences by a factor of two (scenarios 2 and 3, respectively). Table 2 illustrates how the risk of SIDS varies with prevalence of the risk factors. We used WinBUGS to calculate the prediction intervals from the binomial distribution to account for parameter uncertainty.[8]

Results

Using the prevalences given in scenario 1 and the CESDI risk factors, we calculated a predicted incidence of SIDS of 0.69 per thousand births. In the CESDI population (estimated to be 423 000) this predicts 293 deaths. This is comparable to that observed of 325 for the years 1993–95 (rate 0.77 per thousand, about 1 in 1300 given in table 1), and within the lower limit of 289 for the 95% prediction interval based on a Poisson distribution.

Table 3 summarises the results using the three scenarios. For example, among 100 million births in a population where the values of the prevalences of the risk factors are those given in the CESDI study, 3965 parents with no risk factors would experience a first SIDS death (based on a rate of 1:8543). The expected number of second SIDS is 3965/8543 = 0.5. There would be 7830 SIDS in families with three risk factors (based on a rate of 1:214) and 37 of these would be predicted to experience a second SIDS death. Note that in a population with a low prevalence of risk factors a much smaller proportion of first and second SIDS occur in families with three risk factors, because there are fewer such families.

As a separate test of the model, we looked at the numbers of second SIDS in CONI, a cohort of 6373 index cases and the largest published study on recurrence rates of SIDS.[7] In that study, there were 18 deaths categorised as second SIDS and the authors noted that all of these cases were in ''families with high frequencies of SIDS risk factors including smoking, illicit drug use and unemployment'' although the authors did not report the individual risk factors in their study population. Using scenario 2 ''high prevalence'', our model predicts that about 14 SIDS would have occurred in this cohort, with a 95% prediction interval (PI) of 7 to 21 (comparable figures for CESDI prevalence are 5, 95% PI (2 to 11)). Thus, although the observed number is higher than that predicted from our high prevalence figures, it is within the prediction interval. This is only a crude prediction because we do not have the individual risk factors in this population.

As expected, different assumptions for the prevalence of risk factors in the community produce different predictions for the overall risk of recurrence; nevertheless, the predictions all

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Table 2 Proportions of risk factors and combinations of risk factors for three different scenarios of risk prevalence

	Scenario 1 observed	Scenario 2 high*	Scenario 3 low†
Smoking	0.490	0.660	0.320
Parity>1 and age<27	0.190	0.320	0.100
Unemployed/ unwaged	0.180	0.310	0.100
No risk factors P(0)	0.339	0.160	0.551
1 risk factor P(1)	0.479	0.456	0.382
2 risk factors P(2)	0.165	0.319	0.064
3 risk factors P(3)	0.017	0.065	0.003

*Twice the observed odds. †Half the observed odds.

Table 3 The number of second SIDS predicted for a hypothetical population of 100 million births for three different scenarios of risk prevalence

	Scenario 1 observed	Scenario 2 high*	Scenario 3 low†
0 risk factors	0.5	0.2	0.8
1 risk factor	18	17	15
2 risk factors	47	90	18
3 risk factors	37	43	7
Total	102	150	40
Risk‡	1.47	2.19	0.96
Incidence 1:(1000/risk)	1:679	1:456	1:1046

‡per thousand births; *twice the observed odds; †Half the observed odds.

indicate a higher risk of recurrence than the rate in the population as a whole. If the values for the prevalences are changed within realistic limits, predicted values for the risk of a repeat SIDS in a population that has suffered a first SIDS vary between 1:456 (about three times the population risk) for a group with a high prevalence of risk factors, 1:679 for prevalences observed in CESDI and 1:1046 for a group with low prevalence of risk factors (which is still higher than the population risk).

DISCUSSION

The steep social gradient in the risk, and the dramatic change in incidence after the importance of sleeping position was recognised, together suggest that environmental influences play a major role in the pathogenesis of SIDS.[2] The fact that a family has suffered one such tragedy increases the probability that they have raised risk factors. However, even taking these risk factors into account, the risk of a second event may be raised further since the most thorough review may fail to reveal that a death attributed to SIDS was in fact due to familial disorders or covert homicide.

We have shown that in order to answer the question we posed, the rate of second and subsequent deaths must be compared with the rate predicted from the risk factors of the index cases. The analysis shows that the predicted number of second SIDS and the distribution both of index cases and of second SIDS cases depend on the distribution of risk factors in the community at the time of the study. Thus in a community with high rates of smoking, unemployment and young multiparous mothers, most of the second SIDS cases would occur in such families, and the overall recurrence rate would be high. But in a community where these factors were not common, high-risk families would account for only a minority of second SIDS and the overall recurrence rate would be much lower.

None of the published studies on recurrence rates of SIDS quantified the extent to which the risk of recurrence exceeds what would be predicted by our analysis, nor do they provide the risk factor information required to determine this.

We made a number of assumptions to simplify the analysis; for example, we assumed that the risk factors varied independently and that the net effect of changes over time in the risk factors would be zero. We did not attempt to evaluate the effect of different levels of smoking or of varying degrees of poverty. However, we used the risk factors that appeared in all the multivariate analyses of the CESDI study and we tested the sensitivity of the results to a realistic range of values for the prevalence of these factors. The use of additional risk factors or of a more detailed risk classification might modify the predicted

risk of repeat SIDS. In particular, families who suffer a SIDS tend to have large families (CESDI table 3.12)[6] and so have a greater number at risk of SIDS than controls do. If we included further risk factors in our model, we would find a higher risk of recurrence in those families initially at high risk.

Our predictions appear to slightly underestimate the observed numbers suggesting that there are indeed risk factors that as yet we cannot identify. However, the overall message of this paper would not be altered. Notwithstanding the claims in the literature, we do not know the magnitude of the increased risk, if any, for a second SIDS in the same family. We question whether further cohort studies are likely to resolve the issue. Our modelling exercise suggests that the risk of a second SIDS in families with no risk factors is very low. Of course, statistics are of no help in an individual case; parents deserve a high standard of investigation for any unexplained infant death to identify biological or social factors that affect the risk to subsequent children.[9]

Finally, we wish to point out that the analysis described in this paper has a more general application. Recurrence risk studies based on a cohort that is identified by members having experienced a relevant event must adjust the predicted risk to that of the cohort rather than using the risks in the general population.

APPENDIX

Let the prevalence of the three factors be p_1, p_2 and p_3. Then, assuming these factors are independent the proportion of cases having no risk factors is given by $q_0 = (1-p_1).(1-p_2).(1-p_3)$. There are three groups with one risk factor with proportions $q_1 = p_1.(1-p_2).(1-p_3)$, $q_2 = (1-p_1).p_2.(1-p_3)$ and $q_3 = (1-p_2).p_3$ There are three groups with two risk factors with proportions $q_4 = p_1.p_2.(1-p_3)$, $q_5 = p_1.(1-p_2).p_3$ and $q_6 = (1-p_1).p_2.p_3$ Finally the proportions of cases with all three risk factors is $q_7 = p_1.p_2.p_3$.

Then the proportions of cases with zero, one, two or three risk factors are given respectively by $P(0) = q_0$, $P(1) = q_1+q_2+q_3$, $P(2) = q_4+q_5+q_6$ and $P(3) = q_7$

CESDI Table 3.58 derived two sets of rates. One was the rates for groups with zero, one, two or three risk factors which are shown in table 1. The second was the rates for groups with and without each of the three risk factors separately. This leads to two approaches for prediction. The first uses the first set of rates and assumes essentially that groups with one risk factor had the same risk irrespective of the factor, and similarly for combinations of two risk factors. The second approach uses the rates for individual risk factors, and we have to derive risks for each group of subjects who have two risk factors. If Risk(1) is the risk for a group with only risk factor one relative to a group

with zerp risk factors and Risk (1,2) is the risk for a group with risk factors one and two relative to a group with zero risk factors, we assume $Risk(1,2) = \lambda.Risk(1).Risk(2)$ and similarly for risks 1,3 and 2,3. Here λ is a measure of the correlation between the risk factors, which is assumed the same for each pair. We then have the risk for a group with all three risk factors as $Risk(1,2,3) = \lambda^2 Risk(1) \times Risk(2) \times Risk(3)$. CESDI gave $R(1) = 6.82$, $R(2) = 4.29$ and $R(3) = 3.32$, with $R(1,2,3) = 39.95$. From this we deduce that $\lambda = 0.64$, and from which we can deduce the risks for each combination of risk factors. We found both approaches gave similar answers and so present the first approach.

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