Sudden infant death syndrome—insights from epidemiological research

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Sudden infant death syndrome (SIDS) was not recognised as an entity until the early 1960s, and an accepted definition did not emerge until 1969. At that time it was anticipated that the condition might contain subgroups. However, investigators have proceeded in the main as if it was a single condition. The original definition, "the sudden death of any infant or young child which is unexpected by history and in which a thorough postmortem examination fails to demonstrate an adequate cause for death," 1 was revised by the National Institutes of Health, USA, in 1989. The revised definition included only infants dying suddenly under one year of age whose deaths remain unexplained after a complete necropsy examination, including death scene investigation and case history review, had been conducted. 2 Thus the current definition of SIDS remains one of exclusion. However, using standard necropsy protocols to define SIDS as a cause of death it is now possible to obtain good agreement between pathologists independently assessing a case.

It might have been expected that following the identification of the syndrome the first epidemiological studies would have been of a descriptive nature, with analytical studies chasing the leads generated by that work and by concurrent laboratory studies. However, since 1969 both descriptive and analytical epidemiological investigations have proceeded in parallel and it is not at all clear that the hypotheses generated in the descriptive studies have been the basis for much of the analytical work. We shall nonetheless discuss some of the major findings from the two areas in turn, recognising that some of these distinctions between study types are somewhat arbitrary.

Descriptive studies

GEOGRAPHIC AND CLIMATIC FACTORS

Several findings have emerged from the descriptive studies conducted in different geographical locations over the last two decades. The incidence of SIDS is more frequent in winter than summer in most locations where studies have been conducted. 3 However, a winter predominance of SIDS cases was not found in Alaska from 1976 to 1980 or in Sweden from 1973 to 1977. 4 5 Furthermore, the incidence is higher as latitude increases, although this is not universally so. Rates in Scandinavia are much lower than those in locations such as New Zealand and the United Kingdom, which are closer to the equator. 6 Nonetheless, a clear North to South gradient of increasing SIDS incidence is evident in New Zealand and Australia, countries which cover a wide range of latitude. In New Zealand the SIDS rates per 1000 live births vary from 2.5 in Auckland, North Island, with a latitude of 37°, to 7.3 in Dunedin in the Southland, at latitude 45°. 7 In Australia the rate in Queensland (latitude 29° to 12°) was 1.6 per 1000 live births in the period 1975–88 compared to Tasmania at latitude 41° to 43° where the rate was 3.5 per 1000 live births in the same period. 7 The inverse association between SIDS rate and climatic temperature explains much of the regional variation in SIDS rate within these two countries. 6 7 The incidence of SIDS has been found to correlate with a climatic index reflecting mean annual percentage of cold wet weather for many locations. 8

There have been attempts to link this climatic variation to other potential causal factors in ecological studies. Williams et al have proposed that respiratory viral infection may play an important role based on the following observations: the incidence of SIDS correlates with the seasonal and annual incidence of bronchiolitis and also the isolation rate of certain viruses; respiratory viral infection is a common finding at the necropsy examination of SIDS infants; 9 also, signs of respiratory viral illness such as tracheitis have been more commonly reported in older SIDS infants, and the proportion of SIDS infants aged over three months increases as one moves southward in Australia and New Zealand. 10 11 Others have suggested that the effect of climatic temperature may be mediated through hypothermia or paradoxical hyperthermia. Beal and Porter have observed that “in Sweden during the winter virtually all infants sleep in an artificially heated environment with clothing and bedclothes appropriate for a warm temperature” and this may reduce the winter incidence of SIDS. 12 Murphy and Campbell have examined the relationship between temperature and SIDS in detail, observing that there was a latent period between a drop in temperature and a rise in the occurrence of SIDS. This time lagged effect was of four to six days' duration and was independent of the seasonal trend in SIDS incidence. 13 This report also confirmed the lack of space-time epidemiology in SIDS, which has been shown in several previous studies. 13–15

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Epidemiology of SIDS

Demographic factors
SIDS occurs with a peak incidence of two to four months of age with the rate decreasing thereafter. It has been proposed that this age at death curve reflects a physiological vulnerability at the relevant postnatal development phase of the infant. SIDS has a male case predominance with an odds ratio in the order 1:4, although this is not seen in some non-Caucasian races, and it is more common among infants of high birth order.

An association between lower socioeconomic status and SIDS has been documented in many studies. The independent contribution of poverty, after adjustment for factors such as maternal age, parity, bottle feeding, and smoking, remains to be fully assessed. Differences in SIDS rate have been observed between ethnic groups. Some of the rate difference between ethnic groups can be explained by differences in socioeconomic status, and in fact the NICHD study showed that the higher SIDS rates for black Americans was entirely explained by this factor. However, the ethnic differences between Caucasians (3-9/1000 live births) and the more socially disadvantaged Pacific Islanders (1-9/1000 live births) and Maoris (6-5/1000 live births) in New Zealand cannot readily be explained in this way. In Birmingham, England, the significantly lower risk of SIDS among Asians persisted after controlling for maternal age, social class, and birthweight.

In California, the incidence of SIDS in Hispanics varied according to whether the mother was born in the United States (1-5/1000 live births) or Mexico (0-8/1000 live births). These findings suggest that culturally related infant care practices may be an important determinant of SIDS.

Another clear demographic relationship is that between maternal age and risk of SIDS. The vast majority of studies have found that young mothers are considerably more likely to have an infant die of SIDS than older mothers. Adjustment for parity reduces this risk. While some of this association between SIDS and young maternal age can be explained by socioeconomic status, it cannot entirely be explained by this. For example, in the NICHD study, the crude odds ratio for teenage motherhood was 3.5. After adjustment for socioeconomic status, the risk estimate dropped to 2.4. The SIDS recurrence rate in subsequent siblings varies depending on the risk factor profile of the family. Two large scale population studies have found the overall recurrence rate of SIDS in subsequent siblings to be four to five times the rate in the general population.

A framework for developing hypotheses for analytical studies
It can be postulated that the pathogenesis of SIDS is a biphasic event. Antenatal factors may predispose an infant to sudden death. Other risk factors may then operate during a critical period of postnatal vulnerability to trigger a SIDS event in the predisposed infant. In considering what hypotheses might be tested in either analytical epidemiological studies or in the laboratory it is useful to consider the stages of infant development at which abnormalities might occur.

Findings from the descriptive studies have provided some information for the decision on whether prenatal or postnatal influences are likely to be the more important determinant of SIDS. It has been shown that the SIDS seasonal pattern is predominantly due to month of death variation, although Osmond and Murphy also found a small, independent month of birth effect as well. These findings imply that the seasonal effect of SIDS is most likely to be mediated through postnatal factors. It follows that a risk factor with a strong seasonal trend is likely to be exerting its effect during the postnatal period.

Analytical studies
The descriptive work clearly points to the need to investigate hypotheses related to climate and to economic deprivation. In pursuing these leads and in the testing of hypotheses not directly related to this set of factors, epidemiologists have concentrated on the case-control approach. Concerns have reasonably been expressed that the retrospective approach could be plagued by recall bias. For most of the findings we shall consider in this section, these concerns cannot be set aside because there has been little work done to validate the retrospective approach in the study of SIDS. What work has been done has shown that there is likely to be recall bias present for some factors but not others. Drews et al compared interview data from a case-control study to hospital record data and found that case-control differences in recall accuracy did exist, leading to changes in the magnitude, direction, or significance of the odds ratios for some associations. This should be borne in mind in considering the findings presented below.

Prenatal factors
Infant birthweight is inversely related to SIDS risk. Black et al, in a large study (nSIDS=233), found this relationship to be exponential. Low gestational age is also associated with increased risk. The Oxford Record Linkage Survey found an increased risk in premature (<35 weeks) infants (odds ratio = 3.9) and low birthweight (<2500 g) infants (odds ratio = 1.9). After adjustment for gestational age, low weight infants remain at increased risk of SIDS. Intrauterine growth retardation has also been found to be associated with SIDS in other studies. The poorer growth appears to be symmetrical in type, that is, SIDS infants have a reduction in length as well as weight. This type of growth retardation has been suggested to reflect mechanisms which operate in early pregnancy, before peak growth velocity is reached.

Maternal smoking during pregnancy is an independent risk factor for SIDS, with odds ratios generally reported to be between 1.5 and 5.0. A dose-response relationship for maternal smoking and SIDS risk has been demonstrated. Ten years ago, Peterson suggested that the link between maternal smoking and intrauterine growth retardation might be involved in the aetiology of SIDS. A residual association of maternal smoking with SIDS remains after adjustment for birthweight, suggesting that...
other pathways such as passive inhalation of smoke postnatally may also be involved. Our understanding of how the risk factor “maternal smoking” may operate has been enhanced by a recent study which showed modification by maternal smoking of the association between maternal anaemia and SIDS. Low packed cell volume was not a risk factor for SIDS among non-smokers but became an important predictor among heavy smokers. This suggests the two factors may interact through the mechanism of chronic fetal hypoxia.

POSTNATAL FACTORS
Throughout much of the last 20 years the dominant hypothesis concerning postnatal influences has been that SIDS infants experience abnormal respiratory development. Central nervous system abnormalities associated with hypoxia-ischaemia and neural maturational delay have been reported in SIDS infants. The peak age incidence of SIDS coincides with a period of change in the neural control of cardiorespiratory function and sleep-wake cycles. However, prospective studies involving measurements of cardiorespiratory function during early infant life have not provided strong evidence that abnormal apnoea is associated with SIDS. The multicentre NICHD study found two to four per cent of SIDS cases had a hospital record of apnoea of prematurity and less than seven per cent had a history of an apparent life threatening event. Home monitoring is still recommended in selected circumstances, but is yet to be assessed by a prospective randomized trial.

As previously mentioned, the residual effect of maternal smoking, after adjustment for birthweight, may reflect passive smoking by the infant postnatally. Infants of parents who smoke have higher admission rates for lower respiratory tract infection in the first year of life, particularly during winter; and SIDS infants frequently have evidence of respiratory viruses at death. Further work is required to determine the magnitude of the independent effect of postnatal passive smoking by the infant on SIDS risk and to establish if this effect is mediated purely through increased respiratory illness.

A significant negative association between breast feeding and SIDS has been found in some case-control studies but not others, while Kraus et al found the lower frequencies of breast feeding among SIDS cases could be explained, for the most part, by prematurity and maternal education. However, the national case-control study in New Zealand found the odds ratio for not breast feeding changed little (to 2·5) after adjustment for several potential confounders including socio-economic status, young maternal age, birthweight, and gestation. The NICHD study also found breast feeding to have significant protective effect after adjustment for confounders including those listed above. While smoking and breast feeding are related to many other disease outcomes in infancy, recent work has identified two risk factors which appear more specific for SIDS—hyperthermia and prone sleeping position. Until 1990, the evidence supporting a role for thermal stress in SIDS was mainly limited to case series reports. These included reporting of overheating among cot death victims, post mortem pathological changes consistent with heat stroke for some infants, and signs of perspiration. In 1990, Fleming et al published results from a case-control study which found SIDS infants were more likely to have been heavily wrapped (odds ratio = 1·14 per tog of thermal insulation above 8 tog of thermal insulation) and to have had heating on all night (odds ratio = 2·7) than population based controls. Recently, we have found evidence that SIDS infants were more likely to be overwrapped than control infants for a given room temperature. These two case-control studies were, in addition, two of many which have found a higher SIDS risk for infants who slept in the prone position.

PRONE SLEEPING POSITION
Froggatt published data in 1970 which showed there was a significant difference in the normal sleeping position of SIDS cases compared to controls. Since that time there have been more than 10 case-control studies, all of which have demonstrated a positive association between prone sleeping position and SIDS, with odds ratios ranging from 1·7 to 12, although the association has not always been significant. Two issues have been raised in relation to these findings. Firstly, recall bias occurring during the interview with bereaved parents may have influenced the results. The second concern was that potentially important confounding variables need to be considered when examining the link between sleeping position and SIDS and this had not always been done. In 1991, our Centre was able to publish the results from the follow up of the first 3110 infants enrolled in an ongoing prospective cohort study in Tasmania, of whom 20 had died after reaching the home visit age of approximately four postnatal weeks. Complete measurements were available on 15 of these infants. After adjusting for the confounding effects of maternal age and birthweight, the odds ratio for usual prone sleeping position at one month of age and SIDS was 4·5. A comparison of answers obtained in a concurrent retrospective case-control study showed that there was little recall bias in relation to sleeping position, the implication being that the observations from previous retrospective studies were likely to be valid. Since then, data on the first 21 deaths have confirmed this prospective association between prone sleeping position and SIDS. The population attributable risk percentage for the prone position in this updated study sample is 38%. The New Zealand national case-control study estimate was that the population attributable risk percentage for the prone sleeping position was 52%. The retrospective and prospective data are supported in the published reports by the results of interventions in Holland and South Australia. Engleberts and de Jong reported that the SIDS rate in The Netherlands increased after a recommendation was made in 1972 that parents place their infants prone and then fell by 40% between 1987 and 1988, after that advice was reversed. This was paralleled by a similar fall in the prevalence of prone sleeping position. A
similar reduction in SIDS incidence following intervention to change the prone position was observed in South Australia.60 Adequate control for confounding variables was not possible in either of these settings because of the unavailability of relevant data. Inferences from this type of observation can, of course, be potentially unreliable—that is, the “ecologic fallacy” may apply.61 However, in support of these observations is the fact that SIDS rates have not necessarily followed trends in breast feeding prevalence or maternal smoking prevalence over time.62 65 Population interventions to reduce the prevalence of prone sleeping position and other SIDS risk factors have been initiated in several countries including England, Australia, and New Zealand, and formal evaluation of the outcome of these programmes is awaited with great interest.

**Future directions**

Given the consistency of the findings on prone sleeping position, the fact that the hypothesis has survived challenges relating to confounding and measurement bias, and that the first results from interventions, albeit uncontrolled, are positive, the most important next step is to establish the mechanism of prone sleeping in increasing the risk of SIDS and to determine whether effect modification exists. Several possible mechanisms have been proposed, including oropharyngeal obstruction, obstructive apnoea secondary to partial nasal obstruction, and interactions between prone sleeping position and the thermal balance or arousal state of the infant.62–65 The recent findings of Kemp and Thach that “accidental suffocation by rebreathing” was the most likely cause of death in a series of infants found prone on cushions filled with polystyrene beads66 is also important in this regard.

There has been less progress on what factors might be modifying the effect of prone sleeping position, but if we accept a population attributable risk of 0.5 and the fact that sleeping position varies little with season or climate there certainly must be some effect modification to explain seasonal and climatic variation in risk. The next step in epidemiological research must involve research to investigate hypotheses concerning effect modification. For example, is the prone sleeping position a more important risk factor for infants who are heavily wrapped, have an upper respiratory tract infection, or have been placed on soft bedding? The hypothesis that the prone sleeping position and hyperthermia interact64 would explain many of the epidemiological features of SIDS, but two case-control studies have found that the prone position and overheating appear to be independent risk factors.65 66

At the end of this process it is still likely that some of the risk will remain unexplained. It is essential that in the investigation of this remaining aetiological fraction emphasis is placed on obtaining better data on factors already identified as strong candidates. The most important task now is to determine the causal significance of factors for which the evidence is already reasonably strong, such as maternal age, maternal smoking, intrauterine growth retardation, bottle feeding, and thermal imbalance. The qualification of the contribution of these factors to individual and population risk will also be important. This is not to say that the identification of new risk factors does not have a place in the future. However, in this particular field of research the emphasis must shift from the testing of novel theories to the rigorous collection and analysis of data directed at providing a greater understanding of how the well identified risk factors operate and interact.


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