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Sudden Infant Death Syndrome and parental smoking[☆]

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KEYWORDS

SIDS;
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 Prenatal exposure;
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 Causal mechanisms;
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Abstract

Prenatal exposure to tobacco smoke is a major risk factor associated with Sudden Infant Death Syndrome (SIDS) and the risk has increased despite continued advice against this practice. Evidence from the UK suggests the prevalence of maternal smoking during pregnancy has risen amongst SIDS mothers (from 50% to 80%) when the rate amongst expectant mothers in the general population has fallen (from 30% to 20%) confirming pooled estimates from recent studies of a four-fold risk. An additional risk from postnatal exposure has also been identified; increasing with the number of smokers in the household or the daily hours the infant is subjected to a smoke-filled environment. Exposure may lead to a complex range of effects upon normal physiological and anatomical development in fetal and postnatal life that places infants at greatly increased risk of SIDS. Recent legislation prohibiting smoking in public places needs to emphasise the adverse effects of tobacco smoke exposure to infants and amongst pregnant women.

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[☆] Article for Best practice guideline on smoking in pregnancy. Early Human Development.

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1. Introduction

The diagnosis of Sudden Infant Death Syndrome (SIDS), or cot death (crib death), is unique in that it is derived by

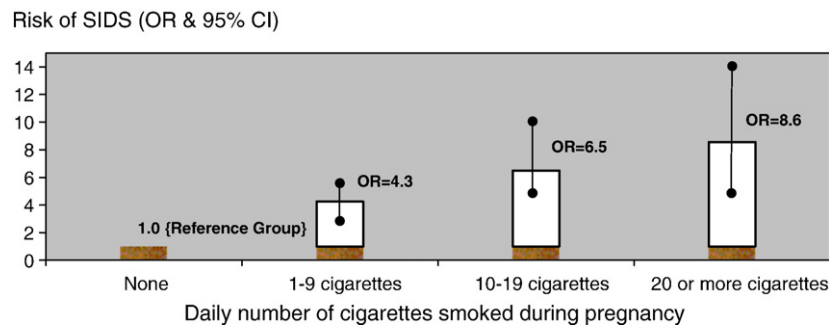


Figure 1 Risk of SIDS related to maternal smoking during pregnancy. Source: The CESDI SUDI study [4].

exclusion, by failing to demonstrate an adequate cause of death after reviewing the clinical history of the infant, investigating the death scene and conducting a thorough postmortem examination. Death often occurs unobserved, during infant sleep, with no discernable signs of a major illness. This mysterious syndrome has been intensely studied and many risk factors and characteristics have been reported that distinguish these infants and their families from randomly chosen surviving controls to the extent that SIDS has been described as an “epidemiological entity” [1]. The majority of deaths occur within the first 9 months of life, with a peak around the third and fourth month. A higher prevalence has been reported amongst males and infants with a lower birth weight, shorter gestation and more neonatal problems at delivery. Studies also show a strong correlation with young maternal age and higher parity and the risk increases with multiple births, single motherhood and a poor obstetric history. However only two consistent background characteristics differentiate unexplained SIDS deaths from infants who die suddenly from identified causes:

1. the distinct age distribution and
2. the high level of exposure to tobacco smoke.

Infant death rates from all causes are highest amongst the most socially deprived groups in society, and many of the epidemiological factors associated with SIDS (particularly those factors related to socio-economic deprivation) are also strongly associated with infant deaths from other causes [2]. Tobacco exposure is one of these markers but the degree of tobacco exposure associated with SIDS far exceeds expected levels, even when socio-economic status is taken into account. A highly significant association between SIDS and

maternal smoking during pregnancy has been consistently reported, and more recently an additional risk from postnatal exposure to tobacco smoke has been identified, particularly within the household.

This is a review of the growing evidence of the link between exposure to tobacco smoke and the risk of SIDS, the role of tobacco smoke as part of a causal mechanism and the potential impact of intervention campaigns aimed at reducing this exposure.

2. Evidence of association

2.1. SIDS and prenatal exposure to tobacco smoke

Anderson and Cook [3] conducted a systematic review of 34 case-control and cohort studies investigating maternal prenatal smoking and SIDS; 31 of these showed a significant association, and a further 2 showed a (non-significant) trend in this direction. The pooled odds ratio adjusted for potential confounders suggested a two to three-fold risk associated with *in utero* tobacco exposure. Nine of these studies also examined the possibility of an increasing risk of SIDS with the number of cigarettes smoked and all but one found a dose-response effect. In our study conducted in five English Health Regions during the 1990's two thirds of the SIDS mothers (66%) smoked during pregnancy compared to 27% of control mothers of surviving infants [4]. The unadjusted five-fold risk halved after controlling for potential confounders including low birth weight, parental alcohol and drug consumption and a range of markers for socio-economic deprivation (OR=2.6 [95% CI:1.4–4.8]), but still remained significant. To try and untangle the relationship between smoking and deprivation further we also adopted an

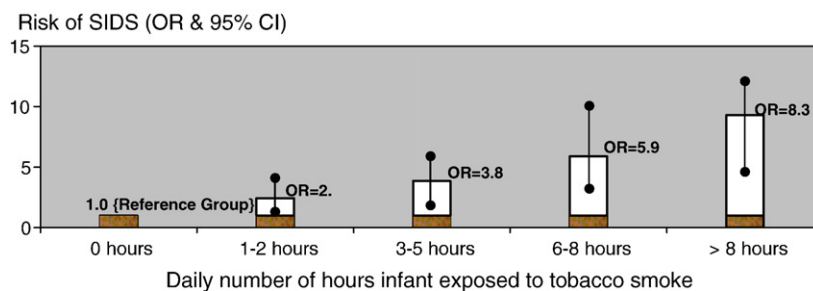


Figure 2 Risk of SIDS related to hours of daily postnatal exposure. Source: The CESDI SUDI study [4].

alternative approach by rigorously matching the socio-economic status of each SIDS family with a similar control family using unemployment status, housing tenure, household occupancy and the availability of motorised transport. The prevalence of maternal smoking during pregnancy for these more deprived control families was 42%, (compared to 27% in the whole population) but the resultant adjusted risk (OR=2.5 [95% CI: 1.6–3.7]) remained significant, confirming our previous findings. The risk associated with maternal smoking during pregnancy is moderated by known confounders but still appears to be an independent risk after adjustment. As in other studies we identified a dose-response effect, the risk increasing with the number of cigarettes smoked by the mother during pregnancy (Fig. 1).

The great majority (91%) of mothers in our study who smoked during pregnancy continued to smoke once the infant was born, making it difficult to disentangle infant tobacco smoke exposure before and after birth. Three studies have now reported that the risk of maternal smoking is mainly limited to those SIDS deaths that occur during night-time sleep, suggesting either an effect upon infant diurnal physiology or an effect upon night-time responsiveness in mothers who smoke [5–7]. A significant interaction, with a 10-fold increase in risk, has also been found between habitual parental smoking and infants co-sleeping in the parental bed, which is most commonly a night-time practice [8,9].

It is not clear whether prenatal exposure, postnatal exposure or both are linked to night-time SIDS deaths, particularly in the co-sleeping environment, but further study is needed in terms of both infant vulnerability and the propensity for arousal amongst sleeping infants and the co-sleeping adults.

2.2. SIDS and postnatal exposure to tobacco smoke

Postnatal exposure is difficult to assess, Mitchell and Milerad have attempted to do this by pooling studies that have reported a prevalence of paternal smoking in households where the mother does not smoke [10]. The pooled risk from seven such studies was significant (RR=1.5 [95% CI: 1.2–1.8]). In our study paternal smoking remained a significant risk factor in those households where the mother did not smoke, showed a clear dose-response effect and a significant interaction with night-time deaths suggesting, as with maternal smoking, that for some unknown reason parental smoking was more strongly associated with nocturnal deaths

[7]. We also looked at the number of smokers in the household, and showed a linear increase in risk with the number of smokers: an odds ratio of 4.7 for one smoker, 11.3 for two smokers and 16.9 for three or more smokers in the household. As a more direct measure of postnatal exposure we also asked the parents and household members to estimate the number of hours on an average day during which the infant was exposed to tobacco smoke, both inside and outside the household (Fig. 2). This may have underestimated the real exposure, as some parents claimed that because they ‘blew the smoke away from the baby’ or ‘always opened the window’ that their infant was never exposed. Nevertheless there was a clear biological gradient: the greater the daily duration of exposure, the greater the associated risk [4].

Maternal smoking during pregnancy is clearly the main source of tobacco smoke exposure, but this evidence suggests a smaller but independent effect from the mother and other household members after the infant is born. These data suggest that always keeping the infant in an environment that is free from tobacco smoke from birth may help reduce the risk of SIDS, even if mothers smoke during pregnancy.

3. Impact of intervention campaigns

The “Back to Sleep” intervention campaign, initiated in the UK in 1991, had several messages the most prominent of which was to encourage parents to place their infant in the supine position to sleep. In the last 15 years the number of SIDS deaths per 1000 livebirths has fallen by 75% (Fig. 3) and a similar decline in SIDS rates has been observed in other countries in which campaigns with broadly the same advice have been conducted.

One of the messages consistently highlighted in most campaigns was specific advice against smoking in pregnancy but this message seems to have achieved less effect than the message on sleeping position. The recent review conducted by Mitchell and Milerad suggests that the pooled risk associated with maternal smoking during pregnancy has risen from two to three-fold prior to these campaigns to almost four-fold (RR=3.9 [95% CI: 3.8, 4.1]) since the intervention campaigns, despite advice against smoking forming part of the campaigns [10].

The overall prevalence of maternal smoking during pregnancy varies between countries; in Sweden or Japan

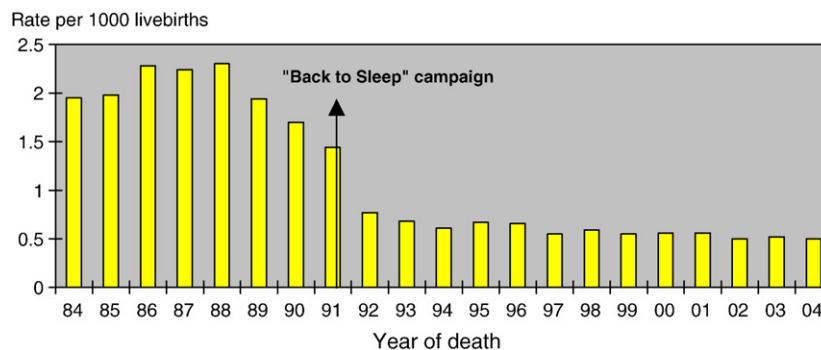


Figure 3 SIDS rate in England and Wales 1984–2004. Source: Office for National Statistics (ONS) and Foundation for the Study of Infant Death (FSID).

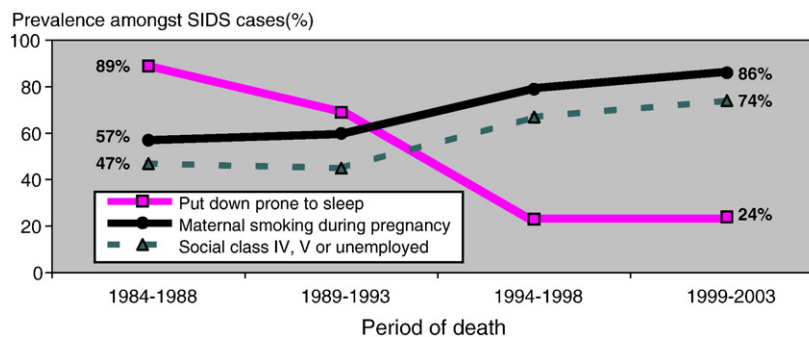


Figure 4 Prevalence of SIDS risk factors. Trends in Avon (1984 to 2003). Source: Avon Longitudinal study [11].

for instance the prevalence is relatively low (<10%) whilst in other countries such as Denmark or Australia the prevalence is much higher (>30%) [11], although the overall trend in most countries over the last decade has been towards a decline in rates. National statistics from the United Kingdom suggests smoking amongst pregnant mothers has fallen from 30% to 20% in the last 15 years, whilst in the United States the prevalence has declined from 20% to around 10%. However the prevalence also varies by maternal age and socio-economic status and the proportion of younger and poorer mothers who smoke during pregnancy (whose infants are already at much higher risk of SIDS), has fallen much less. Longitudinal data of 300 consecutive SIDS cases from Avon over a 20 year period from 1984 to 2003 [12] clearly show that the 'Back to Sleep' message has been taken on board whilst the advice against smoking has not (Fig. 4). The proportion of SIDS infants found in the prone position has fallen from 89% to 24% over the 20-year period but over the same time the proportion of SIDS mothers smoking during pregnancy has increased from 57% to 86%.

The increase in the prevalence of maternal smoking may be explained by the concomitant increase in the proportion of SIDS families from the more deprived socio-economic groups as shown in Fig. 4. Nearly three-quarters of SIDS parents now have occupations described as semi-skilled (social class IV), unskilled (social class V) or have never been employed. This is further supported by evidence from the Avon longitudinal study of a proportional increase in SIDS amongst infants of short gestation or low birth weight, multiple births, infants in larger families, and infants of single mothers, with fewer mothers of SIDS infants having ever attempted to breastfeed.

The target population of families with infants at greatest risk may therefore have changed with the widespread adoption of the supine sleeping position and an increased proportion of SIDS deaths in the most deprived groups. There is however very little evidence that any intervention campaign attempting to reduce maternal smoking within these deprived groups has succeeded. Maternal smoking during pregnancy has often been described as the next major modifiable risk factor to be targeted after the success of changing the position in which infants are put down to sleep. The evidence for smoking being a major risk factor is not in doubt but, given the power that tobacco addiction holds over its victims, there is grave concern as to whether it will be a successfully modifiable risk factor without fundamental changes in tobacco availability to vulnerable individuals.

4. Possible causal mechanisms

The consistency and strength of the association between exposure to tobacco smoke and the risk of SIDS is sufficient to suggest a role for one or more of the constituents of tobacco smoke in the causal mechanism leading to death.

Impairment of the ability of infants to arouse from sleep in response to hypoxic stimuli has been postulated as a potentially important component of the pathophysiology leading to SIDS, and several studies have shown functional impairment of both arousal and of the respiratory response to hypoxia in infants exposed to tobacco smoke *in utero* [13].

Greenough showed impairment of lung growth in preterm infants of mothers who smoked, particularly affecting specific airway conductance [14], which is likely to lead to an increased vulnerability to the adverse consequences of viral respiratory infections, which in turn are more common in infants of smoking parents [4].

Studies on the brainstems of infants who have died as SIDS have shown abnormalities of the serotonergic system, but not of nicotinic receptors [15], although it is not clear whether these represent genetic abnormalities or a response to *in utero* exposure to tobacco smoke. Animal studies have shown that fetal nicotine exposure results in decreased serotonin transporter density in multiple brain sites in the brainstem, midbrain and forebrain, but no consistent effect on nicotinic receptors [16].

Studies on stillborn fetuses and infants dying in the first year after birth have shown that for those whose deaths were unexplained, *in utero* exposure to tobacco smoke was associated with low levels of tyrosine hydroxylase activity (the first step in the production of catecholamines) in the locus coeruleus in the brainstem. Thus decreased noradrenergic activity in this area may be a contributory factor in unexpected deaths both before birth, and in infancy [17]. This possible mechanism is supported by experimental studies on rat brainstem preparations in which prenatal exposure to nicotine led to a loss of the biphasic GABAergic response and its replacement with an immediate precipitous decrease in activity [18]. Such a response could explain the observed terminal bradycardia noted in the reported recordings made from infants at the time of sudden unexpected deaths that occurred whilst being monitored [19].

Morphological abnormalities of the brainstem affecting the arcuate nucleus, a key centre in cardiorespiratory control, have been described in SIDS victims, and Lavezzi has shown that these are most marked in infants of mothers who smoked during pregnancy [20].

The relationship between the pro-inflammatory cytokine IL1- β and the risk of SIDS is complex, and Moscovis et al. [21] have shown potentially important ethnic differences in the patterns of gene polymorphisms and the relationship to maternal smoking. In both Aboriginal Australian and Bangladeshi infants a particular polymorphism (TT) is found, that is uncommon in infants of European origin. This polymorphism is associated with a marked increase in IL1- β production, and increased pro-inflammatory responses on exposure to tobacco smoke. This may partially explain the major difference between Aboriginal Australian infants with high maternal smoking rates and high SIDS rate, and Bangladeshi infants, who are genetically similar with regard to IL1- β , but have very low rates of maternal smoking and very low SIDS rates.

The potential interaction between genetic and environmental factors is further exemplified by the anti-inflammatory cytokine IL10, production of which is markedly decreased by exposure to tobacco smoke [21].

Thus exposure to tobacco smoke, either prenatally or postnatally will lead to a complex range of effects upon normal physiological and anatomical development in fetal and postnatal life, together with an increased incidence of acute viral infection, that places infants at greatly increased risk of SIDS.

5. Implications for reduction of the risk of SIDS in 2007

The introduction in 2007 of legislation prohibiting smoking in all public buildings in the UK (including bars and restaurants), may lead to an increase in smoking in the home, and could thus lead to an increase in exposure of young infants to tobacco smoke. Increasing public awareness of the adverse effects of tobacco smoke exposure of infants and of pregnant women will thus become potentially even more important. Smoking in the presence of pregnant women or young infants should be seen as being antisocial, potentially dangerous, and unacceptable.

6. Key guidelines

1. The risk of unexpected infant death is greatly increased by both prenatal and postnatal exposure to tobacco smoke – we should aim to achieve a “smoke free zone” around pregnant women and infants.
2. Reduction of prenatal exposure to tobacco smoke (by reducing smoking in pregnancy) and of postnatal exposure to tobacco (e.g. by not allowing smoking in the home) will substantially reduce the risk of SIDS.
3. Although the mechanisms of the adverse effects of tobacco smoke are complex and interact with both social deprivation and genetic factors, reduction of exposure to tobacco will reduce the risk of SIDS.
4. Prohibition of smoking in public places should not be allowed to lead to increased exposure of infants or pregnant women at home.

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