WHO/NCD/TFI/99.11

Background Paper

# Smoking and Sudden Infant Death Syndrome

*E.A. Mitchell, Associate Professor in Paediatrics, University of Auckland, Auckland, New Zealand*

*J. Milerad, Associate Professor of Paediatrics, Department of Women and Child Health, Astrid Lindgren Children Hospital at Karolinska Institute, Stockholm, Sweden*

Tel: +64 9 373 7599; Fax: +64 9 373 7486; Email: e.mitchell@auckland.ac.nz

## Abstract
There is substantial evidence to conclude that maternal smoking caused a marked increased in SIDS. There have been almost 50 studies that have examined this relationship and all indicate an increased risk. Since the reduction in the prevalence of prone sleeping position there have been 8 studies examining maternal smoking and SIDS. The pooled unadjusted RR from these studies is almost 5, which suggests that infants of mothers that smoke have almost a five times risk of SIDS compared with infants of mothers who do not smoke. Adjustment for potential confounders lowers the risk estimate; however, many studies over adjust, such as controlling for birthweight, resulting in an inappropriate low estimate of the risk.

Epidemiologically it is difficult to distinguish the effect of active maternal smoking during pregnancy from involuntary postnatal tobacco smoking of the infant to smoking by the mother. The mechanism for SIDS is unknown; however, it is generally believed that the predominant effect from maternal smoking is from *in utero* exposure of the fetus.

Clear evidence for environmental tobacco smoke exposure can be obtained by examining the risk of SIDS from paternal smoking where the mother is non-smoker. There have been 6 such studies. The pooled unadjusted RR was 1.4, which is much smaller than the effect seen for maternal smoking (RR = 4.7).

### 1. Case-control/cohort studies of maternal smoking in pregnancy
There are now almost 50 cohort and case-control studies that have investigated the relationship between maternal smoking in pregnancy and sudden infant death syndrome (SIDS) [1-48] (Table 1; Reviews of smoking and SIDS by Mitchell (1995) [49] and Anderson & Cook (1997) [50] provided the basis of this Table. Also a Medline search using the MeSH terms sudden infant death and smoking was performed. Additional studies were identified by personal contact with other SIDS researchers and the authors who kindly allowed me to include their data). The distinction between cohort and case-control studies is often indistinct, as some cohort studies are analysed by taking all the cases and a sample of controls from the remainder (nested case-control study), and in some case-control studies the data is recorded on all infants e.g. obstetric records, but only a sample is analysed. There is only a minor increase in the power of cohort studies compared with sampling four controls per case in case-control studies. In general the case-control studies have larger number of cases, which increases their power substantially. The studies in Table 1 come from the United States, Canada, the United Kingdom, Ireland, Sweden, Finland, Norway, the Netherlands, Austria, Germany, Brazil, Hong Kong, New Zealand and Australia. (In general where the same data has been analysed and reported in two or more papers the first report has been taken. Where the length of the study has been extended the larger dataset has been used, e.g. Sweden 1983-86 (Nordstom, 1993) [51] replaced by 1883-90 (Haglund, 1995) [35]).

A number of difficulties will be encountered when comparing studies. Case definition is particularly important and may introduce selection bias [52]. Most of the studies had high autopsy rates or did not report it.

The choice of controls is one of the most difficult decisions in designing case-control studies. Some studies matched by date of birth, others by ethnicity or birth weight. Some used population surveys of maternal smoking behaviour which collected data at a different time. Unmatched controls, which are a probability sample of all the infants from the source population, is considered to be the single best control group [52].

Smoking can be defined in a number of ways and can be classified by the amount smoked. Unfortunately authors have defined the categories in different ways making comparisons difficult.

All the studies have relied on questioning the mother. This may occur after the death of the infant, which introduces the possibility of recall bias, or during the antenatal period. Although this is prospectively recorded data, almost all mothers are aware of the health consequences of tobacco use and may under-report it. It is, however, unlikely that there would be differential misclassification and any non-differential misclassification would tend to reduce the likelihood of detecting a difference.
An objective measure of tobacco exposure in pregnancy would eliminate any minor concerns about the definition of maternal smoking, but studies using such measures have yet to be conducted for SIDS.

The early studies did not control for potential confounders. More recently studies have controlled for a number of potential confounders, especially birth weight and socio-economic status. As smoking reduces

birth weight, controlling for birth weight inappropriately reduces the relative risk of SIDS (i.e. over control) observed for smoking [53].

Publication bias is a potential problem, although it seem unlikely as in the majority of the studies smoking was only one of many variables reported.

Despite the difficulty in comparing studies there is a remarkable consistency in the results. Table 1 shows the percentage of mothers who smoked in pregnancy for cases and controls. Unadjusted odds ratios and their 95% confidence intervals have been recalculated. The studies have been divided into two groups, those that were done before the prevalence of prone sleeping position declined and those after the intervention studies where the prevalence of prone sleeping has become very low. To improve the precision of the estimates from the studies a meta-analysis (Mantel Haenszel weighted odds ratio, which uses a fixed effects model with studies weighted by the inverse of the variance) was done [54]. The pooled relative risk associated with maternal smoking before the intervention programmes was 2.91 (95% CI = 2.82, 3.01; excludes 2 studies where the raw data was not available [11,36]; $\chi^2_{45}$ for homogeneity = 30.42, p = 0.94), and after was 4.67 (95% CI = 4.04, 5.35; $\chi^2_7$ for homogeneity = 2.72, p = 0.91).

**2. Maternal smoking after pregnancy**

At least eleven studies have examined maternal smoking after birth and risk of SIDS (Table 2) [3,16,23,26,28,38,41,43,47,48]. Table 2 also compares the ORs for SIDS for maternal smoking after birth with the ORs obtained from the same study for maternal smoking during pregnancy. The correlation between the ORs for the two time periods is very high (r = 0.95, p<0.0001) as few mothers change their smoking behaviour. It is thus almost impossible to disentangle these two time periods as they are highly correlated. One study compared smoking after birth, but not during pregnancy, with non-smoking in both time periods. The adjusted ORs were 2.33 (95% CI = 1.48, 3.67) and 1.75 (95% CI = 1.04, 2.95) for black and white infants respectively. However, adjustment for potential confounders was limited and non-smoking in pregnancy referred to the period after the mother knew she was pregnant and may have included smoking before she knew she was pregnant. This study also showed that where mothers have only smoked in one of these time periods, they were usually light smokers.

**3. Paternal smoking**

Most attention has been directed at the mother's smoking behaviour, although there are 13 studies that have examined smoking by fathers (Table 3) [3,9,16,17,23,27,40,41,43,44,47,48,55]. The pooled relative risk associated with paternal smoking was 2.31 (95% CI = 2.09, 2.59; $\chi^2_{12}$ for homogeneity = 9.06, p = 0.70). However, as maternal smoking behaviour is associated with smoking by the father and other household members, it is important to control for maternal smoking when examining this. An alternative method is to examine the effect of father smoking where the mother is a non-smoker. There are 6 such studies [27,41,43,44,47,55]. Table 4 shows the percentage of fathers who smoked in pregnancy where the mother is a non-smoker for cases and controls. Odds ratios and their 95% confidence intervals have been recalculated. The pooled relative risk was 1.39 (95% CI = 1.11, 1.74; $\chi^2_5$ for homogeneity = 4.20, p = 0.52). Although this is statistically significant no adjustment for other potential confounders, such as socioeconomic status, have been done. As the adjusted ORs for SIDS from maternal smoking generally are much less than the univariate ORs, it is likely that adjustment for confounders would result in a non-significant result.

**4. Smoking by other household members**

Several studies have examined the effect of smoking by other household members. The definition of other household smokers varies between studies, making comparisons difficult. Some have included smoking by the parents within the definition. Ideally it should only refer to smokers other than parents. Such analyses are complicated by household size and the concordance with maternal (and paternal) smoking. Table 5 shows the 4 studies that have examined smoking by other household members and have either adjusted for maternal smoking [38,47,55] or have restricted the analysis to maternal non-smokers [41]. None of the studies have adjusted for household size. Two studies showed a small statistically significant increased risk [38,41], and two showed no additional risk [47,55].

**5. Locality and duration of exposure to environmental tobacco smoke**

Studies examining the location of smoking are conflicting. Mitchell et al [56] found the risk of SIDS to be no different between those that smoked in the house compared with infants of smokers who claimed never to smoke in the house. In contrast Klonoff-Cohen et al [38] found a strikingly higher risk if respondents

reported smoking in the same room as the infant and Blair et al [41] found a dose response relationship with parental reports of daily duration of exposure to tobacco smoke. However, Blair et al did not adjust those results for maternal smoking in pregnancy and the amount smoked.

**6. Smoking in ethnic minorities/indigenous people/high risk groups**

There have been several studies that have examined the risk of maternal smoking between different ethnic groups. These studies come from the United States [28,40], United Kingdom [31], and New Zealand [57]. The remarkable feature is that the odds ratios appear to be very consistent even when the prevalence of smoking is so different between ethnic groups.

In many countries smoking rates are higher in ethnic minorities/indigenous groups [57]. The major exceptions are in the United States where smoking rates are lower in Afro-Americans than whites [28,40] and in the United Kingdom where smoking rates are lower in Bangledeshi than Anglo-Europeans [58].

In communities where few infants now sleep prone SIDS is mainly seen in low socio-economic groups. Table 6 shows the relative risk of SIDS associated with maternal smoking among subgroups of socio-economic groups from the New Zealand Cot Death Study [49]. Maternal smoking increases the risk of SIDS in each socio-economic group, and the magnitude of the risk is similar. However, the prevalence of maternal smoking differs markedly, increasing from 12% in the high socio-economic group to 33% and 49% in the middle and lower groups respectively.

**7. Smoking-risk factor interactions**

Recently a number of studies have reported that maternal smoking modifies the effect of some risk factors for SIDS. One reported an interaction between maternal smoking and low haematocrit during pregnancy [21]. Another study did not find this interaction [59]. A recent study from Germany found that preterm birth, low birthweight and low number of antenatal visits did not increase the risk of SIDS among infants of maternal non-smokers, but were important risk factors for infants of maternal smokers [45]. For example, compared with normal birthweight (2500+ g) infants, low birthweight (<2500 g) was associated with an increased risk of SIDS in infants of mothers who smoked (RR = 2.62), but not in infants of non-smoking mothers (RR = 1.17). Alternatively, the relative risk of SIDS associated with maternal smoking was 7.96 for infants less than 2500 g and 3.56 for infants more than 2500 g.

The best known example of an interaction is that seen between bed sharing (maternal-infant co-sleeping) and maternal smoking. A recent meta-analysis of 6 studies showed that bed sharing was a major risk factor for SIDS if the mother was a smoker (OR = 2.06, 95% CI = 1.70, 2.50), but was associated with only a slightly increased risk if the mother was a non-smoker (OR = 1.42, 95%CI = 1.12, 1.79) [60].

The increased odds ratio for maternal smoking since the reduction in the prevalence of infants sleeping prone was unexpected. We have recently reported that the risk of SIDS associated with smoking is lower if the infant sleeps prone than for infants sleeping non-prone [61]. Thus with the decline in infants sleeping prone, the odds ratio for smoking will increase. However, the biological explanation for this observation is unknown.

**8. Pathology** (Table 7)

Objective measurements of nicotine and its metabolites in babies diagnosed as dying from SIDS indicate that significant exposure has occurred around the time of death [62,63]. When comparing two similar studies, one performed before and one after the "back to sleep" campaign, more SIDS infants were found to be exposed in the latter study (70% vs 92 %) [63]. Although the prevalence of smoking in the population of the latter study was also higher, the observed increase is consistent with epidemiological findings that the majority of victims after the change of sleep position are infants of smoking parents. High postmortem concentrations of nicotine metabolites appear to be more frequent in infants who were co-sleeping and who had focal organ lesions that could reflect previous hypoxic-ischemic insults [64]. The high percentage of exposed infants also means that tobacco smoke exposure is a major confounder in evaluating postmortem findings since few investigations have been stratified to take parental smoking into account.

Morphological findings considered to be indicative of SIDS include decreases in the size of visceral organs [65,66], delays in the normal pattern of maturation [65] and tissue scar formation conceivably after hypoxic or ischemic insults [67,68]. Similar abnormalities have also been described as being consequences of fetal growth retardation [69], which in turn is frequently caused by maternal smoking.

Schellscheidt and collaborators investigated if the association between SIDS and low birthweight may be attributed to maternal smoking [70]. Their data suggest that maternal smoking could account for the lower birthweight and BMI found in SIDS victims. In a larger population based study by Oyen et al the lower birth weight of SIDS victims could not be attributed to maternal smoking alone [71]. These differences of opinion emphasize the complex nature of prenatal and postnatal tobacco smoke exposure and suggest in addition, that many postmortem findings previously attributed to delayed or retarded organ growth may have been caused by exposure to *in utero* tobacco smoke exposure.

The effects of prenatal smoking are believed to be mediated by nicotine and carbon monoxide effects on placental circulation leading to fetal ischemia or hypoxia [72-74]. There is however experimental evidence that many pathological findings in the central nervous system can be induced by levels of nicotine that do not compromise utero-placental function [75], the tentative mechanisms being nicotine induced disturbances of the neuronal network organisation in the developing brain [76].

**Fetal size and body composition**

A reduction in birthweight has long been recognised as a consequence of maternal tobacco use [74, 77-79]. Recent investigations based on objective measurements of tobacco consumption have also documented that the reduction in both birth weight and length at birth show a clear dose–response relationship to maternal tobacco consumption [74,77,79]. Infants born to smoking mothers are disproportionately growth retarded, they have a reduced ponderal index, smaller arm circumference (i.e. lower fat and muscle mass) but a preserved head circumference [80] and liver size. The physiological consequences of a reduced ponderal index are known as “the metabolic syndrome” and include a lower glucose tolerance, elevated blood pressure and a disturbed lipid metabolism with a raised serum low density lipoproteins in later life.

**Respiratory system**

Infants born to smoking mothers have lower lung volumes [81,82], higher airway resistance [83] lower lung compliance and lower expiratory airflow velocities [84], i.e. changes in pulmonary function suggestive of alterations in lung collagen and elastin content [85,86] and a decrease in the elastic properties of the lung and elevated bronchial tone. Since the majority of these changes are already present at birth they are not likely to be produced by the irritant effect of tobacco smoke but are rather a consequence of a suboptimal fetal organ growth.

The mechanism by which maternal smoking induces the reduction in lung size has not been specifically elucidated. One important factor is that smoking decreases fetal breathing and the decrease in rhythmic mechanical distension of airways by fetal breathing movements hampers normal lung growth [87].

**Cardiovascular system.**

Smoking and nicotine exposure do not have primary adverse effects on myocardial development [88], however, it is believed that impaired fetal circulation due to placental ischemia may decrease the size and elasticity of the vascular bed. One obvious consequence would be a blood elevation of systolic blood pressure, a feature commonly seen in infants of smoking mothers [89].

**Immune system**

Nicotine has powerful effects on cytokine synthesis. It tends to depress IgG and IgA synthesis [90]. It has been suggested that the link between airway infections and SIDS may be mediated by nicotine induced activation of the immune system [91].

**Central nervous system, neurotransmission and sympathetic innervation**

Nicotine is the only major neuroactive agent in tobacco smoke of which we are aware. It stimulates cholinergic neurons and the release of dopamine and noradrenaline from synaptic nerve terminals in the brain and elsewhere [92]. Dopaminergic neurons are predominantly involved with regulation of neuroendocrine functions, locomotion and reward-seeking behaviour like food intake [93-95]. Dopamine mediated functions adversely changed by fetal nicotine exposure include hyperactivity [96] and disturbances in cortisone and pituitary hormones release [97]. Noradrenergic neurons regulate a variety of autonomic functions including responses to stress [98-100]. Noradrenaline mediated functions adversely affected by nicotine include a decreased ability for sympathetic activation in response to exogenous stress [99].

Other effects of prenatal nicotine exposure include changes in the regulation of circadian rhythm [100]. Although nicotine is not in itself teratogenic, high doses to the fetus are associated with effects on both cell replication and programmed cell death (apoptosis) [103]. The neuronal damage in the brain stem found in many SIDS victims has consequently been ascribed to tobacco smoke exposure [104], although it is not clear whether the neuronal damage is a primary toxic effect of substances in tobacco smoke or secondary to hypoxic or ischemic episodes that may be associated with smoking exposure [105].

**Summary**
Exposures to tobacco products during fetal life seem to restrict visceral organ growth and alter the neural control of autonomic, behavioural and homeostatic functions. High concentrations of nicotine in fetal circulation may induce structural cell loss and damage in many parts of the central nervous system. None of these effects are life threatening but they may decrease the tolerance to exogenous stress factors such as hyperthermia, airway obstruction, CO2 - rebreathing or infection.

**9. Biological mechanisms** (Table 8)
A number of tentative mechanisms by which maternal smoking may increase the risk of SIDS have been proposed, but so far none of them has been conclusively proven. Two theories for which there is experimental support will be reviewed here. It has to be noted that these physiological mechanisms have not been conclusively shown to be operational in human infants.

*Theory I. Maternal smoking decreases pulmonary function and impairs cardio-respiratory defence mechanisms by altering the development of the nervous system*

**I. Prenatal exposure**
Data derived from experiments where maternal smoking during pregnancy has been mimicked by chronic nicotine exposure of the animal fetus suggest that exposure may impair or attenuate several mechanisms associated with the ability to survive asphyxia or hypoxia. Rat pups exposed during fetal life have a deficient adrenomedullary catecholamines release (i.e. impaired stress response) to hypoxia and they died at hypoxic levels that unexposed rat pups would survive without major ill effects [101]. They also lacked the normal increase in heart rate suggesting that they were unable to increase cardiac output when challenged with low oxygen tension [106]. Similar findings of a deficient "fight or flight response" during hypoxia were also observed in young lambs, both those chronically treated during fetal life and those acutely exposed to nicotine after birth [107]. Exposed lambs had a decreased ability to increase heart rate during hypoxia and had a lower ability to increase respiration and to awake (arouse) from sleep [108]. The respiratory and arousal impairment suggest that nicotine may also alter neurotransmission in the brain and possibly also in the carotid bodies [109].

In contrast to the findings in rats and lambs, a deficient cardio-respiratory response to hypoxia has not been demonstrated in infants born to smoking mothers, although the same delay in awakening response when challenged with hypoxia during sleep has been documented [110]. The more pronounced impairment in cardiopulmonary control mechanisms found in laboratory animals as compared to infants may to some extent reflect differences in experimental designs; comparable experiments involving asphyxia or hypoxia can for obvious reasons not be performed on human babies.

**II. Postnatal exposure**
Only a few studies have addressed the effects of passive smoking on young subjects not exposed during fetal life [107-109]. These investigations have been focused on respiratory defence mechanisms to hypoxia particularly oxygen sensitivity of carotid body chemoreceptors. Exposure has been mimicked by injections or slow infusions of nicotine. High-dose injections given to young rats were found to decrease carotid body oxygen sensitivity by increasing the release of dopamine, which in this context acts as an inhibitory neuromodulator [109]. Such effects were not observed in young lambs after a low dose nicotine infusion [107]. However these animals were found to have a decreased ventilatory response to hypoxemia[107]. More importantly during sleep both ventilatory arousal and heart rate responses were depressed [108]. Collectively these experiments suggest that acute exposure to environmental tobacco smoke or nicotine may adversely affect hypoxic defence mechanisms by altering the oxygen sensing mechanism.

*Theory II. The effects of maternal smoking are mediated by an increased risk of respiratory infections.*

Infants and toddlers who live in smoking environment have more frequent upper airway infections than infants in non-smoking homes [111]. Recently it has been shown that nicotine may enhance adverse

immunological reactions to trivial bacterial infections and induce fatal outcomes at least in chick embryos [91]. The proposed mechanism may be an immunological potentiation of the antigenic properties of staphylococcal toxins by nicotine [112]. Although these experiments can not at present be translated to human physiology they provide new and plausible biological explanation of the risk of tobacco smoke exposure.

**Summary**

Maternal smoking during pregnancy predisposes the newborn to compromised oxygenation by decreasing lung function and inducing sleep related respiratory problems particularly obstructive apneic episodes [113]. Exposed individuals are less able to terminate apneic episodes [114] and appear to have weaker defence reactions to these episodes in terms of a lower sympathetic and cardio-respiratory activation [101,106,108]. These effects are most prominent after prenatal exposure but can also be replicated in naive individuals after an acute exposure to nicotine. These infants do have weaker defence reactions to these episodes in terms of a lower sympathetic and cardio-respiratory activation. In addition nicotine exposure may also increase the release of inflammatory mediators leading to disturbances in homeostatic control during trivial infections.

## 10. Criteria of causation in observational studies

The strongest evidence for causation would be a randomised controlled study, but this of course would be impossible. Hill suggested nine criteria should be considered in trying to assess causation in observational studies [115]. These were:

**Strength**

The stronger the association the more likely that it is causal. The odds ratio for maternal smoking in pregnancy is moderately strong. In contrast the effect of paternal smoking where the mother is a non-smoker and the effect of smoking by other household members is weak.

**Consistency**

This refers to the association being observed in multiple studies. The studies reported here come from different countries, different times and have used different methods. All (except one from Ireland [7] and one from Hong Kong [17], where no mothers smoked) have reported an increased risk of SIDS with maternal smoking.

**Specificity**

Hill and others have argued that if the association is specific to certain categories then causality is more likely. Others have rejected this criterion. The increased risk of SIDS with maternal smoking appears to apply to all subgroups.

**Temporal sequence**

The putative risk factor must precede the event (death) and not be a consequence of it. Clearly this criterion is fulfilled.

**Biological gradient**

If the association shows a dose-response relationship, then causality is more likely. All the studies of maternal smoking in pregnancy and SIDS, with one exception [14] that have examined the amount mothers smoked have found that the risk of SIDS increases with amount smoked. This effect is not seen with smoking by the father, possibly because smoking is done away from the pregnant mother and infant.

**Biological plausibility**

A plausible biological mechanism provides support for a causal relationship. This is addressed in the section above.

**Coherence**
By coherence Hill meant that the assumption of a causal relationship should not conflict with what is known about the disease. This would appear to be the situation with the association between maternal smoking and SIDS.

**Experiment**
Experimental evidence is seldom available in epidemiology. If the prevalence of smoking could be reduced and SIDS rates declined then this would be strong evidence for a causal relationship. Advice not to smoke in pregnancy and around the baby has been included in the SIDS prevention programmes in several countries. Reducing the prevalence of maternal smoking is difficult and the prevention programmes in New Zealand, Australia and the United Kingdom have not resulted in a significant change in the smoking rates.

**Analogy**
If we conclude that maternal smoking in pregnancy is a cause of SIDS, then it is not unreasonable to accept that environmental tobacco smoke from smoking by the mother or partner might also cause SIDS.

**11. Conclusions**
There is substantial evidence to conclude that maternal smoking causes a 3-fold increased risk of SIDS, and possibly 4.7-fold increased risk now that few infants sleep prone. It is difficult based on current epidemiological studies to distinguish the effects of maternal smoking during pregnancy and postnatal exposure of the infant to environmental tobacco exposure from smoking by the mother. The mechanism for SIDS is unknown; however it is generally believed that the predominant effect from maternal smoking is from *in utero* exposure of the fetus. There is some evidence that environmental tobacco exposure due to other household members, particularly the father, may increase the risk of SIDS, but any such effect is likely to be small (RR = 1.4).

Population attributable risk (PAR) estimates the proportion of the cases that can be attributed to the risk factor. For maternal smoking in pregnancy, using the lower pooled relative risk (before intervention programmes: OR = 2.91) and a conservative estimate that 25% of mothers smoke in pregnancy, then the PAR is 0.32. The same calculation for the higher pooled relative risk (after the intervention programmes: OR = 4.67) gives a PAR of 0.48. This suggests that SIDS mortality might be reduced by between a third and a half if no fetus was exposed to maternal tobacco smoke. In contrast the PAR for father's smoking where the mother is a non-smoker is 0.06 (OR = 1.39 and proportion exposed = 0.15).

In many countries prone sleeping position is no longer an issue as few infants are exposed to this risk factor. Maternal smoking, probably due to an utero effect, is clearly the next and major risk factor, which is potentially modifiable. Elimination of this risk factor has the potential to substantially reduce the SIDS rate and would have major health benefits for the child and mother.

There are no contraindications to the advice not to smoke in pregnancy and around the infant. Indeed adherence to this would reduce the risk of SIDS and have a marked benefit to the general health of the child, as well as improving maternal health. Advice not to smoke in pregnancy has been part of antenatal care for many years, and it seems likely that most parents who will respond to advice will have done so already. Increased taxation on cigarettes is one of the most effective strategies for reducing tobacco consumption and should be strongly supported. Other strategies include enforcing minors'-access laws, restricting smoking in public places, stronger health warnings, plain packaging and banning advertising and sport sponsorship.

**Table 1. Studies examining the relationship between maternal smoking in pregnancy and SIDS before and af listed by year of publication. Number of cases and controls are those with known smoking status.**

| Author | Date of study | Country | Case % exposed | Control % exposed | Unadjusted OR (95% CI) | Case n | Contro n |
|---|---|---|---|---|---|---|---|
| **Before interventions to reduce prone sleeping position** | | | | | | | |
| Steele (1966) [1] | 1960-61 | Canada | 61 | 38 | 2.49 (1.38, 4.52) | 80 | 157 |
| Schrauzer (1975) [2] | 1970-72 | US | 39 | 21 | 2.41 (0.82, 7.23) | 46 | 38 |
| Bergman (1976) [3] | 1970-74 | US | 61 | 42 | 2.15 (1.02,4.53) | 56 | 86 |
| Naeye (1976) [4] | 1959-66 | US | 59 | 48 | 1.57 (1.02, 2.42) | 125 | 375 |
| Lewak (1979) [5] | 1960-67 | US | 71 | 35 | 4.40 (2.10, 9.86) | 34 | 14,823 |
| Murphy (1982) [6] | 1965-77 | England | 67 | 42 | 2.79 (1.79, 4.36) | 96 | 46,412 |
| Matthews (1985) [7] | 1979-80 | Ireland | 47 | 44 | 0.70 (0.24, 2.03) | 34 | 34 |
| VandenBerg (1985) [8] | 1978-79 | New Zealand | 62 | 44[#] | 2.10 (1.49, 2.96) | 151 | 51,602 |
| Cameron (1986) [9] | 1980-82 | Australia | 66 | 33 | 3.90 (2.69, 5.66) | 208 | 393 |
| Rintahaka (1986) [10] | 1969-90 | Finland | 52 | 21 | 4.12 (2.32,7.33) | 124 | 141 |
| Victora (1987) [11] | 1984-85 | Brazil | ? | ? | 1.06 (1.00, 1.11) per cigarette/day | 72 | 144 |
| Stebbens (1987) [12] | 1979-81 | England | 62 | 32 | 3.35 (0.97, 11.98) | 13 | 478 |
| Hoffman (1988) [13] | 1978-79 | US | 69 | 39 | 3.41 (2.81, 4.12) | 757 | 1514 |
| Malloy (1988) [14] | 1979-83 | US | 55 | 30 | 2.86 (2.32, 3.51) | 372 | 305,73 |
| McLoughlin (1988) [15] | 1982-86 | England | 62 | 33 | 3.29 (1.47, 7.45) | 45 | 90 |
| McGlashan (1989) [16] | 1980-86 | Australia | 32 | 20 | 1.85 (1.19, 2.89) | 167 | 334 |
| Lee (1989) [17] | 1986-87 | Hong Kong | 0 | 0 | Undefined | 16 | 32 |
| Petru (1989) [18] | 1982-87 | Germany | 25 | 9 | 3.38 (1.24, 9.51) | 80 | 80 |
| Gilbert (1990) [19] | 1987-89 | England | 55 | 33 | 2.44 (1.43, 4.17) | 95 | 190 |

**Table 1 (cont'd)**

| Author | Date of study | Country | Case % exposed | Control % exposed | Unadjusted OR (95% CI) | Case n | Contro n |
|---|---|---|---|---|---|---|---|
| Haglund (1990) [20] | 1983-85 | Sweden | 51 | 31 | 2.35 (1.75, 3.15) | 179 | 260,90 |
| Bulterys (1990) [21] | 1959-90 | US | 58 | 45 | 1.66 (1.20, 2.29) | 178 | 1693 |
| Wierenga (1990) [22] | 1983 | Netherlands | 80 | 40 | 6.00 (1.20,38.57) | 15 | 30 |
| Engelberts (1991) [23] | 1985-87 | Netherlands | 44 | 36 | 1.37 (0.88, 2.12) | 108 | 567 |
| Li (1991) [24] | 1984-89 | US | 50 | 25 | 2.98 (2.55, 3.49) | 855 | 3,464 |
| Nilsen (1991) [25] | 1985-89 | Norway | 71 | 34 | 4.22 (1.99, 9.00) | 73 | 73 |
| Mitchell (1992) [26] | 1987-90 | New Zealand | 65 | 31 | 4.09 (3.26, 5.14) | 440 | 1652 |
| Nicholl (1992) [27] | 1976-79 | England | 56 | 35 | 2.38 (1.63, 3.47) | 242 | 251 |
| Schoendorf (1992) [28] | 1988 | US blacks | 36 | 16 | 2.59 (1.90, 3.55) | 201 | 3,254 |
| Schoendorf (1992) [28] | 1988 | US whites | 53 | 24 | 3.66 (2.77, 4.85) | 234 | 2,844 |
| Einspieler – personal communication | 1982-93 | Austria | 28 | 15 | 2.26 (1.38, 3.70) | 158 | 300 |
| Irwin (1992) [29] | 1984-88 | US | 27 | 21 | 1.36 (1.04, 1.78) | 284 | 114,03 |
| Karagas (1993) [30] | 1984-88 | US | 50 | 25 | 3.00 (2.52,3.58) | 688 | 2,835 |
| Hilder (1994) [31] | 1989-90 | England | 56 | 34 | 2.47 (1.06, 5.82) | 25 | 13,246 |
| Jorch (1994) [32] | 1990-92 | Germany | 58 | 20 | 5.44 (3.99, 7.44) | 175 | 90,426 |
| Ponsonby (1995) [33] | 1988-91 | Australia | 68 | 35 | 4.02 (1.95, 8.36) | 57 | 120 |
| Poets (1995) [34] | 1986-90 | Germany | 55 | 28 | 3.17 (2.27, 4.42) | 157 | 4,616 |
| Haglund (1995) [35] | 1983-90 | Sweden | 46 | 28 | 2.16 (1.86, 2.52) | 698 | 753,30 |
| Taylor (1995) [36] | 1988 | US | 46 | 22 | 3.00 (2.54, 3.53) | 649 | 9,864 |
| Sanghavi (1995) [37] | 1992 | US | ? | ? | 1.92 ($p<0.01$, per pack/day | 70 | 41,598 |

**Table 1 (cont'd)**

| Author | Date of study | Country | Case % exposed | Control % exposed | Unadjusted OR (95% CI) | Case n | Contro n |
|---|---|---|---|---|---|---|---|
| Klonoff-Cohen (1995) [38] | 1989-92 | US | 34 | 18 | 2.35 (1.44, 3.84) | 200 | 200 |
| Wigfield (1995) [39] | 1987-89 | England | 59 | 34 | 2.83 (1.48, 5.43) | 67 | 134 |
| Wigfield (1995) [39] | 1990-91 | England | 63 | 27 | 4.61 (1.70, 12.68) | 32 | 64 |
| MacDorman (1997) [40] | 1983-92 | Sweden | 46 | 27 | 2.30 (2.00, 2.63) | 863 | 979,38 |
| MacDorman (1997) [40] | 1990-91 | US whites | 47 | 20 | 3.54 (3.33, 3.76) | 4,412 | 3,965,5 |
| MacDorman (1997) [40] | 1990-91 | US blacks | 29 | 14 | 2.45 (2.24, 2.69) | 2,210 | 1,016,3 |
| MacDorman (1997) [40] | 1990-91 | US Hispanic | 18 | 6 | 3.60 (2.82, 4.58) | 461 | 553,38 |
| MacDorman (1997) [40] | 1990-91 | US American Indian | 38 | 20 | 2.39 (1.69, 3.38) | 147 | 52,130 |
| MacDorman (1997) [40] | 1990-91 | US Asian & Pacific Islands | 13 | 5 | 2.91 (1.55, 5.35) | 104 | 126,77 |
| **After interventions to reduce prone sleeping position** | | | | | | | |
| Blair (1996) [41] | 1993-95 | England | 63 | 25 | 4.98 (3.53, 7.04) | 195 | 780 |
| Taylor (1996) [42] | 1992-94 | US | 52 | 13 | 7.54 (3.27, 17.60) | 44 | 142 |
| Mitchell (1997) [43] | 1991-93 | New Zealand | 67 | 25 | 6.05 (3.90, 9.40) | 114 | 853 |
| Brooke (1997) [44] | 1992-95 | Scotland | 79 | 34 | 7.26 (4.43, 11.94) | 146 | 275 |
| Schellscheidt (1997) [45] | 1990-94 | Germany | 46 | 18 | 4.02 (3.06, 5.28) | 222 | 258,19 |
| Schellscheidt (1997) [46] | 1993-94 | Germany | 53 | 19 | 4.65 (2.32, 9.37) | 59 | 156 |
| Alm (1998) [47] | 1992-95 | Nordic | 62 | 29 | 3.88 (2.85, 5.28) | 243 | 861 |
| L'Hoir (1998) [48] | 1995-96 | Netherlands | 40 | 18 | 3.06 (1.56, 5.98) | 74 | 148 |

# Rate estimated from census data and refers to postnatal maternal smoking

**Table 2. Studies examining the relationship between maternal smoking after pregnancy and SIDS, listed by year are those with known smoking status. Odds ratios for smoking during pregnancy (from Table 1) are also displa**

| Maternal smoking | Case | | Control | | Unadjusted OR (95% CI) after pregnancy | Unadjus OR duri |
|---|---|---|---|---|---|---|
| | Yes | No | Yes | No | | |
| Bergman (1976) [3] | 33 | 26 | 32 | 54 | 2.14 (1.03, 4.46) | 2.15 |
| McGlashan (1989) [16] | 55 | 112 | 68 | 266 | 1.92 (1.24, 2.980 | 1.50 |
| Engelberts (1991) [23] | 47 | 61 | 195 | 372 | 1.47 (0.95, 2.28) | 1.37 |
| Mitchell (1992) [26] | 262 | 131 | 510 | 1081 | 4.24 (3.33, 5.40) | 4.09 |
| Schoendorf (1992)[28]: black | 98 | 103 | 831 | 2423 | 2.77 (2.06, 3.74) | 2.91 |
| Schoendorf (1992)[28]: white | 145 | 89 | 877 | 1967 | 3.65 (2.75, 4.86) | 3.66 |
| Klonhoff-Cohen (1995) [38] | 55 | 142 | 23 | 174 | 2.93 (1.66, 5.19) | 2.35 |
| Blair (1996) [41] | 129 | 66 | 209 | 571 | 5.34 (3.76, 7.58) | 4.98 |
| Mitchell (1997) [43] | 78 | 38 | 215 | 687 | 6.56 (4.24, 10.17) | 6.05 |
| Alm (1998) [47] | 146 | 97 | 263 | 594 | 3.40 (2.50, 4.62) | 3.88 |
| L'Hoir (1998) [48] | 30 | 44 | 29 | 119 | 2.80 (1.44, 5.43) | 3.63 |

**Table 3. Studies examining the relationship between paternal smoking and SIDS, listed by year of publication.**

| Author | Date of study | Country | % exposed | | OR (95% CI) | Case N | Control N | Study de |
|---|---|---|---|---|---|---|---|---|
| | | | Case | Control | | | | |
| Bergman (1976) [3] | 1970-74 | US | 53 | 43 | 1.53 (0.74, 3.18) | 56 | 86 | Case-co |
| Cameron (1986) [9] | 1980-82 | Australia | 67 | 42 | 2.78 (1.93, 4.02) | 208 | 393 | Case-co |
| McGlashan (1989) [16] | 1980-86 | Australia | 62 | 49 | 1.73 (1.16, 2.58) | 167 | 334 | Case-co |
| Lee (1989) [17] | 1986-87 | Hong Kong | 50 | 19 | 5.00 (0.84, 35.87) | 16 | 32 | Case-co |
| Engelberts (1991) [23] | 1985-87 | Netherlands | 50 | 50 | 1.02 (0.66, 1.50) | 107 | 567 | Case-co |
| Nicholl (1992) [27] | 1976-79 | England | 65 | 49 | 1.99 (1.36, 2.91) | 242 | 251 | Case-co |
| Mitchell (1993) [55] | 1987-90 | New Zealand | 54 | 33 | 2.41 (1.91, 3.04) | 440 | 1652 | Case-co |
| Klonoff-Cohen (1995) [38] | 1989-92 | US | 41 | 18 | 3.17 (1.96, 5.14) | 200 | 200 | Case-co |
| Blair (1996) [41] | 1993-95 | England | 61 | 36 | 2.71 (1.94, 3.78) | 195 | 780 | Case-co |
| Mitchell (1997) [43] | 1991-93 | New Zealand | 61 | 29 | 3.84 (2.49, 5.92) | 109 | 879 | Case-co |
| Brooke (1997) [44] | 1992-95 | Scotland | 64 | 33 | 3.54 (2.27, 5.51) | 146 | 275 | Case-co |
| Alm (1998) [47] | 1992-95 | Nordic | 51 | 37 | 1.72 (1.28, 2.33) | 235 | 855 | Case-co |
| L'Hoir (1998) [48] | 1995-96 | Netherlands | 57 | 26 | 3.63 (1.94, 6.84) | 74 | 147 | Case-co |

**Table 4. Risk of SIDS associated with paternal smoking where the mother is a non-smoker**

| Author | Date of study | Country | Case | | Control | |
|---|---|---|---|---|---|---|
| | | | Father smokes | Father non-smoker | Father smokes | Father non-smoker |
| | | | Number | Number | Number | Number |
| Nichol (1992) [27] | 1976-79 | England | 52 | 54 | 67 | 97 |
| Mitchell (1993) [55] | 1987-90 | New Zealand | 28 | 103 | 228 | 840 |
| Blair (1996) [41] | 1993-95 | England | 40 | 33 | 163 | 421 |
| Mitchell (1997)[43] | 1991-93 | New Zealand | 10 | 25 | 138 | 531 |
| Brooke (1997) [44] | 1992-95 | Scotland | 11 | 20 | 45 | 137 |
| Alm (1998) [47] | 1992-95 | Nordic | 18 | 74 | 138 | 462 |

**Table 5. Studies examining the relationship between other household smokers, which have adjusted for materna**

| Author (year) | Unadjusted OR (95% CI) | Adjusted OR 995% CI) |
|---|---|---|
| Mitchell (1993) [55] | 1.5 (1.2, 2.0) | 1.2 (0.8, 1.6) |
| Klonhoff-Cohen (1995) [38] | 2.4 (1.2, 4.7) | 2.2 (1.1, 4.4) |
| Blair (1996) [41] | 3.0 (1.7, 5.3) | 3.0 (1.2, 7.4)* |
| Alm (1998) [47] | 2.0 (1.3, 3.3) | 1.2 (0.6, 2.2) |

* analysis restricted to mothers being non-smokers. No other adjustment made.

**Table 6. Risk of SIDS associated with maternal smoking in pregnancy by socio-economic status (occupation) in t**

| Socio-economic group | Case | | Control | | OR |
|---|---|---|---|---|---|
| | Smoker | Non-smoker | Smoker | Non-smoker | |
| | N (%) | N (%) | N (%) | N (%) | |
| High | 28 (42) | 39 (58) | 61 (12) | 436 (88) | 5.13 |
| Middle | 97 (59) | 68 (41) | 233 (33) | 467 (67) | 2.86 |
| Low | 100 (76) | 31 (24) | 140 (49) | 143 (51) | 3.29 |

**Table 7. Morphological and morphometric effects of tobacco smoke or nicotine exposure**

| Study subjects | Organs or tissue | Dose & type of exposure | Observed effects |
|---|---|---|---|
| **1. Body size and tissue composition** | | | |
| Human fetuses | Antenatal growth velocity | Maternal smoking in pregnancy | Tobacco consumption retards fetal growth |
| Newborn infants | Size at birth | Maternal smoking in pregnancy | Length at birth and ponderal index lower in exposed infants. |
| SIDS – infants | Size at birth (not matched for gestational age) | Heavy parental smoking | Length , weight and BMI lower in exposed infants |
| SIDS – infants | Size at birth | Parental smoking | Lower birth weight compared to siblings |
| SIDS – infants | Size at birth | Maternal smoking | Lower birthweight of SIDS attributed to lower gestational age and maternal smoking. |
| **2. Organ growth and development** | | | |
| SIDS – infants | Visceral organs | Heavy parental smoking | Focal necrosis in heart and liver |
| Young rats | Myocardial cells | Nicotine injections | Decreased DNA-synthesis, cell damage if concomitant hypoxia |
| SIDS – infants | Lung neuroepithelial cells | Maternal smoking in pregnancy | Hyperplasia of lung neuroepithelial cells (altered airway sensitvity to air oxygen content) |
| Newborn rats | Brain stem | High dose nicotine during pregnancy | Brain stem gliosis resembling SIDS |
| Newborn and fetal rats | Brain | High dose nicotine during pregnancy | Activation of genes inducing delayed neuronal cell death |

**Table 8. Effects of prenatal and/or postnatal experimental nicotine administration or maternal or paternal sı**

| Species | Type of exposure | Dose | Observed effects |
|---|---|---|---|
| **1. Cardiovascular effects** | | | |
| Newborn rat Awake | Chronic prenatal | Pharm Phys | Increased mortality in hypoxia |
| Newborn rat Awake | Chronic prenatal | Phys | Absent heart rate increase during hypoxia |
| Newborn lamb Asleep | Acute postnatal infusion | Phys | Diminished heart rate increase during hypoxia |
| Newborn lamb Awake | Chronic postnatal infusion | Phys | Severe bradycardia during apnea |
| 2. **Respiratory effects** | | | |
| Newborn infants | Maternal smoking in pregnancy | Phys | Decreased expiratory flow velocity Decreased lung volume |
| Newborn infants | Maternal smoking in pregnancy | Phys | Persistent decrease in lungfunction at 18 mo |
| Newborn infants | Maternal smoking in pregnancy | Phys | Decreased expiratory flow velocity Decreased lung compliance |
| Newborn lamb Awake | Acute postnatal infusion | Phys | Decreased ventilatory response to hypoxia |
| Newborn lamb Asleep | Acute postnatal infusion | Phys | Decreased ventilatory response to hypoxia |
| Newborn lamb Awake | Chronic postnatal infusion | Phys | Prolonged reflex apnea |
| Newborn rat Awake | Acute postnatal injection | Pharm | Decreased ventilatory response to hyperoxia |
| 3. **CNS effects** | | | |
| Newborn lamb Asleep | Acute postnatal infusion | Phys | Delayed arousal from sleep during mild hypoxia |
| Infants Asleep | Parental smoking | Phys | Delayed arousal from sleep during mild hypoxia |
| Newborn rat Awake | Acute postnatal injection | Pharm | Abnormal turnover rate of dopamine |
| Young and adult rats | Smoke & nicotine (several studies) | Pharm/phys | Abnormalities in pituitary hormone secretion |

Abbreviations
Pharm = pharmacological dose (comparable to 6 mg/kg/24 h or more )
Phys = physiological dose (comparable to 2 mg/kg/24 h or l

**References**


1. Steele R, Langworth JT. The relationship of antenatal and postnatal factors to sudden unexpected death in infancy. Canad Med Ass J 1966; 94: 1165-1171

2. Schrauzer GN, Rhead WJ, Saltzstein SL. Sudden infant death syndrome: plasma vitamin E level and dietary factors. Ann Clin Lab Sci 1975; 5: 31-37.

3. Bergman AB, Wiesner LA. Relationship of passive cigarette-smoking to sudden infant death syndrome. Pediatrics 1976; 58: 665-668

4. Naeye RL, Ladis B, Drage JS. Sudden infant death syndrome: a prospective study. Am J Dis Child 1976; 130: 1207-1212

5. Lewak N, Berg BJ van den, Beckwith JB. Sudden infant death syndrome risk factors: prospective data review. Clin Pedaitr 1979; 18: 404-411

6. Murphy J, Newcombe R, Sibert J. The epidemiology of sudden infant death syndrome. J Epidemiol Community Health 1982; 36: 17-21

7. Matthews TG, O'Brien SJ. Perinatal epidemiological characteristics of the sudden infant death syndrome in an Irish population. Ir Med J 1985; 78: 251-3

8. VandenBerg M. Smoking during pregnancy and post-neonatal death. NZ med J 1985; 98: 1075-1078.

9. Cameron MH, Williams AL. Development and testing of scoring systems for predicting infants with high-risk of sudden infant death syndrome in Melbourne. Aust Paediatr J 1986 Suppl: 37-45.

10. Rintahaka PJ, Hirvonen J. The epidemiology of sudden infant death syndrome in Finland in 1969-1980. For Sci Int 1986: 30: 219-233

11. Victora CG, Nobre LC, Lombardi C, Texeira AMB, Fuchs SMC, Moreira LB. Epidemiology of sudden infant deaths in cities of Rio Grande do Sul, Brazil. A comparative study of cases and controls. Revista Saude Publica 1987; 21: 490-6

12. Stebbens VA, Alexander JR, Southall DP. Pre and perinatal clinical characteristics of infants who suffer sudden infant death syndrome. Biol Neonate 1987; 51: 129-137

13. Hoffman HJ, Hunter JC, Ellish NJ, Janerick DT, Goldberg J. Adverse reproductive factors and the sudden infant death syndrome. In: Harper RM, Hoffman HJ (eds) Sudden infant death syndrome: risk factors and basic mechanisms. PMA Publishing Corp, New York, 1988: 153-175.

14. Malloy MH, Kleinman JC, Land GH, Schramm WF. The association of maternal smoking with age and the cause of infant death. Am J Epidemiol 1988; 128: 46-55

15. McLoughlin A. Sudden infant deaths in Tameside. Health Visitor 1988; 61: 235-237

16. McGlashan ND. Sudden infant deaths in Tasmania, 1980-1986: a seven year prospective study. Soc Sci Med 1989; 29: 1015-1026

17. Lee NNY, Chan YF, Davis DP, et al. Sudden infant death syndrome in Hong Kong: confirmation of a low incidence. BMJ 1989; 298: 721-722

18. Petru E, Einspieler C, Rosanelli K, Gmoser G, Heydarfadai M, Kenner T. Are there pre- or perinatal risk factors for sudden infant death? Geburtshilfe Frauenheilkd 1989; 49: 494-7

19. Gilbert RE, Fleming PJ, Azaz Y, Rudd P. Signs of illness preceding sudden unexpected death in infants. BMJ 1990; 300: 1237-1239

20. Haglund B, Cnattingius S. Cigarette smoking as a risk factor for sudden infant death syndrome: a population-based study. Am J Public Health 1990; 80: 29-32

21. Bulterys M. Passive tobacco exposure and sudden infant death syndrome. Pediatrics 1993; 92: 205-6

22. Wierenga H, Brand R, Geudeke T, van Geijn HP, van der Harten H, Verloove-Vanhorick SP. Prenatal risk factors for cot death in very preterm and small for gestational age infants. Early Human Dev 1990; 23: 15-26

23. Engelberts A. Cot death in the Netherlands: an epidemiological study. MD Thesis. VU University Press, 1991.

24. Li D-K, Daling JR. Maternal smoking, low birth weight, and ethnicity in relation to sudden infant death syndrome. Am J Epidemiol 1991; 134: 958-964

25. Nilsen ST, Laerdal A. Krybbedod og royking i svangerskapet. Tidsskr Nor Laegeforen 1991; 111: 3493-5.

26. Mitchell EA, Taylor BJ, Ford RPK, Stewart AW, Becroft DMO, Thompson JMD, et al. Four modifiable and other major risk factors for cot death: the New Zealand study. J Paediatr Child Health 1992; 28 suppl 1: S3-S8

27. Nicholl JP, O'Cathain A. Antenatal smoking, postnatal passive smoking, and sudden infant death syndrome. In: Effects of smoking on the fetus, neonate and child. Ed Poswillo D, Alberman E. Oxford: Oxford Medical Publications 1992

28. Schoendorf KC, Kiely JL. Relationship of sudden infant death syndrome to maternal smoking during and after pregnancy. Pediatrics 1992; 90: 905-908

29. Irwin KL, Mannino S, Daling J. Sudden infant death syndrome in Washington State; why are Native American infants at greater risk than white infants? J Pediatr 1992; 121: 242-7

30. Karagas MR, Hollenbach KA, Hickok DE, Daling JR. Induction of labour and risk of sudden infant death syndrome. Obstet Gynaecol 1993;81:497-501

31. HilderAS. Ethnic differences in the sudden infant death syndrome: what we can learn from immigrants to the UK. Early Human Dev 1994, 38:143-9

32. Jorch G, Schmidt-Troschke S, Bajanowski T, Heinecke A, Findeisen M, Nowak C, et al. Risk factors for sudden infant death (SID): epidemiologic study of two German districts 1990-1992. Monatsschr Kinderheilkd 1994; 142: 45-51.

33. Ponsonby AL, Dwyer T, Kasi SV, Cochrane JA. The Tasmanian SIDS case-control study; unvariable and multivariable risk factor analysis. Paediatr Perinatal Epidemiol 1995; 9: 256-72

34. Poets CF, Schlaud M, Kleemann WJ, Rudolph A, Diekmann U, Sens B. Sudden infant death and maternal cigarette smoking: results from the Lower Saxony Perinatal Working Group. Eur J Pediatr 1995; 154: 326-9.

35. Haglund B, Cnattingius S, Otterblad-Olausson P. Sudden infant death syndrome in Sweden, 1983-1990: season at death, age at death, and maternal smoking. Am J Epidemiol 1995; 142:619-24

36. Taylor JA, Sanderson M. A reexamination of the risk factors for the sudden infant death syndromee. J Pediatr 1995; 126: 887-91

37. Sanghavi DM. Epidemiology of sudden infant death syndrome (SIDS) for Kentucky infants born in 1990: maternal, prenatal and perinatal risk factors. J Kentucky Med Assoc 1995; 93: 286-90

38. Klonoff-Cohen HS, Edelstein SL, Lefkowitz ES, Srinivasan IP, Kaegi D, Chang JC, et al. The effect of passive smoking and tobacco exposure through breast milk on sudden infant death syndrome. JAMA 1995, 273: 795-8

39. Wigfield R, Fleming PJ. The prevalence of risk factors for SIDS: Impact of an intervention campaign. In: Sudden infant death syndrome. New Trends for the nineties. Ed. Rognum TO. Scandinavian University Press, Oslo 1995, Chpt 23: 124-128.

40. MacDorman MF, Cnattingius S, Hoffman HJ, Kramer MS, Haglund B. Sudden infant death syndrome and smoking in the United States and Sweden. Am J Epidemiol, 1997; 146: 249-257

41. Blair PS, Fleming PJ, Bensley D, Smith I, Bacon C, Taylor E. et al. Smoking and the sudden infant death syndrome: results from 1993-5 case-control study for the confidential inquiry into stillbirths and death in infancy. Confidential Enquiry into Deaths Regional Coordinators and Researchers. BMJ 1996; 313: 195-8

42. Taylor JA, Krieger JW, Reay DT, Davis RL, Haruff R, Cheney LK. Prone sleep position and the sudden infant death syndrome in King County, Washington: a case-control study. J Pediatr 1996; 128: 626-30

43. Mitchell EA, Tuohy PG, Brunt JM, Thompson JMD, Clements MS, Stewart AW, Ford RPK, Taylor BJ. Risk factors for sudden infant death syndrome following the prevention campaign in New Zealand: A prospective study. Pediatrics 1997; 100: 835-840

44. Brooke H, Gibson A, Tappin D, Brown H. Case-control study of sudden infant death syndrome in Scotland, 1992-5. BMJ 1997; 314: 1516-20.

45. Schellscheidt J, Øyen N, Jorch G. (1997) Interactions between maternal smoking and other prenatal risk factors for sudden infant death (SID). Acta Pædiatrica 86: 857-863

46. Schellscheidt J, Ott A, Jorch G (1997) Epidemiologic features of sudden infant death (SID) after a German intervention campaign in 1992. Eur J Pediatr 156 (8) 655-660

47. Alm B, Milerad J, Wennergren G, Skjærven R, Øyen N, Norvenius G, Daltveit A-K, Helweg-Larsen K, Markestad T, Irgens, LM. A case-control study of smoking and sudden infant death syndrome in the Scandinavian countries, 1992-1995. Arch Dis Child 1998;78:329-334.

48. L'Hoir MP. Cot Death: risk factors and prevention in the Netherlands in1995-1996. Druk; Drukkerij Elinkwijk B.V.

49. Mitchell EA. Smoking: the next major and modifiable risk factor. In: Sudden infant death syndrome. New Trends for the nineties. Ed. Rognum TO. Scandinavian University Press, Oslo 1995, Chpt 21: 114-118.

50. Anderson HR, Cooke DG. Passive smoking and sudden infant death syndrome: review of the epidemiological evidence. Thorax 1997; 52: 1003-9.

51. Nordstrom ML, Cnattingius S, Haglund B. Social differences in Swedish infant mortality by cause of death, 1983 to 1986. Am J Public Health 1993; 83: 26-30.

52. Kraus JF, Bulterys M. The epidemiology of sudden infant death syndrome. In: Kiely M ed Reproductive and Perinatal Epidemiology. Florida: CRC Press, 1990: 219-249.

53. Golding J. Sudden infant death syndrome and parental smoking – a literature review. Paediatr Perinatal Epidemiol 1997; 11: 67-77.

54. Centers for Disease Control and Prevention (CDC). Epi Info Version 6.01, 1994

55. Mitchell EA, Ford RPK, Stewart AW, Taylor BJ, Becroft DMO, Thompson JMD, et al. Smoking and the Sudden Infant Death Syndrome. Pediatrics 1993; 91: 893-896.

56. Mitchell EA, Scragg L, Clements M. Location of smoking and the sudden infant death syndrome (SIDS). Aust NZ J Med 1995; 25: 155-156.

57. Mitchell EA, Stewart AW, Scragg R, Ford RPK, Taylor BJ, Becroft DMO, et al. Ethnic differences in mortality rate from Sudden Infant Death Syndrome in New Zealand. BMJ 1993; 306: 13-16.

58. Hilder AS. Ethnic differences in the sudden infant death syndrome: what we can learn from immigrants to the UK. Early Human Development 1994; 38: 143-9.

59. Stewart AJ, Williams SM, Mitchell EA, Taylor BJ, Ford RPK, Allen EM. Antenatal and intrapartum factors associated with sudden infant death syndrome in the New Zealand Cot Death Study. J Paediatr Child Health 1995; 31: 473-8.

60. Scragg RKR, Mitchell EA. Side sleeping position and bed sharing in the sudden infant death syndrome. Ann Med 1998; 30: 345-9.

61. Thompson JMD, Mitchell EA. Interactions between smoking and other risk factors in SIDS. 11th Australian SIDS Conference, 1997. June 20-22 1997, Melbourne, Australia.

62. Milerad J, Rajs J, Gidlund E. Nicotine and cotinine levels in pericardial fluid in victims of SIDS. Acta Paediatr 1994; 83: 59-62.

63. Milerad J, Vege A, Opdal SH, Rognum TO. Objective measurements of nicotine exposure in victims of sudden infant death syndrome and in other unexpected child deaths. J Pediatr 1998;133:232-236.

64. Rajs J, Rasten-Almqvist P, Falck G, Eksborg S, Andersson BS. Sudden infant death syndrome: postmortem findings of nicotine and cotinine in pericardial fluid of infants in relation to morphological changes and position at death. Pediatr Pathol Lab Med 1997; 17: 83-97.

65. Hinchliffe SA, Howard CV, Lynch MR, Sargent PH, Judd BA, van Velzen D. Renal developmental arrest in sudden infant death syndrome. Pediatr Pathol 1993; 13: 333-343.

66. Kelmanson IA. Retarded heart growth in the victims of sudden infant death: possible implications for lethal mechanisms. Eur JPediatr 1996; 155: 440-444.

67. Rognum TO, Saugstad OD. Biochemical and immunological studies in SIDS victims. Clues to understanding the death mechanism. Acta Paediatr 1993; 82 Suppl 389: 82-85.

68. Kinney HC, Filiano JJ, Harper RM. The neuropathology of the sudden infant death syndrome. A review. J Neuropathol Exp Neurol 1992; 51: 115-126.

69. Kelmanson IA. An impact of birth weight on postnatal body and organ growth capacity in infants under one year of age. General Diagnostic Pathol 1996; 141: 345-351.

70. Schellscheidt J, Jorch G, Menke J. Effects of heavy maternal smoking on intrauterine growth patterns in sudden infant death victims and surviving infants. Euro J Pediatr 1998; 157: 246-51.

71. Oyen N, Haglund B, Skjaerven R, Irgens LM. Maternal smoking, birthweight and gestational age in sudden infant death syndrome (SIDS) babies and their surviving siblings. Paediatr Perinatal Epidemiol 1997; 11 Suppl 1:84-95.

72. Godfrey KM, Redman CW, Barker DJ, Osmond C. The effect of maternal anaemia and iron deficiency on the ratio of fetal weight to placental weight Br J Obstet Gynaecol 1991; 98: 886-891.

73. Philipp K, Pateisky N, Endler M. Effects of smoking on uteroplacental blood flow. Gynecol Obstet Invest 1984; 17: 179-82.

74. Secker-Walker RH, Vacek PM, Flynn BS, Mead PB. Smoking in pregnancy, exhaled carbon monoxide, and birth weight. Obstetr Gynecol 1997; 89: 648-653.

75. Navarro HA, Seidler FJ, Schwartz RD, Baker FE, Dobbins SS, Slotkin TA. Prenatal exposure to nicotine impairs nervous system development at a dose which does not affect viability or growth. Brain Res Bull 1989; 23: 187-192.

76. Lichtensteiger W, Ribary U, Schlumpf M, Odermatt B, Widmer HR. Prenatal adverse effects of nicotine on the developing brain. Progress in Brain Research 1988; 73: 137-157.

77. Wang X, Tager IB, Van Vunakis H, Speizer FE, Hanrahan JP. Maternal smoking during pregnancy, urine cotinine concentrations, and birth outcomes. A prospective cohort study. Int J Epidemiol 1997; 26: 978-988.

78. Vik T, Jacobsen G, Vatten L, Bakketeig LS. Pre- and post-natal growth in children of women who smoked in pregnancy. Early Hum Dev 1996; 45: 245-255.

79. Bardy AH, Seppala T, Lillsunde P, Kataja JM, Koskela P, Pikkarainen J, Hiilesmaa VK. Objectively measured tobacco exposure during pregnancy: neonatal effects and relation to maternal smoking. Br J Obstet Gynaecol 1993; 100: 721-726.

80. Haste FM, Anderson HR, Brooke OG, Bland JM, Peacock JL. The effects of smoking and drinking on the anthropometric measurements of neonates. Paediatr Perinatal Epidemiol 1991; 5: 83-92.

81. Tager IB, Ngo L, Hanrahan JP. Maternal smoking during pregnancy. Effects on lung function during the first 18 months of life. Am J Respir Critical Care Med 1995; 152: 977-983.

82. Hanrahan JP, Tager IB, Segal MR, Tosteson TD, Castile RG, Van Vunakis H, Weiss ST, Speizer FE. The effect of maternal smoking during pregnancy on early infant lung function. Am Rev Respir Dis 1992; 145: 1129-1135.

83. Hanrahan JP, Brown RW, Carey VJ, Castile RG, Speizer FE, Tager IB. Passive respiratory mechanics in healthy infants. Effects of growth, gender, and smoking. Am J Respir Critical Care Med 1996; 154: 670-680.

84. Lodrup Carlsen KC, Jaakkola JJ, Nafstad P, Carlsen KH. In utero exposure to cigarette smoking influences lung function at birth. Eur Respir J 1997; 10: 1774-1779.

85. Kalenga M, Tschanz SA, Burri PH. Protein deficiency and the growing rat lung. I. Nutritional findings and related lung volumes. Pediatr Res 1995; 37: 783-788.

86. Kalenga M, Eeckhout Y. Effects of protein deprivation from the neonatal period on lung collagen and elastin in the rat. Pediatr Res 1989; 26: 125-127.

87. Moessinger AC, Harding R, Adamson TM, Singh M, Kiu GT. Role of lung fluid volume in growth and maturation of the fetal sheep lung. J Clin Invest 1990; 86: 1270-17IS.

88. Tolson CM, Seidler FJ, McCook EC, Slotkin TA. Does concurrent or prior nicotine exposure interact with neonatal hypoxia to produce cardiac cell damage? Teratol 1995; 52: 298-305.

89. Beratis NG, Panagoulias D, Varvarigou A. Increased blood pressure in neonates and infants whose mothers smoked during pregnancy. J Pediatr 1996; 128: 806-812.

90. Fischer A, Konig W. Modulation of in vitro immunoglobulin synthesis of human peripheral blood mononuclear cells by nicotine and cotinine. Clinical Investigator 1994; 72: 225-232.

91. Sayers NM, Drucker DB, Telford DR, Morris JA. Effects of nicotine on bacterial toxins associated with cot death. Arch Dis Child 1995; 73: 549-551.

92. Benowitz NL, Porchet H, Jacob P. ; Wonnacott S, Russell MAH, Stolerman IP, editors.Nicotine Psychopharmacology; Molecular,Cellular, and Behavioural Aspects. New York: Oxford University Press, 1990; 4, Pharmacokinetics, metabolism, and pharmacodynamics of nicotine. p. 112-57.

93. Goldman-Rakic PS. The cortical dopamine system: role in memory and cognition. Adv Pharmacol 1998; 42: 707-711.

94. Schultz W. Dopamine neurons and their role in reward mechanisms. Current Opin Neurobiol 1997; 7: 191-197.

95. Wooten GF. Functional anatomical and behavioral consequences of dopamine receptor stimulation. Annals New York Acad Sci 1997; 835: 153-156.

96. Richardson SA, Tizabi Y. Hyperactivity in the offspring of nicotine-treated rats: role of the mesolimbic and nigrostriatal dopaminergic pathways. Pharmacol Biochem Behav 1994; 47: 331-337.

97. Fuxe K, Andersson K, Eneroth P, Jansson A, von Euler G, Tinner B, Bjelke B, Agnati LF. Neurochemical mechanisms underlying the neuroendocrine actions of nicotine: focus on the plasticity of central cholinergic nicotinic receptors. Prog Brain Res 1989; 79: 197-207.

98. Esler MD, Lambert GW, Ferrier C, Kaye DM, Wallin BG, Kalff V, Kelly MJ, Jennings GL. Central nervous system noradrenergic control of sympathetic outflow in normotensive and hypertensive humans. Clin Exp Hypertension 1995; 17: 409-423.

99. Page ME, Valentino RJ. Locus coeruleus activation by physiological challenges. Brain Res Bull 1994; 35: 557-560.

100. McCormick DA, Pape HC, Williamson A. Actions of norepinephrine in the cerebral cortex and thalamus: implications for function of the central noradrenergic system. Prog Brain Res 1991; 88: 293-305.

101. Slotkin TA, Lappi SE, McCook EC, Lorber BA, Seidler FJ. Loss of neonatal hypoxia tolerance after prenatal nicotine exposure: implications for sudden infant death syndrome. Brain Res Bull 1995; 38: 69-75.

102. Clegg DA, O'Hara BF, Heller HC, Kilduff TS. Nicotine administration differentially affects gene expression in the maternal and fetal circadian clock. Dev Brain Res 1995; 84: 46-54.

103. Slotkin TA, McCook EC, Seidler FJ. Cryptic brain cell injury caused by fetal nicotine exposure is associated with persistent elevations of c-fos protooncogene expression. Brain Res 1997; 750: 180-188.

104. Krous HF, Campbell GA, Fowler MW, Catron AC, Farber JP. Maternal nicotine administration and fetal brain stem damage: a rat model with implications for sudden infant death syndrome. Am J Obstet Gynecol 1981; 140: 743-746.

105. Rognum TO, Saugstad OD. Hypoxanthine levels in vitreous humor: evidence of hypoxia in most infants who died of sudden infant death syndrome. Pediatrics 1991; 87: 306-310.

106. Slotkin TA, Saleh JL, McCook EC, Seidler FJ. Impaired cardiac function during postnatal hypoxia in rats exposed to nicotine prenatally: implications for perinatal morbidity and mortality, and for sudden infant death syndrome. Teratol 1997; 55: 177-184.

107. Milerad J, Larsson H, Lin J, Sundell HW. Nicotine attenuates the ventilatory response to hypoxia in the developing lamb. Pediatr Res 1995; 37: 652-660.

108. Hafström O, Milerad J, Asokan N, Poole S and Sundell H. Nicotine delays arousal during hypoxemia in sleeping lambs. Pediatr Res 1996: 39; 386A.

109. Holgert H, Hoekfelt T, Hertzberg T, Lagercrantz H. Functional and developmental studies of the peripheral arterial chemoreceptors in rat: Effects of nicotine and possible relation to sudden infant death syndrome. Proceedings Nat Acad Sci 1995; 92: 7575-7579.

110. Lewis KW, Bosque EM. Deficient hypoxia awakening response in infants of smoking mothers: Possible relationship to sudden infant death syndrome. J Pediatr 1995; 127: 691-699.

111. Taylor B, Wadsworth J. Maternal smoking during pregnancy and lower respiratory tract illness in early life. Arch Dis Child 1987; 62: 786-791.

112. Blackwell CC, Weir DM, Busuttil A, Saadi AT, Essery SD, Raza MW, James VS, Mackenzie DAC. The role of infectious agents in Sudden Infant Death Syndrome. FEMS Immunol Med Microbiol 1994; 9:91-100.

113. Tirosh E, Libon D, Bader D. The effect of maternal smoking during pregnancy on sleep respiratory and arousal patterns in neonates. J Perinatol 1996; 16: 435-438.

114. Karmo H, Parker R, Milerad J, et al. Nicotine enhances reflex apnea in young lambs. Pediatr Res 1994;35:393

115. Hill AB. The environment and disease: association or causation? Proc Roy Soc Med 1965; 58: 295-300.

116. Cooke RW. Smoking, intra-uterine growth retardation and sudden infant death syndrome. Int J Epidemiol 1998; 27: 238-41.

117. Cutz E, Perrin DG, Hackman R, Czegledy-Nagy EN. Maternal smoking and pulmonary neuroendocrine cells in sudden infant death syndrome. Pediatrics 1996; 98: 668-72.