A case-control study of smoking and sudden infant death syndrome in the Scandinavian countries, 1992 to 1995

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Abstract

Aim—To establish whether smoking is an independent risk factor for sudden infant death syndrome (SIDS), if the effect is mainly due to prenatal or postnatal smoking, and the effect of smoking cessation.

Methods—The analyses were based on data from the Nordic epidemiological SIDS study, a case-control study with 244 cases and 869 controls. Odds ratios were computed by conditional logistic regression analysis.

Results—Smoking emerged as an independent risk factor for SIDS, and the effect was mainly mediated through maternal smoking in pregnancy (crude odds ratio 4.0 (95% confidence interval 2.9 to 5.6)). Maternal smoking showed a marked dose-response relation. There was no effect of paternal smoking if the mother did not smoke. Stopping or even reducing smoking was beneficial. SIDS cases exposed to tobacco smoke were breast fed for a shorter time than non-exposed cases, and feeding difficulties were also more common.

Conclusions—Smoking is an independent risk factor for SIDS and is mainly mediated through maternal smoking during pregnancy. Stopping smoking or smoking less may be beneficial in reducing the risk of SIDS.

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Smoking in pregnancy was first associated with sudden infant death syndrome (SIDS) in 1966.¹ In the Nordic countries, this was observed by Rintahaka,² who attributed the increased risk of SIDS associated with smoking to fetal hypoxaemia during pregnancy. In subsequent studies, it has been a general finding that smoking increases the risk of cot death.³⁻⁴ Moreover, it is not fully established whether the risk is highest for smoking during^{1,2} or after pregnancy,⁵⁻¹¹ to what extent smoking by the father and other members of the household adds to the risk,⁹⁻¹² and whether there are interactions with other risk factors. Thus there is still controversy on how smoking exerts its effects and whether smoking is a confounder for social factors.

The aims of this study were to determine whether smoking is an independent risk factor for SIDS, whether the effect is mainly due to maternal smoking during pregnancy or to passive smoking, and if there is an effect of smoking cessation. Furthermore, we wanted to assess whether the effects on SIDS of other prenatal and postnatal risk factors are different in children of smoking and non-smoking mothers. Finally, we investigated the effects of the different smoking habits in the Scandinavian countries.

Methods

Between 1 September 1992 and 31 August 1995, parents of 294 cases of SIDS in the Scandinavian countries were invited by the local paediatrician (Norway and Sweden) or forensic institute (Denmark) to participate in the study. Of these, 244 families (83%) accepted. For each case, six controls matched for sex, date of birth plus two weeks, and maternity hospital were selected. The delay period of two weeks was allowed in order to obtain a similar age for the controls and the SIDS victims when the questionnaire was completed. The first four were invited to participate in the study. If a family was reluctant to enter the study, one of the two remaining controls was invited. Of 1207 invited control families, 869 (72%) participated.

The cases and controls were sent a questionnaire consisting of 272 questions. The questions analysed here concern maternal and paternal smoking before, during, and after pregnancy. Cigarette doses during pregnancy were recorded for the first and the third trimester separately. The number of persons smoking in the household was reported, as well as the number of cigarettes smoked. Birth weight, age at death/interview, age at weaning, prematurity, and perinatal problems were included in the analysis, as were use of dummies, incidence of infections, use of antibiotics, and hospital admission after the perinatal period. Basic medical and social data concerning the family were also analysed. Unfortunately control questionnaires took longer to complete than anticipated, which resulted in an age difference between cases and controls: cases, 16.1 weeks, 95% confidence interval 14.7 to 17.5; controls, 21.4 weeks, 20.5 to 21.8.

Necropsy was performed in every case. In Denmark and Sweden, 98% of the necropsies were performed at departments of forensic

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Table 1 Parental and other household smoking in SIDS cases and controls with crude and adjusted odds ratios (OR) in Scandinavia 1992 to 1995, the Nordic epidemiological SIDS study

Household smoking	Cases		Controls		Crude			Adjusted for age			Adjusted for age, maternal age, and education		
	No	%	No	%	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Maternal smoking													
Before pregnancy	151	68.3	336	41.4	3.0	2.2 to 4.1	<0.001	3.2	2.2 to 4.7	<0.001	2.5	1.7 to 3.7	<0.001
During pregnancy	150	61.7	253	29.4	4.0	2.9 to 5.6	<0.001	4.5	3.1 to 6.6	<0.001	3.6	2.4 to 5.3	<0.001
After pregnancy	146	60.1	263	30.7	3.8	2.8 to 5.3	<0.001	4.5	3.1 to 6.6	<0.001	3.7	2.5 to 5.5	<0.001
Paternal smoking													
Before pregnancy	114	51.6	322	40.0	1.6	1.2 to 2.1	0.005	1.7	1.2 to 2.5	0.003	0.8	0.5 to 1.2	0.26
During pregnancy	119	50.6	319	37.3	1.7	1.3 to 2.3	<0.001	1.8	1.2 to 2.5	0.002	0.9	0.6 to 1.4	0.62
After pregnancy	117	50.2	284	33.2	2.0	1.5 to 2.8	<0.001	2.3	1.6 to 3.3	<0.001	1.2	0.8 to 1.9	0.30
Other smoking													
After pregnancy	33	14.0	73	8.4	2.0	1.3 to 3.3	0.004	2.1	1.2 to 3.6	0.007	1.2	0.6 to 2.2	0.57

* Paternal and other smoking also adjusted for maternal smoking in pregnancy; CI = confidence interval.

medicine. The SIDS diagnosis was verified according to criteria of the pathology group of the Nordic SIDS study.¹³ In Norway, necropsies were also performed at hospital pathology departments for geographical reasons, but according to the same protocol.¹³ All necropsies can thus be regarded as having the same high validity. The material has been described in more detail by Øyen *et al.*¹⁴

Odds ratios (OR) were calculated by conditional logistic regression¹⁵ using the SPSS statistical software package.¹⁶ The attributable fraction (AF) was calculated for the whole material and for the participating countries from the data in tables 1 and 6 from the formula: $AF = \text{per cent exposed cases} \times ((OR-1)/OR)$.¹⁷ Additive interactions were tested by the EGRET statistical package,¹⁸ and multiplicative interactions by conditional logistic regression.¹⁵

Results

ODDS RATIO AND DOSE-RESPONSE RELATION

Crude odds ratios (95% confidence intervals) for maternal smoking before, during, and after pregnancy were 3.0 (2.2 to 4.1), 4.0 (2.9 to 5.6), and 3.8 (2.8 to 5.3) respectively (table 1). Odds ratios for paternal smoking were 1.6 (1.2 to 2.1), 1.7 (1.3 to 2.3), and 2.0 (1.5 to 2.8), and for other household members smoking postnatally 2.0 (1.3 to 3.3). Odds ratios were adjusted for age of infant as well as age and educational level of mother. Additional adjusting for birth weight reduced the effects marginally. Paternal smoking and other smoking were adjusted for maternal smoking in pregnancy. After adjustment, there was no effect of paternal smoking or other smoking (table 1). This was confirmed in a stratified analysis in which there was no effect of paternal smoking if the mother did not smoke (table 2).

Table 2 Combinations of maternal smoking in pregnancy and paternal smoking after pregnancy in SIDS cases and controls with crude odds ratios (OR) in Scandinavia 1992 to 1995, the Nordic epidemiological SIDS study

Mother smoked in pregnancy	Father smoked after pregnancy	Cases		Controls		OR	95% CI	p
		No	%	No	%			
No	No	74	31.8	462	54.4	1.0	Reference	
No	Yes	18	7.7	138	16.3	0.8	0.5 to 1.5	0.56
Yes	No	42	18.0	108	12.7	2.6	1.7 to 4.0	<0.001
Yes	Yes	99	42.5	141	16.6	4.4	3.0 to 6.5	<0.001

CI = confidence interval.

To evaluate dose-response relations, crude odds ratios for both maternal and paternal smoking before, in the first trimester, in the third trimester, and after pregnancy were calculated in different dose strata (nil, 1–9, 10–19, and > 20 cigarettes/day). We found an obvious dose-response relation for maternal smoking (fig 1).

SMOKING CESSATION

To assess possible effects of maternal smoking cessation, mothers who stopped smoking were divided into three groups. First, those who smoked before pregnancy but stopped permanently when they realised that they were pregnant (early cessation); second, those who stopped when the baby was born (late cessation); and third, those who smoked before pregnancy, stopped during it, but resumed smoking postpartum (partial cessation, table 3). Relatively few mothers changed their smoking behaviour (23 of 151 cases (15%) and 150 of 334 controls (45%)), but in neither group did we find any significant risk increase compared with mothers who never smoked. The odds ratio for early cessation was 0.7 (0.3 to 1.4), late cessation 1.1 (0.5 to 2.4), and partial cessation 1.1 (0.4 to 3.2) (table 3). The mothers who continued to smoke throughout pregnancy and thereafter had an odds ratio of 4.5 (3.1 to 6.5).

To determine why late cessation was not associated with an increased risk, even though the mothers of these infants had smoked during pregnancy, we compared the number of cigarettes consumed by the late ceasers and the non-ceasers. We found that the late ceasers smoked less than the non-ceasers during pregnancy, both in the first and the third trimester. In the first trimester, late ceasers consumed 5.1 cigarettes/day (95% confidence interval 2.1 to 8.2) against 9.3 cigarettes/day (8.7 to 9.9) for non-ceasers. The numbers in the third trimester were 5.3 (2.9 to 7.6) and 8.3 (7.7 to 8.9) respectively. We also tried to adjust for the amount smoked, but the results did not clarify the issue.

PERINATAL AND POSTNATAL PROBLEMS

The differences between SIDS cases and controls exposed and not exposed to maternal smoking in utero and postnatally are shown in tables 4 and 5. The variables initially investigated were: age, birth weight, age at weaning,

Figure 1 Crude odds ratios (log scale) for maternal and paternal smoking doses in different dose strata by exposed period in Scandinavia 1992 to 1995 (the Nordic epidemiological SIDS study); cig = cigarettes.

prematurity, induction of labour, vacuum extraction, caesarean section, resuscitation, admission to neonatal ward, problems during the first week (floppiness, irritability, weak sucking, and vomiting), problems after the first week (floppiness, activity, and irritability), feeding habits, infantile colic, symptoms of infection, antibiotic treatment, admission to hospital after discharge from maternity ward, use of a dummy (pacifier), regurgitation/vomiting, and depth of sleep as estimated by the parents. We chose variables which had effects that might be modified by maternal smoking. Of these variables, only the ones given in tables 4 and 5 showed significant differences. There was no age difference between the groups in this study: mean age at death was 16.1 weeks in the non-exposed group and 15.9 in the exposed group ($p =$

0.90). Cases had lower birth weight than controls, regardless of exposure, and smoke exposed infants had lower birth weight than non-exposed infants. Exposed cases stopped breast feeding earlier (8.0 weeks *v* 11.9 weeks, $p = 0.036$) (table 4).

Among the controls, infants of smoking mothers more often had problems related to breast feeding (49.2% *v* 29.9%), as well as infections (51.8% *v* 48.8%), and were more often admitted to hospital (24.2% *v* 19.0%) and treated with antibiotics (24.2% *v* 17.1%) (table 5). The only exception was poor sucking, which was more prevalent among infants of non-smoking mothers. The effect of poor sucking was much stronger in infants of smoking mothers ($p = 0.01$ in a multiplicative model). The same tendency (not significant) was observed for breast feeding. Otherwise, there was a tendency (not significant) towards smaller effects among infants of smoking mothers. We assessed possible effect modifications of smoking on the following variables: low birth weight, low maternal education, prone sleeping position, high parity, and low maternal age. No significant interactions were observed, except for an additive interaction with position placed to sleep the last time ($p < 0.001$), which is described elsewhere.¹⁴

Table 3 Crude odds ratios (OR) for SIDS by maternal smoking career in Scandinavia 1992 to 1995, the Nordic epidemiological SIDS study

Maternal smoking career	Cases		Controls		OR	95% CI	p
	No	%	No	%			
Never smoked	67	30.7	430	56.3	1.0	Reference	—
Early cessation*	9	4.1	68	8.9	0.7	0.3 to 1.4	0.30
Late cessation†	10	4.6	54	7.1	1.1	0.5 to 2.4	0.73
Partial cessation‡	4	1.8	28	3.7	1.1	0.4 to 3.2	0.92
Non-cessation	128	58.7	184	24.1	4.5	3.1 to 6.5	<0.001

*Stopped smoking when they became pregnant.

†Stopped smoking postpartum.

‡Stopped during pregnancy but resumed smoking postpartum.

Table 4 Age, birth weight, and weaning of SIDS cases and controls exposed to prenatal maternal smoking compared with non-exposed cases and controls in Scandinavia 1992 to 1995, the Nordic epidemiological SIDS study

Characteristics	SIDS cases			p	SIDS controls			p
	Non-exposed	Exposed			Non-exposed	Exposed		
Age (weeks; 95% CI)	16.1 (13.8 to 18.4)	15.9 (14.2 to 17.6)		0.90	21.2 (20.2 to 22.3)	21.9 (20.3 to 23.5)		0.50
Birth weight (g; 95% CI)	3340 (3161 to 3517)	3065 (2950 to 3178)		0.007	3653 (3610 to 3696)	3462 (3399 to 3525)		<0.001
Weaning (weeks; 95% CI)	11.9 (8.1 to 15.6)	8.0 (6.4 to 9.7)		0.036	15.4 (13.7 to 17.1)	11.7 (9.8 to 13.6)		0.004

CI = confidence interval.

Table 5 Interaction between prenatal smoking and perinatal and postnatal characteristics of SIDS cases and controls in Scandinavia 1992 to 1995, the Nordic epidemiological SIDS study

		Cases		Controls		OR	95% CI	p	Test for interaction (p)	
		No	%	No	%				Additive	Multiplicative
Prenatal smoking	Poor sucking									
No	No	86	94.5	545	90.7	1.0	Reference	—	0.07	0.010
No	Yes	5	5.5	56	9.3	0.6	0.2 to 1.6	0.30		
Yes	No	127	86.4	238	95.2	3.5	2.5 to 5.0	<0.001		
Yes	Yes	20	13.6	12	4.8	11.0	4.9 to 24.3	<0.001		
Prenatal smoking	Breast feeding									
No	Yes	62	68.1	425	70.1	1.0	Reference	—	0.31	0.80
No	No	29	31.9	181	29.9	1.2	0.7 to 2.0	0.45		
Yes	Yes	68	45.3	127	50.8	3.8	2.5 to 5.8	<0.001		
Yes	No	82	54.7	123	49.2	5.1	3.3 to 7.9	<0.001		
Prenatal smoking	Infection									
No	No	24	25.8	312	51.2	1.0	Reference	—	0.17	0.15
No	Yes	69	74.2	297	48.8	2.9	1.7 to 4.7	<0.001		
Yes	No	49	32.7	122	48.2	5.4	3.1 to 9.3	<0.001		
Yes	Yes	101	67.3	131	51.8	9.5	5.7 to 15.8	<0.001		
Prenatal smoking	Antibiotics									
No	No	70	75.3	500	82.9	1.0	Reference	—	0.52	0.13
No	Yes	23	24.7	103	17.1	1.8	1.0 to 3.1	0.045		
Yes	No	112	75.7	191	75.8	4.4	3.1 to 6.5	<0.001		
Yes	Yes	36	24.3	61	24.2	4.4	2.7 to 7.4	<0.001		
Prenatal smoking	Hospital admission									
No	No	62	66.7	485	81.0	1.0	Reference	—	0.72	0.097
No	Yes	31	33.3	114	19.0	2.9	1.4 to 6.1	0.004		
Yes	No	107	71.8	188	75.8	4.2	3.0 to 6.0	<0.001		
Yes	Yes	42	28.2	60	24.2	5.4	2.8 to 10.4	<0.001		

CI = confidence interval; OR = odds ratio.

Table 6 Maternal smoking in SIDS cases and controls with crude and adjusted odds ratios (OR) by country, in Scandinavia 1992 to 1995, the Nordic epidemiological SIDS study

Country	Cases		Controls		Crude			Adjusted for age			Adjusted for age, maternal age, and education		
	n	%	n	%	OR	95%CI	p	OR	95%CI	p	OR	95%CI	p
Norway													
In pregnancy	51	71.8	93	34.7	4.1	2.3 to 7.3	<0.001	4.5	2.3 to 8.6	<0.001	3.9	2.0 to 7.9	<0.001
After pregnancy	49	69.0	96	36.2	4.2	2.3 to 7.6	<0.001	4.6	2.3 to 9.2	<0.001	4.2	2.0 to 8.9	<0.001
Sweden													
In pregnancy	66	56.4	101	23.5	4.4	2.8 to 7.0	<0.001	5.5	3.1 to 9.9	<0.001	4.5	2.5 to 8.1	<0.001
After pregnancy	63	53.8	108	25.4	3.8	2.4 to 6.1	<0.001	4.8	2.7 to 8.4	<0.001	4.0	2.3 to 7.2	<0.001
Denmark													
In pregnancy	33	60.0	59	35.8	3.1	1.5 to 6.3	0.002	3.3	1.5 to 7.2	0.004	1.9	0.8 to 4.7	0.17
After pregnancy	34	61.8	59	35.1	3.4	1.7 to 6.8	0.001	4.0	1.7 to 9.2	0.001	2.7	1.1 to 7.0	0.034

CI = confidence interval.

DIFFERENCES BETWEEN THE NORDIC COUNTRIES
Smoking habits differed between the Scandinavian countries. In the control group Sweden had the lowest prevalence of smoking mothers during pregnancy, 23.5% against 34.7% in Norway and 35.8% in Denmark (table 6). The odds ratios for smoking were somewhat lower in Denmark and Norway, but the differences were not statistically significant (table 6). Adjusted for age of infant, maternal age, and education, the odds ratios were somewhat lower, but the pattern was the same, with the exception that the statistical significance for smoking in pregnancy disappeared in the Danish data.

The attributable fraction (AF) was 45% in the whole material. Due to the high prevalence of smoking, Norway had the highest AF (54%), followed by Sweden (44%) and Denmark (41%).

Discussion

Nicotine is a powerful stimulant of cholinergic neurones, and has been postulated to act upon nicotinic acetylcholine receptors either

centrally¹⁹ or peripherally.²⁰ Given prenatally in animal experiments, it alters ventilatory and awakening responses to hypoxia.^{21–23} Nicotine also acts by vasoconstriction and diminution of placental blood flow, thereby reducing the amount of oxygen and nutrients available to the fetus. Prenatal smoking has been shown to have significant negative effects on neonatal airway development and lung elasticity.²⁴ Carbon monoxide might theoretically reduce oxygen transport, and tar and smoke particles are considered responsible for an increased susceptibility to airway infections, a factor associated with SIDS.²⁵

Our major findings were an independent effect of smoking on the risk of SIDS with a dose-response association, no effect of passive smoking, and a strong effect of smoking cessation.

It is well known that smoking reduces birth weight, and it has been argued that adjusting for birth weight carries a risk of over adjustment.²⁶ We therefore calculated odds ratios with and without this adjustment and found slightly lower values with the adjustment, but the effects were

still significant. This suggests an effect in addition to that mediated by the reduction in birth weight.

As in any case-control study, the result is probably affected by recall bias. Smoking might be underreported by control mothers as well as by case mothers.

To evaluate a possible non-response bias, marital status, maternal age, and birth order in the Norwegian cases and controls were compared with data from the Medical Birth Registry of Norway (MBRN) for the same period, including SIDS deaths. The proportions of single mothers, young mothers, and first births were lower in the case-control data than in the MBRN, but the reduction was similar in cases and controls.

The results from the Nordic study confirm that tobacco smoking is an independent risk factor for SIDS, and after the implementation of the supine sleeping position it has now emerged as the most important risk factor. Most infants exposed to smoking were exposed both in utero and postpartum, so the effects of prenatal and postnatal smoking are difficult to separate.^{12, 27} We showed that paternal smoking had no significant effect as such; it tended to augment the effect of maternal prenatal smoking, but the confidence intervals overlapped. This was also found by Blair *et al.*²⁷ In our study, the mean cigarette consumption of the mother in the first trimester, when the father did not smoke, was 8.1 (7.2 to 8.9) cigarettes/day, and when the father did smoke, 9.2 (8.4 to 9.9) cigarettes/day. The figures for the third trimester are similar: 6.3 (5.5 to 7.1) and 7.9 (7.2 to 8.6) cigarettes/day, respectively. An association between maternal and paternal smoking could account for the findings in both studies.

Table 3 contains the components recently suggested by Golding¹²—that is, mothers who smoked only postnatally (partial cessation) as well as mothers who smoked both prenatally and postnatally—and from this it is probable that it is maternal smoking during pregnancy that is important. We consider that paternal and other passive smoking is of relatively minor importance. This is supported by the dose-response figures (fig 1) but we cannot rule out a small effect of maternal smoking postpartum.

The question of the influence of maternal smoking on perinatal and postnatal problems has been raised on the grounds that some children die without having been exposed to tobacco smoke, either prenatally or postnatally. In our study, 30.7% of the case mothers had never smoked. The hypothesis in this section was that it might be shown that there are differences between cases exposed and not exposed to tobacco smoke. Of the 21 variables initially investigated, only those related to feeding (poor sucking, breast feeding) and to infection (infectious symptoms, antibiotics, and hospital admission) remained.

Our interpretation of these findings is that the early feeding difficulties seen in smoke exposed cases are in some way related to the biological effects of tobacco smoke on the fetus, and that the increased risk of SIDS due

to smoking is not caused by an increased risk of infections. Infection might be an additional factor that contributes to the fatal event. It is conceivable that infants who die of SIDS come from a population of infants with compromised health, and the ill effects of this are enhanced by maternal smoking.

In contrast to the findings of Haglund and Cnattingius in 1990,²⁸ we could not show a difference in age at death between the smoke exposed and non-exposed SIDS cases. We have no explanation for this.

Comparing the percentage of smoking mothers in the Scandinavian countries with the incidence of SIDS at the end of the 1980s, we note that both Norway and Denmark had very high SIDS rates, and Sweden a much lower rate.²⁹ During the study period, Norway and Denmark both had a significantly higher proportion of smoking mothers than Sweden. These differences in smoking habits may partly reflect the varying incidences, but none of these analyses provides a convincing explanation of why Denmark and Norway differed as much as they did in the peak years 1985 to 1989. In spite of different smoking habits, all Scandinavian countries now have virtually the same SIDS incidence. This indirectly highlights the major influence on SIDS incidence exerted by the switch to the non-prone sleeping position.

We believe we have shown a remarkable effect of maternal smoking cessation. This conveys an important message—that is, that smoking cessation is potentially beneficial. We find it curious that the infants of mothers who stopped smoking postpartum were not at increased risk, even though they had been exposed to nicotine in utero. One explanation could be that these mothers had already begun to reduce smoking during pregnancy, as was shown in the first and third trimesters. This is consistent with our demonstration of a dose-response relation between smoking dose in pregnancy and SIDS. The fraction of mothers who changed their smoking habits was low, only 23 of 151; therefore the interpretation remains uncertain.

We conclude that smoking is an independent risk factor for SIDS, and that it is mainly mediated through maternal smoking during pregnancy. There are differences in smoking habits among women in Scandinavia, which are probably related to the different odds ratios observed and may have contributed to the varying incidences in the Scandinavian countries at the end of the 1980s. Analysis of smoking careers indicates that smoking cessation, or even a reduction in smoking, may be beneficial in reducing the risk of SIDS.

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