Health effects of passive smoking · 2

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Passive smoking and sudden infant death syndrome: review of the epidemiological evidence

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Abstract

***Background* – This paper provides a systematic, quantitative review of the epidemiological evidence relating parental smoking and sudden infant death.**

***Methods* – Thirty two relevant publications were identified after consideration of 692 articles selected by electronic search of the Embase and Medline databases using keywords and Mesh headings relevant to passive smoking in children. Eleven further articles were identified from reviews and by talking to authors. The search was completed in April 1997 and identified 39 studies.**

***Results* – The unadjusted pooled odds ratio for prenatal maternal smoking was 2.77 (95% CI 2.45 to 3.13). After adjustment for a variety of confounders the pooled odds ratio was reduced to 2.08 (95% CI 1.83 to 2.38) and was similar in cohort and case-control studies. Four studies reported on maternal postnatal smoking after controlling for prenatal maternal smoking (pooled odds ratio 1.94 (95% CI 1.55 to 2.43)). Of three studies reporting on the risk of paternal smoking where the mother was a non-smoker, two found significant effects while one found no effect. Dose-response relationships with both prenatal and postnatal maternal smoking were present in most studies which provided data.**

***Conclusions* – Maternal smoking doubles the risk of sudden infant death syndrome. The relationship is almost certainly causal. There is good evidence that postnatal exposure to environmental tobacco smoke from both mother and father are important. Because prenatal smoking is almost invariably associated with postnatal smoking, the role of prenatal smoking per se will be difficult to resolve using epidemiological studies.**

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Sudden infant death syndrome (SIDS) is currently defined as the sudden death of an infant that remains unexplained by clinical or necropsy evidence. In most developed countries SIDS is the most common single cause of death in the postneonatal period (1–12 months). SIDS became recognised as an entity in the 1960s and was accorded its own code (795) in the 8th Revision of the International Classification of Diseases (ICD) in 1968. From that time until 1988, death rates in Britain rose year on year to a peak of 1.96 per 1000 live births in 1986. A marked reversal of trend then occurred and, by 1992, rates had fallen to 0.63 per 1000. Since then rates have been fairly stable.

It is likely that the immediate cause of death in SIDS is a functional one acting through the cardiorespiratory system. One theory is that infants with SIDS have abnormal arousal or respiratory control mechanisms which may increase the risk of SIDS when combined with other risk factors. A number of risk factors have been identified by epidemiological studies.[1–4] Factors relating to the mother or pregnancy include younger mothers, second or later birth order, low birthweight or gestational age, male sex, and maternal smoking in pregnancy. Postnatal factors include lower socioeconomic status, breast feeding (inconsistent evidence), symptoms of illness (fever, unwell), parental smoking, smoking by others in the household, head covering, overheating, bed sharing with parents, and prone sleeping position. Prone sleeping position, overheating, and smoking have been targeted as the most important modifiable factors for public health action.

The earliest epidemiological study to examine the association between maternal prenatal smoking and SIDS was carried out in Canada in the early 1960s.[5] An odds ratio of 2.4 was obtained and this was not substantially reduced when birthweight, a known risk factor for SIDS which is also related to smoking, was allowed for. Clinical and experimental studies indicate that smoking may be associated with abnormalities in brain development and that one manifestation of this might be a tendency to central apnoea.[6 7] There is also some evidence that maternal smoking is associated with abnormal pulmonary development in neonates independent of a postnatal effect.[8] Such evi-

dence points to the plausibility of an in utero effect, but because mothers who smoke in pregnancy are very likely to smoke postnatally this is difficult to confirm by epidemiological methods.

It is also plausible that postnatal smoking might affect the risk of SIDS, either due to direct irritation of the airways or the promotion of respiratory infection. The relationship between passive smoking and lower respiratory illness in infancy is almost certainly causal.[9] There is also evidence that nicotine may affect the ventilatory response to hypoxia.[6] Because an appreciable proportion of smoking women report giving up smoking during pregnancy but resume postnatally, this hypothesis can be tested using epidemiological methods. Even so, problems of selection and possible informant bias remain and some of the most recent studies have therefore examined the effects of exposure to the cigarette smoke of the father and others in the household controlling for the mother's smoking.

This paper provides a systematic quantitative review of the epidemiological evidence relating to parental smoking and SIDS. In particular, it examines the separate roles of prenatal and postnatal exposure. A number of excellent reviews are already available,[10–12] but this paper incorporates a number of major recent studies as well as including some earlier ones not mentioned in existing reviews.

Methods

SELECTION OF STUDIES FOR REVIEW

Published papers, letters and review articles were selected by an electronic search of the Embase and Medline databases using the research strategy described earlier.[9] Among 692 publications considered relevant to passive smoke exposure in children, 32 were identified as potentially relevant to this review and a further 11 were identified by citation in previous overviews or in individual studies or by contact with authors. No papers with usable data were excluded.

STATISTICAL METHODS

These have been described in more detail in the first paper in this series.[9] In many instances the odds ratio and 95% confidence limits were given or it was possible to calculate them from the raw data. In a few situations it was necessary to derive an approximate standard error (for the log odds ratio) based on the marginal values of the relevant 2×2 table. Where data allowed standardisation for age, sex or occasionally another confounder, the Mantel-Haenszel method was used to provide an adjusted value. In situations where relative odds were given separately for different smoking categories – for example, <10 cigarettes/day and >10 cigarettes per day – a pooled odds ratio and 95% confidence interval were calculated by taking a weighted average (on the log scale) using weights inversely proportional to the variances.

Where quantitative meta-analysis was considered appropriate, odds ratios were tested for heterogeneity using the technique of Breslow and Day.[13] The heterogeneity tests were often statistically significant, implying that a simple "fixed effect" pooling of the logarithms of the odds ratios (using weights inversely proportional to their variances may be inappropriate). Odds ratios were therefore also pooled using a "random effect" model which makes allowances for heterogeneity of effect between studies.

Results

The 43 papers identified related to 39 studies which are listed by year of publication in table 1. Throughout this review the results of the study by Schoendorf and Kiely[37] were analysed separately for black and white subjects and are counted as two separate studies. There were 10 cohort studies; these had the advantage that the smoking habit had nearly always been recorded prospectively and was therefore unbiased by subsequent events. The cohort studies tended to be either planned multipurpose epidemiological studies of pregnancy and the perinatal period or cohorts constructed from national or regional routine databases which included information about maternal smoking in pregnancy. The former tended to have more detail about the pregnancy but were generally less statistically powerful than those based on large routine databases. The major deficiency in cohort studies was the relative lack of information about the postnatal circumstances of the infant; this severely limited the scope of the data to examine the role of postnatal exposure and to take account of postnatal confounding factors.

There were 29 case-control studies, five of which were "nested" in cohort studies. Most of the case-control studies assessed exposure to smoking retrospectively, though some also used prenatal records. Some of the more recent studies were both large and very comprehensive in the variables assessed. These yielded the most useful information about the effects of postnatal exposure to environmental tobacco smoke.

Most studies adopted an age range of 7–365 days, though some earlier studies started at one month and others included infants up to two years of age. Being a diagnosis of exclusion the definition will also be affected by the level of investigation of the death. Some studies included only those diagnosed as SIDS after post mortem examination, with or without clinical review, while other studies included all those with ICD (8th revision) 795 or ICD (9th revision) 798.0. Even where the ICD code was the only criterion, the necropsy rate was generally reported to be high (>80%).

Methods of ascertainment also varied. Some were based on routine death certificates, others on hospital necropsy cases, and others on a mixture of formal and informal systems including networks of health professionals.

The studies varied considerably in their treatment of confounders. Some were confined to univariate analysis but most attempted to control for confounding factors. In some cases this

Table 1 Summary of studies examining effects on sudden infant death syndrome (SIDS) of maternal prenatal and postnatal smoking

Reference	*Place/study period*	*Study design*	*Numbers (cases: controls)*	*Prenatal tobacco smoke exposure*	*Postnatal tobacco smoke exposure*	*Maternal prenatal smoking*			*Maternal postnatal smoking*	
						Sm vs Ns (unadjusted) OR (95% CI)	*Sm vs Ns (adjusted) OR (95% CI)*	*Dose response*	*Sm vs Ns (unadjusted) OR (95% CI)*	*Sm vs Ns (adjusted) OR (95% CI)*
Steele (1996)[5]	Canada 1960–61	Case-control	80:157	Retrospective: interview		2.49 (1.43 to 4.35)	2.4 (1.4 to 4.0)			
Schrauzer (1975)[14]	USA Not stated	Case-control	46:38	Retropective: mailed questionnaire		2.41 (0.9 to 6.42)				
Bergman (1976)[15]	USA 1970–74	Case-control	56:86	Retrospective: written questionnaire	Retrospective: written questionnaire	2.15 (1.08 to 4.26)	2.06 (1.00 to 4.24)	Yes	2.42 (1.22 to 4.82)	
Naeye (1976)[16]	USA 1959–66	Case-control (nested)	125:375	Prospective: record		1.57 (1.04 to 2.37)				
Lewak (1979)[17]	USA 1960–67	Cohort	44:18716	Prospective: records		4.40 (2.10 to 9.22)				
Murphy (1982)[18]	Wales 1965–77	Cohort	99:46422	Prospective: records		2.79 (1.82 to 4.26)				
Matthews (1985)[19]	Republic of Ireland 1979–80	Case-control (nested)	34:34	Prospective: records		0.70 (0.27 to 1.81)				
Rintahaka (1986)[20]	Finland 1969–80	Case-control	124:141	Prospective: record		4.12 (2.40 to 7.06)	Significant after adjustment			
Cameron (1986)[21]	Australia 1980–82	Case-control	208:393	Prospective: records	Retrospective: interview	2.67 (1.89 to 3.78)				
Victora (1987)[22]	Brazil 1984–85	Case-control	72:144	Retrospective: interview		1.79 (1.01 to 2.84) 10 cig/day				
Hoffman (1988)[23 24]	USA 1978–79	Case-control	757:757	Prospective: records		3.40 (2.75 to 4.20)	2.64 (2.20 to 3.17)*			
McLoughlin (1988)[25]	England 1982–86	Case-control	45:90	Retrospective: interview		3.29 (1.56 to 6.94)				
McGlashan (1989)[26]	Australia 1980–86	Case-control	166:234	Retrospective: interview	Retrospective: interview	1.85 (1.22 to 2.82)			1.92 (1.26 to 2.92)	
Kraus (1989)[27]	USA 1959–66	Case-control (nested)	193:1930	Prospective: records		1.99 (1.58 to 2.50)	1.63 (1.29 to 2.06)*	Yes		
Petru (1989)[28]	Germany 1982–87	Case-control	80:80	Prospective: records		3.48 (1.38 to 8.78)				
Wierenga (1990)[29]	Netherlands	Case-control	15:30	Prospective: records			2.38 (0.73 to 7.76)**			
Bulterys (1990)[30]	USA 1959–66	Case-control (nested)	193:1930	Prospective: records		4.14 (2.73 to 6.28)	1.54 (1.30 to 1.82)*	Yes		
Haglund (1990)[31]	Sweden 1983–85	Cohort	190:279938	Prospective: records		2.35 (1.75 to 3.15)	2.24 (1.72 to 2.92)*	Yes		
Gilbert (1990)[32]	England	Case-control	95:190	Retrospective: interview		2.44 (1.47 to 4.04)				
Li (1991)[33]	USA 1984–89	Case-control (nested)	916:3704	Prospective: records		2.98 (2.55 to 3.48)	2.2 (1.8 to 2.6)			
Nilsen (1991)[34]	Norway 1985–89	Case-control	73:73	Source not stated		4.22 (2.11 to 8.45)				
Engelberts (1991)[35]	Netherlands	Case-control	108:675	Retrospective: interview	Retrospective: interview	1.37 (0.90 to 2.08)	1.3 (0.90 to 1.73) per 10 cigs/day	No	1.47 (0.97 to 2.23)	
Malloy (1992)[24 36]	USA 1980–85	Cohort	636:425326	Prospective: record			3.25 (2.04 to 2.71)			
Schoendorf (1992)[37]	USA 1988	Case-control	WH 234:3254 BL 201:2844	Retrospective: interview	Retrospective: interview	W4.07(3.03 to 5.48) B2.94(2.12 to 4.07)	W 3.10 (2.27 to 4.24) B 3.06 (2.19 to 4.29)		2.22 (1.29 to 3.78) 2.40 (1.49 to 3.83)	1.75 (1.04 to 2.95)*** 2.33 (1.48 to 3.67)***
Nicholl (1992)[38]	UK 1976–79	Case-control	303:277	Retrospective: interview	Retrospective: interview	2.42 (1.67 to 3.50)	2.13 (1.45 to 3.13)			
Mitchell (1992)[39–41]	New Zealand 1987–90	Case-control	485:1800	Prospective: records Retrospective: interview	Retrospective: interview	4.09 (3.28 to 5.11) (prospective) 4.29 (3.95 to 5.42) (retrospective)	1.7 (1.2 to 2.3) (prospective) 2.14 (1.61 to 2.84) (retrospective)		4.24 (3.35 to 5.36)	1.79 (1.30 to 2.48)†
Irwin (1992)[42]	USA 1984–88	Cohort	231:114318	Prospective: records			1.36 (1.04 to 1.77)††			
Nordstrom (1993)[43]	Sweden 1983–86	Cohort	324:355277 Nordic origin	Prospective: record		2.10 (1.68 to 2.62)*	1.80 (1.45 to 2.23)*	Yes		
Hilder (1994)[44]	UK 1989–90	Cohort	25:13271	Prospective: records		2.46 (1.12 to 5.43)				
Jorch (1994)[45]	Germany 1990–92	Cohort	175:92062	Prospective: records		5.35 (3.61 to 7.94)				
Ponsonby (1995)[46]	Australia 1988–91	Case-control	58:101		Retrospective: interview				3.96 (1.91 to 8.24)	3.10 (1.36 to 7.09)†††
Haglund (1995)[47]	Sweden 1983–90	Cohort	749:812908	Prospective: records		2.17 (1.87 to 2.51)				
Poets (1995)[48 49]	Germany 1986–90	Case-control	190:5920	Prospective: record		3.17 (2.30 to 4.37)	2.4 (1.71 to 3.36)	Yes		
Taylor (1995)[50]	USA 1988	Case-control	649:9864	Prospective: records		3.06 (2.57 to 3.66)	2.92 (2.30 to 3.69)			
Sanghavi (1995)[51]	USA 1992	Cohort	70:41598	Prospective: record			1.92 (p<0.01) per pack/day			
Klonoff-Cohen (1995)[52]	USA 1989–92	Case-control	200:200	Retrospective: interview	Retrospective: interview	2.48 (1.49 to 4.11)		Yes	3.13 (1.75 to 5.60)	2.28 (1.04 to 4.98)†
Blair (1996)[53]	England 1993–95	Case-control	195:780	Retrospective: interview	Retrospective: interview	4.84 (3.33 to 7.04)	1.78 (1.04 to 3.05)	Yes	5.19 (3.57 to 7.55)	Not significant after adjustment for prenatal smoking
Taylor (1996)[64]	USA 1992–94	Case-control	47:142	Retrospective: interview		4.06 (2.02 to 8.14)				

* Weighted average of different smoking categories taken to produce estimate.
** Confined to birthweight <1500 g or gestation <32 weeks.
*** Mother did not smoke in pregnancy.
† Adjusted for prenatal smoking.
†† Estimated confidence intervals as quoted in paper are incorrect.
††† Not adjusted for prenatal smoking.

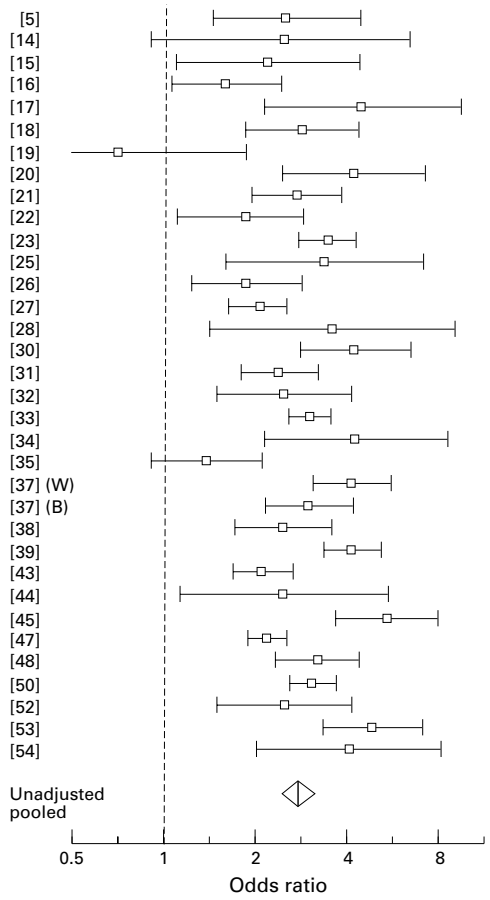

Figure 1 Individual and pooled odds ratios (with 95% confidence interval) for SIDS associated with maternal prenatal smoking ordered by date of publication.

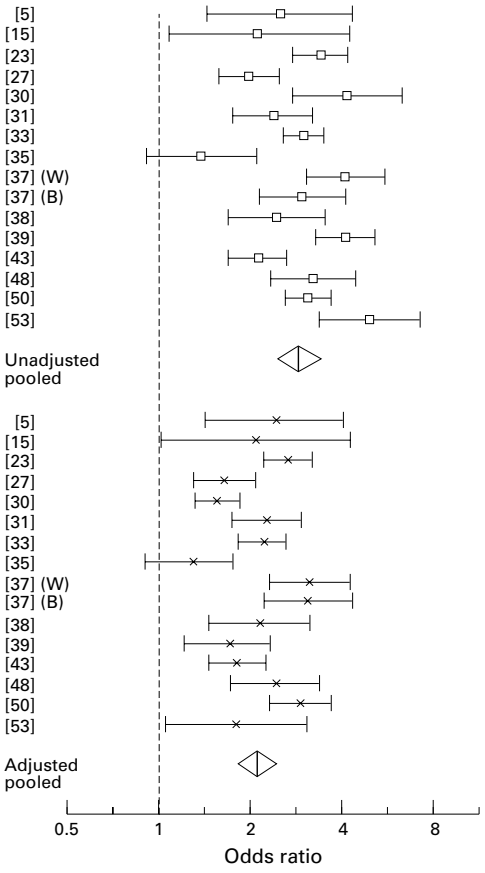

Figure 2 Individual and pooled odds ratios (with 95% confidence intervals) for SIDS in studies with information on adjustment for confounders ordered by date of publication. □ = unadjusted; × = adjusted.

was restricted to controlling for birthweight, whilst others controlled for large numbers of potential confounders. The main categories of confounder were: (1) pregnancy and maternal factors (age, parity); (2) infant factors (sex, birthweight, gestational age); (3) socioeconomic status (ethnicity, social class, education); and (4) infant care practices (breast feeding, sleeping position, wrapping). Of nine studies which examined the effect of postnatal exposure to environmental tobacco smoke four controlled for maternal smoking during pregnancy. The sophistication of analysis increased markedly towards the end of the 1980s, reflecting developments in computing and statistical software.

PRENATAL SMOKING

All but one study reported prenatal smoking habit and this was ascertained either prospectively (25) or retrospectively (13). The odds ratios and 95% confidence intervals for unadjusted effects of prenatal smoking are shown in fig 1. Unadjusted odds ratios for SIDS in smokers compared with non-smokers ranged from about 0.7 to 4.85 with 33 of 34 studies showing an odds ratio greater than unity and with 31 being statistically significant. The pooled estimate was 2.76 (random effects model) with significant heterogeneity between studies (table 2). A dose-response relationship was present in most studies in which this was examined.

Table 2 Summary of pooled odds ratios. Both fixed (FEM) and random (REM) effects models are shown

Group of studies	*Model*	*Pooled unadjusted odds ratios (95% CI)*	*Test for heterogeneity*	*Pooled adjusted odds ratios (95% CI)*	*Test for heterogeneity*
Prenatal smoking (all studies)	REM	2.77 (2.45 to 3.13) (n=34)	$\chi^2(df=33)=124.4$ ($p<0.001$)	2.08 (1.82 to 2.38) (n=19)	$\chi^2(df=18)=68.5$ ($p<0.001$)
	FEM	2.76 (2.61 to 2.92)		2.08 (1.96 to 2.21)	
Prenatal smoking, studies with information on non-adjusted and adjusted odds ratios	REM	2.87 (2.44 to 3.38) (n=16)	$\chi^2(df=15)=61.9$ ($p<0.001$)	2.11 (1.83 to 2.44) (n=16)	$\chi^2(df=15)=55.4$($p<0.001$)
	FEM	2.91 (2.73 to 3.11)		2.08 (1.95 to 2.23)	
Prenatal smoking (cohort studies)	REM	2.75 (2.12 to 3.57) (n=8)	$\chi^2(df=7)=25.1$ ($p<0.001$)	1.90 (1.45 to 2.50) (n=5)	$\chi^2(df=4)=15.6$ ($p=0.004$)
	FEM	2.49 (2.27 to 2.73)		1.99 (1.82 to 2.19)	
Prenatal smoking (case-control studies)	REM	2.77 (2.41 to 3.17) (n=28)	$\chi^2(df=27)=82.1$ ($p<0.001$)	2.13 (1.83 to 2.48) (n=16)	$\chi^2(df=15)=54.0$ ($p<0.001$)
	FEM	2.91 (2.73 to 3.10)		2.09 (1.95 to 2.24)	
Postnatal smoking	REM	2.80 (2.00 to 3.93) (n=9)†	$\chi^2(df=8)=35.0$ ($p<0.001$)	*	$\chi^2(df=3)=1.18$ ($p=0.76$)
	FEM	3.10 (2.70 to 3.56)		1.94 (1.55 to 2.43) (n=4)	

* Below the minimum of five studies for estimation of random effects.
† Schoendorf study results[37] were analysed separately for black and white subjects and in all these analyses are counted as two separate studies.

The studies varied in the number and type of confounding factors for which they were adjusted. Some made no adjustment while others adjusted only for single factors such as maternal age or birthweight. More recent studies tended to adjust for a more extensive number of confounders (see above). The 16 studies for which both adjusted and unadjusted odds ratios for prenatal smoking were available are shown in fig 2. The summary estimate for adjusted odds ratios was 2.11, considerably less than the unadjusted summary estimate of 2.87 for the same studies, but remaining highly significant (table 2). The effect of adjustment tended to be greater for those studies which adjusted for a greater number of confounders, especially those relating to the postnatal period (such as prone sleeping position). For example, the detailed case-control studies of Mitchell and Blair found unadjusted odds ratios of 4.09 and 4.84, whereas the adjusted figures were 1.70 and 1.78, respectively. On the other hand, the detailed study by Schoendorf reported a smaller reduction from 4.07 to 3.1 among white subjects and a small increase from 2.94 to 3.06 in black subjects after adjustment. Not surprisingly, there was evidence of heterogeneity even between the adjusted odds ratios. This heterogeneity was not due to any differences between case-control and cohort studies where the pooled adjusted odds ratios were very similar (table 2).

POSTNATAL MATERNAL SMOKING

Eight of the nine studies with data on postnatal maternal smoking also presented data on prenatal smoking. Five reported greater unadjusted odds ratios for postnatal maternal smoking than for prenatal maternal smoking [15 26 35 52 53] whereas three found a greater effect of prenatal maternal smoking.[37 40]

Of greater relevance were four studies[37 40 52] which controlled also for maternal prenatal smoking, thus enabling the additional contribution of maternal postnatal smoking to be estimated. The adjusted odds ratios were, respectively, 1.75, 2.33, 1.79 and 2.28. The pooled odds ratio was 1.94 (fixed effects model) and was highly statistically significant (table 2). The estimates by Schoendorf were the odds ratios of SIDS in mothers who did not smoke in pregnancy but smoked postnatally, adjusted for obstetric and socioeconomic factors.[37] A fifth study [53] found that the effect of postnatal exposure was not statistically significant ($p = 0.16$) after adjusting for prenatal exposure, but provided no estimate of the odds ratio.

Table 3 Summary of effects of paternal smoking.

Reference	*Unadjusted odds ratio (95% CI)*	*Odds ratio (95% CI) adusted for maternal smoking and other factors*	*Father smoker, mother non-smoker*
Engleberts (1991)[35]	0.96 (0.63 to 1.45)		
Bergmann (1976)[15]	1.53 (0.78 to 3.01)		
Nicholl (1992)[38]	1.99 (1.38 to 2.86)		1.63 (1.11 to 2.40)
Klonoff-Cohen (1995)[52]	3.53 (1.99 to 6.27)	3.46 (1.91 to 6.28)	
Mitchell (1993)[40]	2.41 (1.92 to 3.02)	1.37 (1.02 to 1.84)	1.00 (0.64 to 1.56)
Blair (1996)[53]	3.04 (2.13 to 4.36)	2.50 (1.48 to 4.22)	3.41 (1.98 to 5.88)

PATERNAL AND OTHER SMOKERS IN THE HOUSEHOLD

Because women who do not smoke in pregnancy but smoke afterwards may be a selected group, the hypotheses relating to environmental tobacco smoke may be better tested by including in the analysis data on other smokers in the household. Independent relationships with this source of exposure are unlikely to have been mediated through passive exposure of the fetus during pregnancy and may reasonably be attributed to effects of environmental tobacco smoke. Such analyses are reported by six studies,[15 35 38 40 52 53] the four most recent studies being large case-control studies all of which attempted to control for maternal smoking during pregnancy (table 3).

Nicholl 1992[38] reported an adjusted odds ratio of 1.63 when the mother was a non-smoker and the partner a smoker compared with households in which both were non-smokers. In Klonoff-Cohen's Californian study[52] the adjusted odds ratio for postnatal smoking by fathers (3.53) was only slightly reduced by adjusting for maternal smoking in pregnancy and other confounders (including sleep position). There were also independent effects of other smokers in the house with an adjusted odds ratio of 3.5 for all smokers in the household. There was a dose-response relationship with number of household smokers, number smoking in the same room as the infant, and an estimate of total cigarette exposure per day. For the latter measure, the odds ratio for >20 cigarettes/day was 22.7 (95% CI 4.8 to 107.2).

The New Zealand study by Mitchell *et al*[40] found an effect of paternal smoking (2.41) which, while reduced, remained significant after adjusting for maternal smoking and other confounders (1.37). There were significant effects of other smokers in the household and where there were three smokers or more the odds ratio was 5.72 (95% CI 3.90 to 8.39). However, there was no increased risk of SIDS (OR = 1.00) when the father was a smoker but the mother was reported not to be a smoker.

In England Blair *et al*[53] found an effect of paternal smoking (odds ratio 3.04) which, after controlling for confounders and maternal smoking, fell a little to 2.50. There was a dose response with the number of cigarettes smoked in the household, number of smokers in the household, and an estimate of the infant's daily exposure to tobacco smoke; if this was >8 hours the adjusted odds ratio was 8.30 (95% CI 4.28 to 16.05). When the mother was reported to be a non-smoker, paternal smoking was associated with an odds ratio of 3.41. Because of the small number of studies and given the disparity of results, no meta-analysis was undertaken.

Discussion

Among the 39 studies reviewed, the association between prenatal smoking and SIDS is consistently positive (one study excepted) and often quite strong (odds ratios of over 3). For those 36 studies with sufficient data to include in the meta-analysis, the pooled estimate for

the odds ratio was 2.77. For the 19 studies where adjustment for confounders was carried out the pooled odds ratio of 2.08 was markedly less but remained highly significant. It seems implausible that residual confounding could explain such an association. Not surprisingly there was clear evidence of heterogeneity between studies. Given the variety of different confounders adjusted for and the different constellation of risk factors likely to be operating in different countries, this is not surprising and does not negate the clear evidence of an effect in nearly all studies. In 17 of 19 studies the adjusted odds ratio remained individually significant after adjustment.

The association was not affected by whether case-control or cohort studies were employed. With an uncommon but important and registrable event such as SIDS, it is likely that samples included in case-control studies are very similar to those arising in population cohorts. Assessment of smoking exposure and confounders is a more important methodological issue. Because adverse effects of smoking in pregnancy are well known, prenatal smoking is probably under-reported even when obtained prospectively. This would tend to bias the odds ratios towards unity. However, it is notable that in the study of Mitchell *et al*[40] where prenatal smoking has been measured both prospectively (from records) and retrospectively (by interview), the resulting unadjusted and adjusted estimates of prenatal smoking effect were quite similar.

The association between prenatal smoking and SIDS displays many of the characteristics of a causal relationship including strength, exposure response gradient, consistency across various study designs, environments and investigators, and biological plausibility. It also exhibits a degree of specificity in relation to other causes of infant death; a meta-analysis of 25 studies of infant mortality found that only 11 showed a significant increase in risk and the pooled odds ratio of 1.23 was much lower than that for our estimate of over 2 for SIDS.[11] It is reduced but not explained by known confounders including low birthweight. An outstanding problem, however, is the possibility of confounding by postnatal smoking. Most women who smoke in pregnancy continue to do so postnatally which means that any independent effect of prenatal exposure is difficult to disentangle using epidemiological techniques.

In contrast, in studies with sufficient proportions of mothers who smoke postnatally but not prenatally, an effect of maternal postnatal smoking is still observed after controlling for prenatal smoking (and other confounders, including low birthweight).

The evidence based on smoking by the mother is therefore suggestive of an effect of environmental tobacco smoke independent of any intrauterine effect. Such an interpretation is supported by analyses of exposure of the infant to the cigarette smoke of others in the household, while controlling for the mother's smoking. These studies have found associations with the father's smoking and others smoking, together with dose-response relationships based on number of cigarettes smoked, number of persons in the household, and proximity to the infant. Some of the odds ratios for higher degrees of exposure are very high. These studies are relatively recent and control for known confounders such as sleeping position. Studies of infants whose mothers do not smoke at all are very important for investigating the effects of environmental tobacco smoke alone; two of the three studies which have done this found significant odds ratios for SIDS. To these can be added the finding of a recent study (not eligible for this meta-analysis) which found an odds ratio for only the father smoking of 1.72 (unadjusted) and 2.12 (after adjustment for a large number of other factors).[55] It would be valuable in future research for the non-smoking status of mothers to be objectively validated.

The early history of research into smoking and SIDS is dominated by the idea that smoking has an intrauterine effect. This was before passive smoking was even considered to be a respiratory hazard to children. While this focus on intrauterine effects remains, newer studies are trying to disentangle the separate effects of postnatal exposure.

We conclude that the epidemiological evidence points to a causal relationship between SIDS and postnatal exposure to tobacco smoke. A large part of the association with prenatal exposure is potentially explicable as a postnatal effect. Whether prenatal exposure has an effect independent of postnatal exposure (apart from through effects on birthweight) remains to be determined, but for public health purposes there is a clear indication that both prenatal and postnatal exposure should be avoided.

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1 Chief Medical Officer's Expert Group on the Sleeping Position of Infants and Cot Death. *The sleeping position of infants and cot death*. London: HMSO, 1993.
2 CESDI. *Confidential enquiry into stillbirths and deaths in infancy: 3rd annual report*. London: Department of Health, 1997.
3 Gibson AA. Current epidemiology of SIDS. *J Clin Pathol* 1992;**45**:7–10.
4 Fleming PJ. Understanding and preventing sudden infant death syndrome. *Curr Opin Pediatr* 1994;**6**:158–62.
5 Steele R, Langworth JT. The relationship of antenatal and postnatal factors to sudden unexpected death in infancy. *Can Med Assoc J* 1966;**94**:1165–71.
6 Milerad J, Sundell H. Nicotine exposure and the risk of SIDS. *Acta Paediatr* 1993;**82**(Suppl):70–2.
7 Toubas PL, Duke JC, McCaffree MA, Mattice CD, Bendell D, Orr WC. Effects of maternal smoking and caffeine habits on infantile apnea: a retrospective study. *Pediatrics* 1986;**78**:159–63.
8 Tager IB, Ngo L, Hanrahan JP. Maternal smoking during pregnancy. Effects on lung function during the first 18 months of life. *Am J Respir Crit Care Med* 1995;**152**: 977–83.
9 Strachan DP, Cook DG. Parental smoking and lower respiratory illness in infancy and early childhood. *Thorax* 1997;**52**:0000–0.
10 Di Benedetto G. Passive smoking in childhood. *J R Soc Health* 1995;**115**:13–6.
11 DiFranza JR, Lew RA. Effect of maternal cigarette smoking on pregnancy complications and sudden infant death syndrome. *J Family Pract* 1995;**40**:385–94.
12 Mitchell EA. Smoking: the next major and modifiable risk factor. In: Rognum TO, ed. *Sudden infant death syndrome*. Stockholm: Scandinavian University Press, 1995: 114–8.

13 Breslow N, Day NE. *Statistical methods in cancer research. Volume 1: The analysis of case-control studies*. Lyon, International Agency for Research on Cancer, 1980: 142.
14 Schrauzer GN, Rhead WJ, Saltzstein SL. Sudden infant death syndrome: plasma vitamin E levels and dietary factors. *Ann Clin Lab Sci* 1975;**5**:31–7.
15 Bergman AB, Wiesner LA. Relationship of passive cigarette-smoking to sudden infant death syndrome. *Pediatrics* 1976; **58**:665–8.
16 Naeye RL, Ladis B, Drage JS. Sudden infant death syndrome. A prospective study. *Am J Dis Child* 1976;**130**: 1207–10.
17 Lewak N, van den Berg BJ, Beckwith JB. Sudden infant death syndrome risk factors. Prospective data review. *Clin Pediatr* 1979;**18**:404–11.
18 Murphy JF, Newcombe RG, Sibert JR. The epidemiology of sudden infant death syndrome. *J Epidemiol Community Health* 1982;**36**:17–21.
19 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.
20 Rintahaka PJ, Hirvonen J. The epidemiology of sudden infant death syndrome in Finland in 1969–1980. *Forensic Sci Int* 1986;**30**:219–33.
21 Cameron MA. Development and testing of scoring systems for predicting infants with high-risks of sudden infant death syndrome in Melbourne. *Aust Paediatr J* 1986; Suppl:37–45.
22 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.
23 Hoffman HJ, Damus K, Hillman L, Krongrad E. Risk factors for SIDS. Results of the National Institute of Child Health and Human Development SIDS Cooperative Epidemiological Study. *Ann NY Acad Sci* 1988;**533**:13–30.
24 Malloy MH, Hoffman HJ, Peterson DR. Sudden infant death syndrome and maternal smoking. *Am J Public Health* 1992;**82**:1380–2.
25 McLoughlin A. Sudden infant deaths in Tameside. *Health Visitor* 1988;**61**:235–7.
26 McGlashan ND. Sudden infant deaths in Tasmania, 1980–1986: a seven year prospective study. *Social Sci Med* 1989; **29**:1015–26.
27 Kraus JF, Greenland S, Bulterys M. Risk factors for sudden infant death syndrome in the US Collaborative Perinatal Project. *Int J Epidemiol* 1989;**18**:113–20.
28 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.
29 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.
30 Bulterys M. Passive tobacco exposure and sudden infant death syndrome. *Pediatrics* 1993;**92**:505–6.
31 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.
32 Gilbert RE, Fleming PJ, Azaz Y, Rudd PT. Signs of illness preceding sudden unexpected death in infants. *BMJ* 1990; **300**:1237–9.
33 Li DK, Daling JR. Maternal smoking, low birth weight, and ethnicity in relation to sudden infant death syndrome. *Am J Epidemiol* 1991;**134**:958–64.
34 Nilsen ST, Laerdal A. Crib death and smoking during pregnancy. *Tidsskr Nor Laegeforen* 1991;**111**:3493–5.
35 Engleberts AC. *Cot death in the Netherlands: an epidemiological study.* Amsterdam: VU University Press, 1991.
36 Malloy MH, Kleinman JC, Land GH, Schramm WF. The association of maternal smoking with age and cause of infant death. *Am J Epidemiol* 1988;**128**:46–55.
37 Schoendorf KC, Kiely JL. Relationship of sudden infant death syndrome to maternal smoking during and after pregnancy (see comments). *Pediatrics* 1992;**90**:905–8.
38 Nicholl J, O'Cathain A. Antenatal smoking, postnatal passive smoking, and the sudden infant death syndrome. In: Poswillo D, Alberman E, eds. *Effects of smoking on the fetus, neonate and child*. Oxford: Oxford University Press, 1992: 138–49.
39 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**:S3–8.
40 Mitchell EA, Ford RP, Stewart AW, Taylor BJ, Becroft DMO, Thompson JMD, *et al.* Smoking and the sudden infant death syndrome. *Pediatrics* 1993;**91**:893–6.
41 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.
42 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.
43 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.
44 Hilder AS. Ethnic differences in the sudden infant death syndrome: what we can learn from immigrants to the UK. *Early Human Dev* 1994;**38**:143–9.
45 Jorch G, SchmidtTroschke 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.
46 Ponsonby AL, Dwyer T, Kasl SV, Cochrane JA. The Tasmanian SIDS case-control study: univariable and multivariable risk factor analysis. *Paediatr Perinatal Epidemiol* 1995;**9**:256–72.
47 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.
48 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.
49 Schlaud M, Kleemann WJ, Poets CF, Sens B. Smoking during pregnancy and poor antenatal care: two major preventable risk factors for sudden infant death syndrome. *Int J Epidemiol* 1996;**25**:959–65.
50 Taylor JA, Sanderson M. A reexamination of the risk factors for the sudden infant death syndrome. *J Pediatr* 1995; **126**:887–91.
51 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.
52 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.
53 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 confidential inquiry into stillbirths and deaths in infancy. Confidential Enquiry into Stillbirths and Deaths Regional Coordinators and Researchers. *BMJ* 1996;**313**:195–8.
54 Taylor JA, Krieger JW, Reay DT, Davis RL, Harruff 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.
55 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.