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.

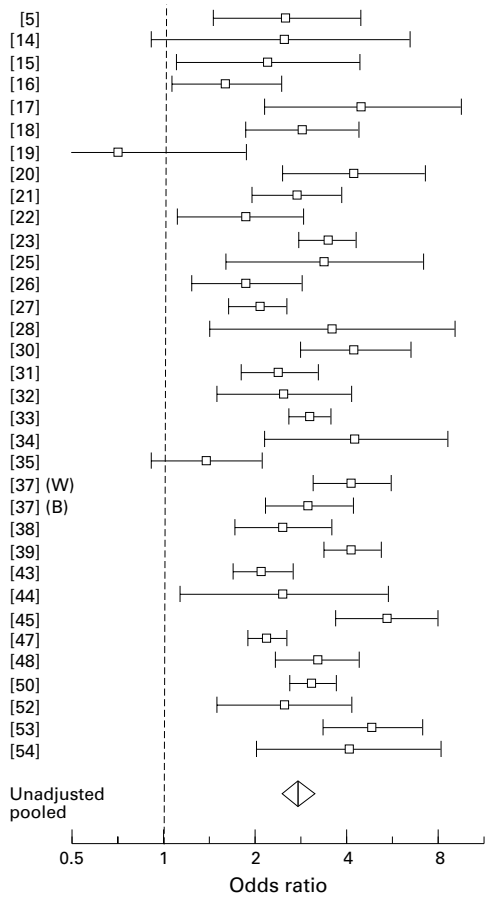

Figure 1 Individual and pooled odds ratios (with 95% confidence interval) for SIDS associated with maternal prenatal smoking ordered by date of publication.

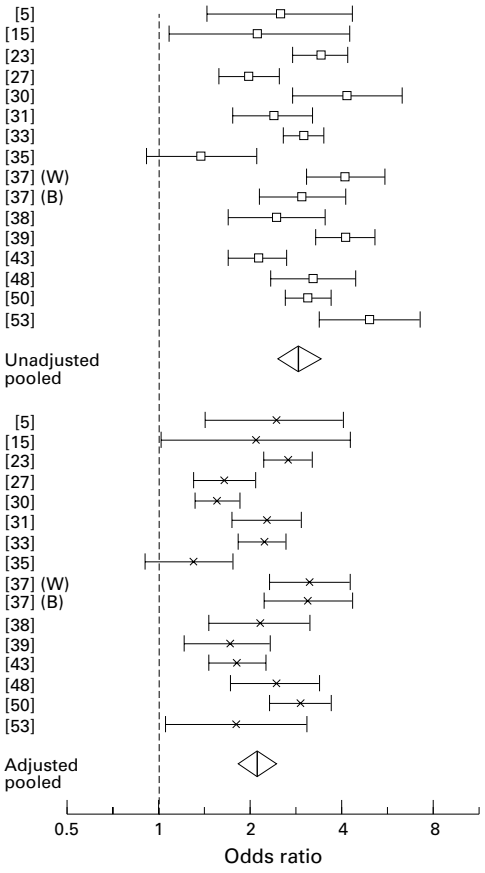

Figure 2 Individual and pooled odds ratios (with 95% confidence intervals) for SIDS in studies with information on adjustment for confounders ordered by date of publication. □ = unadjusted; × = adjusted.

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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Health effects of passive smoking • 10

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Summary of effects of parental smoking on the respiratory health of children and implications for research

Derek G Cook, David P Strachan

Abstract

***Background*—Two recent reviews have assessed the effect of parental smoking on respiratory disease in children.**

***Methods*—The results of the systematic quantitative review published as a series in *Thorax* are summarised and brought up to date by considering papers appearing on Embase or Medline up to June 1998. The findings are compared with those of the review published recently by the Californian Environmental Protection Agency (EPA). Areas requiring further research are identified.**

***Results*—Overall there is a very consistent picture with odds ratios for respiratory illnesses and symptoms and middle ear disease of between 1.2 and 1.6 for either parent smoking, the odds usually being higher in pre-school than in school aged children. For sudden infant death syndrome the odds ratio for maternal smoking is about 2. Significant effects from paternal smoking suggest a role for postnatal exposure to environmental tobacco smoke. Recent publications do not lead us to alter the conclusions of our earlier reviews. While essentially narrative rather than systematic and quantitative, the findings of the Californian EPA review are broadly similar. In addition they have reviewed studies of the effects of environmental tobacco smoke on children with cystic fibrosis and conclude from the limited evidence that there is a strong case for a relationship between parental smoking and admissions to hospital. They also review data from adults of the effects of acute exposure to environmental tobacco smoke under laboratory conditions which suggest acute effects on spirometric parameters rather than on bronchial hyperresponsiveness. It seems likely that such effects are also present in children.**

***Conclusions*—Substantial benefits to children would arise if parents stopped smoking after birth, even if the mother smoked during pregnancy. Policies need to be developed which reduce smoking amongst parents and protect infants and young children from exposure to environmental tobacco smoke. The weight of evidence is such that new prevalence studies are no longer justified. What are needed are studies which allow comparison of the effects of critical periods of exposure to cigarette smoke, particularly in utero, early infancy, and later childhood. Where longitudinal studies are carried out they should be analysed to look at the way in which changes in exposure are related to changes in outcome. Better still would be studies demonstrating reversibility of adverse effects, especially in asthmatic subjects or children with cystic fibrosis.**

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Keywords: parental smoking; passive smoking; children

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In our series of papers in *Thorax* we have presented a systematic and quantitative review of the health effects of passive smoking on children's respiratory health including middle ear disease and sudden infant death syndrome.[1–8] In this paper we (1) summarise the findings of these reviews; (2) comment on papers published since then; (3) compare the findings with a review published by the Californian Environmental Protection Agency (EPA)[9]; (4) discuss the advantages and disadvantages of our systematic quantitative approach; (5) discuss possible mechanisms that might explain the epidemiological findings; (6) identify what further research is needed; and (7) consider the public health issues raised.

Summary of findings from *Thorax* reviews

Tables 1 and 2 summarise the findings of the *Thorax* series. Overall there is a very consistent picture with odds ratios for respiratory illnesses and symptoms and middle ear disease of between 1.2 and 1.6 for either parent smoking, the odds usually being higher in pre-school than school aged children and higher for maternal smoking than for paternal smoking. However, for lower respiratory illness in infancy and for wheeze and cough in schoolchildren the effect of paternal smoking in households where the mother did not smoke

Table 1 Summary of effects of parental smoking on the respiratory health of children

Outcome	*Either parent OR (95% CI)*	*Mother OR (95% CI)*	*Father only OR (95% CI)*	*Both parents OR (95% CI)*
Lower respiratory illnesses (LRI) at age 0–2				
All studies	1.57 (1.42 to 1.74) [27]	1.72 (1.55 to 1.91) [27]	1.29 (1.16 to 1.44) [16]	
Community studies of wheeze	1.55 (1.16 to 2.08) [5]	2.08 (1.59 to 2.71) [7]		
Community studies of LRI, bronchitis and/or pneumonia	1.54 (1.31 to 1.80) [11]	1.57 (1.33 to 1.86) [7]		
Hospital admission for LRI, bronchitis, bronchiolitis or pneumonia	1.71 (1.21 to 2.40) [8]	1.53 (1.25 to 1.86) [9]	1.32 (0.87 to 2.00) [6]	
Prevalence rates at age 5–16				
Wheeze	1.24 (1.17 to 1.31) [30]	1.28 (1.19 to 1.38) [18]	1.14 (1.06 to 1.23) [10]	1.47 (1.14 to 1.90) [11]
Cough	1.40 (1.27 to 1.53) [30]	1.40 (1.20 to 1.64) [14]	1.21 (1.09 to 1.34) [9]	1.67 (1.48 to 1.89) [16]
Phlegm	1.35 (1.13 to 1.62) [6]			1.46 (1.04 to 2.05) [5]
Breathlessness	1.31 (1.08 to 1.59) [6]			
Asthma (cross sectional studies)	1.21 (1.10 to 1.34) [21]	1.36 (1.20 to 1.55) [11]	1.07 (0.92 to 1.24) [9]	1.50 (1.29 to 1.73) [8]
Asthma (case-control studies)	1.37 (1.15 to 1.64) [14]			
Bronchial reactivity		1.29‡ (1.10 to 1.50) [10]		
Skin prick positivity		0.87* (0.64 to 1.24) [8]		
Incidence of asthma				
Under age 6		1.31† (1.22 to 1.41) [4]		
Over age 6		1.13† (1.04 to 1.22) [4]		
Middle ear disease				
Acute otitis media	Range 1.0 to 1.6 [8]			
Recurrent otitis media	1.48 (1.08 to 2.04) [7]			
Middle ear effusion	1.38† (1.23 to 1.55) [4]			
Referral for glue ear	1.21† (0.95 to 1.53) [7]			
Sudden infant death¶		2.13 (1.86 to 2.43) [18]		

*Results relate to maternal smoking during pregnancy or exposure to environmental tobacco smoke (ETS) in infancy. Data for ETS exposure during later childhood are too heterogeneous for meta-analysis.
†Based on fixed effects estimate.
‡Relates largely, but not entirely to maternal smoking.
¶Estimate and confidence limits differ from those in reference 2 due to exclusion of the study by Bulterys *et al* (see Erratum at end of this paper).
Numbers in square brackets are numbers of studies on which pooled odds ratios based.
Source of data: references 1–7.

Table 2 Summary of pooled percentage difference (95% confidence intervals) for effect of parental smoking on lung function

	No. of studies	*% difference (95% CI) fixed effect*	*% difference (95% CI) random effect*
FVC	19	–0.2 (–0.4 to +0.1)	–0.4 (–0.8 to +0.0)
FEV_1	21	–0.9 (–1.2 to –0.7)	–1.4 (–1.9 to –1.0)
MEF	19	–4.8 (–5.4 to –4.3)	–5.0 (–6.6 to –3.3)
EEF	9	–4.3 (–5.3 to –3.3)	–4.3 (–5.5 to –3.1)

FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; MEF = mid expiratory flow rate; EEF = end expiratory flow rate.
Source: reference 8.

was statistically significant. This latter observation suggests that much of the observed association with maternal smoking is probably due to postnatal rather than prenatal (intrauterine) exposure. Because smoking by the mother during pregnancy is almost invariably associated with postnatal smoking, any additional influence of prenatal maternal smoking will be difficult to resolve using epidemiological studies. Except for sudden infant death syndrome (SIDS), the risks associated with parental smoking were largely independent of measured confounding variables, which suggests that residual confounding by unmeasured factors is unlikely to be important.

In June 1998 we re-ran our original search strategy to identify publications since April 1997; this identified 29 articles containing data not included in the original reviews. These are commented on separately in the relevant sections, but the quantitative meta-analyses have not been updated.

Below we summarise the papers published since our original reviews and consider whether any changes in our conclusions are warranted.

LOWER RESPIRATORY ILLNESSES IN INFANCY AND EARLY CHILDHOOD

Two studies published recently from North Carolina, USA,[10] and Norway[11] are broadly consistent with our conclusions, although in one[11] the dose-response gradient was more convincing for smoking by the father than for maternal smoking.

PREVALENCE OF ASTHMA AND RESPIRATORY SYMPTOMS IN SCHOOL AGED CHILDREN

Previously[3] we concluded that there was convincing evidence that parental smoking is associated with increased prevalence of asthma and respiratory symptoms in schoolchildren. Among children with established asthma, parental smoking was associated with more severe disease. A number of cross-sectional studies have been published since our original review, all broadly supporting our conclusions.[12–16] In a methodological study which compared parental reports of nocturnal cough with overnight recording, smoking parents were found to substantially under-report compared with non-smoking parents, resulting in underestimation of the odds ratio relating cough to exposure to environmental tobacco smoke (ETS).[17]

Few studies published before 1997 provided the information required to compare critical periods of exposure or the effects of smoking by the mother during or after pregnancy. On balance, our earlier review suggested that the prevalence of respiratory symptoms in schoolchildren is related more closely to current maternal smoking than to past smoking by the mother, but the retrospective nature of the early exposure data did not allow firm conclusions to be drawn.

More recently three studies have been published comparing current with past expo-

sure, with inconsistent findings. A study of 1129 Polish children found upper and lower respiratory infections were related more strongly to current exposure to ETS than to maternal smoking during pregnancy.[18] A second study of 705 fifth grade children in Chicago found that maternal smoking in pregnancy was more strongly related to doctor diagnosed asthma than current maternal smoking.[19] However, it is worth noting that wheezing was *inversely* associated with current maternal smoking in this study. Consistent with the Chicago study, a large Scandinavian survey of 15 962 children aged 6–12 years in the past year reported that asthma attacks, dry cough and asthma treatment were inversely associated with current smoking in the home but positively associated with smoking in the home in the first two years of life.[20] Again the lack of an association with current exposure is in contrast to the rest of the literature, and the authors suggest that avoidance of risk factors by parents of symptomatic children is likely to be important. Further studies are needed to clarify this potentially important issue.

INCIDENCE OF ASTHMA AND WHEEZING ILLNESSES

The relationship between common lower respiratory illnesses of infancy and asthma in later childhood remains a subject of uncertainty and debate. For this reason we analysed early wheezing illnesses (during the first one or two years of life) separately from the incidence of asthma over a longer period or later in childhood.

Taken together, the evidence suggests that parental smoking is more influential as a cause of early "wheezy bronchitis" than of later onset "asthma".[1] No new references were identified which further informed this issue. However, one recently published paper[21] suggests that Norwegian teenagers with asthmatic symptoms are less likely to receive a diagnosis of asthma if their parents smoke. This finding may not be generalisable to other countries and cultures, but it raises the possibility that the association of ETS with asthma may have been underestimated in studies which rely on physician diagnosis.

NATURAL HISTORY AND SEVERITY OF ASTHMA AND WHEEZING

In our original review we found an inconsistent picture relating ETS exposure to prognosis.[6] Early prognosis appeared to be worse if parents smoked, whereas persistence of symptoms into the teens and twenties was less common in children of smokers. A recently published follow up study of 101 wheezy Swedish infants[22] is intermediate between these two groups of studies. The presence of asthma at age 10 was more common in children exposed to household smoking in infancy (82% versus 59%) although it was not associated with household smoking at age 10 (54% versus 52%), perhaps reflecting changes in parental behaviour associated with persistence of the child's asthma.

The results of 10 case series addressing asthma severity were more consistent with symptom scores, attack frequency, medication use, admissions to hospital, and life threatening attacks being generally positively related to ETS exposure.[6] No new references were identified to change this conclusion.

ALLERGIC SENSITISATION

In contrast to previous reviews, we concluded that the balance of evidence did not support a positive association of allergic sensitisation with parental smoking, either before or after birth.[5] One reason for this discrepancy is that many reviews included asthma and wheezing which may be related to exposure to ETS by mechanisms other than allergy. We chose to review 36 studies of IgE, skin prick positivity, hay fever, or eczema separately from studies of asthma in order to address more directly the influence of exposure to ETS on allergic sensitisation. There was only limited scope here for meta-analysis, with inconsistency in the quantitative results.

Four more recent publications have contributed information in relation to eczema. Three of these, from Denmark, Britain and Hong Kong, show a slightly reduced risk among the offspring of smokers,[13 23 24] and a fourth from Germany[25] found an increased risk cross sectionally which was not sustained on follow up. A British study of skin prick tests among infants of atopic parents[26] reported an inverse association of prick positivity with maternal smoking while a Swedish study also reported a weak inverse association between prick positivity and maternal smoking.[14] These results are consistent with a significantly reduced prevalence of hay fever among the children of smokers in two national British birth cohorts,[24] but not with the slightly raised risk of hay fever in the survey from Hong Kong.[13] These additional publications do not lead us to alter the conclusion of our earlier review.

BRONCHIAL REACTIVITY

Our meta-analysis of the relationship between bronchial reactivity (BHR), as assessed by challenge tests, and exposure to ETS (largely maternal smoking) in 10 population samples suggests a small but real increase in BHR amongst the children of smoking mothers (OR 1.29, 95% CI 1.10 to 1.50).[7] However, it seems likely that this estimate is biased upwards since other studies providing p values but not odds ratios appear to be generally negative, while four studies have collected data but have not been published. The published data relating ETS exposure to bronchial reactivity are therefore not definitive; 60% of all potentially relevant data relating to the issue are either not published or are in papers providing no effect measures. Our literature update identified only one small study of 182 Italian children but no data were presented relating ETS to BHR.[27] The current uncertainty could be resolved by pooling data from all these studies to provide an unbiased estimate of the association.

SPIROMETRIC INDICES

In our earlier review we concluded that maternal smoking is associated with small but statis-

tically significant deficits in forced expiratory volume in one second (FEV_1) and other spirometric indices in school aged children (table 2).[8] This is almost certainly a causal relationship. Much of the effect may be due to maternal smoking during pregnancy which appears to have rather larger effects on neonatal lung mechanics, with the small effects seen in school aged children being attributable to the residual effects of smoking in pregnancy. The effect of the latter is reinforced by a recent Norwegian study of 803 infants in whom tidal flow-volume loops, compliance and resistance were measured 2.7 days after birth.[28] However, the magnitude of effects seems rather smaller in this study than in the earlier studies.

In addition, it is likely that susceptible individuals will experience acute reductions in FEV_1 and peak expiratory flow (PEF) when exposed to ETS.[7] Further work is needed to establish this. It seems likely that the small differences in lung function in children associated with maternal smoking will translate into small differences in adults. Such subtle reductions are unlikely to impact on rates of development of chronic airflow obstruction unless evidence emerges that children exposed to cigarette smoke in early life have faster rates of lung function decline in adult life. In a recent meta-analysis of cross sectional adult data we found a 2.6% deficit in FEV_1 in non-smoking adults exposed to ETS, very similar to the effect reported in children.[29]

Further evidence that exposure to ETS may have some effects on lung function comes from cohort studies. Of the six cohort studies, the Six Cities Study is an order of magnitude larger than any other cohort and thus deserves substantial weight. It reported very small but statistically significant effects of maternal smoking on lung growth (–3.8 ml/year for FEV_1).

To determine whether effects are reversible also requires evidence from cohort rather than cross sectional studies. Unfortunately none of the longitudinal studies have looked at changes in lung function in relation to changes in exposure. It would be an advantage if such studies assessed exposure by measuring cotinine levels. This would take account of changes in exposure to ETS which occur as children grow older and spend less time with their parents resulting in a reduction in their exposure to ETS even though parental smoking habits remain constant. Sources of ETS outside the home may become important, particularly during teenage years.

SUDDEN INFANT DEATH SYNDROME (SIDS)

Unlike other areas, adjustment for confounding variables was important when looking at SIDS.[2] However, an adjusted odds ratio of 2 is difficult to attribute to residual confounding and convincing evidence of dose-response provide further evidence for a causal relationship. Our conclusions differed from most previous reviews in focusing on the relative importance of maternal smoking during pregnancy rather than postnatal exposure to ETS as an explanation for the raised risks. Based on the limited available evidence where mothers claimed to be non-smokers, we concluded that postnatal exposure plays an important role. Recent studies support our interpretation (see below), though none have yet used measurements of cotinine levels to validate maternal non-smoking status.

Four recently published studies (three case-control[30–32] and one nested case-control[33]) containing new data provide further confirmation of the effects of maternal smoking on SIDS. The Munster study provides clear evidence of a dose-response in relation to maternal smoking during pregnancy and of the importance of controlling for confounding variables[31] while the Nordic SIDS study reported only unadjusted odds ratios for maternal smoking in pregnancy.[30] Further data from the New Zealand nested case-control study after their national campaign to prevent SIDS reported a univariate odds ratio for paternal smoking where the mother was a non-smoker of 1.54 (95% CI 0.67 to 3.45)[33] while a Scottish study reported a multivariate odds ratio for father only smoking of 2.12 (95% CI 0.99 to 4.55).[32] A fifth paper re-analysing data from the US and Sweden presents clear evidence that the odds ratio for maternal smoking is little affected by adjustment for birth weight.[34]

MIDDLE EAR DISEASE

Studies of middle ear disease were of various designs including cohort studies, case-control studies, and population surveys. They were reviewed in four groups: 13 studies of acute otitis media, nine of recurrent otitis media, five of middle ear effusion, and nine of glue ear surgery.[4] A meta-analysis was possible for all outcomes except acute otitis media, and the results were consistent with pooled odds ratios in the range 1.2–1.5 (table 1).

Four more recently published case-control studies from Canada,[35] Sweden,[36] Malaysia,[37] and Minnesota, USA[38] present quantitative data for acute or chronic otitis media in relation to parental smoking. The 95% confidence intervals for the odds ratios overlap with the pooled values derived in our meta-analyses. A detailed longitudinal study of 2253 infants in Pennsylvania, USA[39] assessed the presence of middle ear effusion clinically and by tympanometry at monthly intervals throughout the first two years of life. There was a highly significant positive association between the duration of effusion and the number of smokers in the household during both the first and second years of life. Although these results cannot be compared directly with odds ratios derived in other studies, they are qualitatively consistent with our earlier meta-analyses.

Comparison with Californian EPA review

Table 3 contrasts the methods used in our *Thorax* reviews and those of the Californian Environmental Protection Agency[9 40] and table 4 summarises the conclusions of the Californian review. Despite the different approach the conclusions are qualitatively and, from a public health perspective, very similar. The main

Table 3 Comparison of methods used in Thorax series and Californian EPA reviews

	Thorax series	*Californian EPA*
General approach	Systematic search of the literature	Update of previous EPA review
Scope	Children only Respiratory (including SIDS but not CF)	All ages All systems (including SIDS, respiratory and CF)
Inclusions and exclusions	Emphasis on groups of similar studies	Inclusion of all, even isolated studies
Disease definition	Specific outcomes distinguished	Broader groups of diseases
Community versus hospital	Distinguished where possible	Usually combined
Maternal and paternal smoking	Distinguished where possible	Rarely analysed separately
Prenatal and postnatal exposure	Rarely possible to distinguish	Rarely possible to distinguish
Confounding	Addressed in meta-analysis where possible	Discussed in text
Publication bias	Discussed and evaluated where possible	Not discussed
Summarisation	Emphasis on meta-analysis, less narrative	More narrative, selective use of meta-analysis*
Causal inference	Discussed	Discussed
Population attributable risk estimates	Not attempted	Included for USA and California
Experimental (chamber) studies	Very limited evidence in children	Limited evidence, mainly in adults
Mechanisms	Not discussed	Discussed

SIDS = sudden infant death syndrome; CF = cystic fibrosis.
*Only used for asthma induction, including early wheezing illnesses.

differences are a difference in interpretation of the inconsistent data on allergic sensitisation (we hold by our view that allergic sensitisation is not related to in utero or ETS exposure) and greater emphasis in the Californian review on the relationship between exposure to ETS and the incidence of asthma. This arises because the Californian review includes prevalence studies in its assessment of incidence, and also because there is no clear distinction between the incidence of lower respiratory infections and wheezing illness in infancy and the development of later onset asthma.

CYSTIC FIBROSIS

We did not evaluate the effects of ETS on children with cystic fibrosis in our *Thorax* series because there were insufficient studies for a quantitative review. However, the Californian EPA review[9] summarises five studies relating the severity of cystic fibrosis to parental smoking.[41–44] Over half of the children in these studies were exposed to ETS. Hospital admissions for cystic fibrosis exacerbations were significantly related to parental smoking in three of the four studies which reported this association, and in the same three studies exposure to ETS was significantly related to other measures of disease severity. The studies are inconsistent or inconclusive in relation to the effects of parental smoking on growth and ventilatory function.

Value of a systematic quantitative approach

At the end of this series it is worth considering the value of the approach we took to reviewing the evidence. Meta-analyses of observational studies raise a number of difficulties compared with randomised controlled trials.[45] Indeed, some have argued that "the meta-analysis of published non-experimental data should be abandoned".[46] Shapiro argues that meta-analysis is popular because it offers the Holy Grail of attaining statistically stable estimates for effects of low magnitude. This is dangerous, he argues, because, where many studies produce only modest increases in risk, those increases may be due to the same biases in all the studies. In our own case only the twofold increase in the risk of SIDS and possibly lower respiratory infection in infancy are large enough to make confounding unlikely when the relative risk is considered in isolation. However, the approach we adopted of comparing unadjusted and adjusted relative risks in each study permits a more comprehensive evaluation of confounding effects. Although this does not address the possibility of a bias common to all studies, the latter is unlikely if there is consistency of evidence from studies of different design and locations. While such dangers exist, it would seem even more dangerous to rely on a single large study or on narrative reviews. In our view the presentation of all studies on a single graph is an extremely valuable summary of the evidence, even where heterogeneity in effects is so large as to render meta-analysis irrelevant. It is a separate argument to decide whether residual confounding in all studies may explain the findings. Undoubtedly the definitive demonstration of

Table 4 Summary of results and conclusions of Californian EPA review

Outcome	*Odds ratios*	*Conclusions*
Lower respiratory disease in young children	1.5–2	ETS exposure clearly confers an increased risk of acute lower respiratory disease in young children
Asthma "induction"*	1.75–2.25 in summary (n = 37), RR = 1.45 for household exposure, RR = 1.6 for maternal smoking	Compelling evidence of an effect
Asthma exacerbation	Narrative	Disease severity increased by ETS
Respiratory symptoms in children	Narrative	Associated with parental smoking
Lung growth and development	Narrative	Evidence not wholly consistent but suggestive of small effects
Atopy	Narrative	Several studies have shown an increased risk of atopy in children of smoking mothers, though the evidence regarding this issue is mixed
Middle ear infection	Narrative; OR = 1.62	Risk of both acute and chronic middle ear infection increased
Sudden infant death	Narrative	Adequate epidemiological evidence of a causal relationship between maternal smoking and SIDS. Compelling evidence that postnatal ETS exposure is an independent risk factor

ETS = environmental tobacco smoke; SIDS = sudden infant death syndrome.
*Some of the studies included are cross sectional studies of asthma prevalence and thus the conclusion of an effect applies in part to prevalence, not to incidence. Difficult to understand why summary differs from text—in particular from meta-analysis.

Table 5 Mechanisms proposed for respiratory effects of passive smoking

	Effect	*Disease outcomes affected*
Acute	Sensory stimulation	Acute eye/nose irritation Bronchospasm
	Mucosal oedema	Middle ear effusion (Allergic sensitisation)
	Decreased mucociliary clearance	Middle ear effusion Chronic cough and phlegm Lower respiratory infection (leading to other outcomes)
	Goblet cell hypertrophy or hypersecretion	Chronic cough and phlegm Nasal discharge
	Adenoidal hyperplasia	Middle ear effusion Adenotonsillectomy
	Increased risk/severity of respiratory infection (mechanism uncertain)	Early LRTI Exacerbations of asthma Middle ear effusion
	Bronchial inflammation	Bronchial hyperreactivity Spirometric indices
	Postnatal lung development	Spirometric indices Early LRTI (?esp wheezing) ?Bronchial hyperreactivity
Chronic	Prenatal growth*	Spirometric indices

LRTI = lower respiratory tract infection.
*Due to in utero exposure to maternal smoking.

cause and effect requires randomised trials, a point we pick up below.

In our view the major advantage of a systematic quantitative approach is that it has produced a useful corrective to a narrative approach which gives undue weight to highly valued and well published studies. This was particularly valuable in assessing the effect of maternal smoking on allergy. The major disadvantages were the large amount of work needed to extract comparable data and the need to reduce analysis to lowest common denominators. Here the main issue was the variety of ways in which exposure was assessed. Nevertheless, it was possible in most instances to compare maternal with paternal/other household smoking and to gain some insight into dose-response. The effect of adjustment for confounding variables was unimportant except for outcomes other than SIDS. Given the variety of confounders adjusted for and methods of adjustment used, this was fortunate.

Whenever systematic reviews of trials are carried out the quality of studies should be assessed and the sensitivity to inclusion of poor studies investigated. In our reviews the lack of easily agreeable criteria meant we included all studies where possible. For example, response rates were often lowest in some of the "best" studies because they were longitudinal. Equally it was often difficult to extract necessary information from some of the most influential studies, particularly those published early on. Fortunately the consistency of the evidence meant that estimates of effect were little altered by exclusion of specific studies.

It is important not to give undue emphasis to point estimates without considering the consistency and heterogeneity of results lying behind them. For this reason we believe that the figures presenting all studies as well as pooled estimates should be available. This allows distinction of lack of a consistent pattern from statistical heterogeneity where a consistent direction of effect is seen. In our reviews a consistent pattern was seen except for allergic sensitisation. In most instances fixed and random effects estimates were very similar, usually with random slightly greater, while confidence limits for random effects were wider. This reflects the greater emphasis placed on smaller studies by a random effects approach. It is therefore more susceptible to publication bias. In practice, although we were able to detect publication bias for respiratory symptoms and for effects on FEV_1 (in both instances small studies tended to show larger effects), the overall picture and estimates were little altered by excluding small studies.[3 8]

Mechanisms

Evidence relating to mechanisms could potentially assist in interpretation of the epidemiological data we have reviewed. Table 5 summarises the potential mechanisms whereby maternal smoking during pregnancy or exposure to ETS postnatally might influence respiratory disease in children. However, while most of these mechanisms are plausible, remarkably little evidence exists to confirm or refute them.[9]

The most direct evidence on mechanisms is from acute effects on upper respiratory mucosa[9] but, apart from middle ear effusion, this is least relevant to the outcomes we have considered. The most convincing epidemiological evidence relates to early lower respiratory infection in relation to postnatal exposure, yet we are lacking insights into how ETS increases the severity of these early (largely viral) infections.

An early hypothesis was that smoking parents, being more susceptible to respiratory infections themselves, might then transmit them to their children. Thus Colley in two early papers on parental smoking and respiratory symptoms looked at the effect of adjusting for parental phlegm production.[47 48] While adjustment did not adequately explain the higher prevalence rates in children of smoking parents, this hypothesis deserves further consideration in relation to viral infections.

Studies in children which have assessed the effects of acute exposure to ETS in controlled situations are very limited, but there are weak suggestions of acute effects of ETS exposure on lung function.[7] The more extensive evidence in adults has recently been reviewed.[9 49] Coultas[49] reported that "most of the ETS inhalation chamber studies show slight to moderate transient effects on lung function in at least some of the study subjects. In several studies participants experienced decrements in lung function exceeding 20%." Such acute effects might well explain the greater peak flow variability in children of smoking parents.[7] Further studies to confirm these findings in children seem warranted.

The limited evidence relating ETS to bronchial inflammation and airway development is only by extrapolation from active smokers or from sidestream exposure of laboratory animals. Our review has effectively excluded allergic sensitisation as a link between ETS and asthma and casts some doubt on the BHR route. Evidence of acute effects on BHR in chamber studies in adults is limited and not consistent.[9]

Outstanding research issues

While the accumulated evidence for adverse effects of parental smoking on the respiratory health of children is very strong, it is based almost entirely on observational studies. There is no clear demonstration of the effect of reducing exposure. Such studies are needed, either in the form of randomised controlled trials or as observational studies focusing on parents who change their smoking habit.

While randomised controlled trials are the ideal, they would need to be large. Consider a study in which it was proposed to reduce smoking in parents of children with middle ear effusion with the outcome of interest being operative treatment. Middle ear effusion commonly resolves in about one third of cases between outpatient referral and operative treatment some 3–6 months later. We might expect perhaps 10% of parents to stop smoking with usual care and might hope to double this to 20% in the intervention group. Assuming one third of cases resolved spontaneously in children of smokers and an optimistic one half in children of those who quit smoking, we would need to randomise 33 500 children overall (16 750 to each group) to have 90% power at the 0.05 significance level. This is because the majority of parents in each group continue to smoke. The difference in outcome between the intervention and usual care groups is therefore small and the trial needs to be large to detect such a difference. Such considerations explain why there have been so few trials and those that have been carried out have been negative when analysed on an intention to treat basis.

It seems unlikely that many randomised controlled trials will take place. Nevertheless, observational studies looking at changes in health outcome in relation to changes in exposure would be valuable. For example, it would be possible to compare the outcomes in the children of the usual care group comparing the 90% whose parents continued to smoke with the children of the 10% whose parents quit. For such an analysis a sample of only 1000 would suffice.

Further cross sectional studies of lung function or symptoms are unlikely to be informative unless they can compare critical periods of exposure or look at changes in parental smoking—for example, school age versus exposure during pregnancy or early infancy for symptoms, or prenatal versus postnatal exposure for SIDS.

Future studies need to give thought to the assessment of exposure. Key issues are distinguishing between maternal and paternal smoking and looking for dose-response. Objective measures such as cotinine levels are important since actual exposure will vary between individuals and tend to decrease with age despite parental smoking habits being constant. It is also important to consider whether children from non-smoking families are a suitable group to treat as non-exposed. Any background exposure in this group which has an effect on respiratory disease will bias any comparisons between smoking and non-smoking families towards the null hypothesis of no difference. Measurement of cotinine levels will help here. The limited evidence available is not entirely consistent. Studies in British children suggest that the low levels of exposure seen in non-smoking households[50] do not influence either lung function or respiratory symptoms.[51 52] In contrast, an Italian study has reported effects on lung function in children with occasional exposure to ETS.[53] However, the cotinine levels reported in this study are extremely high, even for children from non-smoking households.

Further studies distinguishing current versus cumulative versus early (particularly in utero) exposure in relation to symptoms and lung function would help to elucidate the mechanism and inform preventive measures. While maternal smoking is the most important source of exposure in many countries, it would be valuable to see further large studies measuring dose where mothers are confirmed non-smokers. The studies from China[54–57] have been particularly useful in this context. In the case-control studies of SIDS it would be important to confirm non-smoking status of mothers at interview by measurement of salivary cotinine levels. Such an approach would remove worries about reporting bias.

There is undoubtedly a need to clarify the association between exposure to ETS and BHR—here the solution would be to pool data from all studies published and unpublished. Equally, with only four published studies of peak flow variability there is undoubtedly room for publication bias. However, if there is an acute effect on lung function from ETS exposure in at least a significant minority of subjects this will be better shown by laboratory studies of acute exposure.

Finally, it would be useful to have larger and more comprehensive studies of children with cystic fibrosis. In particular, there is a need for studies of prognosis and severity.

The magnitude of the problem: attributable risks

Throughout our review series we focused on odds ratios as measures of effect since these are what studies provide and they are portable in that studies from different countries produce similar estimates. However, it is important to consider the potential size of the public health problem in any given country and the difference in absolute terms of the different health effects should be recognised. Previous reports have done this for the USA[58] and for California.[9] Such analyses involve a number of assumptions which may be split into two stages. At the first stage the percentage of cases in a population attributable to an exposure (PAR%) can be derived from knowledge of the relative risk (RR) and the proportion of subjects exposed in a population (p):

$$\text{PAR\%} = \frac{p(RR-1)\times 100}{1 + p(RR-1)}$$

The PAR% for a range of relative risks and exposure prevalence rates is given in table 6.

Table 6 Population attributable risk percentages for a range of relative risks and exposure prevalence rates

Relative risk	Prevalence of smoking exposure						
	0.2	*0.25*	*0.3*	*0.35*	*0.4*	*0.45*	*0.5*
1.1	2	2	3	3	4	4	5
1.2	4	5	6	7	7	8	9
1.3	6	7	8	10	11	12	13
1.4	7	9	11	12	14	15	17
1.5	9	11	13	15	17	18	20
1.6	11	13	15	17	19	21	23
1.7	12	15	17	20	22	24	26
1.8	14	17	19	22	24	26	29
1.9	15	18	21	24	26	29	31
2	17	20	23	26	29	31	33

For our purposes we assume that the odds ratios in table 1 are equivalent to relative risks. Where the number of events is known it is then straightforward to move to the second stage to work out the number of cases attributable to the exposure.

Thus, for SIDS, assuming that 25% of women smoke during pregnancy and that this raises the risk of sudden infant death by 2, 20% of deaths from SIDS may be attributed to exposure to ETS (table 6). In England and Wales there are approximately 400 SIDS deaths per year[59] and thus 80 deaths are attributable to maternal smoking. This may be an underestimate as rather more women smoke postnatally and it takes no account of smoking by other household members. One recent study estimated that 63% of sudden infant deaths were attributable to parental smoking,[60] the high percentage arising from a combination of a high relative risk estimate in that study along with an assumption that paternal smoking had a marked effect, thereby increasing the exposure prevalence.

In contrast to sudden infant death which is a fatal but rare condition, lower respiratory infection in infancy, respiratory symptoms in older children, and middle ear disease are much more common but it is difficult to estimate the prevalence of them with any precision. While the number of attributable cases is not easily quantified, even a small relative excess implies many thousands of extra children affected by each of these conditions. The effects range from the very minor to major, and from acute to chronic. Thus, assuming a relative risk of 1.3 and a prevalence exposure of 35%, about 10% of surgical operations for glue ear are attributable to the effects of parental smoking. Given the reported 60 000 operations per year in England,[61] this amounts to an extra 6000 ear operations per year. The number of attributable episodes of glue ear will be far greater.

Public health issues

That exposure to cigarette smoke after childbirth, rather than solely during pregnancy, increases the risk of a range of respiratory problems in infancy as well as later in childhood, appears to alter the agenda. It broadens the problem from maternal smoking to that of family and friends, and hence policy about smoking on public transport, in restaurants, and other public places becomes an important issue. On the other hand, postnatal exposure should be easier to modify as it is theoretically feasible to keep the infant physically apart from the smoker. In practice this is difficult in pre-school children where the mother is a smoker. In particular, it would be wrong to lose sight of the fact that the major part of ETS exposure occurs within the home and that maternal smoking remains the major source in many countries. It seems likely that prevention will remain focused on reducing the percentage of parents who smoke rather than on isolating smokers or increasing ventilation.

ETS pollution is increasingly being tackled in western countries by health promotion campaigns and restrictive interventions—for example, in the workplace. However, few campaigns outside the USA have highlighted the susceptibility of children to ETS exposure. The challenge is to get the message about smoking and health risks in infancy across without making the first six postpartum months even more difficult. While in developed countries "back to sleep" campaigns have successfully altered the sleeping position of babies, smoking rates have been left virtually unchanged. In many undeveloped countries few women smoke, while male smoking rates are very high. It is likely to prove difficult to promote household changes in these groups if education is channelled through mothers because of marked imbalances of power within the family.

It is also important to view the adverse health effects from ETS exposure in context. The effects are small relative to effects of active smoking, but for children ETS exposure is not voluntary. Potentially, the link between parental smoking and uptake of active smoking by their children is of greater long term importance to a child's health. In England parental smoking doubles the risk of smoking uptake by children[62] which, since 50% of children come from smoking households, allows us to estimate that up to one third of children who smoke can be attributed to parental example. For this reason, reduction of parental smoking throughout a child's upbringing, rather than just in the perinatal period, may pay substantial future dividends in the prevention of respiratory diseases.

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Erratum

The following errors appeared in the paper by Anderson HR, Cook DG. "Health effects of passive smoking. 2. Passive smoking and sudden infant death syndrome: review of the epidemiological evidence", *Thorax* 1997; **52**:1003–1009.

In table 1, (i) the study by Bulterys *et al*[30] is a duplicate of that by Kraus *et al*[27] and should be deleted; (ii) the odds ratio for maternal prenatal smoking in the study by Malloy *et al*[36] should have read 2.35 (not 3.25). To take account of the removal of the study by

Bulterys and two minor errors table 2 has been updated below.

The paper by Strachan DP and Cook DG. "Health effects of passive smoking. 5. Parental smoking and allergic sensitisation in children", *Thorax* 1998;**53**:117–123, cited as reference 14 an abstract, which has subsequently been published in full as Ownby DR, Johnson CC, Peterson EL. "Maternal smoking does not influence cord serum IgE or IgD concentrations", *J Allergy Clin Immunol* 1991;**88**:555–560. The authors apologise for this oversight which does not affect the results or conclusions of the review.

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	2.74 (2.42 to 3.10) (n = 33)	χ^2 (df = 32) = 120.7 (p<0.001)	2.13 (1.86 to 2.43) (n = 18)	χ^2 (df = 17) = 54.0 (p<0.001)
	FEM	2.74 (2.59 to 2.90)		2.17 (2.04 to 2.31)	
Prenatal smoking, studies with information on non-adjusted and adjusted odds ratios	REM	2.82 (2.38 to 3.33) (n = 15)	χ^2 (df = 14) = 59.1 (p<0.001)	2.18 (1.89 to 2.51) (n = 15)	χ^2 (df = 14) = 40.7 (p<0.001)
	FEM	2.89 (2.70 to 3.09)		2.20 (2.05 to 2.36)	
Prenatal smoking (cohort studies)	REM	2.75 (1.97 to 3.82) (n = 7)	χ^2 (df = 6) = 22.2 (p = 0.001)	(n = 4)*	χ^2 (df = 3) 14.5 (p = 0.002)
	FEM	2.39 (2.15 to 2.65)		2.04 (1.84 to 2.25)	
Prenatal smoking (case-control studies)	REM	2.73 (2.37 to 3.16) (n = 26)	χ^2 (df = 25) = 78.8 (p<0.001)	2.22 (1.88 to 2.61) (n = 14)	χ^2 (df = 13) 37.0 (p<0.001)
	FEM	2.89 (2.71 to 3.09)		2.26 (2.09 to 2.45)	
Postnatal smoking	REM	2.80 (2.00 to 3.93) (n = 9)	χ^2 (df = 8) = 35.0 (p<0.001)	(n = 4)*†	χ^2 (df = 3) = 1.18 (p= 0 .76)
	FEM	3.10 (2.70 to 3.56)		1.94 (1.55 to 2.43)	

Schoendorf study results[37] were analysed separately for black and white subjects and in all these analyses are counted as two separate studies.
*Below the minimum of five studies for estimation of random effects.
†Excludes reference 46 which did not control for prenatal smoking.