Health effects of passive smoking • 7

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Parental smoking, bronchial reactivity and peak flow variability in children

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Abstract

***Background*—A systematic quantitative review was conducted of the evidence relating environmental tobacco smoke to bronchial hyperresponsiveness (BHR) during childhood.**

***Methods*—Twenty nine relevant studies were identified after consideration of 1593 articles selected by electronic search of the Embase and Medline databases using keywords relevant to passive smoking in children. The search was completed in April 1997.**

***Results*—Of 19 studies using challenge tests in children of school age, 10 (5759 children) could be summarised as the odds ratio of being bronchial hyperreactive in children exposed to environmental tobacco smoke compared with those not exposed. The pooled odds ratio for maternal smoking was 1.29 (95% confidence limits 1.10 to 1.50) with no evidence of heterogeneity between studies. However, in five further studies of 3531 children providing some evidence, but not odds ratios, none were statistically significant. A further four studies on 5233 children have collected data but are not published. In contrast, all four studies of circadian variation in peak expiratory flow found increased variation in children exposed to environmental tobacco smoke.**

***Conclusions*—A clear effect of exposure to environmental tobacco smoke on BHR in the general population has not been established. While the meta-analysis suggests a small but real increase in BHR in school aged children, it seems likely that this estimate is biased upwards due to publication bias. In contrast, limited evidence suggests greater variation in peak expiratory flow in children of smoking parents.**

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Keywords: parental smoking; bronchial hyperresponsiveness; children

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There have been numerous claims that exposure to environmental tobacco smoke in children may induce asthma or increase the frequency or severity of attacks in asthmatic subjects.[1 2] One mechanism for such effects is through the alteration of non-specific bronchial hyperresponsiveness (BHR). Such an effect is plausible given that most studies have reported a relationship between active smoking and bronchial reactivity in adults.[3] However, in a previous paper in this series we suggested that the evidence relating exposure to environmental tobacco smoke with asthma and wheezing was more consistent with the tobacco smoke acting as a trigger than as an underlying cause of the asthmatic tendency.[1] If so, tobacco smoke should be more strongly related to acute manifestations of asthma such as wheezing episodes than with indicators of underlying susceptibility such as BHR. Any effect of exposure to environmental tobacco smoke on BHR would be important, not only because it would suggest an effect on initiation/induction (rather than provocation/exacerbation) of asthma, but also because it is thought that increased BHR may be related to reduced growth in forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC).[4]

This paper systematically reviews the evidence from studies that have measured bronchial reactivity by spirometry or peak expiratory flow (PEF) measurements before and after a bronchoconstrictor provocation such as methacholine, histamine, exercise, or cold air. We also review studies assessing daily variation in individual PEF values and experimental studies of acute exposure to environmental tobacco smoke and their effect on BHR and lung function. The much larger number of studies relating exposure to tobacco smoke with asthma and respiratory symptoms have been reviewed previously.[1 5 6]

Methods

This paper is one of a series of reviews on the respiratory effects of exposure to environmental tobacco smoke in children. For the series published papers, letters and review articles were selected by an electronic search of the Embase and Medline databases using the search strategy described elsewhere.[5] Briefly, all passive smoking references were selected by the MESH heading *Tobacco smoke pollution* and/or the text word combinations ({*passive, second hand, involuntary, parent*, maternal, mother*, paternal, father** or *household*} **and** {*smok*, tobacco** or *cigarette**}) in the title, keywords or

Table 1 Summary of studies reviewed

Reference no.	Year	Country	Age	Sample size	Sample selection	Provoking agent	Outcomes
Studies of bronchial reactivity in neonates							
7	91	Australia	4 weeks	63	Random recruitment at prenatal clinic	Histamine	PC_{40} (g/l) for VmaxFRC
Studies of bronchial reactivity in schoolchildren: odds ratios available							
3,4,8	85	US	11–16	173	Population sample from East Boston	Cold dry air	Decline in FEV_1/VC ⩾9%
9	88	Italy	9	166	Population sample from three towns	Carbachol	Fall in FEV_1 ⩾20%
10	88	Italy	11–14	276	Random sample of children	Methacholine	Fall in FEV_1 ⩾20%
11	89	Germany	10–14	80	Healthy children from three schools	Exercise + cold air	50% Raw increase
12	90	UK	7	770	30 primary schools in Edinburgh	Running for 6 min	Fall in FEV_1 >10% (other cutoffs available)
13,14	92	Germany	8	1461	Children entering primary schools in three towns	Running for 3 min	Decrease in PEF ⩾15%
15–17	91	Australia	5–12	783	Children living near power stations	Histamine	Fall in FEV_1 ⩾20%
18	94	Spain	9–14	338	C-C study based on prevalence survey	Running for 5 min	Fall in PEF >15%
19	94	Italy	7–11	1183	Random sample of schools in two areas	Methacholine	PC_{20} >64 mg/ml
20	95	Norway	7–13	529	Children from two valleys in Western Norway	Methacholine	PC_{20} ⩽8 mg/ml (or 20% increase in FEV_1 after bronchodilator)
Studies of bronchial reactivity in schoolchildren: odds ratios not available							
21,22	89	Denmark	7–16	495	Population sample around Copenhagen University	Histamine	PC_{20} <8.0 mg/ml
23	91	Hungary	9–13	206	Children with "obstructive bronchitis"	Aceticholine	Fall in PEF (or FEV_1 ⩾20%
24	92	Australia	7–12	1217	Schoolchildren from Sydney suburb	Histamine	PC_{20} ⩽3.9 μmol)
25	94	Hong Kong	9–12	412	Four schools in two districts		Fall in FEV_1 ⩾20%
26	94	Croatia	7–14	1201	?	Cold dry air	
Studies of bronchial reactivity in schoolchildren: data not published							
27	90	Germany	7–16	623	Mail invitation to 7500 children	Carbachol	
28	94	Australia	8–11	2765	All schools in three areas	Histamine	Fall in FEV_1 ⩾20% or ⩾15% bronchodilation if FEV_1 <60% predicted
29	96	Australia	8–11	808	Children living near GPO in Sydney	Running for 6 min	Fall in FEV_1 ⩾15%
30	96	New Zealand	9–15	1037	Dunedin birth cohort	Methacholine	PC_{20} FEV_1 ⩽8 mg/ml (or bronchodilation ⩾10% after salbutamol)
Study of bronchial reactivity amongst referrals to an allergy clinic							
2,31–34	86	Canada	7–17	41	Allergy referrals with history of asthma/wheeze	Histamine	PC_{20}
Observational studies of PEF variability							
35	90	USA	5–14	108	Community study in Tucson	Observational	"Diurnal variation" in PEF
36	92	Italy	10–11	40	Unclear	Observational	Circadian rythm of PEF
37	93	Germany	8	1237	All children entering primary school in three towns	Observational	Average over 5 days of PEFhigh–PEFlow/PEF mean
38	96	Holland	9.3	55	Unclear - "Children with allergic asthma at primary school"	Observational	(PEFhigh–PEFlow)/PEFmean
Study of bronchodilation in school aged children							
39	83	US	6–12	183	Children attending school in Iowa city	Isoproterenol	Change in FVC, FEV_1, PEF, FEF_{25}, FEF_{50}, FEF_{75}
Studies of the acute effects of ETS exposure							
40	91	Germany	8–13	11	Asthmatic children	Histamine	Concentration leading to 20% fall in FEV_1
41	93	Germany	8–13	13	Asthmatic children	Cycling for 6 min	% fall in FEV_1 after exercise
42	89	Mexico	6–16	62	Asthmatic children	None	FVC, FEV, MMEF measured before and after ETS exposure

C-C = case-control; FEV_1 = forced expiratory volume in one second; VC = vital capacity; PC_{20} = concentration required to reduce FEV_1 by 20%; PEF = peak expiratory flow; ETS = environmental tobacco smoke.

abstract. Papers were then restricted to children by selecting all papers classified as containing data on neonates to 18 years and/or by relevant textwords in the title or abstract. Embase searches were entirely based on textword searches. This search, completed in April 1997, yielded 3625 references of which 1593 contained keywords relevant to respiratory or allergic disease. These 1593 abstracts were reviewed and 38 relevant papers were identified relating to 28 studies (table 1). One further paper was identified by personal knowledge.[35] Wherever possible it was our aim to identify studies that had assessed both exposure to environmental tobacco smoke and BHR, even if no data were presented.

The studies identified are discussed under five headings (table 1): (1) one study in neonates; (2) 19 population based studies in school age children plus one study of referrals to an allergy clinic using bronchoconstrictor challenge tests; (3) four observational studies of circadian variation in PEF; (4) one study of bronchodilation in school age children; and (5) three experimental studies of the acute effects of exposure to environmental tobacco smoke under controlled conditions. A narrative approach is taken to discussing groups (1), (3), (4), and (5) because of the small number of studies identified. For group (2), which contained most of the studies, a more formal meta-analytical approach is taken.

The findings of most studies in group (2) can be summarised as odds ratios for bronchial hyperreactivity in different environmental tobacco smoke exposure groups (table 2). In all cases these are presented for boys and girls combined, even if the original paper presents sexes separately.

Quantitative meta-analysis was carried out by testing odds ratios for heterogeneity using the technique of Breslow and Day.[43] Both "fixed effects" and "random effects" models were used to produce pooled odds ratios as previously described.[5]

Results

BRONCHIAL REACTIVITY IN NEONATES

Only one study has assessed the relationship of parental smoking to BHR in neonates.[7] Forced expiration at end inspiration was induced by a rapidly inflated jacket to measure expiratory

Table 2 Odds ratios of bronchial hyperreactivity in school aged children by exposure to environmental tobacco smoke

Reference no.	*Provoking agent*	*Prevalence (%)*	*Exposure comparison*	*Odds ratio*	*95% CI*	*Confounding/exclusions†*
3	Cold dry air	23	Mother smokes v not	**0.815**	0.38 to 1.72	Adjusted for sex. Current respiratory illness excluded. Only two children actively smoked
11	Exercise + cold air	40	Smoking families v not	**2.60**	1.02 to 6.65	Asthmatics and active smokers excluded
12	Exercise	12	Salivary cotinine >3.6 ng/ml v ND	**1.01**	0.47 to 2.15	Asthmatics, those with recent symptoms and active smokers excluded
13	Exercise	7	Mother smokes v not	**1.07**	0.68 to 1.68	Unadjusted
			Mother smoked at 1 year	1.53	0.98 to 2.40	
			Mother smoked while pregnant	1.16	0.65 to 2.05	
18	Exercise	7	Mother smokes at home v not	**1.86**	1.07 to 3.26	Matched for sex, age and classroom. Active smoking not mentioned
			Father smokes at home v not	1.05	0.63 to 1.76	
			Mother smokes at home v neither	2.23	1.06 to 4.69	
9*	Carbachol	45	Mother smokes v neither	**1.89**	0.85 to 4.21	Adjusted for sex
			Father smokes v neither	2.21	1.06 to 4.59	
			Both smoke v neither	2.31	1.13 to 4.75	
			Father only smokes	2.88	1.29 to 6.45	
10	Methacholine	16	Smoking mothers v not	**0.77**	0.36 to 1.63	Asthmatics excluded. Active smoking ignored
19*	Methacholine	51	Mother smokes v neither	**1.34**	1.01 to 1.78	Adjusted for sex. Adjustment for a wide range of confounders reduced odds to 1.30
			Both smoke v neither	1.31	0.94 to 1.84	
			Father only v neither	1.13	0.82 to 1.55	
20	Methacholine	43	Mother smokes daily v not	**1.23**	0.76 to 1.99	Unadjusted. Active smoking not mentioned
			Mother smoked first year v not	0.815	0.5 to 1.33	
			Mother smoked when pregnant	0.80	0.48 to 1.33	
			Father smokes daily v not	0.94	0.58 to 1.54	
15	Histamine	24	Any smoker in home v none	1.30	0.92 to 1.84	Adjusted for age, sex, area, house dust mite atopy

*Results presented for girls and boys combined, but adjusted for sex.
†Comment is made on active smoking for all studies including children >11 years.

flow at functional residual capacity (VmaxFRC) before and after inhaled histamine in sedated infants. Four groups were compared: no family history, both parents non-smokers (group 1); family history of asthma, both parents non-smokers (group 2); no family history, one or both parents smoke (group 3); and family history of asthma and one or both parents smoke (group 4). The concentration of histamine resulting in a 40% fall in VmaxFRC was significantly higher in group 1 using pairwise comparisons with each of the other three groups. There were no differences between groups 2, 3 and 4. The overall comparison of exposed and non-exposed children (groups 1 + 2 versus 3 + 4) is not presented, and there is no adjustment for other potential confounders including sex, or information on dose response including paternal versus maternal exposure. Thus, while the data are suggestive of an effect of intrauterine exposure, they require confirmation. The importance of this study is its demonstration that the relationship of parental smoking to BHR can be measured in the neonatal period before the onset of asthmatic symptoms, though the technique is somewhat invasive.

BRONCHIAL REACTIVITY IN SCHOOLCHILDREN

Fifteen studies have published data on the relationship of exposure to environmental tobacco smoke and BHR in population samples (table 1). A further four population based studies have measured both environmental tobacco smoke exposure and BHR but have not, as far as we are aware, published data relating the two (table 1). All studies measured BHR at one point in time; none have looked at longitudinal changes in BHR. Most of the studies were of cross sectional design, with one being a case-control study.[18] Even those that were longitudinal effectively present cross sectional data.[8] Most of the 14 studies characterised BHR as a yes/no response, though several provide more than one cut off point.

The arbitrary nature of the definitions of bronchial reactivity is reflected in the differences in prevalence rates in different studies. Studies using exercise induced BHR[12 13 18] reported the lowest prevalence rates of BHR, while those using methacholine or carbachol reported the highest rates,[9 19 20] except for one study[10] (table 2).

Meta-analysis of effect of mother smoking

For 10 of the 15 studies we were able to extract effect measures in the form of odds ratios of being bronchially hyperreactive in children exposed to environmental tobacco smoke compared with non-exposed children (table 2). Figure 1 presents a summary of the 10 studies. These are based on the odds ratios for maternal smoking except for three studies where specific data for maternal exposure are not given.[11 12 15] There was no evidence of heterogeneity (χ^2_{9df} = 9.1, p = 0.43) between studies and no single study dominated. The pooled fixed effect estimate of the odds ratio was 1.29 (95% CI 1.10 to 1.50). There was no obvious relationship between provocation used or prevalence and likelihood of a positive finding (fig 1, table 2).

Possible publication bias

Of the 10 studies for which odds ratios are available (group 1), eight were focused on the relationship of BHR to environmental tobacco smoke compared with one of five of those studies not providing odds ratios (group 2) and two of four of those not reporting any data (group 3). The total numbers of children included were 5759 in group 1, 3531 in group 2, and 5233 in group 3. Of the five studies in

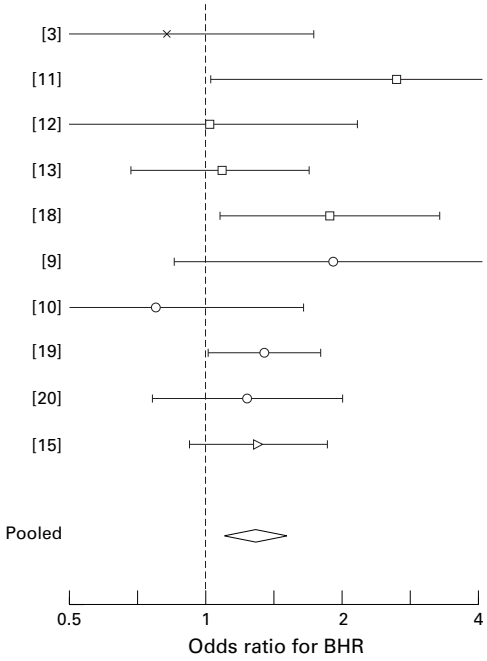

Figure 1 Odds ratios for effects of maternal smoking on BHR. × = cold air; □ = exercise; ○ = methacholine or carbachol; ▷ = histamine.

group 2, all stated they found no effect and three reported p values of 0.29,[23] >0.05,[25] and >0.20.[26] This contrasts with four significant associations being reported among 10 studies reporting odds ratios (table 2). It seems highly likely that the data presented in table 2 are biased towards a positive association between BHR and exposure to environmental tobacco smoke.

Effect of adjustment for potential confounding variables

Most studies did not adjust for potential confounding variables. Where adjustment was carried out it had a relatively small effect,[19] perhaps because social factors have relatively little influence on bronchial reactivity.[44] It seems unlikely that active smoking is an important confounder since the results are similar in studies of younger and older children and in older children they seem unrelated to whether or not active smokers were excluded (table 2).

Exposure/dose response

Only a few studies have reported evidence of exposure or dose response. One reported stronger effects if duration of exposure was more than nine years, current exposure was greater, or there was a younger age at first exposure.[18] However, exposure or dose response is difficult to assess systematically since studies reporting no significant overall effect rarely looked for exposure or dose response, though where they did, none was found.[12 24]

Exposure in different periods and maternal versus paternal exposure

All except one study[12] used questionnaire measures of exposure. These tended to focus on current maternal smoking with a few asking about paternal smoking and two about past smoking by mothers. The only study to use cotinine found no relationship with exercise induced BHR.[12]

Frischer *et al*[13] focused on a statistically significant effect of smoking by the mother during the first year of life while effects of current smoking and smoking in pregnancy were not significant. In contrast, one study[9] found that the effects of smoking during pregnancy or infancy were explained by current exposure, while another[20] found no effects of prenatal smoking on bronchial responsiveness despite clear associations of intrauterine exposure with asthma.

It is difficult to draw any clear conclusions about the effect of paternal smoking. Only four studies report odds ratios for the effect of fathers' smoking, one finding a large effect[9] and three others reporting very small or non-existent effects (table 2).[18–20]

Differences between boys and girls

While one study[19] claimed an effect in girls but not boys (in fact the difference was not statistically significant), another[9] found an effect in boys but not girls. Other authors have either reported no difference by sex[12] or have not addressed possible sex differences in the effect of environmental tobacco smoke exposure.

Susceptibility of children with asthma or a parental history of atopy

Of greater potential importance is whether there are subgroups of children particularly susceptible to cigarette smoke. Five studies commented on the effect of exposure to environmental tobacco smoke on BHR in asthmatic or wheezing subjects compared with normal subjects: two reported a stronger effect in asthmatic subjects[3 9] while two reported stronger effects in non-asthmatic subjects.[12 13] Another study found that the estimated effects were unchanged when the analysis was restricted to asthmatic subjects or to children of non-asthmatic mothers.[18]

Meinert *et al*[14] have proposed that the lack of an association between exposure to environmental tobacco smoke and BHR in asthmatic subjects may be attributed to mothers of asthmatic or bronchially responsive children stopping smoking. While the evidence from their study is persuasive, it is contradicted by that from others.[20]

In a sequence of papers based on referrals to an allergy clinic with a history of asthma or wheeze, Murray and Morrison have claimed an important impact of maternal smoking on bronchial responsiveness. The major problem with all these reports is the lack of any data on sample selection and response rates. In their first paper[2] they reported on 41 children aged 7–17. They found a markedly lower PC_{20} amongst the children of smoking mothers ($p = 0.002$) and evidence of dose response with the number of cigarettes in the home. No confounders were controlled. Subsequently there were papers on expanded numbers of subjects claiming a greater effect in the cold wet season,[32] a greater effect in boys than girls and

Table 3 Summary of results of studies of circadian variation in measurements of peak expiratory flow (PEF)

Reference no.	*Number of PEF measurements*	*Outcome measure used*	*Exposure comparison*	*Results*	*p value*
35	Not given	Not given	Cigarettes smoked in home each day	% classified as "bronchially reactive" was 31% in unexposed, 25% in those exposed to 1–20 cigarettes, and 61% in those exposed to >20 cigarettes	0.03
36	Six measures over 24 hours	Amplitude and mesor of PEF variability analysed by "rhythmometric" analysis	Children exposed and not exposed to cigarette smoke (validated by urinary cotinine)	Amplitude was 0.14 l/s (60%) greater in exposed than in non-exposed children	<0.02
				Mesor (average level) was 0.29 l/s lower in exposed children	<0.02
				Age and sex were controlled for by design	
37	Best of three readings taken morning and evening for one week	Average over week of $\left(\frac{\text{PEFhigh–PEFlow}}{\text{mean PEF}}\right)$	Current maternal smoking v not and no. of smokers in house	Current maternal smoking increased amplitude by 14% (95% CI 4 to 25) in non-asthmatics and by 55% (95% CI 6 to 126) in asthmatics after adjustment for current symptoms, atopy, air temperature and humidity	0.006 0.026
38	Every four hours over a 24 hour period	$\frac{(\text{PEFmax–PEFlow}) \times 100}{(\text{mean PEF})}$	"Exposed" v "not exposed" not defined	Amplitude in exposed group was 29.7% (95% CI 3.9 to 56.6) and in non-exposed was 19.4% (0.0 to 56.6)*	<0.05
				Effect was very similar after adjustment for pets, house dust mite, age and bronchial reactivity	

*Data given are for period off inhaled corticosteroid treatment. Results very similar while on treatment.

in older children,[33] and a reduction in effect over time as parents exposed their children to less cigarette smoke.[34] A number of problems exist when evaluating these papers. For example, if the first report was based on a difference exaggerated by chance variation, then over time there would be regression towards the mean—that is, a smaller difference. At the same time parents advised to smoke less in the presence of children are likely to report that they are doing so. The interpretation of the seasonal analysis is also suspect since p values in different seasons are compared rather than estimates of effect.

VARIATION IN PEF IN SCHOOLCHILDREN

Four studies of variability in PEF amongst schoolchildren have been published, each reporting greater circadian variation in PEF in children exposed to environmental tobacco smoke.[35–38] The results are summarised in table 3. One small study of 40 children aged 10–11 years in Italy reported lower average levels but greater variability in PEF in the 20 children exposed to environmental tobacco smoke.[36] The sample excluded asthmatics and those with acute respiratory problems, but other details are lacking. A larger German study by Frischer *et al* measured PEF twice daily over five days in 991 subjects.[37] The response rate was only 38% to this part of the study, but a wide range of potential confounding variables including the asthmatic status of the child, maternal atopy, and educational level of the parents was measured and controlled. Again greater variability was found in children whose mother smoked. The difference was greater amongst asthmatic children, but this effect modification was not statistically significant. The German study found no evidence of a difference in the level of PEF between children exposed and those not exposed to maternal smoking.

In a third study[35] the odds of having "bronchial reactivity", as assessed by the circadian variability in maximal expiratory flow rate, was 3.6 (95% CI 1.2 to 10.6) in 18 children aged under 15 years who lived with persons smoking more than 20 cigarettes per day compared with 62 children of the same age living with non-smokers. Children living with smokers of 1–20 cigarettes per day were no different from the non-exposed group.

Most recently, a small Dutch study reported that circadian variation in peak flow in children with allergic asthma was greater in 26 children exposed to environmental tobacco smoke in the home than in 29 non-exposed children.[38] The difference was of borderline statistical significance both on and off inhaled corticosteroid therapy, and was little affected by adjustment for potential confounding variables including bronchial reactivity measured by histamine provocation (table 3).

EFFECT OF BRONCHODILATION ON SPIROMETRIC VALUES IN SCHOOL AGED CHILDREN

If exposure to environmental tobacco smoke does have an acute effect on flow rates it might be expected that such effects could be reversed by bronchodilation. One study has examined the effect on spirometric values of administering inhaled isoproterenol[39] and reported small but statistically significant increases in FEV_1, FEF_{50}, FEF_{75}, and $FEF_{25–75}$ in children whose parents smoked (n = 94) but not in children of parents who did not smoke (n = 89). Changes in other indices including PEF, FEF_{25}, and FVC were not statistically significant. While some of the changes remained significant at p = 0.05 after adjustment for multiple significance testing, no formal comparison of the change observed in the exposed group with that observed in the non-exposed group was made. It seems highly unlikely that these differences were significant, but rounding errors preclude calculation from the published data. Information was not available on time since exposure to environmental tobacco smoke.

EXPERIMENTAL STUDIES OF ENVIRONMENTAL TOBACCO SMOKE EXPOSURE UNDER LABORATORY CONDITIONS

We identified three studies that investigated the effect of exposing children to environmental tobacco smoke under controlled laboratory conditions.[40–42] A fourth paper[46] presented the same data on children as in a previous paper.[41] All three studies were of asthmatic children. The first of these studies was of 11 children aged 8–13 years, none of whom smoked but six of whom were exposed to environmental

tobacco smoke at home. Children were studied on three separate days during a two week period. On day 1 baseline data were collected, on day 2 sham exposure occurred, and on day 3 the children were exposed to environmental tobacco smoke. The order of the days was apparently not randomised. While exposure to environmental tobacco smoke resulted in increased symptoms, no significant effect was found on lung volumes or on bronchial reactivity assessed with a histamine challenge. In a similar study by the same group[42] 13 asthmatic children aged 8–13 were studied and BHR assessed by an exercise test. In this study a slightly greater fall in FEV_1 occurred during exposure to environmental tobacco smoke than during exposure to ambient air ($p = 0.04$), but the effects of exercise were similar during both exposure periods. The group carrying out these studies was funded by the tobacco industry.[47] A somewhat larger study of 62 asthmatic children observed the effects of one hour of passive smoking on FVC, FEV_1, and MMEF.[40] BHR was not measured. While a fall in maximum mid-expiratory flow is claimed, no statistical tests were reported.

In summary, only two studies have formally assessed the effects on BHR before and after acute exposure to environmental tobacco smoke. Both were small (11 and 13 children, respectively) and looked at asthmatics only. Details of sample selection are sparse. Given the marked within subject variability apparent in these papers, the studies had limited power to answer the question. We have to conclude that there are too few data at present to make any reasonable statement on the short term effect of exposure to environmental tobacco smoke on BHR, but limited data suggest a small reduction in flow rates after such exposure.

Discussion

Contrary to the claims of previous reports, we do not believe that an adverse effect of environmental tobacco smoke exposure on BHR in the general population has been clearly established. Our meta-analysis of overall effects in general population samples in table 2 and fig 1 suggests a small but real increase in BHR amongst children of smoking mothers (OR 1.29, 95% CI 1.10 to 1.50). 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 that have collected data have not been published. These latter studies contain rather more subjects than the studies included in table 2. There appear to be three reasons given in the literature for the strong positive impression of an association between exposure to environmental tobacco smoke and BHR: (1) there has been extensive reporting of subgroup analyses and selective emphasis by authors of positive findings; (2) there has been selective reporting of positive studies in review articles; and (3) it seems likely that there has been publication bias.

While we cannot rule out a small effect of environmental tobacco smoke exposure on BHR, it is unlikely to be large at average levels of exposure amongst school aged children. However, as nearly all the data relate to school age children and to average exposure levels, the possibility exists that at younger ages or at higher levels of exposure stronger effects would be evident.

In contrast to the equivocal results for BHR, all four published studies suggest an effect of environmental tobacco smoke exposure on daily variation in PEF. The apparent contradiction disappears if we recognise that BHR, as assessed by a challenge test, is measuring something very different from daily variation in PEF.[48] Provocation tests of BHR assess the underlying susceptibility of an individual to environmental stimuli. Increased variation in PEF may well be reflecting acute effects of daily variations in these environmental stimuli rather than a long term effect on an individual's underlying susceptibility.

Conclusion

The published data relating environmental tobacco smoke exposure to bronchial reactivity are not definitive. Sixty percent of all potentially relevant data relating to bronchoconstrictor challenge studies are unpublished or are in papers not providing any effect measures, but reporting no significant associations. It seems likely that the pooled odds ratio, based on the remaining 40%, overestimates the strength of association between exposure to environmental tobacco smoke and BHR.

This uncertainty could be resolved by pooling data from all existing unpublished or partially published studies to provide an unbiased estimate of the effect of environmental tobacco smoke on bronchial reactivity. It would also be useful to obtain more data on circadian variation where studies so far are consistent but generally small, and to carry out larger and better designed studies of the effects of acute environmental tobacco smoke exposure on both ventilatory function and bronchial reactivity.

While the experimental evidence for acute effects on lung function is limited, there is considerable evidence from observational studies relating environmental tobacco smoke exposure to lung function. If our suggestion that exposure to environmental tobacco smoke has acute effects is correct, then we would expect current exposure rather than past exposure to be more important in determining lung function.

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