Exacerbation of asthma

by ETS exposure

A review of the epidemiological evidence

Part II – Literature from 1998 onwards and an overview of the total data

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EXECUTIVE SUMMARY

Part I of this document includes a critical description of those studies thought relevant to study of the relationship of ETS exposure to asthma exacerbation that were published up to 1997. In this part, part II, studies published since then are described, and the overall evidence is assessed.

Studies in children

Sixty relevant publications, apparently relating to 47 separate studies, were identified. 34 of the studies were first reported in the last 10 years (1995 to 2004). Far more studies (18) were conducted in the USA than in other countries, results being available from a total of 21 countries. The median number of asthmatics studied was 167 per subject, the largest study involving 3010. Studies generally were of both sexes, with more boys than girls. Most studies covered an age range of a few years, with 6-9 year olds most commonly studied. A few studies specifically excluded smokers.

There were a variety of study designs, including one experimental and three intervention studies, but most studies were of cases identified through medical records, or cross-sectional studies with the classification of asthma based on questionnaire. Eight of the 47 studies used a nicotine-based marker of ETS exposure, with other studies relying on questionnaire response. Only eight studies recorded maternal smoking in pregnancy.

About half the studies did not adjust for any potential confounding variables, with some potential confounding variables (such as diet, exercise and recent respiratory infections) rarely adjusted for.

A wide variety of indices of asthma exacerbation and severity have been used in the studies, with results summarized under nine different endpoints. The endpoints, the number of studies providing data, the number showing a significant positive (negative) association with ETS exposure are summarized below:

Endpoint	Number of studies	Number significant	Conclusion/comment
Hospitalisation	9	4 (1)	Some evidence of an association, but data from NHANES III conflict
Emergency room visits and urgent consultations	6	4	Evidence of an association
Restricted activity	6	2	Association not demonstrated
Acute and non-acute asthma	4	1	No clear difference in ETS exposure between acutely and non-acutely asthmatic children
Asthma medication	7	3	Association not clearly demonstrated
Health contacts for asthma	3	0	No association shown
Asthma severity	13	6 (1)	Clear positive association
Asthma symptoms and acute episodes	14	7	Results heterogeneous, but strongly suggestive of an association
Quality of life and general health	3	1	Data too limited to draw conclusions
Total	65	28 (2)	Overall data clearly show a positive association, not attributable to chance

Overall, these data show considerable evidence of an association, though the results appear heterogeneous, with a few studies reporting very strong relationships and a number no positive relationship at all. However, interpretation of this association is not completely straightforward for a number of reasons. These include the lack of clear evidence that increases in ETS exposure within child are associated with exacerbations of asthma, limited reporting of relevant study details by many authors (including information on active smoking by the child) and failure to separate out results by sex and by age. Failure to control for potential confounding variables is also a feature of the studies. No studies adjusted for maternal smoking in pregnancy, only six for any social class related variables, only four for infections in the child (and none for infections in the parent) and few even take the sex or age of the child into account. Furthermore, some of the various endpoints used may not be very direct or reliable measures of asthma severity.

Very few studies studied these endpoints in relation to smoking in pregnancy. There were five reported results, of which two (for asthma medication and severity) showed a significant positive association.

Eighteen studies relate ETS exposure to one or more of five lung function variables – FEV_1, FVC, the ratio of FEV_1 to FVC, $FEF_{25-75\%}$ and PEFR. The data for $FEF_{25-75\%}$ are more suggestive of an association with ETS than is the case for FEV_1, FVC or the FEV_1/FVC ratio, but there are still inconsistencies which need resolving. The data on PEFR relate to a variety of endpoints, and the results, which are incompletely reported, are difficult to interpret. Other lung function variables have only very rarely been studied. While a number of statistically significant findings have been reported for lung function, the data generally do not show a very consistent pattern, with associations seen only for subsets of the data or for some indices of exposure and not others, with some studies reporting no significant associations at all. A clear relationship of ETS exposure to reduced lung function has not been established, though the data are somewhat suggestive of a relationship.

Seven studies have related ETS exposure to bronchial responsiveness, but no consistent association has been shown.

Studies in adults

Ten relevant publications, apparently relating to eight studies, were identified. Four of the studies were conducted in the USA, three in India and one in Switzerland. One study was of women aged 20-40, the other studies (where details were known) being of men and women of average age 40. Unlike in children, asthmatic women were generally commoner than asthmatic men. Only two studies were restricted to lifelong never smokers, the rest being of nonsmokers.

Most studies were of cases identified from medical (or insurance) records, but two studies were of cross-sectional design with ETS exposure related to lung function in asthmatics identified by questionnaire. Two studies used a nicotine-based marker of ETS exposure, with other studies relying on questionnaire response. No study recorded ETS exposure in childhood or maternal smoking in pregnancy.

The four studies in the USA and the study in Switzerland took a range of potential confounding variables into account in at least some of their analyses. The three studies in India took no potential confounding variables at all into account, not

even age or sex. One of these three studies was reported only as an abstract, while the other two included major errors in their statistical analyses.

Six of the eight studies reported results for acute exacerbations (including such endpoints as emergency department visits, hospitalisations, acute episodes and restricted activity days). All but one reported significant positive associations in at least one analysis, consistent with the findings for children. Data relating to other endpoints were more rarely studied and, though some associations were reported, more evidence is needed.

Data from four studies gave some support to the possibility that ETS exposure may be associated with reduced lung function, but the limited findings were not always consistent and no firm conclusions can be drawn.

One of the studies in India reported an association of ETS exposure with bronchial responsiveness, but the statistical analysis is open to question. Since no other study provided relevant data, conclusions cannot be drawn here.

Other reviews of the evidence

This document also considers other reviews of this evidence. The California EPA report, and its recent draft update which concludes that ETS exposure exacerbates asthma in children, is limited by failing to include a number of relevant studies, failing to detect obvious flaws in some of the evidence, not discussing sources of potential bias in detail, not summarizing evidence separately for different endpoints, and not describing how its conclusion had been reached from the data available. The reviews by the group from the St George's Hospital Medical School are more thorough but also contain deficiencies. Notably, a mechanism is postulated by which ETS is considered a co-factor, operating with intercurrent infection, to exacerbate asthma, but no consideration is given to the possibility of bias resulting if exposure to infections is greater in households with smokers. There is also no emphasis on the absence of data to distinguish effects of ETS exposure and of maternal smoking in pregnancy. A number of other reviews are also cited, which generally do not consider all the evidence available at the time, and often do not

attempt to separate out potential effects of ETS on induction and exacerbation of asthma.

Comment

Elsewhere, we have reviewed the evidence from experimental chamber studies in which asthmatics were exposed to ETS. These studies showed that ETS can reproducibly exacerbate asthma in a subset of susceptible individuals, but that, for the great majority of asthmatics, ETS exposure, even at extremely high concentrations, does not appear to cause asthmatic attacks.

We have also reviewed the evidence relating ETS exposure to prevalence and incidence of asthma in children and in adults. These reviews showed that there was an association, but that there were difficulties in separating out potential effects on induction and on exacerbation and in distinguishing potential effects of ETS exposure and of smoking in pregnancy. Lack of control for confounding by other variables which may be associated with ETS exposure may also be an issue.

The evidence on asthmatics considered in this document clearly demonstrates an association of ETS exposure with asthma exacerbation, particularly with emergency room visits, hospitalisations, acute episodes and severity, and less clearly with lung function and the other endpoints studied. Certainly, the results are rather heterogeneous, a number of the studies can be criticized, and various possibilities of bias and confounding exist. Furthermore, the role of intercurrent infection has not properly been accounted for. Whether or not ETS exposure can exacerbate asthma in all asthmatics, the findings certainly reinforce the evidence from the chamber studies that ETS exposure can exacerbate asthma.

Conclusion

ETS exposure can exacerbate asthma, though not necessarily in all exposed individuals.

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Abbreviations used

AQOL	Asthma-related quality of life
BHR	Bronchial hyperreactivity
BTS	British Thoracic Society
CCR	Cotinine/creatinine ratio
CI	Confidence interval
ED (or ER)	Emergency department (or room)
EPA	Environmental Protection Agency
ETS	Environmental tobacco smoke
$FEF_{x\%}$	Forced expiratory flow at x% of forced vital capacity
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GP	General practitioner
HDM	House dust mite
ICS	Inhaled corticosteroids
IRR	Incidence rate ratio
IgE	Immunoglobulin E
MMEFR	Mid-maximal expiratory flow rate
NHANES III	Third National Health and Nutrition Survey
OR	Odds ratio
PC_{20} (or PD_{20})	Provocative concentration (or dose) of histamine or methacholine to produce a 20% increase in FEV_1
PC_{100}SRAW	Provocative concentration of histamine or methacholine to produce a 100% increase in specific airway resistance
PEFR	Peak expiratory flow rate
QOL	Quality of life
SES	Socio-economic status
SPT	Skin prick test
SRAW	Specific airway resistance

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Tables

1. Introduction

Part I of this document reviewed the epidemiological evidence relating ETS exposure to exacerbation of asthma based on papers published up to 1997, a period which broadly corresponds to the major reviews carried out by the California EPA (National Cancer Institute, 1999) and the series of reviews published in 1998 and 1999 (summarized in Cook & Strachan, 1999). Part I noted that the overall evidence for adults was too limited and poorly reported to allow a confident conclusion, though it suggested a possible relationship of ETS exposure to asthma exacerbation. The evidence in children was more extensive, and though it did not allow clear conclusions to be drawn as regards lung function and bronchial responsiveness, it was quite highly suggestive as regards ETS being associated with an increased risk of various aspects of asthma severity, such as emergency room visits, hospitalisations, acute episodes of asthma, symptom scores, severity grades or use of therapy.

Part II considers evidence published from 1998 onwards. As before, it starts with a section (2) describing chronologically the various studies that are thought relevant, giving details of the main results and, where appropriate, pointing out apparent weaknesses. Included in this section is mention of some review papers published during this period. Section 3 then summarizes various features of the studies considered, while section 4 brings together the findings, updating the summary in Part I. Conclusions are then drawn. Section 5 compares and contrasts the findings of the review with other recent reviews, including the draft updated review by the California EPA (California Environmental Protection Agency, 2004). Finally, section 6 summarizes the report.

2. The evidence from 1998

Based on a study conducted in Northern California, USA (Eisner et al., 1998), analyses were presented based on 451 nonsmoking adults attending pulmonary or allergy clinics with asthma, aged 18-50 (mean 40 years), 30% male, who had answered questions on ETS exposure and other variables at baseline and at an 18 month follow-up. ETS exposure was based on a question concerning regular exposure to tobacco smoke at home, work or in other locations over the past 12 months (baseline) or past 18 months (follow-up). Four groups of subjects were defined: I. No exposure at either time (n=322); II. Exposure at baseline only (n=43); III. Exposure at follow-up only (n=56); and IV. Exposure at baseline and follow-up (n=30). A wide variety of analyses were presented.

The first set of analyses concerned baseline ETS exposure only, comparing groups II and IV combined vs groups I and III combined. After adjusting for age, sex, race and income, ETS exposure was associated with a significant increase in health care use over the previous 12 months, in terms of emergency department visits (OR = 2.1, 95% CI 1.2-3.5), urgent physician visits (1.9, 1.1-3.3) and hospitalisations (1.9, 1.02-3.6). Restricted activity days were reported to have been recorded, but results were not presented. ETS exposure was also associated with significantly higher asthma severity (p=0.03), worse asthma-specific quality of life (p=0.04) and worse health status as indicated by physical scores (p=0.04) but not mental scores.

Another set of analyses concerned changes in asthma outcomes within groups between baseline and follow-up, after adjustment for age, sex, race, income and baseline asthma severity. Within group II, those who had ceased being ETS exposed, there was a significant reduction in asthma severity (p=0.0003), no significant change in asthma-specific quality of life, and a significant improvement in health status as indicated by physical scores (p=0.05), but not mental scores. Within group III, those who had started being ETS exposed, there was no significant worsening in any of these four asthma outcomes. Nor were there any significant changes in group IV, who had continued ETS exposure.

A third set of analyses related the probability of health care use to exposure cessation, initiation and continuation after adjustment for age, sex, race, income and baseline asthma severity. The only statistically significant relationships noted were between cessation and reduced emergency department visits (OR = 0.4, 95% CI 0.2-0.97) and reduced hospitalisations (0.2, 0.04-0.97). It is unclear here precisely what comparisons are being made. If the comparisons are being made within group, how has adjustment been made for the differing periods to which the health care use refers (12 months vs 18 months)? If the comparisons are being made between group, what reference group is being used in each case?

The authors state that "In conclusion, self-reported ETS exposure is associated with greater asthma severity, worse health status, and increased health care utilization in adults with asthma".

The study has limitations, including relatively small numbers of subjects in some of the groups of interest, inadequate description of some analyses, and perhaps failure to present analyses which more generally relate change in ETS exposure to change in asthma endpoint using the data from all the subjects at once. Nevertheless it is clearly superior to any of the four previous studies on asthmatic adults considered in part I of this report. One interesting feature of the data which might have merited more detailed coverage is the observation that adjustment for covariates substantially reduced the strength of the association of cessation with asthma outcomes. For example, adjustment changed the improvement in asthma severity score from 3.2 to 1.9 points, and made non-significant the improvement in asthma specific quality of life. Which covariates caused the marked changes in the estimates? Could adjustment for other covariates have reduced the estimates further?

A study in Lower Saxony, Germany (Seidler et al., 1998) involved 600 asthmatic children aged up to 8 years who attended a doctor in a baseline phase in 1991, 218 (65% male) of whom visited the same doctor about 3 years

later during a follow-up phase. There were 200 children with information on progression of the asthma; 29% with no attacks, 45% with a decreasing frequency of attacks over the 3 years, 20% in which the frequency had remained the same and 7% in which it had increased. In a polytomous logistic regression analysis involving a number of other variables (age, sex, parental education, frequency of asthmatic episodes, infection-associated asthma, "asthma on exertion", neurodermitis of the child, hospital stay, speciality of treating physician, adequacy of medication, parental asthma, sensitivity to exhaust gases and region) smoking in the home was associated with a marginally significant ($p=0.05$) increased risk of an unfavourable course of the disease with an odds ratio of 1.7 (95% CI 1.0-3.0). It is not totally clear to these reviewers whether all variables were considered simultaneously in the analysis or whether Table 3 of the source paper presents the results of univariate analysis. As a multivariate analysis it would have some objections in that asthma endpoints seem to be included both as independent and dependent variables. An association was reported between having more than 5 asthmatic episodes in the last 12 months and a worsening course of the disease, but these variables to some extent measure the same thing. The authors do not include any simple table relating smoking in the home to progression of the asthma. The paper also reported an almost significant ($0.05<p<0.1$) difference in the prevalence of smoking in the home for the 382 children not followed up (42%) and the 218 followed up (34%). This highlights the possibility of some selection bias.

A study in Marseilles, France (Dubus et al., 1998) involved 46 asthmatic children with a positive skin-prick test to one or more common aeroallergens, normal spirometric values and no upper airway infection. The children were aged 5 to 14 (mean 8.3), with 57% male. Parents were instructed to withhold any asthma therapy for 24h before the tests. Comparisons were made between 23 children with detectable and 23 with non-detectable cotinine in urine, based on a limit of detection of 1 ng/ml. No child was considered an active smoker based on the cotinine values (maximum = 98 ng/ml). There was no significant difference between the exposed (detectable cotinine) and unexposed groups in respect of the number of crises

per year (4.1 vs 4.4), symptoms between crises (OR 0.49, CI 0.15-1.60) or use of anti-inflammatory treatment (0.66, 0.19-2.35). There was also no significant difference as regards FEV_1 (106.5% vs 101.9%, p=0.2), FVC (106.6% vs 101.7%, p=0.13), PEFR (89.1% vs 85.6%, p=0.56) $FEF_{25 \text{ to } 75\%}$ (94.0% vs 104.3%, p=0.34), or SRAW (7.6 vs 7.4 cm H_2O/s, p=0.30). The doubling dose (PC_{100} SRAW) was determined, and was significantly less in the exposed group (108.3 vs 160.9 μg, p=0.04). Following administration of 200 μg albuterol, the percentage of bronchodilatation was defined from the difference between the largest SRAW value obtained and the SRAW value measured 15 minutes later divided by the largest SRAW value. This was significantly higher in the exposed group (74.8% vs 68.8%, p=0.03). No significant relationship was reported between parental smoking and either the doubling dose (mother smoked 98.4 vs 147.2 μg) or the percentage of bronchodilation (data not given). The authors concluded that "environmental tobacco smoke increases bronchial reactivity in asthmatic and allergic children".

A further report from Marseilles, France (Oddoze et al., 1999) concerned 90 children with suspected asthma, aged 4 to 14 (mean 8), with 60% male. The authors noted that urinary cotinine was not associated with basal spirometric tests (FEV_1 and SRAW). Bronchial responsiveness to carbachol was significantly associated with cotinine (p=0.03), but not cotinine/creatinine ratio (p=0.07) or the number of cigarettes smoked by the parents (p=0.19). Detailed results were not reported. Despite these rather marginal results, the lack of consideration of any potential confounding variables and the fact that only 33% of the children had clinical asthma, the authors concluded that "Passive smoke exposure increases the bronchial responsiveness to carbachol in asthmatic children". Whether the children considered in this and the previous paper are separate samples is unclear.

In a study in Chandigarh, India (Jindal et al., 1999) a bronchial provocation test using histamine was performed on 50 asthmatic adult women aged 20-40 years. While the abstract states that they were "nonsmokers", the

methods section states that they were enrolled "without any knowledge of their smoking history" and that "most women were likely to be nonsmokers". 23 of the patients had a history of ETS exposure from the husband. There was no significant difference between the exposed and unexposed women in either FEV_1 (77.9 vs 79.4%) or FEV_1/FVC (83.6 vs 86.3%). PD_{20}, the dose of histamine to produce a 20% fall or greater in FEV_1, was lower in the ETS exposed group (5.66 vs 11.80), a difference they estimate as significant at $p<0.01$ but we do not since, based on the standard deviations given (9.62 and 13.06), the t-value is only 1.91 ($p>0.05$). The authors also claim a significant difference in the proportion of patients requiring continuous bronchodilator therapy, with 9/23 (39%) in the ETS exposed group as against 7/27 (26%) in the unexposed group. This difference is in fact far from statistically significant. Also noted are a non-significant increase in the mean number of acute episodes in the previous year in relation to ETS exposure (4.83 vs 4.00) - which clearly is non-significant - and a statistically significant difference in PD_{20} according to an ETS exposure index calculated by multiplying years of exposure by daily hours of exposure. Here the significance of the difference in PD_{20} (1.8 units for index >15 and 3.2 units for index >0 but <15) cannot be checked from the information presented, but clearly cannot be trusted. The authors' claim that their data show an association of ETS exposure with bronchial responsiveness, which in any case is based on analyses with no adjustment for potential confounding variables, must be regarded as extremely doubtful. As described in part I of this document, a previous paper from this group (Jindal et al., 1994) was also based on erroneous statistical analyses.

In a study conducted in North East England (Shamssain & Shamsian, 1999), data for 3,000 children aged 6-7 years were collected from parents or guardians on smoking habits and on prevalence of various respiratory symptoms. About 685 children (59% male) had ever had asthma. The prevalence of ever asthma in the children was 20.6% if no parent smoked, 26.4% if one parent smoked and 28.7% if both parents smoked. Corresponding prevalences of limitation of speech during attacks in the past year were 2.7%, 3.7% and 4.3%. This implies that, among the asthmatics, the

corresponding proportions with speech limitation were 13.1%, 14.0% and 15.0%, differences which are clearly not significant.

A study based on health maintenance organization members in Portland, USA (Sippel et al., 1999) concerned 619 adult subjects with asthma, including 548 nonsmokers who were of mean age 38, with 43% male. The analyses related quality of life and hospital-based care both to smoking and to ETS exposure at home or at work. Most of the ETS analyses were unrestricted by smoking status and will not be summarized here. However, the results of one longitudinal analysis restricted to nonsmokers was reported. This found that, after adjusting for age, gender, disease severity, diagnosis of COPD and non-asthma medication use, subjects who reported ETS exposure at baseline had more frequent episodes of hospital-based asthma care over the next 30 months than did those who reported no ETS exposure, with a relative risk of 2.87 (95% CI 2.15-3.82).

A study in Nairobi, Kenya (Wafula et al., 1999) involved 150 children with a history of wheezing with a mean age of 4 years (1 month - 10 years) with 60% male. The children were classified as having mild (32%), moderate (47%) or severe (21%) asthma, based on frequency of attacks. There was a non-significant tendency for passive smoke exposure at home to be associated with moderate asthma. Thus 36/71 children (51%) with moderate asthma were exposed to ETS as against 16/48 (33%) with mild asthma (odds ratio 2.06, 95% CI 0.96-4.40). The definition of asthma used in this study required only "At least two previous episodes of wheezing" (excluding cases of pneumonia or cervical tumours) and seems very unrestrictive. It is also unexplained why passive smoking data were not presented for the severe cases. The only other risk factor considered in this study was breastfeeding and then not simultaneously with passive smoking.

A study in the Al-Majmaah region of Saudi Arabia (Al Ghamdy et al., 2000) involved 606 children with asthma aged up to 13 years, 69% male. 292 of these were infants aged less than 1 year. The authors presented a table relating asthma severity (based on national guidelines) to parental smoking

from which the relative risks given below were calculated, showing a significant relationship. No attempt was made to adjust for potential confounding factors.

	Asthma severity		
Parental smoking	Mild	Moderate	Severe
No	279	30	29
Yes	190	37	41
Odds ratio	1.00	1.81	2.08
(95% CI)		(1.08-3.03)	(1.25-3.46)

An abstract summarizing the results of an intervention trial conducted in New Orleans, USA (El-Dahr et al., 2000) involving 16 households containing 21 smokers (presumably adults, and at least one per household) and 18 asthmatic children aged 6-16 with 56% male. In phase 1 of the study the smokers smoked normally for 3 months. In phase 2 smokers received counselling and smoking cessation aids over a 1 month period in order to encourage them to quit and to cease smoking inside the home for 3 months. Although only 2 of the 21 smokers stopped completely, all of them significantly decreased the number of cigarettes smoked in phase II. The number of cigarettes smoked in the home reduced dramatically (from 18.7 to 0.18 cigs/day, $p=0.0001$), as did nicotine levels in the child's bedroom (12.8 to 1.8 $\mu g/m^3$, $p<0.0001$) and in the living rooms (53.1 to 7.3 $\mu g/m^3$, $p<0.0001$), and the cotinine levels of the parents (340.6 to 257.7 ng/ml, $p=0.002$). The cotinine levels of the children (excluding one who was found to be a smoker) did not vary materially (1.7 to 1.5 ng/ml). As regards asthma in the child, there was a significant increase in days with normal sleep (85 to 91%, $p<0.01$), days with normal activity (90 to 95%, $p<0.05$), days without cough (70 to 87%, $p<0.01$) and days without wheeze (78 to 85%, $p=0.06$). Total symptom scores decreased from 1.00 to 0.54 ($p<0.05$). Bronchodilator use was stated to have "decreased in 7/12 (39%)", data which are inconsistent and with no significance test. There is also no statement of significance regarding average daily PEFR, though with increases in 8/15, no change in 6/15

(actually given is 6/35 but presumably a typographical error) and therefore a decrease in 1/15, we estimate p to be <0.05. FEV_1 was noted to have improved significantly (p<0.0001) with 15/17 improving, but metacholine results did not vary, with as many improvements as worsenings. The limitation of this study, from a theoretical point of view, is that there is no formal control group. Had households been randomly assigned to receive or not receive cessation advice, one could have excluded the possibility that changes in asthma status may have, for example, been due to changes in the weather.

A study conducted in Istanbul, Turkey reported only in abstract (Güler et al., 2000) involved 47 asthmatic schoolchildren aged 5 to 15 years, with 68% boys. A questionnaire determined the amount and time of exposure to ETS, and the urinary cotinine/creatinine ratio (CCR) was determined. The patients were followed up for one year and pulmonary function was determined regularly. The abstract states that there was no correlation of asthma severity or pulmonary function to CCR. Asthma severity was, however, significantly correlated with the number of cigarettes smoked by the mother currently (p=0.008), by the mother during pregnancy (p=0.006), and by the father (p=0.04) and with the amount of passive smoking of mothers during pregnancy (p=0.04). FEF_{25-75} reversibility (undefined) was significantly higher if the mother smoked currently (p=0.03) and during pregnancy (p=0.001). PEF reversibility (not defined) was significantly higher if the mother smoked during pregnancy (p not given). The authors considered that they "have established that ETS, primarily smoked by the mother during various periods of life have (sic) long term effects on clinical features of asthma in schoolchildren". They do not comment on the inferences to be drawn from the fact that an objective indicator of ETS exposure (CCR) found no association with asthma severity or pulmonary function but self-reported indicators did. It is unclear from the abstract which of the multiple pulmonary function measurements were used in the analysis. There was also no attempt to separate results for pre- and post-natal smoking.

In a study conducted in Diyarbakir, Turkey (Gürkan et al., 2000) hospital admissions were studied retrospectively over a period of up to 4 years in 140 children with asthma aged 3-15 years, 65% male. Over the follow-up period 30 of the children (21.4%) had a mean of more than one admission per year and qualified as a multiple admission. Results relating multiple admissions to a range of factors were presented on an individual basis. These showed significant associations with both maternal smoking and smoking in the house, as summarized below:

		Multiple admissions		OR
		Yes	No	(95% CI)
Smoker in the house	Yes	16	34	2.55
	No	14	76	(1.12-5.82)
Maternal smoking	Yes	7	8	3.88*
	No	23	102	(1.28-11.8)

Miscalculated as 4.05 (1.47-11.78) by the authors.

The authors also summarize the results of a multivariate logistic regression analysis in which only maternal smoking and age of the child were significant. They cite an adjusted odds ratio of 3.25 (95% CI 1.13-8.85) for maternal smoking.

Based on the SAPALDIA study, a multicentre study involving 8 areas in Switzerland, analyses were presented relating ETS exposure at work to lung function in 3,534 lifelong never smoking adults with acceptable spirometry. 325 were asthmatics, either doctor-diagnosed asthma or wheeze without cold in last 12 months, of mean age 40 years, with 44% male (Künzli et al., 2000). The main results relating to the asthmatic subjects are summarized below:

Subjects	n	% changes (95% CI) in lung function measures associated with ETS exposure at work* FVC	FEV_1	FEF_{25-75}
All	325	-1.7(-5.5 to +2.1)	-4.8(-9.2 to +0.0)	-12.4(-20.4 to -3.7)
Male	142	+1.4(-4.0 to +7.1)	+0.5(-7.9 to +9.6)	-1.4(-18.0 to +18.5)
Female	183	-4.4(-9.6 to +1.1)	-8.7(-14.5 to -2.5)	-20.8(-32.0 to -7.6)
Female: BR**=no	66	Not given	-1.7(-9.4 to +6.7)	-4.7(-19.4 to +12.6)
: BR=yes or not measured	117	Not given	-12.3(-19.9 to -3.9)	-30.6(-43.4 to -14.8)

* Adjusted for log age, log age squared, log height, ETS at home, occupational gas/dust/smoke, and area of residency.
** Bronchial reactivity to methacholine.

The results show no evidence of a relationship of ETS exposure at work to FVC. The data also showed no significant relationship to FEV_1 or FEF_{25-75} in males, but some evidence of a reduction in females, particularly in those who are bronchially reactive or for whom bronchial reactivity could not be measured, mostly due to obstructive pre-test conditions. Additional analysis on extent of ETS exposure among those exposed only at work found a significant dose-response with FEV_1 and FEF_{25-75}, but only among asthmatic women. The authors consider that "differences in the level of [ETS] exposure may be the main reason for the observed sex pattern". However, sampling variation may also be the explanation, as the differences in the % change estimates for men and women are not actually statistically significant for either FEV_1 or FEF_{25-75} ($0.05<p<0.1$).

Based on the first stage (a cross-sectional survey) of a longitudinal study (the Children's Health Study) conducted in southern California, USA (Li et al., 2000), lung function in 5263 children was related simultaneously to sex, asthmatic status, maternal smoking in pregnancy ("in utero exposure") and household ETS exposure after birth, after adjustment for community, school grade, spirometer, pressure, technician, log (height), age and race. Approximately 68% of the children were fourth-graders aged 7-13 years, 16% were seventh-graders aged 11-15 and 16% were tenth-graders aged 14-19 years. The study included 442 asthmatic boys and 307 asthmatic girls. Only 13 of the 749 asthmatics were smokers themselves.

The main findings of this study, which is the first to consider *in utero* exposure in this context, are presented in three tables. Table 3 studies effects of *in utero* exposure ignoring ETS, Table 4 effects of ETS ignoring *in utero* exposure and Table 5 third joint effects. Each table relates to four measures of lung function (FVC, FEV_1, FEV_1/FVC and MMEFR) with results given separately for boys and girls and for asthmatic and non-asthmatic children. The results for single effects in asthmatic children are summarized in the table below:

		Percent change in lung function with statistical significance			
Exposure	Sex	FVC	FEV_1	FEV_1/FVC	MMEFR
In utero vs no *in utero*	Boys	-4.3**	-7.1***	-2.9*	-11.3**
	Girls	+3.3*	-0.5	-3.6***	-8.7*
Past ETS vs no ETS	Boys	-2.2	-4.9*	-2.8*	-9.2*
	Girls	+2.5	+2.1	-0.2	+1.4
One current smoker vs no ETS	Boys	-3.3	-3.9	-0.6	-4.0
	Girls	+1.9	+1.1	-0.8	+7.0
Two or more current smokers vs no ETS	Boys	+0.8	-2.9	-3.6	-5.2
	Girls	+5.9*	+2.7	-2.7	-4.2

*P<0.05 **P<0.01 ***P<0.001

It is clear from these results that the evidence of an association is much stronger for *in utero* exposure than for ETS exposure. For *in utero* exposure 7 of the 8 estimates are of an associated reduction in lung function, with 6 of them statistically significant. The significant result for FVC in girls in the reverse direction is the main conflicting finding. For ETS exposure, the results are far less consistent, with no real evidence of any reduction in lung function in girls and significant reductions in boys only seen in relation to past, not current, ETS exposure.

The analyses in Table 5 compare lung function in 5 groups:

Group	ETS	*In utero*
1 (reference)	No	No
2	Past	No
3	Current	No
4	No	Yes
5	Any	Yes

Based on these data it is possible to estimate differences associated with ETS where *in utero* exposure is not present (weighted average of estimates for groups 2 and 3) and where it is present (difference of estimates for groups 4 and 5). These results are summarized below:

		Percent change in lung function			
Exposure	Sex	FVC	FEV_1	FEV_1/FVC	MMEFR
ETS vs no ETS (no *in utero* exposure)	Boys	-0.2	-1.4	-1.2	-2.9
	Girls	+1.7	+3.0	+1.7	+10.2
ETS vs no ETS (*in utero* exposure)	Boys	-2.7	-0.4	+2.2	+3.0
	Girls	-5.5	-1.1	+4.2	+13.6

While the significance of these individual changes cannot readily be assessed exactly from the data presented, it seems that none of the reductions associated with ETS (adjusted for *in utero* exposure) are statistically significant. Since there are as many increases as reductions in these estimates it seems that the data from this study do not show any evidence of an effect of ETS exposure independent of *in utero* exposure and little consistent evidence of an effect of ETS exposure ignoring *in utero* exposure.

The authors appear to be rather ambivalent about the conclusions of their study. In the abstract they state "In summary both in utero exposure to maternal smoking and ETS exposure were associated with persistent deficits in lung function. The effects of in utero exposure were greatest among

children with asthma". However, reading the last paragraph of the discussion, and most of the paper, one gets the impression that *in utero* effects are much more clearly seen and that it is not so clear whether ETS has any general effect.

In an abstract describing a two-year follow-up of a study of asthmatic children in Stockholm (Melén et al., 2000) results are reported for 144 of the original 189 children. 12 children of mean age 44.3 months were assessed as having severe asthma (based on symptoms and use of inhaled steroids) and 132 children of mean age 49.5 months were assessed as having mild/moderate asthma. Parental smoking was one of a number of variables recorded at baseline (age 1-4) associated with an increased risk of severe asthma at follow-up (age 3-6), with a relative risk estimated as 2.7 (95% CI 0.8-9.8). Parental smoking at follow-up was also stated to have no significant association. It is not stated whether this relative risk was calculated from univariate or multivariate analysis. Although the relative risks for parental smoking were not statistically significant the authors nevertheless concluded that "In children with induction of asthma during the first two years of life, early sensitization, cat allergen exposure at home and parental smoking seem to increase the risk for development of severe asthma with regular use of inhaled steroids later in childhood".

A study conducted in New Delhi, India (Ratageri et al., 2000) included 60 children suffering from severe chronic asthma and 60 children suffering from mild chronic asthma. The children were aged 5-15 years with 72% male. On univariate analysis there was a tendency for the odds of severe asthma to be increased if family members smoked, particularly 10+ cigs/day. In multivariate analysis involving age of onset of asthma, past history of lung diseases, family history of asthma, allergy, breastfeeding, overcrowding, pets, cooking, worm infestation, eosinophil count and air pollution, smoking by the family did not emerge as a factor associated with severity of asthma.

	Mild		Severe		Odds ratio
	No	Yes	No	Yes	(95% CI)
Any family member smoked	32	28	26	34	1.49 (0.73-3.07)
Father smoked	38	22	31	29	1.62 (0.78-3.35)
Grandfather smoked	55	5	54	6	1.22 (0.35-4.24)
Cigs/day smoked by family members					
None		32		26	1.00
1-9		13		7	0.66 (0.23-1.90)
10		15		27	2.22 (0.98-5.01)

A study in Kuopio, Finland (Schwartz et al., 2000) involved 74 asthmatic children aged 7-12, 61% male. For three months the children measured their PEFR every morning and evening and kept a daily diary of respiratory symptoms. They also noted daily whether they had used respiratory medication and whether someone had smoked inside their home. When the data were analysed longitudinally, ETS exposure at home was associated with significant reductions in morning PEFR of 41.9 ℓ/min (95% CI 9.5 to 74.3 ℓ/min) and in evening PEFR of 40.7 ℓ/min (7.6 to 73.7 ℓ/min) after adjustment for age, height, sex, atopic status, father's education, weight, use of maintenance drugs, day of study, previous day's temperature and humidity, bronchodilator use, a random-subject effect, and whether the measurement was taken on a weekend. Similar estimates were obtained using a cross-sectional model. Whether or not adjustment for atopic status, use of maintenance drugs or bronchodilator use made little difference to the estimates, but failure to adjust for father's educational level would have led to markedly lower estimates of 26.0 ℓ/min for morning PEFR and of 23.8 ℓ/min for evening PEFR. Evidence was also presented to support the existence of a dose-related relationship (trend p=0.01) between PEFR and the percentage of days with ETS exposure. The above analyses were based on between-child comparisons. Within-child comparisons showed that ETS exposure on a given day was on average associated non-significantly with a lower PEFR the next day by about 10 ℓ/min.

The previous day's ETS exposure was a significant risk factor for need for bronchodilator use on any given day (OR 10.3, 95% CI 1.3-83.7). Mean ETS exposure over the previous two days was associated with a significant increase in the probability of cough (12.4, 2.4-63.3) and of phlegm production (7.8, 1.4-41.7). Wheezing/breathing difficulties were too rare for analysis.

The authors concluded that "exposure to ETS was associated with a decline in peak flow and increase in symptom reporting and use of bronchodilator drugs by asthmatic children. The effect of ETS on PEFR in this study was largely chronic, but evidence for an effect of daily variations in ETS was seen for bronchodilator use and respiratory symptoms, and there was a suggestion of an acute effect on PEFR".

A review entitled "Environmental tobacco smoke and adult asthma" (Eisner & Blanc, 2000) concluded that "Among adults with pre-existing asthma, ETS appears causally related to adverse health outcomes". In the section on "ETS exposure and exacerbation of pre-existing adult asthma" four studies are cited, one of which (Blanc et al., 1999) does not actually report any results restricted to asthmatics. Of the three relevant studies cited (Jindal et al., 1994; Ostro et al., 1994; Sippel et al., 1999), it should be noted that for one of them (Ostro et al., 1994) the authors only report the results unadjusted for repeated measures and not the adjusted results which are more appropriate and are non-significant with only one exception (restricted activity). As the authors point to weaknesses in the study in Chandigarh (Jindal et al., 1994), it is doubtful whether their conclusions are justified on the evidence they consider, especially when they regard the evidence from the chamber studies they consider as "limited by small sample size, variable subject inclusion criteria and variation in chamber exposure methodology" and only suggesting "a modest adverse effect of acute ETS exposure on pulmonary function".

Another review published in 2000 was entitled "Environmental tobacco smoke, indoor allergens, and childhood asthma" (Gold, 2000). A

brief section on "ETS and exacerbation of asthma" refers to previous reviews (National Cancer Institute, 1993; Strachan & Cook, 1998) and to only a few of the relevant studies (Evans et al., 1987; O'Connor et al., 1987; Murray & Morrison, 1989). It highlights the importance of acute respiratory infections in the exacerbation of asthma, but does not mention the problem of lack of control for such infections in the ETS studies. Nor are the difficulties of distinguishing ETS and *in utero* exposure discussed. The review concludes that ETS "can exacerbate already established childhood asthma".

A third review published that year, on "Environmental tobacco smoke and respiratory diseases" (Jaakkola, 2000) was broad ranging. In its section on "Severity of asthma" it includes a paragraph mainly summarizing the findings of recent major reviews (National Cancer Institute, 1999; Strachan & Cook, 1998). It also notes that "due to highly variable outcomes, a formal meta-analysis was not possible to carry out", and concludes that "several studies carried out all over the world provide strong evidence that ETS exposure is related to a more severe form of asthma and poor overall control of asthma in children $\leq$17 years". It also summarizes much of the data on bronchial hyperresponsiveness and PEF variability considered in Part I of this review, though when, in a later part of the report, it considers "ventilatory lung function" it does not separate out effects in asthmatics. In the summary of the paper the author states that "Parental smoking causes asthma in children, and the evidence strongly supports its role in aggravating asthmatic symptoms" and that "A limited number of studies on ETS and asthma in adults suggest that ETS exposure increases the risk of asthma and contributes to poor overall control of asthma".

A study in Tayside and Fife, Scotland (Crombie et al., 2001) involved 438 asthmatic children aged 2-12, 66% of whom were male. All the children had one or more parents who smoked. They had previously taken part in a randomised controlled trial of advice aimed at reducing passive smoking. Information on health service contacts for asthma over the previous 12 months was collected and a saliva sample taken for cotinine determination. In a

multivariate model including age, severity of asthma (perceived, and based on treatment) and number of children in the household, there was no clear relationship of cotinine to the frequency of contacts for asthma, with incidence rate ratios of 0.95 (95% CI 0.82-1.11) for medium cotinine (2.1-4.5 ng/ml) and of 1.15 (0.98-1.34) for high cotinine (>4.5 ng/ml) as compared to low cotinine (≤2.0 ng/ml). In the same model, there was a significant tendency for the incidence rate ratio to be reduced if the mother only smoked (0.76, 0.64-0.89) or if both parents smoked (0.78, 0.66-0.93) compared to if the father only smoked. In earlier univariate analysis, the authors had also reported a highly significant negative relationship with the amount smoked in the home by the index parent, with incidence ratios of 1.00, 0.81, 0.70, 0.74 and 0.66 for, respectively, 0-5, 6-10, 11-15, 16-20 and >20 cigarettes/day, although amount smoked in the home did not appear in the final multivariate model. The authors conclude that "High levels of parental smoking in the home are associated with a reduction in health care contacts for asthma. This could be due to a lack of awareness of asthma symptoms among heavy smokers or a reluctance to visit the GP. Children with asthma who have parents who smoke heavily may not be receiving adequate management".

A study conducted in Cape Town, South Africa (Ehrlich et al., 2001) included 249 children with asthma aged 6-11, 52% male, all of whom claimed never to have tried cigarettes, who underwent a test of bronchial responsiveness to histamine (or salbutamol if their FEV_1 was less than 75% of normal). In a multivariate analysis involving atopic history, baseline FEV_1, asthma group (reported or multiple symptoms), symptom score and medical insurance, a non-significant negative relationship was found between whether the chid responded to the test and mother's daily cigarettes, with the odds ratio estimated as 0.97 (95% CI 0.67-1.41) for 1-14 cigs/day and 0.62 (0.34-1.11) for 15+ cigs/day. No significant associations were also found between bronchial responsiveness and other indices of parental smoking (current smoking or smoking in the first year of life by either parent individually, maternal smoking in pregnancy, number of smokers in the home or cotinine/creatinine ratio). Nor was cotinine/creatinine ratio related to the

asthma symptom score. Baseline FEV_1, adjusted for age, sex and height, was also related to a variety of indices of smoking habits. There was no association with cotinine/creatinine ratio. As shown in the table below, where selected results have been presented, there was a significant reduction in FEV_1 if the mother currently smoked or if both parents smoked, but a a non-significant increase if the mother had ever smoked or if the father currently smoked.

Exposure to smokers	Mean FEV_1, ml		Mean difference, ml	
	Exposed	Unexposed		(95% CI)
Mother current	1409	1641	-232	(-461 to -2)
Mother ever	1526	1467	+59	(-107* to +225)
Mother in pregnancy	1464	1557	-93	(-296 to +110)
Father current	1561	1449	+112	(-78 to +302)
Mother and father	1385	1591	-150	(-286 to -131)**
Two or more in household	1455	1591	-137	(-366 to +92)

* Given as 107 in the source paper, but clearly erroneous and should be -107.

** There appears to be some error in the data presented for mother and father smoking. The estimate of -150 for the difference is not equal to the difference of the means (-206). Nor is it in the middle of the 95% CI. The width of the CI, 155, is also far too small given the standard errors of 32 and 62 for the two means which imply a width almost twice this.

The authors note that "the findings do not support a mechanism whereby ETS exposure aggravates existing childhood asthma by increasing BHR. This association may be masked, however, by the degree to which mothers of asthmatic children adjust their smoking. The results are consistent with an adverse effect of maternal smoking on lung function in asthmatic children".

In a study conducted in California, USA (Eisner et al., 2001) 50 asthmatic adults with no current personal tobacco smoking and a positive answer to any screening question indicating potential ETS exposure wore a passive nicotine monitor for 7 days. The subjects were of mean age 44.4 years, with 28% male. Compared to the 21 subjects with no measured nicotine, subjects with the higher level of nicotine (>0.05 $\mu g/m^3$) had a significantly increased risk of respiratory symptoms (odds ratio 6.8, 95% CI 1.4-32.3) and of extra bronchodilator use (8.1, 1.3-50). Subjects with the

lower level (>0-0.05 μg/m^3) had a non-significant increase of both respiratory symptoms (1.9, 0.4-8.8) and extra bronchodilator use (2.2, 0.3-15). Self reported ETS exposure was found to correlate significantly ($p<0.001$) with measured nicotine level, but the authors did not analyse it in relation to the risk of respiratory symptoms or bronchodilator use. The discussion and conclusions of the paper were more concerned with the usefulness and validity of the passive badge monitor than in drawing inferences about effects of ETS on health. The subjects in this study are probably a subset of the subjects previously described by Eisner et al., 1998.

In a study in Edmonton, Canada (Mayo, 2001) 31 children of mean age 6.4 years, 17 male, who had been admitted to a pediatric unit with an acute exacerbation of asthma of non-infectious origin and who had one or more parents who smoked at least a pack a day were compared with 31 age- and sex-matched controls with an acute exacerbation of asthma without such ETS exposure. Though the study principally concerned theophylline clearance, it was noted that the duration of the hospital stay was significantly ($p<0.05$) longer in the ETS exposed group (4.35 vs 2.86 days). The author concluded that "Clinically, passive smoke exposure resulted in a longer hospital stay" without discussion or consideration of potential bias and confounding.

In a study conducted in Stockholm, Sweden (Melén et al., 2001) 181 asthmatic children aged 1-4, 76% male, were followed up for 2 years. Of 12 children satisfying the criteria for current severe asthma at follow-up, 9 (75%) had reported ETS exposure at home at baseline whereas, of 158 children with mild/moderate asthma, 85 (54%) did. This was reported as a non-significant odds ratio of 2.59 (95% CI 0.73-9.14) [though from the data presented we calculate it as 2.58 (0.67-9.87)]. After adjustment for age, heredity, and exposure to cat, dog and windowpane condensation, the odds ratio increased to 3.01 (0.74-12.2) but remained non-significant. The unadjusted odds ratio is equivalent to a relative risk of 1.39 (0.61-3.18). The number of children with severe asthma is too small to make any firm conclusion, though the authors noted that "In young asthmatic children, early exposure to … tobacco smoke

increased the risk of … further development of more severe asthma later in childhood". The subjects in this study possibly include subjects previously described by Melén et al., 2000.

A study in Anqing, China (Venners et al., 2001) included 529 never smoking asthmatic children aged 8 to 15 years of age whose mother was a never smoker. 50% of the children were male. As shown in the table below, both in girls and boys, paternal smoking was associated with some reduction in FEV_1 and FVC after adjustment for age, height, height squared, weight and father's education. However these relationships were not statistically significant.

		Decrement in FEV_1 or FVC by father's smoking habits*		
Endpoint	Sex	Never	<30 cigs/day	30+ cigs/day
FEV_1	Boys	0 (base)	-1.9%	-3.7%
	Girls	0	-1.0%	-1.3%
FVC	Boys	0	-1.8%	-3.7%
	Girls	0	-0.4%	-0.8%
Number of subjects				
	Boys	48	179	38
	Girls	50	185	29

* Ex-smoking fathers were excluded

The authors state that they also investigated the ratio of FEV_1 to FVC but did not find an important association.

An intervention trial conducted in California, USA (Wilson et al., 2001b) involved 87 ETS-exposed children aged 3 to 12 years (51% male) who had been seen for acute asthma in the preceding year. Following collection of baseline information, the children were randomly assigned to receive intervention (n = 44) or usual care (n = 43). The intervention involved three counselling sessions led by a nurse which included instruction about asthma and its treatment and the role of ETS in exacerbating and sustaining inflammation, and the collection of urine for cotinine estimation, the estimates then being used at the next session as part of a review of progress in

eliminating the child's exposure to tobacco smoke. The usual care also involved giving basic information about asthma and its treatment, but with no specific focus on ETS except for a generic statement that it is best avoided for children with asthma. In both groups the adequacy of medication was assessed and the regimen adjusted where necessary. Data collected from both groups at baseline and at 6- and 12-month follow-up visits included demographic characteristics, asthma history and symptoms, medication, ETS exposure, smoking restrictions, cotinine and health care use. Lung function was collected at baseline and 12 months only.

At baseline the groups did not differ significantly ($p<0.05$) in respect of any characteristics measured, although the intervention group was almost significantly more likely to have a maternal caregiver who smoked (61% v 42%, $p=0.07$). The main results of the study, presented in Table 2 of the paper, show for each of various primary and secondary outcomes the results of "unadjusted" and "adjusted" tests of the intervention effect. The "unadjusted" comparisons involve a simple comparison of the values observed at the end of follow-up, while the "adjusted" comparisons take into account differences observed at baseline, so are equivalent to comparing changes in the two groups. The adjusted results, which seem more meaningful, showed a significant ($p=0.03$) reduction in the probability of having more than one acute medical visit in the study year in the intervention compared to control group, the percentage falling from 50.0% in the year before baseline to 29.6% in the study year in the intervention group, but rising from 37.2% to 46.5% in the usual care group. This difference was more significant ($p=0.01$) in those with 12 month cotinine data, i.e. subjects who had stayed in the study.

Although this result sounds impressive, it should be noted that there were no other significant differences. The estimated adjusted intervention effect was in the hoped for direction as regards cotinine level, hospitalisation for asthma in the year, allowance of smoking in the home, activity limitations and nights awakened, but not as regards cigarettes smoked per day at home, symptom-free days or FEV_1 (for example, FEV_1 increased by 3.72% in the intervention group but by more, 5.38%, in the control group).

Although health-care utilization had reduced more in the intervention group than in the control group, this could not be explained by a reduction in ETS exposure (as measured either by cotinine or by reported changes in smoking rules in the home). The authors note that adjusting for either of the two indicators of ETS exposure did not affect the significant difference in reduction in health care utilization between the two groups. It would have been helpful here to present data showing, for both groups, how change in ETS exposure correlated with change in health-care utilization, but such results were not shown.

While the results seem consistent with the intervention as a whole being effective in reducing the probability of medical visits and perhaps hospitalisations, it is far from demonstrated that the reduction has actually resulted from ETS reduction. It could be, as the authors admit, that some other part of the intervention nothing to do with ETS had an effect. The study is quite small and it would need a larger study and perhaps one in which attempts are made to "measure ETS exposure and behavioral and disease outcomes concurrently" before a clear picture can be obtained.

A brief review on "Cigarette smoking and asthma" (Ulrik & Lange, 2001) included a section on "Environmental smoke exposure and asthma". This started with the term "Passive exposure to cigarette smoke in utero" which indicates the authors have not understood the essential difference between the effects on the child of ETS exposure and of smoking in pregnancy. As regards asthma exacerbation, evidence is summarized briefly from 10 studies (Chilmonczyk et al., 1993; Frischer et al., 1993; Murray & Morrison, 1986; O'Connor et al., 1987; Evans et al., 1987; Murray & Morrison, 1993; Gürkan et al., 2000; Eisner et al., 1998; Sippel et al., 1999; Jindal et al., 1994) before stating that "From the available evidence, it can be concluded that exposure to environmental tobacco smoke leads to worse asthma control, including a lower level of lung function and more severe

exacerbations, in both children and adults with asthma". There is no discussion of study weaknesses or of sources of bias or confounding.

A study in nine health units/departments across Canada (Dales et al., 2002) involved 3010 schoolchildren aged 5-19 years with current asthma, 52% of whom were male. The odds ratio for having a hospital visit for asthma in the last 12 months in relation to regular ETS exposure at home was 1.55 (95% CI 1.22-1.97) in unadjusted analyses. The odds ratio was noted to vary by household income (<$20000 1.79, $20000 to 60000 1.35, >$60000 1.45) although this variation did not appear to be statistically significant.

Using data from the Third National Health and Nutrition Examination Survey (NHANES III) conducted between 1988 and 1994 in the USA, analyses were conducted relating pulmonary function to ETS exposure, as estimated by serum cotinine, among 440 nonsmoking adults with current asthma (Eisner, 2002b). The adults were of mean age 42, with 44% male. Comparisons were made of subjects in the medium (>0.093 to 3.16 ng/ml) and high (>3.16 to <14 ng/ml) cotinine group with that in the low cotinine group ($\leq$0.093 ng/ml), with adjustment for age, sex, height, education, income, previous smoking and race/ethnicity. Analyses were conducted of FEV_1, FVC and FEV_1/FVC ratio separately for each sex. As shown in the table below, which presents changes in the mean residual value (with 95% CI), statistically significant ($p<0.05$) differences noted were an increase in FEV_1 for medium cotinine in males, a decrease in FEV_1/FVC for high cotinine in males and a decrease in FEV_1 for high cotinine in females. Based on these results, the near significant decrease in FVC for high cotinine in females, and results for the whole population (including non-asthmatics), the authors conclude that "ETS exposure is associated with decreased pulmonary function in adult females, especially those with asthma". The authors also present the results of former analyses using spirometric reference values derived for never smokers with no respiratory symptoms or conditions. Here only the decrease in FEV_1 for high cotinine in females remained statistically significant.

Changes in mean residual spirometric values (95% CI) compared to low* cotinine group

	Medium*	High*
Males		
FEV_1 (ml)	+569 (+78 to +1060)	+242 (-169 to +653)
FVC (ml)	+222 (-92 to +536)	-30 (-331 to +271)
FEV_1/FVC (%)	-0.54 (-1.8 to +0.73)	-1.6 (-2.8 to -0.30)
Females		
FEV_1 (ml)	-87 (-278 to +104)	-261 (-492 to -30)
FVC (ml)	-63 (-278 to +152)	-291 (-601 to +20)
FEV_1/FVC (%)	-0.46 (-2.0 to +1.1)	-1.6 (-3.3 to 0.19)

* See text for cotinine levels.

At the beginning of section 2, results are described (Eisner et al., 1998) from a study of nonsmoking adults in Northern California in which ETS exposure and asthma outcomes were recorded at baseline and again 18 months later. Here, (Eisner et al., 2002), further results are described from the same study. While the first paper concerned 451 nonsmoking adults and related changes in regular ETS exposure over the 18 month period to corresponding changes in asthma outcome, the current paper concerns 326 nonsmoking adults and relates any ETS exposure (home, work or other locations) at baseline to asthma outcomes at follow-up after adjustment for baseline severity of asthma score, age, sex, income and education attainment. Results are presented for five asthma outcomes and for four indices of ETS exposure (any in last 7 days, 1-2 hrs in last 7 days, 3+ hrs in last 7 days or any eye or nose irritation), in each case with the comparison group being no ETS exposure. As shown below, quite a large number of significant associations were noted, all in the direction of worse outcomes in the ETS exposed group. The associations were not materially affected by further adjustment for gas stove or wood-smoke exposure.

	Effect* (95% CI)			
Outcome	Any	1-2 hrs	3+ hrs	Irritation
Severity	+0.6 (-0.1 to +1.4)	+0.1 (-3.0 to +2.9)	+1.5 (+0.4 to +2.6)	+0.4 (-0.5 to +1.4)
Physical health status	-2.0 (-4.4 to +0.5)	-0.1 (-3.0 to +2.9)	-4.9 (-8.4 to –1.3)	-4.0 (-7.0 to -1.0)
Asthma-specific quality of life**	+2.8 (-0.4 to +6.0)	+1.7 (-2.1 to +5.5)	+4.4 (-0.2 to +9.0)	+5.0 (+1.2 to +8.9)
Emergency dept. visits	2.8 (1.2 to 6.4)	2.5 (0.9 to 6.6)	3.4 (1.1 to 10.3)	2.7 (1.1 to 6.6)
Hospital admissions	6.6 (1.3 to 33)	4.6 (0.7 to 40)	12.2 (1.5 to 102)	2.4 (0.4 to 13.1)

* Difference in continuous score for first 3 outcomes, odds ratios for last 2.
** Higher scores are associated with poorer quality of life.
Significant differences are underlined.

In a study conducted in Lisbon, Portugal (Gaspar et al., 2002) 124 children admitted to a hospital for acute asthma during a two-year period (mean age 4.1 years, 57% male) were compared with 124 outpatients individually matched on age, sex and socio-economic status. In univariate analyses asthma admission was significantly associated with parental smoking (odds ratio 3.51, 95% CI 2.1-6.0), paternal smoking (3.0, 1.8-4.9), maternal smoking (1.8, 1.0-3.1, p=0.02) and with any ETS exposure (4.59, 2.6-8.0), but not with other residents at the home (1.28, 0.8-2.0). Similar relationships were seen when analysis was restricted to the 74 pairs of children under 4 years of age – e.g. for any ETS exposure (5.0, 2.3-11.4). In a multiple logistic regression analysis involving all the children, any ETS exposure remained a significant predictor of asthma admission (6.63, 2.5-17.8) after adjustment for prior asthma hospitalisation, atopy, maternal asthma, last year asthma admission, onset of symptoms before 12 months of age, attendance at day care or kindergarten, and family size.

A retrospective study in Tripoli, Lebanon (Kalaajieh, 2002) involved 288 asthmatic children between 6 and 15 years of age, 64% male, who were hospitalised over an 8 year period. Data on ETS exposure at birth and other factors were recorded at the time of first admission and related to the rate of further admissions by the end of the period. 68 of the children had a mean of more than one further admission per year. In univariate analyses, 13 factors were identified as having a significant association with multiple admission. These included maternal smoking (odds ratio 6.10, 95% CI 2.98-12.55) and

indoor smoking (3.06, 1.81-5.18), and also sex, age, residence, frequent respiratory tract infection, atopic dermatitis, allergic conjunctivitis, allergic rhinitis, family history of allergy, total serum IgE, eosinophils in peripheral blood and household number. Although many of these associations were very strong and highly significant (e.g. atopic dermatitis 11.93, 5.81-24.53), only two factors were found to be significant in a multiple logistic regression analysis – maternal smoking and recurrent upper respiratory tract infections (both $p<0.001$; odds ratios not given).

In a further analysis using NHANES III, but this time involving children (Mannino et al., 2002), indicators of asthma severity were related to serum cotinine level, divided into three groups (0.050 to 0.115 ng/ml = low, 0.116 to 0.639 ng/ml = intermediate, and 0.640 to 20 ng/ml = high, with 0.050 ng/ml the limit of detection and levels >20 ng/ml assumed to indicate tobacco use). 523 children aged 4-16 with physician-diagnosed asthma were involved, 59% male. After adjusting for age, race/ethnicity, SES, family size and parental history of asthma, comparisons were made of children in the high and low cotinine group as regards various indices of asthma severity. As shown below, there was a significant positive association with moderate or severe asthma, a significant negative association with any hospitalisation for asthma in the previous year and a non-significant positive association with the other five indices. Adjustment had little effect on the estimated odds ratios, though it did slightly increase and make significant the positive association with moderate or severe asthma, where the unadjusted estimate was 2.5 (0.97-6.2).

Comparing children with highest and lowest cotinine levels

Outcome	Proportion (%)	Odds ratio (95% CI)
Moderate or severe asthma (symptoms/illness ≥12 days*)	21.5	2.7 (1.1-6.8)
Severe asthma (symptoms/illness >300 days*)	14.6	1.9 (0.6-5.7)
Any physician visit for asthma*	41.2	1.8 (0.9-3.8)
Any hospitalisation for asthma*	5.7	0.2 (0.1-0.5)
FEV_1 < 80% predicted	10.3	5.1 (0.7-40.6)
Less than very good health status	43.6	1.3 (0.7-2.5)
≥6 school absences*	44.4	1.8 (0.9-3.6)

* in previous year

Comparisons were also made of the same two groups in respect of lung function, with adjustment for age, sitting height, sex, race/ethnicity, SES, parental history of allergy or asthma and family size. Three of the four parameters (FEV_1, FVC and MMEF but not FEV_1/FVC ratio) tested showed a significantly lower adjusted level in the children with high cotinine levels.

Comparing children with highest and lowest cotinine levels		
Outcome	Mean effect %	95% CI
FEV_1	-8.1	-14.7 to -3.5
FVC	-5.6	-10.6 to -0.6
FEV_1/FVC	-3.0	-6.5 to +0.5
MMEF	-12.5	-23.0 to -2.0

Results were not presented in detail for children with intermediate cotinine levels. For asthma outcomes the authors noted that odds ratios (compared to low cotinine) were **"similar"** to those for high cotinine, but were not statistically significant. However children with intermediate cotinine were noted to have "lung function levels that were similar to the children with low smoke exposure". Overall the authors concluded that "Involuntary smoke exposure is associated with increased asthma severity and worsened lung function in a nationally representative group of US children with asthma". They considered that the negative association of cotinine with hospitalisation in the previous year might have been "because some parents may have altered their home smoking policies" in response to the hospitalisation.

A study in Baltimore and Washington DC, USA (Morkjaroenpong et al., 2002) involved 520 children, predominantly African American, of average age 8.2 years, 40% males. The children were all reported to have doctor-diagnosed asthma or recent symptoms or visit to a hospital or emergency department. Children whose primary care giver smoked but not in the home were excluded from the analysis but it is unclear how children where only other household member(s) smoked were treated. At-home ETS exposure was linked to various aspects of asthma morbidity. No significant relationship was

found between smoking in the home and either nocturnal symptoms, limited physical activity in the past six months, days of work missed by the caregiver in the past 6 months because of the child's asthma or school days missed by the child because of the asthma. These analyses compared 153 children with a caregiver who smoked in the home and 367 with no smokers in the household.

Further analyses were restricted to the former group, dividing them into 71 with "moderate to high" exposure where 10 cigs/day or more were smoked and 82 with low exposure where 1-9 cigs/day were smoked. Again there was no significant association with limited physical activity, days of work missed or school days missed, but there was a significant association with nocturnal symptoms. Compared to the 43 ETS exposed children with mild intermittent symptoms (≤2 nights per month), the 32 with mild persistent symptoms (2-4 nights) [sic] had an odds ratio of 3.4 (95% CI 1.3-8.8) for moderate to high vs low exposure, while the 78 with moderate-severe symptoms had an odds ratio of 2.3 (1.0-5.1).

These analyses were unadjusted for any potential confounding factor, but in an additional analysis the authors presented results of further analysis of nocturnal symptoms in a model that simultaneously investigated the role of the child's age, caregiver education, asthma primary care and use of anti-inflammatory medications as well as that of moderate to high vs low ETS exposure. Here the authors reported an unadjusted odds ratio for ETS of 2.84 (1.25-6.42) and an adjusted odds ratio of 2.83 (1.22-6.55).

The analysis is stated to relate to "presence of nocturnal symptoms", but "presence" is undefined. The previous results seemed to imply that all the children had at least mild intermittent symptoms so it is unclear what the actual definition of the endpoint used was – perhaps it was at least mild persistent symptoms.

The analysis is also unusual in that having three ETS exposure groups – none, low and high to moderate – one would have thought that it would be sensible to make comparisons of the two positive groups with the none group

rather than compare high to moderate with low. Based on the data in the paper one can calculate the following:

	ETS exposure		
	None	Low	High to moderate
Nocturnal symptoms (at least mild persistent)			
No	83	30	13
Yes	283	52	58
Odds ratio (95% CI)	1.00	0.51 (0.30-0.85)	1.31 (0.68-2.50)
	None	Low	High to moderate
Limited physical activity past 6 months			
No	120	38	23
Yes	243	44	48
Odds ratio (95% CI)	1.00	0.57 (0.35-0.93)	1.03 (0.60-1.77)
Days of work missed in past 6 months because of child's asthma			
Mean	3.5	3.9	2.3
SD	5.4	15.3	3.0
p		NS	NS
School days missed by child because of asthma			
Mean	6.7	6.2	8.4
SD	9.0	9.9	10.9
p		NS	NS

It is interesting that when viewed in this, more standard way, the data show no real indication at all of a positive association of ETS exposure with nocturnal symptoms or any of the asthma indices considered, the only significant differences seen being the reduced nocturnal symptoms and limited physical activity in the low ETS exposure group.

In a study in Denver, USA (Wamboldt et al., 2002) 152 children with asthma aged 7-18, 57% male, and their primary parent were evaluated to obtain data on ETS exposure, asthma and other variables. Children with a history of more serious medical treatments for asthma (such as 2 or more hospitalisations in last year) were excluded. A number of the asthma variables (such as asthma knowledge and age at onset) were not of interest to this review, but some were. For the 58 children with a smoker in the household (including if the asthmatic child was a smoker), compared to the 94 with no smoker in the household, no significant difference was noted in functional severity or in quality of life as reported by the child. The score for quality of life as reported by the parent was however significantly lower (poorer) (5.38

vs 6.13, $p<0.005$) where there was a smoker in the household. No adjustment was made for any potential confounding variable.

A review entitled "Environmental tobacco smoke and adult asthma" (Eisner, 2002a) included a section "Environmental tobacco smoke exposure and exacerbation of pre-existing adult asthma", and concluded that "the evidence suggests a causal relationship between ETS exposure and … asthma exacerbation among adults". This is an update of an earlier review by one of the same authors (Eisner & Blanc, 2000) on the same subject. Of the studies cited, two (Blanc et al., 1999; Mannino et al., 1997) do not actually report any results limited to asthmatics, and for another (Ostro et al., 1994) inappropriate results are cited (see comments on Eisner & Blanc, 2000 above). For the other studies cited (Jindal et al., 1994; Sippel et al., 1999; Künzli et al., 2000; Eisner et al., 2001; Eisner, 2002b), all considered earlier in this section, the results are briefly described, but no study-specific limitations are noted.

A second review published in 2002, entitled "Effects of environmental tobacco smoke on the respiratory health of adults" (Jaakkola & Jaakkola, 2002) concluded that "There is limited evidence indicating an increased risk of its [ETS] causing asthma … and for poor control of established asthma". Only eight published studies were cited. Four we consider relevant (Jindal et al., 1994; Ostro et al., 1994; Jindal et al., 1999; Sippel et al., 1999), and four (Dales et al., 1992; Abramson et al., 1995; Blanc et al., 1999; Tarlo et al., 2000) we reject for reasons discussed in the appendices to Parts I and II of this review. Reference was also made to a later published study (Eisner, 2002b) as a personal communication. As with the review considered in the previous paragraph, the data cited from the study by Ostro et al., 1994 seem inappropriate.

Yet another analysis based on NHANES III (Chapman et al., 2003) involved 309 children aged 8-16 with physician-diagnosed asthma, 60% of whom were male. Children who were current smokers or who had ever smoked 5 or more packs of cigarettes in their lifetime were excluded. Model-

predicted lung function values were presented by the number of smokers in the home, separately for each age, for a child of defined age, race/ethnicity, height, body mass, skinfold thickness, use of gas stove, household annual income, pet ownership and physical activity. Expressing these as differences from households with no smokers in the home gives

	Girls		Boys	
	Smokers in home		Smokers in home	
	1	2+	1	2+
FVC (ℓ)	+0.107	-0.075	+0.055	-0.226*
FEV_1 (ℓ)	+0.104	-0.200*	+0.042	-0.219*
FEF_{25-75} (ℓ/sec)	+0.065	-0.738**	+0.154	-0.163
FEV_1/FVC (%)	+0.1	-4.2*	-0.1	-1.1
FEF_{25-75}/FVC (per sec)	-0.022	-0.211**	-0.020	+0.005

*p<0.1 **p<0.05

These results show no association of lung function with having one smoker in the home, but some association with having two or more smokers in the home, with significantly ($p<0.05$) reduced FEF_{25-75} and FEF_{25-75}/FVC in girls. These results should be considered alongside the results relating cotinine levels to lung function in asthmatic children in NHANES III (Mannino et al., 2002).

A study in Istanbul, Turkey (Karadag et al., 2003) involved 32 children admitted to an emergency clinic with an acute asthma attack, 62.5% male. They ranged in age from 1 to 14 (mean 5.7 years). Urinary cotinine and creatinine levels were measured during and 4 weeks after the acute asthma attack. Comparing the period of the acute attack and the asymptomatic period, there was no significant difference in cotinine (295 vs 230 ng/ml), cotinine/creatinine ratio (315 vs 204 ng/mg) or having a cotinine/creatinine ratio above 30 ng/mg (81% vs 96%). It is not clear that the data from this study have been analysed correctly. It appears from the way the results are presented and the lack of reference to appropriate statistical tests that the analyses have been carried out as if two independent groups of 32 children are being compared, when tests should have been based on the distribution of

within-subject differences, e.g. using a paired t-test. Whether this might have altered the significance of the difference between the time periods is not known.

A prospective study conducted by chest specialists throughout France (Soussan et al., 2003) involved 167 children aged 6-12 years (64% boys) with recently diagnosed mild or moderate persistent asthma who had been prescribed inhaled anti-inflammatory treatment. Starting one year after recruitment, the children were followed-up for a further 2 years, with a visit every 4 months. PEF was measured twice a day during the week before each visit. Two endpoints were studied: (1) symptom control = having diurnal or nocturnal exacerbations less than once a week and no symptoms between exacerbations, at all visits and (2) PEF control = daily PEF variability <20% on each of the seven days before each visit. Symptom control was achieved by 42 children and PEF control by 89. 28 factors were considered, of which 10, including the ETS variable at least one smoker in the home, were related to symptom control in univariate analysis ($p<0.2$) and were included in a multiple regression analysis. Three factors remained significantly ($p<0.05$) related to symptom control – taking the prescribed doses (OR = 4.82, 95% CI = 1.87-12.4), understanding how the medication works (3.38, 1.18-9.64) and at least one smoker in the home (0.34, 0.13-0.91). Similarly, of 9 factors, including the ETS variable mother smoking in the home, identified in the univariate analysis for PEF control, taking the prescribed doses (3.58, 1.68-7.67), moulds within the home (0.33, 0.11-0.97) and mother smoking in the home (0.34, 0.14-0.89) remained significant in the multivariate analysis. Although taking the prescribed doses was a major factor for both endpoints, no information was presented on whether children with smokers in the home were more or less likely to take the prescribed doses (or understand how the medication works). It should be noted that the endpoints can be seen as inversely related to asthma severity/exacerbation.

A randomized clinical trial conducted in Rochester NY, USA (Halterman et al., 2004) involved 184 children aged 3 to 7 years (63% male) with mild persistent to severe persistent asthma who were allocated to either

school-based care (daily inhaled corticosteroids provided through the school) or a usual-care group (inhaled corticosteroids not given through the school). For 180 of the children, data were available on at home ETS exposure and on various outcomes assessed monthly for a year. Based on the combined data from the two groups, the following comparisons can be made by ETS exposure.

	ETS exposure		
Variable	No	Yes	Significance of differences[a]
Number of children	101	79	
No of symptom free days[b]	10.97	9.69	p<0.01
No of symptom days[b]	2.07	3.07	p<0.01
No of symptom nights[b]	2.07	3.05	p<0.01
No of days using rescue inhaler[b]	1.97	2.51	NS
Overall change in quality of life[c]	0.36	0.55	NS
Total absences from school	5.92	10.28	p<0.01
			Odds ratio 95% CI)
3+ acute visits	23 (23%)	21 (27%)	1.23 (0.62-2.43)
1+ hospitalisations	6 (6%)	3 (4%)	0.63 (0.15-2.58)

[a] For the first 6 variables the significance is based on a t-test based on the means and standard deviations provided, although the distribution may not be normal.
For the other 2 the significance is based on a chi-squared test.
[b] In two weeks before each monthly interview.
[c] Lower scores indicate poorer quality

The results show that, where there is ETS exposure, the children have significantly greater absence from school and days and nights with symptoms and significantly less symptom free days. The authors also noted that effects of school-based provision of inhaled corticosteroids (improvement in symptoms, quality of life and absenteeism) were only seen among children not exposed to ETS.

3. Studies in children

3.1 The studies

Table 1 summarizes some details of the studies on ETS and asthma exacerbation in children. There are 60 publications involved, seven of which are abstracts (marked by an asterisk in Table 1). Together they appear to relate to 47 studies, though in some cases this is not clear. The table is presented in chronological order of the first publication from the study. Further publications from a study are shown (again in chronological order) on the lines following the first publication, with the location and country columns left blank. Other information in the table (numbers of asthmatics, % male, age and "includes smokers") is shown for each of the multiple publications. In the distributions described below (which are study- rather than publication-based) the value used is that which is not given in parentheses. This selected value is generally taken from the publication that is based on most asthmatic subjects or provides most information.

Publication data The distribution of date of first publication for a study is as follows:

Date	Studies first published
1974	1
1980-1984	2
1985-1989	5
1990-1994	5
1995-1999	12
2000-2004	22

The steeply increasing publication rate is evident.

Location Twenty-two studies have been conducted in North America, 18 in the USA and four in Canada. Thirteen studies have been conducted in Europe in a total of 10 countries, with no more than two from any country. Three studies have been in Turkey, two in the Middle East, three in India or the Far East, three in Africa and one in New Zealand. In all, studies have been

conducted in 22 different countries, which represents quite an extensive geographical coverage (though no studies have been reported from Central or South America).

Most of the studies have been conducted in specific cities or areas of the country, though (see Table 1) results have been reported for two nationwide studies in the USA and one in France. One study in Canada was based on nine regions.

Number of asthmatic subjects Based on the publication that considered the largest number of asthmatic subjects, the distribution of study size is as follows:

Study size	Number of studies
17-50	8
51-100	7
101-250	18
251-500	6
501-1000	7
1001-3010	1

The smallest study involves only 17 asthmatic subjects, while the largest is the nine region study in Canada (Dales et al., 2002) involving 3010. The median study size is 167.

Sex of subjects All studies either included both sexes, or did not state the sex of the subjects. Generally, there were more boys than girls, with the percentage of boys up to 76% (Table 1). Exceptions were the studies in Baltimore (Morkjaroenpong et al., 2002) and Seattle (Abulhosn et al., 1997) with about 40% boys.

Age of subjects Table 1 shows the age range of the subjects where available or, except for one study where no information on age was provided,

the mean or median age. Of the 43 studies that provided age range data, the number of studies where the range covered specific ages was as follows:

Age	0	1	2	3	4	5	6	7	8	9
Studies	7	13	16	22	25	31	35	36	35	35

Age	10	11	12	13	14	15	16	17	18	19
Studies	33	31	28	23	19	16	11	8	5	3

It can be seen that age 7 was the most commonly studied, with over 30 of the 43 studies providing data for ages in the range 5 to 11. The number of studies including infants (aged 0-1) or young adults (aged 16-19) was considerably less. The mean number of ages covered by the studies was 10, so it is clear that the tendency was not to concentrate on a very limited age range, though some studies did.

Smoking habits For 33 of the 47 studies (70%) no mention was made of smoking by the child, though some were based on children so young that smoking could effectively be ruled out. For one study, attention was restricted to children reported never to have smoked (Venners et al., 2001); while a publication from NHANES III (Chapman et al., 2003) was restricted to children with a lifetime consumption of 5 packs at most. In another analysis from NHANES III (Mannino et al., 2002) and in nine other studies (indicated by "No" in the final column in Table 1) current smokers were excluded. In three studies (and in an early analysis from the Vancouver study (Murray & Morrison, 1986) a few smokers were included in the analysis. The largest proportion of smokers was the 5% of all subjects in the study reported by Hu et al., 1997, although the proportion of smokers among the asthmatics was unknown.

TABLE 1

Some details of the studies in children

Publication[a]	Location[b]	Country[b]	Number of asthmatics[c]	% male[c,d]	Age[c,e]	Includes smokers[c,f]
O'Connell & Logan, 1974	Minnesota	USA	35[g]	60	2-16	NK
Aderele, 1982	Ibadan	Nigeria	380	62	1-13	No
Gortmaker et al., 1982	Michigan and Massachusetts	USA	217	NK	0-17	NK
Fergusson & Horwood, 1985	Christchurch	New Zealand	141[h]	NK	0-6	NK
Murray & Morrison, 1986	Vancouver	Canada	(94)	(65)	(7-17)	(2)
Murray & Morrison, 1988			(240)	(68)	(7-17)	(No)
Murray & Morrison, 1989			(414)	70	(1-17)	(No)
Murray & Morrison, 1992			(240)	(NK)	(7-17)	(No)
Murray & Morrison, 1993			807	(NK)	1-17	No
Evans et al., 1987	New York	USA	191	60	4-17	No
O'Connor et al., 1987	Boston	USA	21	62	5-9	No
Martinez et al., 1988	Viterbo	Italy	22	NK	9	NK
Weitzman et al., 1990b	Nationwide	USA	117	NK	0-5	NK
Weitzman et al., 1990a			(110)	63	(2-5)	(NK)
Lilienfeld et al., 1990*	New York	USA	(107)	(NK)	(3-14)	(NK)
Ehrlich et al., 1992			107	62	3-14	No
Frischer et al., 1992	Freiburg	Germany	171	NK	M7.3	NK
Frischer et al., 1993			(113)	(NK)	(D7.3)	(NK)
Meinert et al., 1994			(162)	(NK)	(8)	(NK)
Salmun et al., 1992*	Portland	USA	(199)	(NK)	(0-13)	(NK)
Chilmonczyk et al., 1993			199	72	0-13	NK
Ogborn et al., 1994	Baltimore	USA	56	57	3-11	NK
Abulhosn et al., 1995*	Seattle	USA	(22)	(NK)	(2-9)	(NK)
Abulhosn et al., 1997			22	41	2-13	NK
Chan & Chen, 1995*	Taiwan	Taiwan	46	NK	NK	NK
LeSon & Gershwin, 1995	Davis	USA	300	55	5-12	NK
Strachan & Carey, 1995	Sheffield	England	486	NK	12-18	NK
MacArthur et al., 1996	Toronto	Canada	68	71	D3	NK
Meijer et al., 1996	Zwolle	Netherlands	55	60	M9.3	NK
Callén Blecua et al., 1997	San Sebastian	Spain	312	NK	3-19	1
Hu et al., 1997	Chicago	USA	167	51	10-11[i]	5%[j]
Seidler et al., 1998	Lower Saxony	Germany	200	65	0-8	NK
Dubus et al., 1998	Marseilles	France	(46)	(57)	(5-14)	No
Oddoze et al., 1999			90	60	4-14	(NK)
Shamssain & Shamsian, 1999	N.E.England	England	685[k]	59	6-7	NK
Wafula et al., 1999	Nairobi	Kenya	150	60	0-10	NK
Al Ghamdy et al., 2000	Al-Majmaah	Saudi Arabia	606	69	<13[l]	NK

TABLE 1 (Continued)

Publication[a]	Location[b]	Country[b]	Number of asthmatics[c]	% male[c,d]	Age[c,e]	Includes smokers[c,f]
El-Dahr et al., 2000*	New Orleans	USA	17	56	6-16	No
Güler et al., 2000*	Istanbul	Turkey	47	68	5-15	NK
Gürkan et al., 2000	Diyarbakir	Turkey	140	65	3-15	NK
Li et al., 2000	S.California	USA	749	59	7-19	13
Melén et al., 2000*	Stockholm	Sweden	(144)	(NK)	(1-6)	(NK)
Melén et al., 2001			181	76	1-6	NK
Ratageri et al., 2000	New Delhi	India	120	72	5-15	NK
Schwartz et al., 2000	Kuopio	Finland	74	61	7-12	NK
Crombie et al., 2001	Tayside and Fife	Scotland	438	66	2-12	NK
Ehrlich et al., 2001	Cape Town	South Africa	249	52	6-11	No
Mayo, 2001	Edmonton	Canada	62	55	1-9	NK
Venners et al., 2001	Anqing	China	529	50	8-15	Never
Wilson et al., 2001b	California	USA	87	51	3-12	NK
Dales et al., 2002	9 regions	Canada	3010	52	5-19	NK
Gaspar et al., 2002	Lisbon	Portugal	248	57	1-10	NK
Kalaajieh, 2002	Tripoli	Lebanon	288	64	6-15	NK
Mannino et al., 2002	Nationwide	USA	523	59	4-16	No
Chapman et al., 2003			(309)	(60)	(8-16)	Never[m]
Morkjaroenpong et al., 2002	Baltimore and Washington DC	USA	590	40	5-11	NK
Wamboldt et al., 2002	Denver	USA	152	57	7-18	No?[n]
Karadag et al., 2003	Istanbul	Turkey	32	63	1-14	NK
Soussan et al., 2003	Nationwide	France	167	64	6-12	NK
Halterman et al., 2004	Rochester, NY	USA	184	63	3-7	NK

[a] Publications marked with an asterisk are abstracts.
[b] Where there are multiple publications from the same study, the publications are shown together in the table with the location and country shown only for the earliest.
[c] Where there are multiple publications from the same study, the value shown not in brackets is that used for the distributions discussed in the text.
[d] NK = not known.
[e] Age range is shown if available, otherwise mean preceded by M, or median preceded by D.
[f] NK = not known, No = no current smokers, Never = no ever smokers, number = number of known smokers included in analysis.
[g] In follow-up phase. Selected from 400 asthmatics.
[h] 141 with a maternal report of an asthmatic attack, 134 with a diagnosis of asthma or wheezy bronchitis.
[i] 96% were aged 10-11.
[j] 5% of all children, not of all asthmatic children, were smokers.
[k] Approximate estimate.
[l] 48% were aged <1.
[m] Never or <5 packs during life.
[n] Children were asked if they smoked, but the number who did was not stated.

Study design and subject selection Table 2 summarizes details of the study design and subject selection for the 47 studies of asthma exacerbation in children. The majority of the studies fall into two broad classes, studies of asthma **cases** identified through medical records and **cross-sectional** studies of children generally with the classification of asthma being based on questionnaire. There are 26 studies in the first class, of which 9 included an element of follow-up. For some of these studies the cases had been identified from a previous cross-sectional study or cohort study, or were part of a case-control study. There are 13 studies in the second class, 8 involving surveys in schools (one with follow-up) and 5 surveys in the general population.

There are five rarer study designs:

(a) One **cohort** study (Fergusson & Horwood, 1985) which followed children from birth to 6 years with repeated questionnaires used to identify asthmatics;

(b) Three **case-control** studies (Ehrlich et al., 1992; Ratageri et al., 2000; Gaspar et al., 2002) which compared groups of cases with differing asthma presentation (acute vs non-acute or mild vs severe);

(c) Two **within-person** studies (Ogborn et al., 1994; Karadag et al., 2003) in which children were compared while having an acute attack and later, when symptom-free;

(d) Three **intervention** studies (El-Dahr et al., 2000; Wilson et al., 2001b; Halterman et al., 2004) which investigated effects of advice to reduce ETS exposure or of school-based provision of medication; and

(e) One **experimental** study (Meijer et al., 1996) which investigated effects of treatment withdrawal.

Apart from giving information on broad study design, Table 2 makes clear the wide variety of definitions of asthma used in the studies, whether based on questionnaire or on medical records.

TABLE 2

Details of study design and subject selection for the studies in children

Publication[a]	Study type	Identification of asthma cases
O'Connell & Logan, 1974	Cases followed for 6 mo to 2 yr	Random from clinic files, children affected by ETS followed
Aderele, 1982	Case	Consecutive cases at asthma clinic
Gortmaker et al., 1982	Population cross-sectional	Questionnaire (ever had asthma)
Fergusson & Horwood, 1985	Cohort – from birth to 6 yrs	Repeated questionnaire (physician diagnosis of asthma/wheezy bronchitis; maternal report of attack)
Murray & Morrison, 1986, Murray & Morrison, 1988, Murray & Morrison, 1989, Murray & Morrison, 1992, Murray & Morrison, 1993	Case	Consecutive referrals at allergy clinic
Evans et al., 1987	Case	From outpatient clinics
O'Connor et al., 1987	School cross-sectional, including all household members	Questionnaire (told by physician has asthma in last 12 months)
Martinez et al., 1988	School cross-sectional	Questionnaire (ever had asthma)
Weitzman et al., 1990b, Weitzman et al., 1990a	Population cross-sectional	Questionnaire (has asthma, had it for 3 months, not cured)
Lilienfeld et al., 1990, Ehrlich et al., 1992	Case-control	Acute: emergency room; non-acute: asthma clinic
Frischer et al., 1992, Frischer et al., 1993, Meinert et al., 1994	School cross-sectional	Questionnaire (physician-diagnosis of asthma or wheezy bronchitis)
Salmun et al., 1992, Chilmonczyk et al., 1993	Case	Routine visit to allergy asthma clinic
Ogborn et al., 1994	Within subject comparison during acute episode and when symptom free 3-4 wks later	Emergency room visit with acute asthma attack
Abulhosn et al., 1995, Abulhosn et al., 1997	Cases followed for 1 mo	All admissions with asthma diagnosis only
Chan & Chen, 1995	Cases monitored for 6 mo	Not known
LeSon & Gershwin, 1995	Case	Asthma admission to tertiary-care medical centre
Strachan & Carey, 1995	Case-control (drawn from school cross-sectional, only cases relevant)	Questionnaire (12+ wheezing attacks, or an attack that limited speech, in last 12 months)
MacArthur et al., 1996	Cases followed for 12 mo	Two admissions to hospital within 12 mo (follow-up period starts at second admission)

TABLE 2 (Continued/1)

Publication[a]	Study type	Identification of asthma cases
Meijer et al., 1996	Experimental, of treatment withdrawal	Symptoms of asthma, increased total IgE and allergy to HDM but not others, FEV>70% and increased BR. Recruited at school (no details)
Callén Blecua et al., 1997	Case	First visit to outpatient clinic
Hu et al., 1997	Population cross-sectional	Questionnaire (ever physician diagnosed asthma)
Seidler et al., 1998	Cases followed for 3 yr	Any contact with participating doctor in 6 month baseline phase and any contact with same doctor in 6 months follow-up phase
Dubus et al., 1998, Oddoze et al., 1999	Case	Referred to respiratory function laboratory
Shamssain & Shamsian, 1999	School cross-sectional	Questionnaire (ever had asthma)
Wafula et al., 1999	Case	Consecutive cases at clinic or ward with 2+ previous episodes of wheezing
Al Ghamdy et al., 2000	Case	Consecutive cases at health care centres and clinics
El-Dahr et al., 2000	Intervention trial on cases of effect of cessation advice	Not known
Güler et al., 2000	Cases, followed for 1 yr	Not known
Gürkan et al., 2000	Cases (studied retrospectively for 13 mo – 4 yrs)	All first admissions for asthma during 3 yr period
Li et al., 2000	Population cross-sectional	Questionnaire (physician diagnosed asthma)
Melén et al., 2000, Melén et al., 2001	Cases followed for 2 yrs	Referred to paediatric clinics
Ratageri et al., 2000	Case-control (only cases relevant)	Consecutive cases with severe or mild asthma at clinic of tertiary hospital
Schwartz et al., 2000	School cross-sectional (3 mo diary study)	Questionnaire (ever doctor-diagnosed asthma, or wheezing or shortness of breath with wheezing in last 12 mo)
Crombie et al., 2001	Case	From GP record (and previously took part in intervention trial of advice to reduce ETS)
Ehrlich et al., 2001	Case (drawn from school cross-sectional study)	Questionnaire (parent-reported asthma and 1+ symptom last 12 mo, or 4+ symptoms last 12 mo)
Mayo, 2001	Case	Admitted with acute exacerbation without infection
Venners et al., 2001	Case	Physician diagnosed (had to have at least one sibling and 0 or 1 parents with asthma)
Wilson et al., 2001b	Intervention trial on cases of advice to reduce ETS	Visited emergency room or urgent clinic or hospitalised for acute asthma in last yr, and ETS exposed

TABLE 2 (Continued/2)

Publication	Study type	Identification of asthma cases
Dales et al., 2002	Cases (drawn from school cross-sectional study)	Questionnaire (ever physician-diagnosed asthma and symptoms, attack or medication in last 12 mo)
Gaspar et al., 2002	Case-control	All acute asthma emergency room admissions and matched outpatient cases
Kalaajieh, 2002	Cases followed for up to 8 yr	All acute emergency room admissions
Mannino et al., 2002, Chapman et al., 2003	Population cross-sectional	Questionnaire (ever physician diagnosed asthma)
Morkjaroenpong et al., 2002	Case	All children with asthma diagnosis on school health records
Wamboldt et al., 2002	Cases (drawn from cohort study)	From school (receiving daily medication) or from insurance records (medication in last 6 mo or visit to allergist in last yr) but excluding 6+ steroid bursts or 2+ hospitalisations in last yr, or ever intubated
Karadag et al., 2003	Comparison during acute episode and when symptom free 4 wks later	Consecutive admissions to emergency clinic with acute asthma
Soussan et al., 2003	Cases with 3 yr follow-up	First two cases of recently diagnosed asthma (excluding severe cases) at each chest specialist in France, and on anti-inflammatory medication at 12 mo follow-up
Halterman et al., 2004	Intervention trial on cases of school-based provision of medication	All children with 2+ symptom days/wk, 2+ symptom nights/mo, 3+ acute visits in last yr or 1+ hospitalisation in last yr identified from school medical records.

[a] Multiple publications from the same study are separated by commas.

Markers of exposure

Table 3 shows for each study whether data are available by ETS exposure, by a cotinine-based marker or by smoking in pregnancy, as well as giving details of the actual exposure indices used. Of the 47 studies, all but three (marked by a dash in the relevant column) report results for an index of ETS exposure. Although a few of the studies only present results relating to maternal smoking, the great majority consider smoking by other household members, including the father. Relatively few consider exposure outside the home, such as at day care (Chilmonczyk et al., 1993) or in all locations (Ogborn et al., 1994). Rather more studies take into account not only whether household members smoke, but also whether the smoking occurred inside the home. Eight studies report results for a cotinine based marker, in most cases based on urine samples, though one study reports results based on saliva cotinine (Crombie et al., 2001) and one on serum cotinine (Mannino et al., 2002).

TABLE 3

Indices of exposure to ETS and smoking in pregnancy
for which results are reported for the studies in children

Publication[a]	Index of ETS exposure	Cotinine	Smoking in pregnancy
O'Connell & Logan, 1974	Parents quit or continued		
Aderele, 1982	Household members smoke regularly		
Gortmaker et al., 1982	Mother smokes		
Fergusson & Horwood, 1985	Parents smoke		
Murray & Morrison, 1986, Murray & Morrison, 1988, Murray & Morrison, 1989, Murray & Morrison, 1992, Murray & Morrison, 1993	Parents smoke		
Evans et al., 1987	Household members smoke		
O'Connor et al., 1987	Parents smoke		
Martinez et al., 1988	Parents smoke		
Weitzman et al., 1990b, Weitzman et al., 1990a	-		Mother
Lilienfeld et al., 1990, Ehrlich et al., 1992	Household members smoke	Urine CCR	
Frischer et al., 1992, Frischer et al., 1993, Meinert et al., 1994	Mother, Father smokes[b]		Mother
Salmun et al., 1992, Chilmonczyk et al., 1993	Household or day care smoking	Urine CCR	
Ogborn et al., 1994	ETS in any location in last 48 hours	Urine cotinine, CCR	
Abulhosn et al., 1995, Abulhosn et al., 1997	Parents smoke		
Chan & Chen, 1995	-	Urine CCR	
LeSon & Gershwin, 1995	Parents, family, room-mates smoke		
Strachan & Carey, 1995	Parents smoke (at home)		Mother[c]
MacArthur et al., 1996	Household members smoke		
Meijer et al., 1996	Parents smoke		
Callén Blecua et al., 1997	Parents smoke		
Hu et al., 1997	Mother smokes		Mother
Seidler et al., 1998	Parents smoke (at home)		
Dubus et al., 1998, Oddoze et al., 1999	Parents smoke[d]	Urine cotinine, CCR[d]	

TABLE 3 (Continued)

Publication[a]	Index of ETS exposure	Cotinine	Smoking in pregnancy
Shamssain & Shamsian, 1999	Parents smoke		
Wafula et al., 1999	Household ETS		
Al Ghamdy et al., 2000	Parents smoke		
El-Dahr et al., 2000	Parents smoking normally then reducing		
Güler et al., 2000	Parents smoke		Mother[e]
Gürkan et al., 2000	Mother smokes, Indoor smoking (at home)		
Li et al., 2000	Mother smokes		Mother
Melén et al., 2000, Melén et al., 2001	Parents smoke		
Ratageri et al., 2000	Family members smoke		
Schwartz et al., 2000	Smokers at home		
Crombie et al., 2001	Parents smoke	Saliva cotinine	
Ehrlich et al., 2001	Parents smoke		Mother[f]
Mayo, 2001	Parents 1+ pack/day		
Venners et al., 2001	Father smokes[g]		
Wilson et al., 2001b	Intervention v usual care		
Dales et al., 2002	Regular ETS at home		
Gaspar et al., 2002	Household smoking		
Kalaajieh, 2002	-		Household[h]
Mannino et al., 2002, Chapman et al., 2003	Smokers at home	Serum cotinine[i]	
Morkjaroenpong et al., 2002	Caregiver smokes at home[j]		
Wamboldt et al., 2002	Household members smoke		
Karadag et al., 2003	Household members smoke	Urine cotinine	
Soussan et al., 2003	Household members smoke (at home)		
Halterman et al., 2004	Smokers at home		

[a] Multiple publications from the same study are separated by commas.
[b] Results for father smoking only reported in Frischer et al., 1993.
[c] Around time of birth.
[d] Parental smoking and urinary CCR results only reported in Oddoze et al., 1999.
[e] Also passive smoking by mother in pregnancy.
[f] Also results relating to mother ever smoked and parents smoked in child's first year.
[g] Mothers all never smokers and exsmoking fathers excluded.
[h] At birth.
[i] Household smoking results only used in Chapman et al., 2003; cotinine results only reported in Mannino et al., 2002.
[j] Caregivers who smoke, but not at home, excluded.

Adjustment for potential confounding variables

Of the 47 studies, 23 (49%) did not adjust for any potential confounding variables at all, not even age.

One of these (Ogborn et al., 1994) was a study of changes within child, where adjustment was not relevant. There were also some studies where the groups being compared were noted to be similar in respect of certain variables – such as sex, age, ethnicity and SES (Ehrlich et al., 1992); sex, age and asthma severity (Abulhosn et al., 1997); or body mass index (Dubus et al., 1998) – but in most of these the issues of confounding by other variables had not been addressed at all.

Table 4 gives details of the potential confounding variables taken account of in the different studies. Where a variable is listed for a study, it was taken account of in some of the relevant analyses, though not necessarily in all. Variables indicated in parentheses were considered as potential confounders but found to make little difference, with the analyses presented not actually adjusting for them.

Of the 24 studies listed, two (Martinez et al., 1988; Frischer et al., 1992) involved children of such a limited age range that age adjustment was not needed, and one was a study of changes within child (Wilson et al., 2001b). Of the other 21, only five (Gortmaker et al., 1982; Evans et al., 1987; Ratageri et al., 2000; Gaspar et al., 2002; Halterman et al., 2004) apparently ignored age.

Of the 23 between-child comparison studies considered in Table 4, 14 considered the sex of the child, with 10 actually presenting results adjusted for it.

There are a wide variety of other factors taken into account in at least one study. The broad types of variables considered most commonly, with the number of studies adjusting for them (or determining that they did not have a material confounding effect) are as follows:

child's medical history (18)
family medical history or parental age (12)
socio-economic status (SES) or parental education (9)
height, weight or BMI (6)
pets (5)
location (including urban/rural) (5)
family composition (4)
child's education or day care (4)

Not included among the variables listed in Table 4 are indices of ETS exposure. A few studies presented analyses linking an endpoint of interest to one index of ETS exposure, while adjusting for another (Murray & Morrison, 1988; Murray & Morrison, 1989; O'Connor et al., 1987; Frischer et al., 1992; Crombie et al., 2001).

TABLE 4

Potential confounding variables taken account of in the studies in children

Publication	Age[a]	Sex[a]	Others[a,b]
Gortmaker et al., 1982	No	No	Sample (= urban/rural)
Murray & Morrison, 1986, Murray & Morrison, 1988, Murray & Morrison, 1989, Murray & Morrison, 1992, Murray & Morrison, 1993	Yes	Yes	Recent respiratory infection, recent medication, positive skin test, family history of asthma, hot air heating, wood stove, gas range, pets, duration of asthma, age of onset of asthma, number of siblings, atopic dermatitis
Evans et al., 1987	No	No	Days with asthma symptoms per month
O'Connor et al., 1987	(Yes)	(Yes)	History of cold in last two weeks, predicted FEV, (height, atopy)
Martinez et al., 1988	All 9	Yes	Atopy
Frischer et al., 1992, Frischer et al., 1993, Meinert et al., 1994	All 7-8	Yes	Prematurity, pneumonia in first year, atopy, education
Chilmonczyk et al., 1993	Yes	Yes	Day-care attendance, mother's age and education
Meijer et al., 1996	Yes	No	Pets, house dust mite exposure, PC_{20}
Seidler et al., 1998	Yes	Yes	Parental education, frequency of asthmatic episodes, infection-associated asthma, asthma on exertion, neurodermitis, hospitalisation, speciality of treating physician, parental asthma, sensitivity to exhaust gases, region
Gürkan et al., 2000	Yes	(Yes)	(Allergic conjunctivitis, eczema, frequent URI, familial allergy, +ve SPT, IgE, urban residency, using inhaled steroids)
Li et al., 2000	Yes	No	Community, school grade, spirometer, pressure, technician, height, race
Melén et al., 2000, Melén et al., 2001	Yes	No	Heredity, cat, dog, window condensation, 3+ SPT (possibly cat allergen, IgE cat, but not clear if univariate or multivariate)
Ratageri et al., 2000	No	No	Age of onset, past history lung disease, family history asthma, allergy, breastfeeding, overcrowding, pets, cooking, worm infestation, eosinophil count, air pollution
Schwartz et al., 2000	Yes	Yes	Height, weight, atopy, father's education, medication, day of study, weekend, temperature, humidity
Crombie et al., 2001	Yes	(Yes)	Severity of asthma perceived and based on treatment step, number of children in family (parental age)
Ehrlich et al., 2001	Yes	Yes	Height, atopy, baseline FEV_1, asthma group, symptom score, medical insurance (parental education, mother contributes to income, hay fever, eczema, familial asthma)
Venners et al., 2001	Yes	No	Height, weight, father's education
Wilson et al., 2001b	No[c]	No[c]	Baseline outcome

TABLE 4 (Continued)

Publication	Age[a]	Sex[a]	Others[a,b]
Gaspar et al., 2002	No	No	Prior asthma hospitalisation, atopy, maternal asthma, last year asthma admission, onset of symptoms before 12 mo, attendance at day care or kindergarten, family size
Kalaajieh, 2002	(Yes)	(Yes)	Respiratory infections (atopic dermatitis, allergic rhinitis, IgE, eosinophil)
Mannino et al., 2002, Chapman et al., 2003	Yes	Yes	Race/ethnicity, SES, family size, parental history asthma, sitting height, parental history allergy or asthma, height, body mass, skinfold thickness, gas stove, income, pets, physical activity
Morkjaroenpong et al., 2002	Yes	No	Caregiver education, asthma primary care, medication
Soussan et al., 2003	Yes	Yes	Father's occupation, atopy, sensitisation to mites, cats/dogs, pollen and mould, perennial asthma, perennial/seasonal allergic rhinitis, atopic dermatitis, asthma in father, mother and sibs, gas cooking, mould, cat, dog, carpet, mattress type, medication compliance.
Halterman et al., 2004	No	(Yes)	(Baseline severity, baseline medication, race, ethnicity, parental age, parental education, poverty)

[a] Variables which were considered, found not to have any material confounding effect, but not adjusted for in any analysis are indicated by parentheses.
[b] The list of other variables considered is that taken account of in at least some relevant analysis. Not all analyses necessarily considered all of them.
[c] Within-child study so not necessary to adjust.

3.2 Results

3.2.1 Asthma exacerbation and severity

A wide variety of indices of asthma exacerbation and severity have been used. These have been classified into nine groups, with results presented in Tables 5 to 13.

The layout of each table is similar, with columns for publication, endpoint, exposure and result. In the simplest case there is a single endpoint and single exposure with the result usually expressed as an odds ratio (OR) comparing the exposed and unexposed or as means for the exposed and unexposed. In some cases the comparison is different, e.g. highest vs lowest cotinine group, but this is made clear in the tables. Where results are given by level of endpoint (e.g. mild, moderate, severe asthma) or by level of exposure (e.g. 0, 1-9, 10+ cigs/day by the mother) the results are presented relative to a defined comparison (base) group. Where 95% confidence intervals are not available, p values are presented as $p<0.001$, $p<0.01$, $p<0.05$ or NS ($p\geq0.05$).

Each table in general presents a single set of results from one study. Where there are multiple publications from the same study, the results selected are generally those based on the largest number of subjects, with data given in papers preferred to data given in abstracts.

Hospitalisation (Table 5) Nine studies have related hospital admissions, or in one study (Dales et al., 2002) hospitalisations or emergency room visits, to ETS exposure. Of these four studies (Gürkan et al., 2000; Mayo, 2001; Dales et al., 2002; Kalaajieh, 2002) have reported a significant increase in frequency or length of admissions in relation to parental smoking or other indices of ETS exposure at home. A non-significant positive association was also seen in another study (MacArthur et al., 1996). Of the remaining four studies, two (Evans et al., 1987; Halterman et al., 2004) reported no significant association, but in fact provided little useful information, and one (Wilson et al., 2001b) reported a non-significant reduction in hospitalisation in the intervention group which did not actually show any clear reduction in ETS exposure relative to the usual care group. The final study (Mannino et al., 2002) reported a significantly reduced risk of hospitalisation for asthma in children with the highest cotinine levels. The authors considered that this negative association might have been because parents altered their smoking habits as a result of the hospitalisation, but this seems somewhat speculative. Their study generally found a tendency for cotinine to be positively associated with other asthma severity outcomes, and other studies, such as Dales et al., 2002, reported a positive association between current ETS exposure and previous hospitalisation. The explanation for this aberrant result, which conflicts with the general tendency of a positive relationship is unclear. However, as it was quite highly significant (OR = 0.2, 95% CI 0.1-0.5) and based on a nationally representative US sample from NHANES III, it should not be lightly dismissed.

Only one study (Weitzman et al., 1990b) reported findings for maternal smoking in pregnancy This found that the mean number of overnight hospitalisations (from any cause) was unrelated to the number of cigarettes smoked by the mother (1.1, 1.3 and 1.0 for 0, 1-9 and 10+ cigs/day).

TABLE 5

Summary of results relating hospitalisation in children to ETS exposure

Publication	Endpoint	Exposure	Result[a]
Evans et al., 1987	Hospitalisation for asthma in last year	Household member smokes	Not significant (data not shown)
MacArthur et al., 1996	Readmission for asthma within a year	Household member smokes	OR 1.44 (0.87-2.37)
Gürkan et al., 2000	Multiple admissions per year	Mother smokes Indoor smoking at home	OR 3.25 (1.13-8.85)[b] OR 2.55 (1.12-5.82)[c]
Mayo, 2001	Duration of stay for asthma	Parent(s) smoke 1+ pack/day	Mean 4.35 v 2.86 days ($p<0.05$)
Wilson et al., 2001b	Hospitalisation for asthma in year	Intervention effect	OR 0.34 (NS)[d]
Dales et al., 2002	Hospitalisation for asthma or emergency room visit in last year	Regular ETS at home	OR 1.55 (1.22-1.97)
Kalaajieh, 2002	Multiple admissions for asthma per year	Mother smokes (at birth) Indoor smoking (at birth)	OR 6.10 (2.98-12.55)[e] OR 3.06 (1.81-5.18)
Mannino et al., 2002	Hospitalisation for asthma in last year	Highest v lowest cotinine[f] Intermed v lowest cotinine	OR 0.2 (0.1-0.5)[g] OR similar to that for highest v lowest, but NS
Halterman et al., 2004	Hospitalisation for asthma in study year	Smokers in home	OR 0.63 (0.15-2.58)

[a] Unadjusted for covariates except where stated.
[b] Adjusted for age (for mother smokes result only).
[c] Indoor smoking found to be non-significant in multiple logistic regression analysis with maternal smoking already included in the model
[d] Intervention v control, with adjustment for baseline differences.
[e] OR for maternal smoking noted to be significant ($p<0.001$) in multiple logistic regression analysis, with recurrent upper respiratory tract infection the only other factor included, but OR not given.
[f] Serum cotinine groups are 0.050 to 0.115 ng/ml = low, 0.116 to 0.639 ng/ml = intermediate, and 0.640 to 20 ng/ml = high.
[g] Adjusted for age, race/ethnicity, SES, family size and parental history of asthma.

Emergency room visits (Table 6) Six studies have considered emergency room visits, urgent consultations or other related endpoints. Four of these have also reported results for hospitalisations in Table 5, and for one of them (Dales et al., 2002) the data, for hospitalisations or emergency room visits, are the same as presented there. Three of the studies (Evans et al., 1987; LeSon & Gershwin, 1995; Dales et al., 2002) reported a significant positive association with ETS exposure, the most striking of which was the hugely strong relationship with whether the admission requires intubation (LeSon & Gershwin, 1995). A further study (Wilson et al., 2001b) also reported a significant reduction in acute medical visits in the intervention group though, as noted above, it was not clear if in fact that group had reduced ETS exposure. Other studies (Hu et al., 1997; Halterman et al., 2004) reported no significant association. In total, however, the data provide evidence of an association of emergency room visits with ETS exposure.

Only one study (Hu et al., 1997) has reported results for maternal smoking in pregnancy, finding no association.

TABLE 6

Summary of results relating emergency room visits and urgent consultations in children to ETS exposure

Publication	Endpoint	Exposure	Result[a]
Evans et al., 1987	Emergency room visits for asthma in last year	Household member smokes	Mean 3.46 v 2.12 ($p<0.01$)[b]
LeSon & Gershwin, 1995	Asthma admission requires intubation	ETS from parents, family members or room mates	OR 22.4 (7.4-68.0)[c]
Hu et al., 1997	Emergency room visit for asthma in last year	Mother smoked in last week	OR 0.86 (0.40-1.89)
Wilson et al., 2001b	More than one acute medical visit for asthma in last year	Intervention effect	OR 0.32 ($p<0.05$)[d]
Dales et al., 2002	Hospitalisation for asthma or emergency room visit in last year	Regular ETS at home	OR 1.55 (1.22-1.97)
Halterman et al., 2004	3+ acute visits for asthma in study year	Smokers in home	OR 1.23 (0.62-2.43)

[a] Unadjusted for covariates except where stated.
[b] Adjusted for days with asthma symptoms per month.
[c] From the data presented we estimate OR 22.2 (4.8-102.9).
[d] Intervention v control, with adjustment for baseline difference.

Restricted activity (Table 7) Six studies have related indices of restricted activity to ETS exposure. No significant association was reported in four studies (Gortmaker et al., 1982; Wilson et al., 2001b; Mannino et al., 2002; Morkjaroenpong et al., 2002). However one study (Halterman et al., 2004) reported significantly more school absences where there were smokers in the home, and another (El-Dahr et al., 2000) reported that the child had significantly more days with restricted activity during the three month period where the parents were smoking normally than during the following three month period after encouragement to quit smoking. The design of the latter study, reported only as an abstract, does not include a valid control group. The data for restricted activity, taken as a whole, do not demonstrate the existence of an association with ETS exposure.

No data are available relating restricted activity to smoking in pregnancy.

TABLE 7

Summary of results relating restricted activity in children to ETS exposure

Publication	Endpoint	Exposure	Result[a]
Gortmaker et al., 1982	Functional impairment[b]	Mother smokes cigarettes	OR 1.43 (0.79-2.65)[c]
El-Dahr et al., 2000	% days with restricted activity	Parent smoking normally, then reducing	10% vs 5% ($p<0.05$)
Wilson et al., 2001b	% with activity limitation in 2 wks before interview	Intervention effect	OR 0.64 (NS)[d]
Mannino et al., 2002	6+ school absences in last year	Highest v lowest cotinine[e] Intermed v lowest cotinine	OR 1.8 (0.9-3.6) OR similar to that for highest v lowest, and NS
Morkjaroenpong et al., 2002	Limited physical activity because of asthma in past 6 months	ETS exposure from caregiver: 0 cigs/day (base) 1-9 cigs/day 10+ cigs/day Any	OR 1.00 0.57 (0.35-0.93) 1.03 (0.60-1.77) 0.74 (0.50-1.10)
	School days missed because of asthma in past 6 months	ETS exposure from caregiver: 0 cigs/day (base) 1-9 cigs/day 10+ cigs/day Any	Mean 6.7 6.2 (NS) 8.4 (NS) 7.2 (NS)
Halterman et al., 2004	School absences because of asthma during study year	Smokers in home	Mean 10.28 vs 5.92 ($p<0.01$)

[a] Unadjusted for covariates except where stated.
[b] Functional impairment = affects ability to attend school or do any of the things a child of that age usually does.
[c] Adjusted for study sample (= urban/rural).
[d] Intervention v control, with adjustment for baseline difference.
[e] Serum cotinine groups are 0.050 to 0.115 ng/ml = low, 0.116 to 0.639 ng/ml = intermediate, and 0.640 to 20 ng/ml = high.

Acute and non-acute asthma (Table 8) Two studies (Ogborn et al., 1994; Karadag et al., 2003) have compared ETS exposure in children at a time when they had an acute asthma attack and a few weeks later when they were well. Neither of these studies reported any significant increase in cotinine during the acute period, though one study (Ogborn et al., 1994) reported significantly increased reported ETS exposure based on one index, but not others. There were also two studies of case-control design (Ehrlich et al., 1992; Gaspar et al., 2002), where the cases were acute asthmatics and the controls non-acute asthmatics. The first of these reported no evidence of an association, but the second reported significant associations with various indices of ETS exposure, the strongest being the odds ratio of 6.63 (2.5-17.8) for any ETS exposure. The overall data do not show a clear difference in ETS exposure between acutely and non-acutely asthmatic children.

No data were available relating acute and non-acute asthma to smoking in pregnancy.

TABLE 8

Summary of results comparing ETS exposure in acute and non-acute asthmatic children

Publication	Endpoint	Exposure	Result[a]
Ehrlich et al., 1992	Acute v nonacute asthma (case-control study)	Any smoker in home	OR 0.84 (0.37-1.89)
		Cigs/day by all smokers	Mean 7.7 v 10.7 (NS)
		Maternal caregiver smokes	OR 0.64 (0.28-1.44)
		CCR 30+ ng/mg	OR 0.90 (0.39-2.06)
		CCR ng/ml	Mean 46.2 v 38.5 (NS)
Ogborn et al., 1994	Acute vs when well 3-4 wks later (within child comparison)	Cotinine (ng/ml)	Mean 81 v 77 (NS)
		CCR (ng/mg)	Mean 93 v 97 (NS)
		CCR 30+ ng/mg	80% v 82% (NS)
		Hours exposed last 48 hrs	Mean 32 v 32 (NS)
		N cigs smoked at home last 48 hrs	Mean 31 v 25 (NS)
		ETS some or a lot	56% v 44% ($p<0.05$)
Gaspar et al., 2002	Acute vs outpatient asthmatics (case-control study)	Any ETS	OR 6.63 (2.5-17.8)[b]
		Parents smoke	OR 3.51 (2.1-6.0)
		Father smokes	OR 3.0 (1.8-4.9)
		Mother smokes	OR 1.8 (1.0-3.1)
		Other residents at home smoke	OR 1.28 (0.8-2.0)
Karadag et al., 2003	Acute vs when well 4 wks later (within child comparison)	Cotinine (ng/ml)	Mean 295 v 229.6 (NS)
		CCR (ng/mg)	Mean 314.6 v 203.8 (NS)
		CCR 30+ ng/mg	81% v 96% (NS)

[a] Unadjusted for covariates except where stated.
[b] For exposure "Any ETS" only, the odds ratio is adjusted for the variables given in Table 4.

Asthma medication (Table 9) Seven studies have related use of asthma medication to ETS exposure. In one study of children hospitalised for asthma (Abulhosn et al., 1997), among those living in homes where at least one parent smoked beta-agonist therapy increased slightly over the 4 weeks following discharge, while among those living in nonsmoking homes it substantially reduced. In another study (Schwartz et al., 2000) a within-child analysis estimated that the odds of bronchodilator use were increased 10 fold in association with ETS exposure on the previous day. However, this estimate had very wide confidence limits of 1.3-38.7 and was only marginally significant. Another study (Murray & Morrison, 1988) also reported a marginally significant positive association of recent bronchodilator use with the number of cigarettes smoked by the mother, but not with the number smoked by the father. The other four studies cited in Table 9 reported no significant association or indeed any consistent tendency for asthma medication to be increased where ETS exposure was present. The overall data in Table 9 do not clearly demonstrate an association of ETS exposure with use of asthma medication.

In one of the studies considered in Table 9 (Hu et al., 1997) use of medication was found not to be associated with smoking in pregnancy. Another study (Weitzman et al., 1990b) reported some positive association between current use of asthma medication and maternal smoking in pregnancy. This was not significant for overall smoking, OR 1.75 (0.75-4.07); but was significant for smoking of 10+ cigs/day by the mother, OR 2.66 (1.02-6.91).

TABLE 9

Summary of results relating use of asthma medication in children to ETS exposure

Publication	Endpoint	Exposure	Result[a]
Murray & Morrison, 1988	Recent bronchodilator use	N cigs smoked by mother N cigs smoked by father	Correlation r = 0.12 (p = 0.04) Correlation r = -0.05 (NS)
Abulhosn et al., 1997	Reduction in beta-agonist therapy following hospital discharge (treatments in week 1 and week 4)	Smoking by parents	From 15.3 to 18.0 v 20.8 to 8.9 (p<0.001)
Hu et al., 1997	Medication in last 2 wks	Mother smoked in last wk	OR 0.67 (0.30-1.52)
Dubus et al., 1998	Anti-inflammatory treatment	Detectable cotinine	OR 0.66 (0.19-2.35)
El-Dahr et al., 2000	Bronchodilator use	Parent smoking normally, then reducing	Use said to decrease, but data inconsistent and no statement of significance
Schwartz et al., 2000	Bronchodilator use	ETS on previous day	OR = 10.3 (1.3-38.7)[b]
Halterman et al., 2004	Days using rescue inhaler per 14 days	Smokers in home	Mean 2.51 v 1.97 (NS)

[a] Unadjusted for covariates except where stated.
[b] Adjusted for child (within-child analysis).

Health contacts for asthma (Table 10) Three studies have related ETS exposure to frequency of health contacts. Two studies have reported a somewhat higher frequency of contacts in the most ETS exposed children. In one of these (Fergusson & Horwood, 1985) the increase in frequency was only moderate, and the statistical significance was not known, and in the other (Mannino et al., 2002) the excess was larger but not statistically significant. In the third study (Crombie et al., 2001), no significant relationship was seen with cotinine level, but a statistically significant negative relationship was seen with three questionnaire-based indices of ETS exposure. The authors of this study, which was restricted to children with at least one smoking parent, suggested that "this could be due to a lack of awareness of asthma symptoms among heavy smokers or a reluctance to visit the GP". Factors such as social class or education, which one might expect to be correlated with awareness of asthma symptoms or reluctance to visit the GP, were not adjusted for in this study. It should be noted that the multivariate analysis conducted strangely included both cotinine and parental smoking, two correlated markers of ETS exposure. The interpretation of such an analysis is not straightforward. Clearly the overall data do not demonstrate an increase in health contacts in relation to ETS exposure.

No information is available relating health contacts to smoking in pregnancy.

TABLE 10

Summary of results relating health contacts for asthma in children to ETS exposure

Publication	Endpoint	Exposure	Result[a]
Fergusson & Horwood, 1985	Annual rate of medical consultations for asthma per asthmatic child	Mother smokes cigarettes	Rate
		None	0.80
		1-10/day	0.53
		11+/day	0.96 (Sig NK)
		Father smokes cigarettes	Rate
		None	0.82
		1-10/day	0.64
		11+/day	0.85 (Sig NK)
Crombie et al., 2001	Health contacts for asthma (GP, medication, asthma clinic) in last 12 mo	No. of parents who smoke	IRR[b]
		Father only (base)	1.00
		Mother only	0.76 (0.64-0.89)
		Both parents	0.78 (0.66-0.93)
		Child cotinine level	IRR
		≤2.0 ng/ml (base)	1.00
		2.1-4.5 ng/ml	0.95 (0.82-1.11)
		>4.5 ng/ml	1.15 (0.98-1.34)
		Amount smoked in home by index parent	IRR
		0-5 cigs/day (base)	1.00
		6-10 cigs/day	0.81 (0.71-0.92)
		11-15 cigs/day	0.70 (0.59-0.83)
		16-20 cigs/day	0.74 (0.61-0.91)
		>20 cigs/day	0.66 (0.47-0.93)
		Frequency of smoking in room with child	IRR
		Never (base)	1.00
		Occasionally	0.76 (0.64-0.91)
		Frequently	0.60 (0.48-0.75)
		Every day	0.66 (0.56-0.77)
Mannino et al., 2002	Physician visit in last year for asthma	Highest v lowest cotinine[c]	OR 1.80 (0.9-3.8)[d]
		Intermed v lowest cotinine	OR similar to that for highest v lowest, and NS

[a] Unadjusted for covariates except where stated.

[b] IRR = incidence rate ratio. Results for number of parents who smoke and child cotinine level are from multivariate analysis which also includes age of child, perceived severity of asthma, severity of asthma by BTS treatment step and number of children in family. The study was restricted to children where at least one parent smoked.

[c] Serum cotinine groups are 0.050 to 0.115 ng/ml = low, 0.116 to 0.639 ng/ml = intermediate, and 0.640 to 20 ng/ml = high.

[d] Adjusted for age, race/ethnicity, SES, family size and parental history of asthma.

Asthma severity (Table 11) Twelve studies have related ETS exposure to severity of asthma. In one early study (O'Connell & Logan, 1974) significantly increased asthma improvement was seen in children of parents who quit smoking compared to children whose parents continued to smoke. The other 11 studies have related asthma severity to indices of current ETS exposure. Significant positive associations were reported in seven of these studies (Aderele, 1982; Murray & Morrison, 1993; Strachan & Carey, 1995; Callén Blecua et al., 1997; Al Ghamdy et al., 2000; Güler et al., 2000; Mannino et al., 2002), with nonsignificant positive associations seen in the remaining four, generally smaller, studies (Wafula et al., 1999; Ratageri et al., 2000; Melén et al., 2001; Wamboldt et al., 2002). However, in those studies that did report significant associations, the associations were not always significant (or even positive) in all analyses. This is most notably evident in the Vancouver study (Murray & Morrison, 1993), where a highly significant ($p<0.001$) positive association between asthma severity and maternal smoking was seen in children studied before July 1986, but a significant ($p<0.05$) negative association was seen in children studied later. Also in another study (Aderele, 1982) a significant positive association was seen if the father or older sibling smoked while a nonsignificant negative association was seen if other household members smoked. Overall, however, the data clearly show a positive association.

Only one study (Güler et al., 2000) related asthma severity to smoking in pregnancy, finding a significant ($p<0.01$) relationship with the number of cigarettes smoked by the mother.

TABLE 11

Summary of results relating asthma severity in children to ETS exposure

Publication	Endpoint	Exposure	Result[a]
O'Connell & Logan, 1974	Asthma improved (basis not known)	Parent quit smoking	RR 3.38 (1.44-7.91)
Aderele, 1982	Severity of asthma (basis not known)	Household adult smokes regularly	OR
	Mild (base)		1.00 (base)
	Moderate		1.20 (0.67-2.15)
	Severe		1.48 (0.87-2.53)
		Father or older sib smokes regularly	OR
	Mild (base)		1.00 (base)
	Moderate		1.79 (0.87-3.67)
	Severe		2.61 (1.37-4.96)
		Other smoker in household	OR
	Mild (base)		1.00 (base)
	Moderate		0.68 (0.28-1.67)
	Severe		0.50 (0.20-1.29)
Murray & Morrison, 1993	Severity score (based on wheeze, wheeze on exertion, medication)	Whole study period	
		Cigs/day by mother	Correlation +0.19
		Cigs/day by father (in same room)	($p<0.05$) Correlation –0.04 (NS)
		Before July 1986	
		Mother smokes	Mean 8.2 v 6.4 ($p<0.001$)
		Father smokes	Mean 7.1 v 6.7 (NS)
		After July 1986	
		Mother smokes	Mean 5.8 v 6.6 ($p<0.05$)
		Father smokes	Mean 6.5 v 6.3 (NS)
Strachan & Carey, 1995	Frequent and speech-limiting attacks v only one of these	Mother smokes now[b]	OR
		0 cigs/day (base)	1.00
		1-10 cigs/day	1.69 (0.99-2.88)
		>10 cigs/day	1.86 (0.91-3.77)
		Any	1.74 (1.10-2.76)
		Father smokes now	OR
		0 cigs/day (base)	1.00
		1-10 cigs/day	1.70 (0.93-3.12)
		>10 cigs/day	1.66 (0.73-3.77)
		Any	1.69 (1.01-2.82)
Callén Blecua et al., 1997	Severe (based on FVC, FEV_1, PEFR and $FEF_{25-75\%}$)	Parents smoke	OR 1.84 (1.12-3.03)
Wafula et al., 1999	Severe (based on frequency of attacks)	Any smoking at home	OR
	Mild (base)		1.00
	Moderate		2.06 (0.96-4.40)
	Severe		Not given

TABLE 11 (continued/1)

Publication	Endpoint	Exposure	Result[a]
Al Ghamdy et al., 2000	Severe (based on Saudi national protocol) Mild (base) Moderate Severe	Parents smoke	OR 1.00 1.81 (1.08-3.03) 2.08 (1.25-3.46)
Güler et al., 2000	Severity score (basis unknown)	N cigs smoked by mother N cigs smoked by father CCR	Correlation $p<0.01$ Correlation $p<0.05$ NS (data not shown)
Ratageri et al., 2000	Severe (= wheeze most days/nights, restricted activity, growth affected, frequent medication) v mild	Any family member smokes 0 cigs/day (base) 1-9 cigs/day 10+ cigs/day Any Father smokes Grandfather smokes	OR[c] 1.00 0.66 (0.23-1.90) 2.22 (0.98-5.01) 1.49 (0.73-3.07) 1.62 (0.78-3.35) 1.22 (0.35-4.24)
Melén et al., 2001	Severe (based on inhibited daily activity and steroid use in last year) v mild/moderate	Smoking at home	OR 3.01 (0.74-12.2)[d]
Mannino et al., 2002	Severity (based on frequency of symptoms/respiratory illnesses in last year) Moderate/severe v mild Severe v moderate/mild	Highest v lowest cotinine[e] Intermed v lowest cotinine	OR 2.7 (1.1-6.8) 1.9 (0.6-5.7) ORs similar to those for highest v lowest, but NS
Wamboldt et al., 2002	Functional severity score	Smoker in household	Mean 8.00 v 7.40 (NS)

[a] Unadjusted for covariates except where stated.
[b] Results stated to be similar for mother smoked at time of child's birth.
[c] Unadjusted odds ratios. Odds ratio adjusted for the variables listed in Table 4 were not given, but were not significant.
[d] Adjusted for age, heredity, cat, dog and window condensation.
[e] Serum cotinine groups are 0.050 to 0.115 ng/ml = low, 0.116 to 0.639 ng/ml = intermediate, and 0.640 to 20 ng/ml high.

Asthma symptoms and acute episodes (Table 12) Fourteen studies have related asthma symptoms or acute attacks to ETS exposure. In six of the studies (Evans et al., 1987; Dubus et al., 1998; Shamssain & Shamsian, 1999; Ehrlich et al., 2001; Wilson et al., 2001b; Morkjaroenpong et al., 2002) no significant effect was seen and in another (Fergusson & Horwood, 1985) the pattern of results did not seem consistent with an association, though significance could not be estimated. In another study (Seidler et al., 1998) an increase in frequency of attacks associated with smoking by the parents was only marginally significant (p=0.05). The other six studies have reported a significant association for at least some of the relevant endpoints studied. By far the strongest associations seen were the about 10 fold increase in cough and phlegm related to smoking in the home in the last two days in the daily diary study in Finland (Schwartz et al., 2000). Significant associations with ETS exposure were also noted with frequency of acute exacerbations (Chilmonczyk et al., 1993), frequency of symptomatic days, but not symptomatic nights (Abulhosn et al., 1997), days with disturbed sleep and with cough, but not wheeze (El-Dahr et al., 2000), lack of symptom control (Soussan et al., 2003) and frequency of symptomatic days and nights (Halterman et al., 2004). Of the three studies that studied cotinine as a marker, one reported an association, with acute exacerbations (Chilmonczyk et al., 1993) and two did not, with crises (Dubus et al., 1998) and, with a symptom, score (Ehrlich et al., 2001). While the overall results are certainly heterogeneous they are clearly strongly suggestive of an association.

None of the studies relate asthma symptoms and acute episodes to smoking in pregnancy.

TABLE 12

Summary of results relating asthma symptoms and acute episodes in children to ETS exposure

Publication	Endpoint	Exposure	Result[a]
Fergusson & Horwood, 1985	Asthmatic attacks (maternal report)	Mother smokes 0 cigs/day 1-10 cigs/day 11+ cigs/day	Annual rate (per asthmatic) 1.59 0.96 2.03 (Sig NK)
		Father smokes 0 cigs/day 1-10 cigs/day 11+ cigs/day	 1.55 1.60 1.46 (Sig NK)
Evans et al., 1987	Frequency of days with symptoms	Household member smokes	No significant effect
Chilmonczyk et al., 1993	Acute exacerbations in past 12 months	ETS exposure from household members or at day-care None Mother or other smokes Mother and other smokes Change per category	Mean 2.2 2.5 3.9 +0.83 (+0.39 to +1.26)[b]
		CCR <10 ng/ml 10-39 ng/ml >39 ng/ml Change per category	 2.1 2.8 3.6 +0.63 (+0.10 to + 1.07)[b]
Abulhosn et al., 1997	Symptomatic days (in mo following discharge) 2+ symptomatic days Symptomatic nights	Smoking by parents	Mean 3.3 v 1.4 ($p<0.05$) RR 4.00 (1.08-14.75) Mean 2.3 v 1.4 (NS)
Seidler et al., 1998	Increase in frequency of asthma attacks during follow-up	Smoking by parents	OR 1.7 (1.0-3.0)[b]
Dubus et al., 1998	Crises per year Symptoms between crises	Detectable cotinine	Mean 4.1 v 4.4 (NS) OR 0.49 (0.15-1.60)
Shamssain & Shamsian, 1999	Speech limitation during wheezing attack in past 12 months	Parents smoking Neither One parent Both parents	 13.1% 14.0% 15.0% (NS)
El-Dahr et al., 2000	Symptom score Days with disturbed sleep Days with cough Days with wheeze	Parents smoking normally, then reducing	Mean 1.00 v 0.54 ($p<0.05$) 15% v 9% ($p<0.01$) 30% v 13% ($p<0.01$) 22% v 15% (NS)
Schwartz et al., 2000	Cough Phlegm production	Smoking in the home in last 2 days	OR 12.4 (2.4-63.3) OR 7.8 (1.4-41.7)
Ehrlich et al., 2001	Symptom score 8-10 v 4-7	CCR (ng/mg)	GMean 64.1 v 72.8 (NS)

TABLE 12 (continued/1)

Publication	Endpoint	Exposure	Result[a]
Wilson et al., 2001b	Symptom-free days per 2 wk Nights awakened per 2 wk	Intervention effect	Mean diff -0.22 (NS)[c] Mean diff -0.37 (NS)[c]
Morkjaroenpong et al., 2002	Nocturnal symptoms at least 2 nights per mo	ETS exposure from caregiver 0 cigs/day (base) 1-9 cigs/day 10+ cigs/day Any	OR[d] 1.00 0.51 (0.30-0.85) 1.31 (0.68-2.50) 0.75 (0.49-1.15)
Soussan et al., 2003	Symptom control[e]	Smoker in home Mother smokes in home	OR 0.34 (0.13-0.91)[f] OR 0.53 (0.20-1.37)
Halterman et al., 2004	Symptom free days (per 2 wk) Symptom days (per 2 wk) Symptom nights (per 2 wk)	Smokers in home	Mean 9.69 v 10.97 ($p<0.01$) Mean 3.07 v 2.07 ($p<0.01$) Mean 3.05 v 2.05 ($p<0.01$)

[a] Unadjusted for covariates except where stated.
[b] Adjusted for the variables given in Table 4.
[c] Intervention v control, with adjustment for baseline differences.
[d] ORs are unadjusted. The authors also report an OR, adjusted for the variables given in Table 4, of 2.83 (1.22-6.55) for 10+ v 1-9 cigs/day. This illogical analysis has not been included in the main body of the table.
[e] Symptom control is defined as diurnal and nocturnal asthma <1/wk and no symptoms between attacks at all visits in 2nd and 3rd yrs of follow up.
[f] OR for smoker in the home is adjusted for the variables given in Table 4, but OR for mother smokes in the home is unadjusted.

Quality of life and general health (Table 13) Two studies have related ETS exposure to asthma-related quality of life. In one study (Wamboldt et al., 2002) children with a smoker in the household had a non-significantly lower quality of life as assessed by the child but a significantly lower quality of life as assessed by the parent. In the other study (Halterman et al., 2004) no association was seen between ETS exposure and change in quality of life (in the intervention and usual care groups combined). Table 13 also includes results from one study (Mannino et al., 2002) showing no significant relationship of cotinine level to general health. This endpoint is clearly not very directly related to asthma specifically. These data are too limited for any useful conclusions to be drawn.

TABLE 13

Summary of results relating quality of life and general health in children to ETS exposure

Publication	Endpoint	Exposure	Result[a]
Mannino et al., 2002	Less than very good health	Highest v lowest cotinine[b] Intermed v lowest cotinine	OR 1.3 (0.7-2.5) OR similar to that for highest v lowest, and NS
Wamboldt et al., 2002	Parent-assessed AQOL[c] Child-assessed AQOL	Smoker in household	Mean 5.38 v 6.13 ($p<0.01$) Mean 5.61 v 5.77 (NS)
Halterman et al., 2004	Change in AQOL[c] during study year	Smokers in home	Mean 0.55 v 0.36 (NS)

[a] Unadjusted for covariates except where stated.
[b] Serum cotinine groups are 0.050 to 0.115 ng/ml = low, 0.116 to 0.639 ng/ml = intermediate, and 0.640 to 20 ng/ml = high.
[c] AQOL = Asthma-related qualify of life. Lower scores indicate poorer quality.

Summary of results presented in Tables 5 to 13 The data presented in Tables 5 to 13 relate to a wide variety of endpoints and indices of exposure, with results presented in various ways. Formal meta-analysis of the combined data is not practical. However Table 14 summarises the results for each study in Tables 5 to 13 on a symmetrical 7 point scale as follows:

1. Decrease in risk – significant at $p<0.05$
2. Decrease in risk – not significant – by more than a factor of 1.5
3. Decrease in risk – not significant – by at most a factor of 1.5
4. No effect (association stated to be not significant but data not shown)
5. Increase in risk – not significant – by at most a factor of 1.5
6. Increase in risk – not significant – by more than a factor of 1.5
7. Increase in risk – significant at $p<0.05$

Here an "increase" not only includes cases where an increase in an adverse health effect (or a decrease in a beneficial health effect) was associated with ETS exposure, but where a reduction in risk of an adverse health effect was associated with intervention to reduce ETS exposure (El-Dahr et al., 2000; Wilson et al., 2001b). For each study in each table, only one result is counted. Where there is a choice of ETS exposure indices preference is given to those based on mean cotinine, mean CCR, total ETS exposure and smoking by the mother in that order. Results are normally included in Table 14 based on the exposed/unexposed result, but the highest exposure level is used if only dose-response data are available.

It is evident that the overall data in Table 14 are consistent with a positive association. Of the 65 results summarised, 28 show a significant positive association and only two (Murray & Morrison, 1993 for asthma severity for results after July 1986 and Mannino et al., 2002 for hospitalisation) a significant negative one. Similarly, nonsignificant increases by a factor of 1.5 or more outnumber corresponding nonsignificant decreases 7 to 2. While the data are heterogeneous, with many studies showing little effect if any and a few very strong relationships, it is clear the overall pattern of results is not due to chance. This conclusion would have been unaffected by alternative plausible rules for preferring which results to include from studies providing a choice of ETS exposure variables.

TABLE 14

Summary of associations presented in Tables 5 to 13

Table	Endpoint	No of studies	Decreased risk			No effect	Increased risk		
			Significant	Not significant			Not significant		Significant
			p<0.05	by >1.5	by ≤1.5		by ≤1.5	by >1.5	p<0.05
5	Hospitalisation	9	1	1	0	1	1	1	4
6	Emergency room visits and urgent consultations	6	0	0	1	0	1	0	4
7	Restricted activity	6	0	0	1 [a]	0	1	2	2
8	Acute and non-acute asthma	4	0	0	0	0	3	0	1
9	Asthma medication	7	0	1	1	0	2 [b]	0	3
10	Health contacts for asthma	3	0	0	0	0	2 [c]	1	0
11	Asthma severity	13 [d]	1	0	1	0	3	2	6 [e]
12	Asthma symptoms and acute episodes	14	0	0	4 [f]	1	1	1 [c]	7 [g]
13	Quality of life and general health	3	0	0	1	0	1	0	1 [h]
	TOTAL	65	2	2	9	2	15	7	28

[a] Choosing data for limited physical activity from Morkjaroenpong et al., 2002.
[b] Including result for El-Dahr et al., 2000.
[c] Including results from Fergusson & Horwood, 1985.
[d] Counting as two separate studies results before and after July 1986 from Murray & Morrison, 1993.
[e] Including result for moderate/severe v mild from Mannino et al., 2002.
[f] Choosing data for crises per year from Dubus et al., 1998 and from Wilson et al., 2001b.
[g] Choosing data for symptomatic days from Abulhosn et al., 1997 and for symptom score from El-Dahr et al., 2000.
[h] Choosing data for parent-assessed QOL for Wamboldt et al., 2002.

3.2.2 Lung function

Table 15 summarises results from 18 studies relating ETS exposure to five lung function variables: FEV_1, FVC, the ratio of FEV_1 to FVC, $FEF_{25-75\%}$ and PEFR.

FEV_1 Seven of the 12 studies providing data for FEV_1 reported no significant association with ETS exposure (Evans et al., 1987; O'Connor et al., 1987; Chilmonczyk et al., 1993; Callén Blecua et al., 1997; Dubus et al., 1998; Venners et al., 2001; Wilson et al., 2001b). In the Vancouver study (Murray & Morrison, 1993) no significant association of FEV_1 with parental smoking was seen for children studied after July 1986. However, for children born before July 1986, FEV_1 was significantly reduced if either the mother or the father smoked. In the Southern California study (Li et al., 2000), current smoking was not associated with FEV_1 but past ETS exposure was associated with a significantly ($p<0.05$) reduced FEV_1 in boys but not girls. In the Cape Town study (Ehrlich et al., 2001), current smoking by the mother was associated with a significantly ($p<0.05$) reduced FEV_1, but no significant association was seen with other indices of parental smoking or with cotinine. In the analyses based on NHANES III, no significant association was seen between FEV_1 and smoking at the home (Chapman et al., 2003) but FEV_1 was significantly lower in those with high cotinine (0.640+ ng/ml) than in those with low cotinine (<0.116 ng/ml) (Mannino et al., 2002). The most significant association seen ($p<0.001$) was in the New Orleans study (El-Dahr et al., 2000) where FEV_1 was found to improve in 15 out of 17 children when the parents reduced the amount they smoked. As noted previously, this study lacks a proper control group. Overall these data do not provide very clear evidence that ETS exposure is associated with reduced FEV_1.

FVC Four of the studies with relevant data reported no significant association of FVC with ETS exposure (O'Connor et al., 1987; Callén Blecua et al., 1997; Dubus et al., 1998; Venners et al., 2001). In the Vancouver study (Murray & Morrison, 1989) no relationship was seen with maternal smoking, but a marginally significant ($p=0.05$) reduced FVC was seen where the father smoked. In the study in Southern California (Li et al., 2000) no association of

FVC with ETS exposure was seen in boys, but in girls, children with 2 or more current smokers in the household had a significantly ($p<0.05$) increased FVC. As for FEV_1, the results from NHANES III showed no association of FVC with the number of smokers in the home (Chapman et al., 2003) but did show a significantly ($p<0.05$) reduced FVC in the high cotinine group (Mannino et al., 2002). The combined data for FVC do not clearly demonstrate the existence of an association.

FEV_1/FVC No significant association was reported in most studies (Callén Blecua et al., 1997; Venners et al., 2001; Mannino et al., 2002; Chapman et al., 2003). In the Southern California study (Li et al., 2000) a significantly ($p<0.05$) reduced FEV_1/FVC was seen in relation to past ETS exposure in boys, but no association was seen in relation to current smoking or in girls. The study in Portland (Chilmonczyk et al., 1993) reported a significant ($p<0.05$) reduction in FEV_1/FVC associated with household or day care smoking and cotinine. More data are needed to reach any clear conclusion here.

$FEF_{25-75\%}$ Of the eight studies providing evidence, three (Evans et al., 1987; O'Connor et al., 1987; Dubus et al., 1998) did not find a significant association of $FEF_{25-75\%}$ with ETS exposure. The remaining five did report a significant association, but often only in some analyses. Thus the Vancouver study (Murray & Morrison, 1993) reported a highly significant ($p<0.001$) reduction if the mother smoked for children born before July 1986, but a nonsignificant increase for children born after July 1986, and no association with father smoking in either period. Also, while the study in Southern California (Li et al., 2000) reported a significant ($p<0.05$) reduction in boys but not girls (and then only in relation to past but not current ETS exposure), the NHANES III study (Chapman et al., 2003) reported a significant ($p<0.05$) reduction in girls but not boys associated with having two smokers in the home. Significant ($p<0.05$) reductions were also reported in NHANES III (Mannino et al., 2002) in relation to cotinine level, and in the Portland study (Chilmonczyk et al., 1993) in relation to household or day care smoking and cotinine. The significant results for $FEF_{25-75\%}$ from the Istanbul study (Güler

et al., 2000) are for increased reversibility and are not directly comparable to the other data. Overall, the data for $FEF_{25-75\%}$ are more suggestive of an association with ETS than is the case for FEV_1, FVC or FEV_1, but there are still inconsistencies which need resolving.

PEFR The data included in Table 15, from 10 studies, are for a variety of endpoints, including PEFR variability (Frischer et al., 1993), PEFR amplitude (Meijer et al., 1996), PEFR reversibility (Güler et al., 2000) and PEF control (Soussan et al., 2003) as well as PEFR level (Evans et al., 1987; Chan & Chen, 1995; Callén Blecua et al., 1997; Dubus et al., 1998; El-Dahr et al., 2000; Schwartz et al., 2000). Of the five studies where significant associations were noted, three (Chan & Chen, 1995; El-Dahr et al., 2000; Güler et al., 2000) were only incompletely reported in abstracts, one (Frischer et al., 1993) reported an association only in non-atopic children and one (Chan & Chen, 1995) reported an association with cotinine only for samples collected at night and not during the day. The study in Finland (Schwartz et al., 2000) reported a significantly ($p<0.05$) reduced PEFR associated with ETS exposure in between-child comparisons, but not in within-child comparisons. Taken as a whole, these data are difficult to interpret.

Other lung function variables There are very limited data for other lung function variables that are not shown in Table 15.

SRAW In the study in Marseilles (Dubus et al., 1998; Oddoze et al., 1999) no association was found between cotinine level and SRAW.

$FEF_{25-75\%}$/FVC In NHANES III (Chapman et al., 2003) $FEF_{25-75\%}$/FVC was not associated with smoking in the household in boys (levels 0.791, 0.771, 0.796 for 0, 1, 2+ smokers in the home) but was significantly ($p<0.05$) lower in more heavily exposed girls (levels 1.265, 1.243, 1.054).

Overall conclusions for lung function While there are a number of statistically significant findings in Table 15, the data generally do not show a very consistent pattern. Often associations are seen only for subsets of the

data (Murray & Morrison, 1993; Chan & Chen, 1995; Meijer et al., 1996; Li et al., 2000; Chapman et al., 2003) or for some indices of exposure and not others (Murray & Morrison, 1993; Li et al., 2000; Schwartz et al., 2000; Ehrlich et al., 2001), with some studies reporting no significant associations at all (Evans et al., 1987; O'Connor et al., 1987; Callén Blecua et al., 1997; Dubus et al., 1998; Venners et al., 2001; Wilson et al., 2001b; Soussan et al., 2003). A clear relationship of ETS exposure to reduced lung function has not been established, though the data are somewhat suggestive of a relationship, particularly for $FEF_{25-75\%}$.

TABLE 15

Summary of results relating lung function to ETS exposure

Publication	Exposure	Lung function variable				
		FEV_1	FVC	FEV_1/FVC	$FEF_{25-75\%}$[a]	PEFR
Evans et al., 1987	No household smoker	1.49ℓ			1.42ℓ/sec	2.74ℓ/sec
	Household smoker	1.60ℓ			1.60ℓ/sec	3.19ℓ/sec
	p	NS			NS	NS
O'Connor et al., 1987	Mother nonsmoker	102.9%	104.0%		85.8%	
	Mother smoker	100.8%	107.8%		76.1%	
	p	NS	NS		NS	
Frischer et al., 1993	Effects of mother smoking in non-atopic children					+54.7%[b]
	p					p<0.05
	Effect of mother smoking in atopic children					-8.5%[b]
	p					NS
Chilmonczyk et al., 1993	No household or day-care smoker	109.3%		83.7%	85.4%	
	Mother or others smoke	102.4%		79.4%	71.8%	
	Mother and others smoke	102.2%		80.0%	73.6%	
	Trend p	NS		p<0.05	p<0.05	
	Cotinine <10 ng/ml	108.8%		83.5%	85.4%	
	10-39 ng/ml	105.2%		81.2%	74.9%	
	40+ ng/ml	98.5%		77.5%	67.3%	
	Trend p	NS		p<0.05	p<0.05	
Murray & Morrison, 1993 (FVC data are from Murray & Morrison, 1989)	Before July 1986					
	Mother nonsmoker	84.4%	93.8%		71.7%	
	Mother smoker	77.3%	91.2%		59.5%	
	p	p<0.01	NS		p<0.001	
	Father nonsmoker	84.2%	94.5%		70.0%	
	Father smoker	80.2%	90.6%		67.1%	
	p	p<0.05	p=0.05		NS	
Murray & Morrison, 1993	After July 1986					
	Mother nonsmoker	90.8%			79.4%	
	Mother smoker	91.3%			81.0%	
	p	NS			NS	
	Father nonsmoker	90.1%			78.0%	
	Father smoker	93.0%			84.1%	
	p	NS			NS	

TABLE 15 (continued/1)

Publication	Exposure	Lung function variable				
		FEV_1	FVC	FEV_1/FVC	$FEF_{25-75\%}$[a]	PEFR
Chan & Chen, 1995	Cotinine/creatinine ratio (CCR)					CCR significantly higher where PEFR<80% of predicted for samples collected at night, not during the day
Meijer et al., 1996	During ICS[c]					
	Parents nonsmokers					20.6%
	Parent smokes					28.7%
	p					NS
	After ICS withdrawal[c]					
	Parents nonsmokers					19.4%
	Parent smokes					29.7%
	p					p<0.05
Callén Blecua et al., 1997	Parents nonsmokers	93.7%	97.4%	76.7%		92.6%
	Parent smokes	91.9%	96.9%	72.7%		87.2%
	p	NS	NS	NS		NS
Dubus et al., 1998	No cotinine	101.9%	101.7%		104.3%	85.6%
	Detectable cotinine	106.5%	106.6%		94.0%	89.1%
	p	NS	NS		NS	NS
El-Dahr et al., 2000	Parent smoking normally then reducing	Improved in 15/17 (88%)				Improved in 8/15, worsened in 1/15
	p	<0.001				p<0.05
Güler et al., 2000[d]	Mother smokes now				Higher	?
	p				p=0.03	NS?
	Smoking in pregnancy				Higher	Higher
	p				p=0.001	Sig.(NOS)
Li et al., 2000[e]	Boys					
	Past ETS	-4.9	-2.2	-2.8	-9.2	
	p	p<0.05	NS	p<0.05	p<0.05	
	One current smoker	-3.9	-3.3	-0.6	-4.0	
	p	NS	NS	NS	NS	
	Two+ current smokers	-2.9	+0.8	-3.6	-5.2	
	p	NS	NS	NS	NS	
	Girls					
	Past ETS	+2.1	+2.5	-0.2	+1.4	
	p	NS	NS	NS	NS	
	One current smoker	+1.1	+1.9	-0.8	+7.0	
	p	NS	NS	NS	NS	
	Two+ current smokers	+2.7	+5.9	-2.7	-4.2	
	p	NS	p<0.05	NS	NS	

TABLE 15 (continued/2)

Publication	Exposure	Lung function variable				
		FEV_1	FVC	FEV_1/FVC	$FEF_{25-75\%}$[a]	PEFR
Schwartz et al., 2000[f]	Any ETS at home a.m.					-41.9 ℓ/min
	p					p<0.05
	Any ETS at home p.m.					-40.7 ℓ/min
	p					p<0.05
	ETS previous day					-9.2 ℓ/min
	p					NS
Ehrlich et al., 2001	Mother not current smoker	1.64ℓ				
	Mother current smoker	1.41ℓ				
	p	p<0.05				
	Mother never smoked	1.47ℓ				
	Mother ever smoked	1.53ℓ				
	p	NS				
	Mother did not smoke in child's first year	1.56ℓ				
	Mother smoked in child's first year	1.46ℓ				
	p	NS				
	Father not current smoker	1.45ℓ				
	Father current smoker	1.56ℓ				
	p	NS				
	Father did not smoke in child's first year	1.50ℓ				
	Father smoked in child's first year	1.52ℓ				
	p	NS				
	Not 2+ smokers in household	1.59ℓ				
	2+ smokers in household	1.46ℓ				
	p	NS				
	CCR 1st quartile	1.47ℓ				
	2nd quartile	1.47ℓ				
	3rd quartile	1.65ℓ				
	4th quartile	1.42ℓ				
	Trend p	NS				
Venners et al., 2001[g]	Boys					
	Father current					
	<30 cigs/day	-1.9%	-1.8%	"No		
	p	NS	NS	important		
				association"		
	30+ cigs/day	-3.7%	-3.7%			
	p	NS	NS			
	Girls					
	Father current					
	<30 cigs/day	-1.0%	-0.4%	"No		
	p	NS	NS	important		
				association"		
	30+ cigs/day	-1.3%	-0.8%			
	p	NS	NS			
Wilson et al., 2001b[h]	Intervention	-0.41%				
	effect	NS				

TABLE 15 (continued/3)

Publication	Exposure	Lung function variable				
		FEV_1	FVC	FEV_1/FVC	$FEF_{25-75\%}$[a]	PEFR
Mannino et al., 2002[i]	Difference high					
	v low cotinine	-8.1%	-5.6%	-3.0%	-12.5%	
	p	p<0.05	p<0.05	NS	p<0.05	
	Difference intermediate					
	v low cotinine	Not given	Not given	Not given	Not given	
	p	NS	NS	NS	NS	
Chapman et al., 2003[j]	Boys					
	No smoking at home (base)	2.61ℓ	3.16ℓ	82.6%	2.50 ℓ/s	
	1 smoker at home	2.65ℓ	3.21ℓ	82.5%	2.65 ℓ/s	
	p	NS	NS	NS	NS	
	2 smokers at home	2.39ℓ	2.93ℓ	81.5%	2.33 ℓ/s	
	p	NS	NS	NS	NS	
	Girls					
	No smoking at home (base)	2.92ℓ	3.13ℓ	93.1%	3.96 ℓ/s	
	1 smoker at home	3.02ℓ	3.24ℓ	93.2%	4.03 ℓ/s	
	p	NS	NS	NS	NS	
	2 smokers at home	2.72ℓ	3.06ℓ	88.9%	3.22 ℓ/s	
	p	NS	NS	NS	p<0.05	
Soussan et al., 2003[k]	Smoker in home					0.73
	OR (95% CI)					(0.39-1.38)
	Mother smokes at home					0.34
	OR (95% CI)					(0.14-0.89)

[a] Including MMEFR.
[b] Data are percentage increase in PEFR variability in children with a smoking mother.
[c] ICS = inhaled corticosteroids. PEFR values are PEFR amplitude = (maximum-minimum)/mean based on 24 hour data.
[d] Data are for FEF and PEF reversibility. Significance not stated for PEF reversibility and smoking now but presumably not significant.
[e] Data are percentage differences vs no ETS exposure and are irrespective of *in utero* exposure.
[f] Data are average changes over a 3 month period. For any ETS exposure at home they derive from a between-child analysis, while for ETS previous day they derive from a within-child analysis.
[g] Data are changes relative to father never smoker.
[h] "Intervention effect" is change in intervention group from baseline to follow-up relative to corresponding change in usual care group.
[i] Cotinine groups are 0.050 to 0.115 ng/ml = low, 0.116 to 0.639 ng/ml = intermediate, 0.640 to 20 ng/ml = high.
[j] Values are model-predicted (see Chapman et al., 2003 Table 4)
[k] Data are for PEF control (<20% variability) vs lack of control.

3.2.3 Bronchial responsiveness

Seven studies have related ETS exposure to bronchial responsiveness.

In the Boston study (O'Connor et al., 1987) the response to cold air challenge (fall in FEV_1 as a percentage of predicted FEV_1) was greater if the mother smoked (24% vs 11.9% for mother nonsmoker), but not if the father smoked (15% vs 17.1% for father nonsmoker). The association with maternal smoking was significant ($p=0.02$) using one statistical technique, but not ($p=0.07$) using another.

In the Viterbo study (Martinez et al., 1988) the response to carbachol (fall of >20% FEV_1) was significantly ($p<0.05$) greater if the parents smoked, the odds ratio being estimated as 18.7, but with a very wide confidence interval of 1.5 to 232.3.

In the Vancouver study bronchial responsiveness to histamine was reported to be significantly related to maternal but not paternal smoking in the first few papers describing results (Murray & Morrison, 1986; Murray & Morrison, 1988; Murray & Morrison, 1989; Murray & Morrison, 1992). In the final paper (Murray & Morrison, 1993) the increase in bronchial responsiveness (reduction in lung PC_{20}) in relation to maternal smoking was evident only in children examined before July 1986 (mother smoker –0.23, mother nonsmoker +0.44, $p<0.05$) but not in children examined afterwards (+0.41 vs +0.26, NS). The same tendency was evident for father smoking (+0.12 vs +0.32, NS before July 1986; +0.74 vs +0.10, NS after July 1986).

In the Freiburg study (Frischer et al., 1992; Meinert et al., 1994) bronchial responsiveness to an exercise test (15% decrease in PEFR) was higher if the mother had smoked before pregnancy (OR 1.7) or had smoked when the child was 1 year old (OR 2.2), but was lower if the mother smoked when the test was done at age 8 (OR 0.5). These differences were nonsignificant in univariate analyses. Multivariate analyses claimed a significant 20 fold increase in bronchial responsiveness associated with

maternal smoking at age 1 and a significant 20 fold decrease associated with maternal smoking at age 8. However these analyses are highly open to question because of the inter-correlations of the maternal smoking variables.

In the Marseilles study (Dubus et al., 1998) the response to carbachol (concentration to produce a 2-fold increase in SRAW) was significantly ($p<0.05$) decreased in children with a detectable cotinine (108.3 vs 160.9 for undetectable) but was nonsignificantly decreased if the mother smoked (98.4 vs 147.2 for father smoked or parents did not smoke). The percentage of bronchodilation was significantly ($p<0.05$) increased in children with a detectable cotinine (74.8 vs 68.8), but was not significantly related to parental smoking (data not given).

In the New Orleans study (El-Dahr et al., 2000) the response to methacholine challenge did not vary between the 3 month period where smokers in the child's household smoked normally and the 3 month period where they were encouraged to quit. 7 of 17 children improved, and 7 worsened, with the other 3 showing no change.

In the Capetown study (Ehrlich et al., 2001) bronchial responsiveness to histamine (fall of >20% FEV_1) was found not to be significantly related to cotinine (OR 1.00, 0.86, 0.94, 0.81 for 4 quartiles) or a variety of indices of parental smoking (e.g. mother current smoker OR 0.78, CI 0.54-1.12 or father current smoker OR 0.99, CI 0.78-1.27).

Taken as a whole these data do not show a consistent relationship of ETS exposure to bronchial responsiveness.

4. Studies in adults

4.1 The studies

Ten publications have reported relevant results, three appearing in 1994-1996 and summarized in part I of this review and seven appearing between 1998 and 2002 and summarized in part II.

Three of the publications describe studies conducted in Chandigarh, India (Jindal et al., 1994; Jindal et al., 1996; Jindal et al., 1999) while one describes a study in 8 regions of Switzerland (Künzli et al., 2000). The remaining six publications describe studies conducted in the USA, one nationwide, based on NHANES III (Eisner, 2002b), one in Denver (Ostro et al., 1994), one in Portland (Sippel et al., 1999) and the other three based on a study conducted in northern California (Eisner et al., 1998; Eisner et al., 2001; Eisner et al., 2002). One of the publications is only an abstract (Jindal et al., 1996).

The largest number of asthmatics considered in any study was 548 in the Portland study (Sippel et al., 1999), and varied between 164 and 451 otherwise, except for two studies involving only 50 adults (Jindal et al., 1999; Eisner et al., 2001).

Of the studies conducted in India, one was of women (Jindal et al., 1999) with the sex distribution unknown in the other two (Jindal et al., 1994; Jindal et al., 1996). The other studies all involved both sexes, with men forming between 28% and 44% of the sample, reflecting the known higher frequency of adult asthma in women.

Where the average age of the sample was known it was typically around 40, except for the final Indian study (Jindal et al., 1999), which involved women aged between 20 and 40.

Of the eight studies considered, only two were clearly restricted to lifelong never smokers (Jindal et al., 1994; Künzli et al., 2000), the studies in northern California (Eisner et al., 1998; Eisner et al., 2001; Eisner et al., 2002)

and Portland (Sippel et al., 1999) and the one based on NHANES III (Eisner, 2002b) clearly including exsmokers together with never smokers in their analyses. Two studies (Ostro et al., 1994; Jindal et al., 1996) ambiguously referred to being of "nonsmokers", while one (Jindal et al., 1999) merely considered that "most women were likely to be non-smokers".

Two of the studies (Künzli et al., 2000; Eisner, 2002b) were of cross-sectional design in which ETS exposure was related to lung function in asthmatics identified by questionnaire. The remaining studies were of cases identified, usually at clinics, but in one study (Sippel et al., 1999) from insurance records. Most of these involved follow-up of these cases for varying period of time, though this was not so in two studies (Jindal et al., 1996; Jindal et al., 1999).

In most of the studies ETS exposure (from the spouse, at home, and/or at work) was obtained from questionnaires, but in two studies objective measures were used, one based on nicotine from a personal nicotine badge monitor (Eisner et al., 2001), the other based on serum cotinine (Eisner, 2002b). No study in adults recorded ETS exposure in childhood, or smoking in pregnancy.

The three studies in India (Jindal et al., 1994; Jindal et al., 1996; Jindal et al., 1999) and one of the analyses of the northern California study (Eisner et al., 2001) took no potential confounding variables at all into account, not even age or sex. The remaining papers took into account differing factors as summarized below:

Ostro et al., 1994	Outdoor air pollution, survey day, previous symptoms (temperature, humidity and age also considered – not in final model)
Eisner et al., 1998	Age, sex, race, income. Also baseline severity for follow-up analyses

Sippel et al., 1999	Age, sex, severity of asthma, diagnosis of COPD, non-asthma medication
Künzli et al., 2000	Age, height, ETS at home, occupational gas/dust/smoke, area of residence
Eisner, 2002b	Age, sex, height, education, income, ex-smoking, race/ethnicity
Eisner et al., 2002	Age, sex, income, education, baseline asthma severity

It should also be noted that one of the studies in India (Jindal et al., 1996) was reported only as an abstract, while the other two (Jindal et al., 1994; Jindal et al., 1999) included major statistical errors in their analyses.

4.2 Results

4.2.1 Asthma exacerbation and severity

Table 16 summarizes results from eight publications relating to a variety of endpoints for asthma exacerbation and severity. The endpoints can be broadly classified into groups:

Acute exacerbations These include such endpoints as emergency department visits, hospitalisations, acute episodes and restricted activity days. All but one of the publications (Eisner et al., 2001) report data here. Significant associations are evident in four studies (Ostro et al., 1994; Jindal et al., 1996; Sippel et al., 1999; Eisner et al., 2002) and are not seen in one (Jindal et al., 1999). In one study (Jindal et al., 1994), some significant associations might have been demonstrated, but this is unclear due to doubts about adequacy of the statistical analysis. In the follow-up study in Northern California (Eisner et al., 1998), the data appeared conflicting, with incidence of acute exacerbations higher in those with ETS exposure at baseline and reduced in

those who quit, but not increased in those who started exposure or in those who had continuing exposure at baseline and during the follow-up period.

Severity and symptoms An association with symptoms was reported in one study (Eisner et al., 2001) but not in another (Ostro et al., 1994). Analyses based on the northern California study reported results for an index of severity. In both publications (Eisner et al., 1998; Eisner et al., 2002), some ETS variables showed a significant association with severity, and some did not. As noted above for exacerbations, there was an increase associated with ETS exposure at baseline and a decrease associated with quitting, but no increase in those who started ETS exposure after baseline or who had continuing exposure at baseline and during the follow-up period.

Drug use Bronchodilator use was strongly related to nicotine level as determined by personal monitor in one study (Eisner et al., 2001) but was not significantly related to smoking by the husband in another (Jindal et al., 1999). Reported significant associations of ETS with use of bronchodilators and steroids in the study (Jindal et al., 1994) are not statistically reliable.

Quality of life and general health This was only considered in the northern California study. Asthma-specific quality of life was generally worse in relation to ETS exposure in the later publication (Eisner et al., 2002), although differences were not always significant for every exposure index. In the earlier publication (Eisner et al., 1998), it was worse in those ETS exposed at baseline, but did not change on stopping or starting exposure and was not significantly worse in those who continued to be exposed. Results for two components of a general health index, a physical health score and a mental health score, were also provided. These do not relate so directly to asthma exacerbation. No association was seen between ETS exposure and the mental health score, but some analyses showed a significantly reduced physical health score associated with ETS exposure (or a significant improvement following quitting).

Associations of ETS exposure with severity and symptoms, with drug use, and with quality of life and general health, have not clearly been shown, the data being rather limited for each group of endpoints. The data for acute exacerbations are much more suggestive of an association and seem consistent with the evidence of an association seen in children.

TABLE 16

Summary of results relating asthma exacerbation and severity in adults to ETS exposure

Publication	Endpoint	Results by ETS exposure		
		Unexposed to ETS at home and work	Exposed to ETS at home or work	OR (95% CI)[a]
Jindal et al., 1994	Occurrence in last year of:			
	Emergency department visit	52/100 (52%)	60/100 (60%)	1.38 (0.79-2.42)
	Hospitalisation	30/100 (30%)	30/100 (30%)	1.00 (0.55-1.83)
	Acute episodes	58/100 (58%)	62/100 (62%)	1.18 (0.67-2.08)
	Absence from work due to asthma (>2 weeks)	60/100 (60%)	66/100 (66%)	1.29 (0.73-2.30)
	Parenteral drugs required	64/100 (64%)	64/100 (64%)	1.00 (0.56-1.78)
	Daily bronchodilators[b]	56/100 (56%)	66/100 (66%)	1.53 (0.86-2.70)
	Intermittent steroids	42/100 (42%)	56/100 (56%)	1.76 (1.00-3.08)
	Complications	6/100 (6%)	8/100 (8%)	1.36 (0.45-4.08)
	Mean occurrence per patient per year of:			p[c]
	Emergency department visit	0.60	0.82	<0.01
	Hospitalisation	0.33	0.34	NS
	Acute episodes	0.60	1.32	<0.01
	Parenteral bronchodilators, n	6.0	8.6	<0.01
	Absence from work due to asthma, wks	3.0	3.6	<0.01
	Steroid requirement, wks	8.6	11.3	<0.01
	Bronchodilator required, wks	36.3	38.3	NS
		Unexposed to ETS at home	Exposed to ETS at home	OR (95% CI)[d]
Ostro et al., 1994	Moderate or severe cough			1.15 (0.97-1.36)
	Moderate or severe shortness of breath			1.34 (0.84-2.15)
	Nocturnal asthma			1.08 (0.72-1.56)
	Restricted activity			1.61 (1.08-2.46)

TABLE 16 (continued/1)

Publication	Endpoint	Results by ETS exposure			
		Unexposed to ETS	Exposed to ETS		Association
Jindal et al., 1996	Acute vs nonacute asthma				Exposure higher in acute patients ($p<0.01$)
			OR (95% CI)		
		ETS at baseline vs no ETS	ETS stopped vs ETS continued	ETS started vs no ETS	ETS continued vs no ETS
Eisner et al., 1998	Emergency department visit	2.1 (1.2-3.5)	0.4 (0.2-0.97)	0.9 (0.4-1.8)	Not significant
	Urgent physician visit	1.9 (1.1-3.3)	0.6 (0.3-1.4)	1.0 (0.5-2.0)	Not significant
	Hospitalisation for asthma	1.9 (1.02-3.6)	0.2 (0.04-0.97)	0.6 (0.2-1.9)	Not significant
	Restricted activity	-[e]	0.8 (0.4-1.7)	Not significant	Not significant
			Association		
		ETS at baseline vs no ETS	ETS stopped vs no ETS	ETS started vs no ETS	ETS continued vs no ETS
	Asthma severity score	Greater ($p=0.03$)	Improved ($p<0.001$)	Not significant	Not significant
	Quality of life	Worse ($p=0.04$)	Not significant	Not significant	Not significant
	Mental score	Not significant	Not significant	Not significant	Not significant
	Physical score	Worse ($p=0.04$)	Improved ($p=0.05$)	Not significant	Not significant

TABLE 16 (continued/2)

Publication	Endpoint	Results by ETS exposure			
		Husband nonsmoker	Husband smokes		OR (95% CI)
Jindal et al., 1999	Continuous bronchodilator therapy required	7/27 (26%)	9/23 (39%)		1.84 (0.55-6.10)
					Significance
	Acute episodes in year	4.00	4.83		NS
		Unexposed at home and work	Exposed to ETS at home or work		RR (95% CI)
Sippel et al., 1999	Hospitalisations	89/878 person years	148/528 person years		2.87 (2.15-3.82)
			OR (95% CI) by level		
		No measured nicotine	Nicotine 0-0.05 μg/m^3	Nicotine >0. 05 μg/m^3	Trend p
Eisner et al., 2001	Respiratory symptoms	1.0	1.9 (0.4-8.8)	6.8 (1.4-32.3)	0.017
	Extra bronchodilator use	1.0	2.2 (0.3-15.0)	8.1 (1.3-50.0)	0.022

TABLE 16 (continued/3)

Publication	Endpoint	Results by ETS exposure			
			OR (95% CI)		
		Any ETS vs none	<1-2 hrs/wk vs none	3+ hrs/wk vs none	ETS irritation vs none
Eisner et al., 2002	Emergency department visit	2.8 (1.2-6.4)	2.5 (0.9-6.6)	3.4 (1.1-10.3)	2.7 (1.1-6.6)
	Hospitalisation	6.6 (1.3-33)	4.6 (0.7-40)	12.2 (1.5-102)	2.4 (0.4-13.1)
			Difference in continuous scores (95% CI)		
		Any ETS vs none	<1-2 hrs/wk vs none	3+ hrs/wk vs none	ETS irritation vs none
	Severity	+0.6(-0.1 to +1.4)	+0.1(-3.0 to +2.9)	+1.5(+0.4 to +2.6)	+0.4(-0.5 to +1.4)
	Physical health status	-2.0 (-4.4 to +0.5)	-0.1 (-3.0 to +2.9)	-4.9 (-8.4 to –1.3)	-4.0 (-7.0 to –1.0)
	Asthma-specific QOL[f]	+2.8(-0.4 to +6.0)	+1.7(-2.1 to +5.5)	+4.4(-0.2 to +9.0)	+5.0(+1.2 to +8.9)

[a] Calculated by us from data presented. The authors claim significance at $p<0.01$ for bronchodilators and for intermittent steroids, but this seems inconsistent with the data given.

[b] Results are also given for intermittent bronchodilators, but the percentages given (42% and 56%) seem inconsistent with the results for daily bronchodilators, particularly for the exposed group where the percentage given is 66% and 56% plus 66% = 122%.

[c] The significances were as presented by the authors, and may well be erroneous, although they cannot be checked.

[d] Results used are with correction for autocorrelation and repeated measures

[e] Results for restricted activity were only presented after baseline.

[f] Higher scores are associated with poorer quality of life.

4.2.2 Lung function

Table 17 summarizes lung function results from the four studies providing relevant data for asthmatic adults.

The results for FEV_1 are rather conflicting. ETS was associated with a significant decline in FEV in one Indian study (Jindal et al., 1994) and in females in a Swiss study (Künzli et al., 2000), and high cotinine was associated with a significant decline in females in a US study (Eisner, 2002b). However, no association was evident in another Indian study (Jindal et al., 1999) or in males in the Swiss study (Künzli et al., 2000), and FEV_1 was positively associated with cotinine in males in the US study (Eisner, 2002b).

None of the analyses for FVC show a significant association, with no clear evidence of any consistent relationship.

Three studies reported results for the FEV_1/FVC ratio. No association with ETS exposure was seen in one study (Jindal et al., 1999) or in the medium/low cotinine comparison in the US study (Eisner, 2002b). However, evidence of a reduction in the FEV_1/FVC ratio associated with ETS exposure was seen in another study (Jindal et al., 1994) and in the high/low cotinine comparisons in the US study (Eisner, 2002b), though here only the results for males were statistically significant.

$FEF_{25-75\%}$ was significantly reduced in association with ETS exposure in one study (Jindal et al., 1994) and in females, but not males, in another study (Künzli et al., 2000).

While the data shown in Table 17 give some support to the possibility that ETS exposure may be associated with reduced lung function, the findings are limited, and not always consistent. No firm conclusions can be drawn.

TABLE 17

Summary of results relating lung function in adults to ETS exposure

Publication	Exposure	Lung function variable FEV_1	FVC	FEV_1/FVC	$FEF_{25-75\%}$
Jindal et al., 1994	No ETS exposure	80.8%	90.9%	78.4%	75.7%
	ETS at home or work	68.7%	89.4%	63.5%	54.3%
	Significance[a]	p<0.05	NS	p<0.05	p<0.05
Jindal et al., 1999	Husband does not smoke	79.4%		86.3%	
	Husband smokes	77.9%		83.6%	
	Significance[b]	NS		NS	
Künzli et al., 2000	Difference in lung function associated with ETS exposure at work (95% CI)				
	All subjects	-4.8% (-9.2 to +0.0)	-1.7% (-5.5 to +2.1)		-12.4% (-20.4 to -3.7)
	Male	+0.5% (-7.9 to +9.6)	+1.4% (-4.0 to +7.1)		-1.4% (-18.0 to +18.5)
	Female	-8.7% (-14.5 to –2.5)	-4.4% (-9.6 to +1.1)		-20.8% (-32.0 to -7.6)
Eisner, 2002b	Change in mean residual lung function values (95% CI) compared to low cotinine group[c]				
	Male				
	Medium cotinine	+569 ml (+78 to +1060)	+222 ml (-92 to +536)	-0.54% (-1.8 to +0.73)	
	High cotinine	+242 ml (-169 to +653)	-30 ml (-331 to +271)	-1.6% (-2.8 to -0.30)	
	Female				
	Medium cotinine	-87 ml (-278 to +104)	-63 ml (-278 to +152)	-0.46% (-2.0 to +1.1)	
	High cotinine	-261 ml (-492 to -30)	-291 ml (-601 to +20)	-1.6% (-3.3 to +0.19)	

a Significance as reported by the author. See section 2 of part I of this review for a discussion of statistical errors in this study.

b Significance calculated by us.

c Serum cotinine groups are "low" to 0.093 ng/ml, "medium" >0.093 to 3.16 ng/ml and "high" >3.16 to 14 ng/ml.

4.2.3 Bronchial responsiveness

Only one study (Jindal et al., 1999) presented data for bronchial responsiveness. In this study PD_{20}, the dose of histamine to produce a 20% fall or greater in FEV_1 was noted to be significantly ($p<0.01$) lower if the husband smoked and to be significantly ($p<0.01$) related to an ETS exposure index based on the product of years and hours of exposure. Based on the data presented, we calculate that the first relationship is in fact not significant, and though we cannot check significance for the second, there must be doubt about it. In any event, the very limited data on bronchial responsiveness in adults cannot allow any conclusion to be reached.

5. Recent reviews

5.1 Introduction

In part I of this document, describing the literature up to 1997, section 2 referred to various relevant review papers that had discussed the evidence relating ETS exposure to exacerbation of asthma (Canadian Paediatric Society, 1986; Witorsch, 1992; Shephard, 1992; Ehrlich et al., 1993; National Cancer Institute, 1993; Trédaniel et al., 1994; Di Benedetto, 1995). Section 5 considered in detail the California EPA report (National Cancer Institute, 1999) and the reviews of the St George's Hospital Medical School Group (Strachan & Cook, 1998; Cook & Strachan, 1998) as well as referring to two other reviews published in 1998 and 1999 (Witorsch, 1998; Weiss et al., 1999).

In section 2 of this part (part II), various more recent relevant reviews, published between 2000 and 2002 (Eisner & Blanc, 2000; Gold, 2000; Jaakkola, 2000; Ulrik & Lange, 2001; Eisner, 2002a), have also been discussed.

Below, we discuss the draft updated review by the California EPA (California Environmental Protection Agency, 2004) as well as one other recent review (Janson, 2004).

5.2 Update of the California EPA report

In the recent draft of the "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant" (California Environmental Protection Agency, 2004), the California EPA include "asthma induction and exacerbation in children and adults" in their list of "Effects Causally Associated with ETS Exposure".

5.2.1 Exacerbation in children

In their summary table at the beginning of Chapter 6, the California EPA note that they had considered eight studies in children in their original report (National Cancer Institute, 1999) and 12 additional studies in their

update, with the verdict for causal association remaining "conclusive". In fact, both the text and tables summarizing the new data refer to 14 studies not 12. Of these we rejected two (Willers et al., 2000; Gilliland et al., 2003) as the endpoint was not asthma, but the rest are considered in this report (MacArthur et al., 1996; Meijer et al., 1996; Abulhosn et al., 1997; Dubus et al., 1998; Oddoze et al., 1999; Li et al., 2000; Schwartz et al., 2000; Crombie et al., 2001; Ehrlich et al., 2001; Melén et al., 2001; Venners et al., 2001; Mannino et al., 2002). We noted in Part I that the original California EPA report had missed many relevant references available at the time, and the same is true here. Even restricting attention to those epidemiological studies of asthma exacerbation and severity we considered in section 3.2.1 of this document, and to those published between 1998 and 2002, which one would have expected to appear in the update, there are 15 omissions (Seidler et al., 1998; Shamssain & Shamsian, 1999; Wafula et al., 1999; Al Ghamdy et al., 2000; El-Dahr et al., 2000; Güler et al., 2000; Gürkan et al., 2000; Ratageri et al., 2000; Mayo, 2001; Wilson et al., 2001a; Dales et al., 2002; Gaspar et al., 2002; Kalaajieh, 2002; Morkjaroenpong et al., 2002; Wamboldt et al., 2002), as against only the seven they considered. Clearly, the literature searching is inadequate, though it is possible further studies may appear in the final version.

The main body of the relevant section consists of short summaries of the 14 new studies. The discussion and interpretation was very limited, the relevant section being reproduced below:

"Taken together, the recent evidence supports the original 1997 Cal/EPA report's conclusion that ETS is a causal factor for asthma exacerbation among children. The cross-sectional studies are all limited by the possibility of selection effects, such as smoking reduction by parents who have children with more severe asthma. This bias, which is unavoidable in cross-sectional studies, would attenuate any observed risk estimate. The longitudinal studies, which are less prone to this bias, are most consistent with an adverse effect of ETS on childhood asthma status. In addition, as shown in a recent meta-analysis by Vork *et al*., (2002), hidden environmental

differences between studies may distort risk estimates. Specifically, higher ETS-related asthma risks were reported in areas with lower ambient air pollution. It was suggested that in polluted areas, individuals who are genetically more susceptible to asthma may be more affected by the ambient air pollution than by ETS, thus masking the effects of ETS exposure. If nondifferential, failure to account for the effects of ambient air pollution could bias risk estimates towards unity."

The draft report lacks any attempt to bring together all the relevant data relating to specific endpoints, to give the reader any clue as to the consistency of the findings.

5.2.2 Exacerbation in adults

In their summary table at the beginning of Table 6, the California EPA note that they had considered four studies in adults in their original report (National Cancer Institute, 1999) and eight additional studies in their update, with the verdict for a causal association changing from "suggestive" to "conclusive". In fact, both the text and tables summarizing the new data refer to only 7 studies not 8. Of these, we rejected two (Blanc et al., 1999; Tarlo et al., 2000) for reasons summarized in Appendix A, and considered five (Jindal et al., 1999; Sippel et al., 1999; Künzli et al., 2000; Eisner et al., 2001; Eisner, 2002b). Here the coverage is more complete, the California EPA missing only two studies we considered in our Table 16 (Jindal et al., 1996; Eisner et al., 1998).

Again, there is no attempt to bring together results for specific types of endpoints and no discussion of bias. The draft update concludes that:

"Taken together, the current studies provide conclusive evidence that ETS exposure can cause asthma exacerbation among adults. Although there are fewer studies than in children, the data consistently link ETS exposure with poorer asthma status among adults with the condition and include

evidence of dose response. Based on the available literature, adults with asthma should be protected from ETS exposure."

5.3 Other recent review

In 2004, a short but wide-ranging review on "The effect of passive smoking on respiratory health in children and adults" was published (Janson, 2004). The section on "Passive smoking in childhood" essentially was a summary of the findings of the St George's Hospital Medical School group, citing *inter alia* the two reports relevant to exacerbation (Strachan & Cook, 1998; Cook & Strachan, 1998). The section on asthma in adults was only one paragraph long, citing only three papers we have considered (Eisner, 2002b; Eisner et al., 2002; Künzli et al., 2000). There was no discussion of any potential bias or of separating potential effects of ETS on induction and exacerbation. The review concluded that "Passive smoking is a widespread, important and avoidable risk factor for respiratory symptoms in both children and adults".

6. Summary and conclusions

Part I of this document includes a critical description of those studies thought relevant to study of the relationship of ETS exposure to asthma exacerbation that were published up to 1997. In this part, part II, studies published since then are described, and the overall evidence is assessed.

6.1 Studies in children

Sixty relevant publications, apparently relating to 47 separate studies, were identified. 34 of the studies were first reported in the last 10 years (1995 to 2004). Far more studies (18) were conducted in the USA than in other countries, results being available from a total of 21 countries. The median number of asthmatics studied was 167 per subject, the largest study involving 3010. Studies generally were of both sexes, with more boys than girls. Most studies covered an age range of a few years, with 6-9 year olds most commonly studied. A few studies specifically excluded smokers.

There were a variety of study designs, including one experimental and three intervention studies, but most studies were of cases identified through medical records, or cross-sectional studies with the classification of asthma based on questionnaire. Eight of the 47 studies used a nicotine-based marker of ETS exposure, with other studies relying on questionnaire response. Only eight studies recorded maternal smoking in pregnancy.

About half the studies did not adjust for any potential confounding variables, with some potential confounding variables (such as diet, exercise and recent respiratory infections) rarely adjusted for.

A wide variety of indices of asthma exacerbation and severity have been used in the studies, with results summarized under nine different endpoints. The endpoints, the number of studies providing data, the number showing a significant positive (negative) association with ETS exposure are summarized below:

Endpoint	Number of studies	Number significant	Conclusion/comment
Hospitalisation	9	4 (1)	Some evidence of an association, but data from NHANES III conflict
Emergency room visits and urgent consultations	6	4	Evidence of an association
Restricted activity	6	2	Association not demonstrated
Acute and non-acute asthma	4	1	No clear difference in ETS exposure between acutely and non-acutely asthmatic children
Asthma medication	7	3	Association not clearly demonstrated.
Health contacts for asthma	3	0	No association shown
Asthma severity	13	6 (1)	Clear positive association
Asthma symptoms and acute episodes	14	7	Results heterogenous, but strongly suggestive of an association
Quality of life and general health	3	1	Data too limited to draw conclusions
Total	65	28 (2)	Overall data clearly show a positive association, not attributable to chance

Overall, these data show considerable evidence of an association, though the results appear heterogeneous, with a few studies reporting very strong relationships and a number no positive relationship at all. However, interpretation of this association is not completely straightforward for a number of reasons. These include the lack of clear evidence that increases in ETS exposure within child are associated with exacerbations of asthma, limited reporting of relevant study details by many authors (including information on active smoking by the child) and failure to separate out results by sex and by age. Failure to control for potential confounding variables is also a feature of the studies. No studies adjusted for maternal smoking in pregnancy, only six for any social class related variables, only four for infections in the child (and none for infections in the parent) and few even take the sex or age of the child into account. Furthermore, some of the various endpoints used may not be very direct or reliable measures of asthma severity.

Very few studies studied these endpoints in relation to maternal smoking in pregnancy. There were five reported results, of which two (for asthma medication and severity) showed a significant positive association.

Eighteen studies relate ETS exposure to one or more of five lung function variables – FEV_1, FVC, the ratio of FEV_1 to FVC, $FEF_{25-75\%}$ and PEFR. The data for $FEF_{25-75\%}$ are more suggestive of an association with ETS than is the case for FEV_1, FVC or the FEV_1/FVC ratio, but there are still inconsistencies which need resolving. The data on PEFR relate to a variety of endpoints, and the results, which are incompletely reported, are difficult to interpret. Other lung function variables have only very rarely been studied. While a number of statistically significant findings have been reported for lung function, the data generally do not show a very consistent pattern, with associations seen only for subsets of the data or for some indices of exposure and not others, with some studies reporting no significant associations at all. A clear relationship of ETS exposure to reduced lung function has not been established, though the data are somewhat suggestive of a relationship.

Seven studies have related ETS exposure to bronchial responsiveness, but no consistent association has been shown.

6.2 Studies in adults

Ten relevant publications, apparently relating to eight studies, were identified. Four of the studies were conducted in the USA, three in India and one in Switzerland. One study was of women aged 20-40, the other studies (where details were known) being of men and women of average age 40. Unlike in children, asthmatic women were generally commoner than asthmatic men. Only two studies were restricted to lifelong never smokers, the rest being of nonsmokers.

Most studies were of cases identified from medical (or insurance) records, but two studies were of cross-sectional design with ETS exposure related to lung function in asthmatics identified by questionnaire. Two studies

used a nicotine-based marker of ETS exposure, with other studies relying on questionnaire response. No study recorded ETS exposure in childhood or maternal smoking in pregnancy.

The four studies in the USA and the study in Switzerland took a range of potential confounding variables into account in at least some of their analyses. The three studies in India took no potential confounding variables at all into account, not even age or sex. One of these three studies was reported only as an abstract, while the other two included major errors in their statistical analyses.

Six of the eight studies reported results for acute exacerbations (including such endpoints as emergency department visits, hospitalisations, acute episodes and restricted activity days). All but one reported significant positive associations in at least one analysis, consistent with the findings for children. Data relating to other endpoints were more rarely studied and, though some associations were reported, more evidence is needed.

Data from four studies gave some support to the possibility that ETS exposure may be associated with reduced lung function, but the limited findings were not always consistent and no firm conclusions can be drawn.

One of the studies in India reported an association of ETS exposure with bronchial responsiveness, but the statistical analysis is open to question. Since no other study provided relevant data, conclusions cannot be drawn here.

6.3 Other reviews of the evidence

This document also considers other reviews of this evidence. The California EPA report, and its recent draft update which concludes that ETS exposure exacerbates asthma in children, is limited by failing to include a number of relevant studies, failing to detect obvious flaws in some of the evidence, not discussing sources of potential bias in detail, not summarizing evidence separately for different endpoints, and not describing how its

conclusion had been reached from the data available. The reviews by the group from the St George's Hospital Medical School are more thorough but also contain deficiencies. Notably, a mechanism is postulated by which ETS is considered a co-factor, operating with intercurrent infection, to exacerbate asthma, but no consideration is given to the possibility of bias resulting if exposure to infections is greater in households with smokers. There is also no emphasis on the absence of data to distinguish effects of ETS exposure and of maternal smoking in pregnancy. A number of other reviews are also cited, which generally do not consider all the evidence available at the time, and often do not attempt to separate out potential effects of ETS on induction and exacerbation of asthma.

6.4 Comment

Elsewhere, we have reviewed the evidence from experimental chamber studies in which asthmatics were exposed to ETS. These studies showed that ETS can reproducibly exacerbate asthma in a subset of susceptible individuals, but that, for the great majority of asthmatics, ETS exposure, even at extremely high concentrations, does not appear to cause asthmatic attacks.

We have also reviewed the evidence relating ETS exposure to prevalence and incidence of asthma in children and in adults. These reviews showed that there was an association, but that there were difficulties in separating out potential effects on induction and on exacerbation and in distinguishing potential effects of ETS exposure and of smoking in pregnancy. Lack of control for confounding by other variables which may be associated with ETS exposure may also be an issue.

The evidence on asthmatics considered in this document clearly demonstrates an association of ETS exposure with asthma exacerbation, particularly with emergency room visits, hospitalisations, acute episodes and severity, and less clearly with lung function and the other endpoints studied. Certainly, the results are rather heterogeneous, a number of the studies can be criticized, and various possibilities of bias and confounding exist. Furthermore, the role of intercurrent infection has not properly been accounted

for. Whether or not ETS exposure can exacerbate asthma in all asthmatics, the findings certainly reinforce the evidence from the chamber studies that ETS exposure can exacerbate asthma.

6.5 Conclusion

ETS exposure can exacerbate asthma, though not necessarily in all exposed individuals.

APPENDIX A

Papers not considered in this review with a brief description and reasons for rejecting them

Publication/population	Description	Reasons for rejection
Upton et al., 1998 Adults	2258 men and women aged 30-59 in 1996 who 20 years earlier in Renfrew and Paisley, Scotland had parental smoking habits recorded. In 112 who were currently asthmatic, parental smoking was non-significantly negatively related to FEV_1 adjusted for sex, age, height, SES variables and smoking.	Although results for all subjects are given by smoking status, data for asthmatic never smokers are not given. Also current asthmatics may not have been asthmatics when the parents' smoking was recorded.
Blanc et al., 1999 Adults	2065 adults aged 20-44 randomly selected (with over-sampling of asthmatics) in three regions of Sweden, 1562 with methacholine and skin prick test data. Work characteristics including workplace ETS exposure related to work disability, asthma and airway hyperresponsiveness.	Results for asthmatics not actually given.

Publication/population	Description	Reasons for rejection
Fielder et al., 1999 Children	427 children aged 8-11 years in Wales in which respiratory symptoms, diagnosis of asthma, and smoking in the home was recorded and peak flow variability measured. Peak flow variability was noted to be higher if the child lived with a smoker and "the effect of smoking was greater in children with asthma (diagnosed or wheeze in past year) than in children with no asthmatic tendency".	Results for asthmatics not given or significance stated.
Tarlo et al., 2000 Children and adults	119 adults and children with asthma in Winnipeg and Vancouver, Canada followed for 1 year and comparisons made between 36 cases with and 36 controls without an exacerbation of asthma. 39% of cases and 17% of controls reported ETS exposure in the previous year.	Not restricted to nonsmokers and data not presented separately for the 15 case-control pairs of children.

Publication/population	Description	Reasons for rejection
Willers et al., 2000 Children	112 children aged 8-13 years in Malmö, Sweden with and without symptoms of asthma. "There was no statistically significant difference in cotinine levels between children with previous and current symptoms, nor were there any associations with the severity of symptoms".	Results relate to symptoms (including cough) with no actual group of asthmatics defined.
Gilliland et al., 2001 Children	5,762 children in grades 4, 7 and 10 in Southern California. *In utero* exposure but not ETS exposure was significantly associated with increased asthma, asthma with current symptoms or asthma requiring medication use after adjustment for age, sex and multiple confounders.	It is not possible reliably to relate, within asthmatics, ETS to the probability of symptoms or medication from the data as presented.
Bayona et al., 2002 Children and adults	486 adults and children with asthma in Puerto Rico. Comparisons made between 273 who visited emergency room in last 12 months and 213 who did not. ETS exposure non-significantly higher in the more severe cases.	Not restricted to nonsmokers and data not separated out for adults and children.

Publication/population	Description	Reasons for rejection
Eisner & Blanc, 2002 Adults	Among 374 nonsmoking adults with asthma in California, 111 reported ETS exposure in travel during the 12 months before interview. Symptoms of asthma, use of inhalers or exacerbation of asthma following ETS exposure during travel varied little according to whether these 111 adults had another regular source of ETS exposure.	The response is in relation to ETS exposure during travel, but the exposure variable relates to ETS exposure elsewhere.
Gilliland et al., 2003 Children	Among 1932 fourth grade children in California, school absenteeism was jointly related to ETS exposure and to asthma diagnosis. Respiratory illness related absences were highest in children with asthma living in a household with 2 or more smokers.	The endpoint of respiratory illness related absences is broad and predominantly due to upper respiratory illnesses and not asthma.

Publication/population	Description	Reasons for rejection
Morgan et al., 2004 Children	937 children with atopic asthma aged 5 to 11 years in seven major US cities enrolled into a randomized controlled trial of an environmental intervention that lasted one year and included education and remediation for exposure to both allergens and ETS. Home environmental exposures assessed every 6 months and asthma-related complications assessed during and for a year after the intervention. The intervention group reported significantly fewer symptoms of asthma during and following intervention.	Intervention was to introduce an air purifier into the child's bedroom rather than to reduce ETS. Any effect of ETS exposure cannot be assessed directly.

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