

# **Effects of maternal and paternal smoking on children's respiratory health**

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## ***Abstract***

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

*Methods* - We summarise the results of the systematic quantitative review published as a series in Thorax, and bring it up to date by considering papers appearing on Embase or Medline up to June 1998. The findings are compared with those of the Californian Environmental Protection Agency review.

*Results* –The relationships between parental smoking and acute lower respiratory illness in infancy (LRI) are almost certainly causal. The elevated risks are associated with smoking both by the mother and by other household members, providing good evidence that postnatal exposure is important. Because smoking by the mother during pregnancy is almost invariably associated with post-natal smoking, any additional influence of pre-natal maternal smoking will be difficult to resolve using epidemiological studies.

There is convincing evidence that parental smoking is associated with increased prevalence of asthma and respiratory symptoms in schoolchildren. Among children with established asthma, parental smoking is associated with more severe disease. Parental smoking probably acts, alone or in combination with infection, as a trigger of wheezing attacks rather than as a cause of the underlying asthmatic tendency. Environmental tobacco smoke (ETS) exposure is not consistently related to allergic sensitisation and the case for a relationship with bronchial reactivity (BHR) has not been firmly established.

In contrast to LRI and respiratory symptoms, maternal but not paternal smoking are associated with deficits in FEV1 and other spirometric indices. These deficits are small in school aged children but

much larger in neonates. While this is almost certainly a causal relationship, much of the effect may be due to in utero exposure to maternal smoking rather than to ETS exposure post-natally.

It seems likely that parental smoking causes both acute and chronic middle ear disease in children.

While essentially narrative rather than systematic and quantitative, the findings of the California EPA review are broadly similar. In addition they have reviewed the studies of effects of ETS on children with cystic fibrosis and conclude from the limited evidence that there is a strong case that parental smoking and hospitalization are related.

While a number of mechanisms have been proposed to explain the epidemiological findings the majority remain plausible explanations which lack confirmatory evidence. Acute effects on upper respiratory mucosa have been more thoroughly studied, but these are more relevant to middle ear effusion than to lower respiratory outcomes. Data on the effects in adults of acute exposure to ETS under laboratory conditions suggest ETS has acute effects on spirometric performance rather than on BHR. It seems likely that such effects are also present in children.

Recent publications do not lead us to alter the conclusions of our earlier reviews.

*Conclusions* – Substantial benefits to children would arise if parents stopped smoking after birth, even if the mother smoked during pregnancy. Policies need to be developed which reduce smoking amongst parents and protect infants and young children from exposure to ETS. The weight of evidence is such that new prevalence studies are no longer justified. What are needed are studies which allow comparison of the effects of critical periods of exposure to cigarette smoke, in particular during pregnancy, early infancy and later childhood. Where longitudinal studies are carried out they should be analysed to look at the way in which changes in exposure are related to changes in outcome. Better still would be studies demonstrating reversibility of adverse effects especially in asthmatics or children with cystic fibrosis. While these would ideally be randomised controlled trials, few such studies are likely to be carried out given the large sample sizes implied (tens of thousands of subjects).



## ***Introduction***

During the last two decades many epidemiological studies have reported upon the association of parental smoking and respiratory diseases throughout childhood. Recently a series of papers in *Thorax* have presented a systematic and quantitative review of the health effects of passive smoking on children's respiratory health including middle ear disease<sup>1-7</sup>. In this paper we: (1) summarise the findings of these reviews; (2) comment on papers published since then; (3) compare the findings with a similar review published by the California EPA<sup>8</sup>; (4) discuss possible mechanisms that might explain the epidemiological findings, and (5) identify what further research is needed.

## ***Methods used in Thorax reviews***

Details of our search strategy are published elsewhere<sup>1</sup>. Published papers, letters and review articles relating to ETS exposure in children were selected by an electronic search of the EMBASE and Medline databases. This search, completed in April 1997, yielded 3625 references of which 1593 contained keywords relevant to respiratory or allergic disease. These 1593 abstracts were reviewed and 692 identified as of possible relevance to the assessment of respiratory health effects.

Wherever possible, information was extracted from each study and summarised as an odds ratio for chest illness or symptoms among children with and without smokers in the family. Maternal and paternal smoking were analysed separately where possible as were maternal smoking during pregnancy and current maternal smoking. The odds ratio was chosen as a measure of association which can be derived from all types of study. Where quantitative meta-analysis was considered appropriate, odds ratios were tested for heterogeneity. The heterogeneity tests were often statistically significant, implying that a simple "fixed effect" pooling of the logarithms of the odds ratios may be inappropriate. In most cases therefore the pooling was carried out using a "random effects" model.

For studies of lung function we needed to summarise the effect of ETS exposure on the same scale in different studies. We therefore transformed all reported effect measures to the difference in outcome

measure (e.g. FEV1) between the exposed and non-exposed children expressed as a percentage of the level in the non-exposed group. Approximate confidence limits were derived and pooled percentage differences again produced using both fixed and random effects approaches. In practice using a “random” as opposed to “fixed effects” model made little difference to point estimates, but produced slightly wider confidence limits.

In June 1998 we reran the same search strategy to identify recent publications, this identified 24 articles containing data not included in the original reviews. These are commented on separately in the relevant sections, but the quantitative meta-analyses have not been updated.

### ***Summary of findings from Thorax reviews***

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

For lung function there are small deficits if the mother smokes, with the effect being greater for mid and end expiratory flow rates than for FEV1. In contrast to the symptoms there is little evidence of paternal smoking having an adverse effect. Below we discuss each area in more detail.

#### **Lower respiratory illnesses in infancy and early childhood**

(Figure 1 here)

The most coherent and consistent evidence of adverse health effects from parental smoking comes from 21 studies of lower respiratory illnesses, such as bronchitis, bronchiolitis or pneumonia in infancy and early childhood<sup>1</sup>. These comprised 14 longitudinal studies, 2 controlled trials, 2 case controls studies and 3

retrospective prevalence surveys, mainly of illnesses in the first two years of life. Five studies did not distinguish upper and lower respiratory illnesses, but yielded similar results to the remainder and were therefore included in the meta-analysis. The results were also similar for studies of lower respiratory illnesses in the community setting and those which recruited only cases admitted to hospital.

Overall, the risk of early lower respiratory illness was increased by a factor of about 1.6 if either parent smoked and by about 1.7 if the mother smoked. There was a significantly increased relative risk, about 1.3, associated with smoking by the father if the mother did not smoke. This latter observation suggests that much of the observed association with maternal smoking is probably due to postnatal, rather than prenatal (intrauterine) exposure. The risks associated with parental smoking were largely independent of measured confounding variables, suggesting that residual confounding by unmeasured factors is unlikely to be important.

Two studies published more recently from North Carolina, USA<sup>34</sup> and Norway<sup>35</sup> are broadly consistent with these conclusions, although in one<sup>35</sup> the dose-response gradient was more convincing for smoking by the father than for maternal smoking.

## Prevalence of asthma and respiratory symptoms in school age children

(Figure 2 and 3 here)

Many cross-sectional studies of school age children have reported on the association of respiratory symptoms (wheeze, cough, phlegm and breathlessness) with parental smoking. Not all were suitable for meta-analysis, but the 60 which were offered an opportunity to explore issues of publication bias, confounding, dose-response and symptom specificity in detail.<sup>2</sup>

The prevalence of all respiratory symptoms was increased, with odds ratios typically in the range 1.2-1.4, among children whose parents smoked. The evidence was generally consistent across studies and in

different countries. The magnitude of the effect was altered little by adjustment for a wide range of potential confounding variables, so residual confounding by unmeasured factors is unlikely. Although there was evidence of publication bias (with a deficit of small "negative" studies), the sample size in most studies was large, so the pooled relative risk estimates were robust to exclusion of the smaller published studies. Case-control studies of prevalent asthma gave very similar results to the cross-sectional studies<sup>5</sup>.

A number of cross-sectional studies have been published subsequently, all broadly supporting these conclusions<sup>70-74</sup>. In a methodological study which compared parental reports of nocturnal cough with overnight recording, smoking parents were found to substantially underreport compared to non-smoking parents, resulting in underestimation of the odds ratio relating cough to ETS exposure<sup>75</sup>.

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

More recently, three studies have been published comparing current with past exposure, with inconsistent findings. A study of 1129 Polish children found upper and lower respiratory infections were related more strongly to current ETS exposure than to maternal smoking during pregnancy<sup>76</sup>. A second study of 705 5<sup>th</sup> grade children in Chicago, found that maternal smoking in pregnancy was more strongly related to doctor diagnosed asthma than current maternal smoking<sup>77</sup>. However, it is worth noting that wheezing was *inversely* associated with current maternal smoking in this study. Consistent with the Chicago study, a large Scandinavian survey of 15,962 6-12 year old children reported that asthma attacks, dry cough and asthma treatment in the past year were inversely associated with current smoking in the home, but positively associated with smoking in the home in the first 2 years of life<sup>78</sup>. Again the lack of an association with current exposure stands in contrast to the rest of the literature, and the authors suggest that avoidance of risk factors by parents of symptomatic children is likely to be important. Further studies are needed to clarify this potentially important issue.

## Incidence of asthma and wheezing illnesses

(Figure 4 here)

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

Among the 21 studies of early lower respiratory illness,<sup>1</sup> there were 10 which focused specifically on illnesses associated with wheezing. Although the effect of either parent smoking was of similar magnitude for wheezing and non-wheezing illnesses, maternal smoking was more strongly associated with wheezing than non-wheezing illnesses.

Studies of the incidence of asthma later in childhood<sup>5</sup> provided less information on patterns of household smoking and a quantitative meta-analysis was possible only for maternal smoking. The incidence of asthma or wheezing illness after the first year of life (four longitudinal studies) was weakly but significantly associated with maternal smoking, with an odds ratio of 1.13, considerably less than the odds ratio of 2.08 for wheezing illnesses in infancy. Four cohort studies of asthma or wheezing from birth to age 5-7 give intermediate results: the odds ratio for smoking by the mother being 1.31.

Taken together, the evidence suggests that parental smoking is more influential as a cause of early "wheezy bronchitis" than of later onset "asthma". No new references were identified which further informed this issue. However, one recently published paper<sup>85</sup> suggests that Norwegian teenagers with asthmatic symptoms are less likely to receive a diagnosis of asthma if their parents smoke. This finding may not be generalisable to other countries and cultures, but it raises the possibility that the association of ETS with asthma may have been underestimated in studies which rely on physician diagnosis.

## Natural history and severity of asthma and wheezing

Eight studies of the prognosis of asthma or wheezing illness were inconsistent in relation to the effects of parental smoking.<sup>5</sup> Early prognosis appeared to be worse if parents smoke, whereas persistence of symptoms into the teens and twenties was less common in children of smokers. A recently published follow-up study of 101 wheezy Swedish infants<sup>86</sup> is intermediate between these two groups of studies. The presence of asthma at age 10 was more common in children exposed to household smoking in infancy (82% v 59%), although not associated with household smoking at age 10 (54% v 52%), perhaps reflecting changes in parental behaviour associated with persistence of the child's asthma.

The results of ten case-series addressing asthma severity were more consistent, with symptom scores, attack frequency, medication use, hospitalisations and life-threatening attacks being generally positively related to ETS exposure.<sup>5</sup> No new references were identified to change this conclusion.

## Allergic sensitisation

Previous narrative reviews had concluded that parental smoking increased the risk of allergic disease. However, these included asthma and wheezing which may be related to ETS exposure by mechanisms other than allergy. We chose to review 36 studies of IgE, skin prick positivity, hay fever or eczema separately from studies of asthma in order to address more directly the influence of ETS exposure on allergic sensitisation<sup>4</sup>. There was only limited scope here for meta-analysis, with inconsistency in the quantitative results. In contrast to previous reviews, we concluded that the balance of evidence did not support a positive association of allergic sensitisation with parental smoking, either before or after birth.

Four more recent publications have contributed information in relation to eczema. Three of these, from Denmark, Britain and Hong Kong, show a slightly reduced risk among the offspring of smokers<sup>71; 87; 88</sup>, and a fourth, from Germany,<sup>89</sup> found an increased risk cross-sectionally which was not sustained on follow-up. A British study of skin prick tests among infants of atopic parents<sup>90</sup> reported an inverse association of prick positivity with maternal smoking while a Swedish study also reported a weak inverse association between

prick positivity and maternal smoking<sup>72</sup>. These results are consistent with a significantly reduced prevalence of hay fever among the children of smokers in two national British birth cohorts<sup>88</sup>, but not with the slightly raised risk of hay fever in the survey from Hong Kong<sup>71</sup>. These additional publications do not lead us to alter the conclusion of our earlier review.

## Bronchial reactivity

Our meta-analysis of the relationship between bronchial reactivity (BHR), as assessed by challenge tests, and ETS exposure (largely maternal smoking) in 10 population samples, suggests a small but real increase in BHR amongst the children of smoking mothers (OR=1.29, 95%CI 1.10 to 1.50)<sup>6</sup>. However, it seems likely that this estimate is biased upwards since other studies providing P-values but not odds ratios appear to be generally negative, while 4 studies have collected data but have not published on the relationship between BHR and ETS. The published data relating ETS exposure to bronchial reactivity are therefore not definitive. Our literature update identified only one small study of 182 Italian children, but no data were presented relating ETS to BHR<sup>91</sup>. The current uncertainty could be resolved by pooling data from all these studies to provide an unbiased estimate of the association.

## Peak flow variability

In contrast to the equivocal results for BHR, all 4 published studies report an effect of ETS exposure on daily variation in PEF<sup>6</sup>. Although the evidence is limited, this suggests that the increased variation in PEF may be the result of acute effects of daily variations in exposure, rather than on an individual's underlying susceptibility. No new studies on this issue have appeared.

## Spirometric indices

(Figure 5 here)

Cross-sectional studies in school aged children show a consistent small deficit in lung function indices among children whose parents smoke (Table 2 and Figure 5)<sup>7</sup>. Not surprisingly given the variety of exposure measures used there is some heterogeneity in effect between studies, though much of this heterogeneity arises from 4 small studies reporting relatively large effects (3 negative, 1 positive), while the largest studies reported rather smaller effects (Figure 5). The random effects estimate, which gives greater weight to smaller studies, is thus slightly greater than the fixed effect estimate. The proportionate reduction is smallest for FVC (-0.4%) and FEV1(-1.4%), but larger for mid and end expiratory flow rates (-5.0% and -4.3% respectively, Table 2). Adjustment for potential confounding variables had little effect on the estimates. A number of studies reported clear evidence of a graded exposure response relationship. Where exposure was explicitly identified it was usually maternal smoking with only one Chinese study reporting a clear effect of paternal smoking<sup>103</sup>.

It has been suggested that the small deficits seen in flow rates for children of smoking mothers may be attributable not to current ETS exposure, but to residual effects of maternal smoking during pregnancy. Three studies have measured neonatal lung mechanics and related them to maternal smoking. In two, measurements were sufficiently close to birth to effectively exclude effects due to postnatal ETS exposure. The reported effects were much larger than those seen in school aged children. These findings are reinforced by a recent Norwegian study of 803 babies where tidal flow volume loops, compliance and resistance were measured 2.7 days after birth<sup>107</sup>. However, the magnitude of effects seems rather smaller in this study than the earlier studies. Of five cross-sectional studies in school aged children that compared the effects of perinatal exposure (retrospectively assessed) with current exposure to maternal smoking in later childhood, the three largest concluded that the major effect was in utero or neonatal exposure.

We conclude that maternal smoking is associated with small but statistically significant deficits in FEV1 and other spirometric indices in school aged children. This is almost certainly a causal relationship. Much of the effect may be due to maternal smoking during pregnancy which appears to have rather larger effects on neonatal lung mechanics. In addition it seems likely that susceptible individuals will experience acute reductions in FEV1 and PEF when exposed to ETS. Further work

is needed to establish this. It seems likely that the small differences in lung function in children associated with maternal smoking will translate into small differences in adults. Such subtle reductions are unlikely to impact on rates of development of chronic airflow obstruction, unless evidence emerges that children exposed to cigarette smoke in early life have faster rates of lung function decline in adult life. In a recent meta-analysis of cross-sectional adult data we found a 2.6% deficit in FEV1 in ETS exposed non-smoking adults, very similar to the effect in children's studies<sup>108</sup>.

Further evidence that ETS exposure may have some effects on lung function comes from cohort studies. Of the 6 cohort studies, the Six Cities Study is an order of magnitude larger than any other cohort and thus deserves substantial weight. It reported very small, but statistically significant effects of maternal smoking on lung growth (-3.8ml/yr for FEV1).

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

## Middle ear disease

(Figure 6 here)

Studies of middle ear disease were of a variety of designs, including cohort studies, case-control studies and population surveys. They were reviewed in four groups: 13 studies of acute otitis media, nine of recurrent otitis media, five of middle ear effusion and nine of glue ear surgery<sup>3</sup>. A meta-analysis was possible for all outcomes except acute otitis media, and the results were consistent, with pooled odds ratios in the range 1.2-1.5.

Four more recently published case-control studies, from Canada<sup>127</sup>, Sweden<sup>128</sup>, Malaysia<sup>129</sup> and Minnesota, USA<sup>130</sup> present quantitative data for acute or chronic otitis media in relation to parental smoking. The 95% confidence intervals for the odds ratios overlap with the pooled values derived in our meta-analyses. A detailed longitudinal study of 2253 infants in Pennsylvania, USA<sup>131</sup> assessed the presence of middle ear effusion clinically and by tympanometry at monthly intervals throughout the first two years of life. There was a highly significant positive association between the duration of effusion and the number of smokers in the household, during both the first and second years of life. Although these results cannot be compared directly with odds ratios derived in other studies, they are qualitatively consistent with our earlier meta-analyses.

### ***Comparison with California EPA review***

(Tables 3 and 4 here)

Table 3 contrasts the methods used in our earlier reviews and those of the California EPA<sup>8</sup>. Table 4 summarises the conclusions of the Californian review. Despite the different approach the conclusions are qualitatively and from a public health perspective very similar. The main differences are: (i) difference in interpretation of the inconsistent data on allergic sensitisation. We hold by our view that allergic sensitization is not related to in utero or ETS exposure; (ii) greater emphasis in the Californian review on the relationship of ETS and incidence of asthma. This arises because the Californian review includes prevalence studies in its assessment of incidence and also because there is no clear distinction of the incidence of LRI and wheezing illness in infancy from the development of later onset asthma.

### **Cystic fibrosis**

We did not evaluate the effects of ETS on children with cystic fibrosis (CF) in our Thorax series because there were insufficient studies for a quantitative review. However, the California EPA review<sup>8</sup> summarises five studies<sup>132-136</sup> relating the severity of CF to parental smoking (see CalEPA table 6.6). Over half of the children in these studies were exposed to ETS. Hospital admissions for CF exacerbations were significantly

related to parental smoking in three of the four studies which reported this association, and in the same three studies ETS exposure was significantly related to other measures of disease severity. The studies are inconsistent or inconclusive in relation to the effects of parental smoking on growth and ventilatory function.

## ***Discussion***

While maternal smoking during pregnancy is generally bad for the foetus and has a demonstrable effect on infant lung function, there is good evidence that postnatal ETS exposure plays an important role in the respiratory health of children. We conclude that substantial benefits to children would arise if their parents stopped smoking, even if their mother smoked during pregnancy.

### **Modifying factors/ Subgroups at high risk**

While it is of considerable interest to ask whether there are any subgroups who are particularly vulnerable to the effects of ETS, with the exception of age and to a limited extent sex it is remarkably difficult to review this issue in any systematic way. This is due to the fact that: (i) subgroup analyses within studies are usually presented only if differences appear large or are statistically significant; (ii) studies of diseased children (eg asthmatics or those with cystic fibrosis) rarely include “normal” subjects with whom effects can be compared.

There is little doubt that all effects are greater in infancy. This may be partly due to effects of in-utero exposure (e.g. on spirometry), but also due to higher ETS exposure. For the same level of maternal smoking, exposure to ETS as assessed by cotinine declines markedly between infancy and school age<sup>137</sup>. Even after school entry there is evidence of both differential exposure (as assessed by salivary cotinine levels) and by sex and geographical area and time of year<sup>138-140</sup>.

It has been claimed that the effects of ETS on lung function are greater in boys. In 7/9 studies in school aged children where we were able to compare effects it was greater in boys, but the gender difference was rarely statistically significant<sup>7</sup>. A pooled analysis of all 9 studies estimated the effect

on FEV1 to be –2.1% in boys and –1.3% in girls with the gender difference not being significant at the 5% level (P=0.06). Reported gender differences are inconsistent in studies of respiratory mechanics in neonates and in studies of effects of ETS on BHR in older children.

Based on limited information we found no evidence that effects of ETS on LRI in infants were modified by a parental history of allergy or prematurity<sup>1</sup>. Nor did we find that atopic children were a susceptible sub-group for ETS in relation to wheeze or asthma. Indeed, our conclusion was that the evidence favours a stronger association of parental smoking with non-atopic “wheezy bronchitis” than with “allergic asthma”<sup>5</sup>.

Similarly while ETS appears to increase the risk of hospitalisation in children with cystic fibrosis, the direction of the effect is the same as that in normal populations. However, if a similar relative risk is operating on a high baseline risk for illness or admission, the absolute increase in risk will be largest in high risk groups.

## Mechanisms

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

The most direct evidence on mechanisms is from acute effects on upper respiratory mucosa (see pages 6.29 to 6.34 of California EPA review<sup>8</sup>), but apart from middle ear effusion, this is least relevant to the outcomes we have considered. The most convincing epidemiological evidence concerns early LRI in relation to postnatal exposure, yet we are lacking insights into how ETS increases the severity of these early (largely viral) infections.

An early hypothesis was that smoking parents, being more susceptible to respiratory infections themselves, might then transmit them to their children. Thus Colley in two early papers on parental smoking and respiratory symptoms, looked at the effect of adjusting for parental phlegm production<sup>141: 142</sup>. While adjustment did not adequately explain the higher prevalence rates in children of smoking parents, this hypothesis deserves further consideration.

Studies in children which have assessed the effects of acute exposure to ETS in controlled situations are very limited, but there are weak suggestions of acute effects of ETS exposure on lung function<sup>6</sup>. The California EPA reviewed the more extensive evidence in adults<sup>8</sup> (see pages 6-12 to 6-17). They reported that “most of the ETS inhalation chamber studies show slight-to-moderate, transient effects on lung function in at least some of the study subjects. In several studies, participants experienced decrements in lung function exceeding 20%.” Such acute effects might well explain the peak flow variability results. Further studies to confirm these findings in children, seem warranted.

The limited evidence relating ETS to bronchial inflammation and airway development is only by extrapolation from active smokers, or from side-stream exposure of laboratory animals. Our review has effectively excluded allergic sensitisation as a link between ETS and asthma, and casts some doubt on the BHR route. Evidence of acute effects on BHR in chamber studies in adults is limited and not consistent<sup>8</sup>.

## Outstanding research issues

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

While randomised controlled trials are the ideal, they would need to be large. Consider a study in which it was proposed to reduce smoking in parents of children with middle ear effusion with the outcome of interest being operative treatment. MEE commonly resolves in about 1/3 of cases between

outpatient referral and operative treatment some 3 to 6 months later. We might expect perhaps 10% of parents to stop smoking with usual care and might hope to double this to 20% in the intervention group. Assuming 1/3 of cases resolved spontaneously in children of smokers and an optimistic 1/2 in children of those who quit smoking, we would need to randomise 33,500 children overall (16,750 to each group) to have 90% power at the 0.05 significance level. This is because the majority of parents in each group continue to smoke. The difference in outcome between the intervention and usual care groups is therefore small and the trial needs to be large to detect such a difference. Such considerations explain why there have been so few trials and those that have been carried out have been negative when analysed on an intention to treat basis.

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

Further cross-sectional studies of lung function or symptoms are unlikely to be informative unless they compare critical periods of exposure or look at changes in parental smoking – e.g. now compared to during pregnancy or early infancy.

Future studies need to give thought to the assessment of exposure. Key issues are distinguishing between maternal and paternal smoking and looking for dose response. Objective measures such as cotinine are important since actual exposure will vary between individuals and tend to decrease with age despite parental smoking habits being constant. It is also important to consider whether children from non-smoking families are a suitable group to treat as non-exposed. Any background exposure in this group which has an effect on respiratory disease will bias any comparisons between smoking and non-smoking families towards the null hypothesis of no difference. Measurement of cotinine will help here. The limited evidence available is not entirely consistent. Studies in British children suggest that the low levels of exposure seen in non-smoking households<sup>143</sup> do not influence either lung

function or respiratory symptoms<sup>94; 100</sup>. In contrast an Italian study has reported effects on lung function in children with occasional exposure to ETS<sup>93</sup>. However, the cotinine levels reported in this study are extremely high, even for children from smoking households.

Further studies distinguishing current versus cumulative versus early (particularly in-utero) exposure in relation to symptoms and lung function would help to elucidate mechanism and inform preventive measures. While maternal smoking is the most important source of exposure in many countries, it would be valuable to see further large studies measuring dose where mothers are confirmed non-smokers. Studies from China<sup>15; 29; 33; 103</sup> have been particularly useful in this context.

There is undoubtedly a need to clarify the association of ETS and BHR – here the solution would be to pool data from all studies published and unpublished. Equally with only 4 published studies of peak flow variability there is undoubtedly room for publication bias. However, if there is an acute effect on lung function from ETS exposure in at least a significant minority of subjects this will be better demonstrated by laboratory studies of acute exposure.

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

## Public Health Issues

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

source in many countries. It seems likely that prevention will remain focussed on reducing the percentage of parents who smoke rather than on isolating smokers or increasing ventilation.

ETS pollution is increasingly being tackled in western countries by health promotion campaigns and restrictive interventions (e.g. in the workplace). However, few campaigns outside the United States have highlighted the susceptibility of children to ETS exposure. The challenge is to get the message about smoking and health risks in infancy across without making the first 6 postpartum months even more difficult. While in developed countries back to sleep campaigns have successfully altered sleeping position of babies, smoking rates have been left virtually unchanged. In many undeveloped countries few females smoke, while male smoking rates are very high. At the same time there are marked imbalances of power within the family. It is likely to prove difficult to promote household changes in these groups if education is channeled through mothers.

It is also important to view the adverse health effects from ETS exposure in context. The absolute risks are small relative to those of active smoking, but for children in particular exposure is not voluntary, and this involuntary exposure can cause serious and completely avoidable health effects. Of even greater potential long term significance, is the link between parental smoking and uptake of active smoking by their children. In England, parental smoking doubles the risk of smoking uptake by children<sup>144</sup> which since 50% of children come from smoking households allows us to estimate that up to 1/3 of the cases of children smoking may be attributable to parental example.

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

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

<sup>+</sup> Based on fixed effects estimate

\* Relates largely, but not entirely to maternal smoking

<sup>§</sup> Results relate to maternal smoking during pregnancy or ETS exposure in infancy. Data for ETS exposure during later childhood are too heterogeneous to meta-analyse.

n]=number of studies on which pooled odds ratios based

**Table 2** *Summary of pooled percentage difference (95% confidence intervals) for effect of parental smoking on lung function. Data are from REF [7].*

	No. of studies	% difference (95% CI)	
		Fixed effect	Random effect
FVC	19	-0.2 (-0.4 to +0.1)	-0.4 (-0.8 to +0.0)
FEV1	21	-0.9 (-1.2 to -0.7)	-1.4 (-1.9 to -1.0)
MEF	19	-4.8 (-5.4 to -4.3)	-5.0 (-6.6 to -3.3)
EEF	9	-4.3 (-5.3 to -3.3)	-4.3 (-5.5 to -3.1)

MEF = Mid expiratory flow rate

EEF = End expiratory flow rate

Source reference [7]

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

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

# only used for asthma induction, including early wheezing illnesses

**Table 4 Summary of results and conclusions of Californian EPA review**

<u>Outcome</u>	<u>Odds ratios</u>	<u>Conclusions</u>
Lower respiratory disease in young children	1.5 to 2	ETS exposure clearly confers an increased risk of acute lower respiratory disease in young children
Asthma “induction”*	1.75 to 2.25 in summary N=37, RR=1.45 any Mat RR=1.6 in chapter	Compelling evidence of an effect
Asthma exacerbation	Narrative	Disease severity increased by ETS
Respiratory symptoms In children	Narrative	Associated with parental smoking
Lung growth and development	Narrative	Evidence not wholly consistent but suggestive of small effects
Atopy	Narrative	Several studies have shown an increased risk of atopy in children of smoking mothers, though the evidence regarding this issue is mixed
Middle Ear Infection	Narrative. OR=1.62	Risk of both acute and chronic middle ear infection increased

\*Some of the studies included are cross sectional studies of asthma prevalence and thus the conclusion of an effect applies in part to prevalence, not to incidence. Difficult to understand why summary differs from text – in particular from meta-analysis.

† Odds ratio quoted in summary appears to be based on one study. The emphasis placed on this one study appears inappropriate.

**Table 5**      ***Mechanisms proposed for respiratory effects of passive smoking***

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

\*Due to in-utero exposure to maternal smoking

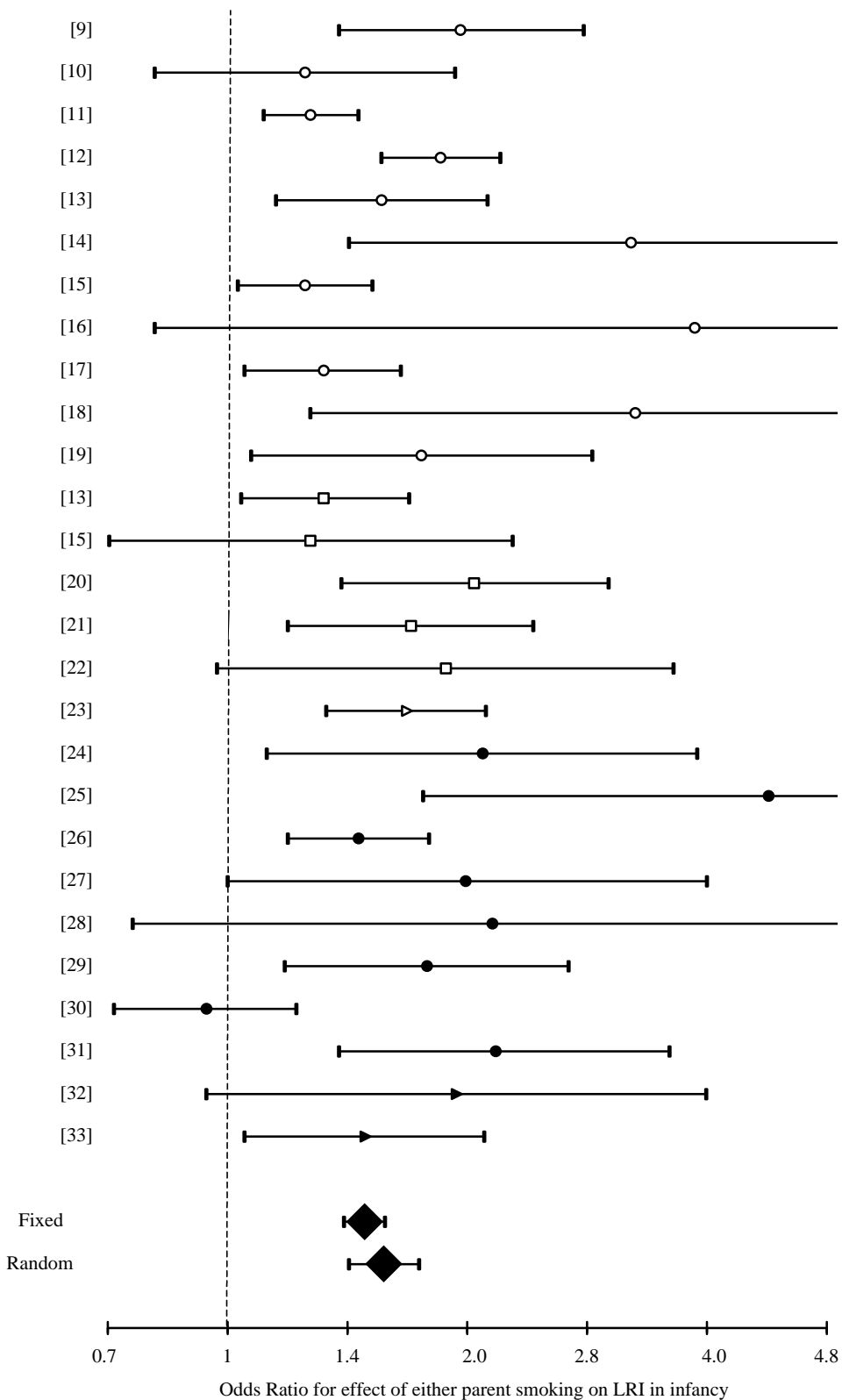


Figure 1. Odds ratios and 95% confidence intervals for effect of either parent smoking (compared with neither smoking) on lower respiratory illness in infancy. The pooled odds ratio derived by fixed effects and random effects methods appear at the foot of the figure. The horizontal scale is logarithmic. Individual studies are denoted thus: circles = studies of lower respiratory illnesses; squares = studies of wheezing illnesses; triangles = studies of upper and lower respiratory illnesses; open = community studies; filled symbols = studies of hospitalised illnesses (Adapted from Figure 1 in reference 1).

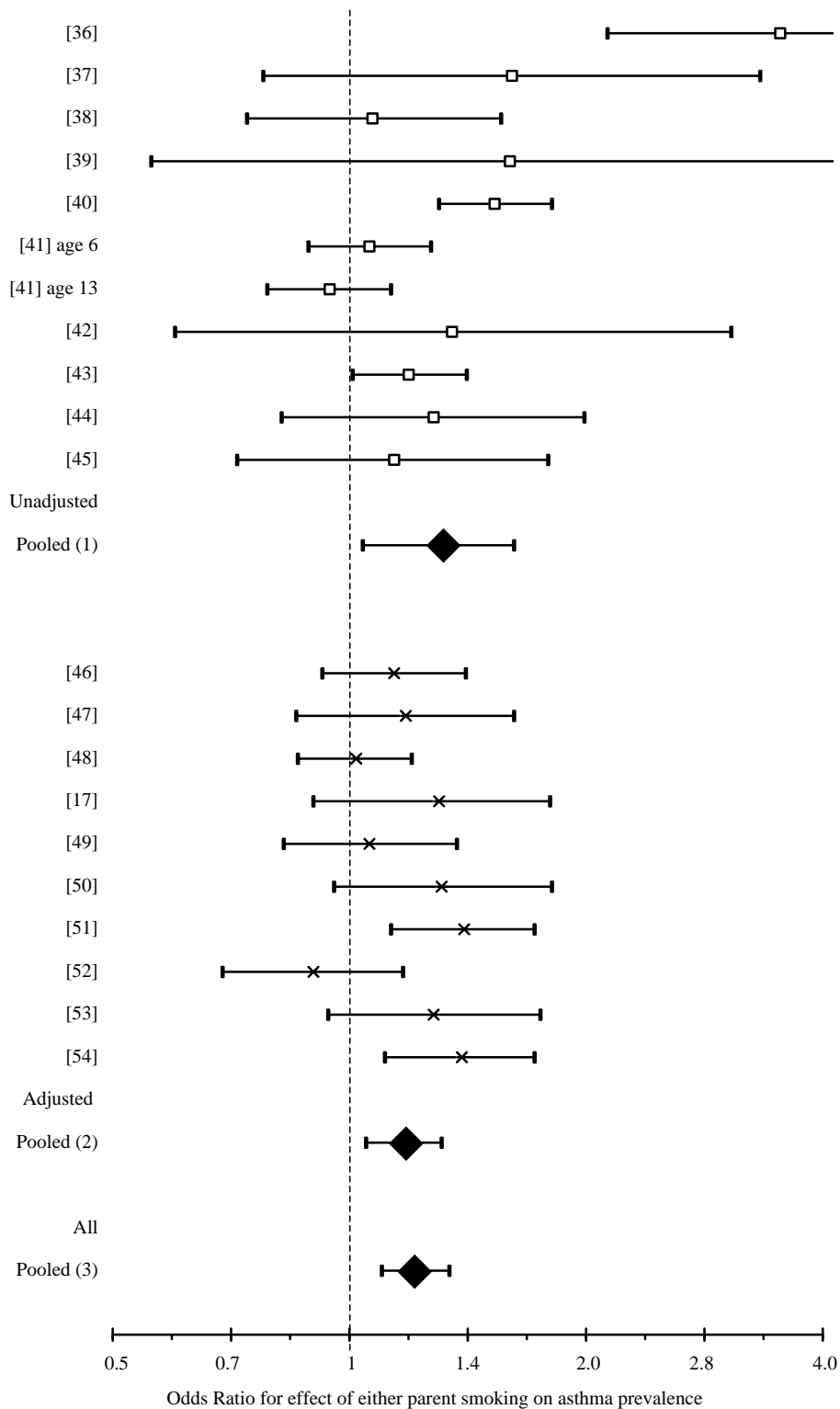


Figure 2. Odds ratios and 95% confidence intervals for effect of either parent smoking on asthma prevalence: upper part, studies not adjusting for potential confounders, contribute to pooled odds ratio (1); lower part, studies adjusting for a variety of potential confounders contribute to pooled odds ratio (2); pooled odds ratio (3) is based on all studies. Studies ordered by date of publication. The pooled odds ratios were derived by random effects methods. The horizontal scale is logarithmic. (Adapted from Figure 1 in reference 2).

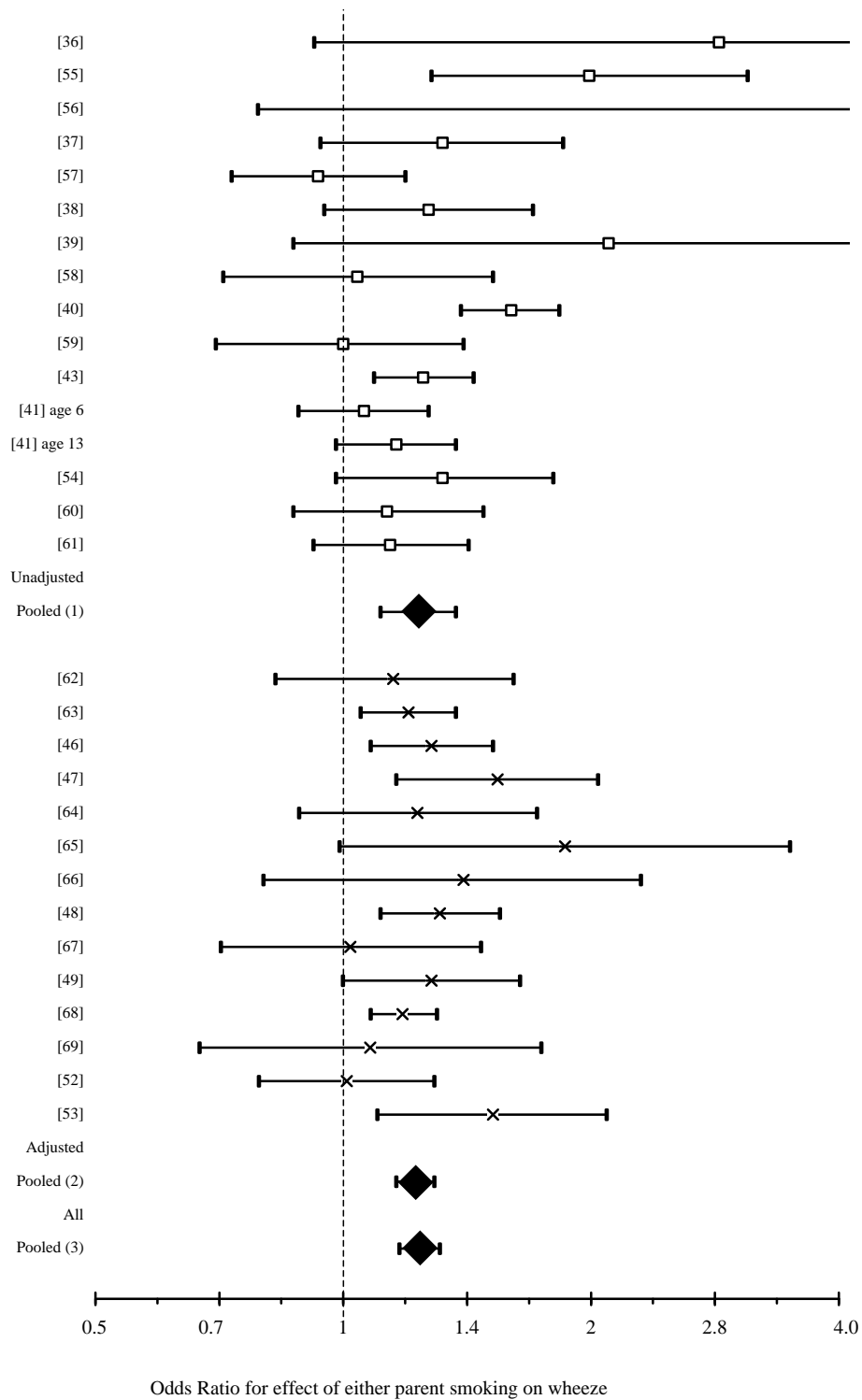


Figure 3. Odds ratios and 95% confidence intervals for effect of either parent smoking on wheeze prevalence: upper part, studies not adjusting for potential confounders contribute to pooled odds ratio (1); lower part, studies adjusting for a variety of potential confounders contribute to pooled odds ratio (2); pooled odds ratio (3) is based on all studies. Studies ordered by date of publication. The pooled odds ratios were derived by random effects methods. The horizontal scale is logarithmic.(Adapted from Figure 2 in reference 2).

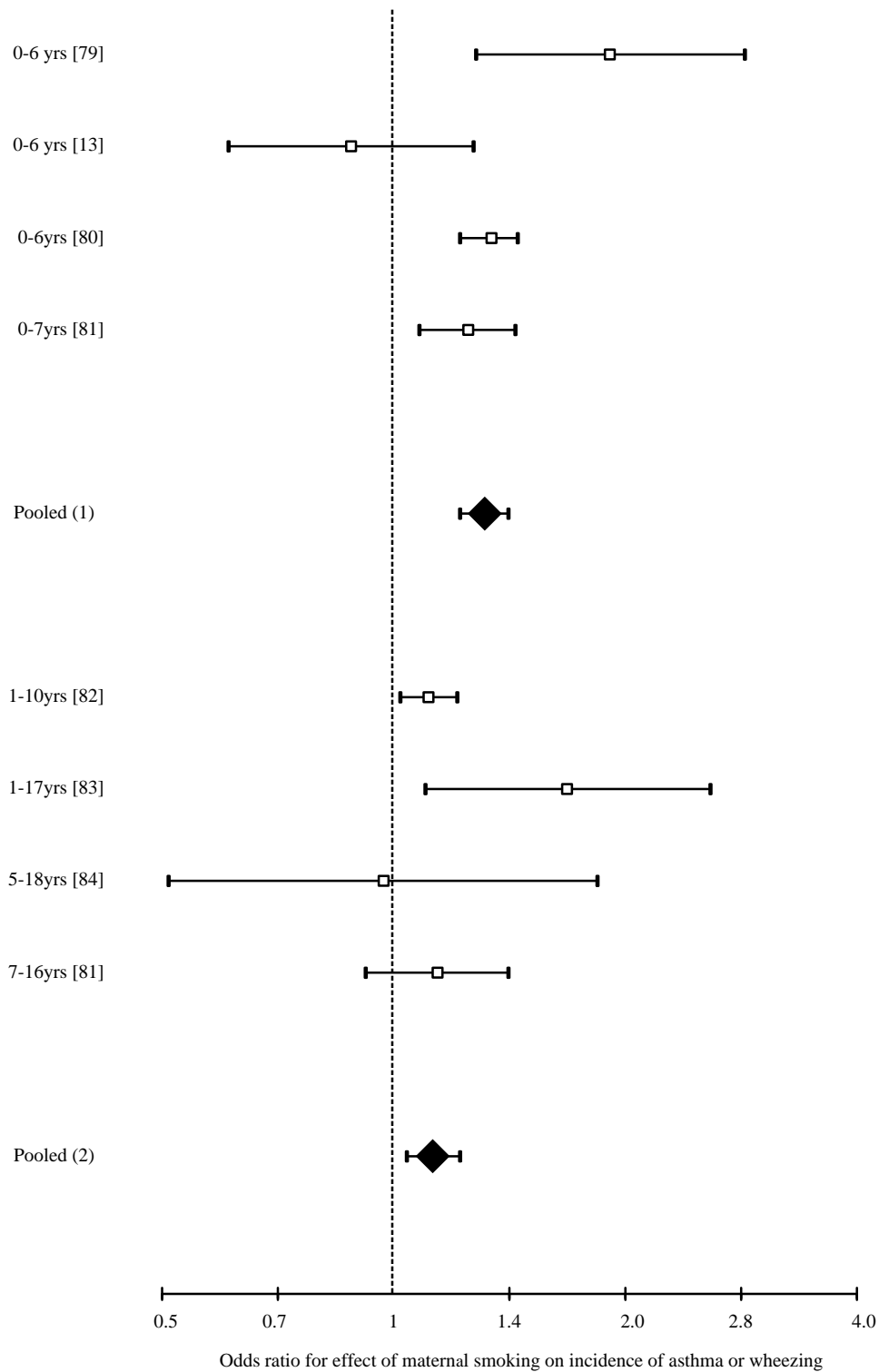


Figure 4. Odds ratios and 95% confidence intervals for effect of maternal smoking on the incidence of asthma or wheezing throughout childhood, cohort studies. The upper part lists studies which include the first year of life (exact incidence period shown on left) contributing to pooled odds ratio (1) and the lower part lists studies which exclude the first year of life contributing to the pooled odds ratio (2). Studies ordered by date of publication. The pooled odds ratios were derived by fixed effects methods. The horizontal scale is logarithmic. (Adapted from Figure 1 in reference 5).

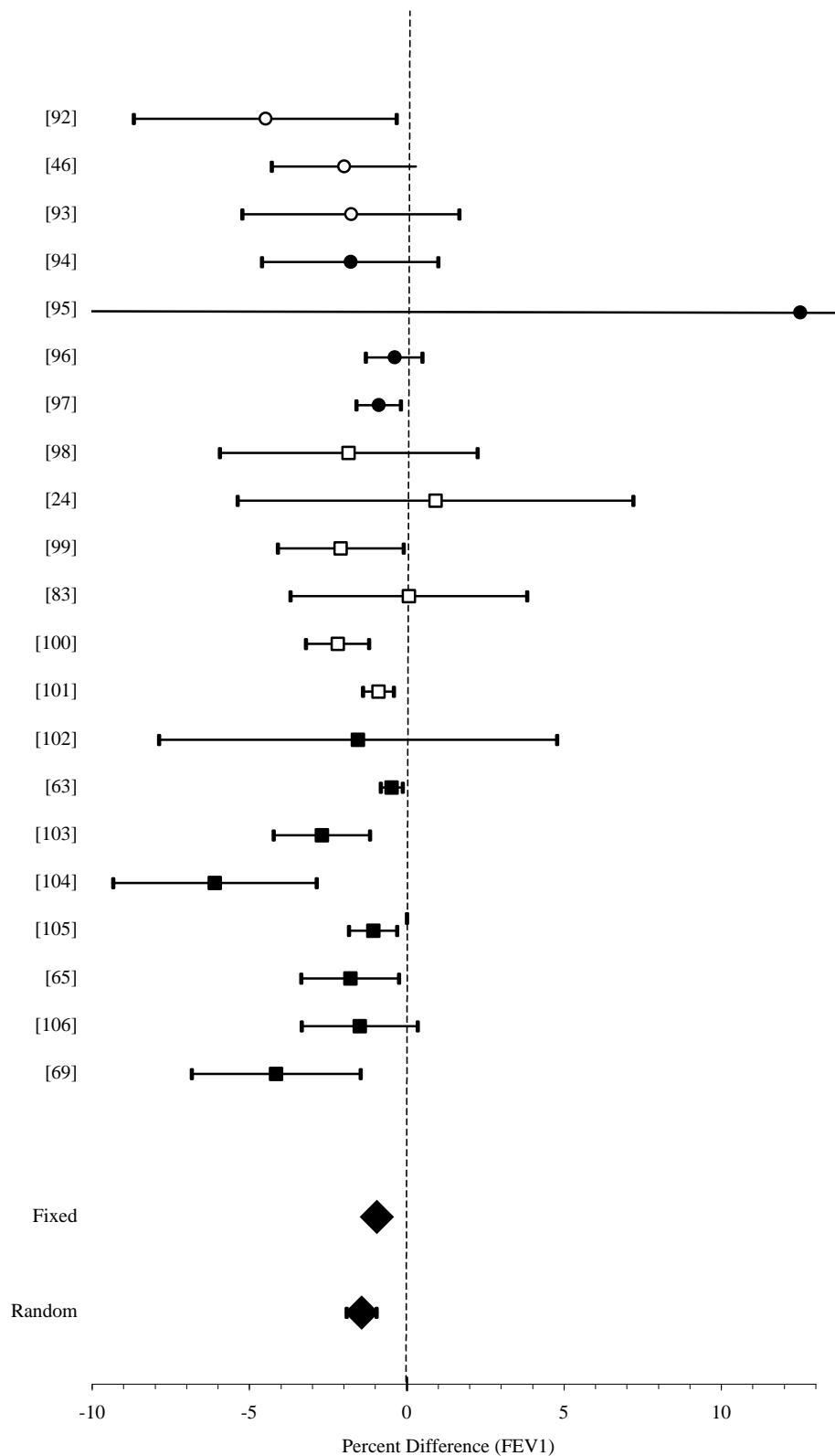


Figure 5. Percentage difference in FEV1 between children of smokers and non-smokers from cross sectional studies: open symbols are studies not adjusting for confounders other than age, height or sex; filled symbols are studies which adjusted for a variety of confounders. Squares = “low exposure comparison” such as maternal smoking versus not; Circles = “high exposure comparison” such as both parents smoke versus neither. (Adapted from Figure 1 in reference 7).

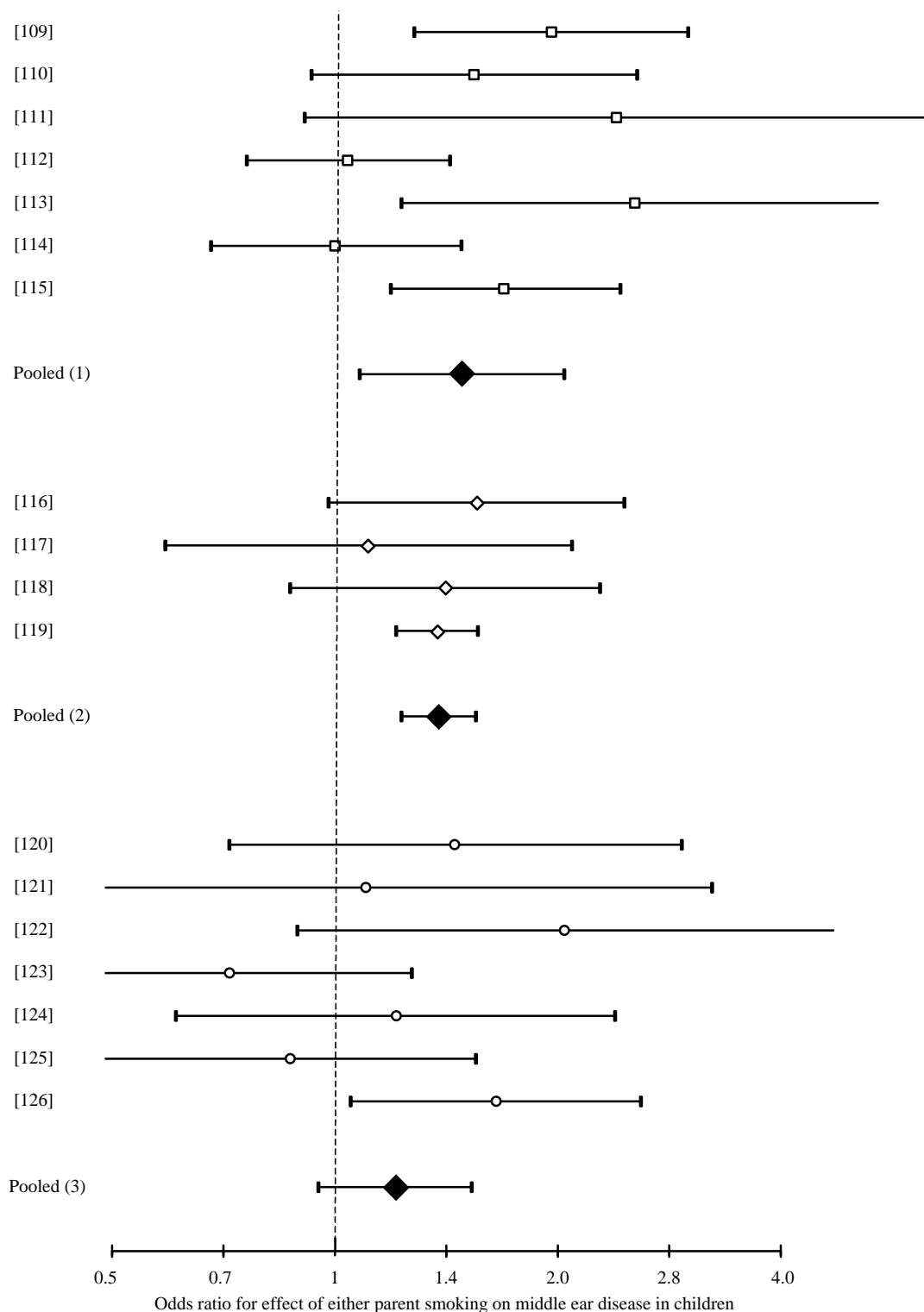


Figure 6. Odds ratios and 95% confidence intervals for effect of either parent smoking (compared with neither smoking) on middle ear disease in children. Open squares = recurrent otitis media (contributing to pooled odds ratio 1, based on random effects); open diamonds = middle ear effusion (contributing to pooled odds ratio 2, based on fixed effects); open circles = outpatient referral for glue ear (contributing to pooled odds ratio 3, based on fixed effects). The horizontal scale is logarithmic. (Adapted from figure 1 in reference 3).