Chapter 6
Respiratory Effects in Children from Exposure to Secondhand Smoke

Introduction

Adverse effects of parental smoking on the respiratory health of children have been a clinical and public health concern for decades. As early as 1974, two articles published in the journal *Lancet* alerted readers to a possible link between parental smoking and the risk of a lower respiratory illness (LRI) among infants (Colley et al. 1974; Harlap and Davies 1974). Although adverse effects on children from exposure to secondhand tobacco smoke had already been suggested (Cameron et al. 1969; Norman-Taylor and Dickinson 1972), the association with early episodes of acute chest illnesses was of immediate and continuing interest because of the suspected long-term consequences for lung growth, chronic respiratory morbidity in childhood, and adult chronic obstructive lung disease (Samet et al. 1983).

Subsequently, many epidemiologic studies have associated parental smoking with respiratory diseases and other adverse health effects throughout childhood. The exposures covered include maternal smoking during pregnancy and afterward, paternal smoking, parental smoking generally, and smoking by others. In 1986, the evidence was sufficient for the U.S. Surgeon General to conclude that the children of parents who smoked had an increased frequency of acute respiratory illnesses and related hospital admissions during infancy (U.S. Department of Health and Human Services [USDHHS] 1986). The 1986 Surgeon General's report also noted that in older children, there was an increased frequency of cough and phlegm and some evidence of an association with middle ear disease. The report also commented on an association between slowed lung growth in children and parental smoking. Several authoritative reviews by various agencies followed the 1986 report (U.S. Environmental Protection Agency [EPA] 1992; National Cancer Institute [NCI] 1999). Some researchers have systematically reviewed the literature and, where appropriate, carried out meta-analyses (DiFranza and Lew 1996; Uhari et al. 1996; Li et al. 1999); the most comprehensive systematic review was commissioned by the Department of Health in England (Scientific Committee on Tobacco and Health 1998). Updated versions of these reviews were then published as a series of articles in the journal *Thorax* (Cook and Strachan 1997, 1998, 1999; Strachan and Cook 1997, 1998a,b,c; Cook et al. 1998). These papers later served as a foundation for the 1999 World Health Organization (WHO) consultation report on environmental tobacco smoke and child health (WHO 1999). This chapter of the Surgeon General's report presents a major update of those reviews based on literature searches carried out through March 2001. The methodology for these reviews is described later in this chapter (see "Methods Used to Review the Evidence"). Selected key references published subsequent to these reviews are included in an appendix of significant additions to the literature at the end of this report.

The section that follows focuses on the biologic basis for respiratory health effects; Chapter 2 (Toxicology of Secondhand Smoke) of this report provides further background. Separate sections review the evidence for different adverse effects of secondhand smoke exposure of children: LRIs in infancy and early childhood, middle ear disease and adenotonsillectomy, frequency of respiratory symptoms and prevalent asthma in school-age children, and cohort and case-control studies of the onset of asthma in childhood. There is also a review of the evidence for the effects of parental smoking on several physiologic measures, lung function, bronchial reactivity, and atopic sensitization. Each section concludes with a summary and an interpretation of the evidence.

Mechanisms of Health Effects from Secondhand Tobacco Smoke

This section reviews the biologic impact of secondhand smoke on the respiratory system of the child. Subsequent sections summarize the evidence for adverse health effects on infants and children and describe postulated mechanisms for these effects. Chapter 2 of this report provides additional general data on these mechanisms.

Introduction

Pregnant women who smoke expose the fetus to tobacco smoke components during a critical window of lung development, with consequences that may be persistent. In infancy and early childhood, the contributions of prenatal versus postnatal exposures to secondhand smoke are difficult to separate because women who smoke during pregnancy almost invariably continue to smoke after their children are born. For children, exposure to secondhand smoke may lead to respiratory illnesses as a result of adverse effects on the immune system and on lung growth and development.

Lung Development and Growth

Active smoking by the mother during pregnancy has causal adverse effects on pregnancy outcomes that are well documented (USDHHS 2001, 2004). Exposure of pregnant women to secondhand tobacco smoke has also been associated with prematurity (Hanke et al. 1999), reduced birth weight (Mainous and Hueston 1994; Misra and Nguyen 1999), and small for gestational age outcomes in some studies (Dejin-Karlsson et al. 1998). However, the developmental effects on the respiratory system from maternal smoking during pregnancy extend beyond those that might be expected based on prematurity alone—the airways are particularly affected. Studies have demonstrated that lower measured airflows associated with secondhand smoke exposure are not completely explained by the reduction in somatic growth caused by maternal smoking (Young et al. 2000b). Researchers suspect that fetal growth limitations are mediated in part by the vasoconstrictive effects of nicotine, which may limit uterine blood flow and induce fetal hypoxia (Philipp et al. 1984). Fetal hypoxia, in turn, may lead to slowed fetal growth and may have direct effects on the lung, possibly affecting lung mechanics by suppressing the fetal respiratory rate. Studies have demonstrated a decrease in fetal movement for at least one hour after maternal smoking, which is consistent with fetal hypoxia (Thaler et al. 1980). Smoking during pregnancy may also negatively affect the control of respiration in the fetus (Lewis and Bosque 1995).

Researchers have proposed several mechanisms that explain the effects of maternal smoking during pregnancy on infant lung function. Animal and human studies suggest that morphologic and metabolic alterations result from in utero exposure to tobacco smoke components that cross the placental barrier (Bassi et al. 1984; Philipp et al. 1984; Collins et al. 1985; Chen et al. 1987). One study with monkeys that involved infusion of nicotine into the mother during pregnancy showed lung hypoplasia and changes in the developing alveoli (Sekhon et al. 1999). The investigators postulated that the effect was mediated by the nicotine cholinergic receptors, which showed an increased expansion and binding with nicotine administration. Further research with this model indicated altered collagen in the developing lung (Sekhon et al. 2002). Studies with this and similar models have shown a variety of effects from nicotine on the neonatal lung (Pierce and Nguyen 2002). The programming of fetal growth genes in utero may have a lifelong effect on lung development and disease susceptibility, areas of ongoing research in other diseases. There is now substantial research in progress on early life events and future disease risk that follows the general hypothesis proposed by Barker and colleagues (1996).

Exposure to secondhand smoke may also lead to structural changes in the developing lung. In a rat model, Collins and colleagues (1985) found that intrauterine exposure of the pregnant rat to secondhand smoke was associated with pulmonary hypoplasia in the baby rats with decreased lung volumes; in this rat model, exposure reduced the number of sacules but increased their size. Brown and colleagues (1995) assessed respiratory mechanics in 53 healthy infants, and interpreted the pattern of findings to suggest that prenatal tobacco smoke exposure from smoking by the mother may lead to a reduction in airway size and changes in lung properties.

Lung maturation in utero is regulated by the endocrine environment, and the timing of secondhand smoke exposures with regard to lung development

may have a lifelong impact on respiratory function. Secondhand smoke components may increase in utero stress responses that then speed lung maturation at the expense of lung growth. Several studies have demonstrated an effect on the fetal endocrine milieu secondary to secondhand smoke exposure (Divers et al. 1981; Catlin et al. 1990; Lieberman et al. 1992). Studies have also associated maternal smoking with more advanced lung maturity measured by lectin/sphingomyelin (L/S) ratios that were out of proportion to fetal size in human infants (Mainous and Hueston 1994). Cotinine levels measured in the amniotic fluid were positively correlated with L/S ratios. Studies also noted an increase in free, conjugated, and total cortisol levels, suggesting a potentially direct or indirect role for hormonal effects of secondhand smoke on the fetus (Lieberman et al. 1992). Other researchers have demonstrated higher levels of catecholamines in amniotic fluid in pregnant smokers compared with pregnant nonsmokers, further supporting an endocrine mechanism for the effect of secondhand smoke (Divers et al. 1981).

Multiple studies suggest that the effect of secondhand smoke on the development of the respiratory system begins with in utero exposure (Tager et al. 1995; Stick et al. 1996; Lodrup Carlsen et al. 1997). Stick and colleagues (1996) reported a dose-dependent effect of in utero cigarette smoke exposure in decreasing tidal flow patterns that were measured during the first three days of life (i.e., before any postnatal exposure). This effect was independent of the effect of smoking on birth weight. Hoo and colleagues (1998) evaluated respiratory function in preterm infants of mothers who did and did not smoke during pregnancy, with the goal of investigating whether the effect of prenatal tobacco smoke exposure is limited to an influence during the last weeks of gestation. The researchers observed that respiratory function was impaired in infants born preterm (an average of seven weeks early), suggesting that the adverse effect of prenatal tobacco smoke exposure is not limited to the last weeks of in utero development. The ratio of time to peak tidal expiratory flow to expiratory time (T_{PTEF}:T_E) was lower in infants exposed to secondhand smoke in utero compared with unexposed infants (mean 0.369 standard deviation [SD] 0.109 versus mean 0.426 SD 0.135, $p \leq 0.02$). Because T_{PTEF}:T_E is associated with airway caliber, these data imply that cigarette smoke exposure in utero may affect airway development. Lower maximal forced expiratory flow at functional residual capacity ($Vmax_{FRC}$) (Hanrahan et al. 1992) and diminished expiratory flows (Brown et al. 1995) in infants exposed in utero to secondhand smoke provide further support for the contention that infants of mothers who smoke during pregnancy have smaller airways. Increased airway wall thickness and increased smooth muscle, which can both lead to a decreased airway diameter, were found in infants exposed to tobacco smoke in utero who had died of sudden infant death syndrome (SIDS) (Elliot et al. 1999). In animal models of secondhand smoke exposure, fetuses of rats exposed to mainstream smoke (from active smoking) or to secondhand (sidestream) smoke had reduced lung volume, decreased elastic tissue within the parenchyma, increased density of interstitial tissue, and inadequate development of elastin and collagen (Collins et al. 1985; Vidic 1991). These animal and human data provide clear evidence for an adverse effect of in utero exposure to tobacco smoke on the developing lung. Studies also document structural changes in animal models and in exposed children who have died from SIDS. The physiologic findings suggest altered lung mechanics and reduced airflow consistent with changes in structure.

Immunologic Effects and Inflammation

The development of lung immunophenotype (i.e., the pattern of immunologic response in the lung) is considered to have a key role in determining the risk for asthma, particularly in regard to the T-helper 1 (Th1) pathway (which mediates cellular immunity) and the Th2 pathway (which mediates allergic responses). Secondhand smoke exposure may promote immunologic development along Th2 pathways, thus contributing to the intermediate phenotypes associated with asthma and with a predilection to chronic respiratory disease. Gene-environment interactions that begin in utero and persist during critical periods of development after birth represent the least understood, but potentially the most important, mechanistic route for a lasting influence of secondhand smoke. Although a meta-analysis of epidemiologic evidence suggests that parental smoking before birth (or early childhood secondhand smoke exposure) does not increase the risk for allergic sensitization, other lines of mechanistic investigation do show a variety of influences from secondhand smoke on immune and inflammatory responses (Strachan and Cook 1998b).

Secondhand smoke effects on T cells may influence gene regulation, inflammatory cell function, cytokine production, and immunoglobulin E (IgE) synthesis. These effects are particularly important to consider in regard to immune system ontogeny and for the subsequent development of allergies in

childhood. Researchers have demonstrated that mainstream and sidestream smoke condensates selectively suppress the interferon gamma induction of several macrophage functions, including phagocytosis of Ig-opsonized sheep red blood cells, class II major histocompatibility complex expression, and nitric oxide synthesis, which are all representative of effects on immunity (Braun et al. 1998; Edwards et al. 1999). Alterations in antigen presentation may occur not only in the respiratory tract but also in the rest of the body where absorbed toxicants are distributed. Macrophages are potent effector cells for immune responsiveness; suppression of their ability to respond to environmental challenges could have lifelong consequences on immune function.

Immune responses may also be increased as a result of secondhand smoke exposure. Animal studies demonstrate increases in IgE, eosinophils, and Th2 cytokines (especially interleukin [IL]-4 and IL-10) with exposure to secondhand smoke. These increases may augment the potential for allergic sensitization and the development of an atopy phenotype. In mice sensitized to the ovalbumin (OVA) antigen and exposed to secondhand smoke for six hours per day, five days per week, for six weeks, researchers measured increases in total IgE, OVA-specific immunoglobulin G1, and eosinophils in the blood (Seymour et al. 1997). These measures indicate an increase in the allergic response to inhaled antigens. On the basis of the results from this mouse model, the investigators concluded that allergen sensitization with the increase in Th2 responses may contribute to the development of allergies in individuals exposed to secondhand smoke (Seymour et al. 1997). Other studies have demonstrated an increase in IL-5, granulocyte-macrophage colony-stimulating factor, and IL-2 in bronchoalveolar lavage fluid in mice exposed to OVA along with secondhand smoke. In these mouse models, interferon gamma levels decreased. Because mice exposed to OVA alone did not experience these cytokine changes, secondhand smoke appears able to induce a sensitization phenotype to a usually neutral antigen (Rumold et al. 2001). Although the animal data are stronger than the human epidemiologic data, studies in humans are supportive of an effect of tobacco smoke exposure on allergic phenotypes.

Allergies are caused by multiple interacting factors in people with underlying susceptibility. Secondhand smoke exposure both in utero and after birth may promote the development of an allergic phenotype. Antigens presented during the neonatal period in mice skew the immune development and response along a Th2 pathway (i.e., toward an allergic phenotype) (Forsthuber et al. 1996). Human fetuses, under the influence of the maternal system mediated through the placenta, may develop a Th2 preference as a response to an antigen (Michie 1998). Magnusson (1986) studied newborn children of nonallergic parents and found evidence suggesting that tobacco smoke exposure in utero may promote an allergic phenotype. A threefold increase in risk for an elevated IgE level was observed in children whose mothers smoked compared with the IgE levels in children born to nonsmoking mothers. Total cord blood IgE concentrations were substantially higher in infants of mothers who smoked (60.8 international units [IU]) compared with infants of nonsmoking mothers (9.8 IU).

Atopy may be characterized by either a positive IgE-mediated skin test or elevated specific IgE serum levels. Atopy represents a risk factor for asthma, and an increase in bronchial responsiveness has been associated with higher serum IgE levels. Human studies provide mixed evidence as to whether secondhand smoke exposures are associated with an increase in IgE-mediated responses (Weiss et al. 1985; Martinez et al. 1988; Ownby and McCullough 1988; Stankus et al. 1988). Weiss and colleagues (1985) demonstrated that maternal smoking was associated with atopy in children aged five through nine years who were evaluated by skin tests to four common allergens. Ronchetti and colleagues (1990) demonstrated an effect of exposure on IgE levels and on eosinophil counts. Eosinophil counts were at least three times higher in boys exposed to secondhand smoke compared with unexposed boys. There was a dose-response relationship between the number of cigarettes to which each boy had been exposed and the level of eosinophilia (Ronchetti et al. 1990).

Researchers showed decades ago that mainstream cigarette smoke causes airway inflammation (Niewoehner et al. 1974) and an increase in airway permeability to small and large molecules in young smokers (Simani et al. 1974; Jones et al. 1980). Given the qualitative similarities between mainstream smoke and secondhand smoke, these effects may be relevant to involuntary smoking (USDHHS 1986).

There are many specific components of secondhand smoke that may adversely affect a child's lung. For example, a bacterial endotoxin known as lipopolysaccharide (LPS) can be detected in both mainstream and sidestream tobacco smoke. Studies have detected biologically active LPS in mainstream and sidestream smoke from regular and light experimental reference cigarettes used in the studies (mainstream: 120 ± 64 nanograms [ng] per regular cigarette, 45.3 ± 16 ng per light cigarette; sidestream: 18 ± 1.5 ng per regular

cigarette, 75 ± 49 ng per light cigarette). The investigators suggested that chronic LPS exposure from cigarette smoke may contribute to the inflammatory effects of secondhand smoke (Hasday et al. 1999). Other studies show that LPS exposure may alter responses to allergen challenge (Tulić et al. 2000).

Researchers need to consider this hypothesized role of endotoxin because of the known pathologic effects of endotoxins on susceptible individuals. As a component of the cell wall of gram-negative bacteria, endotoxins are ubiquitous in the environment and may be found in high concentrations in household dust (Michel et al. 1996) and in ambient air pollution (Bonner et al. 1998). Macrophage activation may result from exposure to low concentrations of an endotoxin, leading to a cascade of inflammatory cytokines (such as IL-1, IL-6, and IL-8) and arachidonic acid metabolites, which are important in the formation of prostaglandin molecules (Bayne et al. 1986; Michie et al. 1988; Ingalls et al. 1999). Studies have documented increased levels of neutrophils in bronchoalveolar lavage fluid after a challenge with dust that contained endotoxins (Hunt et al. 1994). Reversible airflow obstruction has been associated with the inhalation of endotoxins in the air. In a cohort study of infants in Boston, Park and colleagues (2001) used a univariate model and found a significant association of wheeze in the first year of life with elevated dust endotoxin levels (relative risk [RR] = 1.29 [95 percent confidence interval (CI), 1.03–1.62]). In a multivariate model, elevated endotoxin levels in dust were associated with an increased risk for repeated wheeze illness in the first year of life (RR = 1.56 [95 percent CI, 1.03–2.38]) (Park et al. 2001). Exposure to endotoxins from secondhand smoke in utero, during infancy, and in childhood may increase airway inflammation and may interact synergistically with additional secondhand smoke exposures.

Smoking contributes generally to the particulate load in indoor air, and research documents that inhaling particles in the respirable size range contributes to pulmonary inflammation (National Research Council 2004). One consequence of particle-induced inflammation may be an intermediate phenotype with cough and wheeze in early childhood. Investigators used a guinea pig model of secondhand smoke exposure to study sensory nerve pathways for cough and airway narrowing in an effort to explain the development of cough and wheeze symptoms in children of smokers. When guinea pigs were exposed to sidestream smoke for six hours per day, five days per week, from one through six weeks of age, they demonstrated an increase in excitability of pulmonary C fibers (Mutoh et al. 1999) and rapidly adapting receptors (Bonham et al. 1996), which are believed to be primarily responsible for eliciting the reflex responses in defending the lungs against inhaled irritants and toxins (Lee and Widdicombe 2001). These studies have led to the conclusion that cough and wheeze may be produced by neural pathway stimulation and irritation.

Summary

Childhood respiratory disease covers a spectrum of diseases and underlying pathogenetic mechanisms that include infection, prenatal alterations in lung structure, inflammation, and allergic responses. There is a potential for secondhand smoke to contribute over the long term to the development of respiratory disease through altered organ maturation and immune function. Mechanisms underlying the adverse health effects of secondhand smoke vary across the phases of lung growth and development, extending from the in utero period to the completion of lung growth in late adolescence. The long-term effects of secondhand smoke is a field of ongoing research. These effects may vary among individuals because of individual genetic susceptibilities and gene-environment interactions. The discussions that follow summarize the available observational evidence concerning health effects of secondhand tobacco smoke on children, which are presumed to reflect the mechanisms reviewed above. The discussions also interpret the evidence in the context of this mechanistic understanding.

Methods Used to Review the Evidence

The search strategies and statistical methods for pooling that were used for this report were identical to those applied to the earlier reviews of this topic carried out by Strachan and Cook (1997). The authors conducted an electronic search of the EMBASE Excepta Medica and Medline databases using Medical Subject Headings (MeSH) to select published papers, letters, and review articles relating to secondhand tobacco smoke exposure in children. The EMBASE strategy was based on text word searches of titles, keywords, and related abstracts; non-English language articles were not included. The search was carried out through 2001.

Information relating to the odds ratio (OR) for the outcome of interest among children with and without smokers in the family was extracted from each study. Data regarding children exposed and unexposed to maternal smoking prenatally or postnatally were extracted separately. This review also specifically addresses the effects on children of smoking by other household members (usually the father) when the mother was not a smoker. Not every study provided information on all of these indices. The most common measures were smoking by either parent versus neither parent, and the effects of smoking by the mother versus only by the father or by neither parent. Few studies distinguished in any detail between prenatal and postnatal maternal smoking, but those that did were included in the discussion. The ORs for the effects of smoking by both parents compared with neither parent were also extracted from cross-sectional surveys of school-age children.

Because most studies have used self-reported parental smoking behaviors as the principal exposure indicator, and because the major sources of exposure in western countries are overwhelmingly maternal followed by paternal smoking (Cook et al. 1994), the terms parental, maternal, and paternal smoking are used throughout this chapter to refer to major sources of secondhand tobacco smoke exposure for children. The OR was chosen as a measure of association because it can be derived from all types of studies—case-control, cross-sectional, and cohort. In general, ORs and their 95 percent CIs were calculated from data in published tabulations using the actual numbers of participants, or numbers estimated from percentages of published column or row totals. This approach allowed for flexibility in combining categories of household tobacco smoke exposure for comparability across studies. If the number of participants was not provided, the published OR and its 95 percent CI were used. For some studies, it was necessary to derive an approximate standard error (for the log OR) based on the marginal values of the relevant multiplication table (2×2). In situations where ORs were given separately for different genders, a pooled OR and 95 percent CI were calculated by taking a weighted average (on the log scale) using weights inversely proportional to the variances. The papers that quoted an incidence rate ratio rather than an OR are identified in the summary tabulations.

The literature review also identified information on the extent to which the effects of parental smoking were altered by adjustment for potential confounding variables, and whether there was evidence of an exposure-response relationship with, for example, the amount smoked by either parent. Where the presented data could be standardized for age, gender, or occasionally for another confounder, the Mantel-Haenszel method was used to provide an adjusted value. Because there may be multiple published reports for a single study, only one paper from each study (usually the most recently published) was included in the quantitative meta-analyses. In some studies, however, information from other papers contributed to the assessment of potential confounding or a dose-response relationship.

Updated meta-analyses of the health effects from parental smoking were conducted specifically for this chapter. All pooled estimates were calculated using both fixed and random effects models (Egger et al. 2001). All updated analyses were carried out using Stata. For some outcomes, studies were grouped according to the timing of the secondhand smoke exposure (e.g., maternal smoking during pregnancy, parental smoking from infancy to four years of age, and parental smoking at five or more years of age).

The meta-analysis of the cross-sectional evidence relating parental smoking to spirometric indices in children updates the 1998 meta-analysis (Cook et al. 1998). Both the earlier and the more recent meta-analyses used the same effect measure: the average difference in the spirometric index between exposed and unexposed children, expressed as a percentage of the level in the unexposed group. The updated synthesis considered four different spirometric indices: forced vital capacity (FVC), forced expiratory volume in one

second (FEV_1), mid-expiratory flow rate (MEFR), and flow rates at end expiration. Pooled estimates of the percentage differences were calculated using both fixed and random effects models (Egger et al. 2001).

To determine whether the exposure classification influenced the relationship between parental smoking and lung function, studies were pooled within the following exposure groups: both parents did versus did not smoke, mother did versus did not smoke, either parent versus neither parent smoked, the highest versus the lowest cotinine category, and high levels of household secondhand smoke versus none. To test for effects on the relationship between parental smoking and lung function from adjustment for variables other than age, gender, and body size, studies were pooled separately depending on adjustment for other variables. Lastly, this meta-analysis also assessed whether adjusting for socioeconomic measures, such as parental education and social class, affected the pooled results.

Lower Respiratory Illnesses in Infancy and Early Childhood

This section summarizes the evidence relating specifically to acute LRIs in the first two or three years of life and updates the previous review by Strachan and Cook (1997). Separate discussions review studies of asthma incidence, prognosis, and severity as well as studies (mostly cross-sectional) of school-age children.

In developed countries, the specific microbial etiology and determinants of some common lower respiratory tract illnesses in infancy remain a subject of uncertainty and research (Silverman 1993; Wilson 1994; Monto 2002; Klig and Chen 2003). Although many LRIs result from viral infections, there is an indication of a prenatally determined susceptibility related to lung function abnormalities that is already detectable at birth (Dezateux and Stocks 1997). As reviewed in the introduction to this chapter, lasting effects of in utero exposure to tobacco smoke from maternal smoking may increase airway resistance and the likelihood of a more severe LRI with infection. This review covers the full spectrum of LRIs, including categories considered to reflect infection and the category of wheeze, which may be a consequence of infection but may also indicate an asthma phenotype.

There is also an emerging consensus that there are several phenotypes of childhood wheeze, each with a different pattern of incidence, prognosis, and risk factors (Wilson 1994; Christie and Helms 1995). However, there is much less certainty about how these different "asthma phenotypes" should be characterized for either research or clinical purposes. Findings from the Tucson (Arizona) birth cohort study suggest physiologic and immunologic differences between the phenotypic syndromes of early childhood wheeze, the onset of asthma symptoms later in childhood, and persistent disease (Martinez et al. 1995; Stein et al. 1997). These findings have yet to be replicated in a comprehensive way in other large population samples, and few large cohort studies are in progress that provide the needed longitudinal data. The classification of phenotype in the epidemiologic studies is relevant to secondhand smoke if the association of secondhand smoke with risk varies across the phenotypes.

Relevant Studies

In the 1997 review, 75 publications were considered in detail as possibly relevant to illnesses in infancy and early childhood. Of those studies, 50 were included in the review, and 38 of those 50 were included in quantitative meta-analyses: 21 cohort studies, 10 case-control studies, 2 controlled trials, and 5 cross-sectional surveys of school-age children (Strachan and Cook 1997). The latter were included because they related parental smoking to a retrospective history of chest illness before two years of age, information that was obtained using the American Thoracic Society's children's questionnaire (Ferris 1978). No additional references were identified by citations in the above papers or in previous overviews.

Of 26 papers published since 1997, 17 contain quantitative information relevant to this review without duplicating the content of the other papers (Margolis et al. 1997; Nafstad et al. 1997; Baker et al. 1998; Gergen et al. 1998; Chen and Millar 1999; Dezateux et al. 1999; Gold et al. 1999; Karaman et al.

1999; Mrazek et al. 1999; Nuesslein et al. 1999; Rusconi et al. 1999; Yau et al. 1999; Diez et al. 2000; Gürkan et al. 2000b; Hjern et al. 2000; Lux et al. 2000; Young et al. 2000a). Most of these papers are community studies of wheeze illnesses: seven cohort studies, two case-control studies, and four surveys that ask about past illnesses. Only a few studies included data on the effects of smoking by only the father. The two most substantial papers analyze data from the Third National Health and Nutrition Examination Survey (NHANES III) (Gergen et al. 1998) and from a large Swedish study of hospital admissions that focused mostly on pneumonia (Hjern et al. 2000). A complement to the Swedish study examined asthma admissions, but only from two years of age and older, and was therefore not included in the quantitative synthesis (Hjern et al. 1999). That study does provide evidence relevant to effect modification by age.

Publications listed in another systematic review (Li et al. 1999) were also considered, but those studies were already included in other reviews for either LRI or asthma. Three studies from this new search were excluded: one Danish study of hospitalizations for any reason that described findings of respiratory problems, but presented no data related to secondhand smoke (Wisborg et al. 1999); a case-control study from The Gambia that considered admissions for acute LRI and implied that neither maternal nor paternal smoking was significantly associated with the outcome at $p < 0.05$, but presented no data (Weber et al. 1999); and a cohort study of acute respiratory infections in children younger than five years of age that reported increased risks of 2.5 for pneumonia and 2.3 for other "severe disease" in children of smoking parents, but included no standard errors (Deb 1998).

Evidence Review

Community Studies of Lower Respiratory Illnesses

Combining studies from the 1997 review with subsequent publications, 34 community studies were related to parental smoking and LRIs in a community or ambulatory clinic setting (Table 6.1). There were 20 prospective cohort studies, 1 panel (short-term cohort) study, 1 cohort study carried out through record linkage, 2 controlled trials, 4 case-control studies, and 6 prevalence surveys of schoolchildren that asked parents about past illnesses. Seven studies combined all lower respiratory diagnoses (Gardner et al. 1984; Ferris et al. 1985; Pedreira et al. 1985; Wright et al. 1991; Forastiere et al. 1992; Marbury et al. 1996; Richards et al. 1996), six contributed information on bronchitis and pneumonia (Leeder et al. 1976; Fergusson and Horwood 1985; Chen et al. 1988a; Håkansson and Carlsson 1992; Gergen et al. 1998; Nuesslein et al. 1999), and two focused on illnesses diagnosed as bronchiolitis (McConnochie and Roghmann 1986b; Hayes et al. 1989). Twenty-three studies focused specifically on illnesses associated with wheeze (Fergusson and Horwood 1985; Bisgaard et al. 1987; Chen et al. 1988a; Burr et al. 1989; Lucas et al. 1990; Halken et al. 1991; Arshad et al. 1993; Tager et al. 1993; Martinez et al. 1995; Elder et al. 1996; Margolis et al. 1997; Nafstad et al. 1997; Baker et al. 1998; Gergen et al. 1998; Chen and Millar 1999; Dezateaux et al. 1999; Gold et al. 1999; Karaman et al. 1999; Mrazek et al. 1999; Rusconi et al. 1999; Yau et al. 1999; Diez et al. 2000; Lux et al. 2000; Young et al. 2000a). The studies by Baker and colleagues (1998) and Lux and colleagues (2000) both reported on the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC), and three publications contributed independent data on both bronchitis/pneumonia and wheeze illnesses (Fergusson and Horwood 1985; Chen et al. 1988a; Gergen et al. 1998).

Table 6.2 and Figures 6.1–6.3 summarize the results of these studies. All except one study (Nuesslein et al. 1999) found an elevated risk of LRI associated with parental smoking, including by the father only, among the studies where that exposure variable was included. The one study not finding an increased OR associated with maternal smoking reported a significant association with cotinine levels measured in meconium (Nuesslein et al. 1999). Table 6.3 presents the results of meta-analyses that pooled the results from studies of early wheeze separately from those of an unspecified LRI, bronchitis, bronchiolitis, or pneumonia. Although the effect of smoking by either parent was similar for both wheeze and LRI, maternal smoking appeared to have a somewhat greater effect than paternal smoking in studies that specifically ascertained wheeze illnesses (Table 6.3).

Studies of Hospitalizations for Lower Respiratory Illnesses

The literature search identified 14 studies on hospitalizations for lower respiratory complaints in early life (Harlap and Davies 1974; Sims et al. 1978; Mok and Simpson 1982; Ekwo et al. 1983; Hall et al. 1984; Taylor and Wadsworth 1987; Anderson et al. 1988; Stern et al. 1989b; Reese et al. 1992; Jin and Rossignol 1993; Victora et al. 1994; Rylander et al. 1995;

Table 6.1 Design, sample size, and recruitment criteria for studies of illness associated with parental smoking included in meta-analyses

Study	Design/population	Sample size	Case definition	Source of cohort or controls	Outcome
Community studies of lower respiratory illnesses (LRIs)					
Leeder et al. 1976	Cohort Aged <1 year United Kingdom	2,074	Acute bronchitis (BR)/pneumonia (PN) (reported)	Population-based birth cohort	BR/PN
Gardner et al. 1984	Panel Aged <1 year United States (Texas)	131	LRI (reported)	Virologic surveillance panel	LRI
Fergusson and Horwood 1985	Cohort Aged <2 years New Zealand	1,144	BR/PN consultation	Population-based birth cohort	BR/PN
Ferris et al. 1985	Survey Aged <2 years United States (Six cities)	8,528	Physician-diagnosed respiratory illness before 2 years of age	Population survey (children aged 6–9 years)	LRI
Pedreira et al. 1985	Cohort Aged <1 year United States (District of Columbia)	1,144	LRI consultation	Pediatric practice	LRI
McConnochie and Roghmann 1986b	Case-control Aged <2 years United States (New York)	212	First physician-diagnosed acute bronchiolitis (BL)/wheeze	Pediatric outpatient lists (no wheeze)	BL/wheeze
Chen et al. 1988a	Cohort Aged <18 months China	2,227	Physician-diagnosed BR/PN	Population-based birth cohort	BR/PN
Hayes et al. 1989	Case-control Aged <1 year Samoa	80	Respiratory syncytial virus (RSV); epidemic LRI	Well-child clinics	BL
Wright et al. 1991	Cohort Aged <1 year United States (Arizona)	797	Physician-diagnosed LRI	Health maintenance organization (HMO)-based cohort	LRI
Forastiere et al. 1992	Survey Aged <2 years Italy	2,797	BR/BL/PN before 2 years of age	Population survey (children aged 7–11 years)	LRI
Hakansson and Carlsson 1992	Cohort Aged <12 months Sweden	192	Antibiotics for BR/PN	Population-based birth cohort	BR/PN
Marbury et al. 1996	Cohort Aged <2 years United States (Minnesota)	1,424	LRI consultation	HMO-based cohort	LRI

Table 6.1 Continued

Study	Design/population	Sample size	Case definition	Source of cohort or controls	Outcome
			Community studies of LRIs		
Richards et al. 1996	Survey Aged <2 years South Africa	726	Physician-diagnosed respiratory illness before 2 years of age	Survey of 2 schools (children aged 14–18 years)	LRI
Gergen et al. 1998	Survey Aged 2–36 months United States	7,680	Parental report/ recall of physician-diagnosed asthma (ever)	Representative sample from NHANES III*	Chronic BR
Nuesslein et al. 1999	Cohort Aged <6 months Germany	65	Parental report/ recall of cold with cough	Population-based birth cohort	LRI
			Community studies of wheeze illnesses		
Fergusson and Horwood 1985	Cohort Aged <2 years New Zealand	1,144	Wheeze/chest cold	Population-based birth cohort	Wheeze
Bisgaard et al. 1987	Cohort Aged <1 year Denmark	5,953	>1 episode of wheeze	Population-based birth cohort	Wheeze
Chen et al. 1988a	Cohort Aged <18 months China	2,227	Physician-diagnosed asthma	Population-based birth cohort	Wheeze
Burr et al. 1989	Trial Aged <1 year United Kingdom	480	Wheeze by 1 year of age (reported)	Infants from families with allergies	Wheeze
Lucas et al. 1990	Trial Aged <18 months United Kingdom	777	>3 episodes of wheeze or asthma	Infants <37 weeks of gestation	Wheeze
Halken et al. 1991	Cohort Aged <18 months Denmark	276	>2 episodes of wheeze	Random sample of births	Wheeze
Arshad et al. 1993	Cohort Aged <2 years United Kingdom	1,172	>3 episodes of wheeze	Population-based birth cohort	Wheeze
Tager et al. 1993	Cohort Aged <12 months United States (Massachusetts)	97	Wheeze or LRI admission	Special lung function study	Wheeze
Martinez et al. 1995	Cohort Aged <3 years United States (Arizona)	762	LRI with wheeze	HMO-based birth cohort	Wheeze

Table 6.1 Continued

Study	Design/population	Sample size	Case definition	Source of cohort or controls	Outcome
			Community studies of wheeze illnesses		
Elder et al. 1996	Cohort Aged <1 year Australia	525	Bronchodilator therapy	Infants <33 weeks of gestation	Wheeze
Margolis et al. 1997	Cohort Aged ≤12 months United States	325	Parental report/ recall of cough or wheeze	Population-based birth cohort (no high-risk infants)	Wheeze
Nafstad et al. 1997	Cohort Aged ≤24 months Norway	3,038	Bronchial obstruction confirmed by physician diagnosis	Births in 2 clinics (no high-risk infants)	Bronchial obstruction
Baker et al. 1998; Lux et al. 2000	Cohort Aged ≤30 months United Kingdom	8,561	Parental report/ recall of wheeze by 6 months of age	ALSPAC[†] birth cohort	Wheeze
Gergen et al. 1998	Survey Aged 2–36 months United States	7,680	Parental report/ recall of physician diagnosis (ever) of asthma	Representative sample from NHANES III	Asthma
			Parental report/ recall of ≤3 episodes in 12 months		Wheeze
Chen and Millar 1999	Survey Aged ≤36 months Canada	5,888	Parental report/ recall of physician diagnosis of asthma (ever)	Representative sample of Canadian population	Asthma
Dezateux et al. 1999	Cohort Aged <12 months United Kingdom	101	>1 episode of physician-diagnosed wheeze	Population-based birth cohort	Wheeze
Gold et al. 1999	Cohort Aged <12 months United States (Massachusetts)	499	Parental report/ recall of >1 episode of wheeze	Birth cohort of parents with asthma and allergies	Wheeze
Karaman et al. 1999	Case-control Aged 6–24 months Turkey	68	Parental report/ recall of >1 episode of wheeze	A general practice (children with no allergies)	Wheeze
Mrazek et al. 1999	Cohort Aged ≤36 months United States (Colorado)	150	Recurrent asthma in medical records	Birth cohort of mothers with asthma	Wheeze
Rusconi et al. 1999	Survey Aged ≤24 months Italy	16,333	Parental report/ recall of wheeze at 6–7 years of age	Population survey (children aged 6–7 years)	LRI with wheeze

Table 6.1 Continued

Study	Design/population	Sample size	Case definition	Source of cohort or controls	Outcome
Community studies of wheeze illnesses					
Yau et al. 1999	Cohort Aged <24 months Taiwan	71	Parental report/ recall of LRI with wheeze	Healthy full-term infants	Wheeze
Diez et al. 2000	Nested case-control Aged ≤12 months Germany	310	Parental report/ recall of wheeze	Premature infants or others at high risk	Wheeze
Young et al. 2000a	Cohort Aged <24 months Australia	160	Parental report/ recall and/or physician diagnosis of wheeze	Population-based birth cohort	Wheeze
Community studies of upper and lower respiratory illnesses (U/LRIs)					
Ogston et al. 1987	Cohort Aged <12 months United Kingdom	1,542	U/LRIs recorded by a health visitor to the home	Population-based birth cohort	U/LRIs
Woodward et al. 1990	Case-control Aged 1–3 years Australia	489	High U/LRIs "score" based on values assigned to responses to questionnaires	Population survey (children with low scores)	U/LRIs
Hospitalizations for LRIs					
Harlap and Davies 1974	Cohort Aged <1 year Israel	10,672	BR/PN admission	Population-based birth cohort	BR/PN (inpatients)
Sims et al. 1978	Case-control Infants United Kingdom	70	RSV-positive BL admission	Schoolmates at 8 years of age	BL (inpatients)
Mok and Simpson 1982	Case-control Aged <1 year United Kingdom	400	LRI admission	Classmates at 7 years of age	BR/PN (inpatients)
Ekwo et al. 1983	Survey Aged <2 years United States (Iowa)	1,139	LRI admission before 2 years of age	Population survey (children aged 6–12 years)	LRI (inpatients)
Hall et al. 1984	Case-control Aged <2 years United States (New York)	87	RSV and LRI admission	Acute nonrespiratory admission	BL (inpatients)
Taylor and Wadsworth 1987	Cohort Aged <5 years United Kingdom	12,727	LRI admission	Population-based birth cohort	LRI (inpatients)

Table 6.1 Continued

Study	Design/population	Sample size	Case definition	Source of cohort or controls	Outcome
			Hospitalizations for LRIs		
Anderson et al. 1988	Case-control Aged <2 years United States (Georgia)	301	PN/BL admission	Outpatient clinics	PN/BL (inpatients)
Stern et al. 1989b	Survey Aged <2 years Canada	4,099	LRI admission before 2 years of age	Population survey (children aged 7–12 years)	LRI (inpatients)
Reese et al. 1992	Case-control Aged 5–15 months Australia	96	BL admission	Nonrespiratory admission	BL (inpatients)
Jin and Rossignol 1993	Cohort Aged <18 months China	1,007	BR/PN admission	Population-based birth cohort	BR/PN (inpatients)
Victora et al. 1994	Case-control Aged <2 years Brazil	1,020	PN (x-ray)	Neighbors	PN (inpatients)
Rylander et al. 1995	Case-control Aged 4–18 months Sweden	308	Wheeze and breathlessness	Population sample (same area)	Wheeze (inpatients)
Gürkan et al. 2000b	Case-control Aged 2–18 months Turkey	58	Symptoms plus RSV antigen	Infants without respiratory distress seen in the emergency room	RSV (outpatients)
Hjern et al. 2000	Record linkage Aged 0–24 months Sweden	350,648 patient-years‡	ICD-9§ 480–487 at discharge	All children in 3 metropolitan areas (1990–1994)	PN (inpatients)
			Hospitalizations for URIs or LRIs		
Rantakallio 1978	Cohort Aged <5 years Finland	3,644	URI or LRI admission	Birth cohort drawn from smoking and nonsmoking mothers	URI or LRI (inpatients)
Ogston et al. 1985	Cohort Aged <12 months United Kingdom	1,542	URI or LRI admission	Population-based birth cohort	URI or LRI (inpatients)
Chen 1994	Cohort Aged <18 months China	3,285	Any respiratory admission	2 population birth cohorts	URI or LRI (inpatients)

*NHANES III = Third National Health and Nutrition Examination Survey.
†ALSPAC = Avon Longitudinal Study of Pregnancy and Childhood.
‡Patient-years only were reported in this study.
§ICD-9 = *International Classification of Diseases, 9th Revision* (USDHHS 1989).

Table 6.2 Unadjusted relative risks (odds ratios) of illness associated with parental smoking

Study	Cases/ controls	Dose-response relationship	Outcome	Odds ratio for smoking (95% confidence interval)			
				Either parent	Mother	Father/other*	Both parents
Community studies of lower respiratory illnesses (LRIs)							
Leeder et al. 1976	239/1,835	Yes; number of smokers	Acute bronchitis (BR)/ pneumonia (PN)	1.96 (1.38–2.80)	NR†	NR	2.79 (1.87–4.15)
Gardner et al. 1984	31/‡	NR	LRI	1.25 (0.81–1.93)	NR	NR	NR
Fergusson and Horwood 1985	204/940	Yes; cigarettes/ day by the mother	BR/PN	1.56 (1.15–2.12)	1.83 (1.35–2.49)	1.04 (0.65–1.65)	1.83 (1.22–2.74)
Ferris et al. 1985	820/7,708	Yes; cigarettes/ day by the mother	LRI	1.85 (1.56–2.20)	1.69 (1.47–1.96)	1.51 (1.22–1.86)	1.36 (1.11–1.66)
Pedreira et al. 1985	221/‡	NR	LRI	1.27 (0.97–1.66)	NR	NR	NR
McConnochie and Roghmann 1986b	53/159	NR	Acute bronchiolitis (BL)	3.21 (1.42–7.25)	2.33 (1.19–4.57)	NR	NR
Chen et al. 1988a	925/1,302	Yes; cigarettes/ day in the home	BR/PN	1.25 (1.03–1.52)	None smoked	1.25 (1.03–1.52)	NR
Hayes et al. 1989	20/60	NR	BL	3.86 (0.81–18.4)	NR	NR	NR
Wright et al. 1991	256/541	Yes; cigarettes/ day by the mother	LRI	NR	1.52§ (1.07–2.15)	NR	NR
Forastiere et al. 1992	473/2,324	NR	LRI	1.32 (1.05–1.65)	1.21 (0.99–1.48)	1.25 (0.97–1.62)	1.34 (1.02–1.75)
Hakansson and Carlsson 1992	20/172	NR	BR/PN	3.25 (1.27–8.34)	NR	NR	NR
Marbury et al. 1996	1,107/‡	NR	LRI	NR	1.50§ (1.20–1.80)	NR	NR

Table 6.2 Continued

Study	Cases/ controls	Dose-response relationship	Outcome	Odds ratio for smoking (95% confidence interval)			
				Either parent	Mother	Father/other*	Both parents
Community studies of LRIs							
Richards et al. 1996	100/626	NR	LRI	1.75 (1.07–2.87)	2.18 (1.25–3.78)	NR	NR
Gergen et al. 1998	155/4,264	Yes; cigarettes/ day in the home	Chronic bronchitis	1.97 (1.42–2.61)	2.44[Δ] (1.74–3.40)	NR	NR
Nuesslein et al. 1999	49/16	NR	LRI	1.08[¶] (0.17–6.81)	0.87[Δ,¶] (0.17–4.53)	NR	NR
Community studies of wheeze illnesses							
Fergusson and Horwood 1985	733/411	No; cigarettes/ day by the mother	Wheeze	1.32 (1.04–1.69)	1.43 (1.10–1.86)	1.09 (0.77–1.53)	1.50 (1.05–2.12)
Bisgaard et al. 1987	120/5,833	No; cigarettes/ day by the mother	Wheeze	NR	2.85 (1.93–4.19)	NR	NR
Chen et al. 1988a	78/2,149	NR	Wheeze	1.27 (0.71–2.28)	None smoked	1.27 (0.71–2.28)	NR
Burr et al. 1989	166/314	NR	Wheeze	2.04 (1.39–3.01)	2.25 (1.52–3.33)	1.38 (0.81–2.37)	NR
Lucas et al. 1990	175/602	NR	Wheeze	1.70 (1.19–2.42)	NR	NR	NR
Halken et al. 1991	59/217	NR	Wheeze	1.88 (0.97–3.63)	NR	NR	NR
Arshad et al. 1993	127/1,045	NR	Wheeze	NR	2.24 (1.51–3.32)	NR	NR
Tager et al. 1993	59/38	NR	Wheeze	NR	3.16 (1.24–8.04)	NR	NR
Martinez et al. 1995	247/515	NR	Wheeze	NR	2.07 (1.34–3.19)	NR	NR
Elder et al. 1996	76/449	Yes; cigarettes/ day by the mother	Wheeze	NR	1.98 (1.21–3.23)	NR	NR
Margolis et al. 1997	[‡]	NR	Wheeze	1.62**	NR	NR	NR

Table 6.2 Continued

Study	Cases/ controls	Dose-response relationship	Outcome	Odds ratio for smoking (95% confidence interval)			
				Either parent	Mother	Father/other*	Both parents
Community studies of wheeze illnesses							
Nafstad et al. 1997	271/2,777	Yes; cigarettes/ day by both parents	Bronchial obstruction	1.6[¶] (1.3–2.1)	1.6[¶] (1.0–2.6)	1.5[¶] (1.1–2.2)	1.5[¶] (1.0–2.2)
Baker et al. 1998; Lux et al. 2000	1,565/ 6,885	Yes; number of hours/ day of secondhand smoke exposure	Wheeze	1.32 (1.19–1.47)	1.55[Δ] (1.36–1.77)	NR	NR
Gergen et al. 1998	197/4,222	Yes; cigarettes/ day in the home	Asthma	1.33 (0.99–1.77)	1.75[Δ] (1.29–2.39)	NR	NR
	432/3,981	Yes; cigarettes/ day in the home	Wheeze	1.88 (1.54–2.29)	2.15[Δ] (1.74–2.67)	NR	NR
Chen and Millar 1999	326/5,214	NR	Asthma	NR	1.56 (1.24–1.96)	NR	NR
Dezateux et al. 1999	28/73	NR	Wheeze	4.08 (1.12–14.9)	5.10 (1.97–13.3)	NR	NR
Gold et al. 1999	96/403	NR	Wheeze	NR	2.29[§,Δ] (1.44–3.63)	p >0.05	NR
Karaman et al. 1999	38/30	NR	Wheeze	5.6 (1.9–15.9)	4.2[Δ] (1.2–14.6)	NR	NR
Mrazek et al. 1999	14/136	NR	Wheeze	NR	1.5 (0.29–7.16)	NR	NR
Rusconi et al. 1999	1,892/ 14,441	NR	Wheeze	NR	1.55[Δ] (1.37–1.74)	NR	NR
Yau et al. 1999	8/23	NR	Wheeze	1.04 (0.35–3.05)	NR	NR	NR
Diez et al. 2000	64/246	NR	Wheeze	2.0 (1.1–3.5)	NR	NR	NR
Young et al. 2000a	81/79	NR	Wheeze	NR	2.7[Δ] (1.3–5.2)	NR	NR

Table 6.2 Continued

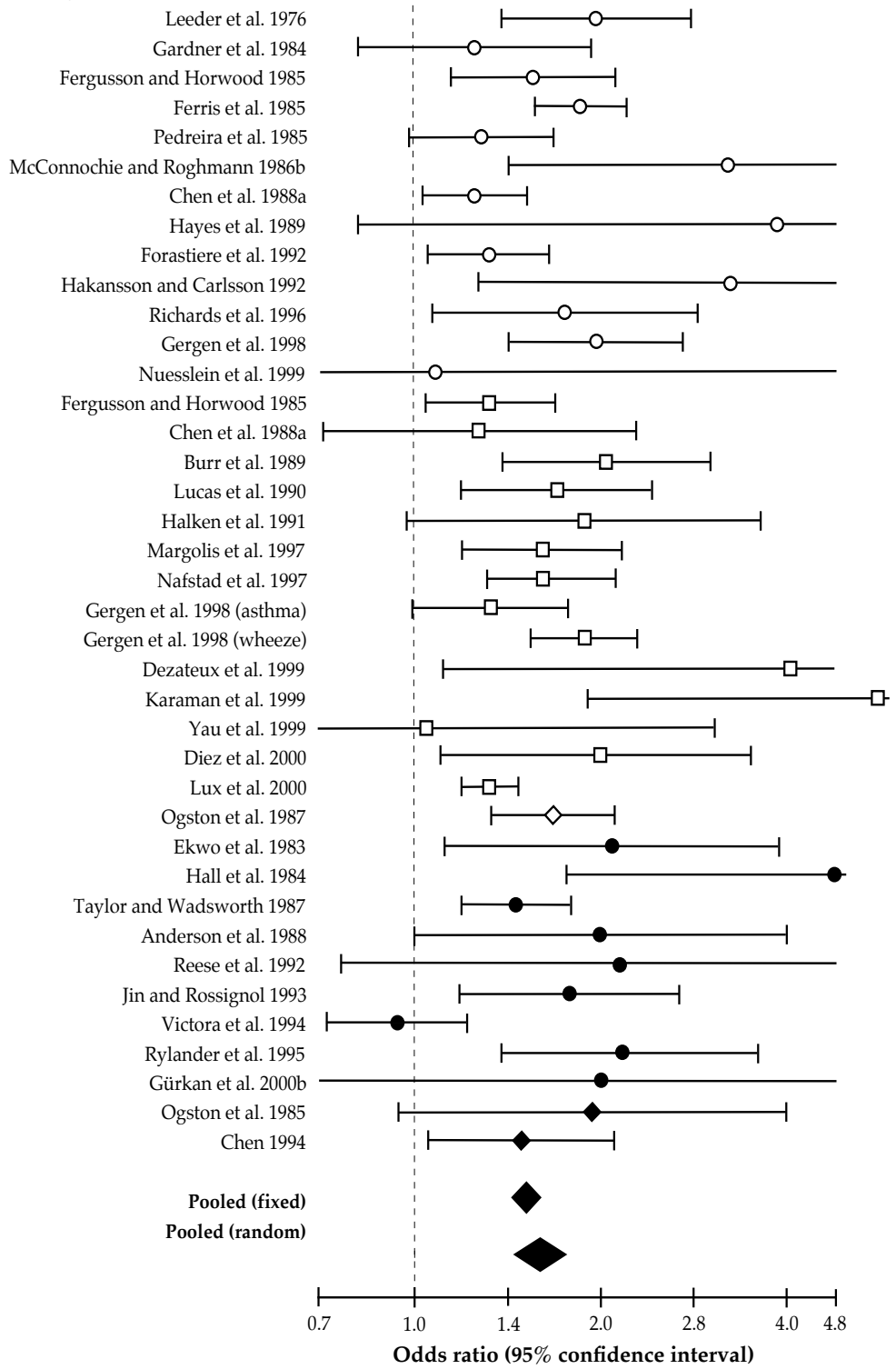
Study	Cases/ controls	Dose-response relationship	Outcome	Odds ratio for smoking (95% confidence interval)			
				Either parent	Mother	Father/other*	Both parents
Community studies of upper and lower respiratory illnesses (U/LRIs)							
Ogston et al. 1987	486/1,056	No; number of smokers	U/LRIs	1.68 (1.33–2.11)	1.52 (1.22–1.89)	1.50 (1.12–2.01)	1.74 (1.33–2.27)
Woodward et al. 1990	200/200	NR	U/LRIs	NR	2.43§ (1.63–3.61)	NR	NR
Hospitalizations for LRIs							
Harlap and Davies 1974	1,049/ 9,623	Yes; cigarettes/ day by the mother	BR/PN	NR	1.43 (1.18–1.75)	NR	NR
Sims et al. 1978	35/35	NR	BL	NR	2.65 (0.99–7.11)	NR	NR
Mok and Simpson 1982	200/200	NR	BR/PN	NR	1.26 (0.83–1.92)	NR	NR
Ekwo et al. 1983	53/1,086	Inverse to the number of smokers	LRI	2.09 (1.12–3.89)	1.32 (0.74–2.32)	2.30 (1.13–4.70)	1.59 (0.74–3.44)
Hall et al. 1984	29/58	NR	BL	4.78 (1.76–13.0)	NR	NR	NR
Taylor and Wadsworth 1987	434/ 12,293	Yes; cigarettes/ day by the mother	LRI	1.46 (1.19–1.79)	1.63 (1.34–1.97)	1.05 (0.78–1.41)	1.69 (1.33–2.14)
Anderson et al. 1988	102/199	NR	BL	1.99§ ($p < 0.05$)††	NR	NR	NR
Stern et al. 1989b	NR	NR	LRI	NR	1.85§ (1.53–2.23)	NR	NR
Reese et al. 1992	39/57	Yes; urinary cotinine	BL	2.15 (0.76–6.10)	2.66 (1.15–6.15)	1.27 (0.38–4.22)	3.29 (1.77–6.14)
Jin and Rossignol 1993	164/843	Yes; cigarettes/ day in the home	BR/PN	1.78 (1.18–2.68)	None smoked	1.78 (1.18–2.68)	NR

Table 6.2 Continued

Study	Cases/ controls	Dose-response relationship	Outcome	Odds ratio for smoking (95% confidence interval)			
				Either parent	Mother	Father/other*	Both parents
Hospitalizations for LRIs							
Victora et al. 1994	510/510	No; cigarettes/ day in the home	PN	0.94 (0.72–1.22)	1.02 (0.79–1.30)	0.89 (0.64–1.24)	0.94 (0.69–1.29)
Rylander et al. 1995	112/196	Yes; urinary cotinine	Wheeze	2.17 (1.38–3.59)	2.04 (1.26–3.28)	1.77 (0.85–3.66)	2.23 (1.23–4.05)
Gürkan et al. 2000b	28/30	NR	Respiratory synctial virus	2.0 (0.6–6.8)	3.6 (0.7–18.3)	1.1 (0.2–4.8)	2.3 (0.5–10.1)
Hjern et al. 2000	‡	NR	LRI	NR	1.3[Δ] (1.2–1.4)	NR	NR
Hospitalizations for URIs or LRIs							
Rantakallio 1978	490/3,154	NR	URI or LRI	NR	1.89 (1.55–2.30)	NR	NR
Ogston et al. 1985	41/1,501	Yes; number of smokers	URI or LRI	1.94 (0.94–3.99)	2.68 (1.41–5.10)	0.87 (0.29–2.56)	2.76 (1.28–5.96)
Chen 1994	239/3,046	No; cigarettes/ day in the home	URI or LRI	1.49 (1.05–2.10)	None smoked	1.49 (1.05–2.10)	NR

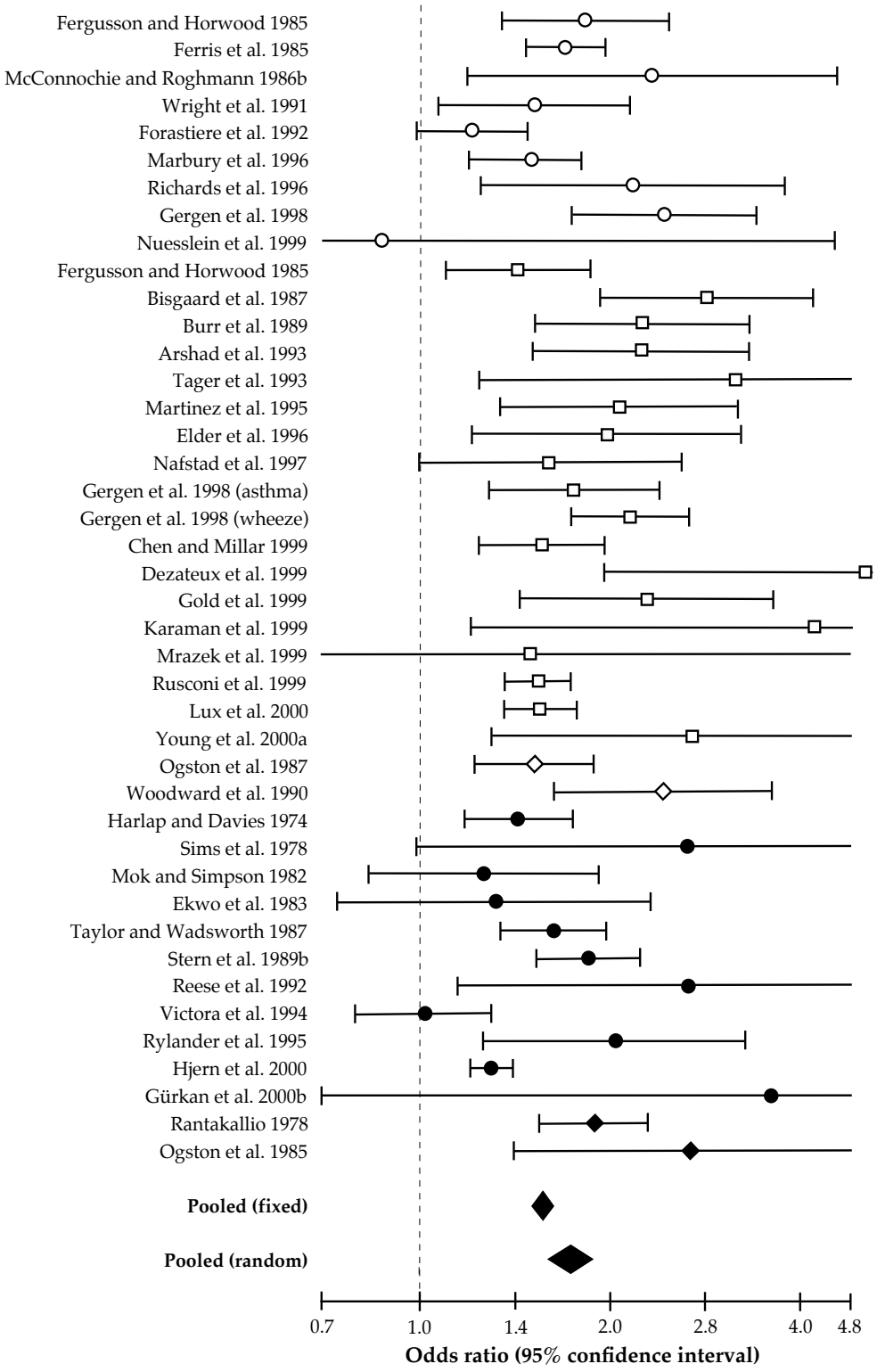
*In households where the mother did not smoke (compared with smoking by neither parent).
[†]NR = Data were not reported.
[‡]Results were published as person-time incidence rates; rate ratios, rather than odds ratios, are shown.
[§]Odds ratio or relative risk was cited in the paper without tabulated numerical data. (Elsewhere, odds ratios were calculated from tabulated numbers or percentages.)
[Δ]Maternal smoking during pregnancy. (Elsewhere, maternal postnatal smoking was used.)
[¶]Adjusted rates only were available (see Table 6.4 for factors adjusted for).
**Based on children exposed to ≤10 cigarettes/day vs. none, as so few were exposed more heavily. Confidence limits for the meta-analysis were assumed to be based on confidence limits for the adjusted analysis (1.20–2.18).
[††]95% confidence interval was estimated at 1.0–3.96 for purposes of the meta-analysis.

Figure 6.1 Odds ratios for the effect of smoking by either parent on lower respiratory illnesses during infancy



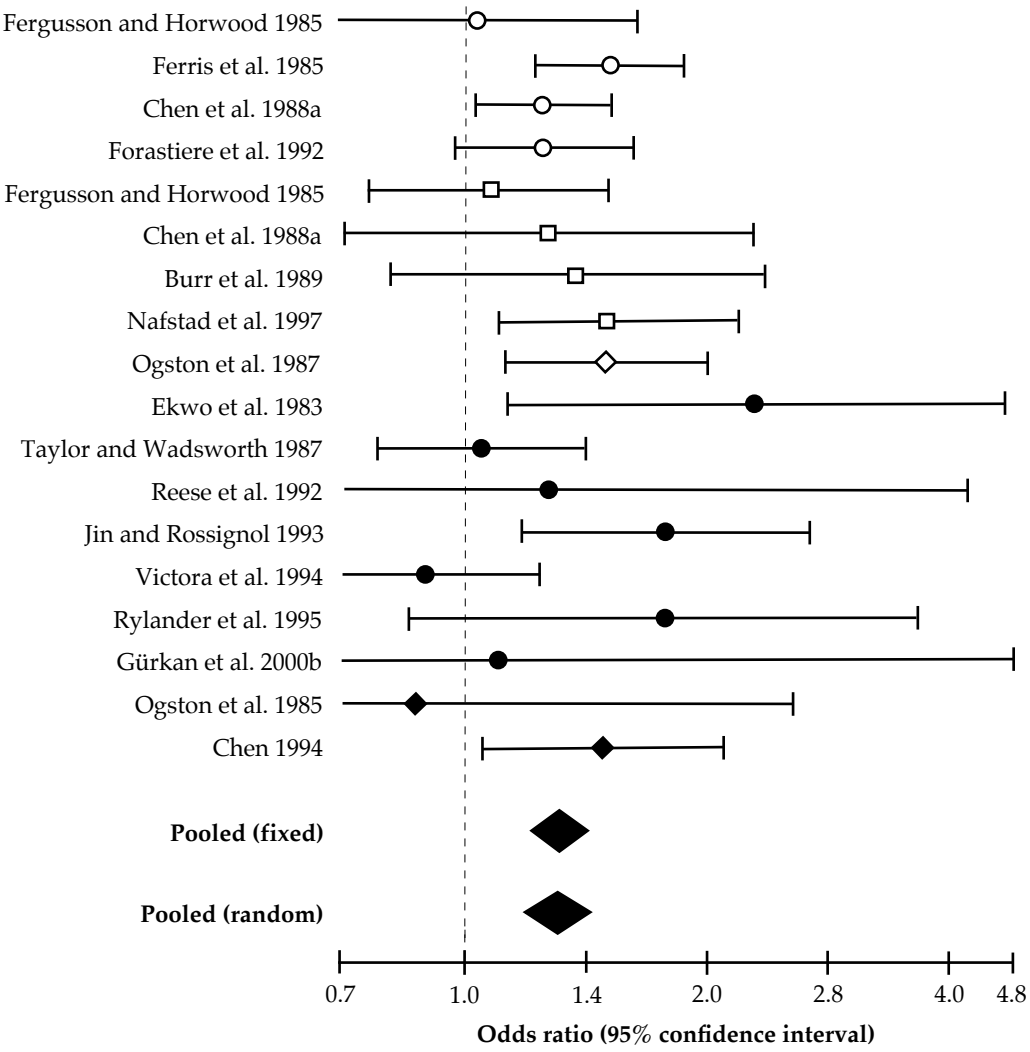
Note: Individual studies are denoted with the following symbols:
Circles = Studies of lower respiratory illnesses.
Squares = Studies of wheeze illnesses.
Diamonds = Studies of upper and lower respiratory illnesses.
Open symbols = Community studies.
Closed symbols = Studies of hospitalized illnesses.

Figure 6.2 Odds ratios for the effect of maternal smoking on lower respiratory illnesses during infancy



Note: Individual studies are denoted with the following symbols:
Circles = Studies of lower respiratory illnesses.
Squares = Studies of wheeze illnesses.
Diamonds = Studies of upper and lower respiratory illnesses.
Open symbols = Community studies.
Closed symbols = Studies of hospitalized illnesses.

Figure 6.3 Odds ratios for the effect of paternal smoking on lower respiratory illnesses during infancy



Note: Individual studies are denoted with the following symbols:
Circles = Studies of lower respiratory illnesses.
Squares = Studies of wheeze illnesses.
Diamonds = Studies of upper and lower respiratory illnesses.
Open symbols = Community studies.
Closed symbols = Studies of hospitalized illnesses.

Table 6.3 Pooled odds ratios (ORs), 95% confidence intervals (CIs), and heterogeneity tests from meta-analyses of lower respiratory illnesses associated with parental smoking

		Findings		
Study description		**Either parent smoked**	**Mother smoked**	**Father smoked**
All studies	Number of studies	38	41	18
	Heterogeneity χ^2	73.1 ($p < 0.001$)	110.5 ($p < 0.001$)	19.3 ($p = 0.311$)
	ORs (95% CIs) (fixed)	1.51 (1.44–1.59)	1.56 (1.51–1.62)	1.31 (1.20–1.42)
	ORs (95% CIs) (random)	1.59 (1.47–1.73)	1.72 (1.59–1.86)	1.31 (1.19–1.43)
Excluded studies with upper respiratory illnesses	Number of studies	35	37	15
	Heterogeneity χ^2	71.8 ($p < 0.001$)	99.0 ($p < 0.001$)	17.2 ($p = 0.247$)
	ORs (95% CIs) (fixed)	1.50 (1.43–1.58)	1.54 (1.48–1.61)	1.28 (1.17–1.40)
	ORs (95% CIs) (random)	1.59 (1.46–1.74)	1.70 (1.56–1.84)	1.28 (1.15–1.42)
Community studies of lower respiratory illnesses (LRIs), bronchitis, and/or pneumonia	Number of studies	13	9	4
	Heterogeneity χ^2	24.7 ($p = 0.016$)	18.2 ($p = 0.020$)	3.03 ($p = 0.387$)
	ORs (95% CIs) (fixed)	1.55 (1.42–1.69)	1.61 (1.47–1.75)	1.31 (1.16–1.48)
	ORs (95% CIs) (random)	1.60 (1.38–1.84)	1.66 (1.42–1.94)	*
Community studies of wheeze illnesses	Number of studies	13	17	4
	Heterogeneity χ^2	23.7 ($p = 0.022$)	29.9 ($p = 0.018$)	1.72 ($p = 0.633$)
	ORs (95% CIs) (fixed)	1.48 (1.38–1.59)	1.71 (1.60–1.83)	1.29 (1.05–1.59)
	ORs (95% CIs) (random)	1.57 (1.39–1.79)	1.85 (1.66–2.06)	*
Studies based on surveys that relied on recall over many years	Number of studies	4	6	3
	Heterogeneity χ^2	6.0 ($p = 0.109$)	12.08 ($p = 0.034$)	3.02 ($p = 0.221$)
	ORs (95% CIs) (fixed)	1.66 (1.46–1.89)	1.58 (1.47–1.71)	1.43 (1.22–1.68)
	ORs (95% CIs) (random)	1.65 (1.33–2.06)	1.58 (1.38–1.81)	*
All studies excluding those that were based on recall over many years	Number of studies	34	35	15
	Heterogeneity χ^2	64.1 ($p < 0.001$)	98.3 ($p < 0.001$)	14.4 ($p = 0.419$)
	ORs (95% CIs) (fixed)	1.49 (1.41–1.57)	1.56 (1.49–1.63)	1.26 (1.14–1.39)
	ORs (95% CIs) (random)	1.58 (1.45–1.73)	1.77 (1.62–1.94)	1.26 (1.14–1.39)
Hospitalizations for LRIs, bronchitis, bronchiolitis, or pneumonia	Number of studies	9	11	7
	Heterogeneity χ^2	22.5 ($p = 0.004$)	28.4 ($p = 0.002$)	11.8 ($p = 0.067$)
	ORs (95% CIs) (fixed)	1.46 (1.27–1.66)	1.39 (1.31–1.47)	1.20 (1.0–1.44)
	ORs (95% CIs) (random)	1.73 (1.31–2.28)	1.49 (1.29–1.73)	1.31 (0.98–1.76)

*The number of studies was too small for reliable random effects modeling; there was no significant heterogeneity of effects.

Gürkan et al. 2000b; Hjern et al. 2000). Four did not distinguish between different forms of chest illnesses (Ekwo et al. 1983; Taylor and Wadsworth 1987; Stern et al. 1989b; Hjern et al. 2000), four examined bronchitis and/or pneumonia (Harlap and Davies 1974; Mok and Simpson 1982; Jin and Rossignol 1993; Victora et al. 1994), and six focused on hospital admissions for wheeze illnesses (Rylander et al. 1995) or for bronchiolitis with (Sims et al. 1978; Hall et al. 1984; Gürkan et al. 2000b) or without (Anderson et al. 1988; Reese et al. 1992) confirmation of respiratory syncytial virus (RSV) infection.

One cohort study included in the meta-analysis presented detailed findings only for hospital admissions of children from birth to five years of age, and not just for early life (Taylor and Wadsworth 1987). Data presented by age at admission suggest a similar strength of association between maternal smoking and admissions across this age span for bronchitis or pneumonia. The results for all ages were therefore included in the meta-analyses.

Only one of these studies, which was carried out in Brazil, did not find an elevated risk associated with parental smoking (Table 6.2 and Figures 6.1–6.3) (Victora et al. 1994). Table 6.3 summarizes the results of the meta-analyses; the pooled ORs are similar in magnitude to those derived from community studies.

One case-control study from South Africa (Kossove 1982) and one from the United Kingdom (Spencer et al. 1996) were excluded from the quantitative overview because they present only general results for a smoky atmosphere in the home and not specifically for secondhand smoke. In the South African study, the principal source of exposure was wood smoke. In the British study, infants admitted with suspected bronchiolitis were almost three times more likely to have a smoky atmosphere recorded by health visitors after visiting the home when the infant was one month of age (OR = 2.93 [95 percent CI, 1.95–4.41]).

Studies of Upper and Lower Respiratory Illnesses Combined

Five studies related parental smoking to all respiratory illnesses without distinguishing upper from lower respiratory tract diagnoses (Table 6.1) (Rantakallio 1978; Ogston et al. 1985, 1987; Woodward et al. 1990; Chen 1994). Two of these studies were based in the community (Ogston et al. 1987; Woodward et al. 1990), three related to hospitalizations for respiratory illnesses (Rantakallio 1978; Ogston et al. 1985; Chen 1994), and one (Chen 1994) synthesized the results of three earlier papers (Chen et al. 1986, 1988b; Chen 1989).

The findings of these studies are summarized in Table 6.2. Their inclusion in the overall meta-analysis changes the estimates of the effects only slightly (Table 6.3).

Effects of Retrospective Recall

For the six studies based on surveys of school-age children that relied on parental recall of LRIs during early childhood (Ekwo et al. 1983; Ferris et al. 1985; Stern et al. 1989b; Forastiere et al. 1992; Richards et al. 1996; Rusconi et al. 1999), separate meta-analyses were carried out and overall estimates that excluded these studies were calculated (Table 6.3). A separate analysis was carried out because this outcome measure is subject to a greater degree of misclassification than that of a prospective recording of illnesses. There was no clear pattern of differences for the findings of this group of studies compared with the other groups. Excluding the six studies from the overall meta-analysis had only a small effect on the pooled ORs.

Independence of Potential Confounding

About half of the cohort studies, but only a quarter of the case-control or cross-sectional studies, included estimates of the effects of parental smoking both with and without adjustment for potential confounding variables. Although different potential confounding variables were controlled for in each study, the effects of parental smoking changed little or only modestly after adjustment for the potential confounders measured in these studies (Table 6.4).

Exposure-Response Relationships

Of the 22 studies that present evidence of an exposure-response relationship within smoking families, 17 found a statistically significant relationship either with the number of smokers or with the amount smoked in the household, or specifically with the amount of maternal smoking (Table 6.2). However, a formal dose-response meta-analysis could not be carried out because of the nature of the data. In contrast, the risk when both parents smoked compared with smoking by either parent only was not substantially greater. Thirteen studies compared smoking by both parents with smoking by neither parent (Leeder et al. 1976; Ekwo et al. 1983; Fergusson and Horwood 1985; Ferris et al. 1985; Ogston et al. 1985, 1987; Taylor and Wadsworth 1987; Forastiere et al. 1992; Reese et al. 1992; Victora et al. 1994; Rylander et al. 1995; Nafstad et al. 1997; Gürkan et al. 2000b). The pooled OR is 1.67 (95 percent CI, 1.42–1.96).

Table 6.4 Effects of adjusting for potential confounders of illness associated with parental smoking

Study	Exposure	Factors adjusted for*	Outcome	Odds ratio	
				Unadjusted	Adjusted
Community studies of lower respiratory illnesses (LRIs)					
Leeder et al. 1976	Both parents vs. none	Family history of chest symptoms, gender, siblings, sibling illnesses	Acute bronchitis (BR)/pneumonia (PN)	2.95	2.78
Gardner et al. 1984	NR†	None	LRI	NR	NR
Fergusson and Horwood 1985	NR	‡	BR/PN	NR	NR
Ferris et al. 1985	NR	None	LRI	NR	NR
Pedreira et al. 1985	NR	None	LRI	NR	NR
McConnochie and Roghmann 1986b	Mother smoked	(Age), socioeconomic status (SES), breastfeeding, siblings, crowding, family history of asthma	Acute bronchiolitis (BL)	2.33	2.68
Chen et al. 1988a	Mother did not smoke, but others smoked ≥10 cigarettes/day	Gender, birth weight, day care, education, cooking fuel	BR/PN	1.33	1.31
Hayes et al. 1989	NR	(Age)	BL	NR	NR
Wright et al. 1991	Mother smoked ≥10 cigarettes/day	Family history of chest illness, season of birth, day care, crowding	LRI	1.82	1.74
Forastiere et al. 1992	Either parent smoked	Age, gender, area, SES, siblings, domestic crowding, heating	LRI	1.32	1.3
Hakansson and Carlsson 1992	NR	None	BR/PN	NR	NR
Marbury et al. 1996	Mother smoked	Family history of asthma, breastfeeding, birth order, day care, housing	LRI	§	1.5
Richards et al. 1996	NR	None	LRI	NR	NR
Gergen et al. 1998	Mother smoked prenatally	Age, gender, ethnicity, birth weight, day care, family history of allergy	Chronic bronchitis (CBR)	2.44	2.2
	≥20 cigarettes/day in the home vs. none	Age, gender, ethnicity, birth weight, day care, family history of allergy	CBR	3.0	2.5
Nuesslein et al. 1999	NR	None	NR	NR	NR

Table 6.4 Continued

Study	Exposure	Factors adjusted for*	Outcome	Odds ratio	
				Unadjusted	Adjusted
Community studies of wheeze illnesses					
Fergusson and Horwood 1985	NR	‡	Wheeze	NR	NR
Bisgaard et al. 1987	Mother smoked ≥20 cigarettes/ day	Gender, SES	Wheeze	2.85	2.7
Chen et al. 1988a	Family members who smoked ≥20 cigarettes/day	None	Wheeze	NR	NR
Burr et al. 1989	NR	None	Wheeze	NR	NR
Lucas et al. 1990	NR	None	Wheeze	NR	NR
Halken et al. 1991	Any smoking	Gender, SES	Wheeze	1.88	2.4
Arshad et al. 1993	Mother smoked	Gender, low birth weight, family history of allergy, season of birth[Δ]	Wheeze	2.24	2.2
Tager et al. 1993	NR	None	Wheeze	NR	NR
Martinez et al. 1995	Mother smoked	Gender, ethnicity, past allergy, family history of asthma	Wheeze	2.07	2.25
Elder et al. 1996	Mother smoked	Duration of breastfeeding	Wheeze	1.98	1.77
Margolis et al. 1997	≤10 cigarettes/ day in child's presence	Age, season, SES, crowding, family history of respiratory disease, day care	Wheeze	1.6	1.5
Nafstad et al. 1997	Secondhand smoke in the home	Gender, family history of atopy, duration of breastfeeding, day care, having siblings	Wheeze	1.52	1.6
Baker et al. 1998	Mother smoked prenatally at 8 months	(Age), housing tenure, mother's education, persons per room, parity, breastfeeding	Wheeze	NR	1.38

Table 6.4 Continued

Study	Exposure	Factors adjusted for*	Outcome	Odds ratio	
				Unadjusted	Adjusted
Community studies of wheeze illnesses					
Gergen et al. 1998	Mother smoked prenatally	Age, gender, ethnicity, birth weight, day care, family history of allergy	Asthma	1.75	1.7
	Mother smoked prenatally	Age, gender, ethnicity, birth weight, day care, family history of allergy	Wheeze	2.15	2.1
	>20 cigarettes/ day in the home vs. none	Age, gender, ethnicity, birth weight, day care, family history of allergy	Asthma	1.63	2.0
	>20 cigarettes/ day in the home vs. none	Age, gender, ethnicity, birth weight, day care, family history of allergy	Wheeze	2.26	2.7
Chen and Millar 1999	Mother was a current smoker	Age, gender, mother's age and education, family type, income, birth weight, gestational age	Asthma	1.56	1.3
Dezateux et al. 1999	NR	None	Wheeze	NR	NR
Gold et al. 1999	Mother smoked prenatally	LRI, low birth weight, maternal asthma, dog exposure, cockroach allergen, ethnicity, income	Wheeze	2.29	1.61
Karaman et al. 1999	NR	None	NR	NR	NR
Mrazek et al. 1999	NR	None	NR	NR	NR
Rusconi et al. 1999	Mother smoked prenatally	(Age), gender, area, father's education, respondent to questionnaire, family history of asthma, birth weight, maternal age, breastfeeding, number of siblings, day care, child's eczema or rhinitis	Transient wheeze	1.48	1.33
	Mother smoked prenatally	(Age), gender, area, father's education, respondent to questionnaire, family history of asthma, birth weight, maternal age, breastfeeding, number of siblings, day care, child's eczema or rhinitis	Persistent wheeze	1.71	1.77
Yau et al. 1999	NR	None	NR	NR	NR

Table 6.4 Continued

Study	Exposure	Factors adjusted for*	Outcome	Odds ratio	
				Unadjusted	Adjusted
Community studies of wheeze illnesses					
Diez et al. 2000	NR	None	NR	NR	NR
Lux et al. 2000¶	Mother smoked prenatally	(Age), housing tenure, mother's education, persons per room, parity, breastfeeding	Wheeze	1.55	NR
Young et al. 2000a	Mother smoked prenatally	NR	Wheeze	2.7	NR
Community studies of upper and lower respiratory illnesses (U/LRIs)					
Ogston et al. 1987	Both parents vs. none	Mother's age, heating fuel	U/LRIs	1.74	1.54
Woodward et al. 1990	Mother smoked	Gender, siblings, family history of respiratory disease, day care, SES, stress, breastfeeding	U/LRIs	2.43	2.06
Hospitalizations for LRIs					
Harlap and Davies 1974	Mother smoked	Birth weight, SES	BR/PN	NR	NR
Sims et al. 1978	NR	(Age, gender, SES)	BL	NR	NR
Mok and Simpson 1982	NR	(Age, height, school)	BR/PN	NR	NR
Ekwo et al. 1983	NR	Gas cooking	LRI	NR	NR
Hall et al. 1984	NR	(Age, gender, race, season, form of health insurance)	BL	NR	NR
Taylor and Wadsworth 1987	NR	None	LRI	NR	NR
Anderson et al. 1988	NR	(Age, gender)	PN/BL	NR	NR
Stern et al. 1989b	NR	None	LRI	NR	NR
Reese et al. 1992	NR	None	BL	NR	NR
Jin and Rossignol 1993	Others smoked ≥20 cigarettes/ day	Gender, breastfeeding, birth weight, education, maternal age, cooking fuel	BR/PN	2.0	2.4
Victora et al. 1994	NR	(Age)	PN	NR	NR
Rylander et al. 1995	Both parents smoked	(Age), family history of asthma, duration of breastfeeding	Wheeze	2.23	2.0
Gürkan et al. 2000b	NR	None	NR	NR	NR

Table 6.4 Continued

Study	Exposure	Factors adjusted for*	Outcome	Odds ratio	
				Unadjusted	Adjusted
Hospitalizations for LRIs					
Hjern et al. 2000	Mother smoked prenatally	Age, gender, maternal education, living in apartment, single parent, country of birth, number of siblings	LRI	1.42	1.3
Hospitalizations for URIs or LRIs					
Rantakallio 1978	NR	None	URI or LRI	NR	NR
Ogston et al. 1985	NR	None	URI or LRI	NR	NR
Chen 1994	Any smoking	Low birth weight	URI or LRI	1.49	1.48

*Matching variables are in parentheses.
†NR = Data were not reported.
‡An analysis of incidence to 1 year of age (Fergusson et al. 1980) shows that smoking effects are independent of breastfeeding and housing.
§No unadjusted relative risk was reported.
ΔAdditional adjustments for family history of asthma, pets, and SES (in Arshad and Hide 1992); matched for incidence to 1 year of age.
¶Same study as Baker et al. 1998 but with different definitions of exposure.

Biomarkers of Exposure

Cotinine was measured as an objective marker of tobacco smoke exposure in four studies that used urine (Reese et al. 1992; Rylander et al. 1995), serum (Gürkan et al. 2000b), or meconium (Nuesslein et al. 1999). In all four studies, cotinine levels were significantly higher in the case group. These results are consistent with another small case-control study of emergency room visits for wheeze illnesses (Duff et al. 1993), which measured urinary cotinine but did not report details of parental smoking patterns.

Specific Respiratory Diagnoses

Some studies assessed the effects of parental smoking on specifically diagnosed illnesses. One study addressed tracheitis and bronchitis (Pedreira et al. 1985), another examined wheeze and pneumonia but not bronchitis or bronchiolitis (Marbury et al. 1996), and the NHANES III study found stronger effects for chronic bronchitis, asthma, and wheeze than for pneumonia (Gergen et al. 1998). One cohort study explicitly distinguished between LRIs with and without wheeze (Wright et al. 1991). The proportion of cases exposed to maternal smoking (defined as ≥20 cigarettes per day) was 14 percent in each subgroup. This finding is not entirely consistent with the pooled ORs obtained from community studies that suggest a stronger effect from maternal smoking specifically in studies of wheeze than in studies that included a broader range of chest illnesses (Table 6.3).

Seven case-control studies that focused specifically on bronchiolitis or illnesses associated with evidence of RSV infection yielded a somewhat stronger effect compared with studies of other outcomes (Sims et al. 1978; Hall et al. 1984; McConnochie and Roghmann 1986b; Anderson et al. 1988; Hayes et al. 1989; Spencer et al. 1996; Gürkan et al. 2000b). This finding, however, may reflect a positive publication bias (see "Publication Bias and Meta-Analyses" later in this chapter).

Parental Smoking at Different Ages

The early report by Colley and colleagues (1974) suggested that the effects of parental smoking on bronchitis and pneumonia incidence were most marked in the first year of life (OR = 1.96 [95 percent CI, 1.30–2.99]), and declined thereafter with the increasing age of the child to an inverse relationship in the fifth year. Results from the Dunedin (New Zealand) cohort

showed a similar pattern, with a slightly greater effect in the first year than in the second year (Fergusson et al. 1981) and little evidence of an association with consultation for bronchitis or pneumonia after two years of age (Fergusson and Horwood 1985). One study reported a decline in the risk ratio for pneumonia admissions and maternal smoking during pregnancy from between 1.2 to 1.3 up to three years of age and to 1.0 at three to four years of age, but a formal test of statistical significance was not carried out for the trend (Hjern et al. 2000).

A study in Shanghai documented that the effects of smoking by persons other than the mother on hospitalizations for respiratory diseases were stronger for admissions before 6 months of age than for admissions at 7 through 18 months of age (Chen et al. 1988a). However, a significantly increased risk persisted after six months of age for children exposed to more than 10 cigarettes per day in the home (incidence ratio = 1.83 [95 percent CI, 1.03–3.24]). In the 1970 British cohort, the effects of maternal smoking on hospitalizations for wheeze illnesses, bronchitis, or pneumonia were similar at all ages up to five years (Taylor and Wadsworth 1987).

The ALSPAC is a cohort study that examined and measured both maternal smoking during pregnancy and secondhand smoke exposure during the first six months of life. The study measured the number of hours the infant was exposed as a predictor of wheeze between 6 and 18 months of age and from 18 through 30 months of age (Lux et al. 2000). There was no evidence of any reduction in the ORs across age strata. In the Isle of Wight cohort study (Arshad et al. 1993), ORs of asthmatic wheeze with maternal smoking declined from 2.5 (95 percent CI, 1.7–3.7) at one year of age to 2.2 (95 percent CI, 1.5–3.4) at two years of age and to 1.2 (95 percent CI, 0.3–2.7) at four years of age (Tariq et al. 2000).

In a Swedish study based on record linkage (Table 6.1), the authors reported a clear decrease with increasing age of the child in the OR for hospital admissions for asthma associated with maternal smoking during pregnancy (Hjern et al. 1999). The OR was 1.6 (95 percent CI, 1.4–1.8) at two years of age, but was lower and not significantly different from 1 at three to six years of age. In the NHANES III study (Gergen et al. 1998), patterns of effect by age varied with the outcome. The OR for chronic bronchitis in children under two years of age (2.2 [95 percent CI, 1.6–3.0]) was higher than the OR for children three to five years of age (1.0 [95 percent CI, 0.6–1.8]). ORs for the younger age group were also higher for wheeze (2.1 [95 percent CI, 1.5–2.9] versus 1.3 [95 percent CI, 0.8–2.0], respectively), but not for diagnosed asthma (1.7 [95 percent CI, 1.1–2.6] versus 1.7 [95 percent CI, 1.1–2.8], respectively).

Susceptible Subgroups

Infants born prematurely are one group potentially at an increased risk from parental smoking because of the still immature lungs at birth and, for some, the development of bronchopulmonary dysplasia after birth. The effects of parental smoking on early respiratory illnesses were reported in two controlled trials (Burr et al. 1989; Lucas et al. 1990), three cohort studies (Elder et al. 1996; Gold et al. 1999; Mrazek et al. 1999), and one nested case-control study (Diez et al. 2000) that recruited infants at high risk based on prematurity (Lucas et al. 1990; Elder et al. 1996), a parental history of allergy (Burr et al. 1989; Gold et al. 1999; Mrazek et al. 1999), or both (Diez et al. 2000). The ORs obtained from these studies are within the general range of the data (Table 6.2) and have therefore been included in the meta-analyses.

Only one study permits a direct comparison between high- and low-risk infants (Chen 1994). In two Chinese cohorts, an adverse effect of household smoking on hospitalizations for a respiratory disease was evident among both low birth weight (<2.5 kilograms) (OR = 6.87 [95 percent CI, 0.89–53.0]) and normal birth weight (OR = 1.36 [95 percent CI, 0.96–1.93]) infants. There was an indication of a significant effect modification by birth weight (test for interaction: $p = 0.06$).

Smoking by Other Household Members

The effects of smoking by other household members when the mother did not smoke are summarized in Tables 6.2 and 6.3. These findings are derived from three studies in China (Chen et al. 1988a; Jin and Rossignol 1993; Chen 1994) that included nonsmoking mothers, and 14 studies from westernized countries with data only for paternal smoking. The results are quantitatively consistent and only two of the OR estimates are less than unity. The pooled OR obtained in the meta-analysis is 1.31 (95 percent CI, 1.19–1.43). In the Chinese studies, this effect is independent of birth weight and a range of other potential confounding factors (Jin and Rossignol 1993; Chen 1994). Another study from Malaysia, which was not included in the meta-analysis because the age range of the participants was one to five years, also found an increased risk when the fathers smoked and the mothers did not report smoking (OR = 1.20 [95 percent CI, 0.86–1.67]) (Quah et al. 2000). A large national survey

from Australia with an age range from birth to four years reported a significant risk of asthma associated with maternal smoking (adjusted OR = 1.52 [95 percent CI, 1.19–1.94]); there was evidence of a dose-response relationship, but no effect from paternal smoking (OR = 0.77 [95 percent CI, 0.60–0.98]) when adjusted for maternal smoking (Lister and Jorm 1998).

Prenatal Versus Postnatal Exposure

Few studies have evaluated the effects of prenatal and postnatal maternal smoking in the same sample. In western countries, too few mothers change their smoking habits in the perinatal period to offer the statistical power to reliably separate prenatal from postnatal effects. For example, in a large study based on a national British cohort, half of the children were born to mothers who had smoked during pregnancy (Taylor and Wadsworth 1987). Only 8 percent of those mothers subsequently quit, and 6 percent of the prenatal nonsmokers smoked after the child was born. The rate of having a hospitalization for LRI differed between these two groups, but not significantly (5.9 percent for those whose mothers smoked only during pregnancy versus 3.1 percent for those whose mothers smoked only after the child's birth; OR = 1.94 [95 percent CI, 0.96–3.94]). Postnatal smoking by mothers who did not smoke during pregnancy compared with lifetime nonsmoking mothers increased the risk, but not significantly (OR = 1.36 [95 percent CI, 0.73–2.54]). The magnitude of the effect is consistent with the pooled effect in this study and in other studies when only the father smoked (Table 6.3). More recent evidence for the independent effects of prenatal and postnatal maternal smoking comes from the ALSPAC cohort study (Lux et al. 2000). The effects of maternal smoking during pregnancy were compared with those of secondhand smoke exposure by assessing the number of hours the mother smoked in the child's presence and by including both prenatal and postnatal smoking in the same logistic regression model. For wheeze illnesses occurring between 18 and 30 months of age, independent effects were found for each smoking pattern: ORs of 1.19 (95 percent CI, 1.02–1.39) for prenatal maternal smoking and 1.17 (95 percent CI, 1.03–1.32) for postnatal secondhand smoke exposure. These effects were adjusted for the other exposure as well as for multiple other potential confounding variables.

The reported ORs in the NHANES III survey for diagnosed asthma, chronic bronchitis, wheeze, and pneumonia were similar for prenatal and postnatal maternal smoking (Gergen et al. 1998). The authors noted the difficulty of distinguishing between the two time periods and did not assess the independent effects of smoking by fathers only.

One controlled intervention study (the control arm is included in the meta-analysis) (Margolis et al. 1997) monitored the incidence of acute LRI after an intervention that was designed to reduce postnatal tobacco smoke exposure (Greenberg et al. 1994). Among 581 infants followed to six months of age, there was no difference in the incidence of episodes of cough, wheeze, or rattling in the chest between the intervention group (1.6 episodes per year of observation) and the control group (1.5 episodes per year of observation). However, the effectiveness of the intervention in reducing tobacco smoke exposure was uncertain because the mean cotinine levels did not differ between the study groups despite a reduction in reported tobacco smoke exposure of infants in the intervention group.

Publication Bias and Meta-Analyses

Publication bias might occur if studies were more likely to be published that were "positive" (i.e., with statistically significant increases in risk), or that tended to show greater effect estimates of secondhand smoke ("Use of Meta-Analysis" in Chapter 1). Figure 6.1 suggests evidence of such a bias because there are few small studies with wide confidence limits below the pooled estimate of effect, an interpretation confirmed formally by Begg's test (Begg and Mazumdar 1994) for a nonparametric correlation between effect estimates and their standard errors ($p = 0.030$ after continuity correction). Egger's test (Egger et al. 1997) provides even stronger evidence for a publication bias ($p = 0.002$). Maternal smoking data also showed evidence of a publication bias (Begg's test, $p = 0.221$; Egger's test, $p < 0.001$). For smoking by fathers only, there was no evidence of heterogeneity in the ORs and no evidence of a publication bias (Begg's test, $p = 0.880$; Egger's test, $p = 0.890$), perhaps reflecting the fact that publication was unlikely to hinge on the presentation or significance of the data for paternal smoking.

One approach that mitigates the consequences of any publication bias is to restrict analyses to the largest studies; for this sensitivity analysis, all studies with more than 800 cases were selected. For maternal smoking, there were six studies with a pooled random effects estimate of 1.49 (95 percent CI, 1.36–1.64). For smoking by either parent, such an analysis was not possible. Of only three large studies that provided estimates, one Chinese study included only fathers

who smoked (Chen et al. 1988a), and the findings of the other two studies were too divergent in their estimated ORs of 1.85 (Ferris et al. 1985) and 1.32 (Lux et al. 2000).

Three studies (Fergusson and Horwood 1985; Chen et al. 1988a; Gergen et al. 1998) appear in more than one row in Table 6.2 and were thus included as separate and independent studies in the meta-analysis. However, a sensitivity analysis confirmed that restricting the inclusion of each study to its most frequent outcome had little effect on the pooled estimates.

Evidence Synthesis

The finding of an association between parental smoking and LRI is consistent across diverse study populations and study designs, methods of case ascertainment, and diagnostic groupings (Table 6.2). The association cannot be attributed to confounding or publication bias. Only two studies found an inverse association. One small study that reported an inverse association for maternal smoking had wide confidence limits and a positive association with cotinine levels in meconium (Nuesslein et al. 1999). A study from Brazil found an inverse association with pneumonia (Victora et al. 1994). Studies in developing countries generally have tended not to find an increased risk associated with exposure of infants and children to parental smoking. This pattern may reflect the different nature of LRIs in developing countries where bacteria are key pathogens and there is a powerful effect from biomass fuel combustion (Smith et al. 2000; Black and Michaelsen 2002), and where levels of secondhand smoke exposure are possibly lower because of housing characteristics and smoking patterns.

Some variation among studies in the magnitude of OR estimates would be anticipated as patterns of smoking differed among countries and over time, and the methods of the studies were not consistent in all respects. This variation is reflected in statistically significant heterogeneity in some of the pooled analyses (Table 6.3). For this reason, the summary ORs derived under the fixed effects assumption should be interpreted with caution. The random effects method may be more appropriate in these circumstances because its wider confidence limits reflect the heterogeneity between studies. This method is, however, more susceptible to the effects of any publication bias because the random effects method gives greater weight to smaller studies. Thus, considering the largest studies only, the fixed effects estimate for maternal smoking was 1.56 and the random effects estimate was 1.72. Regardless, the pooled estimates were statistically significant and it is highly unlikely that the association emerged by chance.

The papers that have been cited were selected using keywords relevant to passive/involuntary smoking and children in the title or abstract. When cross-checked against previous reviews of involuntary smoking in children, major omissions were not identified (USDHHS 1986; USEPA 1992; DiFranza and Lew 1996; Li et al. 1999), whereas the systematic search identified relevant references not cited elsewhere. There is a possibility that the selection was biased toward studies reporting a positive association; it is more likely that statistically significant findings would be mentioned in the abstract in comparison with nonsignificant or null findings. Three of the higher ORs were derived from small case-control studies in which involuntary smoking was not the focus of the original research (Hall et al. 1984; McConnochie and Roghmann 1986b; Hayes et al. 1989), and for these three studies publication bias may have been operative. The slightly higher pooled ORs obtained by the random effects compared with the fixed effects method (Table 6.3) reflect the greater weight assigned by the random effects approach to these small studies with a relatively large OR. However, inclusion of the large Chinese studies (Chen et al. 1988a; Jin and Rossignol 1993; Chen 1994) in the meta-analysis of the effects of smoking by either parent would have had a conservative effect (i.e., a smaller pooled estimate), because few mothers smoked in these communities.

The biologic basis for the association of paternal smoking with LRI is possibly complex, and may reflect mechanisms of injury that are in play before and after birth. These mechanisms operate to make respiratory infections more severe or to possibly increase the likelihood of infection. Although viral infection is a well-characterized etiologic factor (Graham 1990), there is evidence that the severity of the illness may be determined in part by lung function abnormalities detectable from birth that result from maternal smoking during pregnancy (Dezateux and Stocks 1997). Many early childhood episodes of wheeze, including bronchiolitis, probably form part of this spectrum of viral illnesses, although other episodes may be the first evidence of more persistent childhood asthma with associated atopic manifestations (Silverman 1993; Martinez et al. 1995). The evidence does not indicate that parental smoking increases the rate of infection with respiratory pathogens. Respiratory viruses are isolated with equal frequency among infants in smoking and nonsmoking households (Gardner et al. 1984).

The effect of parental smoking on the incidence of wheeze and nonwheeze illnesses appears similar, suggesting a general increase in susceptibility to clinical illness upon exposure to respiratory infections rather than to influences on mechanisms more specifically related to asthma.

The pooled results from families with nonsmoking mothers suggest that the effects of parental smoking are at least partly attributable to postnatal (i.e., environmental) exposure to tobacco smoke in the home. The somewhat stronger effects of smoking by the mother compared with other household members may be related to the role of the mother as the principal caregiver, which would explain a higher degree of postnatal exposure of the child from the mother's smoking. However, there is also evidence pointing to altered intrauterine lung development as a specific adverse effect of maternal smoking during pregnancy (Tager et al. 1993).

The effect of parental smoking is largely independent of potential confounding variables in studies that have measured and incorporated such variables into the analyses, suggesting that residual confounding by other factors is unlikely. It thus appears that smoking by the parents, rather than characteristics of the family related to smoking, adversely affect children and cause LRIs. The evidence supports the conclusion found in other recent reviews that there is a causal relationship between parental smoking and acute LRIs (USDHHS 1986; USEPA 1992; DiFranza and Lew 1996; WHO 1997; Li et al. 1999; California EPA 2005). The findings are consistent, properly temporal in the exposure-outcome relationship, and biologically plausible. The evidence is strongest for the first two years of life. The studies that were reviewed also suggest a clear reduction in the estimated effect after two to three years of age, particularly for pneumonia and bronchitis. The failure to find statistically significant associations in some studies of older children should not be interpreted, however, as indicative of no effect of secondhand smoke exposure at older ages.

Conclusions

1. The evidence is sufficient to infer a causal relationship between secondhand smoke exposure from parental smoking and lower respiratory illnesses in infants and children.

2. The increased risk for lower respiratory illnesses is greatest from smoking by the mother.

Implications

Respiratory infections remain a leading cause of childhood morbidity in the United States and other developed countries and are a leading cause of childhood deaths worldwide. The effect of parental smoking, particularly maternal smoking, is of a substantial magnitude. Reducing smoking by parents, beginning with maternal smoking during pregnancy, should reduce the occurrence of LRI. Health care practitioners providing care for pregnant women, infants, and children should urge smoking cessation; parents who are unable to quit should be encouraged not to smoke in the home.

Middle Ear Disease and Adenotonsillectomy

A possible link between parental smoking and the risk of otitis media (OM) with effusion (OME) in children was first suggested in 1983 (Kraemer et al. 1983). A number of subsequent epidemiologic studies have investigated the association of secondhand tobacco smoke exposure with diseases of the ear, nose, and throat (ENT), and the evidence has been summarized in narrative reviews (USEPA 1992; Gulya 1994; Blakley and Blakley 1995; NCI 1999) and quantitative meta-analyses (DiFranza and Lew 1996; Uhari et al. 1996). Strachan and Cook (1998a) systematically reviewed the evidence relating parental smoking to acute otitis media (AOM), recurrent otitis media (ROM), OME (glue ear), and ENT surgery in children. This section updates that 1998 review following the methods described earlier. Full journal publications cited in an overview by Thornton and Lee (1999) were also considered, but abstracts and conference proceedings were not included.

Relevant Studies

In combination with the 45 reports included in the previous review, there are now 61 relating to 59 studies of possible associations between parental smoking and AOM, ROM, middle ear disease, and adenotonsillectomy in children: 19 cross-sectional surveys, 20 prospective cohort studies, 17 case-control studies, 2 uncontrolled case-series, and 1 controlled trial of surgical intervention for middle ear effusion.

Studies were grouped according to the outcome measure and whether they were included in the meta-analysis, as shown in Tables 6.5 and 6.6. Some studies contributed data to more than one outcome or age group. In total, there were 17 studies of AOM (5 were included in the meta-analysis); 28 studies of ROM with 1 study (Ståhlberg et al. 1986) that also included adenotonsillectomy (13 in the meta-analysis); 7 studies of ear infections or hearing loss in schoolchildren (all were unsuitable for the meta-analysis); and 6 studies of adenoidectomy, tonsillectomy, or sore throat (4 were included in the meta-analysis). Studies of middle ear effusion were subdivided into 2 studies of incidence (not suitable for the meta-analysis), 8 prevalence studies (reported in 9 papers) based on population surveys (6 were included in the meta-analysis), and 11 clinic-based studies of referral for glue ear surgery (all were included) and postoperative natural history (1 trial was reported in 2 papers).

Evidence Review

Acute Otitis Media

Episodes of acute middle ear infection are common in young children, and a variety of methods have been used to establish the diagnosis and identify the incidence of the condition. For this reason, and because few studies present quantitative information in relation to parental smoking, a quantitative meta-analysis was not included in the previous review (Strachan and Cook 1998a). However, a conclusion was reached that the limited available evidence was consistent with a weak adverse effect of parental smoking on the incidence of AOM in children, with ORs ranging from 1.0 to 1.5.

More recent publications address AOM. Some specifically excluded recurrent episodes (Gryczyńska et al. 1999; Lubianca Neto et al. 1999), but others offered no clear distinction between infrequent and frequent ear infections (Lister and Jorm 1998; Stathis et al. 1999; Tariq and Memon 1999; Rylander and Mégevand 2000). As in the previous review (Strachan and Cook 1998a), several publications offered insufficient quantitative data for a meta-analysis (Jackson and Mourino 1999; Rylander and Mégevand 2000). In one study of Swiss children attending preschool medical examinations, the OR for ear infection (not clearly defined as single or recurrent) was 1.04 (95 percent CI, 0.54–1.98) for exposures of 1 to 19 cigarettes daily at home, and 1.18 (95 percent CI, 0.58–2.39) for exposures of 20 or more cigarettes per day, with an apparent reference group of unexposed children (Rylander and Mégevand 2000). The other report only stated that parental smoking was not a significant risk factor for AOM ($p = 0.52$) (Jackson and Mourino 1999).

Several papers compared the effects of parental smoking on AOM and recurrent or subacute OM in the same population sample. Although the effect was stronger for AOM among Inuit children in Greenland, for example, the effect did not reach statistical significance (Table 6.6) (Homøe et al. 1999). In an Australian birth cohort, the risks associated with maternal smoking did not differ significantly across the outcomes considered: AOM, subacute OM, and a history of ear surgery (predominantly grommet insertion) (Table 6.6) (Stathis et al. 1999). In another Australian national health survey, OM (not further specified) was associated with maternal smoking (OR = 1.31 [95 percent CI, 0.95–1.80]), but the OR for health services utilization was weaker (OR = 1.04 [95 percent CI, 0.71–1.53]) (Lister and Jorm 1998).

Stathis and colleagues (1999) examined the independent effects of exposure to prenatal and postnatal maternal cigarette smoking on the three outcomes in their study at different ages. However, results were not presented for the various specific combinations of exposure, thus limiting the interpretation. In general, maternal smoking at the first prenatal visit had a greater effect compared with exposure at older ages. Smoking during the third trimester and at five years of age had few independent effects. These results need to be interpreted cautiously as there is likely to be co-linearity between early prenatal and postnatal smoking patterns.

The pooled OR for the three studies that document the effects of smoking by either parent provides less convincing evidence (OR = 0.99 [95 percent CI, 0.70–1.40]) (see "Respiratory Symptoms and Prevalent Asthma in School-Age Children" later in this chapter; see also Table 6.14).

Recurrent Otitis Media

The epidemiologic evidence is more abundant for ROM, which is usually defined as greater than a

Table 6.5 Design, sample size, and recruitment criteria of studies of illness associated with parental smoking excluded from meta-analyses

Study	Design/population	Sample size	Case definition	Source of cohort or controls	Outcome
Acute otitis media (AOM) in preschool children					
Vinther et al. 1979	Cohort Aged 3 years Denmark	494	AOM episodes	Random sample of children	AOM
Pukander 1982	Case-control Aged 0–4 years Finland	200	AOM in the past year	Health center controls	AOM
van Cauwenberge 1984	Survey Aged 2–6 years Belgium	2,065	AOM, tympanogram	"Healthy" kindergarten pupils	AOM, otitis media with effusion (glue ear) (OME)
Vinther et al. 1984	Cohort Aged 3–4 years Denmark	681	History of AOM	Random sample of birth cohort	AOM, OME
Fleming et al. 1987	Survey Aged 0–4 years United States (Georgia)	609	AOM in the past 2 weeks	Random sample of households	AOM
Sipila et al. 1988	Cohort Aged 0–3 years Finland	1,294	AOM episodes	Random sample of urban area	AOM
Harsten et al. 1990	Cohort Aged 0–3 years Sweden	414	AOM, OME, upper respiratory tract illness (URTI), lower respiratory tract illness (LRTI)	Population-based birth cohort	Acute RTI
Alho et al. 1996	Cohort Aged 0–2 years Finland	825	AOM episodes	Population-based birth cohort	AOM
Salazar et al. 1997	Cohort Aged <6 months United States (Minnesota)	414	>1 physician-diagnosed AOM by 6 months of age	Health maintenance organization (HMO)-based birth cohort	AOM
Jackson and Mourino 1999	Survey Aged <1 year United States (Virginia)	200	Physician-diagnosed AOM	General pediatric clinic	AOM
Tariq and Memon 1999	Case-series Aged <2 years Pakistan	75	AOM presented to the outpatient department	1,724 outpatient visits	AOM

Table 6.5 Continued

Study	Design/population	Sample size	Case definition	Source of cohort or controls	Outcome
			AOM in older children		
Tariq and Memon 1999	Case-series Aged 2–14 years Pakistan	38	AOM presented to the outpatient department	5,401 outpatient visits	AOM
Rylander and Megevand 2000	Survey Aged 4–5 years Switzerland	304	Reported ear infection	Routine preschool screening	AOM, recurrent otitis media (ROM)
			ROM		
Daly et al. 1999	Cohort Aged <6 months United States (Minnesota)	596	>1 physician-diagnosed AOM by 6 months of age	HMO-based birth cohort	AOM
			Middle ear effusion (MEE) incidence		
Paradise et al. 1997	Cohort Aged 0–2 years United States (Pennsylvania)	2,253	Tympanometry and otoscopy	Primary care-based birth cohort	OME
Engel et al. 1999	Cohorts Aged 0–2 years Holland	250	Tympanometry and otoscopy	Healthy and high-risk birth cohort	OME
			Ear infections in schoolchildren		
Goren and Goldsmith 1986	Survey Age data were not provided Israel	1,449	Ear infection (ever)	2nd and 5th graders	Infection
Porro et al. 1992	Survey Aged 6–14 years Italy	2,304	Otitis (ever)	Random sample of schoolchildren	"Otitis"
Goren and Hellmann 1995	Survey Age data were not provided Israel	6,302	Ear infection (ever)	2nd and 5th graders	Infection
Chayarpham et al. 1996	Survey Aged 6–10 years Thailand	2,384	History and examination	3 primary schools	AOM or OME
			MEE prevalence		
Reed and Lutz 1988	Survey Age data were not provided United States (Utah)	45	Flat tympanogram	Outpatients (half with AOM)	OME

Table 6.5 Continued

Study	Design/population	Sample size	Case definition	Source of cohort or controls	Outcome
		MEE prevalence			
Zielhuis et al. 1988*	Cohort Aged 3 years Holland	1,439	Flat tympanogram	Population-based birth cohort	OME
Takasaka 1990	Case-control Aged 4–5 years Japan	201	Tympanometry plus examination	Population screening survey	OME
		MEE natural history			
Maw and Bawden 1993	Trial Aged 2–11 years United Kingdom	66	No effusion	Untreated ears with OME	Resolution
Maw and Bawden 1994	Trial Aged 3–9 years United Kingdom	133	No effusion	Trial participants with OME	Resolution
		Hearing loss			
Lyons 1992	Survey Aged 10 months Ireland	87	Distraction test	Routine postnatal screening	Impairment
Bennett and Haggard 1998	Cohort Aged 5 years United Kingdom	10,880	Parental report	Population-based birth cohort	Hearing loss
Stathis et al. 1999	Cohort Aged 5 years Australia	5,627	Physician consultation	Population-based birth cohort	Hearing loss
		Sore throat, tonsils, and adenoids			
Gryczynska et al. 1999	Survey Aged 3–14 years Poland	60	Histology of excised tissue	General population sample	Adenoidectomy
Rylander and Megevand 2000	Survey Aged 4–5 years Switzerland	304	>1 sore throat/year	Routine preschool screening	Sore throat

*Zielhuis et al. 1988 and 1989 analyze the same study, but the 1989 paper provides more details (OME prevalence).

Table 6.6 Design, sample size, and recruitment criteria of studies of illness associated with parental smoking included in meta-analyses

Study	Design/population	Sample size	Case definition	Source of cohort or controls	Outcome
			Acute otitis media (AOM)		
Lister and Jorm 1998	Survey Aged <5 years Australia	4,281	Definition unclear	Population sample with no AOM	AOM
Daly et al. 1999	Cohort Aged <6 months United States (Minnesota)	596	Physician-diagnosed AOM by 6 months of age	Health maintenance organization-based birth cohort	AOM
Homøe et al. 1999	Survey Aged 3–8 years Greenland	740	Only 1 reported AOM	Population sample with no AOM	AOM
Lubianca Neto et al. 1999	Survey Aged <3 years Brazil	192	>4 physician-diagnosed AOM/year, no otitis media with effusion (glue ear) (OME)	Same hospital outpatient department as cases	AOM
Stathis et al. 1999	Cohort Aged 5 years Australia	5,627	AOM lasting <1 month	Population-based birth cohort	AOM
			Recurrent otitis media (ROM)		
Pukander et al. 1985	Case-control Aged 2–3 years Finland	395	>3 physician-diagnosed AOM (outpatient clinic)	Same health center as cases	ROM
Ståhlberg et al. 1986*	Survey Aged <4 years Finland	321	≥3 recorded physician-diagnosed AOM	≤3 AOM (population sample)	ROM
Tainio et al. 1988	Cohort Aged <2 years Finland	108	>5 physician-diagnosed AOM by 2 years of age	No physician-diagnosed AOM, same physician	ROM
Teele et al. 1989†	Cohort Aged <1 year United States (Massachusetts)	877	>3 physician-diagnosed AOM by 1 year of age	Clinic-based birth cohort	ROM
	Cohort Aged <3 years United States (Massachusetts)	698	>3 physician-diagnosed AOM by 3 years of age	Clinic-based birth cohort	ROM
	Cohort Aged <7 years United States (Massachusetts)	498	>3 physician-diagnosed AOM by 7 years of age	Clinic-based birth cohort	ROM

Table 6.6 Continued

Study	Design/population	Sample size	Case definition	Source of cohort or controls	Outcome
			ROM		
Daigler et al. 1991	Case-control Aged about 4 years United States (New York)	246	>2 physician-diagnosed AOM in 8 months	Private clinic health check	ROM
Alho et al. 1993	Cohort Aged <2 years Finland	2,512	>3 physician-diagnosed AOM by 2 years of age	Population-based birth cohort	ROM
Stenstrom et al. 1993	Case-control Aged <5 years Canada	170	>4 physician-diagnosed AOM in 12 months	Ophthalmology clinic	ROM
Collet et al. 1995	Cohort Aged <4 years Canada	918	>4 recalled AOM	Population-based birth cohort	ROM
Ey et al. 1995	Cohort Aged <1 year United States (Arizona)	1,013	>3 physician-diagnosed AOM in 6 months	Population-based birth cohort	ROM
Stenström and Ingvarsson 1997	Case-control Aged 3–7 years Sweden	484	>4 reported AOM	General pediatric clinic	ROM
Adair-Bischoff and Sauve 1998	Case-control Aged 4–5 years Canada	625	>3 reported AOM or OME	Population survey (nested case-control)	ROM
Homøe et al. 1999	Survey Aged 3–8 years Greenland	740	>4 reported AOM	Population sample with no AOM	ROM
Stathis et al. 1999	Cohort Aged 5 years Australia	5,627	Subacute OM (duration of 1–3 months)	Population-based birth cohort	ROM
			Middle ear effusion (MEE) prevalence		
Iversen et al. 1985	Cohort Aged 3–6 years Denmark	337	Flat tympanogram	Day care center (6 tests)	OME
Zielhuis et al. 1989	Cohort Aged 2–4 years Holland	435	Flat tympanogram	Population sample (9 tests)	OME
Strachan 1990	Survey Aged 7 years United Kingdom	864	Flat tympanogram	Population sample (1 test)	OME
Etzel et al. 1992	Cohort Aged <3 years United States (North Carolina)	132	Otoscopy plus symptoms	Day care center	OME

Table 6.6 Continued

Study	Design/population	Sample size	Case definition	Source of cohort or controls	Outcome
			MEE prevalence		
Saim et al. 1997	Survey Aged 5–6 years Malaysia	1,097	Flat tympanogram and no reflex	Population sample (1 test)	OME
Apostolopoulos et al. 1998	Survey Aged 6–12 years Greece	4,838	Flat or C2 tympanogram and no reflex	Population sample (1 test)	OME
			MEE referral for surgery		
Kraemer et al. 1983	Case-control Age data were not provided United States (Washington state)	152	Operation for OME	General surgical clinic	OME (outpatients)
Black 1985	Case-control Aged 4–9 years United Kingdom	442	Operation for OME	Clinic and community conrols	OME (outpatients)
Hinton and Buckley 1988	Case-control Aged about 6 years United Kingdom	70	Ear, nose, and throat outpatient referrals	Orthoptic clinic	OME (outpatients)
Hinton 1989	Case-control Aged 1–12 years United Kingdom	151	Grommet insertion	Orthoptic clinic	OME (outpatients)
Barr and Coatesworth 1991	Case-control Aged 1–11 years United Kingdom	230	Grommet insertion	Orthopedic and eye clinics	OME (outpatients)
Green and Cooper 1991	Case-control Aged 1–8 years Germany	328	Otalgia and deafness	Various pediatric clinics	OME (outpatients)
Rowe-Jones and Brockbank 1992	Case-control Aged 2–12 years United Kingdom	163	Bilateral OME >3 months	Orthopedic and surgical clinics	OME (outpatients)
Rasmussen 1993	Cohort Aged <7 years Sweden	1,022	Grommet insertion	Population-based birth cohort	OME (outpatients)
Kitchens 1995	Case-control Aged <3 years United States (Alabama)	350	Grommet insertion	General pediatric clinic	OME (outpatients)
Ilicali et al. 1999	Case-control Aged 3–7 years Turkey	332	Grommet insertion	Otorhinolaryngology clinic	OME (outpatients)
Stathis et al. 1999	Cohort Aged 5 years Australia	5,627	Ear surgery (93% grommets)	Population-based birth cohort	OME (outpatients)

Table 6.6 Continued

Study	Design/population	Sample size	Case definition	Source of cohort or controls	Outcome
		Tonsillectomy and/or adenoidectomy			
Said et al. 1978	Survey Aged 10–20 years France	3,920	Recall of surgery	General population sample	Adenoidectomy/ tonsillectomy
Ståhlberg et al. 1986*	Case-controls Aged <4 years Finland	425	Adenoidectomy and ROM	General population sample	Adenoidectomy
Willatt 1986	Survey Aged 2–15 years United Kingdom	154	Tonsillectomy	Children of hospital visitors	Tonsillectomy
Hinton et al. 1993	Case-control Aged about 6 years United Kingdom	120	Tonsillectomy	Orthoptic clinic	Tonsillectomy

*Ståhlberg et al. 1986 appears twice but with mutually exclusive comparisons.
†Teele et al. 1989 appears with three potentially overlapping comparisons but with sample attrition.

specified number of episodes of physician-diagnosed AOM in a defined interval (Table 6.6) (Pukander et al. 1985; Ståhlberg et al. 1986; Tainio et al. 1988; Teele et al. 1989; Daigler et al. 1991; Alho et al. 1993; Stenström et al. 1993; Collet et al. 1995; Ey et al. 1995; Stenström and Ingvarsson 1997; Adair-Bischoff and Sauve 1998; Homøe et al. 1999; and Stathis et al. 1999). Studies that tested for the presence of a dose-response relationship generally found significant relationships (Table 6.7). Several studies adjusted for multiple potential confounding factors and found similar ORs before and after adjustment (Table 6.8). These results suggest that uncontrolled confounding is unlikely to be a major issue in the interpretation of the crude ORs.

One birth cohort study documented the relationship of parental smoking to ROM at one, three, and seven years of age (Teele et al. 1989). The size of the cohort differed for each age because of sample attrition, but the case group increased because of an accumulation of children with at least three episodes of OM. For purposes of the meta-analysis, results from the three-year follow-up were used because this age corresponds most closely to the populations in other similar studies.

Four additional studies were included in the updated meta-analysis (Stenström and Ingvarsson 1997; Adair-Bischoff and Sauve 1998; Homøe et al. 1999; Stathis et al. 1999). In the previous review, not enough papers provided results for smoking by each parent separately to derive summary measures for maternal and paternal smoking. All four additional studies contribute to a pooled estimate for maternal smoking and three contribute estimates for paternal smoking. The findings suggest that the effects are stronger for maternal smoking.

Figure 6.4 summarizes the results comparing children from smoking and nonsmoking parents. There was some evidence for heterogeneity among the nine ORs for smoking by either parent ($\chi^2 = 16.3$, degrees of freedom [df] = 8, $p = 0.038$). Some variation is to be expected given the different age ranges and case definitions in the studies. Under the fixed effects assumption, the pooled OR for ROM if either parent smoked is 1.32 (95 percent CI, 1.14–1.52). Using the random effects model, the pooled estimate is 1.37 (95 percent CI, 1.10–1.70). Under the fixed effects assumption, the pooled OR for ROM is 1.37 (95 percent CI, 1.19–1.59) for an association with maternal smoking and 0.90 (95 percent CI, 0.70–1.15) for an association with paternal smoking.

Middle Ear Effusion: Population Surveys and Birth Cohorts

The 1997 review identified four cross-sectional or longitudinal studies of general population samples

Table 6.7 Unadjusted relative risks for updated meta-analysis of illness associated with parental smoking

Study	Cases/ controls	Dose-response effect	Outcome	Odds ratio for smoking (95% confidence interval)		
				Either parent	Mother	Father
Acute otitis media (AOM)						
Lister and Jorm 1998	232/4,049	NR*	AOM	NR	1.31 (0.95–1.80)	NR
Daly et al. 1999	221/346	NR	AOM	0.98 (0.60–1.59)	NR	NR
Homøe et al. 1999	102/193	NS† (p = 0.51)	AOM	1.64 (0.85–3.19)	NR	NR
Lubianca Neto et al. 1999	71/121	NR	AOM	0.82 (0.67–1.02)	NR	NR
Stathis et al. 1999	722/4,591	Slight (p = 0.054)	AOM	NR	1.23 (1.04–1.44)‡	NR
Recurrent otitis media (ROM)						
Pukander et al. 1985	188/207	NR	ROM	1.96 (1.28–3.0)	NR	NR
Ståhlberg et al. 1986	100/221	NR	ROM	1.54 (0.93–2.56)	NR	NR
Tainio et al. 1988	28/80	NR	ROM	2.40 (0.91–6.33)	NR	NR
Teele et al. 1989	129/748	NR	ROM before 1 year of age	1.42 (0.96–2.11)	NR	NR
	303/395	NR	ROM before 3 years of age	1.04 (0.76–1.43)	NR	NR
	368/130	NR	ROM before 7 years of age	1.18 (0.77–1.80)	NR	NR
Daigler et al. 1991	125/246	NR	ROM	NR	0.90 (0.54–1.50)	0.83 (0.50–1.39)
Alho et al. 1993	960/1,552	NR	ROM	1.0 (0.68–1.48)	NR	NR
Stenstrom et al. 1993	85/85	Yes; total cigarettes/day	ROM	2.54§ (1.23–5.41)	NR	NR
Collet et al. 1995	164/754	Yes; total cigarettes/day	ROM	1.69 (1.19–2.43)	NR	NR
Ey et al. 1995	169/844	Yes; mother smoked >20 cigarettes/day	ROM	NR	1.33 (0.90–1.95)	NR
Stenström and Ingvarsson 1997	179/305	NS (p = 0.71); mother smoked >20 cigarettes/ day	ROM	NR	1.30 (0.89–1.88)	0.73 (0.48–1.10)

Table 6.7 Continued

Study	Cases/ controls	Dose-response effect	Outcome	Odds ratio for smoking (95% confidence interval)		
				Either parent	Mother	Father
			ROM			
Adair-Bischoff and Sauve 1998	227/398	NS; mother smoked >10 cigarettes/day	ROM	1.11 (0.78–1.57)	1.37 (0.93–2.0)	1.11 (0.77–1.63)
Homøe et al. 1999	117/193	NS (p = 0.64)	ROM	0.96 (0.55–1.69)	NR	NR
Stathis et al. 1999	360/4,852	NS (p = 0.56)	ROM	NR	1.53‡ (1.24–1.91)	NR
			Middle ear effusion prevalence (MEE)			
Iversen et al. 1985	183/154	NR	OME	1.55 (0.98–2.46)	NR	NR
Zielhuis et al. 1989	128/307	No; total cigarettes/day	OME	1.11 (0.59–2.09)	NR	NR
Strachan 1990	82/782	Yes; number of smokers$^{\Delta}$	OME	1.41 (0.87–2.28)	NR	NR
Etzel et al. 1992	Total = 132	NR	OME	1.38¶ (1.21–1.56)	NR	NR
Saim et al. 1997	151/946	NR	OME	0.87 (0.61–1.24)	NR	NR
Apostolopoulos et al. 1998	308/4,530	NS (p = 0.85)	OME	1.60 (1.23–2.08)	NR	NR
			OME referral for surgery			
Kraemer et al. 1983	76/76	Yes; number of smokers	OME (outpatients)	1.45 (0.72–2.94)	NR	NR
Black 1985	150/292	Yes; cigarettes times years	OME (outpatients)	NR	NR	NR
Hinton and Buckley 1988	26/44	No; total cigarettes/day	OME (outpatients)	1.10 (0.37–3.23)	NR	NR
Hinton 1989	115/36	NR	OME (outpatients)	2.04 (0.89–4.71)	NR	NR
Barr and Coatesworth 1991	115/115	No; total cigarettes/day	OME (outpatients)	0.72§ (0.41–1.27)	1.23§ (0.70–2.15)	NR
Green and Cooper 1991	164/164	No; total cigarettes/day	OME (outpatients)	NR	1.92 (1.20–3.06)	1.37 (0.87–2.17)
Rowe-Jones and Brockbank 1992	100/63	NR	OME (outpatients)	1.21 (0.61–2.39)	NR	NR
Rasmussen 1993	176/846	NR	OME (outpatients)	0.87 (0.49–1.55)	NR	NR

Table 6.7 Continued

Study	Cases/ controls	Dose-response effect	Outcome	Odds ratio for smoking (95% confidence interval)		
				Either parent	Mother	Father
OME referral for surgery						
Kitchens 1995	175/175	No; number of smokers	OME (outpatients)	1.65 (1.05–2.59)**	1.28 (0.65–2.54)**	1.54 (0.89–2.66)**
Ilicali et al. 1999	166/166	NS (p = 0.61)	OME (outpatients)	NR	3.93 (2.42–6.41)	1.57 (1.01–2.45)
Stathis et al. 1999	290/4,971	NS (p = 0.13)	OME (outpatients)	NR	1.71 (1.35–2.17)‡	NR
Tonsillectomy and/or adenoidectomy						
Said et al. 1978	1,490/2,430	Yes; cigarettes smoked by each parent	Adenoidectomy/ tonsillectomy	2.07 (1.80–2.38)	1.68 (1.44–1.95)	1.89 (1.64–2.17)
Ståhlberg et al. 1986	114/321	NR	Adenoidectomy	2.06 (1.30–3.26)	NR	NR
Willatt 1986	93/61	NR	Tonsillectomy	2.06 (1.06–4.0)	NR	NR
Hinton et al. 1993	60/60	Yes; estimated secondhand smoke exposure	Tonsillectomy	2.10 (1.01–4.35)	2.29 (1.02–5.13)	1.26 (0.55–2.90)

*NR = Data were not reported.
†NS = Not significant.
‡Maternal smoking during pregnancy at first prenatal visit. For maternal smoking when their children were 5 years of age, odds ratios were 1.14 (0.97–1.34) for AOM, 1.38 (1.11–1.72) for ROM, and 1.47 (1.16–1.87) for middle ear surgery (OME outpatients). OME = Otitis media with effusion (glue ear).
§Matched analysis.
ΔDose-response effect was assessed by salivary cotinine levels that appear in a separate paper (Strachan et al. 1989).
¶Incidence density ratio.
**95% confidence interval was derived from the p value.

that objectively measured the presence of OME by tympanometry (Iversen et al. 1985; Zielhuis et al. 1989; Strachan 1990) or otoscopy (Etzel et al. 1992). Regardless of the diagnostic method, all studies found an increase in the prevalence of OME in children exposed to parental smoking (Table 6.7). Two additional cross-sectional studies, one from Malaysia (Saim et al. 1997) and the other from Greece (Apostolopoulos et al. 1998), were included in this meta-analysis (Figure 6.4, middle). The former study showed no association of OME with household smoking but the latter study found a significant relationship, with an OR of 1.60 (95 percent CI, 1.23–2.08) for smoking by either parent but no dose-response trend in relation to the number of cigarettes smoked daily by the parents (p = 0.85). The pooled (random effects) OR for smoking by either parent is 1.33 (95 percent CI, 1.12–1.58).

Two more recent studies followed children prospectively from birth with examinations by tympanometry and otoscopy at intervals of three months throughout the first two years of life (Paradise et al. 1997; Engel et al. 1999). These studies are not readily integrated into the earlier meta-analysis, but they do show that OME in infancy is extremely common. For instance, among 2,253 children in Pittsburgh, 48 percent had at least one episode of effusion by 6 months of age, 79 percent by 12 months of age, and 91 percent by 24 months of age (Paradise et al. 1997). In the Netherlands, parental smoking was not a risk factor for early OME (OR = 1.09 [95 percent CI, 0.84–1.41]),

Table 6.8 Effects of adjusting for potential confounders in each study of illness associated with parental smoking

Study	Outcome	Odds ratio for smoking			Factors adjusted for or addressed in the text
		Exposure	Unadjusted	Adjusted	
Acute otitis media (AOM)					
Lister and Jorm 1998	AOM	Mother	NR*	1.31	Gender, lived in the capital, income, occupation, no English at home, maternal education, family size, paternal smoking
Daly et al. 1999	AOM	Both parents	1.5	1.3	Family history of OM, birth season, day care, infections, infant feeding, number of siblings
Homøe et al. 1999	AOM	Either parent	NR	NR	NR
Lubianca Neto et al. 1999	AOM	Either parent	0.82	0.80	Gender, age, race, socioeconomic status (SES), infant feeding
Stathis et al. 1999	AOM	Mother smoked 10–19 cigarettes/ day vs. 0†	2.3	2.6	Gender, age, maternal age, SES, infant feeding, day care, number of siblings
Recurrent otitis media (ROM)					
Pukander et al. 1985	ROM	NR	NR	NR	None
Ståhlberg et al. 1986	ROM	NR	NR	NR	None
Tainio et al. 1988	ROM	NR	NR	NR	SES was similar in cases and controls
Teele et al. 1989	ROM before 1 year of age	NR	NR	NR	None
	ROM before 3 years of age	NR	NR	NR	None
	ROM before 5 years of age	NR	NR	NR	None
Daigler et al. 1991	ROM	NR	NR	NR	None
Alho et al. 1993	ROM	Either parent	1.0	0.99	Gender, siblings, day care, breastfeeding
Stenstrom et al. 1993	ROM	Either parent	2.54	2.68	Age, gender, family history of OM, atopy, SES, day care, breastfeeding

Table 6.8 Continued

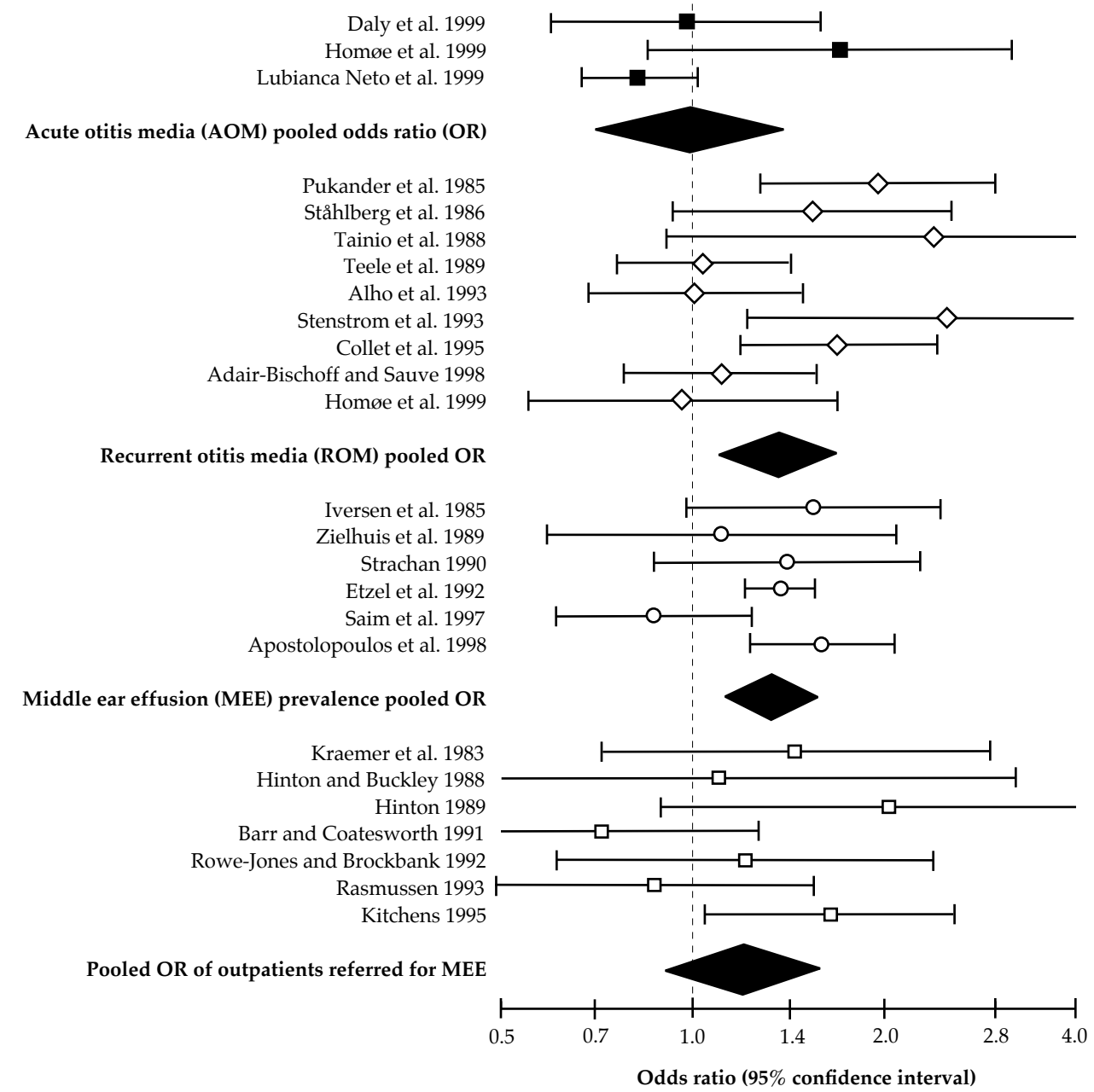
Study	Outcome	Odds ratio for smoking			Factors adjusted for or addressed in the text
		Exposure	Unadjusted	Adjusted	
		ROM			
Collet et al. 1995	ROM	Both parents	2.08	1.80	Gender, family history of OM, day care, SES
Ey et al. 1995	ROM	Mother smoked >20 cigarettes/day	2.10	1.78	Gender, siblings, day care, breastfeeding, family history of hay fever
Stenström and Ingvarsson 1997	ROM	Both parents	NR	NR	Age was similar in cases and controls
Adair-Bischoff and Sauve 1998	ROM	2 or more household smokers vs. 1 or 0	1.85	1.88	Day care, infant feeding, SES, prenatal and postnatal health service utilization
Homøe et al. 1999	ROM	Both parents	NR	NR	NR
Stathis et al. 1999	ROM	Mother smoked 10–19 cigarettes/day vs. 0[†]	2.4	2.6	Gender, age, maternal age, SES, infant feeding, day care, number of siblings
		Middle ear effusion prevalence (MEE)			
Iversen et al. 1985	OME[‡]	Either parent	1.55	1.60	Age
Zielhuis et al. 1989	OME	NR	NR	NR	None
Strachan 1990	OME	Both parents	1.89	1.80	SES, crowding, cooking fuel, dampness
Etzel et al. 1992	OME	NR	NR	NR	Gender, race, infection, atopy, breastfeeding, heating
Saim et al. 1997	OME	Either parent	NR	NR	NR
Apostolopoulos et al. 1998	OME	Either parent	NR	NR	Gender, age, SES, area, medical history
		MEE referral for surgery			
Kraemer et al. 1983	OME (outpatients)	Both parents	2.81	2.80	Age, gender
Black 1985	OME (outpatients)	NR	NR	NR	None
Hinton and Buckley 1988	OME (outpatients)	NR	NR	NR	None
Hinton 1989	OME (outpatients)	NR	NR	NR	None

Table 6.8 Continued

Study	Outcome	Odds ratio for smoking			Factors adjusted for or addressed in the text
		Exposure	Unadjusted	Adjusted	
MEE referral for surgery					
Barr and Coatesworth 1991	OME (outpatients)	NR	NR	NR	Age, gender, race, SES (by matching)
Green and Cooper 1991	OME (outpatients)	NR	NR	NR	Age, gender (by matching), SES (all armed forces)
Rowe-Jones and Brockbank 1992	OME (outpatients)	NR	NR	NR	Area and SES were similar in cases and controls
Rasmussen 1993	OME (outpatients)	NR	NR	NR	None
Kitchens 1995	OME (outpatients)	NR	NR	NR	Age, area, and SES were similar in cases and controls
Ilicali et al. 1999	OME (outpatients)	Both parents	NR	NR	Gender, age, and SES were similar in cases and controls
Stathis et al. 1999	OME (outpatients)	Mother smoked 10–19 cigarettes/ day vs. 0[†]	1.4	1.7	Gender, age, maternal age, SES, infant feeding, day care, number of siblings
Tonsillectomy or adenoidectomy					
Said et al. 1978	Adenoidectomy/ tonsillectomy	NR	NR	NR	Gender, siblings (separate stratified tabulations)
Ståhlberg et al. 1986	Adenoidectomy	NR	NR	NR	None
Willatt 1986	Tonsillectomy	NR	NR	NR	None
Hinton et al. 1993	Tonsillectomy	NR	NR	NR	Age, gender, and SES were similar in cases and controls

*NR = Data were not reported.
[†]Maternal smoking during pregnancy at first prenatal visit, adjusted for smoking prenatally in the third trimester and 6 months and 5 years postnatally.
[‡]OME = Otitis media with effusion (glue ear).

Figure 6.4 Odds ratios for the effect of smoking by either parent on middle ear disease in children



■ AOM studies contributing to the pooled OR.

◇ ROM studies contributing to the pooled OR.

○ MEE studies contributing to the pooled OR.

□ Outpatient referral for MEE studies contributing to the pooled OR.

but a more appropriate measure for such a common outcome may be the duration of the effusion (Engel et al. 1999). The Pittsburgh study documented consistent gradients in the cumulative percentage of days with OME during the first year of life, from 18.4 percent among children not exposed to smokers in the home to 24.8 percent among children living with three or more smokers; in the second year of life the gradients ranged from 15.7 percent to 19.4 percent, respectively. Each dose-response trend was statistically significant ($p < 0.001$), but there were no adjustments for potential confounding variables. The effects of secondhand smoke exposure during the first year of life remained significant after adjustment for area of residence, gender, socioeconomic status (SES), family size, day care, and infant feeding. The adjusted effect of having smokers in the home was not significant in the second year of life (Paradise et al. 1997).

Middle Ear Effusion: Clinic Referrals

The 1998 review considered nine studies that examined the relationship between secondhand smoke exposure and outpatient referrals or operative interventions for glue ear (Table 6.6) (Kraemer et al. 1983; Black 1985; Hinton and Buckley 1988; Hinton 1989; Barr and Coatesworth 1991; Green and Cooper 1991; Rowe-Jones and Brockbank 1992; Rasmussen 1993; Kitchens 1995). Seven of these studies that were suitable for the meta-analysis (Figure 6.4, bottom) yielded a pooled OR for smoking by either parent of 1.20 (95 percent CI, 0.90–1.60). Two additional studies from Australia (Stathis et al. 1999) and Turkey (Ilicali et al. 1999) that have also been included strengthen the evidence for an association with parental smoking, particularly by the mother (Table 6.7). The pooled OR for maternal smoking is 1.84 (95 percent CI, 1.54–2.20) compared with 1.49 (95 percent CI, 1.13–1.96) for paternal smoking.

Most of the studies in this category use the case-control design. Only one compared ORs before and after adjusting for confounders but only for age and gender (Kraemer et al. 1983). However, several case-control studies were either matched for age, gender, and SES, or the reports comment that these variables were similarly distributed among cases and controls (Table 6.8). The Australian cohort study controlled for a wider range of covariates and found a stronger association after adjustment compared with the univariate tabulations (Table 6.8) (Stathis et al. 1999). This finding weighs against residual confounding.

Middle Ear Effusion: Natural History

Studies document that OME commonly resolves spontaneously, and about one-third of the cases may remit between outpatient referrals and operative treatments. For example, in a follow-up of a case series in the United Kingdom, the rate of spontaneous resolution in children with at least one smoking parent was 31.5 percent, similar to the rate in children of nonsmoking parents (31 percent) (Hinton 1989).

Insights into the long-term natural history of untreated effusions emerge from controlled trials of operative interventions for glue ear (Maw and Bawden 1993, 1994). Among 133 children followed for five years after adenoidectomy or adenotonsillectomy, the persistence of fluid at the end of the study was three times more likely if either parent smoked (OR = 3.32 [95 percent CI, 1.17–9.41]) (Maw and Bawden 1994). A similar finding emerged using a survival analysis from a trial of unilateral grommet insertion for OME (Maw and Bawden 1993). Among 66 untreated ears followed for five or more years, a spontaneous resolution of fluid was less common among children of smokers (hazard ratio = 0.44 [95 percent CI, 0.22–0.87]), implying a twofold or threefold difference in the rates of resolution between children of smokers and children of nonsmokers.

Hearing Loss

Researchers have related middle ear effusion to hearing loss (Roland et al. 1989; Roberts et al. 1995). However, only one study was found that related parental smoking to objectively confirmed hearing impairments (Lyons 1992). This study was based on a sample of 87 Irish children having routine developmental screening at 10 months of age. A persistently abnormal distraction test was five times more common in infants involuntarily exposed to cigarette smoke, and the authors calculated that 75 percent of the cases of hearing loss were attributable to secondhand smoke exposure.

Parental reports of "suspected or confirmed hearing difficulty" by five years of age were analyzed in a British birth cohort of more than 10,000 children born in 1970 (Bennett and Haggard 1998). The lifetime incidence was 8.4 percent, and was somewhat higher among children five years of age whose mothers had smoked (unadjusted OR = 1.22; no CIs were supplied). After adjustment for gender, SES, day care, and mouth breathing, the adjusted OR for maternal smoking was 1.31 (95 percent CI, 1.14–1.51).

In a birth cohort of more than 5,000 children from Brisbane (Australia), 10 percent of the children had parental reports of consultations with a physician for hearing problems by five years of age (Stathis et al. 1999). There were significant univariate associations with maternal smoking at the first prenatal clinic visit (OR = 1.35 [95 percent CI, 1.13–1.62]) and at five years of age (OR = 1.31 [95 percent CI, 1.09–1.57]).

Adenoidectomy and Tonsillectomy

The 1997 review identified four studies relating to adenoidectomy, tonsillectomy, or adenotonsillectomy without a specific reference to OME as an indicator (Table 6.6) (Said et al. 1978; Ståhlberg et al. 1986; Willatt 1986; Hinton et al. 1993). These studies documented consistent ORs relating to smoking by either parent, with a pooled OR of 2.07 (95 percent CI, 1.82–2.35). However, that pooled analysis was dominated by one large population survey of French secondary schoolchildren (Said et al. 1978). A large British cohort study was identified that showed an OR of 1.0 for parental smoking with tight 95 percent CIs (0.90–1.11) (Strachan et al. 1996) that did not overlap with those of the French study (Said et al. 1978).

More recently published data do not add substantially to this contradictory evidence, but one Polish study reported large differences in adenoid histology between children involuntarily exposed to cigarette smoke and those who were not exposed (Gryczyńska et al. 1999). Epithelial thickening, significantly fewer ciliated cells, and an increase in squamous epithelium were more common in the exposed children. These findings are consistent with chronic inflammatory changes related to cigarette smoke exposure.

Evidence Synthesis

Evidence from different study designs and for different chronic or recurrent disease outcomes related to the middle ear in young children is remarkably consistent in showing a modest elevation in risk associated with parental smoking. Although the outcome measures used are subject to misclassification, the evidence is nonetheless consistent in spite of this heterogeneity.

Subsequent publications over the last four years have not substantially affected the findings of the 1997 meta-analysis (Strachan and Cook 1998a), although quantitative summarization can now be extended to AOM. No single study addresses all of the potential methodologic concerns about selection (referral) bias, information (reporting) bias, or confounding. However, multiple studies that have considered these potential methodologic problems using objective measurements, matched designs, or multivariate analyses have found that the association of secondhand smoke exposure with middle ear disease persists with little alteration in the magnitude of the effect across studies, or within studies that controlled for potential confounding. There are multiple potential pathogenetic mechanisms related to the effects of tobacco smoke components on the upper airway (Samet 2004) (Chapter 2, Toxicology of Secondhand Smoke). A causal association between acute and chronic middle ear disease and secondhand smoke exposure is thus biologically plausible.

Conclusions

1. The evidence is sufficient to infer a causal relationship between parental smoking and middle ear disease in children, including acute and recurrent otitis media and chronic middle ear effusion.

2. The evidence is suggestive but not sufficient to infer a causal relationship between parental smoking and the natural history of middle ear effusion.

3. The evidence is inadequate to infer the presence or absence of a causal relationship between parental smoking and an increase in the risk of adenoidectomy or tonsillectomy among children.

Implications

The etiology of acute and chronic middle ear disease is still a focus of investigation. Nonetheless, the finding that parental smoking causes middle ear disease offers an opportunity for the prevention of this common problem. Health care providers making diagnoses of acute and chronic middle ear disease need to communicate with parents who smoke concerning the consequences for their children.

Respiratory Symptoms and Prevalent Asthma in School-Age Children

The first reports (based on telephone surveys) documenting an adverse effect of parental smoking on the health of children were published in the late 1960s (Cameron 1967; Cameron et al. 1969). By the early 1970s, studies with more formal designs addressed respiratory symptoms (Norman-Taylor and Dickinson 1972; Colley 1974; Colley et al. 1974). Since then, many epidemiologic studies have found an association between parental smoking and respiratory symptoms and diseases throughout childhood. These outcomes were considered in the 1984 and 1986 reports of the Surgeon General (USDHHS 1984, 1986). The narrative review of the 1992 EPA risk assessment (USEPA 1992) concluded that the evidence causally relating secondhand smoke exposure at home to respiratory symptoms was very strong among preschool-age children, but less compelling in school-age children. A subsequent quantitative review did not distinguish between different types of secondhand smoke exposure and their effects at different ages (DiFranza and Lew 1996).

This section summarizes the evidence on the prevalence of respiratory symptoms and asthma in children aged 5 through 16 years, assessed from surveys carried out in schools or populations. This review includes primarily cross-sectional studies and cohorts studied at a single point in time, and updates an earlier 1997 review by Cook and Strachan (1997). A subsequent section of this chapter addresses studies on the onset of asthma and exposure to secondhand smoke. These two sets of outcome measures for asthma—prevalent and incident disease—were separated because disease prevalence reflects not only factors determining incidence, but factors affecting persistence. The studies of asthma prevalence, however, receive further consideration when assessing the evidence related to asthma onset. There are additional complexities in comparisons across studies of varied designs that arise from the different approaches used to ascertain the presence of asthma, and from the heterogeneity of the asthma phenotype by age. Additionally, wheeze, cough, phlegm, and breathlessness are common symptoms for children with asthma.

Relevant Studies

In the 1997 review, 100 articles were identified from their abstracts as possibly containing data that related the prevalence of respiratory symptoms or asthma to secondhand smoke exposure (Cook and Strachan 1997). If a study resulted in additional publications, those publications were used to extract the necessary data. Data from cohort studies were included only if a prevalence estimate for the cohort was available at some point. However, 39 studies were excluded for various reasons.

Out of 47 new studies identified as possibly relevant, 19 were excluded for the following reasons: 7 papers did not present any findings despite having data on symptoms and secondhand smoke (Asgari et al. 1998; Jedrychowski et al. 1998; Goren et al. 1999; Kalyoncu et al. 1999; Suárez-Varela et al. 1999; Hölscher et al. 2000; Moreau et al. 2000); 3 studies presented data that were insufficient for inclusion in a meta-analysis, although there was usually a comment about either the lack of statistical significance (Garcia-Marcos et al. 1999) or the statistical significance of the findings (Faniran et al. 1998; Peters et al. 1999); 1 study presented no separate data on children (Nriagu et al. 1999); 3 were non-English language publications (Galván Fernández et al. 1999; Vitnerova et al. 1999; Kardas-Sobantka et al. 2000); 2 publications related to studies already included (Renzoni et al. 1999; Forastiere et al. 2000); 2 studies presented data on other endpoints (Gomzi 1999; Heinrich et al. 1999); and 1 study was based on sharing a room with a smoker as the exposure indicator (Odhiambo et al. 1998).

Three additional papers presented relevant data but were not considered suitable for inclusion in a meta-analysis: a study in Taiwan (Wu et al. 1998) that merited some attention because of its size but appears to overlap with a study already included that is based on another report (Wang et al. 1999); a Danish study that focused on the underdiagnosis of asthma (Siersted et al. 1998); and a study with cohorts of secondhand smoke-exposed and unexposed children aged nine years. This study addressed postnatal secondhand smoke exposure versus in utero exposure in relation to risk for all respiratory infections, upper and lower combined (Jedrychowski and Flak 1997).

In addition, a publication from 2001 that lies outside the period of the search is also included because it is based on NHANES III data and is therefore relevant to the United States (Mannino et al. 2001).

Table 6.9 summarizes the characteristics of 88 studies that were included in the quantitative overview. Some papers cover more than one study and, because they may present data on different age groups or outcomes, results may be included in several rows in subsequent tables. The rows that are included in any particular meta-analysis are clearly identified.

One study that was not published in the peer-reviewed literature (Florey et al. 1983) is presented separately from the main meta-analyses because of the uniform protocol, the size of the study (approximately 22,000 children), and because only two centers appear to ever have separately published their findings on secondhand smoke in a peer-reviewed journal (Gepts et al. 1978; Melia et al. 1982). Using a standard questionnaire to parents that was based on the WHO questionnaire (Colley and Brasser 1980), the main purpose of this European study was to investigate the relationship between air pollution and respiratory health in schoolchildren; data were also collected on the number of smokers in each home.

Symptom Questionnaires

With a few exceptions, the studies reviewed here are based on data collected from questionnaires filled out by the parents. Inevitably, definitions of asthma and symptoms varied and reflected the state of development of standard questionnaires. Many early studies, particularly in the United Kingdom, used the respiratory questionnaire developed by the Medical Research Council (MRC) for adults as a starting point (MRC 1966). The purpose of this questionnaire was to study chronic respiratory symptoms, and its two most important characteristics are (1) that it did not ask about symptoms in a defined period but asked whether "a person *usually* coughed first thing in the morning" (cough usually in the a.m.), or whether "a child's chest *ever* sounded wheezy or whistling" (wheeze ever); and (2) if the answer was yes, a second question was usually asked to elicit the severity: "Does he/she cough like this on most days or nights for as much as three months each year?" (persistent cough) or "Does he/she get this [wheeze] on *most* days or nights?" (persistent wheeze). In 1978, the American Thoracic Society's Epidemiology Standardization Project published a questionnaire for children based on the adult questionnaires (Ferris 1978). The children's questionnaire determined whether symptoms occurred only with or apart from colds, and provided information used to distinguish allergic from nonallergic asthma (Ferris 1978). More recently developed questionnaires focus on symptoms in the past 12 months and use a number of methods to assess severity (Asher et al. 1995). One particularly important questionnaire was developed for the International Study of Asthma and Allergy in Childhood (ISAAC) (Asher et al. 1995). This questionnaire has been used in many recent studies. The differences in definitions are explicitly identified in this review where possible, but for some studies a clear definition was not provided in the published report.

Many papers published since the 1997 review have been based on the multicountry ISAAC protocol (Asher et al. 1995). A parental questionnaire was used for younger children in ISAAC while the adolescents themselves completed the questionnaire or, in some locations, were administered a video questionnaire. As a result of the widespread use of the ISAAC study protocol, more of the recent publications relate to asthma (N = 17) and wheeze (N = 21) than to cough (N = 12), phlegm (N = 5), or breathlessness (none).

Evidence Review

Asthma

A total of 41 studies contained quantitative information (Table 6.10); 2 studies presented two separate sets of results (Søyseth et al. 1995; Selçuk et al. 1997). Most studies reported on "asthma ever," which is typically a positive response to "Has this child ever had asthma?" Some studies focused on current asthma, usually defined as in the past year, while other studies specifically asked whether the diagnosis had been made by a physician. One study that reported physician consultations for wheeze is included under asthma for purposes of consistency (Strachan and Elton 1986).

The OR estimates for asthma in children from families in which either parent smoked compared with children of nonsmoking parents were consistently above 1; only three ORs were below 1 (Moyes et al. 1995; Peters et al. 1996; Lam et al. 1999), but the majority of confidence limits included 1. The pooled estimate was 1.23 (95 percent CI, 1.14–1.33), but there is evidence of heterogeneity among the studies ($\chi^2_{30} = 78.8$, $p < 0.001$). The studies reporting the highest ORs were more likely to be early publications that had small study populations and did not adjust for potential confounders Table 6.10 and Figure 6.5. The pooled OR for the unadjusted studies is

Table 6.9 List of secondhand smoke exposure analyses included in the meta-analysis

Study	Population (sample size)	Response rate (%)	Respiratory symptoms
Norman-Taylor and Dickinson 1972	All St. Albans school entrants Aged 5 years (1,119) United Kingdom	NR*	Chronic cough
Colley 1974	7 schools in Aylesbury Aged 6–14 years (2,426) United Kingdom	93	Chronic cough
Lebowitz and Burrows 1976	Stratified cluster sample of Tucson homes Aged 0–15 years (626) United States (Arizona)	72	Asthma, wheeze, chronic cough, chronic phlegm
Schilling et al. 1977	Families from 3 towns Aged 7–18 years (816) United States	NR	Wheeze, chronic cough
Bland et al. 1978	Random sample of Derbyshire schools Aged 11–12 years (5,835) United Kingdom	86	Chronic cough, breathlessness
Kasuga et al. 1979	2 schools Aged 6–11 years (1,896) Japan	99	Wheeze
Stanhope et al. 1979	1 college Aged 12–18 years (715) New Zealand	96	Wheeze
Weiss et al. 1980	Random sample of children aged 5–9 years attending school in East Boston in 1974, plus siblings (383) United States (Massachusetts)	42	Wheeze, chronic cough
Dodge 1982	Schools in 3 Arizona communities Aged 8–12 years (628) United States	76	Asthma, wheeze, chronic cough, chronic phlegm
Ekwo et al. 1983	Primary school in Iowa City Aged 6–12 years (1,138) United States (Iowa)	55	Chronic cough
Schenker et al. 1983†	Stratified sample of Pennsylvania schools Aged 5–14 years (4,071) United States	93	Wheeze, chronic cough, chronic phlegm
Charlton 1984	65 schools in northern England Aged 8–19 years (6,988) United Kingdom	NR	Chronic cough
Ware et al. 1984	6 cities Aged 6–9 years (8,380) United States	NR	Wheeze, chronic cough
Burchfiel et al. 1986	Residents of Tecumseh Aged 0–19 years (3,460) United States (Michigan)	NR	Asthma, wheeze, chronic cough, chronic phlegm

Table 6.9 Continued

Study	Population (sample size)	Response rate (%)	Respiratory symptoms
Goren and Goldsmith 1986	Sampling unclear; near coal-fired power station 2nd and 5th graders (sample size not reported) Israel	86	Asthma, wheeze, chronic cough, breathlessness
McConnochie and Roghmann 1986a	Historical birth cohort Aged 6–10 years (223) United States	62	Wheeze
Park and Kim 1986	Households in Wonsung County Aged 0–14 years (3,651) Korea	NR	Chronic cough
Strachan and Elton 1986	Born in 1976 from 1 general practice Aged 7–8 years (165) United Kingdom	83	Asthma, wheeze, chronic cough
Andrae et al. 1988	7 areas near Norrkoping Aged 6 months–16 years (4,990) Sweden	94	Chronic cough
Somerville et al. 1988	Stratified sample from 22 areas in England Aged 5–11 years (5,169) United Kingdom	75	Asthma, wheeze, chronic cough
Strachan 1988‡	30 primary schools in Edinburgh Aged 7 years (1,001) United Kingdom	91	Wheeze, chronic cough
Hosein et al. 1989	3 North American towns Aged 7–17 years (1,357) United States	>90	Wheeze, chronic cough, chronic phlegm, breathlessness
Stern et al. 1989a	2 rural communities Aged 7–12 years (1,317) Canada	81	Asthma, wheeze, chronic cough
Stern et al. 1989b§	5 rural communities in Ontario and 5 in Saskatchewan Aged 7–12 years (4,003) Canada	81	Asthma, wheeze, chronic cough, chronic phlegm
Dijkstra et al. 1990	9 schools in southeast Holland Aged 6–12 years (1,051) Netherlands	72	Wheeze, chronic cough, breathlessness
Chinn and Rona 1991	National stratified sample Aged 5–11 years (14,256) United Kingdom	>90	Asthma, wheeze, chronic cough
Dekker et al. 1991	30 communities Aged 5–8 years (14,059) Canada	83	Asthma, wheeze
Henry et al. 1991	2 schools: 1 in a polluted area and 1 in a control area Aged 5–12 years (602) Australia	72	Wheeze

Table 6.9 Continued

Study	Population (sample size)	Response rate (%)	Respiratory symptoms
Forastiere et al. 1992	Random sample of schools in 3 areas Aged 7–11 years (2,929) Italy	94	Asthma, chronic cough
Duffy and Mitchell 1993	Stratified sample of 36 schools Aged 8 and 12 years (4,549) Australia	94	Wheeze
Florey et al. 1983	19 European centers Aged 6–10 years (22,078) Europe	62–99	Wheeze
Halliday et al. 1993	2 areas Aged 5–12 years (787) Australia	86	Wheeze
Jenkins et al. 1993	Children born in 1961 (7 years of age) (8,585) Australia (Tasmania)	99	Wheeze
Schmitzberger et al. 1993	3 zones of air pollution Aged 6–15 years (1,626) Austria	88	Asthma
Brabin et al. 1994	15 primary schools in 3 areas around Liverpool Aged 5–11 years (1,872) United Kingdom	92	Asthma, wheeze, breathlessness
Shaw et al. 1994	1 town Aged 8–13 years (708) New Zealand (Kawerau)	82	Wheeze
Soto-Quiros et al. 1994[Δ]	Stratified random sample of 98 schools Aged 5–17 years (2,534) Costa Rica	89	Asthma
Bråbäck et al. 1995	All schools in 1 area Aged 10–12 years (665) Sweden	97	Wheeze, chronic cough
	1 school in Konin Aged 10–12 years (410) Poland	97	Wheeze, chronic cough
	11 schools in Tallin and 4 in Tartu Aged 10–12 years (1,519) Estonia	96	Wheeze, chronic cough
Cuijpers et al. 1995	2 primary schools Aged 6–12 years (470) Netherlands	88	Wheeze, chronic cough, breathlessness
Goren and Hellmann 1995[¶]	3 coastal towns 2nd and 5th graders (6,822) Israel	95	Asthma, wheeze, chronic cough

Table 6.9 Continued

Study	Population (sample size)	Response rate (%)	Respiratory symptoms
Kay et al. 1995	Large, urban general practices Aged 3–11 years (1,077) United Kingdom	98	Asthma
Lau et al. 1995	4 selected Chinese middle-class schools Aged 3–10 years (433) Hong Kong	89	Asthma
Moyes et al. 1995	All children in defined area Aged 6–14 years (2,614) New Zealand	85	Asthma, wheeze, chronic cough
Ninan et al. 1995	Primary schools in Aberdeen Aged 8–13 years (259) United Kingdom	NR	Chronic cough
Søyseth et al. 1995	2 western valleys Aged 7–13 years (620) Norway	96	Asthma
Stoddard and Miller 1995	Stratified cluster sample of all U.S. households Aged <18 years (7,578) United States	NR	Wheeze
Volkmer et al. 1995	All school entries Aged 4–5 years (14,124**) Southern Australia	73	Asthma, wheeze, chronic cough
Abuekteish et al. 1996	Primary schools in and around 1 city Aged 6–12 years (3,186) Jordan (Irbid)	90	Wheeze
Beckett et al. 1996	Older children of mothers who gave birth in hospitals Aged 1–18 years (5,171) United States	91	Asthma
Bener et al. 1996	Sampling unclear Aged 6–14 years (729) United Arab Republic	86	Asthma
Chen et al. 1996	1 town Aged 6–17 years (892) Canada (Humboldt)	NR	Asthma
Peters et al. 1996††	17 schools in 2 areas with different air pollution levels Aged 10–13 years (3,521) Hong Kong	96	Asthma, wheeze, chronic phlegm
Wright et al. 1996	Birth cohort from Tucson Aged 6 years (987) United States (Arizona)	78	Wheeze, chronic cough

Table 6.9 Continued

Study	Population (sample size)	Response rate (%)	Respiratory symptoms
Zejda et al. 1996	Cluster sample of primary schools in 2 towns Aged 7–9 years (1,622) Poland	75	Chronic cough
Austin and Russell 1997	Schools in Scottish Highlands Aged 12 and 14 years (1,537) United Kingdom	85	Wheeze, chronic cough
Butland et al. 1997	All children attending school in Croydon Aged 7.5–8.5 years (7,237) United Kingdom	81–87	Wheeze
Dales et al. 1997	Sampling unclear; 1 community (138) Canada	NR	Chronic cough
Farber et al. 1997	The 1992–1994 Bogalusa Heart Study survey Aged 5–17 years (2,975) United States	NR	Asthma
Forsberg et al. 1997	Schools in Oslo, Malmo, Umea, and Kuopio Aged 6–12 years (15,962) Scandinavia	90	Asthma, chronic cough
Hu et al. 1997	13 schools in Illinois with mostly Black students Aged 10–11 years (707) United States	NR	Asthma, wheeze
Leung et al. 1997	13 randomly selected schools Aged 13–14 years (>3,733) Hong Kong	NR	Wheeze
Maier et al. 1997	Schools in Seattle Aged 5–9 years (925) United States (Washington state)	31	Asthma, wheeze
Selçuk et al. 1997	Random sample Aged 7–12 years (5,412) Turkey	86	Asthma, wheeze
Chen et al. 1998	1 town Aged 6–17 years (892) Canada	88	Chronic cough
Chhabra et al. 1998	2 schools in Delhi Aged 4–17 years (2,609) India	91	Wheeze
Kendirli et al. 1998	Random selection of schools in Adana Aged 6–14 years (2,334) Turkey	88	Asthma, wheeze
Lam et al. 1998	2-stage cluster sample from 172 classes in 61 schools Aged 12–15 years (4,482) Hong Kong	88	Asthma, wheeze, chronic cough, chronic phlegm

Table 6.9 Continued

Study	Population (sample size)	Response rate (%)	Respiratory symptoms
Lewis and Britton 1998	Birth cohort born in 1 week in 1970 Aged 16 years (6,000) United Kingdom	NR	Wheeze
Lewis et al. 1998	Primary schoolchildren from industrial and nonindustrial areas Aged 8–11 years (2,340) Australia	77	Wheeze, chronic cough
Peters et al. 1998	27 schools within 2 districts Aged 8–13 years (10,615) Hong Kong	95	Wheeze, chronic cough, chronic phlegm
Rönmark et al. 1998	3 areas in northernmost Sweden Aged 7–8 years (3,431)	97	Asthma
Saraçlar et al. 1998	12 schools in Ankara Aged 7–14 years (2,784) Turkey	88	Wheeze
Withers et al. 1998	86 general practitioners in Southampton Aged 14–16 years (2,289) United Kingdom	75	Asthma, wheeze, chronic cough
Agabiti et al. 1999	School-based sample aged 6–7 years from 10 centers in northern Italy; SIDRIA[‡‡] (children) sample (18,737)	96	Asthma, wheeze
	School-based sample aged 13–14 years from 10 centers in northern Italy; SIDRIA (adolescent) sample (21,068)	93	Asthma, wheeze
Belousova et al. 1999	All primary schools in 7 regions within New South Wales Aged 8–11 years (6,394) Australia	76	Wheeze
Burr et al. 1999	93 schools in Great Britain Aged 12–14 years (25,393) United Kingdom	79	Wheeze, chronic cough, chronic phlegm
Chhabra et al. 1999	9 randomly selected schools in Delhi Aged 5–17 years (18,955) India	NR	Asthma, wheeze
Lam et al. 1999	30 schools in Hong Kong Aged 8–13 years (3,480) China	NR	Wheeze, chronic cough, chronic phlegm
Nilsson et al. 1999	Residents of Ostergotland Aged 13–14 years (1,878) Southwest Sweden	NR	Asthma

Table 6.9 Continued

Study	Population (sample size)	Response rate (%)	Respiratory symptoms
Shamssain and Shamsian 1999	78 schools in northeast England Aged 6–7 years (3,000) United Kingdom	80	Asthma, wheeze, chronic cough
Wang et al. 1999	Cross-sectional study of 2 communities Aged 11–16 years (165,173) Taiwan	97	Wheeze
Csonka et al. 2000	All 40 primary schools in 1 city (Tampere) Aged 6–13 years (1,814) Finland	90	Wheeze
Ponsonby et al. 2000	All children aged 7 years from Tasmania who had participated in an earlier infant health survey (863) Australia	NR	Asthma
Qian et al. 2000	3 large cities Aged 5–14 years (2,060) China	NR	Asthma, wheeze, chronic cough, chronic phlegm
Räsänen et al. 2000	5 consecutive birth cohorts of 16-year-old twins (4,538) Finland	NR	Asthma

*NR = Data were not reported.
†Data for standard errors are from Wright et al. 1996.
‡Data for cotinine are in Strachan et al. 1990.
§Prevalence data are from Beckett et al. 1996.
ΔNote error in Table 3 in this paper.
¶See also Bener et al. 1996.
**Number of families.
††1991 data were used.
‡‡SIDRIA = Italian Studies on Respiratory Disorders in Childhood and the Environment.

1.26 (95 percent CI, 1.15–1.38, $\chi^2_{21} = 51.3$, $p < 0.001$). In contrast, the relative odds for the 18 studies that adjusted for various potential confounders are quantitatively consistent and slightly lower than those for the unadjusted studies (pooled OR = 1.22 [95 percent CI, 1.12–1.32], χ^2_{17} for heterogeneity = 39.1, $p = 0.002$). For the 11 studies reporting both adjusted and unadjusted ORs, the adjustment had very little effect (Table 6.10) (Somerville et al. 1988; Dekker et al. 1991; Forastiere et al. 1992; Brabin et al. 1994; Kay et al. 1995; Beckett et al. 1996; Maier et al. 1997; Selçuk et al. 1997; Agabiti et al. 1999; Chhabra et al. 1999; Ponsonby et al. 2000).

Only one of the ORs for asthma where either parent smoked was below 1; the highest ORs were from small studies that had not adjusted for potential confounders (Figure 6.5). There was clear evidence of heterogeneity of effect estimates among the unadjusted studies (pooled OR = 1.30 [95 percent CI, 1.20–1.41], χ^2_{28} for heterogeneity = 152.1, $p < 0.001$). Among the adjusted studies, the pooled OR was only slightly lower at 1.25 (95 percent CI, 1.17–1.33), again with evidence of heterogeneity ($\chi^2_{24} = 88.4$, $p < 0.001$). Studies that provided both adjusted and unadjusted ORs found a similar but very small effect of adjustment (Table 6.11), except for one early Japanese study (Kasuga et al. 1979). The overall pooled OR from all of the studies, using adjusted values if available, was 1.23 (95 percent CI, 1.14–1.33) (see Table 6.14).

One foreign language article published in the *Chinese Journal of Public Health* also merits attention

because of the study size: 359,000 children aged 12 through 14 years were screened, making it larger than all other cross-sectional studies combined. There is an overlap between this study in Taiwan and the data presented in another publication included in the meta-analysis (Wang et al. 1999). Disease definitions were based on an ISAAC protocol that included both a written questionnaire to parents and a video questionnaire to children. "Asthma" was based on a somewhat restrictive definition requiring the following three criteria: (1) in the parent's questionnaire, the student's asthma was diagnosed by a physician; (2) after watching the video, the student reported a shortness of breath similar to what was depicted in a particular scene of the video; and (3) in the past 12 months, the student reported a shortness of breath similar to what was shown in the first scene of the video and had also awakened during the night (Crane et al. 2003). "Suspected asthma" was based on a much broader definition that included cough as well as wheeze.

Although the univariate analyses of the larger study did not show an association between either the number of cigarettes per day smoked by household members or the number of household smokers and asthma risk, there was an exposure-response relationship for "suspected asthma" with the number of cigarettes smoked by household members. However, these univariate results were potentially confounded by age, gender, air pollution, and area as well as by correlates of SES. Adjusted ORs were presented only for asthma (not suspected asthma), and were controlled for gender, school grade, air pollution, burning incense, area, and physical activity. Although unadjusted ORs tended to be below 1.0 for students living in smoking households, the adjusted ORs showed an elevated risk that increased with an increasing number of household smokers. Adjusted data for the number of cigarettes smoked by household members are difficult to interpret because the results were adjusted for the number of household members who smoked. The ORs of 1.1, 1.2, and 1.3 in households with one to two, three to four, and four or more smokers, respectively, are compatible with results from the related Taiwanese paper that offers an OR of 1.08 for any exposure after adjustment. An overall effect of household smoking cannot be derived because the number of children exposed in the different groups was not reported. Two other design issues are unclear: consideration does not appear to have been made for active smoking by these 12- through 14-year-olds, although it was controlled in the analysis reported by Wang and colleagues (1999); and secondhand smoke exposure is not specified as to the source: maternal smoking, paternal smoking, and/or other household members. Data from Taiwan were not presented in the 1997 WHO publication *Tobacco or Health: A Global Status Report* (WHO 1997), but in mainland China it was uncommon for women to smoke. Although the ORs presented in both papers from Taiwan are thus broadly compatible with those in Table 6.14, they are more in keeping with the effects of smoking by fathers or others only, as opposed to maternal smoking or smoking by either parent.

Wheeze

Using a variety of definitions (Table 6.11), 58 studies were identified with data on wheeze that could be broadly grouped under three headings: wheeze ever, current wheeze, and persistent wheeze. Wheeze is a common but nonspecific manifestation of asthma, as it has other underlying causes, including respiratory infection.

Of the 43 studies reporting effects of smoking by either parent, the 2 studies with the highest ORs reported on wheeze that was classified as both current and persistent (Weiss et al. 1980) and on wheeze most days or nights (Lebowitz and Burrows 1976), rather than wheeze ever or current wheeze. These two studies also reported the lowest prevalence rates (Table 6.11), suggesting that the definitions probably reflected more severe wheeze. In two studies that reported on both wheeze ever and wheeze most days or nights, the ORs were greater for wheeze most days or nights (Somerville et al. 1988; Chinn and Rona 1991). More recently, one study in Hong Kong reported a slightly higher OR for current than for severe wheeze (Table 6.11) (Leung et al. 1997). Two large studies from the United Kingdom found higher odds for maternal smoking in relation to frequent attacks than for less frequent attacks (Butland et al. 1997), and for speech-limiting wheeze than for all wheeze in the past year (Table 6.11) (Burr et al. 1999). However, a smaller United Kingdom study reported stronger associations with wheeze ever than for wheeze in the past year or for speech-limiting attacks (Table 6.11) (Shamssain and Shamsian 1999). The overall pooled OR from all studies using adjusted values if available was 1.26 (Figure 6.6) (see also Table 6.14).

Similar to the findings for asthma, all but one of the ORs for smoking by either parent were above 1. The highest ORs were from small studies that had not adjusted for potential confounders (Figure 6.6). There was clear evidence of heterogeneity of effect among the unadjusted studies (pooled OR = 1.30 [95 percent CI, 1.20–1.41], χ^2_{28} for heterogeneity = 152.1,

Table 6.10 Studies of asthma prevalence associated with parental smoking

Study	Population age (years)/ location	Definition of asthma	Prevalence in unexposed (%)	Odds ratio for smoking (95% confidence interval)	
				Either parent (unadjusted)	Either parent (adjusted)
Lebowitz and Burrows 1976	0–15 United States	Physician diagnosis	7.6	3.53 (2.13–5.86)	NR*
Dodge 1982	8–12 United States	NR	4.1	1.61 (0.78–3.33)	NR
Burchfiel et al. 1986	0–19 United States	NR	11.5	NR	1.14 (0.92–1.41)
Goren and Goldsmith 1986	2nd and 5th graders Israel	Ever	8.9	1.07 (0.74–1.56)	NR
Strachan and Elton 1986	5–7 United Kingdom	Wheeze consultations	13	1.60 (0.56–4.60)	NR
Somerville et al. 1988	5–11 United Kingdom	An attack in the past year	4	1.0 (0.78–1.28)	1.18 (0.86–1.62)
Stern et al. 1989a	7–12 Canada	Current	3.6	NR	NR
Stern et al. 1989b	7–12 Canada	Physician diagnosis (ever)	4§	NR	NR
Chinn and Rona 1991	5–11 United Kingdom	In the past year	NR	NR	1.02 (0.86–1.20)
Dekker et al. 1991	5–8 Canada	Current	4.8	1.53 (1.30–1.81)	1.49 (NR)
Forastiere et al. 1992	7–11 Italy	Ever (or symptoms)	6.3	1.4 (NR)	1.3 (0.9–1.8)
Schmitzberger et al. 1993	6–15 Austria	Physician diagnosis	3.4	NR	NR
Brabin et al. 1994	5–11 United Kingdom	Ever	17	1.09 (0.85–1.41)	1.06 (0.83–1.37)
Soto-Quiros et al. 1994	6–12 Costa Rica	NR	NR	NR	NR
Goren and Hellmann 1995	2nd and 5th graders Israel	Ever	9.6	1.19 (1.01–1.41)	NR
Kay et al. 1995	3–11 United Kingdom	Current (definition unclear)	17	1.42 (1.05–1.92)	1.31 (0.96–1.81)

Odds ratio for smoking (95% confidence interval)				
One parent only vs. neither	**Both parents vs. neither**	**Mother only vs. neither**	**Father only vs. neither**	**Confounders adjusted for**
NR	NR	NR	NR	NR
1.36 (0.57–3.21)	1.94 (0.81–4.50)	NR	NR	NR
0.84 (0.63–1.13)	1.62 (1.18–2.22)	1.28 (0.68–2.40)	0.76 (0.56–1.04)	Age, gender, socioeconomic status (SES), family size
NR	NR	1.36 (0.87–2.14)	0.91 (0.59–1.39)	NR
NR	NR	NR	NR	NR
NR	NR	NR	NR	Child's age, gender, birth weight, and triceps skinfold; mother's age and education; number of siblings; and father's social class and job
NR	NR	1.11[†] (0.63–1.98)	1.41[‡] (0.80–2.48)	NR
NR	NR	1.43[Δ] (1.09–1.88)	NR	NR
NR	NR	NR	NR	Birth weight; father's social class and job; mother's age, education, and smoking during pregnancy; and family size and ethnic origin
1.4 (1.13–1.73)	1.59 (1.28–1.98)	NR	NR	Dampness, gas cooking, type of heating, pets
NR	1.50 (1.04–2.20)	1.70 (1.04–2.70)	1.0 (0.70–1.50)	Age, gender, area, SES
NR	NR	2.11[†] (1.22–3.67)	NR	NR
NR	NR	NR	NR	Area
NR	NR	1.53[†] (1.14–2.04)	1.19[‡] (0.97–1.45)	NR
1.13 (0.94–1.36)	1.33 (1.07–1.66)	1.27[†] (1.04–1.55)	1.19[‡] (1.0–1.41)	NR
NR	1.81 (1.16–2.84)	1.13 (0.71–1.80)	1.3 (0.86–1.97)	SES

Table 6.10 Continued

Study	Population age (years)/ location	Definition of asthma	Prevalence in unexposed (%)	Odds ratio for smoking (95% confidence interval)	
				Either parent (unadjusted)	Either parent (adjusted)
Lau et al. 1995	3–10 Hong Kong	Current (definition unclear)	7	1.35 (0.60–3.06)	NR
Moyes et al. 1995	6–7 New Zealand	Ever	25	1.06 (0.89–1.27)	NR
	13–14 New Zealand	Ever	23	0.94 (0.79–1.13)	NR
Søyseth et al. 1995¶	7–13 Norway	Ever	7.7	NR	NR
	7–13 Norway	Ever	NR	NR	NR
	7–13 Norway	Ever	NR	NR	NR
Volkmer et al. 1995¶	4–5 Australia	Ever	NR	Not significant	Not significant
Beckett et al. 1996	1–18 United States	Physician diagnosis	10.3	1.56 (1.30–1.88)	1.40 (1.13–1.72)
Bener et al. 1996	6–14 United Arab Republic	Ever	12.7	1.28 (0.82–1.99)	NR
Chen et al. 1996##	6–17 Canada	Physician diagnosis (ever)	10.0	1.14 (0.72–1.79)	NR
Peters et al. 1996	8–11 Hong Kong	Current physician diagnosis (definition unclear)	6.1§	NR	0.90 (0.69–1.17)
Farber et al. 1997	5–17 United States	Ever	15.9§	NR	1.39 (1.11–1.72)
Forsberg et al. 1997	6–12 Scandinavia	Treatment by physician in the past 12 months	3.5§	NR	1.4 (1.1–1.7)
Hu et al. 1997	10–11 United States (Illinois)	Physician diagnosis (ever)	25.3	NR	NR
Maier et al. 1997	5–9 United States (Washington state)	Physician diagnosis (ever)	11§	1.5 (1.0–2.4)	1.6 (0.9–2.7)

Odds ratio for smoking (95% confidence interval)				
One parent only vs. neither	**Both parents vs. neither**	**Mother only vs. neither**	**Father only vs. neither**	**Confounders adjusted for**
NR	NR	NR	NR	NR
NR	NR	NR	NR	NR
NR	NR	NR	NR	NR
NR	NR	1.17† (0.66–2.07)	0.72‡ (0.39–1.31)	NR
NR	NR	1.26**	NR	NR
NR	NR	1.99†† (1.08–3.67)	NR	NR
NR	NR	NR	NR	NR
NR	NR	NR	NR	Ethnicity, gas stove, mold, maternal age, maternal allergy, number of children at home
NR	NR	NR	NR	NR
0.92 (0.53–1.63)	1.55 (0.84–2.84)	1.17† (0.71–1.95)	1.0‡ (0.61–1.64)	NR
0.76 (0.55–1.07)	1.22 (0.78–1.92)	NR	NR	NR
NR	NR	NR	NR	Age, gender, ethnicity
NR	NR	NR	NR	Age, gender, area, fitted carpets, pets, mold, stove use, parental asthma, early day care
NR	NR	1.22 (0.79–1.89)	NR	None
NR	NR	NR	NR	Gender, ethnicity, allergy, SES, parental asthma

Table 6.10 Continued

Study	Population age (years)/ location	Definition of asthma	Prevalence in unexposed (%)	Odds ratio for smoking (95% confidence interval)	
				Either parent (unadjusted)	Either parent (adjusted)
Selçuk et al. 1997	7–12 Turkey	Ever	13.1	1.41 (1.19–1.67)	1.35[¶] (1.12–1.62)
	7–12 Turkey	Current	4.6	1.34 (1.02–1.77)	1.28 (0.94–1.75)
Kendirli et al. 1998	6–14 Turkey	Ever (by questionnaire)	12.9[§]	1.41 (1.16–1.72)	NR
Lam et al. 1998	12–15 Hong Kong	Physician diagnosis (ever)	8.5	NR	NR
Rönmark et al. 1998	7–8 Sweden	Physician diagnosis and current	6.4[§]	NR	NR
Withers et al. 1998	14–16 United Kingdom	Physician diagnosis (ever)	22.3[§]	NR	p >0.05
Agabiti et al. 1999	6–7 Italy	Asthma with symptoms in the past year	5.0	1.33 (1.10–1.60)	1.34 (1.11–1.62)
	13–14 Italy	Asthma with symptoms in the past year	5.9	1.26 (1.07–1.49)	1.17 (0.99–1.39)
Chhabra et al. 1999	5–17 India	Current	10.8	1.61 (NR)	1.51 (1.34–1.69)
Lam et al. 1999	8–13 Hong Kong	Physician diagnosis (ever) (definition unclear)	6.8	NR	0.91[¶¶] (0.69–1.18)
Nilsson et al. 1999	13–14 Sweden	Ever (International Study of Asthma and Allergy in Childhood [ISAAC] child questionnaire)	9.3[§]	1.0 (0.7–1.4)	NR
Shamssain and Shamsian 1999	6–7 United Kingdom	Ever	20.6	NR	NR
Ponsonby et al. 2000	6–7 Australia	Has your child ever had asthma	30.0	1.16 (0.85–1.57)	1.03 (0.83–1.26)

Odds ratio for smoking (95% confidence interval)				
One parent only vs. neither	**Both parents vs. neither**	**Mother only vs. neither**	**Father only vs. neither**	**Confounders adjusted for**
NR	NR	NR	NR	Age, gender, place, animals, atopic family, breastfeeding
NR	NR	NR	NR	NR
NR	NR	NR	NR	NR
0.89 (0.69–1.12)	NR	1.32 (0.71–2.45)	0.92[§§] (0.72–1.17)	Age, gender, area, housing type
NR	NR	1.6[ΔΔ] (1.1–2.3)	NR	Gender, area, pets, dampness, family history
NR	NR	1.50 (1.14–1.98)	p >0.05	Parent and child atopy, sibling with asthma
NR	1.35 (1.09–1.69)	1.46 (1.13–1.87)	1.26 (1.01–1.58)	Age, gender, area, father's education, crowding, dampness, gas heating, parental asthma, other smokers
NR	1.29 (1.06–1.56)	1.23 (0.98–1.53)	1.04 (0.86–1.27)	Age, gender, area, father's education, crowding, dampness, gas heating, parental asthma, other smokers, active smoking
NR	NR	NR	NR	Age, gender, atopic family
NR	NR	NR	NR	Age, gender, area, active smoking
NR	NR	1.4** (1.0–2.0)	NR	None
1.35 (NR)	1.55 (NR)	1.39[†] (1.12–1.74)	NR	None
NR	NR	1.08** (0.90–1.30)	NR	Gender, family history, breastfeeding, gas heat, mother's education, number in household

Table 6.10 Continued

Study	Population age (years)/ location	Definition of asthma	Prevalence in unexposed (%)	Odds ratio for smoking (95% confidence interval)	
				Either parent (unadjusted)	Either parent (adjusted)
Qian et al. 2000	5–14 China	Recall of asthma ever with physician diagnosis	0.8–3.6	NR	2.11 (0.79–5.66)
Räsänen et al. 2000	16 Finland	Physician diagnosis (ever) by questionnaire	3.2	NR	NR

*NR = Data were not reported.
†Mother currently smoked vs. did not smoke.
‡Father currently smoked vs. did not smoke.
§Overall prevalence.
ΔMother smoked vs. did not smoke during pregnancy and infancy.
¶Not included in the meta-analysis.
**Mother smoked vs. did not smoke prenatally.
††Mother smoked vs. did not smoke postnatally.
‡‡Estimates were determined by combining data for allergic and nonallergic participants.
§§Father smoked vs. neither parent smoked where only 2.5% of the mothers smoked.
ΔΔApproximate confidence limits were derived from the given p value.
¶¶Analyses excluded active smokers.
***Mother ever vs. never smoked.

p <0.001). Among the adjusted studies, the pooled OR was only slightly lower (OR = 1.25 [95 percent CI, 1.17–1.33]), which again provided evidence of heterogeneity (χ^2_{24} = 88.4, p <0.001). For those studies with both adjusted and unadjusted ORs, there was a similar, very small effect of adjustment except for one early Japanese study (Table 6.11) (Kasuga et al. 1979).

For the 19 centers participating in the European Communities (EC) Study, it was possible to extract data for wheeze ever. There was no evidence of heterogeneity between centers (χ^2_{18} = 18.6, p = 0.42); the pooled OR across the 19 centers was 1.20 (95 percent CI, 1.09–1.32).

Chronic Cough

A total of 44 published studies of cough have used a variety of symptom definitions (Table 6.12). Although most of the studies were based on either the MRC or American Thoracic Society questionnaires, the largest study was based on a study-specific questionnaire (Charlton 1984). Two studies reported raised ORs for cough without wheeze (Ninan et al. 1995; Wright et al. 1996), thus emphasizing the importance of cough as a symptom. There is no suggestion that the studies reporting the lowest prevalence rates (implying a more restrictive definition) contributed the highest ORs. The pooled OR for the 26 studies with no adjustments for potential confounders was 1.45 (95 percent CI, 1.34–1.58, χ^2_{25} for heterogeneity = 84.0, p <0.001), somewhat greater than for the 16 studies that adjusted for various factors: pooled OR = 1.27 (95 percent CI, 1.21–1.33, χ^2_{15} for heterogeneity = 18.0, p = 0.26) (Figure 6.7). In four studies reporting both adjusted and unadjusted estimates, the adjustments had little impact (Bland et al. 1978; Somerville et al. 1988; Wright et al. 1996; Burr et al. 1999); the study conducted by Forastiere and colleagues (1992) was excluded because CIs were not reported for the unadjusted category. It is worth noting, however, that Wright and colleagues (1996) and Burr and colleagues (1999) adjusted for active smoking.

Chronic Phlegm

Out of 12 studies reporting on phlegm, 4 used a definition of persistent phlegm and 3 were unclear with regard to the definition in the study report

Odds ratio for smoking (95% confidence interval)				
One parent only vs. neither	Both parents vs. neither	Mother only vs. neither	Father only vs. neither	Confounders adjusted for
NR	NR	NR	NR	Age, gender, ventilation, family history, mother's education, coal use, area
NR	NR	1.49*** (1.02–2.18)	NR	Gender, parental asthma and hay fever, number of older siblings, father's occupation

(Table 6.13); 7 out of 10 studies reported significant ORs for smoking by either parent, although all ORs were above 1 (Figure 6.8). The pooled OR for smoking by either parent was 1.35 (95 percent CI, 1.30–1.41), with no evidence of heterogeneity between studies (χ^2_9 for heterogeneity = 4.6, p = 0.87).

Breathlessness

Six studies reported on shortness of breath using various definitions (Table 6.13). Only two studies reported statistically significant effects even though results were above 1 for all but one of the ORs (Figure 6.8). The pooled OR for smoking by either parent was 1.31 (95 percent CI, 1.14–1.50), with no evidence of heterogeneity (χ^2_5 for heterogeneity = 4.6, p = 0.47).

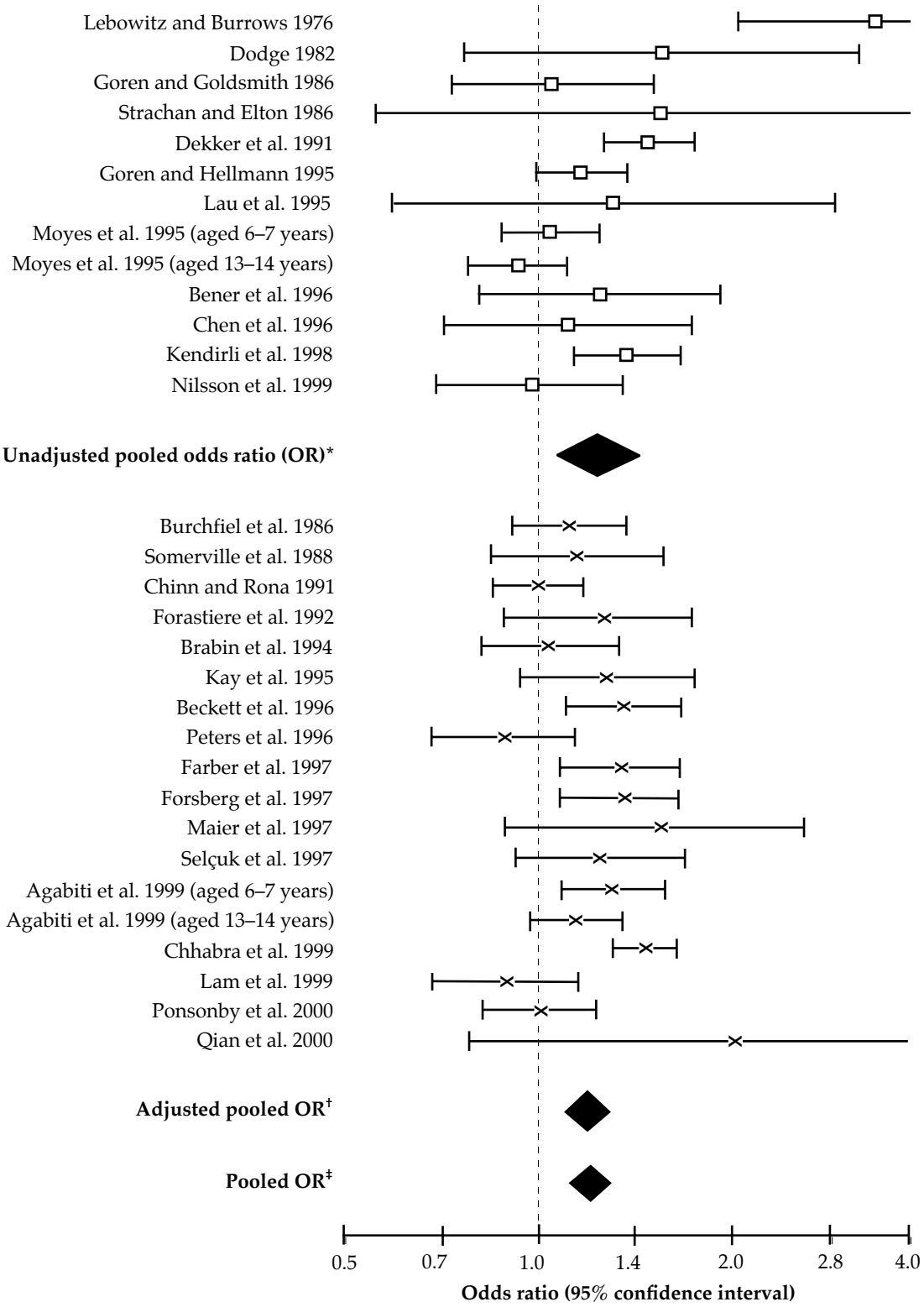
Pooled Odds Ratios

The pooled ORs for smoking by either parent compared with smoking by neither parent are consistent across different outcomes, ranging from 1.23 for asthma to 1.35 for cough and phlegm (Table 6.14). For asthma, wheeze, and cough—for which there are sufficient studies to justify a pooled analysis—there is clear evidence of an increased risk of respiratory symptoms if only one parent smokes, regardless of whether it is only the mother or the father. Exposure to smoking only by the mother appears to have a greater effect, but a formal comparison of smoking by only the mother or father is not possible because it requires within-study estimates of standard errors for the calculation. Evidence exists of a dose-response relationship with the number of parents who smoke; the summary ORs for smoking by both parents are greater than for one parent only in all cases (Table 6.14).

Restricting Analyses to Preteens

Because a number of the cited studies cover teenagers who may be active smokers, and only some studies have included controls for active smoking, the analyses have been repeatedly restricted to those studies in Table 6.9 with no children older than 11 years of age. The results are presented in Table 6.15. Although the number of studies is markedly reduced and confidence limits are widened, the estimated ORs are similar to those in Table 6.14.

Figure 6.5 Odds ratios for the effect of smoking by either parent on asthma prevalence



*Studies that did not adjust for potential confounders.
†Studies that adjusted for a variety of potential confounders.
‡Based on all studies.

Effect of Parental Smoking at Different Ages

Modification of the effect of parental smoking as children age is quite plausible. The relationship of parental smoking to the personal exposure of their children may change as the children age, and susceptibility to secondhand smoke may also change. In addition, the constellation of symptoms, signs, and physiologic abnormalities leading to a diagnosis of asthma may vary by age. A comparison across different studies is unlikely to provide a valid assessment of the risks associated with exposure to parental smoking at different ages because of the considerable overlap of age range in many studies, different definitions of symptoms, and the need to control for active smoking in older children. However, within-study comparisons can be made if comparable information is available across age groups. For example, a large U.S. study found evidence of a reduction in the OR associated with maternal smoking and current wheeze from 1.9 among infants to 1.07 among teenagers (Table 6.11) (Stoddard and Miller 1995). Recent analyses of NHANES III data documented similar results, where ORs for current wheeze in the top versus the bottom tertile of cotinine levels declined from 4.8 (95 percent CI, 2.4–9.9) at 4 through 6 years of age to 1.5 (95 percent CI, 0.7–3.3) at 7 through 11 years of age, and to 0.9 (95 percent CI, 0.3–2.2) at 12 through 16 years of age (Mannino et al. 2001). Similarly, a large questionnaire survey in the United Kingdom found a reduction in the OR for cough from 1.60 at 8 through 10 years of age to 1.50 at 11 through 13 years of age, and to 1.12 at 14 through 19 years of age (Table 6.12) (Charlton 1984). A Korean study found that the OR for cough during a two-week period fell from 3.9 for 5-year-olds and younger to 2.6 for 6- through 11-year-olds, and to 2.0 for 12- through 14-year-olds (Park and Kim 1986). The Italian Studies on Respiratory Disorders in Childhood and the Environment reported a reduction in the odds of current asthma from 1.34 at 6 through 7 years of age to 1.17 in adolescents (Table 6.10) (Agabiti et al. 1999). In contrast, a relatively small New Zealand study found slightly higher ORs for current wheeze and cough at 13 through 14 years of age than at 6 through 7 years of age (Tables 6.11 and 6.12) (Moyes et al. 1995).

For a given level of parental smoking, the reported ORs in this review of the effects of parental smoking on LRIs in schoolchildren were somewhat lower than ORs found in infancy and early childhood. For LRIs, the pooled OR for either parent smoking was 1.57 (95 percent CI, 1.42–1.74). This pattern is consistent with previous claims of smaller effects in older children, but the contrast is less marked than has been suggested (USEPA 1992). Moreover, it is necessary to consider the level of exposure when comparing estimates of the effects, which some earlier reviews did not provide (DiFranza and Lew 1996). For the same level of maternal smoking, biomarker cotinine assessments showed that personal exposure of children to secondhand smoke declined markedly between infancy and school age (Irvine et al. 1997).

Even after entering school, salivary cotinine levels provided evidence that exposure of nonsmoking children to secondhand smoke continues to fall as children grow older; exposures also are affected by gender, geographic area, and time of year (Jarvis et al. 1992; Cook et al. 1994; Pirkle et al. 1996). This decline in cotinine levels with an increase in age is consistent with large, nationwide U.S. study data, and strongly suggests that the adverse effects of parental smoking on respiratory symptoms in their children decline with age even among schoolchildren (Stoddard and Miller 1995).

Prenatal and Postnatal Exposure

Few studies have separately analyzed the effects of past versus current exposure to secondhand smoke. An early study reported a slightly lower prevalence of cough during the day or at night in children of former smokers (14.2 percent of 634) than in the offspring of lifetime nonsmokers (15.6 percent of 320) (Colley 1974). A more recent New Zealand study found that smoking by the current primary caregiver was associated with current wheeze (OR = 1.4 [95 percent CI, 1–2.1]), whereas maternal smoking during pregnancy was not (OR = 0.9 [95 percent CI, 0.7–1.4]) (Shaw et al. 1994). In a Norwegian study, postnatal smoking by the mother was more strongly related to asthma compared with either prenatal or current smoking (Table 6.10) (Søyseth et al. 1995). A recent Scottish study reported slightly stronger effects for current maternal smoking versus prenatal maternal smoking for both wheeze (OR = 1.15 versus 1.10, respectively) and cough (1.93 versus 1.42, respectively) (Beckett et al. 1996).

Findings of an analysis of NHANES III data are relevant to the U.S. experience. In general, the effects of in utero exposure to maternal smoking did not explain the effects of current secondhand smoke exposure (Mannino et al. 2001). Specifically, being in the top tertile of current cotinine levels, after excluding any active smokers, was associated with an increased risk of both current asthma and wheeze, regardless of prenatal maternal smoking. In contrast, a small U.S.

Table 6.11 Studies of wheeze prevalence associated with parental smoking

Study	Population age (years)/ location	Definition of wheeze	Prevalence in unexposed (%)	Odds ratio for smoking (95% confidence interval)	
				Either parent (unadjusted)	Either parent (adjusted)
Lebowitz and Burrows 1976	0–15 United States	Most days	1.4	2.86 (0.92–8.87)	NR*
Schilling et al. 1977	7–15 United States	Ever	11.7	1.99 (1.28–3.10)	NR
Kasuga et al. 1979	6–11 Japan	Current (or asthma)	9.8	2.08 (1.49–2.91)	1.15 (0.83–1.61)
Stanhope et al. 1979	12–18 New Zealand	Current (or asthma)	NR	NR	NR
Weiss et al. 1980	5–9 United States	Current and persistent	1.8	5.89 (0.79–44.1)	NR
Dodge 1982	8–12 United States	Ever	27.9	1.32 (0.94–1.85)	NR
Schenker et al. 1983	5–14 United States	Persistent	7.2	0.93 (0.73–1.19)	NR
Ware et al. 1984	6–9 United States	Persistent	9.9	NR	1.2 (1.05–1.37)
Burchfiel et al. 1986	0–19 United States	NR	18.4	NR	1.28 (1.08–1.52)
Goren and Goldsmith 1986	Grades 2–5 Israel	Wheeze with a cold	12.7	1.27 (0.95–1.70)	NR
McConnochie and Roghmann 1986a	6–10 United States	Current	10.2	NR	NR
Strachan and Elton 1986	7–8 United Kingdom	Ever	20	2.1 (0.87–5.1)	NR
Somerville et al. 1988	5–11 United Kingdom	Ever	11	1.09§ (0.95–1.26)	1.22 (1.02–1.45)
	5–11 United Kingdom	Most days/nights	3	1.66 (1.01–2.12)	1.54 (1.16–2.04)
Strachan 1988	7 United Kingdom	In the past year	12.1	1.04 (0.72–1.52)	NR
Hosein et al. 1989	7–17 United States	Current	13	NR	1.23 (0.88–1.72)
Stern et al. 1989a	7–12 Canada	Ever	22.9	NR	NR
Stern et al. 1989b	7–12 Canada	Persistent	9Δ	NR	NR

Odds ratio for smoking (95% confidence interval)				
One parent only vs. neither	**Both parents vs. neither**	**Mother only vs. neither**	**Father only vs. neither**	**Confounders adjusted for**
NR	NR	NR	NR	NR
1.47 (0.90–2.4)	4.57 (2.45–8.51)	2.08 (1.14–3.79)	1.07 (0.57–1.99)	NR
NR	NR	NR	NR	Distance from a major road
NR	NR	0.53 (0.26–1.05)†	NR	NR
4.12 (0.52–32.9)	7.52 (0.99–57.3)	NR	NR	NR
1.01 (0.67–1.52)	1.8 (1.19–2.73)	NR	NR	NR
1.08 (0.82–1.40)	0.74 (0.53–1.04)	NR	NR	NR
1.11 (0.95–1.29)	1.32 (1.14–1.53)	1.18 (0.95–1.48)	1.08 (0.92–1.28)	Age, gender, city
1.1 (0.87–1.39)	1.53 (1.19–1.97)	1.42 (0.85–2.36)	1.03 (0.80–1.33)	Age, gender, parental education
NR	NR	0.98 (0.66–1.46)	1.44 (1.05–1.98)	NR
NR	NR	2.16† (0.97–4.80)	1.20‡ (0.55–2.62)	NR
NR	NR	NR	NR	NR
NR	NR	NR	NR	Age, gender, birth weight, obesity, socioeconomic status (SES), mother's age, number of siblings
NR	NR	NR	NR	Age, gender, birth weight, obesity, SES, mother's age, number of siblings
1.0 (0.65–1.54)	1.13 (0.67–1.90)	NR	NR	NR
1.32 (0.91–1.91)	1.14 (0.78–1.68)	NR	NR	Gender, active smoking
NR	NR	1.59 (1.24–2.03)	1.03 (0.80–1.31)	NR
NR	NR	1.26 (0.95–1.67)	NR	NR

Table 6.11 Continued

Study	Population age (years)/ location	Definition of wheeze	Prevalence in unexposed (%)	Odds ratio for smoking (95% confidence interval)	
				Either parent (unadjusted)	Either parent (adjusted)
Dijkstra et al. 1990	6–12 Netherlands	In the past year	7.1[Δ]	NR	1.86 (0.99–3.49)
Chinn and Rona 1991	5–11 United Kingdom	Ever	NR	NR	1.11[§] (1.0–1.22)
	5–11 United Kingdom	Most days or nights	NR	NR	1.31 (1.11–1.55)
Dekker et al. 1991	5–8 Canada	Current	7.2	1.6 (1.39–1.83)	1.55 (NR)
Henry et al. 1991	5–12 Australia	In the past year	17.3	NR	1.4 (0.8–2.3)
Duffy and Mitchell 1993	8 and 12 Australia	Ever	22[Δ]	NR	NR
Halliday et al. 1993	5–12 Australia	Current	NR	NR	1.02 (0.71–1.47)
Jenkins et al. 1993	7 Australia	Ever (or asthma)	NR	NR	NR
Brabin et al. 1994	5–11 United Kingdom	Ever	18	1.32 (1.03–1.69)	1.28 (1.0–1.64)
Shaw et al. 1994	8–13 New Zealand	Current	22	1.0 (0.7–1.4)	NR
	8–13 New Zealand	Current	18	NR	NR
	8–13 New Zealand	Current[§]	22	NR	NR
Bråbäck et al. 1995	10–12 Sweden	NR	11.9	NR	NR
	10–12 Poland	NR	9.4	NR	NR
	10–12 Estonia	NR	7.1	NR	NR
Cuijpers et al. 1995	6–12 Netherlands	Ever (definition unclear)	14.7[Δ]	NR	1.08 (0.67–1.74)
Goren and Hellmann 1995	2nd and 5th graders Israel	Wheeze with a cold	13.1	1.25 (1.09–1.44)	NR

Odds ratio for smoking (95% confidence interval)				
One parent only vs. neither	**Both parents vs. neither**	**Mother only vs. neither**	**Father only vs. neither**	**Confounders adjusted for**
NR	NR	NR	NR	Age, parental education
NR	NR	NR	NR	Age, gender, country, birth weight, obesity, SES, mother's age, number of siblings, ethnicity, gas cooking
NR	NR	NR	NR	Age, gender, country, birth weight, obesity, SES, mother's age, number of siblings, ethnicity, gas cooking
1.39 (1.17–1.65)	1.72 (1.44–2.05)	NR	NR	Dampness, gas cooking
NR	NR	NR	NR	Age, gender, area, dust mite allergy
NR	NR	1.36 (0.96–1.93)	0.94 (0.70–1.26)	NR
NR	NR	NR	NR	Age, gender, area, atopy
NR	NR	1.35† (1.2–1.52)	1.10‡ (0.97–1.23)	NR
NR	NR	NR	NR	Area
NR	NR	NR	NR	NR
NR	NR	1.4¶ (1.0–2.1)	NR	NR
NR	NR	0.9** (0.7–1.4)	NR	NR
NR	NR	0.73 (0.41–1.29)	NR	Gender, atopy, dampness, overcrowding
NR	NR	1.54 (0.91–2.60)	NR	Gender, atopy, dampness, overcrowding
NR	NR	1.45 (0.94–2.24)	NR	Gender, atopy, dampness, overcrowding
NR	NR	NR	NR	Age, gender, dampness, father's education, dog, unvented geyser
1.24 (1.07–1.45)	1.27 (1.06–1.53)	1.25† (1.06–1.48)	1.27‡ (1.10–1.47)	NR

Table 6.11 Continued

Study	Population age (years)/ location	Definition of wheeze	Prevalence in unexposed (%)	Odds ratio for smoking (95% confidence interval)	
				Either parent (unadjusted)	Either parent (adjusted)
Moyes et al. 1995	6–7 New Zealand	Current	23	1.06 (0.88–1.27)	NR
	13–14 New Zealand	Current	28	1.16 (0.98–1.37)	NR
Stoddard and Miller 1995	0–17 United States	Current (or asthma)[§]	NR	NR	NR
	0–2 United States	Current (or asthma)	11.6	NR	NR
	3–5 United States	Current (or asthma)	8	NR	NR
	6–12 United States	Current (or asthma)	7.5	NR	NR
	13–17 United States	Current (or asthma)	8.5	NR	NR
Volkmer et al. 1995	4–5 Australia	In the past year	NR	1.12 (NR)	Not significant[§]
	4–5 Australia	Ever	NR	1.24 (NR)	1.18 (1.08–1.30)
Abuekteish et al. 1996	6–12 Jordan	In the past 3 years	12.4[Δ]	NR	NR
Peters et al. 1996	10–13 Hong Kong	NR	7.1[Δ]	NR	1.01 (0.79–1.29)
Wright et al. 1996	6 United States	Current	26.4	1.32 (0.98–1.80)	NR
Austin and Russell 1997	12 and 14 United Kingdom	Current	16.6	1.13 (0.87–1.48)	NR
Butland et al. 1997	7.5–8.5 United Kingdom	≤4 attacks in the past year; parent questionnaire	6.6	NR	NR
	7.5–8.5 United Kingdom	>4 attacks in the past year; parent questionnaire	2.6	NR	NR
Hu et al. 1997	10–11 United States (Chicago)	In the past year	29.0	NR	NR

Odds ratio for smoking (95% confidence interval)				
One parent only vs. neither	**Both parents vs. neither**	**Mother only vs. neither**	**Father only vs. neither**	**Confounders adjusted for**
NR	NR	NR	NR	NR
NR	NR	NR	NR	NR
NR	NR	1.36 (1.14–1.62)	0.83 (0.67–1.02)	Gender, race, area, SES, family size
NR	NR	1.90 (1.23–2.94)	NR	Gender, race, area, SES, family size
NR	NR	1.53 (0.99–2.37)	NR	Gender, race, area, SES, family size
NR	NR	1.35 (1.01–1.81)	NR	Gender, race, area, SES, family size
NR	NR	1.07 (0.76–1.49)	NR	Gender, race, area, SES, family size
NR	NR	NR	NR	Method of heating and ventilating
NR	NR	NR	NR	Method of heating and ventilating
NR	NR	1.87† (1.28–2.75)	1.31‡ (1.05–1.63)	NR
0.94 (0.69–1.28)	1.70 (1.15–2.54)	NR	NR	Age, gender, district, father's education, housing
NR	NR	NR	NR	NR
NR	NR	1.15 (0.84–1.56)	NR	NR
NR	NR	1.27** (0.93–1.74)	1.04†† (0.76–1.43)	Study period
NR	NR	1.55** (1.02–2.34)	1.06†† (0.69–1.62)	Study period
NR	NR	0.79 (0.51–1.21)	NR	None

Table 6.11 Continued

Study	Population age (years)/ location	Definition of wheeze	Prevalence in unexposed (%)	Odds ratio for smoking (95% confidence interval)	
				Either parent (unadjusted)	Either parent (adjusted)
Leung et al. 1997	13–14 Hong Kong	Current[‡‡]	12[Δ]	1.14 (0.92–1.42)	NR
	13–14 Hong Kong	Severe attack[‡‡]	2.4[Δ]	1.05[§] (0.64–1.74)	NR
Maier et al. 1997	5–9 United States (Washington state)	In the past year (no asthma diagnosis)	7[Δ]	1.7 (1.0–2.9)	1.8 (1.0–3.2)
Selçuk et al. 1997	7–12 Turkey	Ever	16.1	1.29 (1.10–1.51)	1.25[§] (1.05–1.48)
	7–12 Turkey	Current	4.1	1.39 (1.02–1.90)	1.52 (1.10–2.09)
Chhabra et al. 1998	4–17 India	Current wheeze	15.3	1.62 (1.27–2.05)	NR
Kendirli et al. 1998	6–14 Turkey	Wheeze (ever)	8.4	1.63 (1.29–2.08)	NR
Lam et al. 1998	12–15 Hong Kong	In the past 3 months	4.8	NR	NR
Lewis and Britton 1998	16 United Kingdom	Current wheeze	NR	NR	NR
Lewis et al. 1998	8–11 Australia	>3 episodes of wheeze in the past year	8.6	NR	1.16 (0.85–1.59)
Peters et al. 1998	8–13 Hong Kong	Physician consultation for wheeze in the past 3 months	2.2	1.22 (0.96–1.57)	NR
Saraçlar et al. 1998	7–14 Turkey	Ever (International Study of Asthma and Allergy in Childhood [ISAAC])	4.7[Δ]	NR	1.33 (1.03–1.76)
Withers et al. 1998	14–16 United Kingdom	Current wheeze	18.2[Δ]	NR	1.48 (1.17–1.88)
Agabiti et al. 1999	6–7 Italy	Wheeze in the past year (no asthma diagnosis); parent questionnaire	5.2	1.09 (0.90–1.32)	1.13 (0.93–1.37)
	13–14 Italy	Wheeze in the past year (no asthma diagnosis); child questionnaire	8.4	1.42 (1.23–1.63)	1.24 (1.07–1.44)

Odds ratio for smoking (95% confidence interval)				
One parent only vs. neither	**Both parents vs. neither**	**Mother only vs. neither**	**Father only vs. neither**	**Confounders adjusted for**
NR	NR	NR	NR	NR
NR	NR	NR	NR	NR
NR	NR	NR	NR	Gender, ethnicity, allergy, SES, parental asthma
NR	NR	NR	NR	Age, gender, place, animals, atopic family, breastfeeding
NR	NR	NR	NR	NR
NR	NR	NR	NR	NR
NR	NR	NR	NR	NR
1.21 (0.91–1.60)	NR	1.71 (0.84–3.49)	1.24[††] (0.93–1.64)	Age, gender, area, housing type
NR	NR	1.27** (1.16–1.39)	NR	Gender, SES, breastfeeding, maternal age, parity, birth weight, gestational age
NR	NR	NR	NR	Age, gender, PM_{10}[§§], SO_2[ΔΔ], gas heating, maternal allergy
1.04 (0.76–1.41)	1.57 (1.02–2.43)	NR	NR	Age, gender, housing type, area, father's education
NR	NR	NR	NR	Age, gender, pets, parental atopy, SES
NR	NR	p >0.05	p >0.05	Maternal asthma, child eczema and hay fever, atopic sibling, pets, gas cooking; active smoking was "not significant"
NR	1.24 (0.99–1.56)	1.18 (1.0–1.39)	1.14 (0.97–1.36)	Age, gender, area, father's education, crowding, dampness, gas heating, parental asthma, other smokers
NR	1.31 (1.11–1.56)	1.26 (1.13–1.41)	1.09 (0.96–1.24)	Age, gender, area, father's education, crowding, dampness, gas heating, parental asthma, other smokers, active smoking

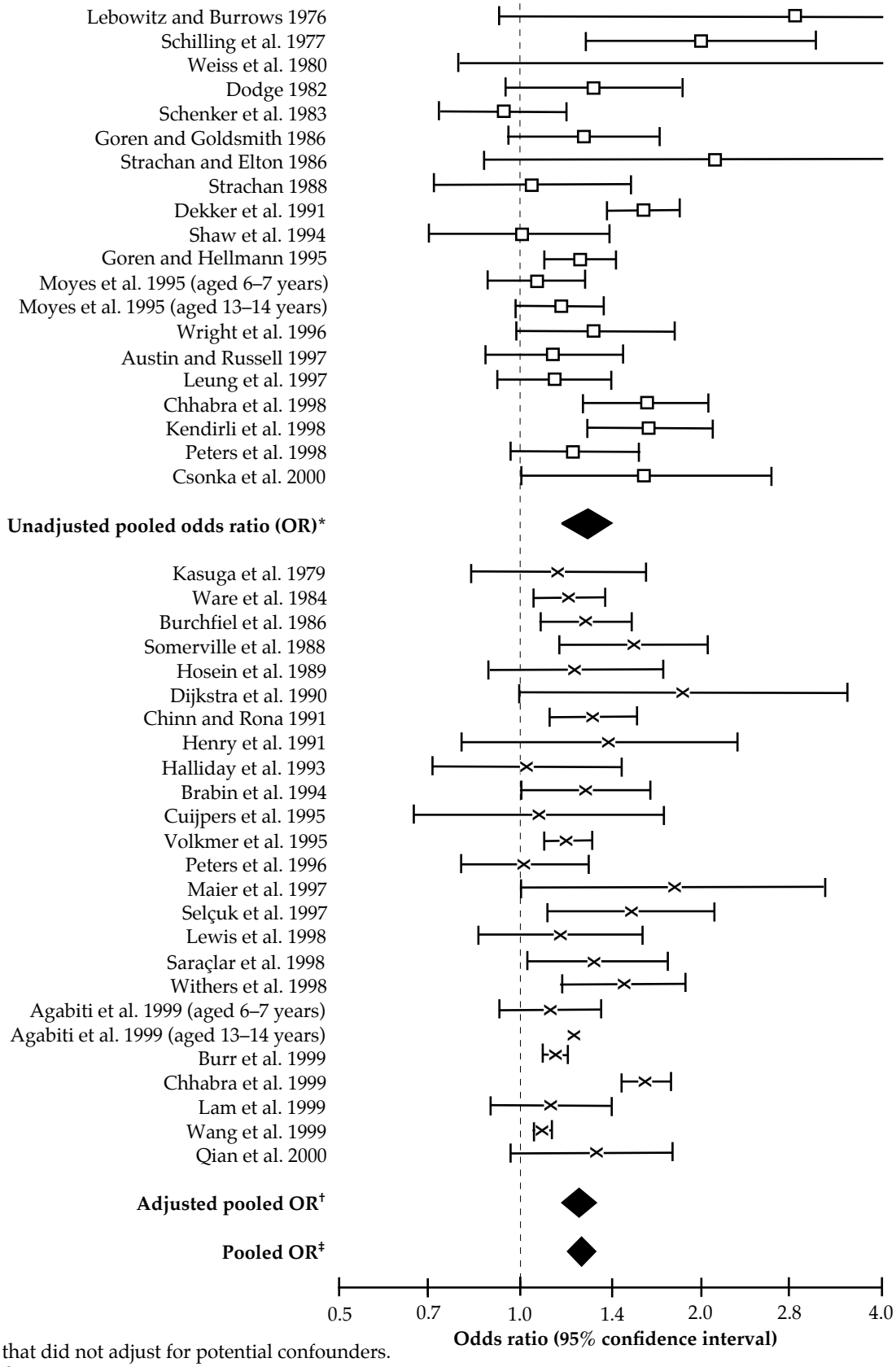
Table 6.11 Continued

Study	Population age (years)/ location	Definition of wheeze	Prevalence in unexposed (%)	Odds ratio for smoking (95% confidence interval)	
				Either parent (unadjusted)	Either parent (adjusted)
Belousova et al. 1999	8–11 Australia	Wheeze in the past year	23.8	NR	NR
Burr et al. 1999	12–14 United Kingdom	Wheeze in the past 12 months; child questionnaire	31.8	1.22 (1.15–1.28)	1.14[¶¶] (1.09–1.19)
	12–14 United Kingdom	Speech-limiting wheeze in the past 12 months	7.6	1.40 (1.28–1.52)	1.27[§,¶¶] (1.17–1.36)
Chhabra et al. 1999	5–17 India	Current wheeze (definition unclear)	10.8	1.69 (NR)	1.61 (1.47–1.78)
Lam et al. 1999	8–13 Hong Kong	Wheeze (ever)	9.6	NR	1.12 (0.89–1.41)[¶¶]
Shamssain and Shamsian 1999	6–7 United Kingdom	Wheeze in the past year	15.5	NR	NR
	6–7 United Kingdom	Speech-limiting attack in the past year	2.7	NR	NR
	6–7 United Kingdom	Wheeze (ever)	25.6	NR	NR
Wang et al. 1999	11–16 Taiwan	Wheeze in the past year; video; written questionnaires	13.2	1.02 (0.99–1.05)	1.08 (1.05–1.12)
Csonka et al. 2000	6–13 Finland	Current wheeze or asthma	>9.6	1.6 (1.0–2.6)	NR
Qian et al. 2000	5–14 China	Wheeze (ever)	6.9–17.4	NR	1.31 (0.96–1.78)

*NR = Data were not reported.
[†]Mother currently smoked vs. did not smoke.
[‡]Father currently smoked vs. did not smoke.
[§]Not included in the meta-analysis.
[Δ]Overall prevalence.
[¶]Primary caregiver smoked vs. did not smoke.
**Mother smoked vs. did not smoke prenatally.
[††]Father smoked vs. neither parent smoked where only 2.5% of the mothers smoked.
[‡‡]Based on a written questionnaire.
[§§]PM_{10} = Particulate matter (levels of particles [particulate pollution] with an aerodynamic diameter of less than 10 micrometers).
[ΔΔ]SO_2 = Sulfur dioxide.
[¶¶]Derived from pooled results of all household smokers.

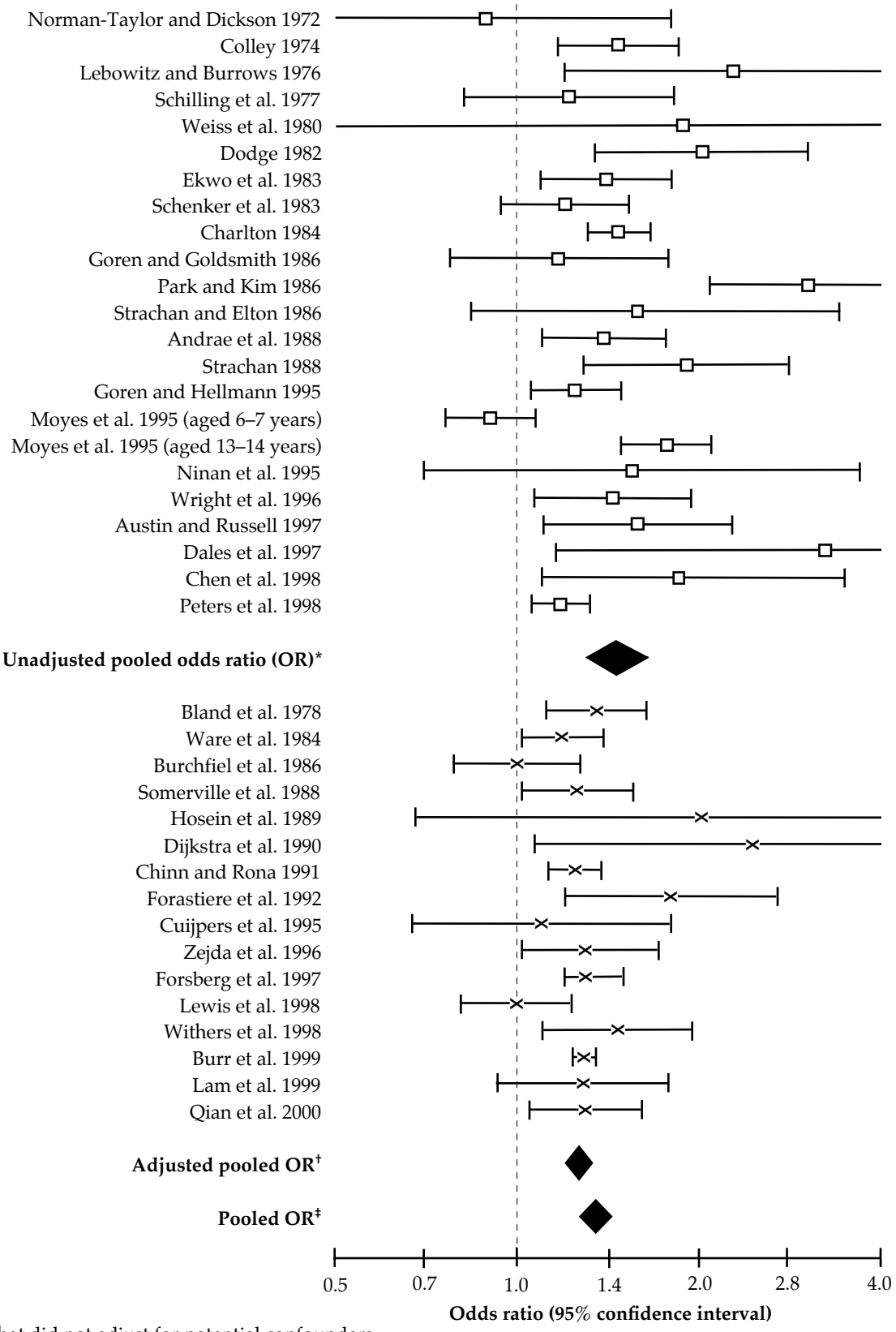
Odds ratio for smoking (95% confidence interval)				
One parent only vs. neither	**Both parents vs. neither**	**Mother only vs. neither**	**Father only vs. neither**	**Confounders adjusted for**
NR	NR	1.33† (1.2–1.5)	NR	Atopy, parental asthma, early life bronchitis
NR	NR	NR	NR	Gender, area, pets, cooking fuel, heating fuel, housing type, active smoking
NR	NR	NR	NR	Gender, area, pets, cooking fuel, heating fuel, housing type, active smoking
NR	NR	NR	NR	Age, gender, family atopy
NR	NR	NR	NR	Age, gender, area, active smoking
1.11 (NR)	1.50 (NR)	1.15 (0.86–1.54)	NR	None
NR	NR	1.12 (0.66–1.90)	NR	None
NR	NR	1.46 (1.19–1.79)	NR	None
NR	NR	NR	NR	Age, gender, parental education, area, Chinese incense, exercise, active smoking, alcohol consumption
NR	NR	NR	NR	NR
NR	NR	NR	NR	Age, gender, ventilation, family history, mother's education, coal use, area

Figure 6.6 Odds ratios for the effect of smoking by either parent on wheeze prevalence



*Studies that did not adjust for potential confounders.
†Studies that adjusted for a variety of potential confounders.
‡Based on all studies.

Figure 6.7 Odds ratios for the effect of smoking by either parent on cough prevalence



*Studies that did not adjust for potential confounders.
†Studies that adjusted for a variety of potential confounders.
‡Based on all studies.

Table 6.12 Studies of cough prevalence associated with parental smoking

Study	Population age (years)/ location	Definition of cough	Prevalence in unexposed (%)	Odds ratio for smoking (95% confidence interval)	
				Either parent (unadjusted)	Either parent (adjusted)
Norman-Taylor and Dickinson 1972	5 United Kingdom	Recent recurrence	3.1	0.89 (0.44–1.80)	NR*
Colley 1974	6–14 United Kingdom	Usually, in winter	14.7	1.47 (1.17–1.85)	NR
Lebowitz and Burrows 1976	0–15 United States	Persistent	4.8	2.28 (1.20–4.32)	NR
Schilling et al. 1977	7–18 United States	Cough and/or phlegm, usually (definition unclear)	12.8	1.22 (0.82–1.82)	NR
Bland et al. 1978	11–12 United Kingdom	Day or night	19.4	1.56 (1.36–1.79)	1.36 (1.12–1.64)
Weiss et al. 1980	5–9 United States	Cough and phlegm	1.7	1.88 (0.24–15.0)	NR
Dodge 1982	8–12 United States	NR	14.1	2.03 (1.35–3.06)	NR
Ekwo et al. 1983	6–12 United States	With colds	30	1.40 (1.09–1.80)	NR
Schenker et al. 1983	5–14 United States	Chronic	6.3	1.21 (0.95–1.54)	NR
Charlton 1984	8–19 United Kingdom	Frequent recurrences	22	1.47 (1.31–1.66)	NR
	8–10 United Kingdom	Frequent recurrences	33.5	1.60† (1.33–1.96)	NR
	11–13 United Kingdom	Frequent recurrences	17.5	1.50† (1.26–1.79)	NR
	14–19 United Kingdom	Frequent recurrences	8.5	1.12† (0.83–1.52)	NR
Ware et al. 1984	6–9 United States	Persistent	7.7	NR	1.19 (1.02–1.39)
Burchfiel et al. 1986	0–19 United States	NR	8.5	NR	1.0 (0.78–1.27)
Goren and Goldsmith 1986	2nd and 5th graders Israel	With sputum	6	1.17 (0.77–1.78)	NR

Odds ratio for smoking (95% confidence interval)				
One parent only vs. neither	**Both parents vs. neither**	**Mother only vs. neither**	**Father only vs. neither**	**Confounders adjusted for**
0.62 (0.25–1.46)	1.4 (0.61–3.2)	NR	NR	NR
1.25 (0.94–1.66)	1.66 (1.28–2.16)	NR	NR	NR
NR	NR	NR	NR	NR
1.06 (0.68–1.63)	1.99 (1.06–3.73)	1.1 (0.56–2.15)	1.04 (0.64–1.69)	NR
1.2 (0.96–1.49)	1.57 (1.25–1.94)	NR	NR	Active smoking, gender
1.64 (0.18–15.0)	2.09 (0.25–17.8)	NR	NR	NR
1.84 (1.15–2.95)	2.29 (1.41–3.73)	NR	NR	NR
1.33 (1.0–1.78)	1.50 (1.10–2.04)	1.38 (0.87–2.17)	1.32 (0.96–1.80)	NR
1.12 (0.84–1.49)	1.35 (1.0–1.83)	NR	NR	NR
1.36 (1.19–1.56)	1.64 (1.41–1.91)	1.36 (1.15–1.62)	1.34 (1.13–1.59)	NR
NR	NR	NR	NR	NR
NR	NR	NR	NR	NR
NR	NR	NR	NR	NR
1.09 (0.91–1.30)	1.38 (1.16–1.63)	0.99 (0.75–1.29)	1.13 (0.94–1.36)	Age, gender, city
0.93 (0.67–1.30)	1.27 (0.89–1.81)	0.78 (0.37–1.64)	0.97 (0.67–1.41)	Age, gender, parental education
NR	NR	1.22 (0.72–2.07)	1.15 (0.73–1.81)	NR

Table 6.12 Continued

Study	Population age (years)/ location	Definition of cough	Prevalence in unexposed (%)	Odds ratio for smoking (95% confidence interval)	
				Either parent (unadjusted)	Either parent (adjusted)
Park and Kim 1986	0–14 Korea	In the past 2 weeks	5	3.04 (2.09–4.43)	NR
Strachan and Elton 1986	7–8 United Kingdom	Night	49.1	1.7 (0.85–3.44)	NR
Andrae et al. 1988	6 months–16 years Sweden	Exercise induced	5.1	1.39 (1.10–1.76)	NR
Somerville et al. 1988	5–11 United Kingdom	Usually in the morning	4	1.24 (1.0–1.53)	1.24† (0.94–1.65)
	5–11 United Kingdom	Usually day/night	8	1.46 (1.27–1.68)	1.26 (1.02–1.56)
Strachan 1988	7 United Kingdom	At night in the past month	9	1.91 (1.29–2.82)	NR
Hosein et al. 1989	7–17 United States	Persistent	0.9	NR	2.02 (0.68–6.03)
Stern et al. 1989a	7–12 Canada	With phlegm	5.3	NR	NR
Stern et al. 1989b	7–12 Canada	Persistent	8‡	NR	NR
Dijkstra et al. 1990	6–12 Netherlands	Persistent	4.6‡	NR	2.46 (1.07–5.64)
Chinn and Rona 1991	5–11 United Kingdom	Usually	NR	NR	1.25 (1.13–1.38)
Forastiere et al. 1992	7–11 Italy	With phlegm	5.5	1.3 (NR)	1.3† (0.9–1.9)
	7–11 Italy	Night	3.4	1.8 (NR)	1.8 (1.2–2.7)
Bråbäck et al. 1995	10–12 Sweden	Night	8.4	NR	NR
	10–12 Poland	Night	6.7	NR	NR
	10–12 Estonia	Night	7.4	NR	NR

Odds ratio for smoking (95% confidence interval)				
One parent only vs. neither	**Both parents vs. neither**	**Mother only vs. neither**	**Father only vs. neither**	**Confounders adjusted for**
3.2 (2.11–4.85)	3.0 (2.05–4.38)	NR	NR	NR
NR	NR	NR	NR	NR
NR	NR	NR	NR	NR
NR	NR	NR	NR	Age, gender, birth weight, obesity, socioeconomic status (SES), mother's age, number of siblings
NR	NR	NR	NR	Age, gender, birth weight, obesity, SES, mother's age, number of siblings
1.64 (1.05–2.56)	2.45 (1.5–4.02)	NR	NR	NR
1.84 (0.55–6.18)	2.23 (0.69–7.19)	NR	NR	Gender, active smoking
NR	NR	0.98 (0.60–1.62)	0.85 (0.52–1.39)	NR
NR	NR	1.45[§] (1.13–1.87)	NR	NR
NR	NR	NR	NR	Age, parental education
NR	NR	NR	NR	Age, gender, country, birth weight, obesity, SES, mother's age, number of siblings, ethnicity, gas cooking
NR	1.7 (1.1–2.5)	1.2 (0.7–2.0)	1.0 (0.7–1.6)	Age, gender, area, SES
NR	2.5 (1.6–3.9)	1.5 (0.8–2.8)	1.2 (0.8–2.0)	Age, gender, area, SES
NR	NR	2.09[Δ] (1.51–2.90)	NR	Gender, atopy, dampness, overcrowding
NR	NR	1.10[Δ] (0.62–1.93)	NR	Gender, atopy, dampness, overcrowding
NR	NR	2.27[Δ] (1.55–3.32)	NR	Gender, atopy, dampness, overcrowding

Table 6.12 Continued

Study	Population age (years)/ location	Definition of cough	Prevalence in unexposed (%)	Odds ratio for smoking (95% confidence interval)	
				Either parent (unadjusted)	Either parent (adjusted)
Cuijpers et al. 1995	6–12 Netherlands	Chronic	12.6‡	NR	1.10 (0.67–1.8)
Goren and Hellmann 1995	2nd and 5th graders Israel	With sputum	8.1	1.25 (1.06–1.49)	NR
Moyes et al. 1995	6–7 New Zealand	Night	30	0.91 (0.77–1.08)	NR
	13–14 New Zealand	Night	24	1.78 (1.50–2.11)	NR
Ninan et al. 1995	8–13 United Kingdom	Isolated, persistent, nocturnal	NR	1.61 (0.70–3.70)	NR
Volkmer et al. 1995†	4–5 Australia	Dry	NR	Not significant	Not significant
Wright et al. 1996	6 United States	Persistent	27.4	1.44** (1.07–1.94)	NR
	6 United States	Persistent, without wheeze	11.8	1.67†,** (1.10–2.54)	1.93†,** (1.09–3.45)
Zejda et al. 1996	7–9 Poland	Chronic	31.9‡	NR	1.3 (1.02–1.71)
Austin and Russell 1997	12 and 14 United Kingdom	Chronic	7.2	1.58 (1.11–2.27)	NR
Dales et al. 1997	NR Canada	Recorded night cough	86	3.25 (1.16–9.09)	NR
Forsberg et al. 1997	6–12 Scandinavia	Dry cough at night apart from colds in the past year	8–19‡	NR	1.3 (1.2–1.5)
Chen et al. 1998	6–17 Canada	Night	5.5‡	1.97 (1.10–3.52)	NR
Lam et al. 1998	12–15 Hong Kong	Saw a physician for cough in the past 3 months	7.3	NR	NR

Odds ratio for smoking (95% confidence interval)				
One parent only vs. neither	**Both parents vs. neither**	**Mother only vs. neither**	**Father only vs. neither**	**Confounders adjusted for**
NR	NR	NR	NR	NR
1.12 (0.93–1.36)	1.51 (1.22–1.87)	1.42[Δ] (1.17–1.73)	1.25[¶] (1.05–1.48)	Age, gender, dampness, father's education, dog, unvented geyser
NR	NR	NR	NR	NR
NR	NR	NR	NR	NR
NR	NR	NR	NR	NR
NR	NR	NR	NR	NR
NR	NR	NR	NR	NR
NR	NR	NR	NR	Gender, hay fever, lower respiratory infection in the first year
NR	NR	NR	NR	Crowding
NR	NR	1.93 (1.30–2.85)	NR	NR
NR	NR	NR	NR	NR
NR	NR	NR	NR	Age, gender, area, fitted carpets, pets, mold, stove use, parental asthma, early day care
2.01 (1.04–3.88)	1.91 (0.84–4.33)	NR	NR	None
1.19 (0.94–1.51)	NR	0.73 (0.32–1.70)	1.31[††] (1.03–1.65)	Age, gender, area, housing type

Table 6.12 Continued

Study	Population age (years)/ location	Definition of cough	Prevalence in unexposed (%)	Odds ratio for smoking (95% confidence interval)	
				Either parent (unadjusted)	Either parent (adjusted)
Lewis et al. 1998	8–11 Australia	Dry night cough that lasted >2 weeks in the past 12 months without a cold	19.1	NR	1.0 (0.81–1.23)
Peters et al. 1998	8–13 Hong Kong	Physician consultation for cough in the past 3 months	12.5	1.18 (1.06–1.32)	NR
Withers et al. 1998	14–16 United Kingdom	Current	12.4‡	NR	1.47 (1.11–1.95)
Burr et al. 1999	12–14 United Kingdom	Cough without colds in the past 12 months	25.5	1.49 (1.41–1.57)	1.29ΔΔ (1.24–1.35)
Lam et al. 1999	8–13 Hong Kong	Cough for 3 months	4.8	NR	1.29¶¶ (0.93–1.78)
Shamssain and Shamsian 1999	6–7 United Kingdom	Nighttime cough in the past 12 months	NR	NR	NR
Qian et al. 2000	5–14 China	Often, with or without colds	41–84	NR	1.30 (1.05–1.61)

*NR = Data were not reported.
†Not included in the meta-analysis.
‡Overall prevalence.
§Mother smoked vs. did not smoke during pregnancy and infancy.
ΔMother currently smoked vs. did not smoke.
¶Father currently smoked vs. did not smoke.
**Reference group = Children without cough or wheeze.
††Father smoked vs. neither parent smoked where only 2.5% of the mothers smoked.
‡‡PM_{10} = Particulate matter (levels of particles [particulate pollution] with an aerodynamic diameter of less than 10 micrometers).
§§SO_2 = Sulfur dioxide.
ΔΔDerived from pooled results of all household smokers.
¶¶Analyses excluded active smokers.

Odds ratio for smoking (95% confidence interval)				
One parent only vs. neither	**Both parents vs. neither**	**Mother only vs. neither**	**Father only vs. neither**	**Confounders adjusted for**
NR	NR	NR	NR	Age, gender, PM_{10}[##], SO_2[§§], gas heating, maternal allergy
1.15 (1.01–1.32)	1.33 (1.08–1.64)	NR	NR	Age, gender, housing type, area, father's education
NR	NR	p >0.05	p >0.05	Maternal hay fever, child's eczema and hay fever, active smoking, single parent
NR	NR	NR	NR	Gender, area, pets, cooking and heating fuel, housing type, active smoking
NR	NR	NR	NR	Age, gender, area, active smoking
1.04 (NR)	1.10 (NR)	1.05 (0.85–1.29)	NR	None
NR	NR	NR	NR	Age, gender, ventilation, family history, mother's education, coal use, area

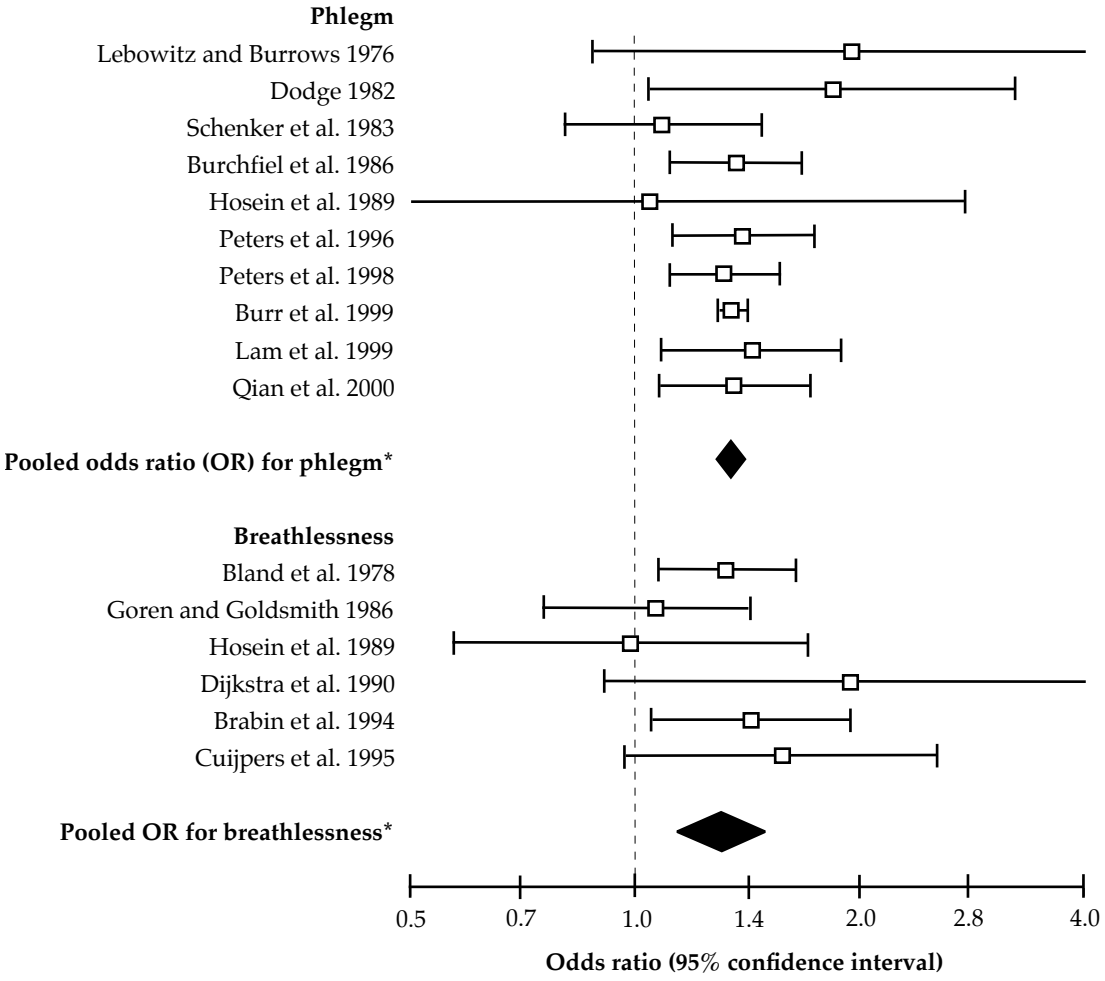
Table 6.13 Studies of phlegm and breathlessness associated with parental smoking

Study	Population age (years)/ location	Prevalence in unexposed (%)	Odds ratio for smoking (95% confidence interval)		
			Either parent (unadjusted)	Either parent (adjusted)	One parent
Lebowitz and Burrows 1976	0–15 United States	3.1	1.96 (0.88–4.38)	NR*	NR
Bland et al. 1978	11–12 United Kingdom	9.8	1.42 (1.22–1.66)	1.33 (1.08–1.65)	1.26 (0.99–1.60)
Dodge 1982	8–12 United States	6.7	1.85 (1.05–3.25)	NR	1.77 (0.93–3.37)
Schenker et al. 1983	5–14 United States	4.1	1.09 (0.81–1.48)	NR	1.18 (0.84–1.67)
Burchfiel et al. 1986	0–19 United States	11	NR	1.37 (1.12–1.68)	1.25 (0.95–1.65)
Goren and Goldsmith 1986	2nd and 5th graders Israel	10.7	1.07 (0.76–1.43)	NR	NR
Hosein et al. 1989	7–17 United States	1.4	NR	1.05 (0.40–2.79)	0.76 (0.23–2.51)
	7–12 United States	4.6	NR	0.99 (0.57–1.71)	1.05 (0.57–1.95)
Stern et al. 1989b	7–12 Canada	8.0†	NR	NR	NR
Dijkstra et al. 1990	6–12 Netherlands	4.6†	NR	1.95 (0.91–4.19)	NR
Brabin et al. 1994	5–11 United Kingdom	10	1.54 (1.13–2.09)	1.44 (1.06–1.95)	NR
Cuijpers et al. 1995	6–12 Netherlands	11.9†	NR	1.58 (0.98–2.56)	NR
Peters et al. 1996	10–13 Hong Kong	8.7†	NR	1.40 (1.13–1.75)	1.26 (0.96–1.64)
Lam et al. 1998	12–15 Hong Kong	4.8	NR	NR	1.14 (0.86–1.52)
Peters et al. 1998	8–13 Hong Kong	4.7	1.32 (1.12–1.57)	NR	1.26 (1.02–1.54)
Burr et al. 1999	12–14 United Kingdom	17.7	1.58 (1.48–1.67)	1.35Δ (1.30–1.42)	NR
Lam et al. 1999	8–13 Hong Kong	6.7	NR	1.44 (1.09–1.90)	NR
Qian et al. 2000	5–14 China	14–57	NR	1.36 (1.08–1.72)	NR

*NR = Data were not reported.
†Overall prevalence.
‡Mother currently smoked vs. did not smoke.
§Father smoked vs. neither parent smoked where only 2.5% of the mothers smoked.
ΔDerived from pooled results for all household smokers.

Odds ratio for smoking (95% confidence interval)				
Both parents	**Mother only**	**Father only**	**Outcome**	**Confounders adjusted for**
NR	NR	NR	Persistent phlegm	NR
1.42 (1.11–1.83)	NR	NR	Shortness of breath (SOB) on exertion	Gender, active smoking
1.95 (1.0–3.81)	NR	NR	Sputum	NR
0.98 (0.66–1.49)	NR	NR	Chronic phlegm	NR
1.53 (1.14–2.05)	1.3 (0.71–2.39)	1.24 (0.91–1.70)	Phlegm	Age, gender, socioeconomic status, family size
NR	1.26 (0.85–1.87)	0.92 (0.64–1.32)	SOB	NR
1.37 (0.47–4.03)	NR	NR	Persistent phlegm	Gender
0.93 (0.49–1.77)	NR	NR	SOB when hurrying	Gender, active smoking
NR	1.15‡ (0.90–1.47)	NR	Persistent phlegm	Parental symptoms, gas cooking (not area)
NR	NR	NR	SOB plus wheeze in the past year	Age, parental education (not school)
NR	NR	NR	SOB (ever)	Area
NR	NR	NR	SOB	Age, gender, dampness, father's education, dog, unvented geyser
1.75 (1.19–2.56)	NR	NR	Phlegm	Age, gender, area, housing type, father's education
NR	2.03 (1.05–3.92)	1.22§ (0.92–1.62)	Phlegm in the past 3 months	Age, gender, area, housing type
1.33 (0.97–1.83)	NR	NR	Physician diagnosis of phlegm in the past 3 months	Age, gender, housing type, area, father's education
1.38 (1.25–1.53)	1.24 (1.12–1.37)	1.26 (1.14–1.38)	Phlegm without colds in the past 12 months	Gender, area, pets, cooking and heating fuel, housing type, active smoking
NR	NR	NR	Phlegm in the past 3 months	Age, gender, area, active smoking
NR	NR	NR	Frequent phlegm	Age, gender, ventilation, family history, mother's education, coal use, area

Figure 6.8 Odds ratios for the effect of smoking by either parent on phlegm and breathlessness



*Adjusted and unadjusted studies.

study found stronger effects of maternal smoking during pregnancy compared with current postnatal maternal smoking (Hu et al. 1997).

A study in Tasmania found that prenatal and postnatal exposure had similar health effects, with some evidence for an effect of smoking in the child's presence (Ponsonby et al. 2000). A Swedish study reported a borderline significant effect from maternal smoking during pregnancy (1.4 [95 percent CI, 1.0–2.0]) but no effect from current parental smoking (1.0 [95 percent CI, 0.7–1.4]) (Nilsson et al. 1999). The Italian collaborative group study tended to find greater ORs in preadolescent children from prenatal maternal smoking than from current maternal smoking, but not among adolescents (Agabiti et al. 1999). Moreover, the authors acknowledged that even in this very large study, disentangling current from past effects was problematic.

Raised ORs for respiratory symptoms in studies from China (Qian et al. 2000), Hong Kong (Lau et al. 1995; Peters et al. 1996, 1998; Leung et al. 1997; Lam et al. 1998, 1999), and Taiwan (Wang et al. 1999), where maternal smoking is uncommon, also suggest a role for postnatal secondhand smoke exposure. One Hong Kong study found that symptoms were more strongly related to smoking by grandparents than by fathers, which fit the role of grandparents as caregivers (Lam et al. 1999).

Table 6.14 Summary of pooled random effects (odds ratios) of respiratory symptoms associated with parental smoking

Symptom	Number of studies	Odds ratio for smoking (95% confidence interval)				
		Either parent	One parent	Both parents	Mother only	Father only
Asthma	31*	1.23 (1.14–1.33)				
	7		1.01 (0.84–1.22)			
	10			1.42 (1.30–1.56)		
	21				1.33 (1.24–1.43)	
	12					1.07 (0.97–1.18)
Wheeze[†]	45*,[‡]	1.26 (1.20–1.33)				
	13		1.18 (1.10–1.26)			
	14			1.41 (1.23–1.63)		
	27[§]				1.28 (1.21–1.35)	
	14					1.13 (1.08–1.20)
Cough	39	1.35 (1.27–1.43)				
	18		1.27 (1.14–1.41)			
	18			1.64 (1.48–1.81)		
	16[§]				1.34 (1.17–1.54)	
	10					1.22 (1.12–1.32)
Phlegm[Δ]	10	1.35 (1.30–1.41)				
	7		1.24 (1.10–1.39)			
	6			1.42 (1.19–1.70)		
Breathlessness[Δ]	6	1.31 (1.14–1.50)				

*Two age groups from Moyes et al. 1995 were included as separate studies.
[†]Excluded the European Communities Study, which had a pooled odds ratio of 1.20.
[‡]Agabiti et al. 1999 was included as two separate studies.
[§]Bråbäck et al. 1995 was included as three separate studies.
[Δ]Data for phlegm and breathlessness are restricted because several comparisons were based on fewer than five studies.

Former Parental Smoking

On balance, limited evidence suggests that there is no increase in the prevalence of respiratory symptoms among children of former smokers (Colley 1974; Shaw et al. 1994). Symptom prevalence seems to be more closely related to current maternal smoking than to prenatal maternal smoking (Søyseth et al. 1995; Beckett et al. 1996; Mannino et al. 2001), although the data are not entirely consistent (Agabiti et al. 1999). Although the data are compatible with the hypothesis that current rather than past exposure makes the predominant contribution to symptoms, the evidence is not strong. There are only a few relevant studies. One major limitation of these studies is that the exposure data were not collected prospectively and consequently, recall bias is a potential problem.

Publication Bias and Wheeze

Researchers have found evidence of publication bias, particularly for wheeze, in small published studies that have higher ORs. Some studies that reported estimated effects and confidence limits only for those exposure and outcome combinations that were statistically significant further sugest publication bias (Withers et al. 1998). However, the effect of this source of bias on the pooled ORs is small because there are so many large published studies. The similarity between the pooled OR for wheeze in published studies and in the unpublished EC Study provides further reassurance that the association is not an artifact of selective publication. Notably, however, the two EC centers whose published data have appeared in journals—Middlesbrough (Melia et al. 1982) and Ardennes

Table 6.15 Summary of pooled random effects (odds ratios) associated with parental smoking restricted to studies of children aged ≤11 years

Symptom	Number of studies	Odds ratio for smoking (95% confidence interval)				
		Either parent	One parent	Both parents	Mother only	Father only
Asthma	13	1.18 (1.06–1.31)				
			Insufficient			
	5		studies	1.47 (1.29–1.68)		
	7				1.31 (1.15–1.50)	
	4					1.13 (0.99–1.29)
Wheeze*	15	1.27 (1.16–1.38)				
	4		1.21 (1.10–1.45)			
	5			1.41 (1.16–1.71)		
	8				1.26 (1.15–1.38)	
	5					1.10 (1.02–1.20)
Cough	13	1.28 (1.13–1.44)				
	4		1.17 (0.84–1.61)			
	5			1.85 (1.29–2.64)		
	4				1.07 (0.91–1.24)	
	3					1.12 (0.95–1.38)

Note: The symptoms "phlegm" and "breathlessness" were not included in this table because of an insufficient number of studies.
*Excluded the European Communities Study, which had a pooled odds ratio of 1.20.

(Gepts et al. 1978)—had ORs of 1.36 and 1.37, respectively, which were above the overall average for the EC Study.

Evidence Synthesis

This report has described multiple mechanisms by which secondhand smoke exposure could increase the prevalence of respiratory symptoms and asthma in childhood. Secondhand smoke exposure might increase the prevalence of respiratory symptoms and asthma through in utero effects or through inflammation and an altered lung immunophenotype from postnatal exposure. Multiple studies from diverse countries consistently show that parental smoking is positively associated with the prevalence of asthma and respiratory symptoms (including wheeze) in schoolchildren; the findings of individual studies as well as the pooled analyses show that these associations are unlikely to be attributable to chance alone. The magnitude of the effects is similar for the different outcome measures. The estimated effects, particularly for wheeze, were robust to adjustments for a wide range of potentially confounding environmental and other factors. This robustness supports the conclusion that residual confounding is unlikely to be an issue and that the associations between parental smoking and the prevalence of asthma and respiratory symptoms in schoolchildren are causal.

The case for a causal interpretation is further strengthened by the trend for the OR to increase with the number of parents who smoke (i.e., none, one, or both). In the meta-analysis, the trends with the number of smoking parents were statistically significant for asthma, wheeze, and cough, and trends were evident in most of the individual studies as well. The effect of maternal smoking is greater than that of paternal smoking, but there is nevertheless evidence for a small effect of paternal smoking. Maternal smoking is associated with higher cotinine levels in school-age children, implying that maternal smoking probably has a greater impact on the exposure of children to secondhand smoke (Cook et al. 1994). These results also imply that the increased risk for asthma and other symptoms reflects postnatal exposure, although prenatal exposure may also be a contributing factor. First, there is an effect of paternal smoking; second, risk tends to rise with the number of

household smokers; third, many women who do not smoke while pregnant smoke after the birth of their children; and fourth, limited evidence shows no increase in symptoms in children of former smokers. Few studies have examined dose-response trends with the number of cigarettes smoked in the household per day or dose-response trends among exposed children alone.

The prevalence of symptoms ascertained by cross-sectional surveys is determined by both disease incidence and prognosis, and the pattern of morbidity tends to be dominated by a large number of children with mild symptoms. There are indications that secondhand smoke exposure is associated with more severe wheeze, both in studies where ORs were reported for different severity measures and in studies where ORs were highest when the prevalence of wheeze was low.

Conclusions

1. The evidence is sufficient to infer a causal relationship between parental smoking and cough, phlegm, wheeze, and breathlessness among children of school age.

2. The evidence is sufficient to infer a causal relationship between parental smoking and ever having asthma among children of school age.

Implications

Respiratory symptoms are common among children, even among those without asthma. Secondhand smoke exposure increases the risk for the major symptoms; these symptoms should not be dismissed as minor because they may impact the activities of the affected children. Secondhand smoke exposure is causally associated with asthma prevalence, perhaps reflecting a greater clinical severity associated with exposure. Secondhand smoke exposure, particularly at home, should be addressed by clinicians caring for any child with a respiratory complaint and particularly children with asthma.

Childhood Asthma Onset

As discussed earlier in this chapter (see "Lower Respiratory Illnesses in Infancy and Early Childhood"), parental smoking is causally associated with an increased incidence of acute LRIs, including illnesses with wheeze, in the first one or two years of a child's life. Prevalence surveys of schoolchildren show that wheeze and diagnosed asthma are more common among children of smoking parents, with a greater elevation in risk for outcomes based on definitions of wheeze that reflect a greater severity. Evidence presented in the prior section supported conclusions that parental smoking was causally associated with respiratory symptoms and prevalent asthma; the cross-sectional evidence did not address asthma onset. This section reviews cohort and case-control studies of wheeze illnesses that provide evidence concerning the effects of parental smoking on the incidence, prognosis, and severity of childhood asthma. The design of these studies addresses the temporal relationship between exposure and disease onset. This discussion also considers case-control studies of prevalent asthma that provide findings complementary to the surveys of schoolchildren. This section represents an update of the 1998 review by Strachan and Cook (1998c).

Relevant Studies

The study findings are separated into categories by outcomes: incidence, natural history, and prevalence. Incidence data come largely from prospective cohort studies that follow groups of children without asthma and monitor the development of wheeze illnesses or a new diagnosis of asthma. Incidence studies provide evidence for factors that cause the development of asthma, including exposure to secondhand smoke. The prevalence of asthma reflects not only the incidence but also the duration of the disease or its natural history. Factors that increase the severity of asthma tend to increase prevalence, particularly if the definition of prevalent asthma incorporates elements of clinical severity.

This review includes cohort and case-control studies of asthma or wheeze that occurred after infancy and includes case series of patients with asthma that investigated parental smoking and disease severity. The literature search identified 66 relevant papers that included 11 cohort studies, 24 case-control studies, 16 uncontrolled case series, and 1 large record-linkage study. Because only a small number of cohort studies were identified, ORs relating parental smoking to the incidence and prognosis of wheeze illnesses were pooled using weights inversely proportional to their variance (the "fixed effects" assumption). The ORs from the larger number of case-control studies were pooled using a "random effects" model. A quantitative meta-analysis was not possible for studies of disease severity.

Evidence Review

Cohort Studies of Incidence

The earlier review by Strachan and Cook (1998c) identified 10 papers based on six cohort studies that documented the incidence of wheeze illnesses after the first two years of life in relation to parental smoking behaviors (Table 6.16) (Taylor et al. 1983; Fergusson and Horwood 1985; Horwood et al. 1985; Anderson et al. 1986; Neuspiel et al. 1989; Sherman et al. 1990; Martinez et al. 1992, 1995; Lewis et al. 1995; Strachan et al. 1996). Five papers addressed mainly wheeze during the preschool years (Taylor et al. 1983; Fergusson and Horwood 1985; Horwood et al. 1985; Lewis et al. 1995; Martinez et al. 1995), two studies focused on the prevalence of wheeze for the first time during the school years (Sherman et al. 1990; Strachan et al. 1996), and three papers included both early and later childhood (Anderson et al. 1986; Neuspiel et al. 1989; Martinez et al. 1992). Only one additional birth cohort study, based on very low birth weight infants, has been published since the 1998 review (Darlow et al. 2000). These studies complement the larger number of studies that address wheeze illness incidence in infancy and are reviewed in the next section. The results are summarized in Table 6.17 and Figure 6.9 and are discussed briefly in the next section.

Investigators in Tucson (Arizona) followed a birth cohort registered with a health maintenance organization (Martinez et al. 1995). Among 762 children followed for the first three years of life and also at six years of age, 403 had no history of wheeze, 147 had wheeze by three years of age but not at six years of age ("transient" early wheeze), 112 developed wheeze after three years of age ("late-onset" wheeze), and 100 developed wheeze before three years of age and had wheeze at six years of age ("persistent" wheeze). The incidence of wheeze before three years of age—transient and persistent combined—doubled if the mother smoked 10 or more cigarettes per day. The incidence of a later onset of wheeze was less strongly associated with maternal smoking (Table 6.17). These associations were unchanged after adjustment for gender, ethnicity, eczema, noninfective rhinitis, and maternal asthma. For a comparison with other studies of early childhood wheeze, the cumulative incidence of wheeze by six years of age is also presented in Table 6.17. Although these incidence data are presented and analyzed by maternal smoking, another publication from the same cohort study has suggested that for children in day care, smoking by the caregiver may also be of importance as a determinant of the frequency of wheeze illnesses in the third year of life (Holberg et al. 1993).

In a similar population-based birth cohort study in Christchurch, New Zealand, 1,032 children were followed at annual intervals until six years of age (Fergusson and Horwood 1985; Horwood et al. 1985). In contrast to other studies, the cumulative incidence of asthmatic symptoms that parents reported was lower if the mother smoked and higher if the father smoked. The incidence was also lower if both parents smoked versus if neither parent smoked. Analyses that used medical consultations for asthma (Horwood et al. 1985) and the frequency of asthma attacks in the first six years of life (Fergusson and Horwood 1985) showed a similar pattern.

The incidence of all forms of wheeze in the nationwide 1970 British birth cohort was ascertained retrospectively by parental recall at five years of age. The direction and strength of dose-response relationships with smoking during pregnancy (Table 6.17) and when the child was five years of age were almost identical (Lewis et al. 1995). The cumulative incidence of wheeze among children of smoking mothers was elevated and changed little after adjustment for gender, birth weight, and breastfeeding, which may have potentially confounded or modified the association (Lewis et al. 1995). There was also an increased incidence of asthma by five years of age if the mother smoked (Taylor et al. 1983). Another study based on the same birth cohort explicitly excluded wheeze in the first year of life and included information from follow-up data gathered at 5 and 10 years of age

Table 6.16 Design, sample size, and recruitment criteria for studies of asthma incidence and prognosis associated with parental smoking included in this overview

Study	Design/population	Sample size	Case definition	Source of cohort or controls	Outcome
			Incidence studies		
Taylor et al. 1983 Lewis et al. 1995	Cohort Aged 0–5 years United Kingdom	12,530	Reported wheeze	National birth cohort	Wheeze incidence
Fergusson and Horwood 1985 Horwood et al. 1985	Cohort Aged 0–6 years New Zealand	1,032	Reported asthma	Population-based birth cohort	Asthma incidence
Anderson et al. 1986 Strachan et al. 1996	Cohort Aged 0–16 years United Kingdom	4,583	Reported asthma/bronchitis with wheeze	National birth cohort	Asthma/ bronchitis with wheeze incidence
Neuspiel et al. 1989	Cohort Aged 1–10 years United Kingdom	9,670	Reported wheeze	National birth cohort	Wheeze incidence
Sherman et al. 1990	Cohort Aged 5–17 years United States (Massachusetts)	722	Physician-diagnosed asthma	Schools-based cohort	Asthma incidence
Martinez et al. 1992	Cohort Aged 0–11 years United States (Arizona)	739	Physician-diagnosed asthma	Random household sample	Asthma incidence
Holberg et al. 1993 Martinez et al. 1995	Cohort Aged 0–6 years United States (Arizona)	762	Reported wheeze	Health maintenance organization-based birth cohort	Wheeze incidence
Hjern et al. 1999	Cohort Aged 2–6 years Sweden	Approxi-mately 156,000	Hospitalization	Record linkage in 3 cities	Asthma incidence
Darlow et al. 2000	Cohort Aged 0–7 years New Zealand	299	Reported physician-diagnosed asthma	Very low birth weight babies	Asthma incidence
			Natural history studies		
McConnochie and Roghmann 1984	Cohort Aged 0–9 years United States (New York)	236	Wheeze 8 years later	Bronchiolitis before 2 years of age	Early prognosis
Welliver et al. 1986	Cohort Aged 0–2 years United States (New York)	27	Recurrent wheeze	Parainfluenza bronchiolitis	Early prognosis

Table 6.16 Continued

Study	Design/population	Sample size	Case definition	Source of cohort or controls	Outcome
		Natural history studies			
Geller-Bernstein et al. 1987	Cohort Aged 0–5 years Israel	80	Persistent wheeze at 5 years of age	Atopic infants with wheeze	Early prognosis
Toyoshima et al. 1987	Cohort Aged 1–4 years Japan	48	Wheeze 22–44 months later	Infants with wheeze	Early prognosis
Rylander et al. 1988	Cohort Aged 0–7 years Sweden	67	Wheeze 4 years later	Respiratory syncytial virus plus illness before 3 years of age	Early prognosis
Lewis et al. 1995	Cohort Aged 5–16 years United Kingdom	1,477	Wheeze at 16 years of age	Wheeze before 5 years of age	Later prognosis
Martinez et al. 1995	Cohort Aged 0–6 years United States (Arizona)	247	Wheeze at 6 years of age	Wheeze before 3 years of age	Early prognosis
Strachan 1995	Cohort Aged 7–23 years United Kingdom	1,090	Asthma/ bronchitis with wheeze at 11 and 23 years of age	Asthma/ bronchitis with wheeze before 7 years of age	Later prognosis
Wennergren et al. 1997	Cohort Aged 0–10 years Sweden	92	Asthma at 10 years of age	Bronchitis with wheeze before 2 years of age	Early prognosis
Infante-Rivard et al. 1999	Case-control and follow-up Aged 3–10 years Canada	394	Asthma symptoms at 9–10 years of age	First emergency room asthma visit	Early prognosis
Rusconi et al. 1999	Survey Aged 0–7 years Italy	1,892	Wheeze at 6–7 years of age	Lower respiratory illness with wheeze before 2 years of age	Early prognosis
		Case-control studies			
O'Connell and Logan 1974	Aged 2–16 years United States (Minnesota)	628	Outpatients with asthma	Other outpatients (no atopic disease)	Asthma (outpatients)
Palmieri et al. 1990	Aged 1–12 years Italy	735	Outpatients with asthma	Routine health check	Asthma (outpatients)
Daigler et al. 1991	Aged 0–17 years United States (New York)	383	Hospital admission or 2 outpatient visits	Private pediatric practice	Asthma (inpatients/ outpatients)
Willers et al. 1991	Aged 3–15 years Sweden	126	New outpatient referrals	2 local schools	Asthma (outpatients)

Table 6.16 Continued

Study	Design/population	Sample size	Case definition	Source of cohort or controls	Outcome
		Case-control studies			
Butz and Rosenstein 1992	Aged about 9 years United States (Maryland)	346	Outpatients with asthma	Private pediatric practice	Asthma (outpatients)
Ehrlich et al. 1992	Aged 3–14 years United States (New York)	114	Emergency room visit for asthma	Other emergency room patients	Asthma (emergency room)
Infante-Rivard 1993	Aged 3–4 years Canada	914	First emergency room visit for asthma	Population sample	Asthma (inpatients)
Rylander et al. 1993, 1995	Aged 1½–4 years Sweden	212	Bronchitis with wheeze treated in the hospital	Random population sample	Bronchitis with wheeze (inpatients)
Clark et al. 1994	Aged 5–7 years United Kingdom	62	Outpatients with asthma	Surgical outpatients	Asthma (outpatients)
Fagbule and Ekanem 1994	Aged about 5½ years Nigeria	280	Outpatients with wheeze (no family history)	Neighbors	Wheeze (outpatients)
Leen et al. 1994	Aged 5–11 years Ireland	211	Reported asthma	Population survey	Asthma (survey)
Mumcuoglu et al. 1994	Aged 3–15 years Israel	400	Asthma treatment	Neighbors	Wheeze (outpatients)
Azizi et al. 1995	Aged 0–5 years Malaysia	359	First asthma admission	Nonrespiratory admissions	Asthma (inpatients)
Henderson et al. 1995	Aged 7–12 years United States (North Carolina)	342	≥2 wheeze attacks	Pediatric clinic sample	Wheeze (outpatients)
Lindfors et al. 1995	Aged 1–4 years Sweden	511	Asthma outpatient referral	Random population sample	Asthma (outpatients)
Strachan and Carey 1995	Aged 12–18 years United Kingdom	961	Frequent/severe wheeze	Population survey (no wheeze)	Wheeze (survey)
Ehrlich et al. 1996	Aged 7–9 years South Africa	620	Asthma symptoms	Population survey (no wheeze)	Asthma/ wheeze (survey)
Moussa et al. 1996	Aged 6–18 years United Arab Emirates	406	Physician-diagnosed asthma on therapy	School classmates (survey)	Asthma
Oliveti et al. 1996	Aged 4–9 years United States (Ohio)	262	Physician-diagnosed asthma on therapy	Adjacent birth records	Asthma (outpatients)

Table 6.16 Continued

Study	Design/population	Sample size	Case definition	Source of cohort or controls	Outcome
			Case-control studies		
Jones et al. 1999	Aged 4–16 years United Kingdom	200	Physician-diagnosed asthma on therapy	General practice population	Asthma (primary care)
Chang et al. 2000	Aged 0–16 years United States (Virginia)	271	Wheeze on auscultation	Nonrespiratory emergencies	Wheeze (emergency room)
			Other studies		
Kershaw 1987*	Case-control Aged 0–5 years United Kingdom	1,285	≥3 wheeze attacks	Neonates in locality	Wheeze (outpatients)
Murray and Morrison 1990*	Case-control Aged 1–17 years Canada	620	Asthma diagnosis	Allergy clinic patients	Asthma (outpatients)
Duff et al. 1993*	Case-control Aged 2–16 years United States (Virginia)	114	Emergency room visit for asthma/ bronchiolitis	Other emergency room patients	Wheeze (emergency room)
Chen et al. 1996*	Survey Aged 6–17 years Canada	892	Physician-diagnosed asthma and symptoms	Survey of complete town	Recent asthma (survey)
Knight et al. 1998*	Case-control Aged 2–18 years Canada	152	Physician-diagnosed asthma	General pediatric clinic	Asthma (outpatients)

*Not included in the meta-analysis of case-control studies in Table 6.3.

(Neuspiel et al. 1989). Maternal smoking was associated with wheeze that was labeled as bronchitis with wheeze (incidence ratio 1.44 [95 percent CI, 1.24–1.68]), but not with wheeze that was labeled as asthma (incidence ratio 0.96 [95 percent CI, 0.77–1.22]). Most of the published analyses related only to the former category, which accounted for only 38 percent of all wheeze incidents (Strachan and Cook 1998c). In the absence of maternal smoking, smoking by the father was not associated with an increased risk of bronchitis with wheeze (incidence ratio 0.99 [95 percent CI, 0.76–1.29]) and was not assessed for other forms of wheeze.

An earlier national British birth cohort of persons born in 1958 contributes information on both early and later onset of wheeze illnesses (Anderson et al. 1986; Strachan et al. 1996). As in the 1970 cohort, early wheeze illnesses were ascertained retrospectively, in this case at seven years of age, and were more common if the mother had smoked during pregnancy. This association was independent of other risk factors (Strachan et al. 1996). Among 4,583 children without a history of asthma or bronchitis with wheeze reported by parents at 7 years of age, the incidence from 7 to 16 years of age differed little according to whether the mother had smoked during pregnancy; however, there were weak, nonsignificant, and positive associations with smoking by both the mother and father at the 16-year follow-up (Table 6.17).

A smaller cohort study in Boston also found little evidence for a relationship between parental smoking and asthma incidence (Sherman et al. 1990). The study

Table 6.17 Incidence and prognosis of asthma or wheeze in relation to parental smoking

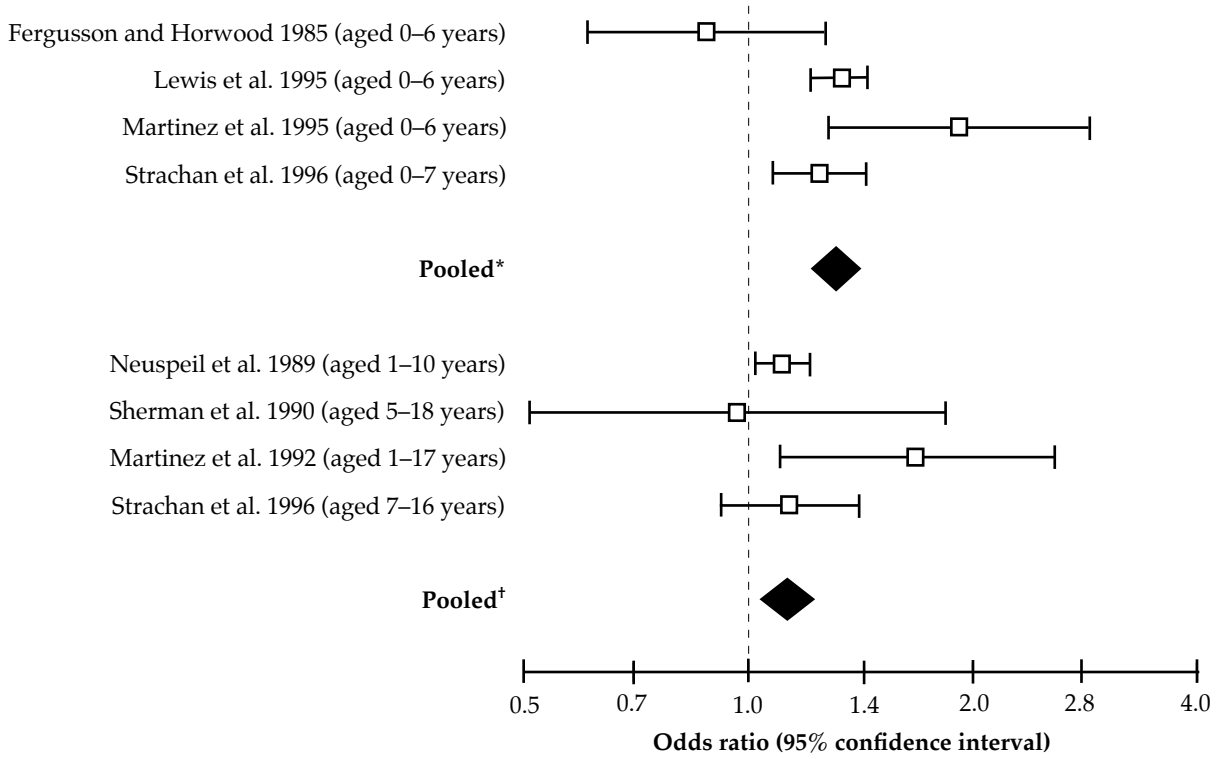
Study	Population		Age (years) at start/end (length of follow-up period)	Smoking exposure	Outcome	Odds ratio for smoking (95% confidence interval)
	Cases	Non-cases				
Incidence studies						
Fergusson and Horwood 1985	141	891	0/6	Mother smoked	Asthma	0.88* (0.61–1.27)
	141	891	0/6	Father smoked	Asthma	1.27 (0.89–1.81)
Neuspiel et al. 1989	1,662	8,016	1/10	Mother smoked at any age	Asthma Wheeze	0.96 (0.77–1.22) 1.44 (1.24–1.68)
Sherman et al. 1990	43	679	5–9/NR† (9 years)	Mother smoked	Asthma	0.97* (0.51–1.84)
	43	679	5–9/NR (9 years)	Father smoked	Asthma	0.91 (0.49–1.69)
Martinez et al. 1992	86	653	<5/NR (12 years)	Mother smoked ≥10 cigarettes/day	Asthma	1.68* (1.10–2.58)
	78	622	<5/NR (12 years)	Father smoked ≥10 cigarettes/day	Asthma	1.06 (0.67–1.69)
Lewis et al. 1995	2,616	9,914	0–1 years	Mother smoked during pregnancy	Wheeze	1.34* (1.22–1.45)
Martinez et al. 1995	247	515	0/3	Mother smoked ≥10 cigarettes/day	Wheeze	2.07 (1.34–3.19)
	112	403	3/6	Mother smoked ≥10 cigarettes/day	Wheeze	1.59 (0.89–2.84)
	359	403	0/6	Mother smoked ≥10 cigarettes/day	Wheeze	1.91* (1.28–2.86)
Strachan et al. 1996	1,026	4,583	0/7	Mother smoked during pregnancy	Asthma or bronchitis with wheeze	1.25* (1.08–1.44)
	368	4,215	7/16	Mother smoked during pregnancy	Asthma or bronchitis with wheeze	0.99 (0.78–1.25)
	368	4,215	7/16	Mother smoked at 16-year follow-up	Asthma or bronchitis with wheeze	1.14* (0.92–1.41)
	368	4,215	7/16	Father smoked at 16-year follow-up	Asthma or bronchitis with wheeze	1.10 (0.88–1.36)

Table 6.17 Continued

Study	Population		Age (years) at start/end (length of follow-up period)	Smoking exposure	Outcome	Odds ratio for smoking (95% confidence interval)
	Cases	Non-cases				
				Natural history studies		
McConnochie and Roghmann 1984	26	33	<2/8	Either parent smoked	Persistent wheeze	1.45* (0.45–4.70)
Geller-Bernstein et al. 1987	26	54	<2/5	Either parent smoked	Persistent wheeze	3.10* (1.08–8.91)
Toyoshima et al. 1987	18	22	<3/NR (22–44 months)	Household members smoked	Recent wheeze	11.80* (1.32–105.0)
Rylander et al. 1988	22	45	<3/NR (4 years)	Either parent smoked	Recent wheeze	0.80* (0.28–2.27)
Lewis et al. 1995	218	1,259	<5/16	Mother smoked during pregnancy	Wheeze in the past year	0.86* (0.64–1.15)
Martinez et al. 1995	100	147	<3/6	Mother smoked ≥10 cigarettes/day	Recent wheeze	0.99* (0.53–1.86)
Strachan 1995	203	887	<7/11	Mother smoked during pregnancy	Asthma/bronchitis with wheeze in the past year	0.56* (0.40–0.78)
	101	989	<7/23	Mother smoked during pregnancy	Asthma/bronchitis with wheeze in the past year	0.70 (0.50–0.98)
Wennergren et al. 1997	28	64	<2/10	Household member(s) smoked during the child's infancy	Asthma symptoms	3.14‡
	28	64	<2/10	Household member(s) smoked when the child was 10 years of age	Asthma symptoms	1.08 (0.69–1.71)
Infante-Rivard et al. 1999	288	105	3–4/9–10	Mother smoked when the child was 3–4 years of age	Asthma symptoms	1.06 (0.67–1.67)
Rusconi et al. 1999	671	1,221	<2/6–7	Mother smoked during pregnancy	Recent wheeze	1.16* (0.92–1.45)

*Odds ratios were used in the meta-analysis.
†NR = Data were not reported.
‡Odds ratios were used in the meta-analysis; confidence intervals were not provided.

Figure 6.9 Odds ratios for the effect of maternal smoking on asthma or wheeze incidence throughout childhood (cohort studies)



*Studies that included the first year of life (exact incidence period shown on left in parentheses), derived by the fixed effects method.
†Studies that excluded the first year of life (exact incidence period shown on left in parentheses), derived by the fixed effects method.

had a mean annual follow-up of nine years among 722 children with no history of asthma upon entry into the study at five to nine years of age (Table 6.17). In a second cohort study in Tucson (Arizona) that was based on a random sample of households, physician-diagnosed asthma was ascertained at one- to two-year intervals (Martinez et al. 1992). Maternal smoking was associated with an increased risk of asthma, whereas smoking by the father was not (Table 6.17). The effect of maternal smoking was stronger among less educated families, although the effect modification by educational level was not statistically significant.

A national cohort study followed 299 very low birth weight children born in New Zealand in 1986 (96 percent of all survivors) through seven years of age (Darlow et al. 2000). In this potentially vulnerable group, maternal smoking during pregnancy was associated with an increased cumulative incidence of physician-diagnosed asthma (OR = 2.0 [95 percent CI, 1.2–3.3]), but a decreased risk of requiring daily medication for asthma at seven years of age (OR = 0.6 [95 percent CI, 0.3–1.3]). This unique group was not included in the meta-analyses described below.

In quantitative meta-analyses of studies of early and later incidence of asthma and wheeze illnesses, the association with maternal smoking was significantly stronger for the first five to seven years of life (the pooled OR for the four studies = 1.31 [95 percent CI, 1.22–1.41], χ^2 for heterogeneity = 8.58, p = 0.036) (Fergusson and Horwood 1985; Lewis et al. 1995; Martinez et al. 1995; Strachan et al. 1996) than for the school years (Sherman et al. 1990; Strachan et al. 1996) or throughout childhood (Neuspiel et al. 1989; Martinez et al. 1992), excluding infancy (the pooled OR for

the four studies = 1.13 [95 percent CI, 1.04–1.22], χ^2 for heterogeneity = 3.71, p = 0.29).

Natural History

Tables 6.16 and 6.17 summarize 11 studies that related parental smoking to the natural history of wheeze illnesses in childhood (McConnochie and Roghmann 1984; Welliver et al. 1986; Geller-Bernstein et al. 1987; Toyoshima et al. 1987; Rylander et al. 1988; Lewis et al. 1995; Martinez et al. 1995; Strachan 1995; Wennergren et al. 1997; Infante-Rivard et al. 1999; Rusconi et al. 1999). Five studies addressed the short-term prognosis of all forms of wheeze from infancy through school age (Geller-Bernstein et al. 1987; Toyoshima et al. 1987; Martinez et al. 1995; Wennergren et al. 1997; Rusconi et al. 1999). Two studies reported specifically on the prognosis of wheeze following RSV infection (Rylander et al. 1988) or bronchiolitis in infancy (McConnochie and Roghmann 1984). The results of these seven studies are all consistent with an association between parental smoking and a small but increased risk of wheeze persisting after early childhood (pooled OR = 1.49 [95 percent CI, 1.24–1.78], χ^2 for heterogeneity = 28.4, p <0.001).

The short-term prognosis of bronchiolitis from a parainfluenza virus infection in infancy was evaluated among 27 children after an approximate follow-up period of three years (ranging from 8 to 51 months) (Welliver et al. 1986). The mean number of subsequent wheeze episodes was significantly higher (p <0.05) in children whose parents smoked compared with children whose parents were nonsmokers (3.0 versus 1.6 episodes, respectively), but the findings cannot be expressed in the form of an OR for a direct comparison with other prognostic studies.

A contrasting pattern of effect of parental smoking on prognosis emerges from a follow-up of a longer duration in two British birth cohort studies (Lewis et al. 1995; Strachan 1995). Among children from the 1958 cohort with a history of asthma or bronchitis with wheeze by 7 years of age, maternal smoking was associated with a significantly reduced risk of these illnesses at 11 and 23 years of age (Strachan 1995), despite the tendency of children of smoking parents to become active smokers, which is strongly associated with the recurrence of symptoms (Strachan et al. 1996). In the 1970 cohort, children younger than 5 years of age with wheeze whose mothers had smoked during pregnancy were less likely to experience wheeze in the past year at 16 years of age. This inverse association was not statistically significant but changed little after adjustment for gender, maternal age, parity, birth weight, and SES (Lewis et al. 1995). The pooled OR for maternal smoking with a follow-up to 11 (1958 cohort) or 16 years of age (1970 cohort) is 0.71 (95 percent CI, 0.57–0.89, χ^2 for heterogeneity = 3.58, p = 0.058).

A study in Canada that initiated a follow-up at three to four years of age found no effect of maternal smoking on the persistence of symptoms six years later (OR = 1.06 [95 percent CI, 0.67–1.67]) (Infante-Rivard et al. 1999). This result is consistent with prevalence studies that found a declining influence of parental smoking on asthmatic symptoms as the child grows older.

Prevalence Case-Control Studies

Tables 6.16 and 6.18 summarize 21 case-control studies that relate parental smoking to asthma or wheeze illnesses after the first year of life (O'Connell and Logan 1974; Palmieri et al. 1990; Daigler et al. 1991; Willers et al. 1991; Butz and Rosenstein 1992; Ehrlich et al. 1992, 1996; Infante-Rivard 1993; Clark et al. 1994; Fagbule and Ekanem 1994; Leen et al. 1994; Mumcuoglu et al. 1994; Azizi et al. 1995; Henderson et al. 1995; Lindfors et al. 1995; Rylander et al. 1995; Strachan and Carey 1995; Moussa et al. 1996; Oliveti et al. 1996; Jones et al. 1999; Chang et al. 2000). The studies are based mostly on outpatient or inpatient cases, although four ascertained more severe forms of wheeze illnesses using a population survey (Leen et al. 1994; Strachan and Carey 1995; Ehrlich et al. 1996; Moussa et al. 1996). These papers complement the results of population surveys of diagnosed asthma or symptoms of wheeze reviewed earlier in this chapter (see "Respiratory Symptoms and Prevalent Asthma in School-Age Children") by more specifically addressing the relationship of parental smoking to the prevalence of more severe forms of asthma that require clinical care.

For asthma, the results for smoking by either parent (from 15 studies) are summarized in Figure 6.10. There is evidence for borderline significant heterogeneity between studies (χ^2 = 23.3, df = 14, p = 0.06), but the size of the effect does not appear to be systematically related to the age ranges studied or to the sources of cases or controls. The pooled OR for smoking by either parent, derived by random effects modeling, is 1.39 (95 percent CI, 1.19–1.64). In a comparison of the effects of maternal and paternal smoking, there is a consistent finding of an association with maternal smoking (pooled OR = 1.54 [95 percent CI, 1.31–1.81]) but not with paternal smoking (pooled OR = 0.93 [95 percent CI, 0.81–1.07]). This finding

Table 6.18 Unadjusted relative risks associated with parental smoking for asthma (meta-analysis of case-control studies)

Study	Population (cases/controls)	Odds ratios for smoking (95% confidence intervals)			Dose-response effect*	Cotinine measured
		Either parent	Mother	Father		
O'Connell and Logan 1974	400/213 Aged 2–16 years	1.30 (0.93–1.83)	NR†	NR	NR	NR
Palmieri et al. 1990	302/433 Aged 1–12 years	1.0 (0.70–1.42)	NR	NR	No‡	NR
Daigler et al. 1991	137/246 Aged 0–17 years	NR	1.43 (0.92–2.23)	0.71 (0.44–1.15)	NR	NR
Willers et al. 1991	49/77 Aged 3–15 years	1.97 (0.90–4.35)	2.56 (1.23–5.32)	0.87 (0.42–1.80)	Yes	Yes
Butz and Rosenstein 1992	102/105 Aged about 9 years	1.43 (0.75–2.71)	NR	NR	NR	NR
Ehrlich et al. 1992	107/121 Aged 3–14 years	1.13 (0.67–1.90)	2.0 (1.16–3.48)	NR	Yes	Yes
Infante-Rivard 1993	457/457 Aged 3–4 years	NR	1.16 (0.89–1.51)	0.81 (0.62–1.06)	NR	NR
Clark et al. 1994	19/43 Aged 5–7 years	0.71 (0.22–2.22)	NR	NR	NR	Yes
Fagbule and Ekanem 1994	140/140 Aged about 5½ years	2.12 (1.32–3.42)	NR	NR	NR	NR
Leen et al. 1994	115/96 Aged 5–11 years	0.76 (0.44–1.31)	NR	NR	NR	NR
Mumcuoglu et al. 1994	300/100 Aged 3–15 years	0.90 (0.57–1.42)	Few smoked	0.95 (0.60–1.50)	NR	NR
Azizi et al. 1995	158/201 Aged 0–5 years	1.80 (1.20–2.70)	NR	NR	NR	NR
Henderson et al. 1995	193/149 Aged 7–12 years	2.0 (1.22–3.27)	NR	NR	NR	Yes
Lindfors et al. 1995	193/318 Aged 1–4 years	1.62 (1.13–2.32)	NR	NR	NR	NR
Rylander et al. 1995	75/137 Aged 1½–4 years	1.46 (0.83–2.58)	1.70 (0.93–3.14)	1.02 (0.42–2.46)	No	Yes
Strachan and Carey 1995	486/475 Aged 12–18 years	NR	1.38 (1.18–1.61)	0.96 (0.69–1.34)	Yes	NR

Table 6.18 Continued

Study	Population (cases/controls)	Odds ratios for smoking (95% confidence intervals)			Dose-response effect*	Cotinine measured
		Either parent	Mother	Father		
Ehrlich et al. 1996	348/272 Aged 7–9 years	1.57 (1.06–2.33)	1.70 (1.23–2.34)	1.23 (0.90–1.70)	Yes	Yes
Moussa et al. 1996	203/203 Aged 6–18 years	NR	Few smoked	1.03 (0.63–1.70)	NR	NR
Oliveti et al. 1996	131/131 Aged 4–9 years	NR	2.79 (1.66–4.67)	NR	Yes	NR
Jones et al. 1999	100/100 Aged 4–16 years	NR	1.17 (0.62–2.21)	0.85 (0.48–1.49)	NR	NR
Chang et al. 2000	165/106 Aged 0–16 years	1.90 (1.10–3.40)	1.30 (0.70–2.30)	NR	Yes	Yes

*Urinary cotinine was measured (not all such studies reported dose-response relationships).
†NR = Data were not reported.
‡Dose-response relationship was only evident for participants with negative skin pricks.

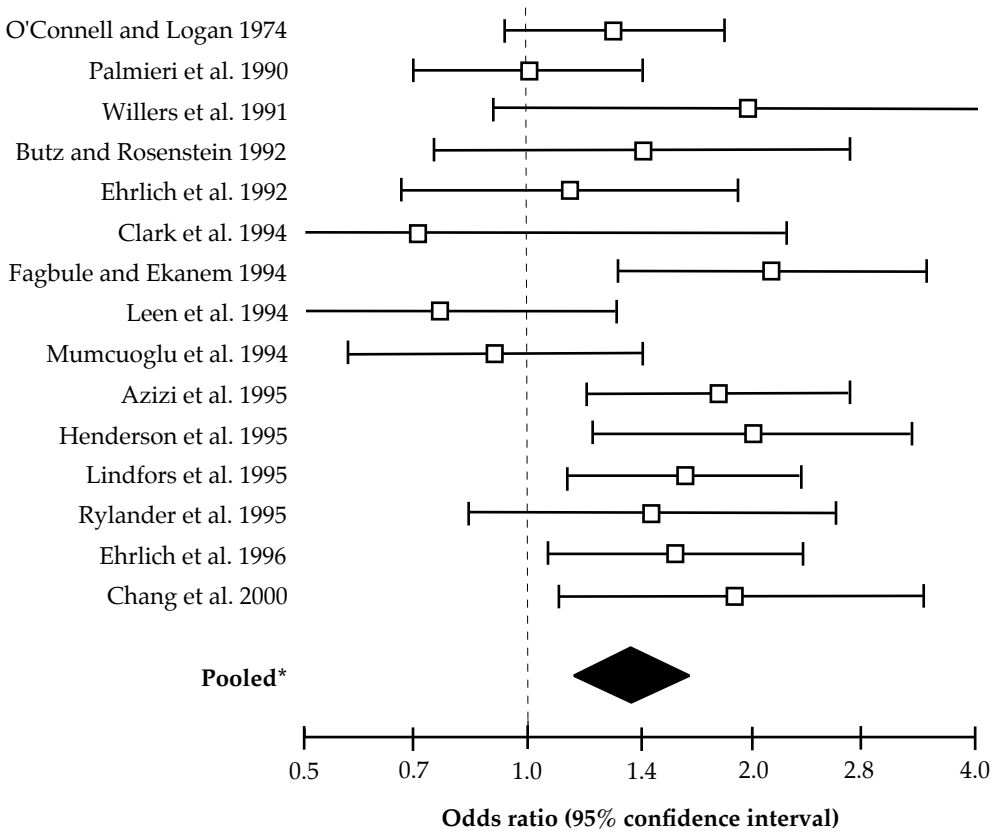
contrasts with prevalence surveys of asthma and wheeze among schoolchildren that found an effect of paternal smoking.

Six studies provided findings before and after adjustment for potential confounding variables (Fagbule and Ekanem 1994; Henderson et al. 1995; Rylander et al. 1995; Strachan and Carey 1995; Ehrlich et al. 1996; Oliveti et al. 1996). Only one study from Nigeria (Fagbule and Ekanem 1994) reported a substantial reduction in the OR for smoking by either parent (from 2.12 to 1.41) after adjustment for potential confounders that included pet ownership, indoor mold, cockroaches, wood smoke, and the use of mosquito coils. The OR for parental smoking changed little (from 1.32 to 1.3) after adjustment for family history of asthma and duration of breastfeeding in Sweden (Rylander et al. 1995); in the United Kingdom the OR changed from 1.44 to 1.49 after adjustment for age, gender, SES, gas cooking, indoor mold, feather bedding, and pet ownership (Strachan and Carey 1995); in the United States the OR changed from 1.74 to 1.8 after adjustment for family history of asthma and skin-prick positivity to common aeroallergens (Henderson et al. 1995); in South Africa the OR changed from 1.97 to 1.87 after adjustment for personal and family histories of atopic disease, SES, indoor mold, and salt preference (Ehrlich et al. 1996); and in the United States the OR changed from 2.79 to 2.82 after adjustment for maternal asthma, history of bronchiolitis, and a range of obstetric and perinatal variables (Oliveti et al. 1996).

Seven studies included measurements of urinary cotinine as an objective marker of tobacco smoke exposure (Willers et al. 1991; Ehrlich et al. 1992, 1996; Clark et al. 1994; Henderson et al. 1995; Rylander et al. 1995; Chang et al. 2000). Generally, the results of questionnaire and biochemical assessments were similar, although one study (Clark et al. 1994) found a stronger association between asthma and exposure classified by cotinine levels rather than by parental smoking assessed from a questionnaire. At least one study suggested that children with asthma may differ from other children exposed to secondhand tobacco smoke in terms of a lower clearance rate for nicotine metabolites, raising the possibility of a pharmacokinetic predisposition underlying the association between parental smoking and childhood asthma (Knight et al. 1998).

Four studies found a significant dose-response relationship of parental smoking with cotinine concentrations (Willers et al. 1991; Ehrlich et al. 1992, 1996; Chang et al. 2000), but a fifth did not (Rylander et al. 1995). Two other studies with findings for exposure-response trends based on a questionnaire assessment have inconsistent results (Palmieri et al. 1990; Strachan and Carey 1995), whereas a third, based

Figure 6.10 Odds ratios for the effect of smoking by either parent on childhood asthma or wheeze prevalence (case-control studies)



*Derived by the random effects method.

on obstetric records, reported a strong exposure-response relationship for daily cigarette smoking by the mother during pregnancy (Oliveti et al. 1996).

Three studies compared the effects of parental smoking at different ages. In the Swedish study by Rylander and colleagues (1993, 1995), the effect of parental smoking was greater at 18 months of age than at a younger age. This pattern was the same, regardless of whether exposure was assessed by the number of smoking parents or by urinary cotinine concentrations (Rylander et al. 1995). A U.S. case-control study that measured urinary cotinine concentrations found a positive association with wheeze before two years of age, but a nonsignificant inverse relationship at older ages (Duff et al. 1993). An Italian case-control study compared the effect of parental smoking before and after six years of age (Palmieri et al. 1990). The ORs for smoking by either parent were, respectively, 1.13 (95 percent CI, 0.71–1.80) and 0.83 (95 percent CI, 0.48–1.44).

In this context, it is relevant to note that a large record-linkage study of hospital admissions for asthma in Sweden (see "Respiratory Symptoms and Prevalent Asthma in School-Age Children" earlier in this chapter) found a significant effect of maternal smoking only on hospital admissions for children under three years of age (Hjern et al. 1999).

Atopic and Nonatopic Wheeze

In the 1958 British birth cohort, the increased incidence of bronchitis with wheeze or asthma by 16 years of age among children whose mothers had smoked during pregnancy occurred only among the 3,815 participants with no history of hay fever, allergic rhinitis, or eczema (cumulative incidence was

24.5 percent versus 18.9 percent among those with a history, OR = 1.39 [95 percent CI, 1.18–1.63]) (Strachan et al. 1996). Among the 1,794 participants reporting hay fever, allergic rhinitis, or eczema at one or more follow-up visits, maternal smoking had little effect on disease incidence (cumulative incidence was 32.2 percent among those whose mothers had smoked during pregnancy versus 33.5 percent among those whose mothers had not smoked during pregnancy, OR = 0.95 [95 percent CI, 0.76–1.18]). The difference in the effect of maternal smoking during pregnancy by the presence or absence of hay fever, allergic rhinitis, or eczema was statistically significant ($p < 0.01$).

In the Italian case-control study, cases (but not controls) were tested by skin prick with six locally relevant aeroallergens (Palmieri et al. 1990). Fewer prick-positive cases were exposed to any parental smoking than were prick-negative cases (77 percent versus 82 percent, respectively, OR = 0.72 [95 percent CI, 0.37–1.41]). The association of exposure with a positive skin-prick result was more marked and statistically significant at the 5 percent level with exposure to more than 20 cigarettes a day (44 percent for those exposed to ≤20 cigarettes per day versus 60 percent for those exposed to >20 cigarettes per day, OR = 0.54 [95 percent CI, 0.31–0.92]). Among 70 children with asthma aged younger than six years in a British outpatient series, maternal smoking was less common if the serum IgE was elevated (>1 SD above the population mean): 54 percent versus 69 percent among those who did not have an elevated serum Ig (OR = 0.54 [95 percent CI, 0.21–1.45]) (Kershaw 1987). A cross-sectional survey of Canadian children also identified a stronger association between parental smoking and recent asthma among children with no reported history of an allergy (OR for current smoking by either parent = 2.93 [95 percent CI, 0.83–10.3]) than among children with an allergy (OR = 0.73 [95 percent CI, 0.37–1.46]) (Chen et al. 1996). Although these differences are nonsignificant, they are consistent with the 1958 British birth cohort study results and thus suggest a stronger association between parental smoking and nonatopic "wheezy bronchitis" than with "allergic asthma."

A recent cross-sectional study of six- to seven-year-old children in northern Sweden presented results separately for atopic and nonatopic asthma defined by the presence or absence of positive skin-prick tests (Rönmark et al. 1999). Maternal smoking was significantly associated with nonatopic asthma (OR = 1.67 [95 percent CI, 1.04–2.68]) but not with atopic asthma (OR = 1.17 [95 percent CI, 0.68–2.01]). Because the study data were not fully displayed, effect modification by atopy cannot be formally evaluated for statistical significance.

A contrasting pattern was found in a study of allergy clinic patients aged 1 through 17 years in Vancouver (Canada) (Murray and Morrison 1990). Among 224 patients with atopic dermatitis, maternal smoking was associated with an increased risk of diagnosed asthma (OR = 3.42 [95 percent CI, 1.60–7.30]), whereas among 396 patients without atopic dermatitis there was no association (OR = 0.93 [95 percent CI, 0.57–1.51]). This interaction is statistically significant at the 1 percent level, but the findings are difficult to interpret biologically without the consideration of possible referral biases in this clinic-based study.

Severity

The severity of an episodic disease such as asthma has several dimensions: frequency of wheeze episodes, persistence of symptoms between "attacks," occurrence of clinically severe or life-threatening bronchospasm, the need for preventive and/or rescue medications, health services utilization, and interference with daily activities. Seven population surveys (Gortmaker et al. 1982; Weitzman et al. 1990a,b; Strachan and Carey 1995; Ehrlich et al. 1996; Chew et al. 1999; Schwartz et al. 2000), 1 case-control study (Henderson et al. 1995), 11 uncontrolled case series (Aderele 1982; Evans et al. 1987; Murray and Morrison 1989, 1993; Chilmonczyk et al. 1993; LeSon and Gershwin 1995; Macarthur et al. 1996; Minkovitz et al. 1999; Wafula et al. 1999; Gürkan et al. 2000a; Sandberg et al. 2000), and 1 record-linkage study (Hjern et al. 1999) present data on asthma severity in relation to parental smoking (Table 6.19). Various dimensions of severity were used and some studies combined a number of indices into a composite "severity score" (Aderele 1982; Murray and Morrison 1989, 1993).

Because each study employed different approaches, a formal quantitative meta-analysis was not carried out, but Table 6.20 presents a qualitative review. These studies suggest greater disease severity in children exposed to smoking at home, a pattern that is more consistently found among persons with asthma who are hospital outpatients or inpatients than among children with asthma identified through population surveys (Table 6.20).

Several studies adjusted for potential confounding variables, and it is possible that some of the associations of parental smoking with health service utilization, in particular, may reflect a common association with a lower SES and correlates of SES that affect

Table 6.19 Design, sample size, and severity index for studies of asthma severity associated with parental smoking included in this overview

Study	Design/population	Severity index
Aderele 1982	Case series of 380 outpatients with asthma Aged 1–13 years Nigeria	Severity score
Gortmaker et al. 1982	Survey of 272 patients with reported current asthma Aged 0–17 years United States (Massachusetts/Michigan)	Functional impairment
Evans et al. 1987	Case series of 276 outpatients with asthma Aged 4–17 years United States (New York)	Emergency room visits per year
Murray and Morrison 1989	Case series of 415 outpatients with asthma Aged 1–17 years Canada	Severity score
Weitzman et al. 1990a	Survey of 99 patients with reported current asthma Aged 2–5 years United States (All states)	Asthma medication
Weitzman et al. 1990b	Survey of 117 patients with reported current asthma Aged 0–5 years United States (All states)	Hospitalizations
Chilmonczyk et al. 1993	Case series of 199 outpatients with asthma Aged 0–13 years United States (Maine)	Attack frequency
Murray and Morrison 1993	Case series of 807 outpatients with asthma Aged 1–17 years Canada	Severity score
Henderson et al. 1995	Case-control study of 149 children from a pediatric clinic sample Aged 7–12 years United States (North Carolina)	>1 wheeze attack
LeSon and Gershwin 1995	Case series of 300 inpatients with asthma Aged 5–12 years United States (California)	Intubation
Strachan and Carey 1995	Survey of 486 patients with current wheeze Aged 12–18 years United Kingdom	Frequent/severe wheeze
Ehrlich et al. 1996	Survey of 325 children with current asthma/wheeze Aged 7–9 years South Africa	Asthma symptoms

Table 6.19 Continued

Study	Design/population	Severity index
Macarthur et al. 1996	Case series of 68 inpatients with asthma Aged 1–10 years Canada	Readmission within 1 year
Chew et al. 1999	Survey of 2,222 children with current wheeze Aged 6–13 years Singapore	"Increased morbidity"
Hjern et al. 1999	Routine data of about 2,500 admissions in 3 cities Aged 2–6 years Sweden	Readmission by 6 years of age
Minkovitz et al. 1999	Case series of 107 inpatients with asthma Aged 0–14 years United States (Maryland)	Readmission within 1 year
Wafula et al. 1999	Case series of 150 inpatients and outpatients with wheeze Aged 0–9 years Kenya	>1 attack in 2 months
Gürkan et al. 2000a	Case series of 140 inpatients with asthma Aged 3–15 years Turkey	Readmission within 4 years
Sandberg et al. 2000	Case series of 90 outpatients with asthma Aged 6–13 years United Kingdom	New asthma attacks
Schwartz et al. 2000	Survey of 74 current patients with asthma Aged 7–12 years Finland	Daily medication and peak expiratory flow

utilization. On the other hand, the striking association of secondhand tobacco smoke exposure with near-fatal asthma, evaluated retrospectively in a tertiary medical care center in California, was stronger than a range of psychosocial variables, which suggests that the association cannot be entirely explained by SES confounding (LeSon and Gershwin 1995). However, a mutually adjusted analysis was not possible as only 2 of the 13 patients who required intubation came from nonsmoking households.

Effects of Reducing Tobacco Smoke Exposure

Information on secondhand smoke exposure and asthma severity can also be found in studies that track the consequences of exposure reduction. According to the early case-control study by O'Connell and Logan (1974), 67 percent of the 265 children who were exposed to parental smoking considered that it had aggravated their symptoms. In addition, tobacco smoke exposure was considered a "significant factor" for symptoms in 10 percent (16/158) of children if one parent smoked and in 20 percent (21/107) if both parents smoked. These 37 children were included in an empirical study of antismoking advice that included a follow-up 6 to 24 months later of 35 of the children. Symptoms improved in 90 percent (18/20) of the children whose parents had stopped smoking, and in 27 percent (4/15) of the children who remained involuntarily exposed to tobacco smoke. These results suggest a benefit from reducing exposure, but interpretation is limited by the nonrandomized nature of the intervention.

Table 6.20 Summary of studies on asthma severity associated with parental smoking

Study	Population age (years)	Index of exposure	Index of severity	Association of disease severity with secondhand smoke exposure		
				Direction	Significance	Comments
			Population-based case series			
Gortmaker et al. 1982	0–17	Mother smoked	Functional impairment	Positive	p = 0.47	Functional impairment was reported for 22% of those with asthma whose mothers smoked (n = 144), and for 18% of the remaining population with asthma (n = 128)
Weitzman et al. 1990a	2–5	Mother smoked	Asthma medication	Positive	p = 0.08	Medication was taken by 41% of those with asthma whose mothers smoked ≥10 cigarettes/day (n = 23), and by 19% of others with asthma (n = 76)
Weitzman et al. 1990b	0–5	Mother smoked	Hospitalizations	No trend	p = 0.88	Mean admission rates were 1.1 per year if mother was a nonsmoker, 1.3 if mother smoked <10 cigarettes/day, and 1.0 if mother smoked ≥10 cigarettes/day
Henderson et al. 1995	7–12	Household smoker	Attack frequency	Inverse	p = 0.59	35% (29/82) of those with infrequent wheeze and 30% (20/67) with ≥5 attacks/year were exposed to secondhand smoke; urinary cotinine levels were similar in the 2 groups
Strachan and Carey 1995	12–18	Mother smoked	Frequency and intensity	Positive	p = 0.02	34% (38/113) of children with both frequent and intense attacks, and 23% (84/373) of children with less severe cases had mothers who smoked
Ehrlich et al. 1996	7–9	Mother smoked	Frequency and intensity	Weak positive	NR*	Published odds ratio (OR) of 2.04 (95% confidence interval [CI] ,1.25–3.34) for severe wheeze (179 cases) is similar to the 1.87 (95% CI, 1.25–2.81) for all wheeze cases (325)

Table 6.20 Continued

Study	Population age (years)	Index of exposure	Index of severity	Association of disease severity with secondhand smoke exposure		
				Direction	Significance	Comments
Population-based case series						
Chew et al. 1999	6–13	Father smoked (<1% of the mothers smoked)	"Increased morbidity"	Weak positive	p = 0.34	Father smoked in 14% (122/899) of cases in children with "increased morbidity," and in 12% (160/1,323) of other cases in children with wheeze
Hjern et al. 1999	2–6	Mother smoked during pregnancy	Multiple admissions	No effect	NR	Large record-linkage study; there was no difference in the adjusted OR for any asthma admission (1.3 [95% CI, 1.1–1.4]) and for multiple admissions (1.3 [95% CI, 1.0–1.6])
Schwartz et al. 2000	7–12	Smoking in the home (day-by-day exposure)	Daily medication	Positive	p = 0.02	Secondhand smoke exposure on the previous day increased the use of bronchodilator medication (OR = 10.3 [95% CI, 1.3–83.7]); there was also a dose-dependent effect of secondhand smoke on morning and evening peak flows
Clinic-based case series						
Aderele 1982	1–13	Household smoker	Composite score	Positive	p = 0.15	Exposure (mainly to nonmaternal smoking): 23% (43/186) mild, 26% (23/87) moderate, and 31% (33/107) severe cases
Evans et al. 1987	4–17	Any secondhand smoke exposure	Emergency room visits per year	Positive	p = 0.008	Mean visits of 3.1 per year in 137 smoking homes, 1.8 per year in 122 nonsmoking homes
Murray and Morrison 1989	1–17	Mother smoked	Composite score	Positive	p <0.01	Severity score was related to maternal smoking (p <0.01) but not to paternal smoking (p >0.5)
Chilmonczyk et al. 1993	0–13	Urinary cotinine	Attack frequency	Positive	p <0.05	Mean of 3.6 episodes per year if cotinine was >39 ng/mL† (n = 30), 2.8 per year if cotinine was 10–39 ng/mL (n = 53), and 2.1 per year if cotinine was <10 ng/mL (n = 116)

Table 6.20 Continued

Study	Population age (years)	Index of exposure	Index of severity	Association of disease severity with secondhand smoke exposure		
				Direction	Significance	Comments
Clinic-based case series						
Murray and Morrison 1993	1–17	Mother smoked	Composite score	Inverse	p <0.01	Reversal of previous relationship in Aderele (1982) after introducing antismoking advice
LeSon and Gershwin 1995	5–12	Any secondhand smoke exposure	Intubation	Positive	p <0.001	85% (11/13) of intubated patients and 20% of 287 nonintubated patients were exposed to secondhand smoke (OR = 22.4 [95% CI, 7.4–68.0])
Macarthur et al. 1996	1–10	Household smoker	Readmission	Positive	p = 0.24	53% (17/32) of children who were readmitted and 36% (13/36) of children not readmitted were from smoking homes (OR = 2.0 [95% CI, 0.8–5.3])
Minkovitz et al. 1999	0–14	Household smoker	Readmission	Inverse	p = 0.19	49% (16/33) of children with multiple admissions compared with 62% (46/74) of single admissions were exposed to smoking in the home
Wafula et al. 1999	0–9	Household smoker	>1 attack in 2 months	Positive	p = 0.09	51% (36/71) of persons with moderate and severe asthma were exposed, compared with 33% of persons with mild asthma cases (OR = 2.1 [95% CI, 0.9–4.7])
Gürkan et al. 2000a	3–15	Household smoker Mother smoked	Readmission	Positive	p = 0.04 p = 0.02	Among children with multiple hospitalizations, 53% (16/30) were from smoking households and 23% (7/30) had mothers who smoked; among other children these figures were 31% (34/110) and 7% (8/110), respectively
Sandberg et al. 2000	6–13	Parents smoked	New asthma attacks	Positive	p = 0.05	Adjusted OR for asthma exacerbation during follow-up in offspring of smoking parents was 1.33 (95% CI, 1.01–1.77)

*NR = Data were not reported.
†ng/mL = Nanograms per milliliter.

A composite score was used to grade severity among 415 children aged 1 through 17 years diagnosed with asthma who attended an allergy clinic in Vancouver (Canada) from 1983 to 1986 (Murray and Morrison 1989). The severity score was significantly higher among children of smoking mothers ($p < 0.01$), but when the analysis was repeated for an additional 387 children attending the same clinic from 1986 to 1990, the relationship between maternal smoking and the asthma severity score was reversed, reflecting a highly significant ($p < 0.001$) decline in severity among children of smoking mothers, and little change in severity for children whose mothers did not smoke (Murray and Morrison 1993). The authors attributed this change to an alteration in parental smoking behaviors following advice from clinicians to avoid smoking in the home or in the presence of the child. However, this interpretation was based on anecdotal reports, and no objective data were presented to confirm the postulated reduction in the personal exposure of the children.

Evidence Synthesis

The results summarized in this discussion and in previous sections present a complex picture of the associations of parental smoking with asthma incidence, prognosis, prevalence, and severity. The rates of incidence and recurrence of wheeze illnesses in early life are greater if there is smoking in the home, particularly by the mother, whereas the incidence of asthma during the school-age years is less strongly affected by parental smoking. A similar age-related decline in the strength of the effect of secondhand smoke exposure is evident in cross-sectional studies. These findings may simply reflect the diminishing level of secondhand tobacco smoke exposure from household sources as children age (Irvine et al. 1997; Chang et al. 2000). Alternatively or additionally, parental smoking may have differential effects on the incidence of various forms of wheeze illnesses; there may be a stronger effect on the viral infection associated with wheeze that is common in early childhood, and a weaker effect on the atopic wheeze that occurs often as a later onset component of asthma (Wilson 1989). Five studies comparing the effect of smoking on wheeze in atopic and nonatopic children lend support to the latter hypothesis (Kershaw 1987; Palmieri et al. 1990; Chen et al. 1996; Strachan et al. 1996; Rönmark et al. 1999), but a sixth does not (Murray and Morrison 1990).

The earlier section on LRIs in infancy presented evidence of an increased risk from postnatal exposure to smoking by the father in households where the mother did not smoke, but there was insufficient evidence to distinguish the separate effects of prenatal and postnatal smoking by the mother. Several of the cohort studies reviewed here have reported findings in relation to maternal smoking during pregnancy. These data are limited, and the potential role of prenatal exposure as an independent cause of asthma is still unclear. The published data are insufficient to assess the independent effect of nonmaternal smoking on the incidence or natural history of childhood asthma after the first few years of life. Most cohort studies show a weak association of asthma incidence with paternal smoking. In case-control studies, maternal smoking has the dominant effect, with little effect from smoking by the father.

Although wheeze in infancy is more likely to recur if both parents smoke, at least maternal smoking alone is associated with seemingly little long-term risk (Table 6.17). This indication could also reflect a stronger association of parental smoking with nonatopic wheeze ("wheezy bronchitis" than with "allergic asthma"), which is associated with a better prognosis. On the other hand, atopic children tend to have more severe and more frequent or persistent wheeze, and case-control studies of ("clinic") children with more severe asthma show a positive association with maternal smoking that again appears to be of greater importance. Indeed, the pooled OR for smoking by either parent from these case-control studies (1.39) is somewhat greater than the corresponding pooled ORs from cross-sectional surveys of wheeze (1.27) and asthma (1.22) among schoolchildren. Furthermore, most studies have found a greater severity of disease among children with asthma if the parents smoke (Table 6.20), and prevalence surveys among schoolchildren suggest a stronger association with more restrictive (presumably more severe) definitions of wheeze than with any recent wheeze.

These findings by age and phenotype are complex to interpret: studies of incidence and prognosis suggest an association of parental smoking primarily with early, nonatopic wheeze that tends to run a mild and transient course, whereas studies of prevalence and severity suggest that secondhand tobacco smoke exposure increases the risk of more severe symptoms and more outpatient clinic visits or emergency hospital admissions. One explanation for this pattern would be to consider secondhand tobacco smoke as a cofactor operating with intercurrent infections as a trigger

of wheeze attacks, rather than as a factor initiating or inducing persistent asthma. This distinction between induction (initiation) and exacerbation (provocation) also emerges when considering the role of outdoor air pollution as a cause of asthma (Department of Health Committee on the Medical Effects of Air Pollutants 1995). There is also strong familial aggregation for childhood asthma that certainly has genetic determinants, although research on the genetics of asthma is still inconclusive.

The incidence of both wheeze and nonwheeze LRIs in infancy increases to a similar extent if both parents smoke, and the increase reflects, at least in part, postnatal secondhand (environmental) tobacco smoke exposure. It is likely that the clinical severity of viral respiratory infections in older children is also exacerbated by secondhand smoke exposure, which leads to an increased risk of respiratory symptoms in general, including wheeze. Among children at low risk for wheeze, secondhand smoke exposure at the time of an intercurrent infection may be sufficient to cause occasional episodes of asthmatic symptoms and thus increase the risk of a mild, often transient wheeze tendency that the child outgrows as the airways become larger or less reactive with increasing age. In a previous section of this chapter, the conclusion was reached that secondhand smoke exposure from parental smoking causes LRIs in infants and children. The wheezing that accompanies many of these LRIs may be clinically classified as asthma, although the cohort study findings suggest that this phenotype is not generally persistent as the child ages.

Some previous reviews have concluded that exposure to secondhand smoke is causally associated with an increase in the incidence of childhood asthma (USEPA 1992; Halken et al. 1995). This association has been attributed to chronic (but possibly reversible) effects of parental smoking on bronchial hyperreactivity rather than to the acute effects of cigarette smoke on airway caliber (USEPA 1992). The most relevant evidence for secondhand smoke exposure and onset of asthma comes from studies of older children at an age when there is reasonable diagnostic certainty. This evidence comes from only a small number of studies and their statistical power is limited, particularly within specific age strata. In addition, all studies are inherently limited by the difficulty of classifying the outcome, and there may be variations in the phenotypes that were considered across the studies. Within these constraints, the evidence indicating an association of secondhand smoke exposure from parental smoking with asthma incidence is inconsistent. The evidence for asthma prevalence, by contrast, was sufficient to support an inference of causality.

Conclusions

1. The evidence is sufficient to infer a causal relationship between secondhand smoke exposure from parental smoking and the onset of wheeze illnesses in early childhood.

2. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure from parental smoking and the onset of childhood asthma.

Implications

The etiology of childhood asthma includes the interplay of genetic and environmental factors. The asthma phenotype likely comprises several distinct entities. The evidence is clear in showing that secondhand smoke exposure causes wheeze illnesses in early life and makes asthma more severe clinically. This evidence provides a strong basis for limiting exposure of infants and children to secondhand smoke, even though a causal link with asthma onset is not yet established for asthma incidence.

Atopy

The hypothesis that secondhand tobacco smoke exposure might increase allergic sensitization was first proposed more than 20 years ago (Kjellman 1981). However, the role of secondhand smoke exposure (specifically from maternal smoking) in allergic sensitization remains uncertain despite many investigations since that time. Some studies have documented an association between maternal smoking during

pregnancy and elevated cord blood total IgE, as well as an elevated risk for the development of allergic disease (Magnusson 1986; Bergmann et al. 1995). Other studies, however, have not replicated these findings (Halonen et al. 1991; Oryszczyn et al. 1991; Ownby et al. 1991). Many studies have investigated the relationships of secondhand smoke exposure from parental smoking with cord blood IgE concentrations, IgE levels later in childhood, skin-test reactivity, and allergic manifestations such as rhinitis (Strachan and Cook 1998c). The comprehensive, systematic review reported by Strachan and Cook (1998c) of the effects of secondhand smoke exposure from parental smoking covered IgE levels, skin-prick test reactivity, and allergic rhinitis and eczema. The review included 9 studies of IgE levels in neonates, 8 studies of IgE levels in older children, 12 studies of skin-prick tests, and 10 studies of allergic symptoms (Strachan and Cook 1998c). The quantitative summary did not show a significant association of maternal smoking with total serum IgE, allergic rhinitis, or eczema. The meta-analysis for skin-prick test positivity and smoking during infancy and pregnancy yielded a pooled OR estimate of 0.87 (95 percent CI, 0.62–1.24), suggesting no effect of secondhand smoke on skin-prick positivity during these stages of development. The summary estimate supported a conclusion that maternal smoking before birth or parental smoking during infancy is unlikely to increase the risk of allergic sensitization.

This conclusion remains consistent with results from studies conducted since this systematic review, which also found no increase in risk for allergic sensitization from secondhand smoke exposure. The discussion that follows reviews some of the key studies published since 1997 (Table 6.21).

Immunoglobulin E

Evidence for the level of cord blood IgE as a predictor of IgE-mediated disease is inconsistent. Some studies suggest that cord blood IgE predicts the development of allergic disease (Michel et al. 1980; Magnusson 1988), but others do not support that hypothesis (Halonen et al. 1991; Ruiz et al. 1991; Hansen et al. 1992). If maternal smoking during pregnancy influences immune system development and gene expression in the fetus, then the cord blood IgE concentration may be a biomarker for the effects of smoking. However, expression of genes primed in the fetal environment may not be manifest until later in life, so the complete effect of in utero tobacco smoke exposure on allergic phenotypes may not be apparent until adulthood.

A study by Kaan and colleagues (2000) examined cord blood IgE and cotinine levels in a cohort of 62 infants. The infants were part of a randomized trial of primary intervention for the prevention of asthma and allergic disease. As expected, infants of mothers who smoked at the time of study recruitment had significantly higher cotinine levels when compared with unexposed children and with children exposed to secondhand smoke from smoking by the father or other household adults. Although cord blood IgE was a significant predictor of food allergy at 12 months of age, cord blood IgE and cotinine levels were not correlated. The investigators concluded that the cord blood IgE level is not influenced by maternal smoking (Kaan et al. 2000). It should be noted that cord blood IgE values have the weakest relationship with allergy and these data should be considered separate from measures of whole blood IgE obtained at postnatal and childhood time points.

In a cohort study of 342 children followed from birth to early childhood, prenatal and postnatal tobacco smoke exposure was investigated to assess whether secondhand smoke exposure has a role in the development of allergic sensitization to food allergens during infancy and childhood (Kulig et al. 1999). The researchers collected cord blood and used a questionnaire to evaluate secondhand smoke exposure. At three years of age, children with a history of prenatal and postnatal tobacco smoke exposure had a higher risk of food allergen sensitization than children with no exposure (OR = 2.3 [95 percent CI, 1.1–4.6]). There was no association between secondhand smoke exposure and quantitative measures of cord blood IgE ($p = 0.58$) (Kulig et al. 1999). Another birth cohort study of 1,218 infants measured cord blood IgE levels in 1,064 infants (Tariq et al. 2000). Maternal smoking was evaluated at birth and again when the children were one, two, and four years of age; 20.5 percent of the mothers reported smoking during pregnancy and 25.2 percent reported smoking after childbirth. Maternal smoking during pregnancy was not associated with cord blood IgE levels at birth (Tariq et al. 2000).

Allergic Sensitization During Childhood

Other studies published since 1997 have investigated childhood IgE levels and exposure to secondhand tobacco smoke. Lindfors and colleagues (1999) investigated 189 children with asthma aged one to four years. The researchers explored the association between exposures to dog and cat allergens and the

Table 6.21 Atopy studies of markers for exposure to secondhand smoke

Study	Design/population	Measures	Findings	Comments
Farooqi and Hopkin 1998	Retrospective cohort 1975–1984 birth cohort N = 1,934 United Kingdom (Oxfordshire)	• Log regression of predictors of atopic disease • Maternal atopy • Maternal smoking	• 45.4% (879) developed atopic disorder (OR* = 1.16 [95% CI†, 0.95–1.43]) • 25% developed asthma (OR = 1.29 [95% CI, 1.03–1.63], p <0.05) • 25% developed hay fever (OR = 1.04 [95% CI, 0.82–1.32]) • 19% developed eczema (OR = 0.97 [95% CI, 0.75–1.26])	No significant association was found between maternal smoking and atopic symptoms
Lewis and Britton 1998	1970s birth cohort N = 6,068 with complete follow-up data Follow-up at 5, 10, and 16 years of age United Kingdom	• Wheeze • Eczema • Hay fever	• Wheeze increased at 16 years of age in relation to maternal smoking • There was no evidence to support maternal smoking as a contributing factor to the development of atopy	Suggested that an independent effect of smoking reduced the effect of allergic disease; hay fever was less common with high levels of maternal smoking
Tariq et al. 1998	Birth cohort N = 1,218 Followed to 4 years of age	Serum and cord IgE‡	• 27% had symptoms of allergic disease by 4 years of age • Parental smoking did not increase allergen sensitization among children	Family history of atopy was deemed the most important risk
Kalyoncu et al. 1999	N = 738 358 boys, 380 girls Aged 6–13 years Turkey (Ankara)	• Questionnaire • Prevalence of asthma, wheeze, rhinitis, and atopic dermatitis in the last 12 months	• Secondhand smoke exposure affected occurrence of allergic rhinitis (OR = 1.84 [95% CI, 1.3–3.0]) • Occurrence of any type of allergic disease or symptoms in the past 12 months was associated with secondhand smoke exposure (OR = 1.74 [95% CI, 1.18–2.56])	None

Table 6.21 Continued

Study	Design/population	Measures	Findings	Comments
Kulig et al. 1999	Birth cohort N = 342 of 1,314 from initial cohort Studied from infancy to early childhood Measured at 1, 2, and 3 years of age Children were grouped into 4 exposure categories, depending on parental smoking Germany	• Specific IgE • Questionnaire assessed parental smoking at birth, and at 18 and 36 months	• Allergic sensitization to food and aeroallergens • By 3 years of age with prenatal exposure (OR = 2.3 [95% CI, 1.1–4.6]) and postnatal exposure (OR = 2.2 [95% CI, 0.9–5.9]) to secondhand smoke, there was an increased risk of food allergy • There was no association between secondhand smoke and cord blood IgE	Effect was restricted to food allergens; there were no consistent dose-response patterns; no association between secondhand smoke and sensitization to inhaled allergens was found
Lindfors et al. 1999	N = 189 children with asthma Aged 1–4 years Sweden	• Specific IgE antibody to cat and dog allergens • Questionnaire • House dust analysis	Secondhand smoke increased the risk for sensitization to cat (OR = 2.2 [95% CI, 0.9–4.9]) and dog (OR = 2.0 [95% CI, 0.9–4.5])	There was an interaction between secondhand smoke exposure, window pane condensation, and a high level of cat allergen (OR = 42 [95% CI, 3.7–472.8]); wide CI
Suárez-Varela et al. 1999	Cross-sectional N = 3,948 Aged 6–7 years Spain (Valencia)	• Rhinitis • Atopic dermatitis • Asthma • Secondhand smoke exposure	• Severity of atopic disease increased in lower social classes • Secondhand smoke exposure increased in lower social classes	None
Vinke et al. 1999	N = 20 10 exposed and 10 unexposed	Immunohistochemical staining for Langerhans cells, T cells, B cells, granulocytes, macrophages, mast cells, and eosinophils in the nasal mucosa	There were more IgE-positive cells and eosinophils in the nasal mucosa of children exposed to secondhand smoke	Secondhand smoke leads to a tissue infiltrate that resembles infiltrates in the nasal mucosa of children with allergy; no significant sensitization was found in nasal mucosa with increased IgE on cell surface
Kaan et al. 2000	397 high-risk infants in a controlled trial to prevent asthma and allergic disease Canada (Vancouver and Winnepeg)	• Total IgE • Serum cotinine in cord blood taken at birth	There was no correlation between cord blood IgE and cotinine levels	None

Table 6.21 Continued

Study	Design/population	Measures	Findings	Comments
Tariq et al. 2000	Birth cohort N = 1,218 Tested at 1, 2, and 4 years of age 981 were skin-prick tested Cord IgE from 1,064 United Kingdom (Isle of Wight)	• Skin testing • Cord blood IgE	• Maternal smoking did not increase allergen sensitization at 4 years of age • There was an inverse association between maternal smoking during and after pregnancy and allergen sensitization at 4 years of age	Smoking while pregnant has no effect on cord blood IgE at birth
Ulrik and Backer 2000	408 participants from case histories of 983 children Aged 7–17 years Longitudinal surveys were 6 years apart Denmark (Copenhagen)	• Skin-prick test • Total serum IgE • Pulmonary function • Airway responsiveness	There was an increased risk of a positive skin prick at second survey with exposure to maternal smoking (OR = 2.0 [95% CI, 1.3–3.1], p = 0.002)	None
Zacharasiewicz et al. 2000	N = 18,606 children Aged 6–9 years Austria	Nasal symptoms suggestive of atopic rhinitis	• Maternal smoking during pregnancy and/or breastfeeding increased risks for rhinitis in the last 12 months (OR = 1.28 [95% CI, 1.07–1.52]) • ≥50 cigarettes smoked at home: OR = 2.9 (95% CI, 1.21–6.95)	There was a demonstrated dose-response pattern for allergic symptoms depending on the amount of secondhand smoke exposure

*OR = Odds ratio.
†CI = Confidence interval.
‡IgE = Immunoglobulin E.

risk for allergic sensitization, and assessed whether the risk of allergen sensitization was modified by secondhand smoke exposure (Lindfors et al. 1999). In this study, questionnaires were completed regarding exposures to dogs, cats, home dampness as indicated by window pane condensation, and secondhand smoke, which was evaluated from questions about parental smoking in the home during the child's first two years of life; house dust was also analyzed. Exposure to secondhand tobacco smoke increased the risk for allergic sensitization to cats (Radioallergosorbent Test [RAST] e1 cat ≥0.35 kilounit per liter (kU/L), OR = 2.2 [95 percent CI, 0.9–4.9]; RAST e1 cat ≥0.70 kU/L, OR = 2.1 [95 percent CI, 0.7–6.5]). Exposure to secondhand smoke also increased the risk for sensitization to dogs (RAST e5 dog ≥0.35 kU/L, OR = 2.0 [95 percent CI, 0.9–4.5]). With joint exposure to cats, secondhand smoke, and home dampness, the OR of 42.0 indicated a very high risk for allergic sensitization to cats, although CIs were broad (95 percent CI, 3.7–472.8). The investigators concluded that secondhand smoke exposure may promote atopic sensitization in children with asthma. The study did not control for in utero exposure to smoking (Lindfors et al. 1999).

A six-year prospective cohort study of 408 Danish children and adolescents aged 7 to 17 years initially included measurements of IgE and skin tests to common allergens. Only a single measurement of IgE was available when the study began. An analysis of individuals who were not atopic at the time of the first

examination showed that exposure to secondhand tobacco smoke from maternal smoking increased the risk for a positive skin-prick test at the second evaluation (OR = 2.0 [95 percent CI, 1.3–3.1]), but changes in IgE levels could not be assessed. The authors concluded that exposure to secondhand smoke was associated with an increased risk of sensitization to common aeroallergens in adolescence (Ulrik and Backer 2000).

Other recent investigations have focused on children in the first three to four years of life, a critical time for alveolar and immune system development. In a birth cohort study, 981 children of the original cohort of 1,218 children were tested by skin prick for common aeroallergens at one, two, and four years of age (Tariq et al. 2000). An inverse association was noted for exposure to maternal smoking during pregnancy and childhood and the development of allergic sensitization at four years of age. Among children whose mothers smoked during pregnancy and/or after birth, 31.4 percent were not sensitized to aeroallergens versus 21.2 percent who were ($p < 0.05$). Paternal smoking was not associated with allergen sensitization or skin-test reactivity (17.2 percent of those exposed versus 20.5 percent who were not exposed to paternal smoking). The investigators noted that secondhand smoke exposure from paternal sources may have been underestimated because more mothers than fathers were available for interviews (Tariq et al. 2000). Kulig and colleagues (1999) found that in children three years of age who had been exposed to secondhand smoke prenatally and postnatally, secondhand smoke exposure and sensitization to aeroallergens were not associated.

For the updated meta-analysis of the evidence relating parental smoking to allergic sensitization in children as measured by a skin-prick test (Strachan and Cook 1998b), 50 potentially relevant studies were identified, 3 of which yielded sufficient data to calculate the effect measure of interest. One of these papers was not included in the synthesis (Burr et al. 1997) because it measured allergic sensitization in neonates instead of in children. Two papers (Arshad et al. 1993; Tariq et al. 2000) analyzed the same data, and the more recent results (Tariq et al. 2000) are included here. In both the 1998 synthesis and this meta-analysis, the effect measure compared the relative odds of positive skin-prick reactions in exposed versus unexposed children. Studies were grouped according to the timing of secondhand smoke exposure: perinatal (maternal smoking during pregnancy and parental smoking from infancy to four years of age) and childhood (parental smoking at five or more years of age). The updated meta-analysis includes 10 papers (Table 6.22). There was significant heterogeneity among the studies. The heterogeneity does not seem to be explained by study characteristics such as design, location, age group, or exposure measure.

The results of studies of perinatal exposure were the least heterogeneous; the pooled ORs suggest a nonsignificant reduction in risk among children exposed to secondhand smoke (Table 6.23 and Figure 6.11). The evidence is less consistent for childhood exposures (Figure 6.12 and Table 6.23). The random effects estimate, which is more appropriate than the fixed effects given the significant heterogeneity, shows a small and nonsignificant increase in risk associated with exposure, although this conclusion is limited by the small number of studies included in this analysis.

Considering all of the studies together, the random effects estimate is 1.10 (95 percent CI, 0.85–1.42), a nonsignificant increase in risk among exposed children (Figure 6.13 and Table 6.23). The results of these studies confirm those of the previous meta-analysis: parental smoking during pregnancy or childhood is not consistently associated with an increased risk of allergic sensitization.

Atopic Disease

Findings from recent investigations of atopic disease indicators such as allergic symptoms, eczema, rhinitis, and dermatitis are generally consistent with the earlier systematic review. Studies document that secondhand smoke exposure affects cellular biomarkers. Vinke and colleagues (1999) demonstrated that IgE-positive cells and eosinophils were higher in the nasal mucous of children exposed to secondhand smoke than in unexposed children. The researchers concluded that although secondhand tobacco smoke exposure led to a tissue infiltrate in biopsy specimens that resembles that in the nasal mucosa of children with allergy, a key difference was the lack of IgE-positive mast cells in biopsy specimens from the nonatopic children exposed to secondhand smoke (Vinke et al. 1999).

In a prospective cohort study of 6,068 children born in 1970, a follow-up for indicators of atopy was carried out at 5, 10, and 16 years of age by questioning parents (Lewis and Britton 1998). Maternal smoking was measured as "maternal smoking during pregnancy" and "current maternal smoking." The findings did not support the hypothesis that maternal smoking during pregnancy or current maternal smoking contributes to the development of atopy. In fact, the occurrence of hay fever at 16 years of age was less

Table 6.22 Studies relating parental smoking to skin-prick positivity in children

Study/location	Design/ population	Exposure measure	Outcome measure	Odds ratio (95% confidence interval)
Perinatal secondhand smoke exposure				
Kuehr et al. 1992 Germany	Survey N = 1,470 Aged 6–8 years	Mother smoked during pregnancy	Any of 7 SPT* ≥3 mm†	0.6 (0.3–1.1)
Bråbäck et al. 1995 Estonia	Survey N = 1,519 Aged 10–12 years	Secondhand smoke in home during infancy	Any of 8 SPT ≥0 mm	1.2 (0.9–1.8)
Poland	Survey N = 410 Aged 10–12 years	Secondhand smoke in home during infancy	Any of 8 SPT ≥0 mm	0.6 (0.3–1.1)
Sweden	Survey N = 665 Aged 10–12 years	Secondhand smoke in home during infancy	Any of 8 SPT ≥0 mm	1.3 (0.9–1.8)
Henderson et al. 1995 United States (North Carolina)	Survey N = 219 Aged 7–12 years	Mother smoked during pregnancy	Any of 14 SPT ≥4 mm	0.8 (0.4–2.0)
Søyseth et al. 1995 Norway	Survey N = 529 Aged 7–13 years	Mother smoked during pregnancy	Any of 8 SPT ≥3 mm	0.6 (0.4–1.0)
Tariq et al. 2000 United Kingdom	Cohort N = 1,456 Aged 0–4 years	Mother smoked when child was 4 years of age	Any of 12 SPT ≥3 mm	1.1 (0.6–1.6)
Childhood secondhand smoke exposure				
Weiss et al. 1985 United States (Massachusetts)	Cohort N = 163 Aged 12–16 years	Mother currently smoked	Any of 4 SPT >0 mm	2.2 (1.1–4.4)
Ronchetti et al. 1992 Italy	Cohort N = 142 Aged 13 years	Either parent smoked	Any of 10 positive SPT	1.7 (0.8–3.8)
von Mutius et al. 1994 Germany	Survey N = 8,653 Aged 9–11 years	Mother currently smoked	Any of 6 SPT ≥3 mm	0.8 (0.7–0.9)
Henderson et al. 1995 United States (North Carolina)	Survey N = 219 Aged 7–12 years	Parental smoking when child was 5 years of age	Any of 14 SPT ≥4 mm	1.1 (0.6–1.9)
Søyseth et al. 1995 Norway	Survey N = 529 Aged 7–13 years	Mother currently smoked	Any of 8 SPT ≥3 mm	0.8 (0.5–1.2)

Table 6.22 Continued

Study/location	Design/ population	Exposure measure	Outcome measure	Odds ratio (95% confidence interval)
		Childhood secondhand smoke exposure		
Zeiger and Heller 1995 United States	Trial N = 165 Aged 7 years	Regular smoking at home	Any of 9 positive SPT	2.9 (1.1–7.7)
Ulrik and Backer 2000 Denmark	Cohort N = 408 Aged 7–17 years	Maternal smoking during childhood	Any of 9 SPT ≥3 mm	2 (1.2–3.1)

*SPT = Skin-prick test.
†mm = Millimeter.

Table 6.23 Summary of pooled odds ratios (95% confidence intervals) in skin-prick positivity comparing unexposed children with children exposed to secondhand smoke at various time points

	Perinatal exposure	Childhood exposure	Perinatal or childhood exposure
Number of studies	7	7	12
Fixed effects	0.97 (0.81–1.15)	0.90 (0.81–1.01)	0.92 (0.84–1.02)
Random effects	0.90 (0.68–1.18)	1.35 (0.91–2.01)	1.10 (0.85–1.42)
Q (p value)	13.1 (0.042)	29.5 (0.000)	42.2 (0.000)

Note: Q is the chi-square distributed test statistic for the null hypothesis of no heterogeneity between studies.

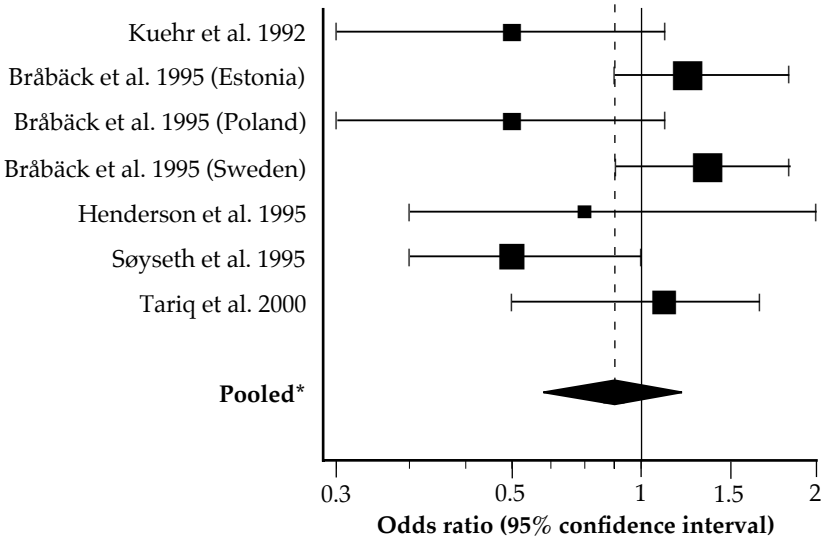
common in those with the highest levels smoked by the mother (current smoking OR = 0.78 [95 percent CI, 0.67–0.92]). A risk for eczema at 16 years of age was not associated with current maternal smoking.

Kalyoncu and colleagues (1999) conducted two questionnaire surveys five years apart to evaluate prevalence rates for asthma, allergic disease, and risk factors among primary school-age children. The second survey included 358 boys and 380 girls aged 6 through 13 years. In this sample, smoking at home was associated with the occurrence of allergic rhinitis (OR = 1.84 [95 percent CI, 1.3–3.0]), and the occurrence of allergic symptoms during the past 12 months was associated with secondhand tobacco smoke exposure (OR = 1.74 [95 percent CI, 1.18–2.56]) (Kalyoncu et al. 1999).

In a retrospective cohort study of 1,934 children, there was no significant association between maternal smoking and atopy (OR = 1.16 [95 percent CI, 0.95–1.43]), hay fever (OR = 1.04 [95 percent CI, 0.82–1.32]), or eczema (OR = 0.97 [95 percent CI, 0.75–1.26]) (Farooqi and Hopkin 1998). The authors concluded that genetic factors constitute the main risk for the development of atopy in children. With an OR of 1.97 (95 percent CI, 1.46–2.66), maternal atopy was a predictor of the development of atopy in these children (Farooqi and Hopkin 1998).

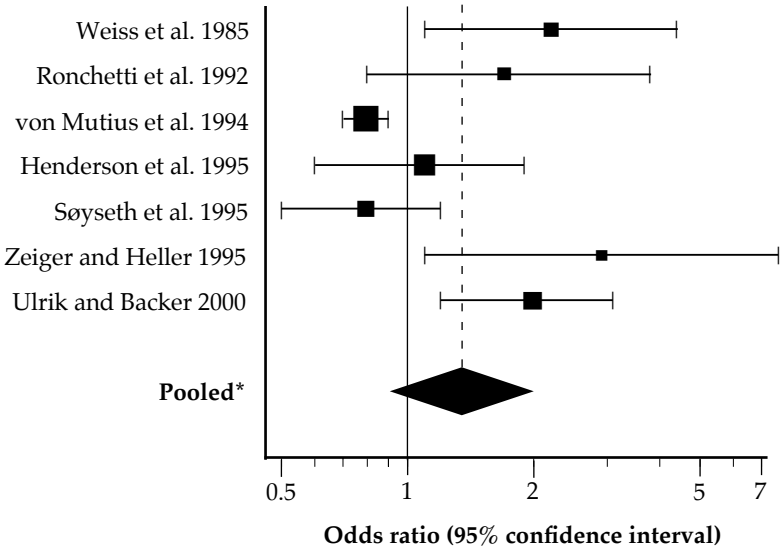
As part of ISAAC, parents answered a supplemental questionnaire regarding indoor environmental exposures and childhood symptoms of atopic rhinitis. For participants in Austria, there were questionnaire responses for 18,606 children aged six through nine years (Zacharasiewicz et al. 2000). Multiple indoor environmental exposures were considered in the analyses, including maternal smoking during pregnancy and/or while breastfeeding, secondhand smoke exposure, mattress and bedding type, home dampness, cooking fuels, home heating, and indoor pets. Overall, there was no difference between indoor environmental exposures in children with rhinitis symptoms only during the pollen season versus those with symptoms year round. Maternal smoking during pregnancy and

Figure 6.11 Odds ratios for the association between parental smoking during pregnancy and infancy and skin-prick positivity



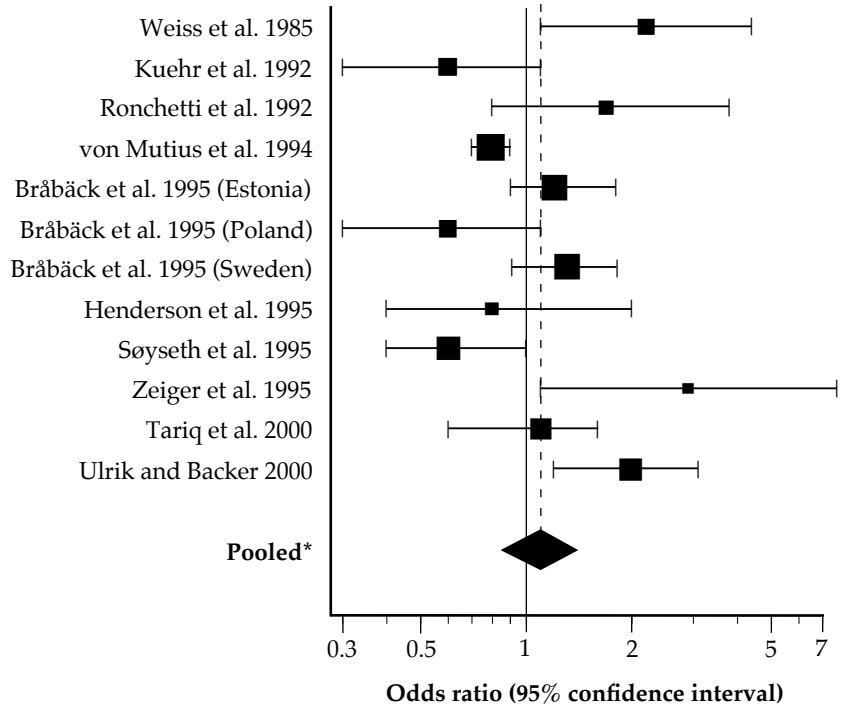
Note: Size of boxes is proportional to the weight of each study in the pooled odds ratio (OR). Solid line represents an OR of 1, dotted line is the combined result.
*From random effects meta-analysis.

Figure 6.12 Odds ratios for the association between parental smoking during childhood and skin-prick positivity



Note: Size of boxes is proportional to the weight of each study in the pooled odds ratio (OR). Solid line represents an OR of 1, dotted line is the combined result.
*From random effects meta-analysis.

Figure 6.13 Odds ratios for the association between parental smoking and skin-prick positivity



Note: Size of boxes is proportional to the weight of each study in the pooled odds ratio (OR). Solid line represents an OR of 1, dotted line is the combined result.
*From random effects meta-analysis.

after birth while the mother breastfed was associated with an increased risk for atopic rhinitis symptoms in the 12 months before the interview (OR = 1.28 [95 percent CI, 1.07–1.52]). There was also evidence of a dose-response relationship: nasal symptoms in the previous 12 months increased if household smokers smoked 50 or more cigarettes per day in the home (OR = 2.9 [95 percent CI, 1.21–6.95]) (Zacharasiewicz et al. 2000).

Heterogeneity in the measures of allergic sensitization across the studies limits comparisons. There are no prospective cohort studies that demonstrate longitudinal changes in IgE levels associated with prenatal and postnatal secondhand smoke exposure. Assessments of parental and sibling symptoms are critical to these studies, as those children predisposed to the development of allergic sensitization secondary to secondhand smoke exposure may be those most genetically predisposed to the development of atopy, and gene-environment interactions will need to be considered in future studies of secondhand smoke exposure in children.

Evidence Synthesis

There are multiple mechanisms by which secondhand smoke exposure might alter the risk for allergic diseases in infants and children. Exposure to tobacco smoke components from maternal smoking during pregnancy might have lasting effects on lung and systemic immunophenotypes. Exposures after birth might also affect immunophenotype or increase susceptibility to sensitization by common allergens.

The observational evidence across a range of outcome measures is inconsistent, however. The inconsistency may partially reflect the limited number of studies for any particular outcome and the methodologic complexities of studies on atopic disorders.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between parental smoking and the risk of immunoglobulin E-mediated allergy in their children.

Implications

Studies on secondhand smoke exposure and atopy need to be prospective in design and should track exposures back to the pregnancy. Further studies on secondhand smoke and atopy in childhood are needed, but the studies need to be large enough and need to have sufficient and valid measurements of allergic phenotype. Future studies also need to address potential genetic determinants of susceptibility, particularly as they modify the effect of secondhand smoke.

Lung Growth and Pulmonary Function

Beginning with the 1984 report (USDHHS 1984), the U.S. Surgeon General's reports in this series have covered the adverse effects of exposure to secondhand smoke, including effects from maternal smoking during pregnancy and effects on lung growth from exposure during infancy and childhood. Both cross-sectional and cohort studies on this topic have used lung function level as the primary indicator (Table 6.24). The level of lung function achieved at any particular age and measured cross-sectionally is an indicator of the rate of growth of function up to that age; cohort studies with repeated measurements of lung function directly estimate the rate of growth. The 1986 Surgeon General's report, *The Health Consequences of Involuntary Smoking*, reviewed 18 cross-sectional and cohort studies and concluded that "available data demonstrate that maternal smoking reduced lung function in young children" (USDHHS 1986, p. 54). The report further suggests that although this reduction is small, with an average of 1 to 5 percent, "some children might be affected to a greater extent, and even small differences might be important for children who become active cigarette smokers as adults" (USDHHS 1986, p. 54). The EPA issued its risk assessment in 1992 and concluded that the decline in lung function associated with exposure to secondhand smoke represented a causal effect (USEPA 1992). Similar conclusions were reached by the California Environmental Protection Agency (NCI 1999) and WHO (1999). Thus, for nearly two decades the weight of evidence has been sufficient to conclude that prenatal and postnatal tobacco smoke exposure is associated with a decrease in lung function in childhood. As discussed earlier in this chapter (see "Mechanisms of Health Effects from Secondhand Tobacco Smoke"), lung maturation and growth decrements secondary to exposure are reflected in changes in measured pulmonary function.

A 1998 meta-analysis by Cook and colleagues (1998) concluded that maternal smoking was associated with reduced ventilatory function assessed by spirometry. In a quantitative synthesis of 21 cross-sectional studies, the effects of parental smoking on lung function were reductions of the FVC by 0.2 percent (95 percent CI, -0.4–0.1), the FEV_1 by 0.9 percent (95 percent CI, -1.2 to -0.7), the MEFR by 4.8 percent (95 percent CI, -5.4 to -4.3), and the end-expiratory flow rate (EEFR) by 4.3 percent (95 percent CI, -5.3 to -3.3). The meta-analysis also considered six prospective cohort studies and found only a small effect of current exposure on decreased growth in lung function. The researchers attributed most of the decreased growth to a lasting consequence of in utero exposure from maternal smoking (Cook et al. 1998).

This discussion considers some of the studies included in this 1998 meta-analysis in addition to studies published subsequently. The studies are both cross-sectional and cohort in design, include data on maternal smoking during pregnancy and after birth, and indicate that maternal smoking during pregnancy has a substantially greater adverse effect. As discussed above, maternal smoking affects lung development in utero perhaps by a direct toxic effect, by gene regulation, or by leading to developmental abnormalities. The number of airways in the lung is considered fixed

Table 6.24 Cross-sectional and cohort studies that used lung function level as the primary indicator of adverse effects of exposure to secondhand smoke

Study	Design/population	Measures	Findings	Comments
Cook et al. 1993	Random population-based sample N = 2,511 children Aged 5–7.9 years 10 towns in England and Wales	• Questionnaire • Salivary cotinine • FEV_1* • FVC† • FEF_{25}‡ • FEF_{50} • FEF_{75}	• PFT§ results were negatively associated with cotinine • FEV_1/FVC^{Δ} was not correlated with salivary cotinine • FEV_1 decreased linearly with an increase in salivary cotinine	Cannot distinguish as an early effect
Rona and Chinn 1993	Cross-sectional national health survey N = 2,756 children Aged 6.5–12 years Great Britain	Data were not reported	• There was a significant association between maternal smoking and decreased FEF_{25-75}¶ and FEF_{75-85} in boys but not in girls • The FEV_1 decreased in boys exposed to maternal secondhand smoke	Concluded that reduced childhood lung function was associated with maternal smoking
Cunningham et al. 1994	N = 8,863 children Aged 8–12 years 24 cities United States	• Questionnaire • FEV_1 • FVC • FEV_1/FVC • FEV_{75} • PEFR** • FEF_{25-75} • FEF_{65-75}	• FEV_{75} decreased by 1.8% • FEV_1 decreased by 1.4% • FEV_1/FVC decreased by 1.3% • PEFR decreased by 2.1% • FEF_{25-75} decreased by 5.2% (findings are unadjusted for covariates)	When adjusted for prenatal smoking, effects of current smoking decreased; there was no significant association of secondhand smoke exposure with a decrease in lung function between birth and 2 years of age except in the FEF_{25-75}
Haby et al. 1994	N = 2,765 children Aged 7–12 years Australia	• FEV_1 • FVC • PEFR • FEF_{25-75}	Dose-related decrease in FEV_1, PEFR, and FEF_{25-75} but not in FVC with secondhand smoke exposure	Dose was the number of cigarettes smoked in the home; there was no report on gender difference in maternal or paternal smoking

Table 6.24 Continued

Study	Design/population	Measures	Findings	Comments
Wang et al. 1994	N = 8,796 children Aged 6–18 years Exposure was measured in preschool (first 5 years of life), cumulative exposure from 6 years of age to 1 year before the exam China	• Regression splines to model pulmonary function as a function of secondhand smoke exposure were adjusted for age, weight, city, and parental education • Current maternal and paternal smoking	• Preschool exposure was a significant predictor of child pulmonary function • There was no difference in effect for boys vs. girls; there was a small but statistically significant reduction in FEV_1/FVC and FEF_{25-75} through adolescence • Early maternal smoking was associated with a small increase in FVC (statistically significant in children aged 11–18 years) • Children aged 6–10 years exposed to current maternal smoking had slower FVC and FEV_1 growth	Early exposure to secondhand smoke had long-lasting effects on lung growth
Cuijpers et al. 1995	N = 535 children Aged 6–12 years Netherlands	• FVC • FEV_1 • PEF • FEF_{25-75}	• Decreases in FVC, FEV_1, PEF, and FEF_{25-75} in boys were related to lifetime secondhand smoke exposure • A decrease in FEF_{25-75} was significant only in girls	None
Cunningham et al. 1995	N = 876 children Aged 9–11 years United States (Pennsylvania)	• Secondhand smoke exposure was determined by questionnaire • Pulmonary function • FEV_1 • FVC • FEV_1/FVC • FEF_{25-75}	• There was a statistically significant decrease in FEF_{25-75} of -8.1% (95% confidence interval [CI], -12.9 to -3.1), and a decrease in FEV_1/FVC of -2% (95% CI, -3.0 to -0.9) with maternal smoking during pregnancy • There was no statistically significant decrease in FEV_1 • There was no decrease in FVC	Current secondhand smoke exposure was not associated with lung function decrease after adjustment for maternal smoking during pregnancy; effect on boys was greater than effect on girls
Goren and Hellmann 1995	Cross-sectional N = 8,259 children 2nd and 5th graders (ages not provided) Israel	• FVC • FEV_1 • PEF • FEV_1/FVC	There was no relationship between lung volume and secondhand smoke	None

Table 6.24 Continued

Study	Design/population	Measures	Findings	Comments
Søyseth et al. 1995	N = 573 children (out of a birth cohort of 620) Aged 7–13 years Norway	• Parental smoking • Prenatal smoking	There was a slight (but not statistically significant) decrease in FEV_1/FVC in relation to maternal smoking	None
Richards et al. 1996	N = 395 children Aged 14–18 years South Africa	• FEF_{25-75} • FEV_1	There was no significant difference in the FEV_1 or FEF_{25-75} in exposed vs. unexposed adolescents	None
Behera et al. 1998	N = 2,000 children 77 girls, 123 boys Aged 7–15 years Northern India	• FEV_1 • FVC • PEFR • Maximal MEF†† • FEF_{25} • FEF_{50} • FEF_{75}	• FVC and FEV_1 were lowest in boys whose households used biomass fuels ($p < 0.05$) • All parameters were lower in children exposed to secondhand smoke but were not statistically significant	None
Bono et al. 1998	Longitudinal N = 394 children Aged 14–16 years 2 consecutive years (1992–1993) Northwest Italy	• Questionnaire • Urinary cotinine • FVC • FEV_1 • Maximal MEF_{25} • Maximal MEF_{50} • PEF‡‡	Effect for FEV_1 percentage change as measured for natural log of the mean cotinine concentration was -0.66% ($p < 0.05$)	Active and involuntary exposure to tobacco smoke had a significant effect on lung growth measured by linear change in FEV_1; effect was small but dose-related
Demissie et al. 1998	N = 989 children Aged 5–13 years 1990–1992 Canada (Montreal)	• Questionnaire • FVC • FEV_1 • FEV_1/FVC	• FEV_1/FVC decreased (β = -2.13 [95% CI, -4.07–0.19], the estimated effect for a household exposure of 7.25 cigarettes/day vs. none) in boys exposed to secondhand smoke • Maternal smoking during pregnancy was associated with a lower FEV_1 ($p = 0.04$) • Maternal smoking was associated with a lower FEV_1/FVC	Gender difference could be attributable to the difference in maturation rates of lungs in girls vs. in boys
Hoo et al. 1998	108 preterm infants United Kingdom	• $Vmax_{FRC}$§§ • $T_{PTEF}:T_E$ΔΔ • Infant urine cotinine • Passive respiratory compliance	$T_{PTEF}:T_E$ was lower in infants exposed in utero, $p \leq 0.02$	Measured respiratory function in preterm infants only; concluded that an adverse effect was present and was not limited to the last weeks of pregnancy

Table 6.24 Continued

Study	Design/population	Measures	Findings	Comments
Bek et al. 1999	N = 360 children 169 girls, 191 boys Aged 9–13 years Turkey (Ankara)	• Questionnaire • Spirometry for FEV_1/FVC • FEV_1/FVC • PIF[¶¶]/PEF • FEF_{25-75} • $Vmax_{25}$ • $Vmax_{50}$ • $Vmax_{75}$	• All spirometric indices were lower in those with secondhand smoke exposure • Maternal smoking had no significant effect but paternal smoking was associated with reduced FEF_{25-75} ($p = 0.02$), PEF ($p = 0.03$), $Vmax_{50}$ ($p = 0.008$), and $Vmax_{75}$ ($p = 0.009$) • There was no significant reduction in peak flow in children whose mothers had smoked during pregnancy	79% of fathers smoked, suggesting that fathers should be targeted, although it may be a sampling issue; there was no significant dose-response pattern
Gilliland et al. 2000	Cross-sectional N = 3,357 children 4th, 7th, and 10th graders United States (Southern California)	• Questionnaire • Current/former smoking while pregnant • PEFR • FVC • FEV_1 • FEV_1/FVC	• In utero exposure • Decreased PEFR: -3% (95% CI, -4.4% to -1.4%) • Decreased maximal MEF: -4.6% (95% CI, -7% to -2.3%) • Decreased FEF_{75}: -6.2% (95% CI, -9.1% to -3.1%) • There was no decrease in FEV_1	In utero exposure to maternal smoking was independently associated with decreased lung function in school-age children, especially for small airway flows
Li et al. 2000	Cross-sectional N = 5,263 children 49% boys, 51% girls Aged 7–19 years Two consecutive years (1992–1993)	• Questionnaire • FVC • FEV_1 • FEV_1/FVC • Maximal MEF	• In utero effects were independently associated with lung function deficits, which were greater in children with asthma • Decreased maximal MEF • Decreased FEV_1/FVC	Used regression splines to account for nonlinear effects; effects of secondhand smoke depend on gender and/or asthma status; in utero exposure leads to persistent lung function deficits, with the greatest effects in those with asthma
O'Connor et al. 2000	N = 2,043 children Aged 10–11 years Boys and girls in 8 U.S. and Canadian communities	• Questionnaire • FVC • FEV_1 • FEV_1/FVC ratio • V_{35M} • V_{30M} • V_{25M}	• V_{30M}/V_{30P} ratio was not related to asthma or maternal smoking • V_{30M}/V_{30P} ratio was slightly higher among girls than boys • FVC was lower with a history of asthma or maternal smoking	Spirometric indices such as FEF_{25-75}/FVC are sensitive to effects of asthma and secondhand smoke exposure; volume history has no benefit

Table 6.24 Continued

Study	Design/population	Measures	Findings	Comments
Mannino et al. 2001	Cross-sectional N = 5,400 children Aged 4–16 years NHANES III*** United States	• Questionnaire • Serum cotinine (stratified by tertiles) • Spirometry on children aged 8 or more years • FEV_1 • FVC • Maximal MEF • FEV_1/FVC	• Children with highest cotinine levels had decreased FEV_1 (mean = -1.8% [95% CI, -3.2% to -0.4%]) • At highest cotinine levels, children were more likely to have FEV_1/FVC <0.8 (odds ratio = 1.8 [95% CI, 1.3–2.4]) • Secondhand smoke was associated with decreased lung function at ages 8–11 years without prenatal secondhand smoke exposure but with secondhand smoke exposure during childhood	Used cotinine to decrease misclassification bias; large sample, but may lack power to detect small increases in odds ratio for some outcomes

*FEV_1 = Forced expiratory volume in 1 second during maximal expiratory effort.
†FVC = Forced vital capacity or total volume of air expired after a full inspiration.
‡FEF_{25} = Amount of air expelled in the first 25% of the total forced vital capacity test. This test is useful when looking for obstructive diseases.
§PFT = Pulmonary function test.
ΔFEV_1/FVC = Percentage of the vital capacity that is expired in the first second of maximal expiration.
¶ FEF_{25-75} = Forced mid-expiratory flow rate. Average rate of airflow between 25% and 75% of the FVC, which is reduced in both obstructive and restrictive disorders.
**PEFR = Peak expiratory flow rate.
††MEF = Mid-expiratory flow.
‡‡PEF = Peak expiratory flow or maximum flow achieved after a maximal inhalation and forced exhalation.
§§$Vmax_{FRC}$ = Maximal forced expiratory flow at functional residual capacity.
ΔΔT_{PTEF}:T_E = The ratio of time to peak tidal expiratory flow to expiratory time.
¶¶PIF = Peak inspiratory flow.
***NHANES III = Third National Health and Nutrition Examination Survey.

by the time a child is born, but the number of alveoli in the lung increases until four years of age (Dezateux and Stocks 1997). The period from gestation to four years of age thus represents a vulnerable time for lung growth and development, and exposures during this time are potentially the most critical for structural and functional lung development and performance. This section reviews the evidence that associates different phases of lung growth and development with corresponding ages.

Neonatal and Infant Lung Function and Growth

Evaluating lung function in neonates and infants is challenging because of an inability of the young child to cooperate with testing. However, methods that do not rely on cooperation from the child have been developed and standardized to assess pulmonary function during this period of ongoing lung development. The FRC is the most common measure of lung volumes performed in infants and is an indicator of normal lung volume growth. Measures of FRC can

be completed using gas dilution (nitrogen washout) techniques or plethysmography, although plethysmographic measures are more difficult to perform accurately with this age group. Airway resistance can be measured using plethysmography; lung resistance and compliance can be measured using esophageal manometry and forced oscillation methods. The partial forced expiratory maneuver can be used to obtain estimates of the forced expiratory flow rate (FEFR). This maneuver is performed using an inflatable jacket around the thorax of the infant, who is sedated and in the supine position. A rapid mechanical squeeze of the thorax by the jacket accomplishes the expiratory maneuver. With exhalation data from the FRC, partial expiratory flow maneuvers can be normalized and provide information on lung growth and disease in infants. These methods have been used both clinically and in research. The relationship of these infant lung function tests to standard spirometry, which can be measured reproducibly from around five years of age, is still unclear; researchers have published reviews of infant lung function measurements (Stocks et al. 2001; Davis 2003).

Hanrahan and colleagues (1992) conducted a birth cohort study in east Boston that was designed to measure the effect of maternal smoking during and after pregnancy on infant lung function after birth. Maternal reports of smoking during pregnancy were validated against measures of urinary cotinine. In 80 infants studied at a mean age of 4.2 (±1.9) weeks of age, there was a reduced flow in the FRC among infants born to mothers who had smoked during pregnancy (74.3 milliliters [mL] per second) compared with infants whose mothers had not smoked during pregnancy (150.4 mL per second, $p = 0.0007$). The effects were independent of effects from secondhand smoke on gestational age and birth weight. After stratification by prenatal exposure, the flow rates were not associated with postnatal exposure.

Tager and colleagues (1995) investigated the growth of pulmonary function in 159 infants in the same east Boston cohort. Infant pulmonary function tests were evaluated at 2 to 6 weeks, 4 to 6 months, 9 to 12 months, and 18 months of age using partial expiratory flow volume curves and helium dilution measures for the FVC to evaluate the effects of prenatal tobacco smoke exposure on lung function growth in the first 18 months of life. Maternal smoking during pregnancy was associated with a decrease in the FRC itself (9.4 ± 4.3 mL, $p = 0.03$) and a decrease in the FRC flow rate (33 ± 12.3 mL per second, $p = 0.0008$); these estimates were adjusted for the growth of the child. Because of the longitudinal structure of the data, including lung function assessment shortly after birth, the study data could separate the effects of prenatal and postnatal exposure. The study demonstrated an effect of maternal smoking on the FEFR at the FRC, with a multivariate analysis showing that the effect was secondary to prenatal but not to postnatal exposure.

An Australian cohort study that recruited participants from a prenatal care clinic assessed secondhand smoke exposure from a questionnaire and evaluated cotinine levels. The researchers tested lung function in 461 infants by measuring the $T_{PTEF}:T_E$. Measurements at one to six and one-half days of age showed lower values in infants whose mothers smoked more than one-half pack of cigarettes per day (Stick et al. 1996).

Two studies published since the 1998 meta-analysis (Cook et al. 1998) also assessed the effects of maternal smoking during pregnancy on infants (Hoo et al. 1998; Dezateux et al. 1999). Hoo and colleagues (1998) measured the $Vmax_{FRC}$ and $T_{PTEF}:T_E$ in a cohort of preterm infants born at a mean gestational age of 33.5 weeks. Of the 108 infants in the cohort, 40 were born to mothers who had smoked during pregnancy. The $T_{PTEF}:T_E$ was lower in infants exposed to secondhand smoke in utero (mean 0.369, SD 0.109) compared with unexposed infants (mean 0.426, SD 0.135, $p \leq 0.024$). This was the first study to evaluate preterm infants, and the investigators found an effect of maternal smoking on lung development by the 33rd week of gestation.

A study by Dezateux and colleagues (1999) investigated the association of postnatal maternal smoking with measures of specific airway conductance at eight weeks and at one year of age. The initial cohort consisted of 108 term infants with a lung function assessment at eight weeks of age; 100 were available for a longitudinal follow-up at one year of age. Specific airway conductance at end expiration ($sGaw_{EE}$) was used as a measure of airway function with a correction for airway size. In multivariate models that included physician-diagnosed wheeze, a family history of asthma, $sGaw_{EE}$ measured at eight weeks, and a maternal history of postnatal smoking, there was a decrease of 0.40 seconds per kilopascal (unit of pressure) (95 percent CI, -0.71 to -0.10, $p = 0.01$) in sGaw among infants of mothers who had smoked in the early postnatal period. The authors concluded that early postnatal maternal smoking was an important cause of altered airway function in the infant, with implications for lung growth and development.

Childhood Lung Function and Growth

Researchers have conducted multiple studies of older children to characterize the effects of secondhand smoke exposure on lung growth and development beyond the neonate or infancy stage. Some of these studies evaluated in utero, postnatal, and current tobacco smoke exposures. Although several large, cross-sectional studies (presented below) have been published since the 1998 meta-analysis (Cook et al. 1998), there has been little additional longitudinal evidence since 1997.

One cross-sectional study was carried out in 24 U.S. and Canadian cities to assess the effects of air pollution on child respiratory health. Using data from 8,863 children aged 8 to 12 years in 22 of the cities, Cunningham and colleagues (1994) found that lung function was lower in children whose mothers had smoked during pregnancy. The study recorded maternal smoking histories and pulmonary function measures. Regardless of whether these mothers were still smoking the year before study assessment, their children had lower spirometric measures than children with no in utero or postnatal exposure to maternal smoking. In comparisons of exposed and unexposed children, adjusted findings in exposed children included a 5.7 percent reduction (95 percent CI, -7.7 to -3.6 percent) in the FEF that was between 65 and 75 percent of the FVC, a 4.9 percent reduction (95 percent CI, -6.5 to -3.2 percent) in the FEF measured between 25 and 75 percent of the FVC (FEF_{25-75}), and a 1.7 percent reduction (95 percent CI, -2.4 to -1.0 percent) in the measure of the FEV during the first three-fourths of a second of exhalation ($FEV_{0.75}$). Current maternal smoking was not associated with spirometric decrements. There were 75 children whose mothers had smoked only during the prepartum but not in the postpartum phase. These children had FEF_{25-75} values that were 11 percent lower (95 percent CI, -16.5 to -5.1, $p = 0.0004$) than those in children of mothers who had never smoked. In this cohort, 6,508 mothers had not smoked during pregnancy. Multivariate models that adjusted for gender, height, age, parental education, place of residence, and current tobacco smoke exposure in the home (maternal, paternal, or other smokers in the home) documented an estimated 2.8 percent decrease ($p = 0.026$) in the FEF_{25-75} for postpartum maternal smoking up to two years of age of the child. This estimate is about half the size of the effect of smoking during pregnancy. The authors concluded that the decrements in lung function associated with maternal smoking during pregnancy were not explained by current maternal smoking; the observation that these effects were most significant on flow measures suggests involvement, likely inflammation and obstruction, of the small airways.

Several additional cross-sectional studies have been reported since Cunningham and colleagues (1994) conducted their large, cross-sectional analysis. Gilliland and colleagues (2000) investigated 3,357 children in 12 southern California communities and assessed the effects of maternal prenatal and postnatal smoking on pulmonary function measures in children. Current and past secondhand smoke exposures and in utero maternal smoking were assessed from a questionnaire that was completed by parents of fourth-, seventh-, and tenth-grade students. In utero exposure was associated with reduced flow rates measured by spirometry, but not with reductions in the FEV_1. More specifically, the peak expiratory flow rate was reduced by 3 percent (95 percent CI, -4.4 to -1.4 percent), the mean MEF (closely equivalent to the FEF_{25-75}) was reduced by 4.6 percent (95 percent CI, -7.0 to -2.3 percent), and the FEF at 75 percent of vital capacity (FEF_{75}) was reduced by 6.2 percent (95 percent CI, -9.1 to -3.1 percent). Adjustment for confounding factors such as secondhand smoke from the mother, father, or other adult household smokers; gender; race; school grade; income; personal smoking; or parental education levels did not significantly alter the effect estimate for in utero exposure. The researchers concluded that in utero exposure to maternal secondhand smoke was independently associated with a reduction in lung function among school-age children. The authors also suggested that the predominant reduction in flows may reflect an effect of in utero exposure on distal airway maturation and growth during in utero development.

The Children's Health Study evaluated the effects of in utero and postnatal secondhand smoke exposure on lung function in boys and girls with and without a history of asthma. In utero exposure from maternal smoking and secondhand smoke exposure postnatally (from maternal, paternal, or other adult household members) was associated with a measured decrease in lung function in 5,263 children (Li et al. 2000). Children exposed to tobacco smoke in utero from maternal smoking had reductions in maximal MEF and FEV_1/FVC ratios. Specifically, the maximal MEF decreased by 5.9 percent (95 percent CI, -8.4 to -3.4 percent, $p < 0.001$) in boys and by 3.9 percent (95 percent CI, -6.3 to -1.5 percent) in girls (4.2 and 3.0 percent, respectively, when children with asthma were excluded). The FEV_1/FVC ratio decreased by

2.0 percent (95 percent CI, -2.7 to -1.2 percent, $p < 0.001$) in boys and by 1.7 percent (95 percent CI, -2.3 to -1.0 percent) in girls (1.6 and 1.2 percent, respectively, when children with asthma were excluded). In this study, decreased airflow in children without asthma was significantly associated with current secondhand smoke exposure from two or more current smokers.

The NHANES III included a cross-sectional U.S. national sample of 5,400 children aged 4 through 16 years (Mannino et al. 2001). The study data included a respiratory symptoms questionnaire, spirometric measurements, and serum cotinine levels. Participants were stratified by cotinine levels to assess the effects of secondhand tobacco smoke exposure on a variety of health outcomes including lung function. Prenatal secondhand smoke exposure was also retrospectively assessed in the group of children aged 4 to 11 years. Children in the highest cotinine tertile were more likely to have a FEV_1/FVC ratio of less than 0.8 (OR = 1.8 [95 percent CI, 1.3–2.4]). Children exposed to secondhand smoke had reductions in the FEV_1 (-1.8 percent [95 percent CI, -3.2 to -0.4 percent]), the FEV_1/FVC ratio (-1.5 percent [95 percent CI, -2.2 to -0.8 percent]), and the maximal MEF (-5.9 percent [95 percent CI, -8.1 to -3.4 percent]).

Lung Function

To date, prospective cohort studies have not incorporated measurements of lung function along with serial cotinine level measurements. On the other hand, reports of smoking by key household members have high validity and are likely to provide an adequate index of usual exposure to secondhand smoke. One small, prospective cohort study that assessed the effects of tobacco smoke on lung growth in adolescents used urine cotinine levels as a biomarker for active and secondhand tobacco smoke exposure (Bono et al. 1998). Questionnaires, urinary cotinine levels, and spirometric measurements were used to evaluate 394 schoolchildren aged 14 through 16 years. Approximately one year later, data from 333 adolescents were reassessed in multiple regression analyses. The reassessments revealed a trend for reductions in lung growth suggested by spirometry (FEV_1), in association with active and involuntary smoking measured by serum cotinine levels. The effect on FEV_1 growth, although small, demonstrated a dose-related linear trend (Bono et al. 1998).

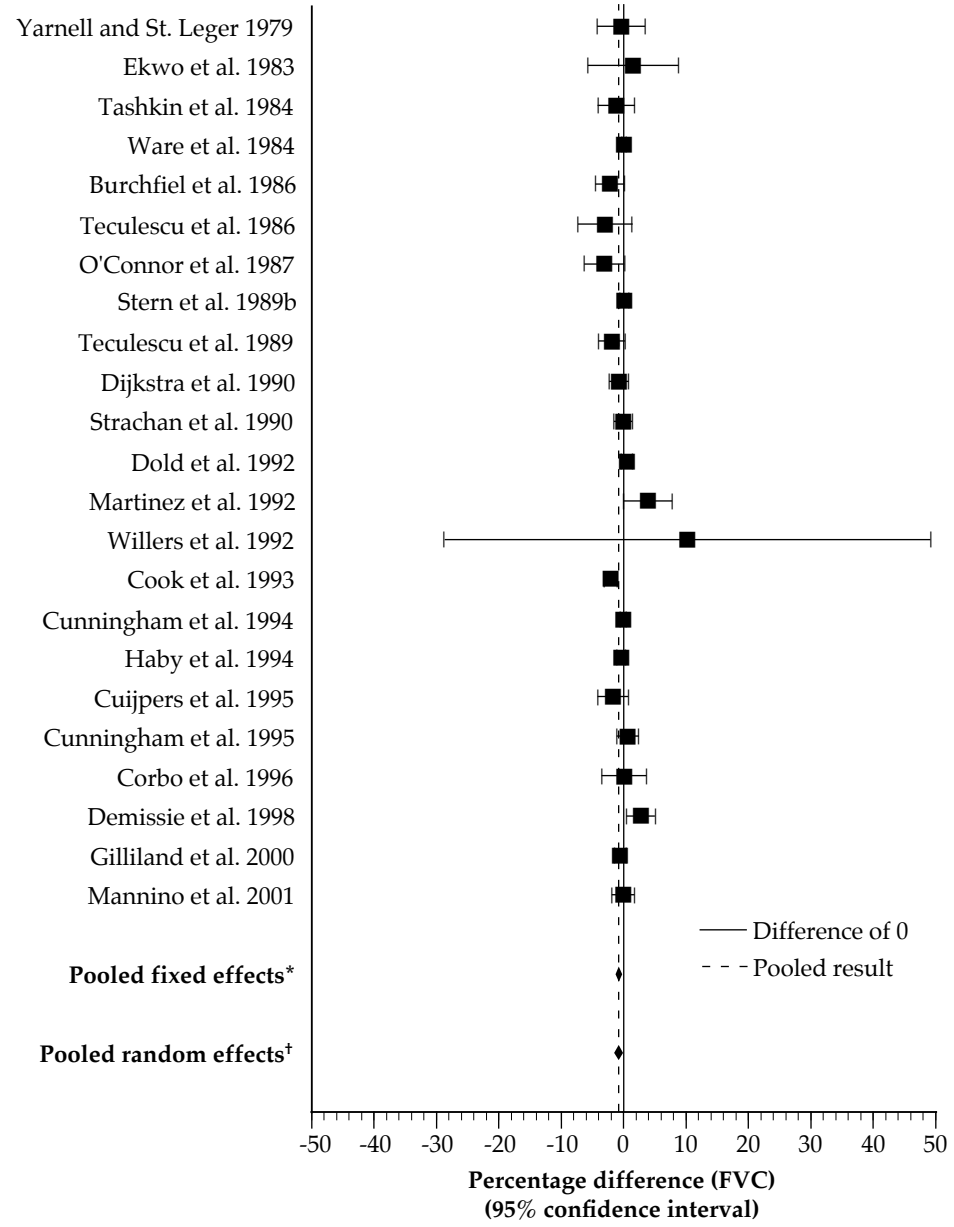
In a meta-analysis of the cross-sectional evidence relating parental smoking to spirometric indices in children (Cook et al. 1998), new cross-sectional studies (published from 1997 to 2000) were identified by using the same search strategy that the 1998 review had used (Cook et al. 1998). Six additional studies were identified (Behera et al. 1998; Demissie et al. 1998; Bek et al. 1999; Gilliland et al. 2000; O'Connor et al. 2000; Mannino et al. 2001). Three of these studies (Behera et al. 1998; Bek et al. 1999; O'Connor et al. 2000) could not be included in this quantitative synthesis because they did not provide sufficient data to calculate the effect measure of interest (average percentage difference in spirometric index between exposed and unexposed children). The other three papers (Demissie et al. 1998; Gilliland et al. 2000; Mannino et al. 2001) were included in the following updated meta-analysis. One additional paper published before the 1998 synthesis (Rona and Chinn 1993) that was included in the present analysis had not been included in the 1998 quantitative synthesis—the data needed to calculate the effect measure of interest were not available at the time; the data have since become available. The data in this study were presented separately for girls and boys, and a combined estimate was obtained with a random effects method (Egger et al. 2001).

This analysis used the same effect measure that was used in the 1998 synthesis: the average difference in spirometric index between the exposed and unexposed children expressed as a percentage of the level in the unexposed group. Four different spirometric indices were considered: FVC, FEV_1, MEFR, and EEFR. Pooled estimates of the percentage differences were calculated using both fixed and random effects models (Egger et al. 2001).

To determine whether the classification of exposure influenced the relationship between parental smoking and lung function, studies were pooled within exposure groups: both parents did versus did not smoke, mother did versus did not smoke, either parent did versus did not smoke, the highest cotinine category versus the lowest, and high levels of household secondhand tobacco smoke versus none. To test whether adjusting for variables other than age, gender, and body size affected the relationship, studies were pooled separately depending on what adjustments were made for other variables. A final assessment was then made as to whether adjustments for SES measures, such as parental education and social class, were assessed for possible effects on the pooled results.

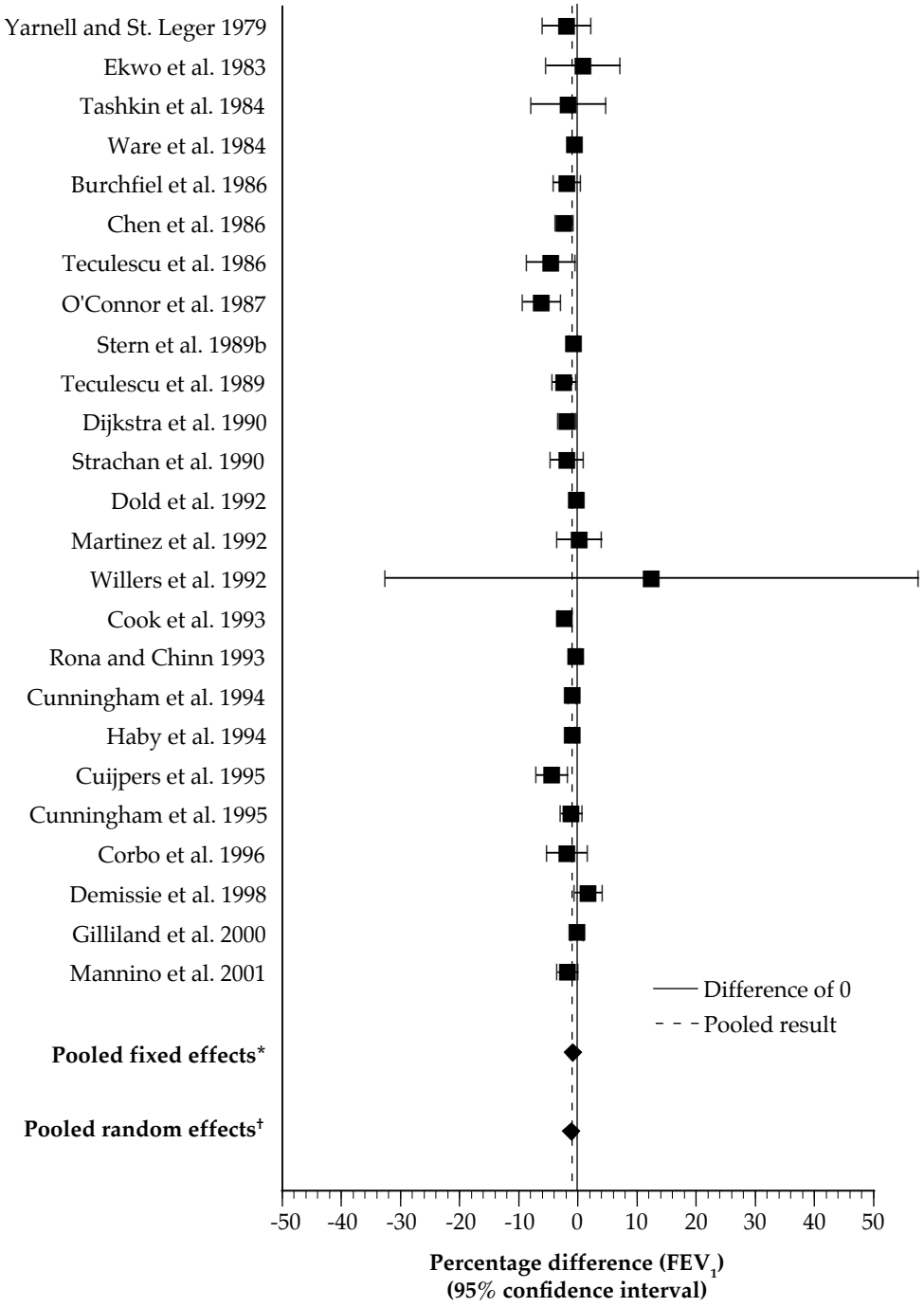
Of the 26 studies included in the updated quantitative synthesis, 4 were not in the 1998 analysis. There was significant variability among studies for all spirometric measures except the EEFR (Figures 6.14–6.17 and Table 6.25). Heterogeneity was

Figure 6.14 Percentage difference in the forced vital capacity (FVC) between children of smokers and children of nonsmokers in studies included in the meta-analysis



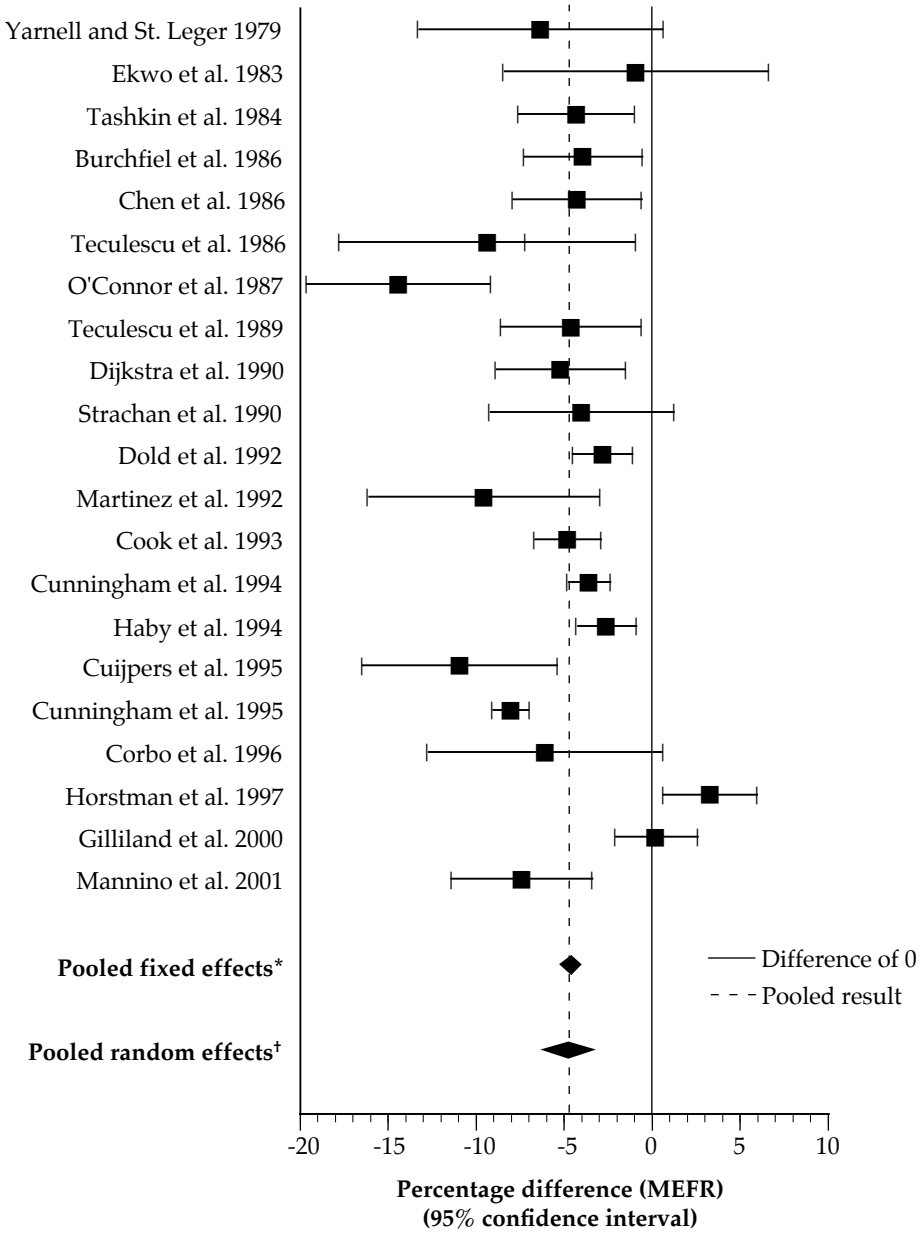
*Pooled difference is from the fixed effects meta-analysis.
†Pooled difference is from the random effects meta-analysis.

Figure 6.15 Percentage difference in the forced expiratory volume in 1 second (FEV_1) between children of smokers and children of nonsmokers in studies included in the meta-analysis



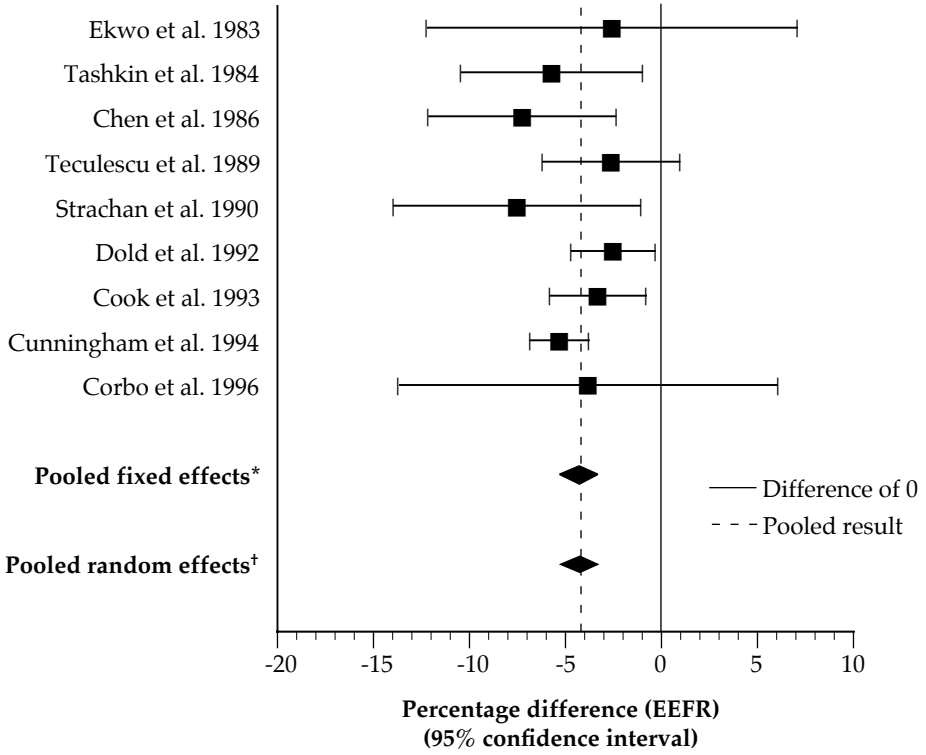
*Pooled difference is from the fixed effects meta-analysis.
†Pooled difference is from the random effects meta-analysis.

Figure 6.16 Percentage difference in the mid-expiratory flow rate (MEFR) between children of smokers and children of nonsmokers in studies included in the meta-analysis



*Pooled difference is from the fixed effects meta-analysis.
†Pooled difference is from the random effects meta-analysis.

Figure 6.17 Percentage difference in the end-expiratory flow rate (EEFR) between children of smokers and children of nonsmokers in studies included in the meta-analysis



*Pooled difference is from the fixed effects meta-analysis.
†Pooled difference is from the random effects meta-analysis.

Table 6.25 Summary of pooled percentage differences in cross-sectional studies of lung function in children exposed to secondhand smoke compared with unexposed children

	Number of studies	% differences, fixed effects (95% CI*)	% differences, random effects (95% CI)	Q (p value)
FVC†	23	-0.15 (-0.37–0.07)	-0.32 (-0.71–0.08)	40.64 (0.009)
FEV_1‡	25	-0.85 (-1.05 to -0.64)	-1.15 (-1.56 to -0.75)	50.12 (0.001)
MEFR§	21	-4.62 (-5.16 to -4.09)	-4.76 (-6.34 to -3.18)	129.3 (0.000)
EEFRΔ	9	-4.30 (-5.30 to -3.30)	-4.26 (-5.34 to -3.19)	8.49 (0.387)

Note: Q is the chi-square distributed test statistic for the null hypothesis of no heterogeneity between studies. The corresponding p values indicate significant heterogeneity between studies.
*CI = Confidence interval.
†FVC = Forced vital capacity.
‡FEV_1 = Forced expiratory volume in 1 second.
§MEFR = Mid-expiratory flow rate.
ΔEEFR = End-expiratory flow rate.

Table 6.26 Pooled percentage differences in lung function according to secondhand smoke exposure category (random effects results)

	FVC*		FEV_1†		MEFR‡		EEFR§	
	% difference (95% CIΔ)	n	% difference (95% CI)	n	% difference (95% CI)	n	% difference (95% CI)	n
Both parents or the mother smoked vs. neither parent smoked	-0.2 (-0.6–0.3)	13	-1.1 (-1.6 to -0.6)	13	-6.0 (-8.1 to -3.9)	10	-4.0 (-5.8 to -2.2)	4
Either parent smoked vs. neither	1.6 (-5.7–8.9)	1	-1.0 (-2.7 to -0.6)	3	-3.7 (-7.0 to -0.4)	2	-6.3 (-10.7 to -1.9)	2
Cotinine (highest vs. lowest level)	-0.9 (-2.5–0.7)	3	-2.1 (-3.0 to -1.2)	3	-4.8 (-6.5 to -3.1)	3	-3.9 (-6.1 to -1.6)	3
Secondhand smoke (highest level vs. none)	-0.2 (-0.9–0.5)	6	-1.0 (-2.0–0.01)	6	-3.3 (-6.6–0.1)	6	Data were not reported	0
All	-0.3 (-0.7–0.0)	23	-1.2 (-1.6 to -0.8)	25	-4.8 (-6.3 to -3.2)	21	-4.3 (-5.3 to -3.2)	9

*FVC = Forced vital capacity.
†FEV_1 = Forced expiratory volume in 1 second.
‡MEFR = Mid-expiratory flow rate.
§EEFR = End-expiratory flow rate.
ΔCI = Confidence interval.

to be expected given the variability in secondhand smoke exposure classifications. Pooling all of the studies found statistically significant reductions in three out of the four measures of lung function (FEV_1, MEFR, and EEFR) for children exposed to secondhand smoke in their homes compared with unexposed children. The pooled percentage differences in lung function were smallest for FVC (-0.3 percent) and FEV_1 (-1.2 percent) and larger for MEFR (-4.8 percent) and EEFR (-4.3 percent). The MEFR and EEFR are more sensitive indicators of airways function compared with the FVC and the FEV_1.

The association between exposure to secondhand smoke and lung function differed according to the exposure classification, but not in a consistent pattern across the four lung function measures (Table 6.26). Adjusting for factors in addition to age, gender, and body size did not significantly affect the associations between secondhand smoke exposure and lung function (Table 6.27). Adjusting for social class had little effect on the FVC, FEV_1, and MEFR measures, but nearly doubled the percentage difference in the EEFR (Table 6.27).

The evidence of associations between secondhand smoke exposure and lung function growth and development continues to come largely from cross-sectional studies. The resulting data indicate the level of lung function at only a single age, which at that point is considered indicative of the cumulative consequences of the various factors influencing lung function growth, including prenatal and postnatal maternal smoking. Prospective cohort studies have the advantages of directly measuring lung function over time and directly estimating the rate of change, but few have been carried out because of cost and logistical constraints.

Evidence Synthesis

Smoking during pregnancy exposes the developing lung to a variety of toxins and reduces the delivery of oxygen to the fetus (USDHHS 2001). Animal models indicate structural consequences that may underlie the physiologic effects that are well documented shortly after birth. Secondhand smoke exposure

Table 6.27 Pooled percentage differences in lung function according to confounders adjusted for (random effects results)

	FVC*		FEV_1†		MEFR‡		EEFR§	
	% difference (95% CIΔ)	n	% difference (95% CI)	n	% difference (95% CI)	n	% difference (95% CI)	n
Adjusted only for age, gender, body size	-0.7 (-1.8–0.4)	8	-1.2 (-2.2 to -0.2)	8	-4.3 (-7.0 to -1.6)	8	-2.7 (-5.9–0.5)	3
Adjusted for more than age, gender, body size	-0.3 (-0.6–0.2)	15	-1.2 (-1.6–0.7)	17	-4.9 (-6.8 to -3.0)	13	-4.5 (-5.9 to -3.0)	6
Not adjusted for social class	-0.7 (-1.4–0.1)	14	-1.3 (-2.1 to -0.6)	14	-4.9 (-6.8 to -2.9)	12	-3.1 (-4.5 to -1.7)	6
Adjusted for social class	-0.1 (-0.5–0.3)	9	-1.1 (-1.6 to -0.6)	11	-4.5 (-7.1 to -2.0)	9	-5.6 (-7.0 to -4.1)	3
All	-0.3 (-0.7–0.0)	23	-1.2 (-1.6 to -0.8)	25	-4.8 (-6.3 to -3.2)	21	-4.3 (-5.3 to -3.2)	9

*FVC = Forced vital capacity.
†FEV_1 = Forced expiratory volume in 1 second.
‡MEFR = Mid-expiratory flow rate.
§EEFR = End-expiratory flow rate.
ΔCI = Confidence interval.

from parents who smoke would be expected to lead to pulmonary inflammation that would be sustained across childhood.

Thus, there is substantial biologic plausibility for causation of reduced lung growth by secondhand smoke exposure. Multiple studies have measured lung function shortly after birth and document the adverse effects on lung function from maternal smoking during pregnancy. The pattern of abnormalities is suggestive of a persistent adverse effect on the airways of the fetus from maternal smoking during pregnancy.

There is also substantial evidence from both cross-sectional and cohort studies of a sustained effect from in utero exposure, as well as an additional adverse effect from postnatal exposure. Multiple studies have shown cumulative consequences of both prenatal and postnatal exposures. Across the set of studies, potentially important confounding factors have been given consideration and the adverse effects of secondhand smoke exposure on lung function cannot be attributed to other factors.

In the context of this body of evidence against causal criteria, the effects of prenatal and postnatal exposures merit separate consideration because they correspond to substantially different phases of development and potential susceptibility. For both exposures, the evidence is substantial and consistent. There are multiple bases for biologic plausibility, and the temporal relationships of exposures with the outcome measures are appropriate.

Conclusions

1. The evidence is sufficient to infer a causal relationship between maternal smoking during pregnancy and persistent adverse effects on lung function across childhood.

2. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke after birth and a lower level of lung function during childhood.

Implications

Lung growth continues throughout childhood and adolescence and is completed by young adulthood, when lung growth peaks and then begins to decline as a result of aging, smoking, and other environmental factors. The evidence shows that parental smoking reduces the maximum achieved level, although not to a degree (on average) that would impair individuals. Nonetheless, a reduced peak level increases the risk for future chronic lung disease, and there is heterogeneity of the effect so that some exposed children may have a much greater reduction than the mean. In addition, children of smokers are more likely to become smokers and thus face a future risk for impairment from active smoking.

Conclusions

Lower Respiratory Illnesses in Infancy and Early Childhood

1. The evidence is sufficient to infer a causal relationship between secondhand smoke exposure from parental smoking and lower respiratory illnesses in infants and children.

2. The increased risk for lower respiratory illnesses is greatest from smoking by the mother.

Middle Ear Disease and Adenotonsillectomy

3. The evidence is sufficient to infer a causal relationship between parental smoking and middle ear disease in children, including acute and recurrent otitis media and chronic middle ear effusion.

4. The evidence is suggestive but not sufficient to infer a causal relationship between parental smoking and the natural history of middle ear effusion.

5. The evidence is inadequate to infer the presence or absence of a causal relationship between parental smoking and an increase in the risk of adenoidectomy or tonsillectomy among children.

Respiratory Symptoms and Prevalent Asthma in School-Age Children

6. The evidence is sufficient to infer a causal relationship between parental smoking and cough, phlegm, wheeze, and breathlessness among children of school age.

7. The evidence is sufficient to infer a causal relationship between parental smoking and ever having asthma among children of school age.

Childhood Asthma Onset

8. The evidence is sufficient to infer a causal relationship between secondhand smoke exposure from parental smoking and the onset of wheeze illnesses in early childhood.

9. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure from parental smoking and the onset of childhood asthma.

Atopy

10. The evidence is inadequate to infer the presence or absence of a causal relationship between parental smoking and the risk of immunoglobulin E-mediated allergy in their children.

Lung Growth and Pulmonary Function

11. The evidence is sufficient to infer a causal relationship between maternal smoking during pregnancy and persistent adverse effects on lung function across childhood.

12. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke after birth and a lower level of lung function during childhood.

Overall Implications

The extensive evidence considered in this chapter causally links parental smoking to adverse health effects in children. The association between parental smoking and childhood respiratory disease is stronger at younger ages, a pattern plausibly explained by a higher level of exposure to secondhand smoke among infants and preschool-age children for any given level of parental smoking. In general, associations with maternal smoking are stronger than with paternal smoking, but for several outcomes, associations were found for smoking by the father in homes where the mother does not smoke. This finding argues strongly for an independent adverse effect of a postnatal involuntary (environmental) exposure to secondhand smoke in the home. There may be an additional hazard related to prenatal exposure of the fetus to maternal smoking during pregnancy (USDHHS 2001, 2004). The published evidence does not adequately separate the independent effects on childhood respiratory health of prenatal versus postnatal exposure to maternal smoking. This unresolved research issue should not detract from the public health message that smoking by either parent is potentially damaging to the health of children.

Interpretation of the evidence is perhaps most complex in relation to childhood asthma, which is a term generally applied to a mixed group of clinical phenotypes. Recurrent wheeze illnesses are common among young children, and there is controversy about whether these illnesses should all be classified as "asthma." Cohort studies show that symptoms do not persist for many children beyond the first few years of life. The balance of evidence strongly supports a causal relationship between parental smoking and the incidence of wheeze illnesses in infancy, the prevalence of wheeze and related symptoms among schoolchildren, and the relative severity of disease among children with physician-diagnosed asthma. These are all important indicators of a substantial and potentially preventable public health burden.

The evidence related to the wheeze illnesses can be separated to an extent from that related to a clearer clinical phenotype of asthma, a chronic condition of variable airflow obstruction with a heightened susceptibility to environmental triggers of bronchospasm. The evidence is less clear as to whether parental smoking initiates the disease among previously healthy children. Because the clinical diagnosis of asthma relies to a large extent upon a history of recurrent wheeze attacks or other chest illnesses, any exposure (including parental smoking) that increases the incidence of such episodes will tend to be associated with an apparent increase in the incidence of diagnosed "asthma," even if secondhand smoke exposure does not contribute to the incidence directly. Studies of nonspecific bronchial responsiveness, a surrogate for the asthma phenotype, offer some insights into the long-term susceptibility that underlies chronic asthma. Secondhand smoke exposure is linked to an increase in responsiveness, beginning with in utero exposure. However, bronchial responsiveness is also nonspecifically and transiently increased following respiratory tract infections. For this reason, the conclusion regarding parental smoking as a cause of childhood asthma has been phrased in less definite terms than the conclusions relating to asthma prevalence and severity.

References

Abuekteish F, Alwash R, Hassan M, Daoud AS. Prevalence of asthma and wheeze in primary school children in Northern Jordan. *Annals of Tropical Paediatrics* 1996;16(3):227–31.

Adair-Bischoff CE, Sauve RS. Environmental tobacco smoke and middle ear disease in preschool-age children. *Archives of Pediatrics & Adolescent Medicine* 1998;152(2):127–33.

Aderele WI. Aetiologic, precipitating and environmental factors in childhood asthma. *Nigerian Journal of Paediatrics* 1982;9(1):26–31.

Agabiti N, Mallone S, Forastiere F, Corbo GM, Ferro S, Renzoni E, Sestini P, Rusconi F, Ciccone G, Viegi G, et al. The impact of parental smoking on asthma and wheezing. *Studi Italiani sui Disturbi Respiratori nell'Infanzia e l'Ambiente*. *Epidemiology* 1999;10(6):692–8.

Alho OP, Kilkku O, Oja H, Koivu M, Sorri M. Control of the temporal aspect when considering risk factors for acute otitis media. *Archives of Otolaryngology—Head & Neck Surgery* 1993;119(4):444–9.

Alho O-P, Läärä E, Oja H. Public health impact of various risk factors for acute otitis media in northern Finland. *American Journal of Epidemiology* 1996;143(11):1149–56.

Anderson HR, Bland JM, Patel S, Peckham C. The natural history of asthma in childhood. *Journal of Epidemiology and Community Health* 1986;40(2):121–9.

Anderson LJ, Parker RA, Strikas RA, Farrar JA, Gangarosa EJ, Keyserling HL, Sikes RK. Day-care center attendance and hospitalization for lower respiratory tract illness. *Pediatrics* 1988;82(3):300–8.

Andrae S, Axelson O, Björkstén B, Fredriksson M, Kjellman N-IM. Symptoms of bronchial hyperreactivity and asthma in relation to environmental factors. *Archives of Disease in Childhood* 1988;63(5):473–8.

Apostolopoulos K, Xenelis J, Tzagaroulakis A, Kandiloros D, Yiotakis J, Papafragou K. The point prevalence of otitis media with effusion among school children in Greece. *International Journal of Pediatric Otorhinolaryngology* 1998;44(3):207–14.

Arshad SH, Hide DW. Effect of environmental factors on the development of allergic disorders in infancy. *Journal of Allergy and Clinical Immunology* 1992;90(2):235–41.

Arshad SH, Stevens M, Hide DW. The effect of genetic and environmental factors on the prevalence of allergic disorders at the age of two years. *Clinical and Experimental Allergy* 1993;23(6):504–11.

Asgari MM, Dubois A, Asgari M, Gent J, Beckett WS. Association of ambient air quality with children's lung function in urban and rural Iran. *Archives of Environmental Health* 1998;53(3):222–30.

Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, Mitchell EA, Pearce N, Sibbald B, Stewart AW, Strachan D, Weiland SK, Williams HC. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *European Respiratory Journal* 1995;8(3):483–91.

Austin JB, Russell G. Wheeze, cough, atopy, and indoor environment in the Scottish Highlands. *Archives of Disease in Childhood* 1997;76(1):22–6.

Azizi BHO, Zulkifli HI, Kasim MS. Indoor air pollution and asthma in hospitalized children in a tropical environment. *Journal of Asthma* 1995;32(6):413–8.

Baker D, Taylor H, Henderson J, ALSPAC Study Team. Inequality in infant morbidity: causes and consequences in England in the 1990s. Avon Longitudinal Study of Pregnancy and Childhood. *Journal of Epidemiology and Community Health* 1998;52(7): 451–8.

Barker K, Mussin E, Taylor DK. Fetal exposure to involuntary maternal smoking and childhood respiratory disease. *Annals of Allergy, Asthma, & Immunology* 1996;76(5):427–30.

Barr GS, Coatesworth AP. Passive smoking and otitis media with effusion. *British Medical Journal* 1991;303(6809):1032–3.

Bassi JA, Rosso P, Moessinger AC, Blanc WA, James LS. Fetal growth retardation due to maternal tobacco smoke exposure in the rat. *Pediatric Research* 1984;18(2):127–30.

Bayne EK, Rupp EA, Limjuco G, Chin J, Schmidt JA. Immunocytochemical detection of interleukin 1 within stimulated human monocytes. *Journal of Experimental Medicine* 1986;163(5):1267–80.

Beckett WS, Belanger K, Gent JF, Holford TR, Leaderer BP. Asthma among Puerto Rican Hispanics: a multi-ethnic comparison study of risk factors. *American Journal of Respiratory and Critical Care Medicine* 1996;154(4 Pt 1):894–9.

Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50(4):1088–101.

Behera D, Sood P, Singh S. Passive smoking, domestic fuels and lung function in north Indian children. *Indian Journal of Chest Diseases & Allied Sciences* 1998;40(2):89–98.

Bek K, Tomaç N, Delibas A, Tuna F, Teziç HT, Sungur M. The effect of passive smoking on pulmonary function during childhood. *Postgraduate Medical Journal* 1999;75(884):339–41.

Belousova EG, Toelle BG, Xuan W, Peat JK. The effect of parental smoking on presence of wheeze or airway hyper-responsiveness in New South Wales school children. *Australian and New Zealand Journal of Medicine* 1999;29(6):794–800.

Bener A, Abdulrazzaq YM, Al-Mutawwa J, Debuse P. Genetic and environmental factors associated with asthma. *Human Biology* 1996;68(3):405–14.

Bennett KE, Haggard MP. Accumulation of factors influencing children's middle ear disease: risk factor modelling on a large population cohort. *Journal of Epidemiology and Community Health* 1998; 52(12):786–93.

Bergmann RL, Schulz J, Gunther S, Dudenhausen JW, Bergmann KE, Bauer CP, Dorsch W, Schmidt E, Luck W, Lau S. Determinants of cord-blood IgE concentrations in 6401 German neonates. *Allergy* 1995;50(1):65–71.

Bisgaard H, Dalgaard P, Nyboe J. Risk factors for wheezing during infancy. A study of 5,953 infants. *Acta Paediatrica Scandinavica* 1987;76(5):719–26.

Black N. The aetiology of glue ear—a case-control study. *International Journal of Pediatric Otorhinolaryngology* 1985;9(2):121–33.

Black RE, Michaelsen KF. *Public Health Issues in Infant and Child Nutrition*. Philadelphia: Lippincott Williams & Wilkins, 2002.

Blakley BW, Blakley JE. Smoking and middle ear disease: are they related? A review article. *Otolaryngology—Head & Neck Surgery* 1995;112(3):441–6.

Bland M, Bewley BR, Pollard V, Banks MH. Effect of children's and parents' smoking on respiratory symptoms. *Archives of Disease in Childhood* 1978;53(2):100–5.

Bonham AC, Kott KS, Joad JP. Sidestream smoke exposure enhances rapidly adapting receptor responses to substance P in young guinea pigs. *Journal of Applied Physiology* 1996;81(4):1715–22.

Bonner JC, Rice AB, Lindroos PM, O'Brien PO, Dreher KL, Rosas I, Alfaro-Moreno E, Osornio-Vargas AR. Induction of the lung myofibroblast PDGF receptor system by urban ambient particles from Mexico City. *American Journal of Respiratory Cell and Molecular Biology* 1998;19(4):672–80.

Bono R, Nebiolo F, Bugiani M, Meineri V, Scursatone E, Piccioni P, Caria E, Gilli G, Arossa W. Effects of tobacco smoke exposure on lung growth in adolescents. *Journal of Exposure Analysis and Environmental Epidemiology* 1998;8(3):335–45.

Bråbäck L, Breborowicz A, Julge K, Knutsson A, Riikjärv M-A, Vasar M, Björkstén B. Risk factors for respiratory symptoms and atopic sensitisation in the Baltic area. *Archives of Disease in Childhood* 1995;72(6):487–93.

Brabin B, Smith M, Milligan P, Benjamin C, Dunne E, Pearson M. Respiratory morbidity in Merseyside schoolchildren exposed to coal dust and air pollution. *Archives of Disease in Childhood* 1994;70(4): 305–12.

Braun KM, Cornish T, Valm A, Cundiff J, Pauly JL, Fan S. Immunotoxicology of cigarette smoke condensates: suppression of macrophage responsiveness to interferon γ. *Toxicology and Applied Pharmacology* 1998;149(2):136–43.

Brown RW, Hanrahan JP, Castile RG, Tager IB. Effect of maternal smoking during pregnancy on passive respiratory mechanics in early infancy. *Pediatric Pulmonology* 1995;19(1):23–8.

Burchfiel CM, Higgins MW, Keller JB, Howatt WF, Butler WJ, Higgins ITT. Passive smoking in childhood: respiratory conditions and pulmonary function in Tecumseh, Michigan. *American Review of Respiratory Disease* 1986;133(6):966–73.

Burr ML, Merritt TG, Dunstan FD, Maguire MJ. The development of allergy in high-risk children. *Clinical and Experimental Allergy* 1997;27(11):1247–53.

Burr ML, Anderson HR, Austin JB, Harkins LS, Kaur B, Strachan DP, Warner JO. Respiratory symptoms and home environment in children: a national survey. *Thorax* 1999;54(1):27–32. [See also erratum in *Thorax* 1999;54(4):376.]

Burr ML, Miskelly FG, Butland BK, Merrett TG, Vaughan-Williams E. Environmental factors and symptoms in infants at high risk of allergy. *Journal of Epidemiology and Community Health* 1989;43(2): 125–32.

Butland BK, Strachan DP, Anderson HR. The home environment and asthma symptoms in childhood: two population based case-control studies 13 years apart. *Thorax* 1997;52(7):618–24.

Butz AM, Rosenstein BJ. Passive smoking among children with chronic respiratory disease. *Journal of Asthma* 1992;29(4):265–72.

California Environmental Protection Agency. *Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant. Part B: Health Effects.*

Sacramento (CA): California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, 2005.

Cameron P. The presence of pets and smoking as correlates of perceived disease. *Journal of Allergy* 1967;40(1):12–5.

Cameron P, Kostin JS, Zaks JM, Wolfe JH, Tighe G, Oselett B, Stocker R, Winton J. The health of smokers' and non-smokers' children. *Journal of Allergy* 1969;43(6):336–41.

Catlin EA, Powell SM, Manganaro TF, Hudson PL, Ragin RC, Epstein J, Donahoe PK. Sex-specific fetal lung development and Müllerian inhibiting substance. *American Review of Respiratory Diseases* 1990;141(2):466–70.

Chang MY, Hogan AD, Rakes GP, Ingram JM, Hoover GE, Platts-Mills TAE, Heymann PW. Salivary cotinine levels in children presenting with wheezing to an emergency department. *Pediatric Pulmonology* 2000;29(4):257–63.

Charlton A. Children's coughs related to parental smoking. *British Medical Journal Clinical Research Ed* 1984;288(6431):1647–9.

Chayarpham S, Stuart J, Chongsuvivatwong V, Chinpairoj S, Lim A. A study of the prevalence of and risk factors for ear diseases and hearing loss in primary school children in Hat Yai, Thailand. *Journal of the Medical Association of Thailand* 1996;79(7): 468–72.

Chen Y. Synergistic effect of passive smoking and artificial feeding on hospitalization for respiratory illness in early childhood. *Chest* 1989;95(5):1004–7.

Chen Y. Environmental tobacco smoke, low birth weight, and hospitalization for respiratory disease. *American Journal of Respiratory and Critical Care Medicine* 1994;150(1):54–8.

Chen J, Millar WJ. Birth outcome, the social environment and child health. *Health Reports* 1999;10(4): 57–67.

Chen MF, Kimizuka G, Wang NS. Human fetal lung changes associated with maternal smoking during pregnancy. *Pediatric Pulmonology* 1987;3(1):51–8.

Chen Y, Li W, Yu S. Influence of passive smoking on admissions for respiratory illness in early childhood. *British Medical Journal Clinical Research Ed* 1986;293(6542):303–6.

Chen Y, Li WX, Yu SZ, Qian WH. Chang-Ning epidemiological study of children's health. I: passive smoking and children's respiratory diseases. *International Journal of Epidemiology* 1988a;17(2):348–55.

Chen Y, Rennie DC, Dosman JA. Influence of environmental tobacco smoke on asthma in nonallergic and allergic children. *Epidemiology* 1996;7(5):536–9.

Chen Y, Rennie DC, Lockinger LA, Dosman JA. Effect of environmental tobacco smoke on cough in children with a history of tonsillectomy or adenoidectomy. *European Respiratory Journal* 1998;11(6):1319–23.

Chen Y, Yu SZ, Li WX. Artificial feeding and hospitalization in the first 18 months of life. *Pediatrics* 1988b;81(1):58–62.

Chew FT, Teo J, Quak SH, Lee BW. Factors associated with increased respiratory symptoms among asthmatic children in Singapore. *Asian Pacific Journal of Allergy and Immunology* 1999;17(3):143–53.

Chhabra SK, Gupta CK, Chhabra P, Rajpal S. Prevalence of bronchial asthma in schoolchildren in Delhi. *Journal of Asthma* 1998;35(3):291–6.

Chhabra SK, Gupta CK, Chhabra P, Rajpal S. Risk factors for development of bronchial asthma in children in Delhi. *Annals of Allergy, Asthma & Immunology* 1999;83(5):385–90.

Chilmonczyk BA, Salmun LM, Megathlin KN, Neveux LM, Palomaki GE, Knight GJ, Pulkkinen AJ, Haddow JE. Association between exposure to environmental tobacco smoke and exacerbations of asthma in children. *New England Journal of Medicine* 1993;328(23):1665–9.

Chinn S, Rona RJ. Quantifying health aspects of passive smoking in British children aged 5–11 years. *Journal of Epidemiology and Community Health* 1991;45(3):188–94.

Christie G, Helms P. Childhood asthma: what is it and where is it going [review]? *Thorax* 1995;50(10): 1027–30.

Clark SJ, Warner JO, Dean TP. Passive smoking amongst asthmatic children: questionnaire or objective assessment? *Clinical and Experimental Allergy* 1994;24(3):276–80.

Collet JP, Larson CP, Boivin JF, Suissa S, Pless IB. Parental smoking and risk of otitis media in preschool children. *Canadian Journal of Public Health* 1995;86(4):269–73.

Colley JRT. Respiratory symptoms in children and parental smoking and phlegm production. *British Medical Journal* 1974;2(912):201–4.

Colley JRT, Brasser LJ, editors. *Chronic Respiratory Disease in Children in Relation to Air Pollution*. Report on a WHO study. Copenhagen: World Health Organization, 1980.

Colley JRT, Holland WW, Corkhill RT. Influence of passive smoking and parental phlegm on pneumonia and bronchitis in early childhood. *Lancet* 1974;2(7888):1031–4.

Collins MH, Moessinger AC, Kleinerman J, Bassi J, Rosso P, Collins AM, James LS, Blanc WA. Fetal lung hypoplasia associated with maternal

smoking: a morphometric analysis. *Pediatric Research* 1985;19(4):408–12.

Cook DG, Strachan DP. Health effects of passive smoking: 3. Parental smoking and prevalence of respiratory symptoms and asthma in school age children. *Thorax* 1997;52(12):1081–94.

Cook DG, Strachan DP. Health effects of passive smoking: 7. Parental smoking, bronchial reactivity and peak flow variability in children. *Thorax* 1998;53(4):295–301.

Cook, DG, Strachan DP. Health effects of passive smoking: 10. Summary of effects of parental smoking on the respiratory health of children and implications for research. *Thorax* 1999;54(4):357–66.

Cook DG, Strachan DP, Carey IM. Health effects of passive smoking: 9. Parental smoking and spirometric indices in children. *Thorax* 1998;53(10): 884–93.

Cook DG, Whincup PH, Jarvis MJ, Strachan DP, Papacosta O, Bryant A. Passive exposure to tobacco smoke in children aged 5–7: individual, family, and community factors. *British Medical Journal* 1994;308(6925):384–9.

Cook DG, Whincup PH, Papacosta O, Strachan DP, Jarvis MJ, Bryant A. Relation of passive smoking as assessed by salivary cotinine concentration and questionnaire to spirometric indices in children. *Thorax* 1993;48(1):14–20.

Corbo GM, Agabiti N, Forastiere F, Dell'Orco V, Pistelli R, Kriebel D, Pacifici R, Zuccaro P, Ciappi G, Perucci CA. Lung function in children and adolescents with occasional exposure to environmental tobacco smoke. *American Journal of Respiratory and Critical Care Medicine* 1996;154:695–700.

Crane J, Mallol J, Beasley R, Stewart A, Asher MI, International Study of Asthma and Allergies in Childhood Phase I Study Group. Agreement between written and video questions for comparing asthma symptoms in ISAAC. *European Respiratory Journal* 2003;21(3):455–61.

Csonka P, Kaila M, Laippala P, Kuusela A-L, Ashorn P. Wheezing in early life and asthma at school age: predictors of symptom persistence. *Pediatric Allergy and Immunology* 2000;11(4):225–9.

Cuijpers CEJ, Swaen GMH, Wesseling G, Sturmans F, Wouters EFM. Adverse effects of the indoor environment on respiratory health in primary school children. *Environmental Research* 1995;68(1):11–23.

Cunningham J, Dockery DW, Gold DR, Speizer FE. Racial differences in the association between maternal smoking during pregnancy and lung function in children. *American Journal of Respiratory and Critical Care Medicine* 1995;152(2):565–9.

Cunningham J, Dockery DW, Speizer FE. Maternal smoking during pregnancy as a predictor of lung function in children. *American Journal of Epidemiology* 1994;139(12):1139–52.

Daigler GE, Markello SJ, Cummings KM. The effect of indoor air pollutants on otitis media and asthma in children. *Laryngoscope* 1991;101(3):293–6.

Dales RE, White J, Bhumgara C, McMullen E. Parental reporting of childrens' coughing is biased. *European Journal of Epidemiology* 1997;13(5):541–5.

Daly KA, Brown JE, Lindgren BR, Meland MH, Le CT, Giebink GS. Epidemiology of otitis media onset by six months of age. *Pediatrics* 1999;103(6 Pt 1): 1158–66.

Darlow BA, Horwood LJ, Mogridge N. Very low birthweight and asthma by age seven years in a national cohort. *Pediatric Pulmonology* 2000;30(4):291–6.

Davis SD. Neonatal and pediatric respiratory diagnostics. *Respiratory Care* 2003;48(4):367–84.

Deb SK. Acute respiratory disease survey in Tripura in case of children below five years of age. *Journal of the Indian Medical Association* 1998;96(4):111–6.

Dejin-Karlsson E, Hanson BS, Ostergren PO, Sjoberg NO, Marsal K. Does passive smoking in early pregnancy increase the risk of small-for-gestational-age infants? *American Journal of Public Health* 1998;88(10):1523–7.

Dekker C, Dales R, Bartlett S, Brunekreef B, Zwanenburg H. Childhood asthma and the indoor environment. *Chest* 1991;100(4):922–6.

Demissie K, Ernst P, Joseph L, Becklake MR. The role of domestic factors and day-care attendance on lung function of primary school children. *Respiratory Medicine* 1998;92(7):928–35.

Department of Health Committee on the Medical Effects of Air Pollutants. *Asthma and Outdoor Air Pollution*. London: HMSO, 1995.

Dezateux C, Stocks J. Lung development and early origins of childhood respiratory illness. *British Medical Bulletin* 1997;53(1):40–57.

Dezateux C, Stocks J, Dundas I, Fletcher ME. Impaired airway function and wheezing in infancy: the influence of maternal smoking and a genetic predisposition to asthma. *American Journal of Respiratory and Critical Care Medicine* 1999;159(2):403–10.

Diez U, Kroessner T, Rehwagen M, Richter M, Wetzig H, Schulz R, Borte M, Metzner G, Krumbiegel P, Herbarth O. Effects of indoor painting and smoking on airway symptoms in atopy risk children in the first year of life results of the LARS-study. *International Journal of Hygiene and Environmental Health* 2000;203(1):23–8.

DiFranza JR, Lew RA. Morbidity and mortality in children associated with the use of tobacco products by other people. *Pediatrics* 1996;97(4):560–8.

Dijkstra L, Houthuijs D, Brunekreef B, Akkerman I, Boleij JSM. Respiratory health effects of the indoor environment in a population of Dutch children. *American Review of Respiratory Disease* 1990;142(5):1172–8.

Divers WA Jr, Wilkes MM, Babaknia A, Yen SS. Maternal smoking and elevation of catecholamines and metabolites in the amniotic fluid. *American Journal of Obstetrics and Gynecology* 1981;141(6):625–8.

Dodge R. The effects of indoor pollution on Arizona children. *Archives of Environmental Health* 1982;37(3):151–5.

Dold S, Reitmeir P, Wjst M, von Mutius E. Effects of passive smoking on the pediatric respiratory tract. *Monatsschrift Kinderheilkunde* 1992;140:763–8.

Duff AL, Pomeranz ES, Gelber LE, Price GW, Farris H, Hayden FG, Platts-Mills TA, Heymann PW. Risk factors for acute wheezing in infants and children: viruses, passive smoke, and IgE antibodies to inhalant allergens. *Pediatrics* 1993;92(4):535–40.

Duffy DL, Mitchell CA. Lower respiratory tract symptoms in Queensland schoolchildren: risk factors for wheeze, cough and diminished ventilatory function. *Thorax* 1993;48(10):1021–4.

Edwards K, Braun KM, Evans G, Sureka AO, Fan S. Mainstream and sidestream cigarette smoke condensates suppress macrophage responsiveness to interferon γ. *Human & Experimental Toxicology* 1999; 18(4):233–40.

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal* 1997;315(7109):629–34.

Egger M, Smith GD, Altman DG, editors. *Systematic Reviews in Health Care: Meta-analysis in Context*. 2nd ed. London: BMJ Publishing Group, 2001.

Ehrlich R, Kattan M, Godbold J, Saltzberg DS, Grimm KT, Landrigan PJ, Lilienfeld DE. Childhood asthma and passive smoking: urinary cotinine as a biomarker of exposure. *American Review of Respiratory Disease* 1992;145(3):594–9.

Ehrlich RI, Du Toit D, Jordaan E, Zwarenstein M, Potter P, Volmink JA, Weinberg E. Risk factors for childhood asthma and wheezing: importance of maternal and household smoking. *American Journal of Respiratory and Critical Care Medicine* 1996;154 (3 Pt 1):681–8.

Ekwo EE, Weinberger MM, Lachenbruch PA, Huntley WH. Relationship of parental smoking and gas cooking to respiratory disease in children. *Chest* 1983;84(6):662–8.

Elder DE, Hagan R, Evans SF, Benninger HR, French NP. Recurrent wheezing in very preterm infants. *Archives of Disease in Childhood Fetal and Neonatal Edition* 1996;74(3):F165–F171.

Elliot J, Vullermin P, Carroll N, James A, Robinson P. Increased airway smooth muscle in sudden infant death syndrome. *American Journal of Respiratory and Critical Care Medicine* 1999;160(1):313–6.

Engel J, Anteunis L, Volovics A, Hendriks J, Marres E. Risk factors of otitis media with effusion during infancy. *International Journal of Pediatric Otorhinolaryngology* 1999;48(3):239–49.

Etzel RA, Pattishall EN, Haley NJ, Fletcher RH, Henderson FW. Passive smoking and middle ear effusion among children in day care. *Pediatrics* 1992; 90(2 Pt 1):228–32.

Evans D, Levison MJ, Feldman CH, Clark NM, Wasilewski Y, Levin B, Mellins RB. The impact of passive smoking on emergency room visits of urban children with asthma. *American Review of Respiratory Disease* 1987;135(3):567–72.

Ey JL, Holberg CJ, Aldous MB, Wright AL, Martinez FD, Taussig LM, Group Health Medical Associates. Passive smoke exposure and otitis media in the first year of life. *Pediatrics* 1995;95(5):670–7.

Fagbule D, Ekanem EE. Some environmental risk factors for childhood asthma: a case-control study. *Annals of Tropical Paediatrics* 1994;14(1):15–9.

Faniran AO, Peat JK, Woolcock AJ. Persistent cough: is it asthma? *Archives of Disease in Childhood* 1998;79(5):411–4.

Farber HJ, Wattigney W, Berenson G. Trends in asthma prevalence: the Bogalusa Heart Study. *Annals of Allergy, Asthma & Immunology* 1997;78(3):265–9.

Farooqi IS, Hopkin JM. Early childhood infection and atopic disorder. *Thorax* 1998;53(11):927–32.

Fergusson DM, Horwood LJ. Parental smoking and respiratory illness during early childhood: a six-year longitudinal study. *Pediatric Pulmonology* 1985;1(2):99–106.

Fergusson DM, Horwood LJ, Shannon FT. Parental smoking and respiratory illness in infancy. *Archives of Disease in Childhood* 1980;55(5):358–61.

Fergusson DM, Horwood LJ, Shannon FT, Taylor B. Parental smoking and lower respiratory illness in the first three years of life. *Journal of Epidemiology and Community Health* 1981;35(3):180–4.

Ferris BG. Epidemiology Standardization Project. *American Review of Respiratory Disease* 1978;118 (6 Pt 2):1–120.

Ferris BG Jr, Ware JH, Berkey CS, Dockery DW, Spiro A III, Speizer FE. Effects of passive smoking on

health of children. *Environmental Health Perspectives* 1985;62:289–95.

Fleming DW, Cochi SL, Hightower AW, Broome CV. Childhood upper respiratory tract infections: to what degree is incidence affected by day-care attendance? *Pediatrics* 1987;79(1):55–60.

Florey C duV, Swan AV, van der Lende R, Holland WW, Berlin A, Di Ferrante E. *Report on the EC Epidemiological Survey on the Relationship Between Air Pollution and Respiratory Health in Primary School Children*. Brussels: Commission of the European Communities Environmental Research Programme, 1983.

Forastiere F, Corbo GM, Michelozzi P, Pistelli R, Agabiti N, Brancato, G, Ciappi G, Perucci CA. Effects of environment and passive smoking on the respiratory health of children. *International Journal of Epidemiology* 1992;21(1):66–73.

Forastiere F, Pistelli R, Sestini P, Fortes C, Renzoni E, Rusconi F, Dell'Orco V, Ciccone G, Bisanti L, SIDRIA (Italian Studies on Respiratory Disorders in Children and the Environment) Collaborative Group, Italy. Consumption of fresh fruit rich in vitamin C and wheezing symptoms in children. *Thorax* 2000;55(4):283–8.

Forsberg B, Pekkanen J, Clench-Aas J, Martensson M-B, Stjernberg N, Bartonova A, Timonen KL, Skerfving S. Childhood asthma in four regions in Scandinavia: risk factors and avoidance effects. *International Journal of Epidemiology* 1997;26(3):610–9.

Forsthuber T, Yip HC, Lehmann PV. Induction of TH1 and TH2 immunity in neonatal mice. *Science* 1996;271(5256):1728–30.

Galván Fernández C, Díaz Gómez NM, Suárez López de Vergara RG. Tobacco exposure and respiratory disease in children. *Revista Española de Pediatría* 1999;55(328):323–7.

Garcia-Marcos L, Guillén JJ, Dinwiddie R, Guillén A, Barbero P. The relative importance of socioeconomic status, parental smoking and air pollution (SO_2) on asthma symptoms, spirometry and bronchodilator response in 11-year-old children. *Pediatric Allergy and Immunology* 1999;10(2):96–100.

Gardner G, Frank AL, Taber LH. Effects of social and family factors on viral respiratory infection and illness in the first year of life. *Journal of Epidemiology and Community Health* 1984;38(1):42–8.

Geller-Bernstein G, Kenett R, Weisglass L, Tsur S, Lahav M, Levin S. Atopic babies with wheezy bronchitis: follow-up study relating prognosis to sequential IgE values, type of early infant feeding, exposure to parental smoking and incidence of lower respiratory tract infections. *Allergy* 1987;42(2):85–91.

Gepts L, Borlee I, Minette A. Prevalence of respiratory symptoms in 1659 school children living in a non polluted area [French]. *Acta Tuberculosea et Pneumologica Belgica* 1978;69(3–4):179–210.

Gergen PJ, Fowler JA, Maurer KR, Davis WW, Overpeck MD. The burden of environmental tobacco smoke exposure on the respiratory health of children 2 months through 5 years of age in the United States: Third National Health and Nutrition Examination Survey, 1988 to 1994. *Pediatrics* 1998; 101(2):E8.

Gilliland FD, Berhane K, McConnell R, Gauderman WJ, Vora H, Rappaport EB, Avol E, Peters JM. Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function. *Thorax* 2000;55(4):271–6.

Gold DR, Burge HA, Carey V, Milton DK, Platts-Mills T, Weiss ST. Predictors of repeated wheeze in the first year of life: the relative roles of cockroach, birth weight, acute lower respiratory illness, and maternal smoking. *American Journal of Respiratory and Critical Care Medicine* 1999;160(1):227–36.

Gomzi M. Indoor air and respiratory health in preadolescent children. *Atmospheric Environment* 1999;33(24–25):4081–6.

Goren A, Hellmann S, Gabbay Y, Brenner S. Respiratory problems associated with exposure to airborne particles in the community. *Archives of Environmental Health* 1999;54(3):165–71.

Goren AI, Goldsmith JR. Epidemiology of childhood respiratory disease in Israel. *European Journal of Epidemiology* 1986;2(2):139–50.

Goren AI, Hellmann S. Respiratory conditions among schoolchildren and their relationship to environmental tobacco smoke and other combustion products. *Archives of Environmental Health* 1995; 50(2):112–8.

Gortmaker SL, Walker DK, Jacobs FH, Ruch-Ross H. Parental smoking and the risk of childhood asthma. *American Journal of Public Health* 1982;72(6):574–9.

Graham NM. The epidemiology of acute respiratory infections in children and adults: a global perspective. *Epidemiologic Reviews* 1990;12:149–78.

Green RE, Cooper NK. Passive smoking and middle ear effusions in children of British servicemen in West Germany—a point prevalence survey by clinics of outpatient attendance. *Journal of the Royal Army Medical Corps* 1991;137(1):31–3.

Greenberg RA, Strecher VJ, Bauman KE, Boat BW, Fowler MG, Keyes LL, Denny FW, Chapman RS, Stedman HC, LaVange LM, et al. Evaluation of a home-based intervention program to reduce infant

passive smoking and lower respiratory illness. *Journal of Behavioral Medicine* 1994;17(3):273–90.

Gryczyńska D, Kobos J, Zakrzewska A. Relationship between passive smoking, recurrent respiratory tract infections and otitis media in children. *International Journal of Pediatric Otorhinolaryngology* 1999;49(Suppl 1):S275–S278.

Gulya AJ. Environmental tobacco smoke and otitis media [review]. *Otolaryngology—Head & Neck Surgery* 1994;111(1):6–8.

Gürkan F, Ece A, Haspolat K, Derman O, Bosnak M. Predictors for multiple hospital admissions in children with asthma. *Canadian Respiratory Journal* 2000a;7(2):163–6.

Gürkan F, Kiral A, Dağli E, Karakoç F. The effect of passive smoking on the development of respiratory syncytial virus bronchiolitis. *European Journal of Epidemiology* 2000b;16(5):465–8.

Haby MM, Peat JK, Woolcock AJ. Effect of passive smoking, asthma, and respiratory infection on lung function in Australian children. *Pediatric Pulmonology* 1994;18(5):323–9.

Håkansson A, Carlsson B. Maternal cigarette smoking, breast-feeding, and respiratory tract infections in infancy: a population-based cohort study. *Scandinavian Journal of Primary Health Care* 1992;10(1): 60–5.

Halken S, Høst A, Husby S, Hansen LG, Østerballe O, Nyboe J. Recurrent wheezing in relation to environmental risk factors in infancy: a prospective study of 276 infants. *Allergy* 1991;46(7):507–14.

Halken S, Host A, Nilsson L, Taudorf E. Passive smoking as a risk factor for development of obstructive respiratory disease and allergic sensitization. *Allergy* 1995;50(2):97–105.

Hall CB, Hall WJ, Gala CL, MaGill FB, Leddy JP. Long-term prospective study in children after respiratory syncytial virus infection. *Journal of Pediatrics* 1984;105(3):358–64.

Halliday JA, Henry RL, Hankin RG, Hensley MJ. Increased wheeze but not bronchial hyperreactivity near power stations. *Journal of Epidemiology and Community Health* 1993;47(4):282–6.

Halonen M, Stern D, Lyle S, Wright A, Taussig L, Martinez FD. Relationship of total serum IgE levels in cord and 9-month sera of infants. *Clinical and Experimental Allergy* 1991;21(2):235–41.

Hanke W, Kalinka J, Florek E, Sobala W. Passive smoking and pregnancy outcome in central Poland. *Human & Experimental Toxicology* 1999;18(4): 265–71.

Hanrahan JP, Tager IB, Segal MR, Tosteson TD, Castile RG, Van Vunakis H, Weiss ST, Speizer FE. The effect of maternal smoking during pregnancy on early infant lung function. *American Review of Respiratory Diseases* 1992;145(5):129–35.

Hansen LG, Host A, Halken S, Holmskov A, Husby S, Lassen LB, Storm K, Østerballe O. Cord blood IgE: II. Prediction of atopic disease: a follow-up at the age of 18 months. *Allergy* 1992;47(4 Pt 2):397–403.

Harlap S, Davies AM. Infant admissions to hospital and maternal smoking. *Lancet* 1974;1(7857):529–32.

Harsten G, Prellner K, Heldrup J, Kalm O, Kornfalt R. Acute respiratory tract infections in children: a three-year follow-up from birth. *Acta Paediatrica Scandinavica* 1990;79(4):402–9.

Hasday JD, Bascom R, Costa JJ, Fitzgerald T, Dubin W. Bacterial endotoxin is an active component of cigarette smoke. *Chest* 1999;115(3):829–35.

Hayes EB, Hurwitz ES, Schonberger LB, Anderson LJ. Respiratory syncytial virus outbreak on American Samoa: evaluation of risk factors. *American Journal of Diseases of Children* 1989;143(3):316–21.

Heinrich J, Hoelscher B, Jacob B, Wjst M, Wichmann H-E. Trends in allergies among children in a region of former East Germany between 1992–1993 and 1995–1996. *European Journal of Medical Research* 1999;4(3):107–13.

Henderson FW, Henry MM, Ivins SS, Morris R, Neebe EC, Leu S-Y, Stewart PW, the Physicians of Raleigh Pediatric Associates. Correlates of recurrent wheezing in school-age children. *American Journal of Respiratory and Critical Care Medicine* 1995;151(6):1786–93.

Henry RL, Abramson R, Adler JA, Wlodarcyzk J, Hensley MJ. Asthma in the vicinity of power stations: I. A prevalence study. *Pediatric Pulmonology* 1991;11(2):127–33.

Hinton AE. Surgery for otitis media with effusion in children and its relationship to parental smoking. *Journal of Laryngology & Otology* 1989;103(6): 559–61.

Hinton AE, Buckley G. Parental smoking and middle ear effusions in children. *Journal of Laryngology and Otology* 1988;102(11):992–6.

Hinton AE, Herdman RCD, Martin-Hirsch D, Saeed SR. Parental cigarette smoking and tonsillectomy in children. *Clinical Otolaryngology and Allied Sciences* 1993;18(3):178–80.

Hjern A, Haglund B, Bremberg S. Lower respiratory tract infections in an ethnic and social context. *Paediatric and Perinatal Epidemiology* 2000;14(1):53–60.

Hjern A, Haglund B, Bremberg S, Ringbäck-Weitoft G. Social adversity, migration and hospital admissions for childhood asthma in Sweden. *Acta Paediatrica* 1999;88(10):1107–12.

Holberg CJ, Wright AL, Martinez FD, Morgan WJ, Taussig LM, Group Health Medical Associates. Child day care, smoking by caregivers, and lower respiratory tract illness in the first 3 years of life. *Pediatrics* 1993;91(5):885–92.

Hölscher B, Heinrich J, Jacob B, Ritz B, Wichmann H-E. Gas cooking, respiratory health and white blood cell counts in children. *International Journal of Hygiene and Environmental Health* 2000;203(1): 29–37.

Homøe P, Christensen RB, Bretlau P. Acute otitis media and sociomedical risk factors among unselected children in Greenland. *International Journal of Pediatric Otorhinolaryngology* 1999;49(1):37–52.

Hoo A-F, Henschen M, Dezateux C, Costeloe K, Stocks J. Respiratory function among preterm infants whose mothers smoked during pregnancy. *American Journal of Respiratory and Critical Care Medicine* 1998;158(3):700–5.

Horstman D, Kotesovec F, Vitnerova N, Leixner M, Nozicka J, Smitkova D, Sram R. Pulmonary functions of school children in highly polluted northern Bohemia. *Archives of Environmental Health* 1997;52(1):56–62.

Horwood LJ, Fergusson DM, Shannon FT. Social and familial factors in the development of early childhood asthma. *Pediatrics* 1985;75(5):859–68.

Hosein HR, Corey P, Robertson JMD. The effect of domestic factors on respiratory symptoms and FEV_1. *International Journal of Epidemiology* 1989;18(2):390–6.

Hu FB, Persky V, Flay BR, Zelli A, Cooksey J, Richardson J. Prevalence of asthma and wheezing in public schoolchildren: association with maternal smoking during pregnancy. *Annals of Allergy, Asthma & Immunology* 1997;79(1):80–4.

Hunt LW, Gleich GJ, Ohnishi T, Weiler DA, Mansfield ES, Kita H, Sur S. Endotoxin contamination causes neutrophilia following pulmonary allergen challenge. *American Journal of Respiratory and Critical Care Medicine* 1994;149(6):1471–5.

Ilicali ÖC, Keleş N, Değer K, Savaş I. Relationship of passive cigarette smoking to otitis media. *Archives of Otolaryngology—Head & Neck Surgery* 1999;125(7):758–62.

Infante-Rivard C. Childhood asthma and indoor environmental risk factors. *American Journal of Epidemiology* 1993;137(8):834–44.

Infante-Rivard C, Gautrin D, Malo J-L, Suissa S. Maternal smoking and childhood asthma. *American Journal of Epidemiology* 1999;150(5):528–31.

Ingalls RR, Heine H, Lien E, Yoshimura A, Golenbock D. Lipopolysaccharide recognition, CD14, and lipopolysaccharide receptors. *Infectious Disease Clinics of North America* 1999;13(2):341–53, vii.

Irvine L, Crombie IK, Clark RA, Slane PW, Goodman KE, Feyerabend C, Cater JI. What determines levels of passive smoking in children with asthma? *Thorax* 1997;52(9):766–9.

Iversen M, Birch L, Lundqvist GR, Elbrond O. Middle ear effusion in children and the indoor environment: an epidemiological study. *Archives of Environmental Health* 1985;40(2):74–9.

Jackson JM, Mourino AP. Pacifier use and otitis media in infants twelve months of age or younger. *Pediatric Dentistry* 1999;21(4):255–60.

Jarvis MJ, Strachan DP, Feyerabend C. Determinants of passive smoking in children in Edinburgh, Scotland. *American Journal of Public Health* 1992;82(9):1225–9.

Jedrychowski W, Flak E. Maternal smoking during pregnancy and postnatal exposure to environmental tobacco smoke as predisposition factors to acute respiratory infections. *Environmental Health Perspectives* 1997;105(3):302–6.

Jedrychowski W, Maugeri U, Flak E, Mroz E, Bianchi I. Predisposition to acute respiratory infections among overweight preadolescent children: an epidemiologic study in Poland. *Public Health* 1998;112(3):189–95.

Jenkins MA, Hopper JL, Flander LB, Carlin JB, Giles GG. The associations between childhood asthma and atopy, and parental asthma, hay fever and smoking. *Paediatric and Perinatal Epidemiology* 1993;7(1):67–76.

Jin C, Rossignol AM. Effects of passive smoking on respiratory illness from birth to age eighteen months, in Shanghai, People's Republic of China. *Journal of Pediatrics* 1993;123(4):553–8.

Jones JG, Minty BD, Lawler P, Hulands G, Crawley JC, Veall N. Increased alveolar epithelial permeability in cigarette smokers. *Lancet* 1980;1(8159):66–8.

Jones RC, Hughes CR, Wright D, Baumer JH. Early house moves, indoor air, heating methods and asthma. *Respiratory Medicine* 1999;93(12):919–22.

Kaan A, Dimich-Ward H, Manfreda J, Becker A, Watson W, Ferguson A, Chan H, Chan-Yeung M. Cord blood IgE: its determinants and prediction of development of asthma and other allergic disorders at 12 months. *Annals of Allergy, Asthma & Immunology* 2000;84(1):37–42.

Kalyoncu AF, Selçuk ZT, Enünlü T, Demir AU, Çöplü L, Şahin AA, Artvinli M. Prevalence of asthma and allergic diseases in primary school children in Ankara, Turkey: two cross-sectional studies, five years apart. *Pediatric Allergy and Immunology* 1999;10(4):261–5.

Karaman Ö, Uguz A, Uzuner N. Risk factors in wheezing infants. *Pediatrics International* 1999;41(2): 147–50.

Kardas-Sobantka D, Stańczyk A, Kubik M. Prevalence of asthma symptoms among adolescents in Łódź. *Alergia Astma Immunologia* 2000;5(1):51–5.

Kasuga H, Hasebe A, Osaka F, Matsuki H. Respiratory symptoms in school children and the role of passive smoking. *Tokai Journal of Experimental and Clinical Medicine* 1979;4(2):101–14.

Kay J, Mortimer MJ, Jaron AG. Do both paternal and maternal smoking influence the prevalence of childhood asthma: a study into the prevalence of asthma in children and the effects of parental smoking. *Journal of Asthma* 1995;32(1):47–55.

Kendirli GS, Altintaş DU, Alparslan N, Akmanlar N, Yurdakul Z, Bolat B. Prevalence of childhood allergic diseases in Adana, Southern Turkey. *European Journal of Epidemiology* 1998;14(4):347–50.

Kershaw CR. Passive smoking, potential atopy and asthma in the first five years. *Journal of the Royal Society of Medicine* 1987;80(11):683–8.

Kitchens GG. Relationship of environmental tobacco smoke to otitis media in young children [review]. *Laryngoscope* 1995;105(5 Pt 2 Suppl 69):1–13.

Kjellman NI. Effect of parental smoking on IgE levels in children [letter]. *Lancet* 1981;1(8227):993–4.

Klig JE, Chen L. Lower respiratory infections in children. *Current Opinion in Pediatrics* 2003;15(1):121–6.

Knight JM, Eliopoulos C, Klein J, Greenwald M, Koren G. Pharmacokinetic predisposition to nicotine from environmental tobacco smoke: a risk factor for pediatric asthma. *Journal of Asthma* 1998;35(1):113–7.

Kossove D. Smoke-filled rooms and lower respiratory disease in infants. *South African Medical Journal* 1982;61(17):622–4.

Kraemer MJ, Richardson MA, Weiss NS, Furukawa CT, Shapiro GG, Pierson WE, Bierman CW. Risk factors for persistent middle-ear effusions: otitis media, catarrh, cigarette smoke exposure, and atopy. *Journal of the American Medical Association* 1983;249(8):1022–5.

Kuehr J, Frischer T, Karmaus W, Meinert R, Barth R, Herrman-Kunz E, Forster J, Urbanek R. Early childhood risk factors for sensitization at school age. *Journal of Allergy and Clinical Immunology* 1992; 90(3 Pt 1):358–63.

Kulig M, Luck W, Lau S, Niggemann B, Bergmann R, Klettke U, Guggenmoos-Holzmann I, Wahn U, Multicenter Allergy Study Group, Germany. Effect of pre- and postnatal tobacco smoke exposure on specific sensitization to food and inhalant allergens during the first 3 years of life. *Allergy* 1999;54(3):220–8.

Lam TH, Chung SF, Betson CL, Wong CM, Hedley AJ. Respiratory symptoms due to active and passive smoking in junior secondary school students in Hong Kong. *International Journal of Epidemiology* 1998;27(1):41–8.

Lam TH, Hedley AJ, Chung SF, Macfarlane DJ, Child Health and Activity Research Group (CHARG). Passive smoking and respiratory symptoms in primary school children in Hong Kong. *Human & Experimental Toxicology* 1999;18(4):218–23.

Lau YL, Karlberg J, Yeung CY. Prevalence of and factors associated with childhood asthma in Hong Kong. *Acta Paediatrica* 1995;84(7):820–2.

Lebowitz MD, Burrows B. Respiratory symptoms related to smoking habits of family adults. *Chest* 1976;69(1):48–50.

Lee LY, Widdicombe JG. Modulation of airway sensitivity to inhaled irritants: role of inflammatory mediators. *Environmental Health Perspectives* 2001;109(Suppl 4):585–9.

Leeder SR, Corkhill R, Irwig LM, Holland WW, Colley JRT. Influence of family factors on the incidence of lower respiratory illness during the first year of life. *British Journal of Preventive & Social Medicine* 1976;30(4):203–12.

Leen MG, O'Connor T, Kelleher C, Mitchell EB, Loftus BG. Home environment and childhood asthma. *Irish Medical Journal* 1994;87(5):142–4.

LeSon S, Gershwin ME. Risk factors for asthmatic patients requiring intubation. I: observations in children. *Journal of Asthma* 1995;32(4):285–94.

Leung R, Wong G, Lau J, Ho A, Chan JKW, Choy D, Douglass C, Lai CKW. Prevalence of asthma and allergy in Hong Kong schoolchildren: an ISAAC study. *European Respiratory Journal* 1997;10(2): 354–60.

Lewis KW, Bosque EM. Deficient hypoxia awakening response in infants of smoking mothers: possible relationship to sudden infant death syndrome. *Journal of Pediatrics* 1995;127(5):691–9.

Lewis PR, Hensley MJ, Wlodarczyk J, Toneguzzi RC, Westley-Wise VJ, Dunn T, Calvert D. Outdoor air pollution and children's respiratory symptoms in the steel cities of New South Wales. *Medical Journal of Australia* 1998;169(9):459–63.

Lewis S, Richards D, Bynner J, Butler N, Britton J. Prospective study of risk factors for early and persistent wheezing in childhood. *European Respiratory Journal* 1995;8(3):349–56.

Lewis SA, Britton JR. Consistent effects of high socioeconomic status and low birth order, and the

modifying effect of maternal smoking on the risk of allergic disease during childhood. *Respiratory Medicine* 1998;92(10):1237–44.

Li JSM, Peat JK, Xuan W, Berry G. Meta-analysis on the association between environmental tobacco smoke (ETS) exposure and the prevalence of lower respiratory tract infection in early childhood. *Pediatric Pulmonology* 1999;27(1):5–13.

Li Y-F, Gilliland FD, Berhane K, McConnell R, Gauderman WJ, Rappaport EB, Peters JM. Effects of *in utero* and environmental tobacco smoke exposure on lung function in boys and girls with and without asthma. *American Journal of Respiratory and Critical Care Medicine* 2000;162(6):2097–104.

Lieberman E, Torday J, Barbieri R, Cohen A, Van Vunakis H, Weiss ST. Association of intrauterine cigarette smoke exposure with indices of fetal lung maturation. *Obstetrics and Gynecology* 1992;79(4):564–70.

Lindfors A, van Hage-Hamsten M, Rietz H, Wickman M, Nordvall SL. Influence of interaction of environmental risk factors and sensitization in young asthmatic children. *Journal of Allergy and Clinical Immunology* 1999;104(4 Pt 1):755–62.

Lindfors A, Wickman M, Hedlin G, Pershagen G, Rietz H, Nordvall SL. Indoor environmental risk factors in young asthmatics: a case-control study. *Archives of Disease in Childhood* 1995;73(5):408–12.

Lister SM, Jorm LR. Parental smoking and respiratory illnesses in Australian children aged 0–4 years: ABS 1989–90 National Health Survey results. *Australian and New Zealand Journal of Public Health* 1998;22(7):781–6.

Lodrup Carlsen KC, Jaakkola JJ, Nafstad P, Carlsen KH. In utero exposure to cigarette smoking influences lung function at birth. *European Respiratory Journal* 1997;10(8):1774–9.

Lubianca Neto JF, Burns AG, Lu L, Mombach R, Saffer M. Passive smoking and nonrecurrent acute otitis media in children. *Otolaryngology—Head & Neck Surgery* 1999;121(6):805–8.

Lucas A, Brooke OG, Cole TJ, Morley R, Bamford MF. Food and drug reactions, wheezing, and eczema in preterm infants. *Archives of Disease in Childhood* 1990;65(4):411–5.

Lux AL, Henderson AJ, Pocock SJ, ALSPAC Study Team. Wheeze associated with prenatal tobacco smoke exposure: a prospective, longitudinal study. *Archives of Disease in Childhood* 2000;83(4):307–12.

Lyons RA. Passive smoking and hearing loss in infants. *Irish Medical Journal* 1992;85(3):111–2.

Macarthur C, Calpin C, Parkin PC, Feldman W. Factors associated with pediatric asthma readmissions. *Journal of Allergy and Clinical Immunology* 1996; 98(5 Pt 1):992–3.

Magnusson CG. Maternal smoking influences cord serum IgE and IgD levels and increases the risk for subsequent infant allergy. *Journal of Allergy and Clinical Immunology* 1986;78(5 Pt 1):898–904.

Magnusson CG. Cord serum IgE in relation to family history and as predictor of atopic disease in early infancy. *Allergy* 1988;43(4):241–51.

Maier WC, Arrighi HM, Morray B, Llewellyn C, Redding GJ. Indoor risk factors for asthma and wheezing among Seattle school children. *Environmental Health Perspectives* 1997;105(2):208–14.

Mainous AG 3rd, Hueston WJ. Passive smoke and low birth weight: evidence of a threshold effect. *Archives of Family Medicine* 1994;3(10):875–8.

Mannino DM, Moorman JE, Kingsley B, Rose D, Repace J. Health effects related to environmental tobacco smoke exposure in children in the United States: data from the Third National Health and Nutrition Examination Survey. *Archives of Pediatrics & Adolescent Medicine* 2001;155(1):36–41.

Marbury MC, Maldonado G, Waller L. The Indoor Air and Children's Health Study: methods and incidence rates. *Epidemiology* 1996;7(2):166–74.

Margolis PA, Keyes LL, Greenberg RA, Bauman KE, LaVange LM. Urinary cotinine and parent history (questionnaire) as indicators of passive smoking and predictors of lower respiratory illness in infants. *Pediatric Pulmonology* 1997;23(6):417–23.

Martinez FD, Antognoni G, Macri F, Bonci E, Midulla F, De Castro G, Ronchetti R. Parental smoking enhances bronchial responsiveness in nine-year-old children. *American Review of Respiratory Diseases* 1988;138(3):518–23.

Martinez FD, Cline M, Burrows B. Increased incidence of asthma in children of smoking mothers. *Pediatrics* 1992;89(1):21–6.

Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life: the Group Health Medical Associates. *New England Journal of Medicine* 1995;332(3):133–8.

Maw AR, Bawden R. Factors affecting resolution of otitis media with effusion in children. *Clinical Otolaryngology and Allied Sciences* 1994;19(2):125–30.

Maw R, Bawden R. Spontaneous resolution of severe chronic glue ear in children and the effect of adenoidectomy, tonsillectomy, and insertion of ventilation tubes (grommets). *British Medical Journal* 1993;306(6880):756–60.

McConnochie KM, Roghmann KJ. Bronchiolitis as a possible cause of wheezing in childhood: new evidence. *Pediatrics* 1984;74(1):1–10.

McConnochie KM, Roghmann KJ. Breast feeding and maternal smoking as predictors of wheezing in children age 6 to 10 years. *Pediatric Pulmonology* 1986a;2(5):260–8.

McConnochie KM, Roghmann KJ. Parental smoking, presence of older siblings, and family history of asthma increase risk of bronchiolitis. *American Journal of Diseases of Children* 1986b;140(8):806–12.

Medical Research Council. Questionnaire on Respiratory Symptoms (1966). London: Medical Research Council, 1966.

Melia RJ, Florey CV, Morris RW, Goldstein BD, John HH, Clark D, Craighead IB, Mackinlay JC. Childhood respiratory illness and the home environment. II: association between respiratory illness and nitrogen dioxide, temperature and relative humidity. *International Journal of Epidemiology* 1982;11(2):164–9.

Michel FB, Bousquet J, Greillier P, Robinet-Levy M, Coulomb Y. Comparison of cord blood immunoglobulin E concentrations and maternal allergy for the prediction of atopic diseases in infancy. *Journal of Allergy and Clinical Immunology* 1980;65(6): 422–30.

Michel O, Kips J, Duchateau J, Vertongen F, Robert L, Collet H, Pauwels R, Sergysels R. Severity of asthma is related to endotoxin in house dust. *American Journal of Respiratory and Critical Care Medicine* 1996;154(6 Pt 1):1641–6.

Michie C. Th1 and Th2 cytokines in pregnancy, from a fetal viewpoint [letter]. *Immunology Today* 1998;19(7):333–4.

Michie HR, Manogue KR, Spriggs DR, Revhaug A, O'Dwyer S, Dinarello CA, Cerami A, Wolff SM, Wilmore DW. Detection of circulating tumor necrosis factor after endotoxin administration. *New England Journal of Medicine* 1988;318(23):1481–6.

Minkovitz CS, Andrews JS, Serwint JR. Rehospitalization of children with asthma. *Archives of Pediatrics & Adolescent Medicine* 1999;153(7):727–30.

Misra DP, Nguyen RHN. Environmental tobacco smoke and low birth weight: a hazard in the workplace? *Environmental Health Perspectives* 1999; 107(Suppl 6):879–904.

Mok JY, Simpson H. Outcome of acute lower respiratory tract infection in infants: preliminary report of seven-year follow-up study. *British Medical Journal Clinical Research Edition* 1982;285(6338):333–7.

Monto AS. Epidemiology of viral respiratory infections. *American Journal of Medicine* 2002;112(6A): 4S–12S.

Moreau D, Ledoux S, Choquet M, Annesi-Maesano I. Prevalence and severity of asthma in adolescents in France: cross-sectional and retrospective analyses of a large population-based sample. *International Journal of Tuberculosis and Lung Disease* 2000;4(7):639–48.

Moussa MAA, Skaik MB, Yaghy OY, Salwanes SB, Bin-Othman SA. Factors associated with asthma in school children. *European Journal of Epidemiology* 1996;12(6):583–8.

Moyes CD, Waldon J, Ramadas D, Crane J, Pearce N. Respiratory symptoms and environmental factors in schoolchildren in the Bay of Plenty. *New Zealand Medical Journal* 1995;108(1007):358–61.

Mrazek DA, Klinnert M, Mrazek PJ, Brower A, McCormick D, Rubin B, Ikle D, Kastner W, Larsen G, Harbeck R, et al. Prediction of early-onset asthma in genetically at-risk children. *Pediatric Pulmonology* 1999;27(2):85–94.

Mumcuoglu KY, Abed Y, Armenios B, Shaheen S, Jacobs J, Bar-Sela S, Richter E. Asthma in Gaza refugee camp children and its relationship with house dust mites. *Annals of Allergy* 1994;72(2):163–6.

Murray AB, Morrison BJ. Passive smoking by asthmatics: its greater effect on boys than on girls and on older than on younger children. *Pediatrics* 1989;84(3):451–9.

Murray AB, Morrison BJ. It is children with atopic dermatitis who develop asthma more frequently if the mother smokes. *Journal of Allergy and Clinical Immunology* 1990;86(5):732–9.

Murray AB, Morrison BJ. The decrease in severity of asthma in children of parents who smoke since the parents have been exposing them to less cigarette smoke. *Journal of Allergy and Clinical Immunology* 1993;91(1 Pt 1):102–10.

Mutoh T, Bonham AC, Kott KS, Joad JP. Chronic exposure to sidestream tobacco smoke augments lung C-fiber responsiveness in young guinea pigs. *Journal of Applied Physiology* 1999;87(2):757–68.

Nafstad P, Kongerud J, Botten G, Hagen JA, Jaakkola JJ. The role of passive smoking in the development of bronchial obstruction during the first 2 years of life. *Epidemiology* 1997;8(3):293–7.

National Cancer Institute. *Health Effects of Exposure to Environmental Tobacco Smoke: The Report of the California Environmental Protection Agency*. Smoking and Tobacco Control Monograph No. 10. Bethesda

(MD): U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 1999. NIH Publication No. 99-4645.

National Research Council. *Research Priorities for Airborne Particulate Matter. IV: Continuing Research Progress*. Washington: National Academies Press, 2004.

Neuspiel DR, Rush D, Butler NR, Golding J, Bijur PE, Kurzon M. Parental smoking and post-infancy wheezing in children: a prospective cohort study. *American Journal of Public Health* 1989;79(2):168–71.

Niewoehner DE, Kleinerman J, Rice DB. Pathologic changes in the peripheral airways of young cigarette smokers. *New England Journal of Medicine* 1974;291(15):755–8.

Nilsson L, Castor O, Löfman O, Magnusson A, Kjellman N-IM. Allergic disease in teenagers in relation to urban or rural residence at various stages of childhood. *Allergy* 1999;54(7):716–21.

Ninan TK, Macdonald L, Russell G. Persistent nocturnal cough in childhood: a population based study. *Archives of Disease in Childhood* 1995;73(5):403–7.

Norman-Taylor W, Dickinson VA. Danger for children in smoking families. *Community Medicine* 1972;128(1):32–3.

Nriagu J, Robins T, Gary L, Liggans G, Davila R, Supuwood K, Harvey C, Jinabhai CC, Naidoo R. Prevalence of asthma and respiratory symptoms in south-central Durban, South Africa. *European Journal of Epidemiology* 1999;15(8):747–55.

Nuesslein TG, Beckers D, Rieger CHL. Cotinine in meconium indicates risk for early respiratory tract infections. *Human & Experimental Toxicology* 1999;18(4):283–90.

O'Connell EJ, Logan GB. Parental smoking in childhood asthma. *Annals of Allergy* 1974;32(3):142–5.

O'Connor GT, Sparrow D, Demolles D, Dockery D, Raizenne M, Fay M, Ingram RH, Speizer FE. Maximal and partial expiratory flow rates in a population sample of 10- to 11-yr-old schoolchildren: effect of volume history and relation to asthma and maternal smoking. *American Journal of Respiratory and Critical Care Medicine* 2000;162(2 Pt 1):436–9.

O'Connor GT, Weiss ST, Tager IB, Speizer FE. The effect of passive smoking on pulmonary function and nonspecific bronchial responsiveness in a population-based sample of children and young adults. *American Review of Respiratory Disease* 1987; 135:800–4.

Odhiambo JA, Ng'ang'a LW, Mungai MW, Gicheha CM, Nyamwaya JK, Karimi F, Macklem PT, Becklake MR. Urban-rural differences in questionnaire-derived markers of asthma in Kenyan school children. *European Respiratory Journal* 1998;12(5):1105–12.

Ogston SA, Florey CDV, Walker CHM. The Tayside infant morbidity and mortality study: effect on health of using gas for cooking. *British Medical Journal (Clinical Research Edition)* 1985;290(6473): 957–60.

Ogston SA, Florey CDV, Walker CHM. Association of infant alimentary and respiratory illness with parental smoking and other environmental factors. *Journal of Epidemiology and Community Health* 1987;41(1):21–5.

Oliveti JF, Kercsmar CM, Redline S. Pre- and perinatal risk factors for asthma in inner city African-American children. *American Journal of Epidemiology* 1996;143(6):570–7.

Oryszczyn MP, Godin J, Annesi I, Hellier G, Kauffmann F. In utero exposure to parental smoking, cotinine measurements, and cord blood IgE. *Journal of Allergy and Clinical Immunology* 1991;87(6): 1169–74.

Ownby DR, Johnson CC, Peterson EL. Maternal smoking does not influence cord serum IgE or IgD concentrations. *Journal of Allergy and Clinical Immunology* 1991;88(4):555–60.

Ownby DR, McCullough J. Passive exposure to cigarette smoke does not increase allergic sensitization in children. *Journal of Allergy and Clinical Immunology* 1988;82(4):634–8.

Palmieri M, Longobardi G, Napolitano G, Simonetti DML. Parental smoking and asthma in childhood. *European Journal of Pediatrics* 1990;149(10):738–40.

Paradise JL, Rockette HE, Colborn DK, Bernard BS, Smith CG, Kurs-Lasky M, Janosky JE. Otitis media in 2253 Pittsburgh-area infants: prevalence and risk factors during the first two years of life. *Pediatrics* 1997;99(3):318–33.

Park J-H, Gold DR, Spiegelman DL, Burge HA, Milton DK. House dust endotoxin and wheeze in the first year of life. *American Journal of Respiratory and Critical Care Medicine* 2001;163(2):322–8.

Park JK, Kim IS. Effects of family smoking on acute respiratory disease in children. *Yonsei Medical Journal* 1986;27(4):261–70.

Pedreira FA, Guandolo VL, Feroli EJ, Mella GW, Weiss IP. Involuntary smoking and incidence of respiratory illness during the first year of life. *Pediatrics* 1985;75(3):594–7.

Peters J, Hedley AJ, Wong CM, Lam TH, Ong SG, Liu J, Spiegelhalter DJ. Effects of an ambient air pollution intervention and environmental tobacco smoke on children's respiratory health in Hong Kong. *International Journal of Epidemiology* 1996;25(4):821–8.

Peters J, McCabe CJ, Hedley AJ, Lam TH, Wong CM. Economic burden of environmental tobacco smoke on Hong Kong families: scale and impact. *Journal of Epidemiology and Community Health* 1998;52(1):53–8.

Peters JM, Avol E, Navidi W, London SJ, Gauderman WJ, Lurmann F, Linn WS, Margolis H, Rappaport E, Gong H Jr, et al. A study of twelve southern California communities with differing levels and types of air pollution. I: prevalence of respiratory morbidity. *American Journal of Respiratory and Critical Care Medicine* 1999;159(3):760–7.

Philipp K, Pateisky N, Endler M. Effects of smoking on uteroplacental blood flow. *Gynecologic and Obstetric Investigation* 1984;17(4):179–82.

Pierce RA, Nguyen NM. Prenatal nicotine exposure and abnormal lung function. *American Journal of Respiratory Cell and Molecular Biology* 2002;26(1): 31–41.

Pirkle JL, Flegal KM, Bernert JT, Brody DJ, Etzel RA, Maurer KR. Exposure of the US population to environmental tobacco smoke: the Third National Health and Nutrition Examination Survey, 1988 to 1991. *Journal of the American Medical Association* 1996; 275(16):1233–40.

Ponsonby A-L, Couper D, Dwyer T, Carmichael A, Kemp A, Cochrane J. The relation between infant indoor environment and subsequent asthma. *Epidemiology* 2000;11(2):128–35.

Porro E, Calamita P, Rana I, Montini L, Criscione S. Atopy and environmental factors in upper respiratory infections: an epidemiological survey on 2304 school children. *International Journal of Pediatric Otorhinolaryngology* 1992;24(2):111–20.

Pukander J. Acute otitis media among rural children in Finland. *International Journal of Pediatric Otorhinolaryngology* 1982;4(4):325–32.

Pukander J, Luotonen J, Timonen M, Karma P. Risk factors affecting the occurrence of acute otitis media among 2–3-year-old urban children. *Acta Oto-Laryngologica* 1985;100(3–4):260–5.

Qian Z, Chapman RS, Tian Q, Chen Y, Lioy PJ, Zhang J. Effects of air pollution on children's respiratory health in three Chinese cities. *Archives of Environmental Health* 2000;55(2):126–33.

Quah BS, Mazidah AR, Simpson H. Risk factors for wheeze in the last 12 months in preschool children. *Asian Pacific Journal of Allergy and Immunology* 2000;18(2):73–9.

Rantakallio P. Relationship of maternal smoking to morbidity and mortality of the child up to the age of five. *Acta Paediatrica Scandinavica* 1978;67(5): 621–31.

Räsänen M, Kaprio J, Laitinen T, Winter T, Koskenvuo M, Laitinen LA. Perinatal risk factors for asthma in Finnish adolescent twins. *Thorax* 2000;55(1):25–31.

Rasmussen F. Protracted secretory otitis media: the impact of familial factors and day-care center attendance. *International Journal of Pediatric Otorhinolaryngology* 1993;26(1):29–37.

Reed BD, Lutz LJ. Household smoking exposure—association with middle ear effusions. *Family Medicine* 1988;20(6):426–30.

Reese AC, James IR, Landau LI, Lesouëf PN. Relationship between urinary cotinine level and diagnosis in children admitted to hospital. *American Review of Respiratory Disease* 1992;146(1):66–70.

Renzoni E, Forastiere F, Biggeri A, Viegi G, Bisanti L, Chellini E, Ciccone G, Corbo G, Galassi C, Rusconi F, et al. Differences in parental- and self-report of asthma, rhinitis and eczema among Italian adolescents. *European Respiratory Journal* 1999;14(3): 597–604.

Richards GA, Terblanche APS, Theron AJ, Opperman L, Crowther G, Myer MS, Steenkamp KJ, Smith FCA, Dowdeswell R, van der Merwe CA, et al. Health effects of passive smoking in adolescent children. *South African Medical Journal* 1996;86(2):143–7.

Roberts JE, Burchinal MR, Medley LP, Zeisel SA, Mundy M, Roush J, Hooper S, Bryant D, Henderson FW. Otitis media, hearing sensitivity, and maternal responsiveness in relation to language during infancy. *Journal of Pediatrics* 1995;126(3):481–9.

Roland PS, Finitzo T, Friel-Patti S, Brown KC, Stephens KT, Brown O, Coleman JM. Otitis media: incidence, duration, and hearing status. *Archives of Otolaryngology—Head & Neck Surgery* 1989;115(9):1049–53.

Rona RJ, Chinn S. Lung function, respiratory illness, and passive smoking in British primary school children. *Thorax* 1993;48(1):21–5.

Ronchetti R, Bonci E, Cutrera R, De Castro G, Indinnimeo L, Midulla F, Tancredi G, Martinez FD. Enhanced allergic sensitisation related to parental smoking. *Archives of Disease in Childhood* 1992; 67(4):496–500.

Ronchetti R, Macri F, Ciofetta G, Indinnimeo L, Cutrera R, Bonci E, Antognoni G, Martinez FD. Increased serum IgE and increased prevalence of eosinophilia in 9-year-old children of smoking parents. *Journal of Allergy and Clinical Immunology* 1990;86(3 Pt 1):400–7.

Rönmark E, Jönsson E, Platts-Mills T, Lundbäck B. Different pattern of risk factors for atopic and nonatopic asthma among children—report from the Obstructive Lung Disease in Northern Sweden Study. *Allergy* 1999;54(9):926–35.

Rönmark E, Lundbäck B, Jönsson E, Platts-Mills T. Asthma, type-1 allergy and related conditions in 7- and 8-year-old children in Northern Sweden: prevalence rates and risk factor pattern. *Respiratory Medicine* 1998;92(2):316–24.

Rowe-Jones JM, Brockbank MJ. Parental smoking and persistent otitis media with effusion in children. *International Journal of Pediatric Otorhinolaryngology* 1992;24(1):19–24.

Ruiz RG, Richards D, Kemeny DM, Price JF. Neonatal IgE: a poor screen for atopic disease. *Clinical and Experimental Allergy* 1991;21(4):467–72.

Rumold R, Jyrala M, Diaz-Sanchez D. Secondhand smoke induces allergic sensitization in mice. *Journal of Immunology* 2001;167(8):4765–70.

Rusconi F, Galassi C, Corbo GM, Forastiere F, Biggeri A, Ciccone G, Renzoni E, SIDRIA Collaborative Group. Risk factors for early, persistent, and late-onset wheezing in young children. *American Journal of Respiratory and Critical Care Medicine* 1999;160 (5 Pt 1):1617–22.

Rylander E, Eriksson M, Freyschuss U. Risk factors for occasional and recurrent wheezing after RSV infection in infancy. *Acta Paediatrica Scandinavica* 1988;77(5):711–5.

Rylander E, Pershagen G, Eriksson M, Bermann G. Parental smoking, urinary cotinine, and wheezing bronchitis in children. *Epidemiology* 1995;6(3): 289–93.

Rylander E, Pershagen G, Eriksson M, Nordvall L. Parental smoking and other risk factors for wheezing bronchitis in children. *European Journal of Epidemiology* 1993;9(5):517–26.

Rylander R, Mégevand Y. Environmental risk factors for respiratory infections. *Archives of Environmental Health* 2000;55(5):300–3.

Said G, Zalokar J, Lellouch J, Patois E. Parental smoking related to adenoidectomy and tonsillectomy in children. *Journal of Epidemiology and Community Health* 1978;32(2):97–101.

Saim A, Saim L, Saim S, Ruszymah BHI, Sani A. Prevalence of otitis media with effusion amongst pre-school children in Malaysia. *International Journal of Pediatric Otorhinolaryngology* 1997;41(1):21–8.

Salazar JC, Daly KA, Giebink GS, Lindgren BR, Liebeler CL, Meland M, Le CT. Low cord blood pneumococcal immunoglobulin G (IgG) antibodies predict early onset acute otitis media in infancy. *American Journal of Epidemiology* 1997;145(11):1048–56.

Samet JM. Adverse effects of smoke exposure on the upper airway. *Tobacco Control* 2004;13(Suppl 1): i57–i60.

Samet JM, Tager IB, Speizer FE. The relationship between respiratory illness in childhood and chronic air-flow obstruction in adulthood. *American Review of Respiratory Disease* 1983;127(4):508–23.

Sandberg S, Paton JY, Ahola S, McCann DC, McGuinness D, Hillary CR, Oja H. The role of acute and chronic stress in asthma attacks in children. *Lancet* 2000;356(9234):982–7.

Saraçlar Y, Şekerel BE, Kalayci Ö, Çetinkaya F, Adalioğlu G, Tuncer A, Tezcan S. Prevalence of asthma symptoms in school children in Ankara, Turkey. *Respiratory Medicine* 1998;92(2):203–7.

Schenker MB, Samet JM, Speizer FE. Risk factors for childhood respiratory disease: the effect of host factors and home environmental exposures. *American Review of Respiratory Disease* 1983;128(6):1038–43.

Schilling RSF, Letai AD, Hui SL, Beck GJ, Schoenberg JB, Bouhuys A. Lung function, respiratory disease, and smoking in families. *American Journal of Epidemiology* 1977;106(4):274–83.

Schmitzberger R, Rhomberg K, Büchele H, Puchegger R, Schmitzberger-Natzmer D, Kemmler G, Panosch B. Effects of air pollution on the respiratory tract of children. *Pediatric Pulmonology* 1993;15(2):68–74.

Schwartz J, Timonen KL, Pekkanen J. Respiratory effects of environmental tobacco smoke in a panel study of asthmatic and symptomatic children. *American Journal of Respiratory and Critical Care Medicine* 2000;161(3 Pt 1):802–6.

Scientific Committee on Tobacco and Health. *Report of the Scientific Committee on Tobacco and Health*. London: The Stationary Office, 1998.

Sekhon HS, Jia Y, Raab R, Kuryatov A, Pankow JF, Whitsett JA, Lindstrom J, Spindel ER. Prenatal nicotine increases pulmonary α7 nicotine receptor expression and alters fetal lung development in monkeys. *Journal of Clinical Investigation* 1999;103(5):637–47.

Sekhon HS, Keller JA, Proskocil BJ, Martin EL, Spindler ER. Maternal nicotine exposure upregulates collagen gene expression in fetal monkey lung: associated with α7 nicotine acetylcholine receptors. *American Journal of Respiratory Cell and Molecular Biology* 2002;26(1):10–3.

Selçuk ZT, Çaglar T, Enünlü T, Topal T. The prevalence of allergic diseases in primary school children in Edirne, Turkey. *Clinical & Experimental Allergy* 1997;27(3):262–9.

Seymour BW, Pinkerton KE, Friebertshauser KE, Coffman RL, Gershwin LJ. Second-hand smoke is an adjuvant for T helper-2 responses in a murine model of allergy. *Journal of Immunology* 1997;159(12): 6169–75.

Shamssain MH, Shamsian N. Prevalence and severity of asthma, rhinitis, and atopic eczema: the north east study. *Archives of Disease in Childhood* 1999;81(4):313–7.

Shaw R, Woodman K, Crane J, Moyes C, Kennedy J, Pearce N. Risk factors for asthma symptoms in Kawerau children. *New Zealand Medical Journal* 1994;107(987):387–91.

Sherman CB, Tosteson TD, Tager IB, Speizer FE, Weiss ST. Early childhood predictors of asthma. *American Journal of Epidemiology* 1990;132(1):83–95.

Siersted HC, Boldsen J, Hansen HS, Mostgaard G, Hyldebrandt N. Population based study of risk factors for underdiagnosis of asthma in adolescence: Odense schoolchild study. *British Medical Journal* 1998;316(7132):651–5.

Silverman M. Out of the mouths of babes and sucklings: lessons from early childhood asthma. *Thorax* 1993;48(12):1200–4.

Simani AS, Inoue S, Hogg JC. Penetration of the respiratory epithelium of guinea pigs following exposure to cigarette smoke. *Laboratory Investigation* 1974;31(1):75–81.

Sims DG, Downham MAPS, Gardner PS, Webb JKG, Weightman D. Study of 8-year-old children with a history of respiratory syncytial virus bronchiolitis in infancy. *British Medical Journal* 1978;1(6104): 11–4.

Sipila M, Karma P, Pukander J, Timonen M, Kataja M. The Bayesian approach to the evaluation of risk factors in acute and recurrent acute otitis media. *Acta Oto-Laryngologica* 1988;106(1–2):94–101.

Smith KR, Samet JM, Romieu I, Bruce N. Indoor air pollution in developing countries and acute lower respiratory infections in children. *Thorax* 2000;55(6):518–32.

Somerville SM, Rona RJ, Chinn S. Passive smoking and respiratory conditions in primary school children. *Journal of Epidemiology and Community Health* 1988;42(2):105–10.

Soto-Quiros M, Bustamante M, Gutierrez I, Hanson LC, Strannegard I-L, Karlberg J. The prevalence of childhood asthma in Costa Rica. *Clinical & Experimental Allergy* 1994;24(12):1130–6.

Søyseth V, Kongerud J, Boe J. Postnatal maternal smoking increases the prevalence of asthma but not of bronchial hyperresponsiveness or atopy in their children. *Chest* 1995;107(2):389–94.

Spencer N, Logan S, Scholey S, Gentle S. Deprivation and bronchiolitis. *Archives of Disease in Childhood* 1996;74(1):50–2.

Ståhlberg M-R, Ruuskanen O, Virolainen E. Risk factors for recurrent otitis media. *Pediatric Infectious Disease* 1986;5(1):30–2.

Stanhope JM, Rees RO, Mangan AJ. Asthma and wheeze in New Zealand adolescents. *New Zealand Medical Journal* 1979;90(645):279–82.

Stankus RP, Menon PK, Rando RJ, Glindmeyer H, Salvaggio JE, Lehrer SB. Cigarette smoke-sensitive asthma: challenge studies. *Journal of Allergy and Clinical Immunology* 1988;82(3 Pt 1):331–8.

Stathis SL, O'Callaghan DM, Williams GM, Najman JM, Andersen MJ, Bor W. Maternal cigarette smoking during pregnancy is an independent predictor for symptoms of middle ear disease at five years' postdelivery. *Pediatrics* 1999;104(2):e16.

Stein RT, Holberg CJ, Morgan WJ, Wright AL, Lombardi E, Taussig L, Martinez FD. Peak flow variability, methacholine responsiveness and atopy as markers for detecting different wheezing phenotypes in childhood. *Thorax* 1997;52(11):946–52.

Stenström C, Ingvarsson L. Otitis-prone children and controls: a study of possible predisposing factors. 2: physical findings, frequency of illness, allergy, day care and parental smoking. *Acta Oto-Laryngologica* 1997;117(5):696–703.

Stenstrom R, Bernard PAM, Ben-Simhon H. Exposure to environmental tobacco smoke as a risk factor for recurrent acute otitis media in children under the age of five years. *International Journal of Pediatric Otorhinolaryngology* 1993;27(2):127–36.

Stern B, Jones L, Raizenne M, Burnett R, Meranger JC, Franklin CA. Respiratory health effects associated with ambient sulfates and ozone in two rural Canadian communities. *Environmental Research* 1989a;49(1):20–39.

Stern B, Raizenne M, Burnett R. Respiratory effects of early childhood exposure to passive smoke. *Environment International* 1989b;15(1–6):29–34.

Stick SM, Burton PR, Gurrin L, Sly PD, LeSouef PN. Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. *Lancet* 1996;348(9034):1060–4.

Stocks J, Godfrey S, Beardsmore C, Bar-Yishay E, Castile R, ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. Plethysmographic measurements of lung volume and airway resistance. *European Respiratory Journal* 2001;17(2): 302–12.

Stoddard JJ, Miller T. Impact of parental smoking on the prevalence of wheezing respiratory illness in children. *American Journal of Epidemiology* 1995;141(2):96–102.

Strachan DP. Damp housing and childhood asthma: validation of reporting of symptoms. *British Medical Journal* 1988;297(6658):1223–6.

Strachan DP. Impedance tympanometry and the home environment in seven-year-old children. *Journal of Laryngology and Otology* 1990;104(1):4–8.

Strachan DP. Epidemiology. In: Silverman M, editor. *Childhood Asthma and Other Wheezing Disorders*. New York: Chapman & Hall, 1995:7–31.

Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *British Medical Journal* 1996;312(7040):1195–9.

Strachan DP, Carey IM. Home environment and severe asthma in adolescence: a population based case-control study. *British Medical Journal* 1995;311(7012):1053–6.

Strachan DP, Cook DG. Health effects of passive smoking. 1: parental smoking and lower respiratory illness in infancy and early childhood. *Thorax* 1997;52(10):905–14.

Strachan DP, Cook DG. Health effects of passive smoking. 4: parental smoking, middle ear disease and adenotonsillectomy in children. *Thorax* 1998a; 53(1):50–6.

Strachan DP, Cook DG. Health effects of passive smoking. 5: parental smoking and allergic sensitisation in children. *Thorax* 1998b;53(2):117–23.

Strachan DP, Cook DG. Health effects of passive smoking. 6: parental smoking and childhood asthma: longitudinal and case-control studies. *Thorax* 1998c; 53(3):204–12.

Strachan DP, Elton RA. Relationship between respiratory morbidity in children and the home environment. *Family Practice* 1986;3(3):137–42.

Strachan DP, Jarvis MJ, Feyerabend C. Passive smoking, salivary cotinine concentrations, and middle ear effusion in 7 year old children. *British Medical Journal* 1989;298(6687):1549–52.

Strachan DP, Jarvis MJ, Feyerabend C. The relationship of salivary cotinine to respiratory symptoms, spirometry, and exercise-induced bronchospasm in seven-year-old children. *American Review of Respiratory Disease* 1990;142(1):147–51.

Suárez-Varela MM, González AL, Martínez Selva MI. Socioeconomic risk factors in the prevalence of asthma and other atopic diseases in children 6 to 7 years old in Valencia, Spain. *European Journal of Epidemiology* 1999;15(1):35–40.

Tager IB, Hanrahan JP, Tosteson TD, Castile RG, Brown RW, Weiss ST, Speizer FE. Lung function, pre- and post-natal smoke exposure, and wheezing in the first year of life. *American Review of Respiratory Disease* 1993;147(4):811–7.

Tager IB, Ngo L, Hanrahan JP. Maternal smoking during pregnancy: effects on lung function during the first 18 months of life. *American Journal of Respiratory and Critical Care Medicine* 1995;152(3):977–83.

Tainio V-M, Savilahti E, Salmenperä L, Arjomaa P, Siimes MA, Perheentupa J. Risk factors for infantile recurrent otitis media: atopy but not type of feeding. *Pediatric Research* 1988;23(5):509–12.

Takasaka T. Incidence, prevalence and natural history of otitis media in different geographic areas and populations: epidemiology of otitis media with effusion in Japan. *Annals of Otology, Rhinology and Laryngology* 1990;99(7 Pt 2 Suppl 149):13–4.

Tariq S, Memon IA. Acute otitis media in children. *Journal of the College of Physicians and Surgeons Pakistan* 1999;9(12):507–10.

Tariq SM, Hakim EA, Matthews SM, Arshad SH. Influence of smoking on asthmatic symptoms and allergen sensitisation in early childhood. *Postgraduate Medical Journal* 2000;76(901):694–9.

Tariq SM, Matthews SM, Hakim EA, Stevens M, Arshad SH, Hide DW. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. *Journal of Allergy and Clinical Immunology* 1998;101(5):587–93.

Tashkin DP, Clark VA, Simmons M, Reems C, Coulson AH, Bourque LB, Sayre JW, Detels R, Rokaw S. The UCLA population studies of chronic obstructive respiratory disease. VII: relationship between parental smoking and children's lung function. *American Review of Respiratory Disease* 1984;129(6):891–7.

Taylor B, Wadsworth J. Maternal smoking during pregnancy and lower respiratory tract illness in early life. *Archives of Disease in Childhood* 1987;62(8):786–91.

Taylor B, Wadsworth J, Golding J, Butler N. Breast feeding, eczema, asthma, and hayfever. *Journal of Epidemiology and Community Health* 1983;37(2):95–9.

Teele DW, Klein JO, Rosner B, Greater Boston Otitis Media Study Group. Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study. *Journal of Infectious Diseases* 1989;160(1):83–94.

Teculescu D, Pham QT, Aubry C, Chau N, Viaggi MN, Henquel JC, Manciaux M. Respiratory health of children and atmospheric pollution: II. Ventilatory function. *Revue Des Maladies Respiratoires* 1989;6:221–8.

Teculescu DB, Pham QT, Varona-Lopez W, Deschamps JP, Marchand M, Henquel JC, Manciaux M. The single-breath nitrogen test does not detect functional impairment in children with passive exposure to tobacco smoke. *Bulletin Europeen De Physiopathologie Respiratoire* 1986;22:605–7.

Thaler I, Goodman JD, Dawes GS. Effects of maternal cigarette smoking on fetal breathing and fetal movements. *American Journal of Obstetrics and Gynecology* 1980;138(3):282–7.

Thornton AJ, Lee PN. Parental smoking and middle ear disease in children: a review of the evidence. *Indoor and Built Environment* 1999;8(1):21–39.

Toyoshima K, Hayashida M, Yasunami J, Takamatsu I, Niwa H, Muraoka T. Factors influencing the prognosis of wheezy infants. *Journal of Asthma* 1987;24(5):267–70.

Tulić MK, Wale JL, Holt PG, Sly PD. Modification of the inflammatory response to allergen challenge after exposure to bacterial lipopolysaccharide. *American Journal of Respiratory Cell and Molecular Biology* 2000;22(5):604–12.

Uhari M, Mäntysaari K, Niemelä M. A meta-analytic review of the risk factors for acute otitis media. *Clinical Infectious Diseases* 1996;22(6):1079–83.

Ulrik CS, Backer V. Atopy in Danish children and adolescents: results from a longitudinal population study. *Annals of Allergy, Asthma and Immunology* 2000;85(4):293–7.

U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Chronic Obstructive Lung Disease. A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, 1984. DHHS Publication No. (PHS) 84-50205.

U.S. Department of Health and Human Services. *The Health Consequences of Involuntary Smoking. A Report of the Surgeon General.* Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Health Promotion and Education, Office on Smoking and Health, 1986. DHHS Publication No. (CDC) 87-8398.

U.S. Department of Health and Human Services. *Reducing the Health Consequences of Smoking: 25 Years of Progress. A Report of the Surgeon General.* Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1989. DHHS Publication No. (CDC) 89-8411.

U.S. Department of Health and Human Services. *Women and Smoking. A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Office of the Surgeon General, 2001.

U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General*. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.

U.S. Environmental Protection Agency. *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders*. Washington: U.S. Environmental Protection Agency, Office of Research and Development, Office of Air and Radiation, 1992. Publication No. EPA/600/6-90/006F.

van Cauwenberge PB. Relevant and irrelevant predisposing factors in secretory otitis media. *Acta Oto-Laryngologica* 1984;414:147–53.

Victora CG, Fuchs SC, Flores JAC, Fonseca W, Kirkwood B. Risk factors for pneumonia among children in a Brazilian metropolitan area. *Pediatrics* 1994;93(6 Pt 1):977–85.

Vidic B. Transplacental effect of environmental pollutants on interstitial composition and diffusion capacity for exchange of gases of pulmonary parenchyma in neonatal rat. *Bulletin de l'Association des Anatomistes (Nancy)* 1991;75(229):153–5.

Vinke JG, KleinJan A, Severijnen LW, Fokkens WJ. Passive smoking causes an 'allergic' cell infiltrate in the nasal mucosa of non-atopic children. *International Journal of Pediatric Otorhinolaryngology* 1999;51(2):73–81.

Vinther B, Brahe Pedersen C, Elbrrnd O. Otitis media in childhood: sociomedical aspects with special reference to day-care conditions. *Clinical Otolaryngology and Allied Sciences* 1984;9(1):3–8.

Vinther B, Elbrond O, Pedersen CB. A population study of otitis media in childhood. *Acta Oto-Laryngologica* 1979;360(Suppl):135–7.

Vitnerova N, Horstman D, Hnizdova E. Prevalence of symptoms of airway diseases in schoolchildren living in areas with different atmospheric contamination. *Hygiena* 1999;44(Suppl 2):30–9.

Volkmer RE, Ruffin RE, Wigg NR, Davies N. The prevalence of respiratory symptoms in South Australian preschool children. II: factors associated with indoor air quality. *Journal of Paediatrics and Child Health* 1995;31(2):116–20.

von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Reitmeir R, Thiemann HH. Skin test reactivity

and number of siblings. *British Medical Journal* 1994;308(6930):692–5.

Wafula EM, Limbe MS, Onyango FE, Nduati R. Effects of passive smoking and breastfeeding on childhood bronchial asthma. *East African Medical Journal* 1999;76(11):606–9.

Wang FL, Love EJ, Liu N, Dai XD. Childhood and adolescent passive smoking and the risk of female lung cancer. *International Journal of Epidemiology* 1994;23(2):223–30.

Wang T-N, Ko Y-C, Chao Y-Y, Huang C-C, Lin R-S. Association between indoor and outdoor air pollution and adolescent asthma from 1995 to 1996 in Taiwan. *Environmental Research* 1999;81(3):239–47.

Ware JH, Dockery DW, Spiro A III, Speizer FE, Ferris BG Jr. Passive smoking, gas cooking, and respiratory health of children living in six cities. *American Review of Respiratory Disease* 1984;129(3):366–74.

Weber MW, Milligan P, Hilton S, Lahai G, Whittle H, Mulholland EK, Greenwood BM. Risk factors for severe respiratory syncytial virus infection leading to hospital admission in children in the western region of The Gambia. *International Journal of Epidemiology* 1999;28(1):157–62.

Weiss ST, Tager IB, Munoz A, Speizer FE. The relationship of respiratory infections in early childhood to the occurrence of increased levels of bronchial responsiveness and atopy. *American Review of Respiratory Diseases* 1985;131(4):573–8.

Weiss ST, Tager IB, Speizer FE, Rosner B. Persistent wheeze: its relation to respiratory illness, cigarette smoking, and level of pulmonary function in a population sample of children. *American Review of Respiratory Disease* 1980;122(5):697–707.

Weitzman M, Gortmaker S, Sobol A. Racial, social, and environmental risks for childhood asthma. *American Journal of Diseases of Children* 1990a;144(11): 1189–94.

Weitzman M, Gortmaker S, Walker DK, Sobol A. Maternal smoking and childhood asthma. *Pediatrics* 1990b;85(4):505–11.

Welliver RC, Wong DT, Sun M, McCarthy N. Parainfluenza virus bronchiolitis: epidemiology and pathogenesis. *American Journal of Diseases of Children* 1986;140(1):34–40.

Wennergren G, Cmark M, Cmark K, Óskarsdóttir S, Sten G, Redfors S. Wheezing bronchitis reinvestigated at the age of 10 years. *Acta Paediatrica* 1997;86(4):351–5.

Willatt DJ. Children's sore throats related to parental smoking. *Clinical Otolaryngology and Allied Sciences* 1986;11(5):317–21.

Willers S, Attewell R, Bensryd I, Schutz A, Skarping G, Vahter M. Exposure to environmental tobacco smoke in the household and urinary cotinine excretion, heavy metals retention, and lung function. *Archives of Environmental Health* 1992;47:357–63.

Willers S, Svenonius E, Skarping G. Passive smoking and childhood asthma: urinary cotinine levels in children with asthma and in referents. *Allergy* 1991;46(5):330–4.

Wilson NM. Wheezy bronchitis revisited. *Archives of Disease in Childhood* 1989;64(8):1194–9.

Wilson NM. The significance of early wheezing. *Clinical and Experimental Allergy* 1994;24(6):522–9.

Wisborg K, Henriksen TB, Obel C, Skajaa E, Østergaard JR. Smoking during pregnancy and hospitalization of the child. *Pediatrics* 1999;104 (4):e46.

Withers NJ, Low L, Holgate ST, Clough JB. The natural history of respiratory symptoms in a cohort of adolescents. *American Journal of Respiratory and Critical Care Medicine* 1998;158(2):352–7.

Woodward A, Douglas RM, Graham NM, Miles H. Acute respiratory illness in Adelaide children: breast feeding modifies the effect of passive smoking. *Journal of Epidemiology and Community Health* 1990;44(3):224–30.

World Health Organization. *Tobacco or Health: A Global Status Report*. Geneva: World Health Organization, 1997.

World Health Organization. *International Consultation on Environmental Tobacco Smoke (ETS) and Child Health: Consultation Report*. Geneva: World Health Organization, Tobacco Free Initiative, 1999. Report No. WHO/NCD/TFI/99.10.

Wright AL, Holberg C, Martinez FD, Taussig LM, Group Health Medical Associates. Relationship of parental smoking to wheezing and nonwheezing lower respiratory tract illnesses in infancy. *Journal of Pediatrics* 1991;118(2):207–14.

Wright AL, Holberg CJ, Morgan WJ, Taussig LM, Halonen M, Martinez FD. Recurrent cough in childhood and its relation to asthma. *American Journal of Respiratory and Critical Care Medicine* 1996;153 (4 Pt 1):1259–65.

Wu J-H, Lin RS, Hsieh K-H, Chiu W-T, Chen L-M, Chiou S-T, Huang K-C, Liu W-L, Chiu HI, Hsiao H-C, et al. Adolescent asthma in Northern Taiwan. *Chinese Journal of Public Health* 1998;17(3):214–25.

Yarnell JWG, St Leger AS. Respiratory illness, maternal smoking habit and lung function in children. *British Journal of Diseases of the Chest* 1979;73(3): 230–6.

Yau K-I, Fang L-J, Shieh K-H. Factors predisposing infants to lower respiratory infection with wheezing in the first two years of life. *Annals of Allergy, Asthma & Immunology* 1999;82(2):165–70.

Young S, Arnott J, O'Keeffe PT, Le Souef PN, Landau LI. The association between early life lung function and wheezing during the first 2 yrs of life. *European Respiratory Journal* 2000a;15(1):151–7.

Young S, Sherrill DL, Arnott J, Diepeveen D, LeSouëf PN, Landau LI. Parental factors affecting respiratory function during the first year of life. *Pediatric Pulmonology* 2000b;29(5):331–40.

Zacharasiewicz A, Zidek T, Haidinger G, Waldhör T, Vutuc C, Zacharasiewicz A, Goetz M, Pearce N. Symptoms suggestive of atopic rhinitis in children aged 6–9 years and the indoor environment. *Allergy* 2000;55(10):945–50.

Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. *Journal of Allergy and Clinical Immunology* 1995;95(6):1179–90.

Zejda JE, Skiba M, Orawiec A, Dybowska T, Cimander B. Respiratory symptoms in children of Upper Silesia, Poland: cross-sectional study in two towns of different air pollution levels. *European Journal of Epidemiology* 1996;12(1):115–20.

Zielhuis GA, Heuvelmans-Heinen EW, Rach GH, van den Broek P. Environmental risk factors for otitis media with effusion in preschool children. *Scandinavian Journal of Primary Health Care* 1989;7(1):33–8.

Zielhuis GA, Rach GH, van den Broek P. Predisposing factors for otitis media with effusion in young children. *Advances in Oto-Rhino-Laryngology* 1988;40:65–9.