

smoked. Estimates of ETS exposure, based on cotinine measurements, suggest that involuntary smokers absorb about 0.5 to 1 percent of the nicotine that active smokers absorb (Jarvis et al. 1984; Haley and Hoffmann 1985; Wald et al. 1984; Russell et al. 1986).

Dose-Response Relationships and Threshold for Risk

Dose-response relationships for active smoking can provide insights into the expected magnitude of disease resulting from the exposure of nonsmokers to ETS. These data are reviewed to determine whether disease can be expected in association with ETS.

Data from cohort and case-control studies demonstrate dose-response relationships for lung cancer, which extend to the lowest levels of reported active smoking. The dose-response relationship of active smoking with lung cancer risk has been described by several investigators in several different data sets (Whittemore and Altshuler 1976; Doll and Peto 1978; Pathak et al. 1986). Although the mathematical forms of these models vary, none have included a threshold level of active smoking that must be passed for lung cancer to develop.

The dose-response relationship for active smoking and lung cancer has been used to project the lung cancer risk for nonsmokers (Vutuc 1984). Such projections yield risk estimates of 1.03 to 1.36 for exposures, considered to be reasonable estimates of involuntary smoking exposures, i.e., 0.1 to 1.0 cigarettes per day. The reference population for these risk estimates is the risk for nonsmokers as a group, including those with higher and those with lower exposures to environmental tobacco smoke. In contrast, the reference population for the risk estimates in studies of involuntary smoking is the lung cancer risk in only that group of nonsmokers who have lower exposure to ETS. Comparisons of lung cancer risk estimates from active smoking studies with those from involuntary smoking studies require reference to the same exposure group for proper interpretation. In general, the lung cancer experience of all nonsmokers (i.e., those with higher and lower involuntary smoking exposure combined) has been used to establish the reference rate of lung cancer occurrence (i.e., set as a risk of 1) in studies of active smoking. The use of all nonsmokers as the reference group averages the lower risks of nonsmokers with less ETS exposure with the higher risks of those with more ETS exposure. Thus, with the relative risk for the entire group of nonsmokers set to unity, the relative risk for nonsmokers with lower exposure is below 1 and that for the group with higher exposure is above 1. As a consequence, relative risk estimates from studies of involuntary exposure cannot be directly compared with risk estimates extrapolated from active smoking, unless comparison to a single level of exposure is possible. Failure to

consider the differences between the reference populations explains the apparent discrepancy noted by Vutuc.

Consider, for example, the mortality study reported by Hirayama (1981a). In this study, the relative risk of lung cancer for nonsmoking wives of smoking husbands (current and former) compared with nonsmoking wives of nonsmoking husbands (as calculated from Figure 1 in Hirayama 1981a) was 1.78. If the relative risk for nonsmoking wives of nonsmoking husbands were expressed in relation to the combined group of nonsmoking women, then a value of 0.63 is obtained, while with a similar calculation, that for nonsmoking wives of smoking husbands (both current and former), yields a value of 1.12. Thus, when the appropriate comparison is made, the risk estimates developed by extrapolation of the active smoking data (1.03 to 1.36) closely approximate those actually found in a study of lung cancer risk due to involuntary smoking.

Dose-response relationships between active smoking and the level of lung function, the rate of decline of lung function in adult life, and the development of chronic airflow obstruction are well established (US DHHS 1984). Different measures of dose have provided the strongest correlation with functional decline in different studies. Pack-years, a cumulative dose measure, was the strongest predictor of the level of forced expiratory volume in 1 second (FEV_1) in the Tucson epidemiologic study (Burrows, Knudson, Cline et al. 1977). Duration of smoking and the amount smoked were found to be the best predictors in male subjects in a study of three U.S. communities (Beck et al. 1981), and pack-years was the best predictor in female subjects. In both of these studies, however, the estimated dose accounted for only about 15 percent of the variation of age- and height-adjusted FEV_1 levels. The relatively low predictive capability of cigarette smoking variables in these studies most likely reflects a lack of information on the determinants of individual susceptibility to tobacco smoke. Further, exposure variables obtained by questionnaire, such as the number of cigarettes smoked daily, may only roughly approximate the dose delivered to target sites in the respiratory tract. Many factors, such as puff volume, lung volume at which inhalation starts, and airways geometry will influence the smoke dose and its distribution within the lungs. Extrapolation from the results of these studies to the pulmonary effects of exposure to ETS is, therefore, likely to be inaccurate.

Another approach for assessing low-dose exposures is to consider the information available from studies involving children and teenagers who have recently taken up smoking. Even with brief smoking experience, cross-sectional studies of active cigarette smoking by children and adolescents have demonstrated an increased frequency of respiratory symptoms (Rawbone et al. 1978; Rush 1974; Bewley et al. 1973; Seely et al. 1971) and small but statistically

significant reductions in lung function (Seely et al. 1971; Peters and Ferris 1967; Lim 1973; Walter et al. 1974; Backhouse 1975; Woolcock et al. 1984). Longitudinal studies involving children and adolescents have demonstrated that a physiologic impairment attributable to smoking may be found in some children by age 14 and may be present after only 1 year of smoking 10 or more cigarettes per week in children with previously normal airways (Woolcock et al. 1984), and that relatively small amounts of cigarette use may lead to significant effects on FEV₁ and on the growth of lung function in adolescents (Figure 1) (Tager et al. 1985).

When considering the risk of low-dose exposures for the development of chronic respiratory disease, the existence of a spectrum of risk and a distribution of dose within the population should be taken into consideration. The characteristics of the part of the population most susceptible to involuntary smoke exposure is still being clarified. Evidence is accumulating that airways hyperresponsiveness, atopy, childhood respiratory illness, and occupational exposures may all influence response to ETS. Current understanding of lung injury suggests that individuals with one or more of these characteristics that place them at the most sensitive end of the susceptibility curve may be the most likely to develop symptoms or functional changes as a result of ETS exposure. Dose of ETS also varies in the population, and the coincidence of high dose and increased susceptibility may convey a particularly high risk. Furthermore, ETS exposure may damage lungs that are also affected by other insults.

Pathophysiologic Considerations

Cancer

Carcinogenesis refers to the process by which a normal cell is transformed into a malignant cell with uncontrolled replication. Carcinogenesis has been conceptualized as a multistage process involving a sequence of alterations in cellular DNA that terminate with the development of a malignant cell. Agents acting early in this sequence are referred to as initiators; those acting later are referred to as promoters. Compounds with both initiating activity and promoting activity have been identified in tobacco smoke.

Carcinogenesis reflects DNA damage; although some repair may take place, biological models have not suggested that there is a threshold of damage that must be exceeded. Rather, carcinogenesis has been considered to involve a series of changes, each occurring at a rate dependent on the dose of a damaging agent. Higher doses increase the probability that the entire sequence will be completed, but lower doses may also lead to malignancy.

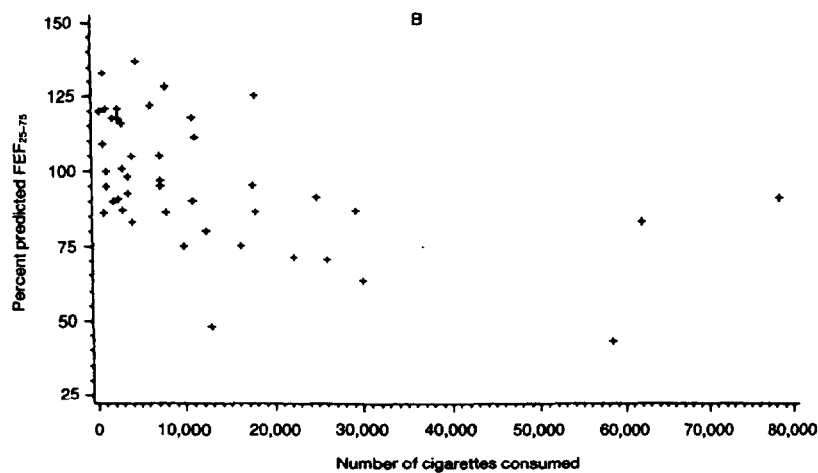
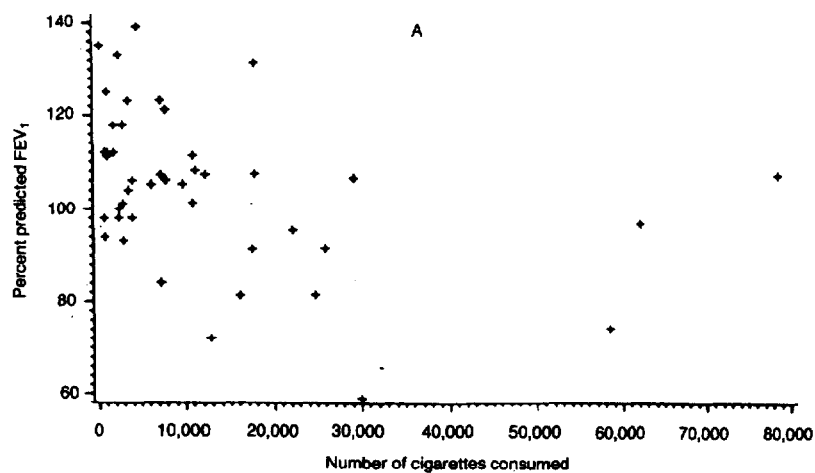


FIGURE 1.—Relationship between levels of predicted for FEV₁ (A) and FEF₂₅₋₇₅ (B) at examination 8 and cumulative number of cigarettes smoked during examinations 4 through 8

NOTE: Men and women combined (N=44).
SOURCE: Tager et al. (1985).

with the PiZZ or other phenotypes, are modest particulate exposures likely to increase the risk for disease to an appreciable extent.

The development of acute and chronic *airway* disease or symptoms of cough, phlegm production, and wheeze may require a considerably smaller exposure than changes in the lung parenchyma, and it is not unreasonable to hypothesize that these symptoms may be related to repeated and continuous exposure to ETS in the susceptible individual. Strong evidence that low-dose active smoking causes increased rates of respiratory symptoms and functional impairment comes from the studies of children and adolescents discussed earlier (Woolcock et al. 1984; Tager et al. 1985). Because of the length of exposure, it is likely that these reflect airway rather than parenchymal effects.

Another pathophysiological mechanism by which exposure to ETS may increase an individual's risk for the development of chronic airflow obstruction is through respiratory viral infections. Mounting evidence indicates that the very young child (under 2 years of age) exposed to ETS is at increased risk for lower respiratory tract viral infections (Harlap and Davies 1974; Colley 1974; Colley et al. 1974; Leeder et al. 1976a; Fergusson et al. 1981; Dutau et al. 1979; Pedreira et al. 1985). There is also increasing, though still inconclusive, epidemiologic evidence that respiratory viral infections in early life may be associated with an accelerated decline in FEV₁ and, therefore, an increased risk for the development of chronic airflow obstruction in adult life in smokers (Burrows, Knudson, Lebowitz 1977; Samet et al. 1983). By increasing the occurrence of viral infections of the lower respiratory tract in early life, exposure to ETS in childhood may have an appreciable, but indirect, effect on the risk for the development of chronic airflow obstruction in adult life. The structural basis for this increased susceptibility has not yet been elucidated, however. Furthermore, the child whose parents smoke is also more likely to take up smoking than is the child of nonsmoking parents. Thus, the child made susceptible to the effects of active smoking by prior ETS exposure is also more likely to become an active smoker.

The possibility that exposure to constituents of tobacco smoke in utero may exert a prenatal effect must also be considered. This exposure is clearly not the same as ETS exposure, since the lungs of the fetus are not being exposed to ETS; rather, the developing fetal lung is exposed to compounds absorbed by the mother and delivered to the fetus transplacentally. Evidence of an in utero effect in pregnant rats has been reported by Collins and coworkers (1985). These investigators reported that pregnant rats exposed to smoke from day 5 to day 20 of gestation, in comparison with control rats, showed reduced lung volume at term and saccules that were reduced in number and increased in size as a result of the reduced formation

Lung Disease

The noncarcinogenic pathophysiologic effects of active smoking on the respiratory tract can be separated into (1) effects on the airways and (2) effects on the lung parenchyma. In the airways, the structural changes include inflammation in the small airways and mucous gland hypertrophy and hyperplasia. In the parenchyma, the main structural change is alveolar wall destruction. Both the airways and the parenchymal changes are caused by active smoking, but the interrelationships of these changes are not clear. They may be independent pathophysiologic processes, linked only by their joint association with tobacco smoking.

As discussed earlier, there is evidence showing an approximately linear dose-response relationship between FEV₁ level and amount smoked; however, the dose-response relationships have not been as well described for the underlying pathophysiologic changes in the airways or in the lung parenchyma. Host factors and other environmental factors presumably interact with active smoking to affect an individual's risk for the development of disease. In this regard, present evidence would suggest that only 10 to 15 percent of smokers develop clinically significant airflow obstruction, although parenchymal and airways changes can be demonstrated in a substantially higher percentage at autopsy (US DHHS 1984).

Extrapolation from the evidence on active smoking to the likely effect of exposure to environmental tobacco smoke on the airways and parenchyma suggests that pathophysiologic effects on both the airways and the lung parenchyma might be expected. Because the dose of smoke components from ETS exposure is small in comparison with the dose from active smoking, the extent of lung injury would most likely also be much smaller than that found in active smokers. Small changes in the lung may be below the threshold for detection on pulmonary function testing. If clinically significant chronic airflow obstruction occurs in nonsmokers exposed to ETS, the risk is likely to be concentrated among those individuals highly susceptible to the airway or parenchymal effects of cigarette smoke. This susceptible group may include individuals with bronchial hyperresponsiveness and with other, as yet unidentified, genetic and familial risk factors. Identifying the risk factors for susceptibility to the airway and parenchymal effects of both mainstream smoke and ETS is an important priority. The dose of environmental tobacco smoke received by the nonsmoker is unlikely, by itself, to be sufficient to cause a clinically significant degree of *parenchymal* disease (emphysema) unless an individual is at the extreme end of the susceptibility distribution. Any particulate load is likely to increase the elastase burden in the lungs by causing an influx of neutrophils. However, only in the individual with very inadequate lung defenses, specifically severe deficiency of protease inhibitor (Pi) associated

of sacculle partitions. These hypoplastic lungs showed an internal surface area that was decreased. Whether this study in rats has any relevance to humans is not yet clear, but this issue deserves further investigation.

Whether continued exposure to ETS during childhood, while the lung is remodeling and growing, affects the process of growth and remodeling is not yet clear. In general, rapidly dividing cells and immature organs are more susceptible to the effects of environmental toxins than are cells undergoing a normal rate of division and mature organs. Apart from the evidence, cited above, linking lower respiratory tract viral infections in very early life to an accelerated decline of FEV₁ in adult life, there is no information yet to link the rate of growth of lung function during childhood to the rate of decline of lung function in adult life because the necessary longitudinal studies have not been done. More information is needed to describe the relationship of exposure to ETS at various times during childhood to the maximal level of lung function achieved at full lung growth.

Methodological Considerations in Epidemiologic Studies

Measurement of Exposure

In assessing the health effects of ETS exposure, as with other environmental pollutants, accurate assessment of exposure is critical for obtaining estimates of this agent's effects. Both random and systematic misclassification of the exposures of subjects in an investigation are of concern. Random misclassification refers to errors that occur at random; the consequence of such random misclassification is to bias toward finding no effect. Systematic misclassification refers to nonrandom errors in exposure assessment; the consequence may be to bias toward a greater or lesser effect than is actually present. Biased answers in response to a questionnaire may introduce systematic misclassification.

Some misclassification occurs in most observational (nonexperimental) epidemiological studies, and is inherent in all epidemiological studies of ETS. Tobacco smoking is ubiquitous in nearly all environments; few people escape being exposed to ETS. Thus, the exposure variables for ETS in epidemiological studies do not separate nonexposed subjects from exposed subjects; rather, they identify groups with more or less exposure, or with a qualitative or semiquantitative gradient of exposure.

In assessing exposure to ETS, the information should cover the biologically appropriate time period for the health effect of interest and be collected in a form that permits the construction of biologically appropriate exposure measures. However, the collection of a full lifetime history of ETS exposure, as in a study of malignancy, may not be feasible, and the accuracy of the informa-

tion may be limited. In evaluating the effects of ETS exposure, cumulative exposure, duration of exposure, and intensity of exposure may each influence the magnitude of effects, as may the timing of exposure in relation to age and level of development.

Because of the difficulties inherent in assessing exposures through questionnaires, increased emphasis has been placed on measuring exposure through the use of molecular or biochemical markers. With available markers, this approach is limited to providing an indication of recent (within 48 hours) exposure, which may not necessarily correlate with past exposure. A marker has not yet been devised for total integrated dose. Nevertheless, biological markers provide another method for classification of current exposure, and a standard for validating questionnaires.

The strengths and weaknesses of the existing methods of measuring exposure are further discussed below.

Atmospheric Markers

A number of different markers of atmospheric contamination by tobacco combustion products can be feasibly measured. Ideally, the atmospheric levels of the air contaminant or class of contaminants that are implicated in producing the adverse health effects would be measured. A variety of contaminants have been measured as indicators of ETS, but no single measure can adequately index all of its myriad components. Further, some contaminants are produced by sources of environmental contamination other than tobacco smoke. Nicotine is absorbed only from tobacco and tobacco combustion products.

Some of the pollutants that have been measured include (1) carbon monoxide, (2) respirable suspended particulates (RSP), (3) nicotine, (4) a number of aromatic hydrocarbons, such as benzene, toluene, benzo-pyrene, and phenols, and (5) acrolein. Some of these are in the vapor phase and some in the particulate phase. Some, such as nicotine, may exist in one phase (particulate) in MS and in the other (gas) phase in SS. Until more is learned about the contaminants and their physical state in ETS, the results of monitoring for a particular ETS component will be difficult to relate to its disease-causing potential. At a practical level, the technology for measuring nicotine levels and RSP levels is available and accurate.

Personal Monitoring

Both active and passive personal monitors can be used to measure an individual's total exposure to an air contaminant at the breathing zone. Active personal monitoring systems employ pumps to concentrate the air contaminants on a collection medium for laboratory analysis or to deliver the air to a continuous monitor. Passive

personal monitoring systems use diffusion and permeation to concentrate gases on a collection medium for laboratory analysis. Personal monitoring should provide a more accurate estimate of the dose of a contaminant than area monitoring, because the actual air in the breathing zone is sampled and the subject's time-activity pattern is inherently considered.

As with area monitoring, the results for a particular component of ETS may not adequately characterize exposure to other components responsible for a particular disease or effect. Respirable suspended particulates can be measured with accuracy and give a reasonably accurate measurement of current exposure.

Questionnaires

The questionnaire has been the most frequently used means of estimating exposures for epidemiological investigations. Questionnaires typically have obtained information about the smoking habits of parents, spouses, or other family members and often about exposure outside the home. From this information, the subject is classified as exposed or not exposed to ETS, and the extent of exposure may be estimated.

The questionnaire approach for exposure estimation has several potential limitations. First, the information obtained cannot exhaustively cover lifetime exposure to ETS; therefore, a completely accurate reconstruction of integrated dose over the years cannot be achieved. Second, in evaluating ETS exposure in the home, the usual daily smoking of the smokers has often been used as a measure of exposure intensity at home. This assumption may not be correct, since smoking does not occur only in the home. For example, a one-pack-a-day smoker may smoke only five cigarettes a day in the home environment and smoke the rest at work or elsewhere outside the home. Third, quantitation of exposure in the workplace is inherently difficult because of changes in jobs and the varying exposure in any particular workplace.

Despite these shortcomings, the information obtained by questionnaires does discriminate between more exposed and less exposed subjects. The evidence validating the questionnaire method is strongest for domestic exposure. In several studies, levels of cotinine in body fluids have varied with reported exposure to tobacco smoke at home (Greenberg et al. 1984; Wald and Ritchie 1984; Matsukura et al. 1984; Jarvis et al. 1984). In fact, residence with a smoker may identify a population that is more tolerant of ETS, and therefore more likely to be exposed outside the home. Evidence in support of this speculation is provided by a study of urinary cotinine levels in nonsmoking men in the United Kingdom (Wald and Ritchie 1984). In this study, the men married to women who smoked reported a

greater duration of exposure outside the home than men married to women who did not smoke.

Until accurate and inexpensive exposure markers are available for cumulative ETS exposure, the questionnaire approach will remain the simplest means of obtaining exposure information. It is, therefore, important to consider the misclassification that can be introduced by using this indirect measure of exposure. In studies of the effect of ETS exposure, two types of misclassification are of concern: misclassification of current or former smokers as never smokers and misclassification of the extent of ETS exposure.

Because active smoking has a greater effect on the lungs than exposure to ETS, the inclusion of active smokers within a larger group of nonsmokers may lead to the finding of a significant effect on lung function, which is actually attributable to active smoking rather than to involuntary smoking. Misclassification of undeclared active smoking is a particularly important source of error in studies involving teenagers. Misclassification of smoking status is also of concern in case-control studies of the association between exposure to ETS and lung cancer. Information about smoking habits for these studies often comes from interviews with a surviving spouse or surrogate, who may have been a close family member, neighbor, or friend, or from a review of medical records. The smoking habits of the subject may be incorrectly reported. Classification of individuals who are current or former smokers as never smokers would lead to a spurious increase in the relative risk for lung cancer in nonsmokers exposed to ETS, because the smoking habits of spouses tend to be correlated. The extent of this bias in the case-control studies is uncertain. The proportion of people reported as never smokers, but who in fact did smoke in the past, is unknown. The proportion of current smokers who report themselves as nonsmokers can be estimated from studies using markers to validate questionnaires. Using biochemical markers of tobacco smoke absorption, the proportion would appear to be about 0.5 to 3 percent, depending on the population studied and the questionnaire used (Wald et al. 1981; Saloojee et al. 1982).

Misclassification of the extent of ETS exposure can also occur, and may reduce the observed risk if a nonsmoking spouse of a smoker is not exposed to smoke at home. Friedman and colleagues (1983), reporting on a survey of 38,000 subjects, noted that 47 percent of nonsmoking women married to smokers reported that they were not exposed to tobacco smoke at home.

Measurements of Absorption

The difficulties inherent in estimating exposure and dose have provided the impetus for the development of biological markers for exposure to both MS and ETS. The marker that at present holds the

highest promise is cotinine, the major metabolite of nicotine. Cotinine may be measured in saliva, blood, or urine. Numerous studies have demonstrated that there is good correlation between these measures of cotinine and the estimated exposure to tobacco smoke under laboratory conditions (Russell and Feyerabend 1975; Hoffmann et al. 1984) and under conditions of daily life (Russell and Feyerabend 1975; Feyerabend et al. 1982; Foliart et al. 1983; Wald et al. 1984; Wald and Ritchie 1984; Jarvis et al. 1984; Matsukura et al. 1984; Greenberg et al. 1984). Cotinine is probably the best marker for tobacco smoke intake because it is highly sensitive and specific for tobacco smoke and because it can be detected both in active smokers and in individuals exposed to ETS. Further details about cotinine and other markers are to be found in Chapter 4.

Potentially Confounding Variables

In any epidemiological study, the confounding factors must be considered and their effects controlled. Confounding refers to the biasing effect of a factor that independently influences the risk for the disease of concern and is also associated with the exposure under evaluation. Confounding is of particular concern when the effects of the exposure of interest are expected to be small.

The potential confounding variables depend on the health outcome of interest. For lung cancer, occupational exposures, diet, and exposure to other combustion products are of concern. For acute and chronic pulmonary effects, potential confounders include airways hyperresponsiveness, other indoor air pollutants, outdoor air pollution, respiratory tract infections, occupational exposure, and socioeconomic status, which may potentially influence disease risk through its environmental correlates. While this list is extensive, it may not be inclusive; in any single investigation it may not be possible to measure and control all potentially confounding variables.

Statistical Issues

In general, the evidence on active smoking in combination with the dosimetry of involuntary smoking leads to the conclusion that the effects of ETS on a population will be substantially less than the effects of active smoking. The effects of ETS on infants and young children are an important exception.

The association of ETS with an adverse effect in an individual study may reflect bias, chance, or a causal relationship. Statistical significance testing is used to quantitate the role of chance; by convention, a p (probability) value less than 0.05 is deemed statistically significant. A p value less than 0.05 means that the observed results would occur by chance less than 5 times out of 100, if there is

truly no association between ETS and the effect. The choice of 0.05 is arbitrary, and as the significance level declines, the probability that the observation could have occurred by chance lessens.

For effects of small magnitude, as may be anticipated for some consequences of exposure to ETS, a large study population may be necessary to demonstrate statistical significance. The absence of statistical significance for an association may reflect an inadequate sample size and is not always indicative of the absence of an association. In this regard, reports describing the absence of effects of ETS should provide the calculations needed to demonstrate the study's statistical power (ability to detect effects of the magnitude expected) or a confidence interval for the estimate of effect.

An additional statistical issue is the directionality of statistical significance testing. Either one-sided or two-sided tests may be used; in the first, only effects in one direction are considered a possibility, whereas two-sided tests consider the possibility of effects in opposing directions, i.e., increase or decrease of risk. Given the strength of the evidence on active smoking and disease risk, one-sided testing in the direction of an adverse effect seems appropriate for most potential consequences of ETS. However, one-sided tests have not been performed in all investigations of ETS; the use of two-sided tests makes these studies conservative, as statistical significance will less often be attained.

Respiratory System Effects of Involuntary Cigarette Smoke Exposure

This section reviews the evidence on involuntary smoking and the adverse physiologic effects, respiratory symptoms, and respiratory diseases in nonsmoking adults and children. Health effects related to fetal exposure in utero from active smoking by the mother are not discussed. Lung growth and development may be influenced by in utero exposure, and the effects of such exposures have not been separated from those of exposure after birth. More complete treatments of this issue have been published (US DHEW 1979; US DHHS 1980; Abel 1980; Weinberger and Weiss 1981).

This section begins with a review of the data on infants and children who are exposed primarily through parental smoking. The health effects examined are increased respiratory illnesses, of both the upper and the lower respiratory tracts, increased chronic respiratory symptoms and illnesses, and alterations in lung growth and development. Studies of adults, whose exposures to environmental tobacco smoke occur in a variety of settings, are examined with regard to symptoms and changes in measures of lung function. The potential for ETS to produce bronchoconstriction in asthmatic and nonasthmatic subjects is also examined.

Infants and Children

Acute Respiratory Illness

Longitudinal Studies

A number of studies, based on a variety of different designs, have examined the effects of involuntary smoking on the acute respiratory illness experience of children (Table 1). Several different end points have been evaluated in these investigations: hospitalization for bronchitis or pneumonia as assessed by hospital records (Harlap and Davies 1974; Rantakallio 1978); questionnaire assessment of hospitalization for bronchitis or pneumonia or of doctor's visits (Colley 1971; Leeder et al. 1976a) or both (Fergusson et al. 1981; Fergusson and Horwood 1985); questionnaire assessment of respiratory illness within the last year (Cameron et al. 1969; Schenker et al. 1983; Ware et al. 1984); chest illness before age 2 (Schenker et al. 1983); hospitalization for respiratory syncytial virus (RSV) infection (Sims et al. 1978; Pullan and Hey 1982); physician-diagnosed bronchitis, tracheitis, or laryngitis (Pedreira et al. 1985); and tonsillectomy as an indication of recurrent respiratory infection (Said et al. 1978). These diverse end points range from illnesses associated with a specific etiologic agent, e.g., RSV bronchiolitis, to clinician-diagnosed syndromes, e.g., bronchitis of undetermined etiology.

The possibility of reporting bias must be considered for the studies that have used questionnaires to measure illness experience. In most of these studies, parents, usually the mother, have responded for the child and reported on the child's illness experience. Some investigators have suggested that mothers with respiratory symptoms are more likely to report symptoms for their children and that stratification of subjects by the symptom status of their parents removes this element of recall bias (Lebowitz and Burrows 1976). Removal of symptomatic parents, however, may result in overcorrection for recall bias because cigarette smoking is associated with symptoms in the adult. This analytical strategy would not be expected to adjust for biased parental recall of early life events. Additionally, in all studies in which potential reporting bias was examined, control for parents' status reduced, but did not eliminate, associations of involuntary smoking with health outcomes (Colley et al. 1974; Leeder et al. 1976a,b; Schenker et al. 1983; Ware et al. 1984). Further, the consistency of these studies, in spite of differing study populations and methods, weighs against bias as the sole explanation for the effect of involuntary smoke exposure.

Harlap and Davies (1974) studied 10,672 births in Israel between 1965 and 1968 and observed that infants, whose mothers, at a prenatal visit, reported that they smoked, had a 27.5 percent greater hospital admission rate for pneumonia and bronchitis than children

TABLE 1.—Early childhood respiratory illness and involuntary cigarette smoking

Study	Subjects	Findings	Illness rates per 100				Comments
			By cigarettes per day				
			0	1-10	11-20	20+	
Harlap and Davies (1974)	10,872 births, 1965-1968, Israel	Hospitalized, bronchitis/pneumonia, first year of life RR=1.38	9.5	10.8	16.2	31.7	Prenatal smoking history; maternal smoking only Longitudinal study
Colley ¹ (1971)	2,205 births, 1963-1965, England	Questionnaire, bronchitis/pneumonia, first year of life RR=1.73 for one parent smoker RR=2.60 for two parent smokers	7.6 10.3	10.4 15.1	11.1 14.5	15.2 23.2	= Asymptomatic parents = Symptomatic parents Neither controlled for sibling number or smoker sex Longitudinal study
Fergusson et al. (1981); Fergusson and Horwood (1985) ²	1,265 births, 4 months, 1977, New Zealand	Questionnaire, doctor or hospital visits, bronchitis/pneumonia; hospital records checked; assessed at 4 months, 1, 2, 3, and 6 years; RR=2.04 if mother smoked	7.0 7.0	12.8 4.6	13.4 8.8	Maternal only Paternal only	Effect significant for maternal smoking in first year of life only; effect present in first 2 years of life
			By number of smoking parents				
			0	1	2		
Ware et al. (1984)	8,528 children, aged 5-9, with two parents' smoking status known, six U.S. cities	Respiratory illness in last year	12.9	13.7	14.8		Adjusted for age, sex, and city cohort effect; significant trends Longitudinal study

TABLE 1.—Continued

Study	Subjects	Findings	Illness rates per 100			Comments
Said et al. (1978)	3,920 children, aged 10-20, France	Tonsillectomy and/or adenoidectomy, generally before age 5, as indicator of frequent respiratory tract infection	28.2	41.4	50.9	Children self-reported; not clear parent smoking habit at report time directly related to exposure approx. 10+ years earlier Cross-sectional study
Schenker et al. (1983)	4,071 children, aged 5-14, United States	Chest illness before age 2 Chest illness >3 days in past year	6.7 8.8	7.9 11.8	11.5 13.6	Trends for both significant Cross-sectional study
			Parent status			
			Nonsmoker	Current smoker		
Cameron et al. (1969)	158 children, aged 6-9; parents' telephone questionnaire, United States	Respiratory illness, restricted activity and/or medical consultation in last year	1.33	7.4		Illness reported not verified; not clear how reporting adult related to child Cross-sectional study
Leeder et al. (1976a, b)	2,149 infants, born 1963- 1965, England	RR ~ 2.0 for infants with two smoking parents	Not provided			Parents' response bias unlikely, effects observed for infants of asymptomatic parents; maternal vs. paternal smoking effects not investigated Longitudinal study
Sims et al. (1978)	35 children, hospitalized, RSV bronchiolitis; 35 controls, England	Borderline significant increase in maternal smoking, first year of life RR=2.65	Not provided			No significant effect for paternal smoking; average amount smoked greater for parents of cases than controls Case-control study

TABLE 1.—Continued

Study	Subjects	Findings	Illness rates per 100		Comments	
			Nonsmoker	Smoker		
Rantakallio (1978)	1,821 children of smoking mothers, 1,823 children of nonsmoking mothers, Finland	Significant increase in hospitalization for respiratory illness during first 5 years of life RR=1.74	Not provided		Prospective followup of doctor visits, hospitalizations, deaths up to age 5; only maternal smoking evaluated Longitudinal study	
Pullan and Hey (1982)	130 children hospitalized, RSV infection, first year of life; 111 nonhospitalized controls, England	Significant effect of maternal (RR=1.96) and paternal (RR=1.53) smoking at time of study; significant maternal smoking effect during first year of life (RR=1.55)	Not provided		Case-control study	
Pedreira et al. (1985)	1,144 infants in pediatric practice, United States	Significant increase in respiratory illnesses among smoke-exposed children	Bronchitis Tracheitis Laryngitis	71 21 4	103 40 7	Pediatricians not blinded to exposure; no effect seen for croup, pneumonia, or bronchiolitis Longitudinal study

¹ These data are considered in a more expanded analysis provided by Leeder et al. (1976a, b).

² Relative risk for children of smoking mothers versus children of nonsmoking mothers calculated from data provided by J.M. Samet (personal communication).

of nonsmoking mothers. In addition, they demonstrated a dose-response relationship between the amount of maternal smoking and the number of hospital admissions for these conditions. The infants were classified by the mothers' prenatal smoking behavior and not by the mothers' smoking behavior during the first year of the child's life. Maternal smoking habits would probably have remained relatively stable across the short observation period.

British investigators (Colley et al. 1974) followed children born between 1963 and 1965 in London and also observed an increased frequency of bronchitis and pneumonia during the first year of life in the children of parents who smoked. This difference did not persist at 2 to 5 years of age. This effect was independent of the parents' personal reports of winter morning phlegm and increased with the amount of smoking by parents. The annual incidence of bronchitis and pneumonia during the first year of life also increased with a greater number of siblings. This variable was not controlled in the original analysis; however, Leeder and colleagues (1976b) subsequently reported that, in this same cohort, a dose-response relationship with parental smoking persisted for bronchitis and pneumonia in the first year of life, after control for parental respiratory symptoms, the sex of the child, the number of siblings, and a history of respiratory illness in the siblings.

Fergusson and colleagues (1981) studied 1,265 New Zealand children from birth to age 3. They demonstrated an increase in bronchitis and pneumonia and in lower respiratory illness during the first 2 years of life in children whose mothers smoked compared with children whose mothers did not smoke. Correction for maternal age, family size, and socioeconomic status did not affect the relationship between the amount of maternal smoking and the rate of respiratory illness. The effect of maternal smoking declined with increasing age of the child.

In a second report (Fergusson and Horwood 1985) the followup was extended to include the first 6 years of life. The results confirmed the initial findings. Maternal, but not paternal, smoking was associated with a statistically significant increase in lower respiratory illnesses during the first 2 years of life. However, after age 2 there was no significant effect of maternal smoking on respiratory illness occurrence.

Rantakallio (1978) followed more than 3,600 children during the first 5 years of life; half of the children had mothers who smoked cigarettes during pregnancy and half did not. The children of mothers who smoked had a 70 percent greater chance of hospitalization for a respiratory illness than the children of nonsmoking mothers.

Pedreira and associates (1985) prospectively studied 1,144 infants and their families in the greater Washington, D.C., area. Maternal

smoking was associated with an excess frequency of acute bronchitis, tracheitis, and laryngitis, as diagnosed by the pediatricians caring for these families. Episodes of croup, pneumonia, and bronchiolitis were not increased by maternal smoking. A family history of chronic respiratory symptoms was also associated with excess respiratory illness.

Ware and coworkers (1984) studied more than 10,000 children in six American cities. Maternal cigarette smoking was associated with increased parental reporting of a doctor-diagnosed respiratory illness before the age of 2 years and of an acute respiratory illness within the past year. The prevalence of positive questionnaire responses increased consistently with the current daily cigarette consumption of the mother; the dose-response relationships were unchanged by adjustment for maternal symptoms and educational status.

Cross-Sectional Studies

Schenker and coworkers (1983) studied 4,071 children between the ages of 5 and 14 years in a cross-sectional study in Pennsylvania. Both chest illness in the past year and severe chest illness before age 2 were more frequently reported in nonsmoking children of parents who smoked. These investigators found that symptom and illness rates were higher in children of parents with respiratory symptoms. However, a significant effect of maternal smoking on these illness variables remained after adjustment for the parents' own respiratory symptom history.

In a study of 1,355 children between 6 and 12 years of age in the Iowa public schools, Ekwo and coworkers (1983) found that the presence in the home of at least one parent who smoked was significantly associated with reported hospitalization of the child for a respiratory illness during the first 2 years of life. As in other studies, the effect was stronger for maternal smoking than for paternal smoking.

Case-Control Studies

In England, Sims and colleagues (1978) examined 35 children at 8 years of age who had been hospitalized during infancy for RSV bronchiolitis and compared them with 35 control children of similar age. Maternal smoking was associated with a relative risk of 2.65 for hospitalization due to bronchiolitis. The sample size was small, and this effect of maternal smoking was not statistically significant.

Pullan and Hey (1982) studied children who had been hospitalized with documented RSV infection in infancy. They found significantly greater smoking by their mothers at the time of the infection, compared with children hospitalized for other illnesses, including respiratory disease for which RSV infection was not documented. At

age 10, the children previously ill with RSV infection had an excess reported occurrence of wheeze and asthma and had lower levels of pulmonary function in comparison with the controls. The researchers could not determine whether the RSV infection had caused persistent damage that affected the maturation of the lung or whether these children were already more susceptible to severe RSV infection because of pulmonary problems that antedated the RSV infection.

In summary, the results of these studies show excess acute respiratory illness in the children of parents who smoke, particularly in children under 2 years of age. This pattern is evident in studies conducted with different methodologies and in different locales. The increased risk of hospitalization for severe bronchitis or pneumonia associated with parental smoking ranges from 20 to 40 percent during the first year of life. Young children appear to represent a more susceptible population for the adverse effects of involuntary smoking than older children or adults. The time-activity patterns of infants, which generally place them in proximity to their mothers, may lead to particularly high exposures to environmental tobacco smoke if the mother smokes.

Acute respiratory illnesses during childhood may have long-term effects on lung growth and development, and might increase the susceptibility of the lung to the effects of active smoking and to the development of chronic obstructive lung disease (Samet et al. 1983; US DHHS 1984).

Cough, Phlegm, and Wheezing

A number of cross-sectional studies from different countries (Table 2) have shown a positive association between parental cigarette smoking and the prevalence of chronic cough and chronic phlegm in children; some studies have shown a relationship for persistent wheeze. However, not all studies have shown a positive relationship for all symptoms. The results of some of these studies may have been confounded by the child's own smoking habits (Colley et al. 1974; Bland et al. 1978; Kasuga et al. 1979). The association with parental smoking was not statistically significant for all symptoms in all studies (Lebowitz and Burrows 1976; Schilling et al. 1977; Schenker et al. 1983). However, the majority of studies showed an increase in symptom prevalence with an increase in the number of smoking parents in the home.

A recent report (Charlton 1984) provides cross-sectional data on parent-reported cough for 15,000 children, 8 to 19 years of age, in northern England. Chronic cough in the children was related to their age and to their own cigarette smoking status. However, with control of these factors by stratification, the number of parental smokers in the home was positively associated with the occurrence of chronic

TABLE 2.—Chronic respiratory symptoms in children in relation to involuntary smoke exposure

Study	Subjects	Respiratory symptoms or illness	Rates per 100 by number of smoking parents			Comments
			0	1	2	
Colley et al. (1974)	2,426 children, aged 6-14, England	Chronic cough; questionnaire completed by parent	15.6	17.7	22.2	Trend significant; reporting bias possible result of parent symptoms or active smoking in children, unlikely to explain full effect of trend Cross-sectional study
Bland et al. (1978)	3,105 children, aged 12-13, did not admit to ever smoking cigarettes, England	Cough during day or at night	16.4	19.0	23.5	Children's self-reported symptoms and smoking history collected simultaneously; morning and daytime cough suggested as different diseases, could be difference in exposure (exposure more likely awake than asleep) Cross-sectional study, adjusted for child's own smoking habits
		Morning cough	1.5	2.8	2.9	
Weiss et al. (1980)	650 children, aged 5-9, United States	Chronic cough and phlegm	1.7	2.7	3.4	Trend not significant
		Persistent wheeze	1.8	6.8	11.8	Trend significant Cross-sectional study, adjusted for parental symptoms and child's own smoking
Charlton (1984)	15,000 children, aged 8-19 years, England	Any cough	40.0	45.0	55.0	Trend significant; percents not age adjusted Cross-sectional study, adjusted for child's own smoking, not parental symptoms

TABLE 2.—Continued

Study	Subjects	Respiratory symptoms or illness	Rates per 100 by number of smoking parents			Comments
			0	1	2	
Dodge (1982)	628 children, grades 3-4, two-parent households; parent questionnaire response, United States	Any wheeze	27.6	27.9	40.0	All trends significant; some effect might relate to parental symptoms, but no trend influence likely Cross-sectional study
		Phlegm	6.4	10.9	12.0	
		Cough	14.6	23.0	27.8	
Schenker et al. (1983)	4,071 children, aged 5-14, United States	Chronic cough	6.2	7.0	8.3	Trend not significant; not adjusted for parental symptoms, although parental symptom effect analyzed Cross-sectional study
		Chronic phlegm	4.1	4.8	4.0	
		Persistent wheeze	7.2	7.7	5.4	
Lebowitz and Burrows (1976)	1,525 children, <15 years old, United States	Persistent cough	Never smoker 3.7	Parent smoker 7.2	Higher rates in symptomatic parent households; trends persisted for asymptomatic households; no adjustment for child's own smoking Cross-sectional study	
		Persistent phlegm	10.0	12.8		
		Wheeze	23.4	24.1		
Schilling et al. (1977)	816 children, age 7+, United States	Cough, phlegm, wheeze	No significant effect			Specific data not provided Cross-sectional study
Kasuga et al. (1979)	1,937 children, aged 6-11, Japan	Wheeze, asthma	Increased prevalence in heavy smoker (>21 cig/day) family; less clear effect in light smoker (<21 cig/day) family			Adjusted for distance of home from main traffic, highway Cross-sectional study
Ekwo et al. (1983)	1,355 children, aged 6-12, United States	Coughs with colds	Odds ratios: 1.4 for smoker father, 1.5 for smoker mother			Gas stove use measured, not controlled for; no consistent dose- response Cross-sectional study
		Wheezing apart from colds	2 if only smoker mother			

cough. The mother's smoking had a greater effect than the father's smoking.

Burchfiel and colleagues (1986) have conducted a longitudinal study of 3,482 subjects from Tecumseh, Michigan. Subjects were initially between the ages of birth and 10 years and were followed up by questionnaire and examination 15 years after entry into the study. Age-specific incidence rates were calculated for a number of chronic respiratory symptoms, including cough, phlegm, wheeze, and bronchitis. Incidence rates for all symptoms were higher for children with two parental smokers when compared with children of non-smokers. Adjustment for potential confounding variables, including age, parental education, family size, and personal smoking, did not explain these results.

British researchers (Leeder et al. 1976b) studying a birth cohort over a 5-year period demonstrated an increased incidence of wheezing among nonasthmatic children with two parents who smoked in comparison with children whose parents did not smoke, one parent who smoked, or parents whose smoking changed during the study (Leeder et al. 1976a). However, when this association was examined by logistic regression with control for other factors, parental smoking was not a significant predictor of wheeze or of asthma.

McConnochie and Roghmann (1984) performed a retrospective cohort study to examine the influence of mild bronchitis in early childhood on wheezing symptoms 8 years later when the subjects had reached a mean age of 8.3 years. Involuntary smoking was a significant predictor of current wheezing (odds ratio 1.9). In a related study (McConnochie and Roghmann 1985) with these same children, involuntary smoking did not affect lower respiratory tract illness experience.

In a study of 650 children aged 5 to 10 years (Weiss et al. 1980), a significant trend in the reported prevalence of chronic wheezing with current parental smoking was found; the rates were 1.9 percent, 6.9 percent, and 11.8 percent for children with zero, one, and two parents who smoked, respectively. Although the data given are for all households, when the analysis was restricted to those households where neither parent reported symptoms, the results were identical. The stability of the findings with this restriction suggests that reporting bias introduced by parental symptoms was not responsible for the observed results.

Schenker and coworkers (1983) examined the influence of parental smoking and symptoms on the reporting of chronic respiratory symptoms of cough, phlegm, and persistent wheezing in children. These investigators found that the mothers were more likely than the fathers and symptomatic mothers were more likely than asymptomatic mothers to report these symptoms in their children.

Parental smoking had no significant effects on chronic respiratory symptoms.

Lebowitz and Burrows (1976) assessed the effects of household members' smoking on respiratory symptoms in 626 Tucson children younger than 15 years of age. Children from homes with current smokers had higher symptom rates than those from homes with ex-smokers and with never smokers. However, the effect of household smoking type was statistically significant only for persistent cough. In a general population study, Schilling and colleagues (1977) reported no association between wheeze and involuntary smoking.

Ware and associates (1984) enrolled 10,106 children between 6 and 9 years of age from six U.S. cities in a prospective study. The prevalence of persistent cough and persistent wheeze, measured at the second examination, was higher in children whose parents smoked. The effect was greater for maternal smoking than for paternal smoking. Symptom prevalence rates increased linearly with the number of cigarettes smoked daily by the mother. In a multiple logistic model, the effect of maternal smoking persisted after adjustment for reported illness in the parents.

Dodge (1982), studying third and fourth grade children in Arizona, found that symptoms, including wheeze, were related to both the presence of symptoms in the parents and the number of smokers in the household.

In summary, children whose parents smoke had a 30 to 80 percent excess prevalence of chronic cough or phlegm compared with children of nonsmoking parents. For wheezing, the increase in risk varied from none to over sixfold among the studies reviewed. Many studies showed an exposure-related increase in the percentage of children with reported chronic symptoms as the number of parental smokers in the home increased. Misclassification as nonsmokers of children who are actively smoking could bias the results of these studies. Adolescent smokers may be reluctant to accurately report their smoking habits, and more objective measures of exposure may not help to distinguish active experimentation with cigarettes from involuntary exposure to smoke (Tager 1986). Although misclassification of children who are actively smoking as nonsmokers must be considered, many studies showing a positive association between parental smoking and symptoms in children, including children at ages before significant experimentation with cigarettes is prevalent. In addition, many studies (Bland et al. 1978; Weiss et al. 1980; Charlton 1984; Schenker et al. 1983; Dodge 1982; Burchfiel et al. 1986) found significant effects of parental smoking after considering active smoking by the children.

Chronic respiratory symptoms represent an immediate health burden for the child. However, the long-term significance of chronic respiratory symptoms for the health of the child is unclear. Most

available data are cross-sectional, and followup studies of chronically symptomatic children are necessary to determine the long-term health consequences of chronic respiratory symptoms.

Pulmonary Function

In recent years, the effect of parental cigarette smoking on pulmonary function in children has been examined in cross-sectional studies (Table 3) and a few longitudinal studies. The cross-sectional studies have demonstrated lower values on tests of pulmonary function ($FEV_{75\%}$, FEV_1 , FEF_{25-75} , and flows at low lung volumes) in children of mothers who smoked compared with children of non-smoking mothers. The longitudinal studies (Table 4) have confirmed the cross-sectional results and provide some insight into the implications of the cross-sectional data.

Dose-response relationships have been found in both cross-sectional and longitudinal studies (Tager et al. 1979; Weiss et al. 1980; Ware et al. 1984; Berkey et al. 1986); the level of function decreases with an increasing number of smokers in the home. As would be anticipated from the mother's greater contact time with the child, maternal smoking tends to have a greater impact than paternal smoking. Younger children seem to experience greater effects than older children (Tager et al. 1979; Weiss et al. 1980), and in older children the effects of personal smoking may be additive with those of involuntary smoking (Tager et al. 1979, 1985).

As noted by Tager (1986), the effect of maternal smoking on lung function may vary with the child's sex. Some studies have reported greater effects on flows at lower lung volumes in girls than in boys (Burchfiel et al. 1986; Tashkin et al. 1984; Yarnell and St. Leger 1979; Vedal et al. 1984). Flows at higher lung volumes seem more affected in boys (Burchfiel et al. 1986; Yarnell and St. Leger 1979; Berkey et al. 1986; Tashkin et al. 1984). Whether these sex effects represent differences in exposure, differences in susceptibility to environmental cigarette smoke, or differences in growth and development is unclear.

Tager and colleagues (1983) followed 1,156 children for 7 years to determine the effect of maternal smoking on the growth of pulmonary function in children (Figure 2). After correcting for previous level of FEV_1 , age, height, personal cigarette smoking, and correlation between mother's and child's pulmonary function level, maternal smoking was associated with a reduced annual increase in FEV_1 and FEF_{25-75} , using two separate methods of analysis. If the effect of maternal smoking is maintained to 20 years of age, then a 3 to 5 percent reduction of FEV_1 and FEF_{25-75} due to maternal smoking would be projected. The validity of this projection remains to be established. Because few mothers changed their smoking habits, the

TABLE 3.—Pulmonary function in children exposed to involuntary smoking

Study	Subjects	Pulmonary function measured	Outcome	Comments
Schilling et al. (1977)	816 children, aged 7-17, Connecticut and South Carolina, United States	FEV ₁ as percent predicted	No effect of parental smoking	No control for sibship size or correlation of sibling pulmonary function; for children who never smoked, V _{max50} significantly less in children with smoking mothers
Tager et al. (1979)	444 children, aged 5-19, East Boston, Massachusetts, United States	MMEF in standard deviation units	Significant effect of parental smoking	Controlled for sibship size and correlation of sibling pulmonary function
Weiss et al. (1980)	650 children, aged 5-9, East Boston, Massachusetts, United States	MMEF in standard deviation units	Significant effect of parental smoking	Controlled for sibship size and correlation of sibling pulmonary function
Vedal et al. (1984)	4,000 children, aged 6-13, United States	FEV ₁ , FVC, V̇ _{max50} , V̇ _{max75} , V̇ _{max90}	FVC positively associated, flows negatively associated	Flows dose-response with amount smoked by mother
Lebowitz and Burrows (1976)	271 households, complete histories of parent smoking and pulmonary function of children, age >6, Tucson, Arizona, United States	FEV ₁ , FVC, V̇ _{max50} , V̇ _{max75} derived from MMEF V curves, as standard deviation units	No effect of parental smoking	Suggestion: may be real differences in indoor levels of exposure compared with more northerly climates
Lebowitz et al. (1982)	229 children, Tucson, Arizona, United States	FEV ₁ , z score	No effect of parental smoking	Higher levels of pulmonary function for children of smoking parents than for non-smoke-exposed children