The Health Consequences of Involuntary Exposure to Tobacco Smoke

A Report of the Surgeon General

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The Health Consequences of Involuntary Exposure to Tobacco Smoke

A Report of the Surgeon General

2006

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Office of the Surgeon General
Rockville, MD

Message from Michael O. Leavitt

Secretary of Health and Human Services

This Surgeon General's report returns to the topic of the health effects of involuntary exposure to tobacco smoke. The last comprehensive review of this evidence by the Department of Health and Human Services (DHHS) was in the 1986 Surgeon General's report, *The Health Consequences of Involuntary Smoking*, published 20 years ago this year. This new report updates the evidence of the harmful effects of involuntary exposure to tobacco smoke. This large body of research findings is captured in an accompanying dynamic database that profiles key epidemiologic findings, and allows the evidence on health effects of exposure to tobacco smoke to be synthesized and updated (following the format of the 2004 report, *The Health Consequences of Smoking*). The database enables users to explore the data and studies supporting the conclusions in the report. The database is available on the Web site of the Centers for Disease Control and Prevention (CDC) at http://www.cdc.gov/tobacco. I am grateful to the leadership of the Surgeon General, CDC's Office on Smoking and Health, and all of the contributors for preparing this important report and bringing this topic to the forefront once again.

Secondhand smoke, also known as environmental tobacco smoke, is a mixture of the smoke given off by the burning end of tobacco products (sidestream smoke) and the mainstream smoke exhaled by smokers. People are exposed to secondhand smoke at home, in the workplace, and in other public places such as bars, restaurants, and recreation venues. It is harmful and hazardous to the health of the general public and particularly dangerous to children. It increases the risk of serious respiratory problems in children, such as a greater number and severity of asthma attacks and lower respiratory tract infections, and increases the risk for middle ear infections. It is also a known human carcinogen (cancer-causing agent). Inhaling secondhand smoke causes lung cancer and coronary heart disease in nonsmoking adults.

We have made great progress since the late 1980s in reducing the involuntary exposure of nonsmokers in this country to secondhand smoke. The proportion of nonsmokers aged 4 and older with a blood cotinine level (a metabolite of nicotine) indicating exposure has declined from 88 percent in 1988–1991 down to 43 percent in 2001–2002, a decline that exceeds the *Healthy People 2010* objective for this measure. Despite the great progress that has been made, involuntary exposure to secondhand smoke remains a serious public health hazard that can be prevented by making homes, workplaces, and public places completely smoke-free. As of the year 2000, more than 126 million residents of the United States aged 3 or older still are estimated to be exposed to secondhand smoke. Smoke-free environments are the most effective method for reducing exposures. *Healthy People 2010* objectives address this issue and seek optimal protection of nonsmokers through policies, regulations, and laws requiring smoke-free environments in all schools, workplaces, and public places.

Foreword

This twenty-ninth report of the Surgeon General documents the serious and deadly health effects of involuntary exposure to tobacco smoke. Secondhand smoke is a major cause of disease, including lung cancer and coronary heart disease, in healthy nonsmokers.

In 2005, it was estimated that exposure to secondhand smoke kills more than 3,000 adult nonsmokers from lung cancer, approximately 46,000 from coronary heart disease, and an estimated 430 newborns from sudden infant death syndrome. In addition, secondhand smoke causes other respiratory problems in nonsmokers such as coughing, phlegm, and reduced lung function. According to the CDC's National Health Interview Survey in 2000, more than 80 percent of the respondents aged 18 years or older believe that secondhand smoke is harmful and nonsmokers should be protected in their workplaces.

Components of chemical compounds in secondhand smoke, including nicotine, carbon monoxide, and tobacco-specific carcinogens, can be detected in body fluids of exposed nonsmokers. These exposures can be controlled. In 2005, CDC released the *Third National Report on Human Exposure to Environmental Chemicals,* which found that the median cotinine level (a metabolite of nicotine) in nonsmokers had decreased across the life stages: by 68 percent in children, 69 percent in adolescents, and 75 percent in adults, when samples collected between 1999 and 2002 were compared with samples collected a decade earlier. These dramatic declines are further evidence that smoking restrictions in public places and workplaces are helping to ensure a healthier life for all people in the United States.

However, too many people continue to be exposed, especially children. The recent data indicate that median cotinine levels in children are more than twice those of adults, and non-Hispanic blacks have levels that are more than twice as high as those of Mexican Americans and non-Hispanic whites. These disparities need to be better understood and addressed.

Research reviewed in this report indicates that smoke-free policies are the most economic and effective approach for providing protection from exposure to secondhand smoke. But do they provide the greatest health impact. Separating smokers and nonsmokers in the same airspace is not effective, nor is air cleaning or a greater exchange of indoor with outdoor air. Additionally, having separately ventilated areas for smoking may not offer a satisfactory solution to reducing workplace exposures. Policies prohibiting smoking in the workplace have multiple benefits. Besides reducing exposure of nonsmokers to secondhand smoke, these policies reduce tobacco use by smokers and change public attitudes about tobacco use from acceptable to unacceptable.

Research indicates that the progressive restriction of smoking in the United States to protect nonsmokers has had the additional health impact of reducing active smoking. In November 2005, CDC's Tobacco-Free Campus policy took full effect in all facilities owned by CDC in the Atlanta area. As the Director of the nation's leading health promotion and disease prevention agency, I am proud to support this effort. With this commitment, CDC continues to protect the health and safety of all of its employees and serves as a role model for workplaces everywhere.

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Preface

from the Surgeon General,
U.S. Department of Health and Human Services

Twenty years ago when Dr. C. Everett Koop released the Surgeon General's report, *The Health Consequences of Involuntary Smoking,* it was the first Surgeon General's report to conclude that involuntary exposure of nonsmokers to tobacco smoke causes disease. The topic of involuntary exposure of nonsmokers to secondhand smoke was first considered in Surgeon General Jesse Steinfeld's 1972 report, and by 1986, the causal linkage between inhaling secondhand smoke and the risk for lung cancer was clear. By then, there was also abundant evidence of adverse effects of smoking by parents on their children.

Today, massive and conclusive scientific evidence documents adverse effects of involuntary smoking on children and adults, including cancer and cardiovascular diseases in adults, and adverse respiratory effects in both children and adults. This 2006 report of the Surgeon General updates the 1986 report, *The Health Consequences of Involuntary Smoking,* and provides a detailed review of the epidemiologic evidence on the health effects of involuntary exposure to tobacco smoke. This new report also uses the revised standard language of causality that was applied in the 2004 Surgeon General's report, *The Health Consequences of Smoking*.

Secondhand smoke is similar to the mainstream smoke inhaled by the smoker in that it is a complex mixture containing many chemicals (including formaldehyde, cyanide, carbon monoxide, ammonia, and nicotine), many of which are known carcinogens. Exposure to secondhand smoke causes excess deaths in the U.S. population from lung cancer and cardiac related illnesses. Fortunately, exposures of adults are declining as smoking becomes increasingly restricted in workplaces and public places. Unfortunately, children continue to be exposed in their homes by the smoking of their parents and other adults. This exposure leads to unnecessary cases of bronchitis, pneumonia and worsened asthma. Among children younger than 18 years of age, an estimated 22 percent are exposed to secondhand smoke in their homes, with estimates ranging from 11.7 percent in Utah to 34.2 percent in Kentucky.

As this report documents, exposure to secondhand smoke remains an alarming public health hazard. Approximately 60 percent of nonsmokers in the United States have biologic evidence of exposure to secondhand smoke. Yet compared with data reviewed in the 1986 report, I am encouraged by the progress that has been made in reducing involuntary exposure in many workplaces, restaurants, and other public places. These changes are most likely the major contributing factors to the more than 75 percent reduction in serum cotinine levels that researchers have observed from 1988 to 1991. However, more than 126 million nonsmokers are still exposed. We now have substantial evidence on the efficacy of different approaches to control exposure to secondhand smoke. Restrictions on smoking can control exposures effectively, but technical approaches involving air cleaning or a greater exchange of indoor with outdoor air cannot. Consequently, nonsmokers need protection through the restriction of smoking in public places and workplaces and by a voluntary adherence to policies at home, particularly to eliminate exposures of children. Since the release of the 1986 Surgeon General's report, the public's attitude and social norms toward secondhand smoke exposure have changed significantly—a direct result of the growing body of scientific evidence on the health effects of exposure to secondhand smoke that is summarized in this report.

Finally, clinicians should routinely ask about secondhand smoke exposure, particularly in susceptible groups or when a child has had an illness caused by secondhand smoke, such as pneumonia. Because of the high levels of exposure among young children, their exposure should be considered a significant pediatric issue. Additionally, exposure to secondhand smoke poses significant risks for people with lung and heart disease. The large body of evidence documenting that secondhand smoke exposures produce substantial and immediate effects on the cardiovascular system indicates that even brief exposures could pose significant acute risks to older adults or to others at high risk for cardiovascular disease. Those caring for relatives with heart disease should be advised not to smoke in the presence of the sick relative.

An environment free of involuntary exposure to secondhand smoke should remain an important national priority in order to reach the *Healthy People 2010* objectives.

Richard Carmona, M.D., M.P.H., F.A.C.S.
Surgeon General

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The Health Consequences of Involuntary Exposure to Tobacco Smoke

Chapter 1
Introduction, Summary, and Conclusions

Introduction

The topic of passive or involuntary smoking was first addressed in the 1972 U.S. Surgeon General's report (*The Health Consequences of Smoking*, U.S. Department of Health, Education, and Welfare [USDHEW] 1972), only eight years after the first Surgeon General's report on the health consequences of active smoking (USDHEW 1964). Surgeon General Dr. Jesse Steinfeld had raised concerns about this topic, leading to its inclusion in that report. According to the 1972 report, nonsmokers inhale the mixture of sidestream smoke given off by a smoldering cigarette and mainstream smoke exhaled by a smoker, a mixture now referred to as "secondhand smoke" or "environmental tobacco smoke." Cited experimental studies showed that smoking in enclosed spaces could lead to high levels of cigarette smoke components in the air. For carbon monoxide (CO) specifically, levels in enclosed spaces could exceed levels then permitted in outdoor air. The studies supported a conclusion that "an atmosphere contaminated with tobacco smoke can contribute to the discomfort of many individuals" (USDHEW 1972, p. 7). The possibility that CO emitted from cigarettes could harm persons with chronic heart or lung disease was also mentioned.

Secondhand tobacco smoke was then addressed in greater depth in Chapter 4 (Involuntary Smoking) of the 1975 Surgeon General's report, *The Health Consequences of Smoking* (USDHEW 1975). The chapter noted that involuntary smoking takes place when nonsmokers inhale both sidestream and exhaled mainstream smoke and that this "smoking" is "involuntary" when "the exposure occurs as an unavoidable consequence of breathing in a smoke-filled environment" (p. 87). The report covered exposures and potential health consequences of involuntary smoking, and the researchers concluded that smoking on buses and airplanes was annoying to nonsmokers and that involuntary smoking had potentially adverse consequences for persons with heart and lung diseases. Two studies on nicotine concentrations in nonsmokers raised concerns about nicotine as a contributing factor to atherosclerotic cardiovascular disease in nonsmokers.

The 1979 Surgeon General's report, *Smoking and Health: A Report of the Surgeon General* (USDHEW 1979), also contained a chapter entitled "Involuntary Smoking." The chapter stressed that "attention to involuntary smoking is of recent vintage, and only limited information regarding the health effects of such exposure upon the nonsmoker is available" (p. 11–35). The chapter concluded with recommendations for research including epidemiologic and clinical studies. The 1982 Surgeon General's report specifically addressed smoking and cancer (U.S. Department of Health and Human Services [USDHHS] 1982). By 1982, there were three published epidemiologic studies on involuntary smoking and lung cancer, and the 1982 Surgeon General's report included a brief chapter on this topic. That chapter commented on the methodologic difficulties inherent in such studies, including exposure assessment, the lengthy interval during which exposures are likely to be relevant, and accounting for exposures to other carcinogens. Nonetheless, the report concluded that "Although the currently available evidence is not sufficient to conclude that passive or involuntary smoking causes lung cancer in nonsmokers, the evidence does raise concern about a possible serious public health problem" (p. 251).

Involuntary smoking was also reviewed in the 1984 report, which focused on chronic obstructive pulmonary disease and smoking (USDHHS 1984). Chapter 7 (Passive Smoking) of that report included a comprehensive review of the mounting information on smoking by parents and the effects on respiratory health of their children, data on irritation of the eye, and the more limited evidence on pulmonary effects of involuntary smoking on adults. The chapter began with a compilation of measurements of tobacco smoke components in various indoor environments. The extent of the data had increased substantially since 1972. By 1984, the data included measurements of more specific indicators such as acrolein and nicotine, and less specific indicators such as particulate matter (PM), nitrogen oxides, and CO. The report reviewed new evidence on exposures of nonsmokers using biomarkers, with substantial information on levels of cotinine, a major nicotine metabolite. The report anticipated future conclusions with regard to respiratory effects of parental smoking on child respiratory health (Table 1.1).

Involuntary smoking was the topic for the entire 1986 Surgeon General's report, *The Health Consequences of Involuntary Smoking* (USDHHS 1986). In its 359 pages, the report covered the full breadth of the

Table 1.1 Conclusions from previous Surgeon General's reports on the health effects of secondhand smoke exposure

Disease and statement	Surgeon General's report
Coronary heart disease: "The presence of such levels" as found in cigarettes "indicates that the effect of exposure to carbon monoxide may on occasion, depending upon the length of exposure, be sufficient to be harmful to the health of an exposed person. This would be particularly significant for people who are already suffering from. . .coronary heart disease." (p. 7)	1972
Chronic respiratory symptoms (adults): "The presence of such levels" as found in cigarettes "indicates that the effect of exposure to carbon monoxide may on occasion, depending upon the length of exposure, be sufficient to be harmful to the health of an exposed person. This would be particularly significant for people who are already suffering from chronic bronchopulmonary disease. . . ." (p. 7)	1972
Pulmonary function: "Other components of tobacco smoke, such as particulate matter and the oxides of nitrogen, have been shown in various concentrations to affect adversely animal pulmonary. . .function. The extent of the contributions of these substances to illness in humans exposed to the concentrations present in an atmosphere contaminated with tobacco smoke is not presently known." (pp. 7–8)	1972
Asthma: "The limited existing data yield conflicting results concerning the relationship between passive smoke exposure and pulmonary function changes in patients with asthma." (p. 13)	1984
Bronchitis and pneumonia: "The children of smoking parents have an increased prevalence of reported respiratory symptoms, and have an increased frequency of bronchitis and pneumonia early in life." (p. 13)	1984
Pulmonary function (children): "The children of smoking parents appear to have measurable but small differences in tests of pulmonary function when compared with children of nonsmoking parents. The significance of this finding to the future development of lung disease is unknown." (p. 13)	1984
Pulmonary function (adults): ". . .some studies suggest that high levels of involuntary [tobacco] smoke exposure might produce small changes in pulmonary function in normal subjects. . . . Two studies have reported differences in measures of lung function in older populations between subjects chronically exposed to involuntary smoking and those who were not. This difference was not found in a younger and possibly less exposed population." (p. 13)	1984
Acute respiratory infections: "The children of parents who smoke have an increased frequency of a variety of acute respiratory illnesses and infections, including chest illnesses before 2 years of age and physician-diagnosed bronchitis, tracheitis, and laryngitis, when compared with the children of nonsmokers." (p. 13)	1986
Bronchitis and pneumonia: "The children of parents who smoke have an increased frequency of hospitalization for bronchitis and pneumonia during the first year of life when compared with the children of nonsmokers." (p. 13)	1986
Cancers other than lung: "The associations between cancers, other than cancer of the lung, and involuntary smoking require further investigation before a determination can be made about the relationship of involuntary smoking to these cancers." (p. 14)	1986
Cardiovascular disease: "Further studies on the relationship between involuntary smoking and cardiovascular disease are needed in order to determine whether involuntary smoking increases the risk of cardiovascular disease." (p. 14)	1986

Table 1.1 Continued

Disease and statement	Surgeon General's report
Chronic cough and phlegm (children): "Chronic cough and phlegm are more frequent in children whose parents smoke compared with children of nonsmokers." (p. 13)	1986
Chronic obstructive pulmonary disease (COPD): "Healthy adults exposed to environmental tobacco smoke may have small changes on pulmonary function testing, but are unlikely to experience clinically significant deficits in pulmonary function as a result of exposure to environmental tobacco smoke alone." (pp. 13–14) "The implications of chronic respiratory symptoms for respiratory health as an adult are unknown and deserve further study." (p. 13)	1986
Lung cancer: "Involuntary smoking can cause lung cancer in nonsmokers." (p. 13)	1986
Middle ear effusions: "A number of studies report that chronic middle ear effusions are more common in young children whose parents smoke than in children of nonsmoking parents." (p. 14)	1986
Pulmonary function (children): "The children of parents who smoke have small differences in tests of pulmonary function when compared with the children of nonsmokers. Although this decrement is insufficient to cause symptoms, the possibility that it may increase susceptibility to chronic obstructive pulmonary disease with exposure to other agents in adult life, e.g., [*sic*] active smoking or occupational exposures, needs investigation." (p. 13)	1986
Other: "An atmosphere contaminated with tobacco smoke can contribute to the discomfort of many individuals." (p. 7)	1972
"Cigarette smoke can make a significant, measurable contribution to the level of indoor air pollution at levels of smoking and ventilation that are common in the indoor environment." (p. 13)	1984
"Cigarette smoke in the air can produce an increase in both subjective and objective measures of eye irritation." (p. 13)	1984
"Nonsmokers who report exposure to environmental tobacco smoke have higher levels of urinary cotinine, a metabolite of nicotine, than those who do not report such exposure." (p. 13)	1984
"The simple separation of smokers and nonsmokers within the same air space may reduce, but does not eliminate, the exposure of nonsmokers to environmental tobacco smoke." (p. 13)	1986
"Validated questionnaires are needed for the assessment of recent and remote exposure to environmental tobacco smoke in the home, workplace, and other environments." (p. 14)	1986

Sources: U.S. Department of Health, Education, and Welfare 1972; U.S. Department of Health and Human Services 1984, 1986.

topic, addressing toxicology and dosimetry of tobacco smoke; the relevant evidence on active smoking; patterns of exposure of nonsmokers to tobacco smoke; the epidemiologic evidence on involuntary smoking and disease risks for infants, children, and adults; and policies to control involuntary exposure to tobacco smoke. That report concluded that involuntary smoking caused lung cancer in lifetime nonsmoking adults and was associated with adverse effects on respiratory health in children. The report also stated that simply separating smokers and nonsmokers within the same airspace reduced but did not eliminate exposure to secondhand smoke. All of these findings are relevant to public health and public policy (Table 1.1). The lung cancer conclusion was based on extensive information already available on the carcinogenicity of active smoking, the qualitative similarities between secondhand and mainstream smoke, the uptake of tobacco smoke components by nonsmokers, and the epidemiologic data on involuntary smoking. The three major conclusions of the report (Table 1.2), led Dr. C. Everett Koop, Surgeon General at the time, to comment in his preface that "the right of smokers to smoke ends where their behavior affects the health and well-being of others; furthermore, it is the smokers' responsibility to ensure that they do not expose nonsmokers to the potential [*sic*] harmful effects of tobacco smoke" (USDHHS 1986, p. xii).

Two other reports published in 1986 also reached the conclusion that involuntary smoking increased the risk for lung cancer. The International Agency for Research on Cancer (IARC) of the World Health Organization concluded that "passive smoking gives rise to some risk of cancer" (IARC 1986, p. 314). In its monograph on tobacco smoking, the agency supported this conclusion on the basis of the characteristics of sidestream and mainstream smoke, the absorption of tobacco smoke materials during an involuntary exposure, and the nature of dose-response relationships for carcinogenesis. In the same year, the National Research Council (NRC) also concluded that involuntary smoking increases the incidence of lung cancer in nonsmokers (NRC 1986). In reaching this conclusion, the NRC report cited the biologic plausibility of the association between exposure to secondhand smoke and lung cancer and the supporting epidemiologic evidence. On the basis of a pooled analysis of the epidemiologic data adjusted for bias, the report concluded that the best estimate for the excess risk of lung cancer in nonsmokers married to smokers was 25 percent, compared with nonsmokers married to nonsmokers. With regard to the effects of involuntary smoking on children, the NRC report commented on the literature linking secondhand smoke exposures from parental smoking to increased risks for respiratory symptoms and infections and to a slightly diminished rate of lung growth.

Since 1986, the conclusions with regard to both the carcinogenicity of secondhand smoke and the adverse effects of parental smoking on the health of children have been echoed and expanded (Table 1.3). In 1992, the U.S. Environmental Protection Agency (EPA) published its risk assessment of secondhand smoke as a carcinogen (USEPA 1992). The agency's evaluation drew on toxicologic information on secondhand smoke and the extensive literature on active smoking. A comprehensive meta-analysis of the 31 epidemiologic studies of secondhand smoke and lung cancer published up to that time was central to the decision to classify secondhand smoke as a group A carcinogen—namely, a known human carcinogen. Estimates of approximately 3,000 U.S. lung cancer deaths per year in nonsmokers were attributed to secondhand smoke. The report also covered other respiratory health effects in

Table 1.2 Major conclusions of the 1986 Surgeon General's report, *The Health Consequences of Involuntary Smoking*

1. Involuntary smoking is a cause of disease, including lung cancer, in healthy nonsmokers.
2. The children of parents who smoke compared with the children of nonsmoking parents have an increased frequency of respiratory infections, increased respiratory symptoms, and slightly smaller rates of increase in lung function as the lung matures.
3. The simple separation of smokers and nonsmokers within the same air space may reduce, but does not eliminate, the exposure of nonsmokers to environmental tobacco smoke.

Source: U.S. Department of Health and Human Services 1986, p. 7.

Table 1.3 Selected major reports, other than those of the U.S. Surgeon General, addressing adverse effects from exposure to tobacco smoke

Agency	Publication	Place and date of publication
National Research Council	*Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects*	Washington, D.C. United States 1986
International Agency for Research on Cancer (IARC)	*Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Tobacco Smoking* (IARC Monograph 38)	Lyon, France 1986
U.S. Environmental Protection Agency (EPA)	*Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders*	Washington, D.C. United States 1992
National Health and Medical Research Council	*The Health Effects of Passive Smoking*	Canberra, Australia 1997
California EPA (Cal/EPA), Office of Environmental Health Hazard Assessment	*Health Effects of Exposure to Environmental Tobacco Smoke*	Sacramento, California United States 1997
Scientific Committee on Tobacco and Health	*Report of the Scientific Committee on Tobacco and Health*	London, United Kingdom 1998
World Health Organization	*International Consultation on Environmental Tobacco Smoke (ETS) and Child Health. Consultation Report*	Geneva, Switzerland 1999
IARC	*Tobacco Smoke and Involuntary Smoking* (IARC Monograph 83)	Lyon, France 2004
Cal/EPA, Office of Environmental Health Hazard Assessment	*Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant*	Sacramento, California United States 2005

children and adults and concluded that involuntary smoking is causally associated with several adverse respiratory effects in children. There was also a quantitative risk assessment for the impact of involuntary smoking on childhood asthma and lower respiratory tract infections in young children.

In the decade since the 1992 EPA report, scientific panels continued to evaluate the mounting evidence linking involuntary smoking to adverse health effects (Table 1.3). The most recent was the 2005 report of the California EPA (Cal/EPA 2005). Over time, research has repeatedly affirmed the conclusions of the 1986 Surgeon General's reports and studies have further identified causal associations of involuntary smoking with diseases and other health disorders. The epidemiologic evidence on involuntary smoking has markedly expanded since 1986, as have the data on exposure to tobacco smoke in the many environments where people spend time. An understanding of the mechanisms by which involuntary smoking causes disease has also deepened.

As part of the environmental health hazard assessment, Cal/EPA identified specific health effects causally associated with exposure to secondhand smoke. The agency estimated the annual excess deaths in the United States that are attributable to secondhand smoke exposure for specific disorders: sudden infant death syndrome (SIDS), cardiac-related illnesses (ischemic heart disease), and lung cancer (Cal/EPA 2005). For the excess incidence of other health outcomes, either new estimates were provided or estimates from the 1997 health hazard assessment were

used without any revisions (Cal/EPA 1997). Overall, Cal/EPA estimated that about 50,000 excess deaths result annually from exposure to secondhand smoke (Cal/EPA 2005). Estimated annual excess deaths for the total U.S. population are about 3,400 (a range of 3,423 to 8,866) from lung cancer, 46,000 (a range of 22,700 to 69,600) from cardiac-related illnesses, and 430 from SIDS. The agency also estimated that between 24,300 and 71,900 low birth weight or preterm deliveries, about 202,300 episodes of childhood asthma (new cases and exacerbations), between 150,000 and 300,000 cases of lower respiratory illness in children, and about 789,700 cases of middle ear infections in children occur each year in the United States as a result of exposure to secondhand smoke.

This new 2006 Surgeon General's report returns to the topic of involuntary smoking. The health effects of involuntary smoking have not received comprehensive coverage in this series of reports since 1986. Reports since then have touched on selected aspects of the topic: the 1994 report on tobacco use among young people (USDHHS 1994), the 1998 report on tobacco use among U.S. racial and ethnic minorities (USDHHS 1998), and the 2001 report on women and smoking (USDHHS 2001). As involuntary smoking remains widespread in the United States and elsewhere, the preparation of this report was motivated by the persistence of involuntary smoking as a public health problem and the need to evaluate the substantial new evidence reported since 1986. This report substantially expands the list of topics that were included in the 1986 report. Additional topics include SIDS, developmental effects, and other reproductive effects; heart disease in adults; and cancer sites beyond the lung. For some associations of involuntary smoking with adverse health effects, only a few studies were reviewed in 1986 (e.g., ear disease in children); now, the relevant literature is substantial. Consequently, this report uses meta-analysis to quantitatively summarize evidence as appropriate. Following the approach used in the 2004 report (*The Health Consequences of Smoking*, USDHHS 2004), this 2006 report also systematically evaluates the evidence for causality, judging the extent of the evidence available and then making an inference as to the nature of the association.

Organization of the Report

This twenty-ninth report of the Surgeon General examines the topics of toxicology of secondhand smoke, assessment and prevalence of exposure to secondhand smoke, reproductive and developmental health effects, respiratory effects of exposure to secondhand smoke in children and adults, cancer among adults, cardiovascular diseases, and the control of secondhand smoke exposure.

This introductory chapter (Chapter 1) includes a discussion of the concept of causation and introduces concepts of causality that are used throughout this report; this chapter also summarizes the major conclusions of the report. Chapter 2 (Toxicology of Secondhand Smoke) sets out a foundation for interpreting the observational evidence that is the focus of most of the following chapters. The discussion details the mechanisms that enable tobacco smoke components to injure the respiratory tract and cause nonmalignant and malignant diseases and other adverse effects. Chapter 3 (Assessment of Exposure to Secondhand Smoke) provides a perspective on key factors that determine exposures of people to secondhand smoke in indoor environments, including building designs and operations, atmospheric markers of secondhand smoke, exposure models, and biomarkers of exposure to secondhand smoke. Chapter 4 (Prevalence of Exposure to Secondhand Smoke) summarizes findings that focus on nicotine measurements in the air and cotinine measurements in biologic materials. The chapter includes exposures in the home, workplace, public places, and special populations. Chapter 5 (Reproductive and Developmental Effects from Exposure to Secondhand Smoke) reviews the health effects on reproduction, on infants, and on child development. Chapter 6 (Respiratory Effects in Children from Exposure to Secondhand Smoke) examines the effects of parental smoking on the respiratory health of children. Chapter 7 (Cancer Among Adults from Exposure to Secondhand Smoke) summarizes the evidence on cancer of the lung, breast, nasal sinuses, and the cervix. Chapter 8 (Cardiovascular Diseases from Exposure to Secondhand Smoke) discusses coronary heart disease (CHD), stroke, and subclinical vascular disease. Chapter 9 (Respiratory Effects in Adults from Exposure to Secondhand Smoke) examines odor and irritation, respiratory symptoms, lung function, and respiratory diseases such as asthma and chronic obstructive pulmonary disease. Chapter 10 (Control of Secondhand Smoke Exposure) considers measures used to control exposure to secondhand smoke in public places, including legislation, education, and approaches based on building designs and operations. The report concludes with "A Vision for the Future." Major conclusions of the report were distilled from the chapter conclusions and appear later in this chapter.

Preparation of the Report

This report of the Surgeon General was prepared by the Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Coordinating Center for Health Promotion, Centers for Disease Control and Prevention (CDC), and U.S. DHHS. Initial chapters were written by 22 experts who were selected because of their knowledge of a particular topic. The contributions of the initial experts were consolidated into 10 major chapters that were then reviewed by more than 40 peer reviewers. The entire manuscript was then sent to more than 30 scientists and experts who reviewed it for its scientific integrity. After each review cycle, the drafts were revised by the scientific editors on the basis of the experts' comments. Subsequently, the report was reviewed by various institutes and agencies within U.S. DHHS. Publication lags, even short ones, prevent an up-to-the-minute inclusion of all recently published articles and data. Therefore, by the time the public reads this report, there may be additional published studies or data. To provide published information as current as possible, this report includes an Appendix of more recent studies that represent major additions to the literature.

This report is also accompanied by a companion database of key evidence that is accessible through the Internet (http://www.cdc.gov/tobacco). The database includes a uniform description of the studies and results on the health effects of exposure to secondhand smoke that were presented in a format compatible with abstraction into standardized tables. Readers of the report may access these data for additional analyses, tables, or figures.

Definitions and Terminology

The inhalation of tobacco smoke by nonsmokers has been variably referred to as "passive smoking" or "involuntary smoking." Smokers, of course, also inhale secondhand smoke. Cigarette smoke contains both particles and gases generated by the combustion at high temperatures of tobacco, paper, and additives. The smoke inhaled by nonsmokers that contaminates indoor spaces and outdoor environments has often been referred to as "secondhand smoke" or "environmental tobacco smoke." This inhaled smoke is the mixture of sidestream smoke released by the smoldering cigarette and the mainstream smoke that is exhaled by a smoker. Sidestream smoke, generated at lower temperatures and under somewhat different combustion conditions than mainstream smoke, tends to have higher concentrations of many of the toxins found in cigarette smoke (USDHHS 1986). However, it is rapidly diluted as it travels away from the burning cigarette.

Secondhand smoke is an inherently dynamic mixture that changes in characteristics and concentration with the time since it was formed and the distance it has traveled. The smoke particles change in size and composition as gaseous components are volatilized and moisture content changes; gaseous elements of secondhand smoke may be adsorbed onto materials, and particle concentrations drop with both dilution in the air or environment and impaction on surfaces, including the lungs or on the body. Because of its dynamic nature, a specific quantitative definition of secondhand smoke cannot be offered.

This report uses the term secondhand smoke in preference to environmental tobacco smoke, even though the latter may have been used more frequently in previous reports. The descriptor "secondhand" captures the involuntary nature of the exposure, while "environmental" does not. This report also refers to the inhalation of secondhand smoke as involuntary smoking, acknowledging that most nonsmokers do not want to inhale tobacco smoke. The exposure of the fetus to tobacco smoke, whether from active smoking by the mother or from her exposure to secondhand smoke, also constitutes involuntary smoking.

Evidence Evaluation

Following the model of the 1964 report, the Surgeon General's reports on smoking have included comprehensive compilations of the evidence on the health effects of smoking. The evidence is analyzed to identify causal associations between smoking and disease according to enunciated principles, sometimes referred to as the "Surgeon General's criteria" or the "Hill" criteria (after Sir Austin Bradford Hill) for causality (USDHEW 1964; USDHHS 2004). Application of these criteria involves covering all relevant observational and experimental evidence. The criteria, offered in a brief chapter of the 1964 report entitled "Criteria for Judgment," included (1) the consistency of the association, (2) the strength of the association, (3) the specificity of the association, (4) the temporal relationship of the association, and (5) the coherence of the association. Although these criteria have been criticized (e.g., Rothman and Greenland 1998), they have proved useful as a framework for interpreting evidence on smoking and other postulated causes of disease, and for judging whether causality can be inferred.

In the 2004 report of the Surgeon General, *The Health Consequences of Smoking*, the framework for interpreting evidence on smoking and health was revisited in depth for the first time since the 1964 report (USDHHS 2004). The 2004 report provided a four-level hierarchy for interpreting evidence (Table 1.4). The categories acknowledge that evidence can be "suggestive" but not adequate to infer a causal relationship, and also allows for evidence that is "suggestive of no causal relationship." Since the 2004 report, the individual chapter conclusions have consistently used this four-level hierarchy (Table 1.4), but evidence syntheses and other summary statements may use either the term "increased risk" or "cause" to describe instances in which there is sufficient evidence to conclude that active or involuntary smoking causes a disease or condition. This four-level framework also sharply and completely separates conclusions regarding causality from the implications of such conclusions.

That same framework was used in this report on involuntary smoking and health. The criteria dating back to the 1964 Surgeon General's report remain useful as guidelines for evaluating evidence (USDHEW 1964), but they were not intended to be applied strictly or as a "checklist" that needed to be met before the designation of "causal" could be applied to an association. In fact, for involuntary smoking and health, several of the criteria will not be met for some associations. Specificity, referring to a unique exposure-disease relationship (e.g., the association between thalidomide use during pregnancy and unusual birth defects), can be set aside as not relevant, as all of the health effects considered in this report have causes other than involuntary smoking. Associations are considered more likely to be causal as the strength of an association increases because competing explanations become less plausible alternatives. However, based on knowledge of dosimetry and mechanisms of injury and disease causation, the risk is anticipated to be only slightly or modestly increased for some associations of involuntary smoking with disease, such as lung cancer, particularly when the very strong relative risks found for active smokers are compared with those for lifetime nonsmokers. The finding of only a small elevation in risk, as in the

Table 1.4 Four-level hierarchy for classifying the strength of causal inferences based on available evidence

Level 1	Evidence is **sufficient** to infer a causal relationship.
Level 2	Evidence is **suggestive but not sufficient** to infer a causal relationship.
Level 3	Evidence is **inadequate** to infer the presence or absence of a causal relationship (which encompasses evidence that is sparse, of poor quality, or conflicting).
Level 4	Evidence is **suggestive of no causal relationship**.

Source: U.S. Department of Health and Human Services 2004.

example of spousal smoking and lung cancer risk in lifetime nonsmokers, does not weigh against a causal association; however, alternative explanations for a risk of a small magnitude need full exploration and cannot be so easily set aside as alternative explanations for a stronger association. Consistency, coherence, and the temporal relationship of involuntary smoking with disease are central to the interpretations in this report. To address coherence, the report draws not only on the evidence for involuntary smoking, but on the even more extensive literature on active smoking and disease.

Although the evidence reviewed in this report comes largely from investigations of secondhand smoke specifically, the larger body of evidence on active smoking is also relevant to many of the associations that were evaluated. The 1986 report found secondhand smoke to be qualitatively similar to mainstream smoke inhaled by the smoker and concluded that secondhand smoke would be expected to have "a toxic and carcinogenic potential that would not be expected to be qualitatively different from that of MS [mainstream smoke]" (USDHHS 1986, p. 23). The 2004 report of the Surgeon General revisited the health consequences of active smoking (USDHHS 2004), and the conclusions substantially expanded the list of diseases and conditions caused by smoking. Chapters in the present report consider the evidence on active smoking that is relevant to biologic plausibility for causal associations between involuntary smoking and disease. The reviews included in this report cover evidence identified through search strategies set out in each chapter. Of necessity, the evidence on mechanisms was selectively reviewed. However, an attempt was made to cover all health studies through specified target dates. Because of the substantial amount of time involved in preparing this report, lists of new key references published after these cut-off dates are included in an Appendix. Literature reviews were extended when new evidence was sufficient to possibly change the level of a causal conclusion.

Major Conclusions

This report returns to involuntary smoking, the topic of the 1986 Surgeon General's report. Since then, there have been many advances in the research on secondhand smoke, and substantial evidence has been reported over the ensuing 20 years. This report uses the revised language for causal conclusions that was implemented in the 2004 Surgeon General's report (USDHHS 2004). Each chapter provides a comprehensive review of the evidence, a quantitative synthesis of the evidence if appropriate, and a rigorous assessment of sources of bias that may affect interpretations of the findings. The reviews in this report reaffirm and strengthen the findings of the 1986 report. With regard to the involuntary exposure of nonsmokers to tobacco smoke, the scientific evidence now supports the following major conclusions:

1. Secondhand smoke causes premature death and disease in children and in adults who do not smoke.

2. Children exposed to secondhand smoke are at an increased risk for sudden infant death syndrome (SIDS), acute respiratory infections, ear problems, and more severe asthma. Smoking by parents causes respiratory symptoms and slows lung growth in their children.

3. Exposure of adults to secondhand smoke has immediate adverse effects on the cardiovascular system and causes coronary heart disease and lung cancer.

4. The scientific evidence indicates that there is no risk-free level of exposure to secondhand smoke.

5. Many millions of Americans, both children and adults, are still exposed to secondhand smoke in their homes and workplaces despite substantial progress in tobacco control.

6. Eliminating smoking in indoor spaces fully protects nonsmokers from exposure to secondhand smoke. Separating smokers from nonsmokers, cleaning the air, and ventilating buildings cannot eliminate exposures of nonsmokers to secondhand smoke.

Chapter Conclusions

Chapter 2. Toxicology of Secondhand Smoke

Evidence of Carcinogenic Effects from Secondhand Smoke Exposure

1. More than 50 carcinogens have been identified in sidestream and secondhand smoke.

2. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and its condensates and tumors in laboratory animals.

3. The evidence is sufficient to infer that exposure of nonsmokers to secondhand smoke causes a significant increase in urinary levels of metabolites of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). The presence of these metabolites links exposure to secondhand smoke with an increased risk for lung cancer.

4. The mechanisms by which secondhand smoke causes lung cancer are probably similar to those observed in smokers. The overall risk of secondhand smoke exposure, compared with active smoking, is diminished by a substantially lower carcinogenic dose.

Mechanisms of Respiratory Tract Injury and Disease Caused by Secondhand Smoke Exposure

5. The evidence indicates multiple mechanisms by which secondhand smoke exposure causes injury to the respiratory tract.

6. The evidence indicates mechanisms by which secondhand smoke exposure could increase the risk for sudden infant death syndrome.

Mechanisms of Secondhand Smoke Exposure and Heart Disease

7. The evidence is sufficient to infer that exposure to secondhand smoke has a prothrombotic effect.

8. The evidence is sufficient to infer that exposure to secondhand smoke causes endothelial cell dysfunctions.

9. The evidence is sufficient to infer that exposure to secondhand smoke causes atherosclerosis in animal models.

Chapter 3. Assessment of Exposure to Secondhand Smoke

Building Designs and Operations

1. Current heating, ventilating, and air conditioning systems alone cannot control exposure to secondhand smoke.

2. The operation of a heating, ventilating, and air conditioning system can distribute secondhand smoke throughout a building.

Exposure Models

3. Atmospheric concentration of nicotine is a sensitive and specific indicator for secondhand smoke.

4. Smoking increases indoor particle concentrations.

5. Models can be used to estimate concentrations of secondhand smoke.

Biomarkers of Exposure to Secondhand Smoke

6. Biomarkers suitable for assessing recent exposures to secondhand smoke are available.

7. At this time, cotinine, the primary proximate metabolite of nicotine, remains the biomarker of choice for assessing secondhand smoke exposure.

8. Individual biomarkers of exposure to secondhand smoke represent only one component of a complex mixture, and measurements of one marker may not wholly reflect an exposure to other components of concern as a result of involuntary smoking.

Chapter 4. Prevalence of Exposure to Secondhand Smoke

1. The evidence is sufficient to infer that large numbers of nonsmokers are still exposed to secondhand smoke.

2. Exposure of nonsmokers to secondhand smoke has declined in the United States since the 1986 Surgeon General's report, *The Health Consequences of Involuntary Smoking*.

3. The evidence indicates that the extent of secondhand smoke exposure varies across the country.

4. Homes and workplaces are the predominant locations for exposure to secondhand smoke.

5. Exposure to secondhand smoke tends to be greater for persons with lower incomes.

6. Exposure to secondhand smoke continues in restaurants, bars, casinos, gaming halls, and vehicles.

Chapter 5. Reproductive and Developmental Effects from Exposure to Secondhand Smoke

Fertility

1. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal exposure to secondhand smoke and female fertility or fecundability. No data were found on paternal exposure to secondhand smoke and male fertility or fecundability.

Pregnancy (Spontaneous Abortion and Perinatal Death)

2. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal exposure to secondhand smoke during pregnancy and spontaneous abortion.

Infant Deaths

3. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and neonatal mortality.

Sudden Infant Death Syndrome

4. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and sudden infant death syndrome.

Preterm Delivery

5. The evidence is suggestive but not sufficient to infer a causal relationship between maternal exposure to secondhand smoke during pregnancy and preterm delivery.

Low Birth Weight

6. The evidence is sufficient to infer a causal relationship between maternal exposure to secondhand smoke during pregnancy and a small reduction in birth weight.

Congenital Malformations

7. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and congenital malformations.

Cognitive Development

8. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and cognitive functioning among children.

Behavioral Development

9. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and behavioral problems among children.

Height/Growth

10. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and children's height/growth.

Childhood Cancer

11. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood cancer.

12. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal exposure to secondhand smoke during pregnancy and childhood cancer.

13. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke during infancy and childhood cancer.

14. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood leukemias.

15. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood lymphomas.

16. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood brain tumors.

17. The evidence is inadequate to infer the presence or absence of a causal relationship between prenatal and postnatal exposure to secondhand smoke and other childhood cancer types.

Chapter 6. Respiratory Effects in Children from Exposure to Secondhand Smoke

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.

Chapter 7. Cancer Among Adults from Exposure to Secondhand Smoke

Lung Cancer

1. The evidence is sufficient to infer a causal relationship between secondhand smoke exposure and lung cancer among lifetime nonsmokers. This conclusion extends to all secondhand smoke exposure, regardless of location.

2. The pooled evidence indicates a 20 to 30 percent increase in the risk of lung cancer from secondhand smoke exposure associated with living with a smoker.

Breast Cancer

3. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke and breast cancer.

Nasal Sinus Cavity and Nasopharyngeal Carcinoma

4. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and a risk of nasal sinus cancer among nonsmokers.

5. The evidence is inadequate to infer the presence or absence of a causal relationship between secondhand smoke exposure and a risk of nasopharyngeal carcinoma among nonsmokers.

Cervical Cancer

6. The evidence is inadequate to infer the presence or absence of a causal relationship between secondhand smoke exposure and the risk of cervical cancer among lifetime nonsmokers.

Chapter 8. Cardiovascular Diseases from Exposure to Secondhand Smoke

1. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and increased risks of coronary heart disease morbidity and mortality among both men and women.

2. Pooled relative risks from meta-analyses indicate a 25 to 30 percent increase in the risk of coronary heart disease from exposure to secondhand smoke.

3. The evidence is suggestive but not sufficient to infer a causal relationship between exposure to secondhand smoke and an increased risk of stroke.

4. Studies of secondhand smoke and subclinical vascular disease, particularly carotid arterial wall thickening, are suggestive but not sufficient to infer a causal relationship between exposure to secondhand smoke and atherosclerosis.

Chapter 9. Respiratory Effects in Adults from Exposure to Secondhand Smoke

Odor and Irritation

1. The evidence is sufficient to infer a causal relationship between secondhand smoke exposure and odor annoyance.

2. The evidence is sufficient to infer a causal relationship between secondhand smoke exposure and nasal irritation.

3. The evidence is suggestive but not sufficient to conclude that persons with nasal allergies or a history of respiratory illnesses are more susceptible to developing nasal irritation from secondhand smoke exposure.

Respiratory Symptoms

4. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and acute respiratory symptoms including cough, wheeze, chest tightness, and difficulty breathing among persons with asthma.

5. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and acute respiratory symptoms including cough, wheeze, chest tightness, and difficulty breathing among healthy persons.

6. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and chronic respiratory symptoms.

Lung Function

7. The evidence is suggestive but not sufficient to infer a causal relationship between short-term secondhand smoke exposure and an acute decline in lung function in persons with asthma.

8. The evidence is inadequate to infer the presence or absence of a causal relationship between short-term secondhand smoke exposure and an acute decline in lung function in healthy persons.

9. The evidence is suggestive but not sufficient to infer a causal relationship between chronic secondhand smoke exposure and a small decrement in lung function in the general population.

10. The evidence is inadequate to infer the presence or absence of a causal relationship between chronic secondhand smoke exposure and an accelerated decline in lung function.

Asthma

11. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and adult-onset asthma.

12. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and a worsening of asthma control.

Chronic Obstructive Pulmonary Disease

13. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and risk for chronic obstructive pulmonary disease.

14. The evidence is inadequate to infer the presence or absence of a causal relationship between secondhand smoke exposure and morbidity in persons with chronic obstructive pulmonary disease.

Chapter 10. Control of Secondhand Smoke Exposure

1. Workplace smoking restrictions are effective in reducing secondhand smoke exposure.

2. Workplace smoking restrictions lead to less smoking among covered workers.

3. Establishing smoke-free workplaces is the only effective way to ensure that secondhand smoke exposure does not occur in the workplace.

4. The majority of workers in the United States are now covered by smoke-free policies.

5. The extent to which workplaces are covered by smoke-free policies varies among worker groups, across states, and by sociodemographic factors. Workplaces related to the entertainment and hospitality industries have notably high potential for secondhand smoke exposure.

6. Evidence from peer-reviewed studies shows that smoke-free policies and regulations do not have an adverse economic impact on the hospitality industry.

7. Evidence suggests that exposure to secondhand smoke varies by ethnicity and gender.

8. In the United States, the home is now becoming the predominant location for exposure of children and adults to secondhand smoke.

9. Total bans on indoor smoking in hospitals, restaurants, bars, and offices substantially reduce secondhand smoke exposure, up to several orders of magnitude with incomplete compliance, and with full compliance, exposures are eliminated.

10. Exposures of nonsmokers to secondhand smoke cannot be controlled by air cleaning or mechanical air exchange.

Methodologic Issues

Much of the evidence on the health effects of involuntary smoking comes from observational epidemiologic studies that were carried out to test hypotheses related to secondhand smoke and risk for diseases and other adverse health effects. The challenges faced in carrying out these studies reflect those of observational research generally: assessment of the relevant exposures and outcomes with sufficient validity and precision, selection of an appropriate study design, identification of an appropriate and sufficiently large study population, and collection of information on other relevant factors that may confound or modify the association being studied. The challenge of accurately classifying secondhand smoke exposures confronts all studies of such exposures, and consequently the literature on approaches to and limitations of exposure classification is substantial. Sources of bias that can affect the findings of epidemiologic studies have been widely discussed (Rothman and Greenland 1998), both in general and in relation to studies of involuntary smoking. Concerns about bias apply to any study of an environmental agent and disease risk: misclassification of exposures or outcomes, confounding effect modification, and proper selection of study participants. In addition, the generalizability of findings from one population to another (external validity) further determines the value of evidence from a study. Another methodologic concern affecting secondhand smoke literature comes from the use of meta-analysis to combine the findings of epidemiologic studies; general concerns related to the use of meta-analysis for observational data and more specific concerns related to involuntary smoking have also been raised. This chapter considers these methodologic issues in anticipation of more specific treatment in the following chapters.

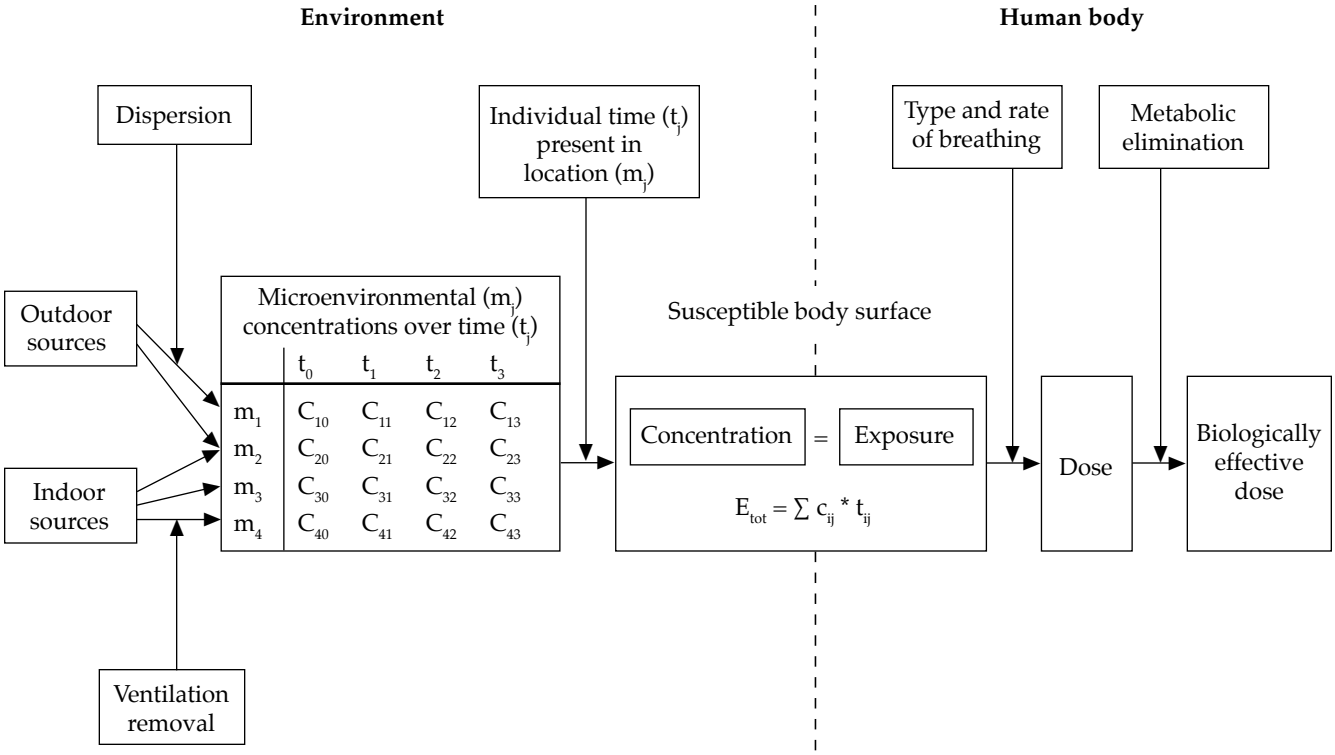
Classification of Secondhand Smoke Exposure

For secondhand smoke, as for any environmental factor that may be a cause of disease, the exposure assessment might encompass the time and place of the exposure, cumulative exposures, exposure during a particular time, or a recent exposure (Jaakkola and Jaakkola 1997; Jaakkola and Samet 1999). For example, exposures to secondhand smoke across the full life span may be of interest for lung cancer, while only more recent exposures may be relevant to the exacerbation of asthma. For CHD, both temporally remote and current exposures may affect risk. Assessments of exposures are further complicated by the multiplicity of environments where exposures take place and the difficulty of characterizing the exposure in some locations, such as public places or workplaces. Additionally, exposures probably vary qualitatively and quantitatively over time and across locations because of temporal changes and geographic differences in smoking patterns.

Nonetheless, researchers have used a variety of approaches for exposure assessments in epidemiologic studies of adverse health effects from involuntary smoking. Several core concepts that are fundamental to these approaches are illustrated in Figure 1.1 (Samet and Jaakkola 1999). Cigarette smoking is, of course, the source of most secondhand smoke in the United States, followed by pipes, cigars, and other products. Epidemiologic studies generally focus on assessing the exposure, which is the contact with secondhand smoke. The concentrations of secondhand smoke components in a space depend on the number of smokers and the rate at which they are smoking, the volume into which the smoke is distributed, the rate at which the air in the space exchanges with uncontaminated air, and the rate at which the secondhand smoke is removed from the air. Concentration, exposure, and dose differ in their definitions, although the terms are sometimes used without sharp distinctions. However, surrogate indicators that generally describe a source of exposure may also be used to assess the exposure, such as marriage to a smoker or the number of cigarettes smoked in the home. Biomarkers can provide an indication of an exposure or possibly the dose, but for secondhand smoke they are used for recent exposure only.

People are exposed to secondhand smoke in a number of different places, often referred to as "microenvironments" (NRC 1991). A microenvironment is a definable location that has a constant concentration of the contaminant of interest, such as secondhand smoke, during the time that a person is there. Some key microenvironments for secondhand smoke include the home, the workplace, public places, and transportation environments (Klepeis 1999). Based

Figure 1.1 The determinants of exposure, dose, and biologically effective dose that underlie the development of health effects from smoking



Source: Samet and Jaakkola 1999. Reprinted with permission.

on the microenvironmental model, total exposure can be estimated as the weighted average of the concentrations of secondhand smoke or indicator compounds, such as nicotine, in the microenvironments where time is spent; the weights are the time spent in each microenvironment. Klepeis (1999) illustrates the application of the microenvironmental model with national data from the National Human Activity Pattern Survey conducted by the EPA. His calculations yield an overall estimate of exposure to airborne particles from smoking and of the contributions to this exposure from various microenvironments.

Much of the epidemiologic evidence addresses the consequences of an exposure in a particular microenvironment, such as the home (spousal smoking and lung cancer risk or maternal smoking and risk for asthma exacerbation), or the workplace (exacerbation of asthma by the presence of smokers). Some studies have attempted to cover multiple microenvironments and to characterize exposures over time. For example, in the multicenter study of secondhand smoke exposure and lung cancer carried out in the United States, Fontham and colleagues (1994) assessed exposures during childhood, in workplaces, and at home during adulthood. Questionnaires that assess exposures have been the primary tool used in epidemiologic studies of secondhand smoke and disease. Measurement of biomarkers has been added in some studies, either as an additional and complementary exposure assessment approach or for validating questionnaire responses. Some studies have also measured components of secondhand smoke in the air.

Questionnaires generally address sources of exposure in microenvironments and can be tailored to address the time period of interest. Questionnaires represent the only approach that can be used to assess exposures retrospectively over a life span, because available biomarkers only reflect exposures

over recent days or, at most, weeks. Questionnaires on secondhand smoke exposure have been assessed for their reliability and validity, generally based on comparisons with either biomarker or air monitoring data as the "gold" standard (Jaakkola and Jaakkola 1997). Two studies evaluated the reliability of questionnaires on lifetime exposures (Pron et al. 1988; Coultas et al. 1989). Both showed a high degree of repeatability for questions concerning whether a spouse had smoked, but a lower reliability for responses concerning the quantitative aspects of an exposure. Emerson and colleagues (1995) evaluated the repeatability of information from parents of children with asthma. They found a high reliability for parent-reported tobacco use and for the number of cigarettes to which the child was exposed in the home during the past week.

To assess validity, questionnaire reports of current or recent exposures have been compared with levels of cotinine and other biomarkers. These studies tend to show a moderate correlation between levels of cotinine and questionnaire indicators of exposures (Kawachi and Colditz 1996; Cal/EPA 1997; Jaakkola and Jaakkola 1997). However, cotinine levels reflect not only exposure but metabolism and excretion (Benowitz 1999). Consequently, exposure is only one determinant of variation in cotinine levels among persons; there also are individual variations in metabolism and excretion rates. In spite of these sources of variability, mean levels of cotinine vary as anticipated across categories of self-reported exposures (Cal/EPA 1997; Jaakkola and Jaakkola 1997), and self-reported exposures are moderately associated with measured levels of markers (Cal/EPA 1997; Jaakkola and Jaakkola 1997).

Biomarkers are also used for assessing exposures to secondhand smoke. A number of biomarkers are available, but they vary in their specificity and in the dynamics of the temporal relationship between the exposure and the marker level (Cal/EPA 1997; Benowitz 1999). These markers include specific tobacco smoke components (nicotine) or metabolites (cotinine and tobacco-specific nitrosamines), nonspecific biomarkers (thiocyanate and CO), adducts with tobacco smoke components or metabolites (4-aminobiphenyl–hemoglobin adducts, benzo[*a*]pyrene–DNA adducts, and polycyclic aromatic hydrocarbon–albumin adducts), and nonspecific assays (urinary mutagenicity). Cotinine has been the most widely used biomarker, primarily because of its specificity, half-life, and ease of measurement in body fluids (e.g., urine, blood, and saliva). Biomarkers are discussed in detail in Chapter 3 (Assessment of Exposure to Secondhand Smoke).

Some epidemiologic studies have also incorporated air monitoring, either direct personal sampling or the indirect approach based on the microenvironmental model. Nicotine, present in the gas phase of secondhand smoke, can be monitored passively with a special filter or actively using a pump and a sorbent. Hammond and Leaderer (1987) first described a diffusion monitor for the passive sampling of nicotine in 1987; this device has now been widely used to assess concentrations in different environments and to study health effects. Airborne particles have also been measured using active monitoring devices.

Each of these approaches for assessing exposures has strengths and limitations, and preference for one over another will depend on the research question and its context (Jaakkola and Jaakkola 1997; Jaakkola and Samet 1999). Questionnaires can be used to characterize sources of exposures, such as smoking by parents. With air concentrations of markers and time-activity information, estimates of secondhand smoke exposures can be made with the microenvironmental model. Biomarkers provide exposure measures that reflect the patterns of exposure and the kinetics of the marker; the cotinine level in body fluids, for example, reflects an exposure during several days. Air monitoring may be useful for validating measurements of exposure. Exposure assessment strategies are matched to the research question and often employ a mixture of approaches determined by feasibility and cost constraints.

Misclassification of Secondhand Smoke Exposure

Misclassification may occur when classifying exposures, outcomes, confounding factors, or modifying factors. Misclassification may be differential on either exposure or outcome, or it may be random (Armstrong et al. 1992). Differential or nonrandom misclassification may either increase or decrease estimates of effect, while random misclassification tends to reduce the apparent effect and weaken the relationship of exposure with disease risk. In studies of secondhand smoke and disease risk, exposure misclassification has been a major consideration in the interpretation of the evidence, although misclassification of health outcome measures has not been a substantial issue in this research. The consequences for epidemiologic studies of misclassification in general are well established (Rothman and Greenland 1998).

An extensive body of literature on the classification of exposures to secondhand smoke is reviewed in this and other chapters, as well as in some publications on the consequences of misclassification (Wu 1999). Two general patterns of exposure misclassification are of concern to secondhand smoke: (1) random misclassification that is not differential by the presence or absence of the health outcome and (2) systematic misclassification that is differential by the health outcome. In studying the health effects of secondhand smoke in adults, there is a further concern as to the classification of the active smoking status (never, current, or former smoking); in studies of children, the accuracy of secondhand smoke exposure classification is the primary methodologic issue around exposure assessment, but unreported active smoking by adolescents is also a concern.

With regard to random misclassification of secondhand smoke exposures, there is an inherent degree of unavoidable measurement error in the exposure measures used in epidemiologic studies. Questionnaires generally assess contact with sources of an exposure (e.g., smoking in the home or workplace) and cannot capture all exposures nor the intensity of exposures; biomarkers provide an exposure index for a particular time window and have intrinsic variability. Some building-related factors that determine an exposure cannot be assessed accurately by a questionnaire, such as the rate of air exchange and the size of the microenvironment where time is spent, nor can concentrations be assessed accurately by subjective reports of the perceived level of tobacco smoke. In general, random misclassification of exposures tends to reduce the likelihood that studies of secondhand smoke exposure will find an effect. This type of misclassification lessens the contrast between exposure groups, because some truly exposed persons are placed in the unexposed group and some truly unexposed persons are placed in the exposed group. Differential misclassification, also a concern, may increase or decrease associations, depending on the pattern of misreporting.

One particular form of misclassification has been raised with regard to secondhand smoke exposure and lung cancer: the classification of some current or former smokers as lifetime nonsmokers (USEPA 1992; Lee and Forey 1995; Hackshaw et al. 1997; Wu 1999). The resulting bias would tend to increase the apparent association of secondhand smoke with lung cancer, if the misclassified active smokers are also more likely to be classified as involuntary smokers. Most studies of lung cancer and secondhand smoke have used spousal smoking as a main exposure variable. As smoking tends to aggregate between spouses (smokers are more likely to marry smokers), misclassification of active smoking would tend to be differential on the basis of spousal smoking (the exposure under investigation). Because active smoking is strongly associated with increased disease risk, greater misclassification of an actively smoking spouse as a nonsmoker among spouses of smokers compared with spouses of nonsmokers would lead to risk estimates for spousal smoking that are biased upward by the effect of active smoking. This type of misclassification is also relevant to studies of spousal exposure and CHD risk or other diseases also caused by active smoking, although the potential for bias is less because the association of active smoking with CHD is not as strong as with lung cancer.

There have been a number of publications on this form of misclassification. Wu (1999) provides a review, and Lee and colleagues (2001) offer an assessment of potential consequences. A number of models have been developed to assess the extent of bias resulting from the misclassification of active smokers as lifetime nonsmokers (USEPA 1992; Hackshaw et al. 1997). These models incorporate estimates of the rate of misclassification, the degree of aggregation of smokers by marriage, the prevalence of smoking in the population, and the risk of lung cancer in misclassified smokers (Wu 1999). Although debate about this issue continues, analyses show that estimates of upward bias from misclassifying active smokers as lifetime nonsmokers cannot fully explain the observed increase in risk for lung cancer among lifetime nonsmokers married to smokers (Hackshaw et al. 1997; Wu 1999).

There is one additional issue related to exposure misclassification. During the time the epidemiologic studies of secondhand smoke have been carried out, exposure has been widespread and almost unavoidable. Therefore, the risk estimates may be biased downward because there are no truly unexposed persons. The 1986 Surgeon General's report recognized this methodologic issue and noted the need for further data on population exposures to secondhand smoke (USDHHS 1986). This bias was also recognized in the 1986 report of the NRC, and an adjustment for this misclassification was made to the lung cancer estimate (NRC 1986). Similarly, the 1992 report of the EPA commented on background exposure and made an adjustment (USEPA 1992). Some later studies have attempted to address this issue; for example, in a case-control study of active and involuntary smoking and breast cancer in Switzerland, Morabia and colleagues (2000) used a questionnaire to assess exposure and

identified a small group of lifetime nonsmokers who also reported no exposure to secondhand smoke. With this subgroup of controls as the reference population, the risks of secondhand smoke exposure were substantially greater for active smoking than when the full control population was used.

This Surgeon General's report further addresses specific issues of exposure misclassification when they are relevant to the health outcome under consideration.

Use of Meta-Analysis

Meta-analysis refers to the process of evaluating and combining a body of research literature that addresses a common question. Meta-analysis is composed of qualitative and quantitative components. The qualitative component involves the systematic identification of all relevant investigations, a systematic assessment of their characteristics and quality, and the decision to include or exclude studies based on predetermined criteria. Consideration can be directed toward sources of bias that might affect the findings. The quantitative component involves the calculation and display of study results on common scales and, if appropriate, the statistical combination of these results across studies and an exploration of the reasons for any heterogeneity of findings. Viewing the findings of all studies as a single plot provides insights into the consistency of results and the precision of the studies considered. Most meta-analyses are based on published summary results, although they are most powerful when applied to data at the level of individual participants. Meta-analysis is most widely used to synthesize evidence from randomized clinical trials, sometimes yielding findings that were not evident from the results of individual studies. Meta-analysis also has been used extensively to examine bodies of observational evidence.

Beginning with the 1986 NRC report, meta-analysis has been used to summarize the evidence on involuntary smoking and health. Meta-analysis was central to the 1992 EPA risk assessment of secondhand smoke, and a series of meta-analyses supported the conclusions of the 1998 report of the Scientific Committee on Tobacco and Health in the United Kingdom. The central role of meta-analysis in interpreting and applying the evidence related to involuntary smoking and disease has led to focused criticisms of the use of meta-analysis in this context. Several papers that acknowledged support from the tobacco industry have addressed the epidemiologic findings for lung cancer, including the selection and quality of the studies, the methods for meta-analysis, and dose-response associations (Fleiss and Gross 1991; Tweedie and Mengersen 1995; Lee 1998, 1999). In a lawsuit brought by the tobacco industry against the EPA, the 1998 decision handed down by Judge William L. Osteen, Sr., in the North Carolina Federal District Court criticized the approach EPA had used to select studies for its meta-analysis and criticized the use of 90 percent rather than 95 percent confidence intervals for the summary estimates (*Flue-Cured Tobacco Cooperative Stabilization Corp. v. United States Environmental Protection Agency*, 857 F. Supp. 1137 [M.D.N.C. 1993]). In December 2002, the 4th U.S. Circuit Court of Appeals threw out the lawsuit on the basis that tobacco companies cannot sue the EPA over its secondhand smoke report because the report was not a final agency action and therefore not subject to court review (*Flue-Cured Tobacco Cooperative Stabilization Corp. v. The United States Environmental Protection Agency*, No. 98-2407 [4th Cir., December 11, 2002], *cited in* 17.7 TPLR 2.472 [2003]).

Recognizing that there is still an active discussion around the use of meta-analysis to pool data from observational studies (versus clinical trials), the authors of this Surgeon General's report used this methodology to summarize the available data when deemed appropriate and useful, even while recognizing that the uncertainty around the meta-analytic estimates may exceed the uncertainty indicated by conventional statistical indices, because of biases either within the observational studies or produced by the manner of their selection. However, a decision to not combine estimates might have produced conclusions that are far more uncertain than the data warrant because the review would have focused on individual study results without considering their overall pattern, and without allowing for a full accounting of different sample sizes and effect estimates.

The possibility of publication bias has been raised as a potential limitation to the interpretation of evidence on involuntary smoking and disease in general, and on lung cancer and secondhand smoke exposure specifically. A 1988 paper by Vandenbroucke used a descriptive approach, called a "funnel plot," to assess the possibility that publication bias affected the 13 studies considered in a review by Wald and colleagues (1986). This type of plot characterizes the relationship between the magnitude of estimates and their precision. Vandenbroucke suggested the possibility of publication bias only in reference to the studies of men. Bero and colleagues (1994) concluded that there

had not been a publication bias against studies with statistically significant findings, nor against the publication of studies with nonsignificant or mixed findings in the research literature. The researchers were able to identify only five unpublished "negative" studies, of which two were dissertations that tend to be delayed in publication. A subsequent study by Misakian and Bero (1998) did find a delay in the publication of studies with nonsignificant results in comparison with studies having significant results; whether this pattern has varied over the several decades of research on secondhand smoke was not addressed. More recently, Copas and Shi (2000) assessed the 37 studies considered in the meta-analysis by Hackshaw and colleagues (1997) for publication bias. Copas and Shi (2000) found a significant correlation between the estimated risk of exposure and sample size, such that smaller studies tended to have higher values. This pattern suggests the possibility of publication bias. However, using a funnel plot of the same studies, Lubin (1999) found little evidence for publication bias.

On this issue of publication bias, it is critical to distinguish between indirect statistical arguments and arguments based on actual identification of previously unidentified research. The strongest case against substantive publication bias has been made by researchers who mounted intensive efforts to find the possibly missing studies; these efforts have yielded little—nothing that would alter published conclusions (Bero et al. 1994; Glantz 2000). Presumably because this exposure is a great public health concern, the findings of studies that do not have statistically significant outcomes continue to be published (Kawachi and Colditz 1996).

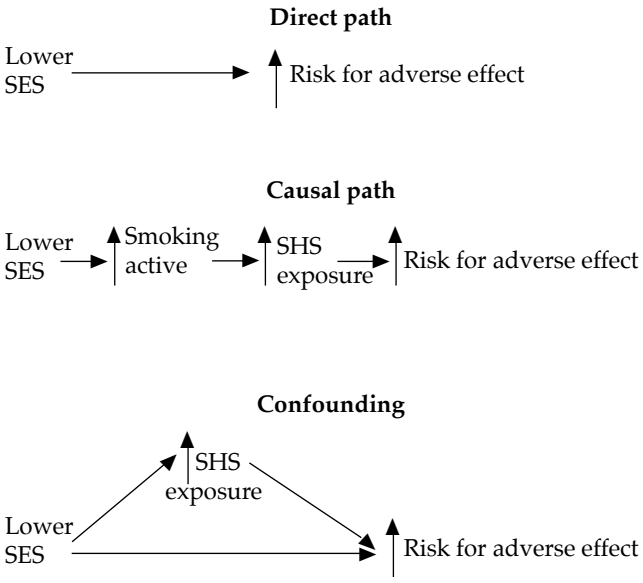
The quantitative results of the meta-analyses, however, were not determinate in making causal inferences in this Surgeon General's report. In particular, the level of statistical significance of estimates from the meta-analyses was not a predominant factor in making a causal conclusion. For that purpose, this report relied on the approach and criteria set out in the 1964 and 2004 reports of the Surgeon General, which involved judgments based on an array of quantitative and qualitative considerations that included the degree of heterogeneity in the designs of the studies that were examined. Sometimes this heterogeneity limits the inference from meta-analysis by weakening the rationale for pooling the study results. However, the availability of consistent evidence from heterogenous designs can strengthen the meta-analytic findings by making it unlikely that a common bias could persist across different study designs and populations.

Confounding

Confounding, which refers in this context to the mixing of the effect of another factor with that of secondhand smoke, has been proposed as an explanation for associations of secondhand smoke with adverse health consequences. Confounding occurs when the factor of interest (secondhand smoke) is associated in the data under consideration with another factor (the confounder) that, by itself, increases the risk for the disease (Rothman and Greenland 1998). Correlates of secondhand smoke exposures are not confounding factors unless an exposure to them increases the risk of disease. A factor proposed as a potential confounder is not necessarily an actual confounder unless it fulfills the two elements of the definition. Although lengthy lists of potential confounding factors have been offered as alternatives to direct associations of secondhand smoke exposures with the risk for disease, the factors on these lists generally have not been shown to be confounding in the particular data of interest.

The term confounding also conveys an implicit conceptualization as to the causal pathways that link secondhand smoke and the confounding factor to

Figure 1.2 Model for socioeconomic status (SES) and secondhand smoke (SHS) exposure



Arrows indicate directionality of association.

disease risk. Confounding implies that the confounding factor has an effect on risk that is independent of secondhand smoke exposure. Some factors considered as potential confounders may, however, be in the same causal pathway as a secondhand smoke exposure. Although socioeconomic status (SES) is often cited as a potential confounding factor, it may not have an independent effect but can affect disease risk through its association with secondhand smoke exposure (Figure 1.2). This figure shows general alternative relationships among SES, secondhand smoke exposure, and risk for an adverse effect. SES may have a direct effect, or it may indirectly exert its effect through an association with secondhand smoke exposure, or it may confound the relationship between secondhand smoke exposure and disease risk. To control for SES as a potential confounding factor without considering underlying relationships may lead to incorrect risk estimates. For example, controlling for SES would not be appropriate if it is a determinant of secondhand smoke exposure but has no direct effect.

Nonetheless, because the health effects of involuntary smoking have other causes, the possibility of confounding needs careful exploration when assessing associations of secondhand smoke exposure with adverse health effects. In addition, survey data from the last several decades show that secondhand smoke exposure is associated with correlates of lifestyle that may influence the risk for some health effects, thus increasing concerns for the possibility of confounding (Kawachi and Colditz 1996). Survey data from the United States (Matanoski et al. 1995) and the United Kingdom (Thornton et al. 1994) show that adults with secondhand smoke exposures generally tend to have less healthful lifestyles. However, the extent to which these patterns of association can be generalized, either to other countries or to the past, is uncertain.

The potential bias from confounding varies with the association of the confounder to secondhand smoke exposures in a particular study and to the strength of the confounder as a risk factor. The importance of confounding to the interpretation of evidence depends further on the magnitude of the effect of secondhand smoke on disease. As the strength of an association lessens, confounding as an alternative explanation for an association becomes an increasing concern. In prior reviews, confounding has been addressed either quantitatively (Hackshaw et al. 1997) or qualitatively (Cal/EPA 1997; Thun et al. 1999). In the chapters in this report that focus on specific diseases, confounding is specifically addressed in the context of potential confounding factors for the particular diseases.

Tobacco Industry Activities

The evidence on secondhand smoke and disease risk, given the public health and public policy implications, has been reviewed extensively in the published peer-reviewed literature and in evaluations by a number of expert panels. In addition, the evidence has been criticized repeatedly by the tobacco industry and its consultants in venues that have included the peer-reviewed literature, public meetings and hearings, and scientific symposia that included symposia sponsored by the industry. Open criticism in the peer-reviewed literature can strengthen the credibility of scientific evidence by challenging researchers to consider the arguments proposed by critics and to rebut them.

Industry documents indicate that the tobacco industry has engaged in widespread activities, however, that have gone beyond the bounds of accepted scientific practice (Glantz 1996; Ong and Glantz 2000, 2001; Rampton and Stauber 2000; Yach and Bialous 2001; Hong and Bero 2002; Diethelm et al. 2004). Through a variety of organized tactics, the industry has attempted to undermine the credibility of the scientific evidence on secondhand smoke. The industry has funded or carried out research that has been judged to be biased, supported scientists to generate letters to editors that criticized research publications, attempted to undermine the findings of key studies, assisted in establishing a scientific society with a journal, and attempted to sustain controversy even as the scientific community reached consensus (Garne et al. 2005). These tactics are not a topic of this report, but to the extent that the scientific literature has been distorted, they are addressed as the evidence is reviewed. This report does not specifically identify tobacco industry sponsorship of publications unless that information is relevant to the interpretation of the findings and conclusions.

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Chapter 2
Toxicology of Secondhand Smoke

Introduction

A full range of scientific evidence, extending from the molecular level to whole populations, supports the conclusion that secondhand smoke causes disease. The scope of this evidence is enormous, and encompasses not only the literature on secondhand smoke but also relevant findings on active smoking and on the toxicity of individual tobacco smoke components. The 2004 report of the Surgeon General provides reviews on biologic considerations in relation to active smoking (U.S. Department of Health and Human Services [USDHHS] 2004). The guidelines for causal inference include coherence, which is defined as the extent to which all lines of scientific evidence converge in support of a causal conclusion. Beginning with the 1964 Surgeon General's report on smoking and health (U.S. Department of Health, Education, and Welfare [USDHEW] 1964), reports in this series have comprehensively evaluated the full scope of evidence supporting causal inference with regard to particular associations of smoking with disease. This chapter reviews the evidence relevant to coherence, and includes the mechanisms relevant to the pathogenesis of diseases caused by secondhand smoke.

Studies reviewed for this chapter were selected from Medline and SciFinder literature searches. Search terms included "carcinogens," "environmental tobacco smoke," "DNA adducts," "protein adducts," "urinary metabolites," "tobacco smoke," and the names of specific carcinogens and their metabolites. Recent reviews and cited references in recent papers provided additional sources for this chapter.

This chapter sets out a foundation for interpreting the observational evidence that is the focus of most of the following chapters. The discussion that follows details the mechanisms that enable tobacco smoke components to injure the respiratory tract and cardiovascular system and to cause nonmalignant and malignant diseases and other adverse effects.

Composition of Tobacco Smoke

The chemical and physical properties of tobacco smoke from mainstream (drawn through the cigarette) and sidestream (released by the smoldering cigarette) smoke have been reviewed in a number of publications (Jenkins et al. 2000; Hoffmann et al. 2001; International Agency for Research on Cancer [IARC] 2004; California Environmental Protection Agency [Cal/EPA] 2005). The IARC (2004) review indicates that some 4,000 mainstream tobacco smoke compounds have been identified (Roberts 1988), and the qualitative composition of the components is nearly identical in mainstream smoke, sidestream smoke, and secondhand smoke. An assessment by the National Research Council (1986) of differences in the composition of mainstream and sidestream smoke indicates that some compounds are emitted at levels up to more than 10 times greater in sidestream smoke compared with mainstream smoke (see also Table III-1 in Cal/EPA 2005). The Cal/EPA (2005) report identified 19 gas-phase and 21 particulate matter compounds in sidestream smoke with known carcinogenic and noncarcinogenic health effects (e.g., pulmonary edema, immune alterations, cardiac arrthythmias, and hepatotoxic and neurologic effects). The National Toxicology Program (USDHHS 2000) estimates that at least 250 chemicals in secondhand smoke are known to be toxic or carcinogenic. Other published reports have additional listings of specific chemical compounds in mainstream and secondhand smoke (Fowles and Dybing 2003; Cal/EPA 2005).

Evidence of Carcinogenic Effects from Secondhand Smoke Exposure

Carcinogens in Sidestream Smoke and Secondhand Smoke

As a result of advances in chemical analytical techniques and an expanded understanding of the mechanisms by which environmental agents are genotoxic, the number of known carcinogens in tobacco smoke increased to 69 in the year 2000 (IARC 2004). Table 2.1 summarizes representative levels of carcinogens found in sidestream and secondhand cigarette smoke, but includes only 30 compounds that have been evaluated by IARC and that have fulfilled certain other criteria: sufficient evidence of carcinogenicity in either laboratory animals or humans and published data on levels found in sidestream or secondhand smoke. Field studies on the carcinogenic composition of secondhand smoke cannot comprehensively evaluate all of the potential carcinogens in secondhand smoke. Some tobacco smoke carcinogens that IARC evaluated were not included in Table 2.1 because there were no published data on their levels in sidestream or secondhand cigarette smoke (Hoffmann et al. 2001). It is likely, however, that these carcinogens (which include some polycyclic aromatic hydrocarbons [PAHs], heterocycles, heterocyclic aromatic amines, nitro compounds, and other miscellaneous organic compounds) are also present in sidestream and secondhand smoke. In addition, there may be carcinogens present that IARC has not yet fully characterized or evaluated.

PAHs are a diverse group of compounds formed in the incomplete combustion of organic material, and are potent, locally acting carcinogens in laboratory animals. PAHs induce tumors of the upper respiratory tract and lung when inhaled, instilled in the trachea, implanted in the lung, or administered by other routes (Shimkin and Stoner 1975), and are found in tobacco smoke, broiled foods, and polluted environments of various types. The best known member of this class of compounds is benzo[*a*]pyrene (B[*a*]P), which induces tumors of the upper respiratory tract and lung when inhaled, instilled in the trachea, implanted in the lung, or administered intraperitoneally, intravenously, subcutaneously, or by other routes (Shimkin and Stoner 1975). When administered systemically, B[*a*]P causes lung tumors in mice but not in rats (IARC 1973, 1983; Culp et al. 1998). Workers in iron and steel foundries and aluminum and coke production plants are exposed to PAHs. These exposures are considered to be a cause of excess cancers among workers in these settings (IARC 1983, 1984).

N-Nitrosamines are a large group of carcinogens that induce cancer in a wide variety of species and tissues and are presumed to cause cancer in humans (Preussmann and Stewart 1984). These carcinogens can be formed endogenously from amines and nitrogen oxides and are found at low levels in foods (Bartsch and Spiegelhalder 1996). Tobacco smoke contains volatile *N*-nitrosamines such as *N*-nitrosodimethylamine and *N*-nitrosopyrrolidine, as well as tobacco-specific *N*-nitrosamines such as *N'*-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (Hoffmann and Hecht 1990). Tobacco-specific *N*-nitrosamines are chemically related to nicotine and other tobacco alkaloids and are therefore found only in tobacco products or related materials (Hecht and Hoffmann 1988). In laboratory animals, many *N*-nitrosamines are powerful carcinogens that display a striking organospecificity and affect particular tissues often independently of the route of administration (Preussmann and Stewart 1984). For example, NNN causes tumors of the esophagus and nasal cavity in rats, while the principal target of NNK in rodents is the lung; NNK is the only tobacco smoke carcinogen that induces lung tumors by systemic administration in all three commonly used rodent models—rat, mouse, and hamster (Hecht 1998).

Among the aromatic amines first identified as carcinogens in dye industrial exposures, 2-naphthylamine and 4-aminobiphenyl are well-established human bladder carcinogens (IARC 1973, 1974). These carcinogens are also found in tobacco smoke. Aromatic amines cause tumors at a variety of sites in laboratory animals. Some members of this class, such as 2-toluidine, are only weakly carcinogenic (Garner et al. 1984).

Formaldehyde and acetaldehyde, weaker carcinogens than PAHs, *N*-nitrosamines, and aromatic amines, have been measured in sidestream and secondhand smoke. When inhaled, formaldehyde and acetaldehyde induce respiratory tract tumors in rodents (Kerns et al. 1983; IARC 1999). Butadiene and benzene are volatile hydrocarbons that also occur in considerable quantities in sidestream and secondhand smoke. Butadiene is a multiorgan carcinogen that is particularly potent in mice; benzene causes leukemia

Table 2.1 Levels of carcinogens in sidestream and secondhand cigarette smoke

Carcinogen	Representative amounts		Study
	Sidestream (per cigarette)	Secondhand (per cubic meter [m^3])	
Polycyclic aromatic hydrocarbons			
Benz[*a*]anthracene	201 nanograms (ng)	0.32–1.7 ng	Grimmer et al. 1987; Chuang et al. 1991
Benzo[*a*]pyrene	45–103 ng	0.37–1.7 ng	Adams et al. 1987; Grimmer et al. 1987; Chuang et al. 1991
Benzo[*b*]fluoranthene Benzo[*j*]fluoranthene Benzo[*k*]fluoranthene	196 ng	0.79–2.0 ng	Grimmer et al. 1987; Chuang et al. 1991
Dibenz[*a,h*]anthracene	NR*	1 ng	Vu-Duc and Huynh 1989
Indeno[1,2,3-*cd*]pyrene	51 ng	0.35–1.1 ng	Grimmer et al. 1987; Chuang et al. 1991
5-Methylchrysene	NR	35.5 ng	Vu-Duc and Huynh 1989
***N*-Nitrosamines**			
N-Nitrosodiethanolamine	43 ng	NR	Brunnemann and Hoffmann 1981
N-Nitrosodiethylamine	8.2–73 ng	0–20 ng	Brunnemann et al. 1977; Hoffmann et al. 1987
N-Nitrosodimethylamine	143–1,040 ng	4–240 ng	Brunnemann et al. 1977; Hoffmann et al. 1987; Klus et al. 1992
N-Nitrosoethylmethylamine	3–35 ng	NR	Brunnemann et al. 1977; Hoffmann et al. 1987
N′-Nitrosonornicotine	110–857 ng	0.7–23 ng	Brunnemann et al. 1983, 1992; Adams et al. 1987; Klus et al. 1992
N-Nitrosopiperidine	4.8–19.8 ng	NR	Adams et al. 1987
N-Nitrosopyrrolidine	7–700 ng	3.5–27.0 ng	Brunnemann et al. 1977; Hoffmann et al. 1987; Klus et al. 1992; Mahanama and Daisey 1996
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone	201–1,440 ng	0.2–29.3 ng	Brunnemann et al. 1983, 1992; Adams et al. 1987; Klus et al. 1992
Aromatic amines			
2-Naphthylamine	63.1–128 ng	NR	Government of British Columbia Ministry of Health Services 2001
2-Toluidine	3,030 ng	NR	Patrianakos and Hoffmann 1979
4-Aminobiphenyl	11.4–18.8 ng	NR	Government of British Columbia Ministry of Health Services 2001
Aldehydes			
Acetaldehyde	961–1,820 micrograms (μg)	268 μg	Martin et al. 1997; Government of British Columbia Ministry of Health Services 2001
Formaldehyde	233–485 μg	143 μg	Martin et al. 1997; Government of British Columbia Ministry of Health Services 2001

Table 2.1 Continued

Carcinogen	Representative amounts: Sidestream (per cigarette)	Representative amounts: Secondhand (per cubic meter [m^3])	Study
Miscellaneous organics			
Acrylonitrile	42–109 μg	NR	Government of British Columbia Ministry of Health Services 2001
Benzene	163–353 μg	4.2–63.7 μg	Scherer et al. 1995; Heavner et al. 1996; Martin et al. 1997; Government of British Columbia Ministry of Health Services 2001; Kim et al. 2001
Catechol	98–292 μg	1.24 μg	Sakuma et al. 1983; Martin et al. 1997; Government of British Columbia Ministry of Health Services 2001
Isoprene	668–1,260 μg	657 μg	Martin et al. 1997; Government of British Columbia Ministry of Health Services 2001
1,3-Butadiene	98–205 μg	0.3–40 μg	Heavner et al. 1996; Martin et al. 1997; Government of British Columbia Ministry of Health Services 2001; Kim et al. 2001
Inorganic compounds			
Cadmium	330–689 ng	4–38 ng	Wu et al. 1995; Government of British Columbia Ministry of Health Services 2001
Chromium	57–79 ng	NR	Government of British Columbia Ministry of Health Services 2001
Hydrazine	94 ng	NR	Liu et al. 1974
Lead	28.9–46.6 ng	NR	Government of British Columbia Ministry of Health Services 2001
Nickel	51 ng	NR	Government of British Columbia Ministry of Health Services 2001
Polonium-210	0.091–0.139 picocurie	NR	Ferri and Baratta 1966

*NR = Data were not reported.
Source: Adapted from Hoffmann et al. 2001.

in humans (IARC 1982, 1992, 1999). Metals such as nickel, chromium, and cadmium are human carcinogens that are also present in sidestream smoke (IARC 1990, 1994).

Mainstream cigarette smoke consists of a gas phase and a particulate phase specifically composed of several million semiliquid particles per cubic centimeter (cm^3) within a mixture of combustion gases (Ingebrethsen 1986; Guerin et al. 1992). Sidestream smoke contains free radicals in about the same concentrations as does mainstream smoke (Pryor et al. 1983). Pryor and colleagues (1998) detected reactive yet long-lived radicals in the gas phase; in the particulate phase, these investigators found a free

radical system that is a mixture of semiquinones, hydroquinones, and quinones (Pryor et al. 1998). Whether such agents can induce tumors in laboratory animals is not known.

Carcinogenicity of Sidestream Smoke and Secondhand Smoke

Numerous studies have demonstrated that mainstream cigarette smoke condensate, the solid materials in the smoke, induces tumors on mouse skin and, by implantation, in rat lungs (IARC 1986, 2004). Inhalation experiments with mainstream smoke have demonstrated that cigarette smoke and its particulate phase induce preneoplastic lesions and benign and malignant tumors of the larynx in Syrian golden hamsters (IARC 1986). Studies with rats and mice documented less consistent results (IARC 1986, 2004; Hecht 1999).

The carcinogenicity of sidestream smoke has been less extensively investigated. Sidestream smoke condensate was significantly more carcinogenic than mainstream smoke condensate when tested on mouse skin: mice treated with sidestream smoke developed two to six times more skin tumors than mice treated with mainstream smoke (Mohtashamipur et al. 1990). In a rat model using implanted sidestream smoke particles, a fraction containing PAHs with four or more rings produced tumors, while a fraction with semivolatiles and a PAH fraction with fewer rings had little effect (Grimmer et al. 1988). Limited histopathologic changes were observed in rats exposed to cigarette sidestream smoke aged in the chamber for 12 months (Haussmann et al. 1998). Researchers have carried out a series of investigations on the effects of secondhand smoke inhalation in A/J mice (Witschi et al. 1995, 1997a,b,c, 1998, 1999, 2000; Witschi 1998, 2000). Table 2.2 summarizes the data from these studies. Lung tumor multiplicity, the most sensitive indicator of response in this model, increased significantly in all experiments, and lung tumor incidence increased in several experiments. The protocol involved exposing mice to secondhand smoke (89 percent sidestream smoke and 11 percent mainstream smoke) for five months followed by a four-month recovery period in air. Other experiments have demonstrated that to observe an increase in lung tumor multiplicity, there must be a recovery period. These same experiments also showed that the response is due to a gas-phase component of secondhand smoke.

Table 2.2 Inhalation studies of secondhand smoke (89% sidestream smoke and 11% mainstream smoke) in A/J mice

Study	Exposure (mg/m^3* of total suspended particulates)	Lung tumor multiplicity†		Lung tumor incidence‡	
		Filtered air control	Smoke	Filtered air control (%)	Smoke (%)
Witschi et al. 1997a	79	0.5 ± 0.1 (24)	1.3 ± 0.3 (26)§	42	58
Witschi et al. 1997b	87	0.5 ± 0.2 (24)	1.4 ± 0.2 (24)§	38	83§
Witschi et al. 1998	83	0.9 ± 0.2 (29)	1.3 ± 0.2 (33)§	69	73
Witschi et al. 1999	132	0.6 ± 0.1 (30)	2.1 ± 0.3 (38)§	50	86Δ
Witschi et al. 2000	137	0.9 ± 0.2 (30)	2.8 ± 0.2 (38)§	60	100Δ
	137	1.0 ± 0.1 (54)	2.4 ± 0.3 (28)§	65	89Δ
Witschi et al., unpublished data	134	1.2 ± 0.2 (25)	2.3 ± 0.3 (26)§	60	88Δ

*mg/m^3 = Milligrams per cubic meter.
†Mean ± standard error (number of animals is in parentheses).
‡Percentage of all animals at risk that had tumors.
§Significantly different ($p < 0.05$) compared with air controls by Welsh's alternate test.
ΔSignificantly different ($p < 0.05$) compared with air controls by Fisher's exact test.
Source: Adapted from Witschi 2000.

Although these results are of interest, there are some poorly understood features of the model. The animals lose weight during exposure and never weigh as much as the air-treated controls even after the recovery period. The consequences of the weight loss are unknown. The reason for the recovery period requirement also is not clear. In addition, the apparent tumor-inducing effect of the gas phase is inconsistent with most of the earlier work on mainstream smoke inhalation and with the tumor-inducing properties of sidestream smoke condensate described above. Finally, recent data from De Flora and colleagues (2003) somewhat contradict the observations of Witschi and colleagues (1995, 1997a,b,c, 1998, 1999, 2000). De Flora and colleagues (2003) exposed Swiss strain mice to environmental tobacco smoke continuously for a period of nine months without a recovery period and observed a significant increase in the lung tumor response.

Collectively, these studies suggest the potential involvement of multiple carcinogens from sidestream and secondhand cigarette smoke in tumor induction. The results of the implanted mouse skin and rat lung carcinogenicity assays demonstrate the importance of PAHs and other nonvolatile carcinogens. Moreover, sidestream and secondhand smoke contain potent lung carcinogens such as NNK. The results of the mouse inhalation studies indicate that gas-phase constituents of secondhand smoke contribute to tumorigenesis. Prominent among these constituents could be formaldehyde, acetaldehyde, butadiene, and benzene because of their tumorigenic activities and relatively high concentrations in secondhand smoke.

Human Carcinogen Uptake from Secondhand Smoke

Tables 2.3 and 2.4 summarize data from biomarker studies on human uptake of specific secondhand smoke carcinogens. These studies demonstrate that human exposures to secondhand smoke lead to the uptake of carcinogens, a topic that Scherer and Richter (1997) have reviewed.

trans,*trans*-Muconic acid is a urinary metabolite of benzene, a known cause of leukemia, that has been widely used to estimate benzene uptake (Scherer et al. 1998). Studies on the relationship of this metabolite to secondhand smoke exposure have documented mixed results, with some studies showing somewhat higher levels in persons exposed to secondhand smoke while others found no effect (Scherer et al. 1995, 1999; Weaver et al. 1996; Yu and Weisel 1996; Ruppert et al. 1997; Carrer et al. 2000). The interpretation of these findings is complicated by differences in excretion rates among participants and by contributions from sources other than benzene, such as sorbate in food, to levels of this metabolite in urine (Yu and Weisel 1996; Ruppert et al. 1997; Scherer and Richter 1997). Benzene itself can be quantified in exhaled breath. Breath measurements of nonsmokers who reported secondhand smoke exposures at work from smokers showed elevated benzene levels, but nonsmokers living with smokers did not have increased levels (Wallace et al. 1987). A second study detected higher levels of exhaled benzene in nonsmokers living with smokers compared with nonsmokers living with nonsmokers (Scherer et al. 1995). Another study documented no difference in levels of exhaled benzene among children living with smokers compared with children living with nonsmokers (Scherer et al. 1999). Collectively, the biomarker data discussed here indicate that benzene uptake in humans is not consistently found to be associated with secondhand smoke exposure, but there are other sources of benzene exposure that complicate efforts to estimate the contribution of secondhand smoke to biomarker levels.

Several methods have been used to estimate PAH uptake by persons exposed to secondhand smoke. 1-Hydroxypyrene and hydroxyphenanthrene are urinary metabolites of pyrene and phenanthrene, respectively. These metabolites are widely used as biomarkers of PAH uptake although the parent compounds, pyrene and phenanthrene, are noncarcinogenic. Exposure to secondhand smoke does not increase 1-hydroxypyrene and hydroxyphenanthrene levels in urine (Hoepfner et al. 1987; Scherer et al. 1992, 2000; Van Rooij et al. 1994; Siwińska et al. 1999). Other factors such as smoking, occupational exposures, and diet are significant contributors to urinary levels of these compounds. Metabolites of B[*a*]P and other PAHs form covalent binding products (adducts) with hemoglobin and serum albumin and have been measured using a variety of methods, including immunoassay and gas chromatography–mass spectrometry (GC–MS). Studies of adduct formation with hemoglobin and albumin have given mixed results. Using an enzyme-linked immunosorbent technique, one group found increased levels of PAH-albumin adducts in children exposed to secondhand smoke (Crawford et al. 1994; Tang et al. 1999), but two other studies did not find increments in these levels (Autrup et al. 1995; Nielsen et al. 1996). Using GC–MS as the detection method, researchers found no effect of secondhand smoke exposure on B[*a*]P albumin and hemoglobin adducts (Scherer et al. 2000). Thus, the evidence that

Table 2.3 Representative biomarker studies of carcinogens in persons exposed to secondhand smoke

Carcinogen	Exposure data (if reported)	Biomarker levels		Exposed vs. unexposed: significant difference?	Study
Benzene	11.5 μg/m³*, personal exposure (nonsmokers, nonsmoking homes, n = 39)	tt-MA†	92 μg/g creatinine	No	Scherer et al. 1995
	13.6 μg/m³ (nonsmokers, smoking homes, n = 43)		126 μg/g creatinine		
Benzene	NR‡	tt-MA	3.84 ± 1.6 ng/μL§ in 53 secondhand smoke-exposed children 4.02 ± 1.1 ng/μL in 26 unexposed children	No	Weaver et al. 1996
			3.5 ± 1.4 ng/μL when urinary cotinine ≤44 ng/mL△ (n = 39) 4.32 ± 1.4 ng/μL when urinary cotinine >44 ng/mL (n = 39)	Yes	
Benzene	<0.19–22 μg/m³, personal exposure, 5 females exposed to secondhand smoke	tt-MA	34–74 μg excreted on nonexposure days	Yes	Yu and Weisel 1996
			42–95 μg excreted on exposure days		
Benzene	2–100 μg/m³, personal exposure (n = 69 nonsmokers from smoking and nonsmoking households)	tt-MA was not correlated with benzene; marginal difference in tt-MA of nonsmokers from smoking homes vs. those from nonsmoking homes		No	Ruppert et al. 1997
Benzene	11.5 μg/m³, personal exposure (children, smoking homes, n = 24)	tt-MA	130 μg/g creatinine	No	Scherer et al. 1999
	19.7 μg/m³ (children, nonsmoking homes, n = 15)		112 μg/g creatinine		
Benzene (geometric means)	16.5 ± 2.3 μg/m³, personal exposure (nonsmokers, no secondhand smoke, n = 42)	tt-MA	38.9 ± 2.4 μg/L	Yes	Carrer et al. 2000
	25.4 ± 2.9 μg/m³ (nonsmokers, secondhand smoke, n = 27)		54.7 ± 2.9 μg/L		

Table 2.3 Continued

Carcinogen	Exposure data (if reported)	Biomarker levels	Exposed vs. unexposed: significant difference?	Study
NNK[¶]	75–263 ng/m^3 in a 16 m^3 room	Significantly increased levels of NNAL[**] plus NNAL-Gluc[††] in urine of 5 men after secondhand smoke exposure	Yes	Hecht et al. 1993
NNK	NR	Significantly increased levels of NNAL-Gluc in hospital workers (n = 9) exposed to secondhand smoke compared with controls	Yes	Parsons et al. 1998
NNK	2.4–50 ng/m^3 in 19 rooms where smoking took place	NNAL plus NNAL-Gluc levels correlated with nicotine on personal sampler in secondhand smoke-exposed persons	Yes	Meger et al. 2000
NNK	NR	NNAL plus NNAL-Gluc levels were significantly higher in women (n = 23) who lived with male smokers compared with women (n = 22) who lived with male nonsmokers	Yes	Anderson et al. 2001
NNK	NR	34% of 204 children with cotinine >5 ng/mL urine; 52/54 of these samples had detectable NNAL plus NNAL-Gluc; NNAL plus NNAL-Gluc levels were significantly higher in secondhand smoke-exposed vs. unexposed children	Yes	Hecht et al. 2001
Polycyclic aromatic hydrocarbons (PAHs)	NR	5 nonsmokers exposed to secondhand smoke from 100 cigarettes (100–180 μg/m^3 cotinine in the room) over an 8-hour period; no effect on urinary hydroxyphenanthrenes	No	Hoepfner et al. 1987
PAHs	Benzo[*a*]pyrene (B[*a*]P), 21.5 ng/m^3; phenanthrene, 6.8 ng/m^3; pyrene, 17.6 ng/m^3 in an experimental room with 5 smokers and 5 nonsmokers	No effects on urinary hydroxyphenanthrenes (2.0 vs. 2.2 μg/24 hours before and after secondhand smoke exposure); no effects on urinary 1-HOP[‡‡] (0.24 μg/24 hours before and after secondhand smoke exposure); no effects on ^{32}P-postlabeling of DNA adducts	No	Scherer et al. 1992
PAHs	NR	No differences in PAH-albumin levels in umbilical cord blood from women exposed to secondhand smoke (n = 49) vs. unexposed women (n = 54)	No	Autrup et al. 1995
PAHs	NR	No effect of secondhand smoke on PAH-albumin adduct levels in 73 persons from Aarhus, Denmark	No	Nielsen et al. 1996

Table 2.3 Continued

Carcinogen	Exposure data (if reported)	Biomarker levels	Exposed vs. unexposed: significant difference?	Study
PAHs	NR	No difference in urinary 1-HOP levels of children exposed to secondhand smoke from their parents' smoking (n = 286) vs. unexposed children (n = 126)	No	Siwińska et al. 1999
PAHs	NR	1-HOP: 0.140 μg/24 hours in 19 secondhand smoke-exposed persons (urinary cotinine 12.3 μg/24 hours) vs. 0.171 μg/24 hours in 23 unexposed persons (urinary cotinine 2.3 μg/24 hours)	NR	Scherer et al. 2000
		B[*a*]P-hemoglobin (Hb) adducts: 0.049 fmol/mg[§§] Hb in secondhand smoke-exposed persons vs. 0.083 fmol/mg Hb in unexposed persons (same persons as above)	No	
		B[*a*]P-albumin adducts: 0.021 fmol/mg albumin in secondhand smoke-exposed persons vs. 0.019 fmol/mg albumin in unexposed persons (same persons as above)	NR	
PAH and 4-aminobiphenyl	NR	Significantly higher levels of 4-aminobiphenyl–Hb adducts and PAH-albumin adducts in children whose mothers smoked (n = 23 for 4-aminobiphenyl Hb, n = 44 for PAH albumin) compared with unexposed children (n = 10 for 4-aminobiphenyl Hb, n = 24 for PAH albumin)	Yes	Tang et al. 1999
4-Aminobiphenyl	Estimated weekly average nicotine concentration ranged from <0.5 to ≥2.0 μg/m^3	Higher 4-aminobiphenyl–Hb adducts (27.8 pg/g[ΔΔ] Hb) in 9 pregnant women with >2.0 μg/m^3 nicotine (personal exposure) than in pregnant women with 0.5–1.9 μg/m^3 (n = 20, 20.8 pg/g Hb) or in pregnant women with <0.5 μg/m^3 (n = 7, 17.6 pg/g Hb)	Yes	Hammond et al. 1993
4-Aminobiphenyl and other aromatic amines	NR	No relationship of aromatic amine-Hb adducts to reported secondhand smoke exposure or cotinine/creatinine ratios in 73 pregnant women	No	Branner et al. 1998

Table 2.3 Continued

Carcinogen	Exposure data (if reported)	Biomarker levels	Exposed vs. unexposed: significant difference?	Study
4-Aminobiphenyl and other aromatic amines	NR	No increase in aromatic amine-Hb adducts among 224 children with increased exposures to secondhand smoke; exposures were confirmed by cotinine testing	No	Richter et al. 2001
Unknown	NR	No effects of secondhand smoke exposure on ^{32}P-postlabeled DNA adducts in monocytes of 5 nonsmokers exposed for 8 hours	No	Holz et al. 1990
Unknown	5 nonsmokers exposed to secondhand smoke in an unventilated room, 4,091 $\mu g/m^3$ respirable suspended particles	A marginal, nonsignificant increase in urinary thioethers was observed	No	Scherer et al. 1992
Unknown	NR	No effect of secondhand smoke exposure on ^{32}P-postlabeled DNA adducts in women (n = 31 exposed, 11 unexposed)	No	Binková et al. 1995
Unknown	NR	No difference in urinary thioethers between persons exposed to low (n = 23) and high (n = 23) levels of secondhand smoke based on plasma cotinine; no difference in urinary thioethers between persons exposed to low (n = 20) and high (n = 19) levels of secondhand smoke exposures in the home	No	Scherer et al. 1996
Unknown	NR	No difference in placental levels of 8-OH-dG[¶¶] in 10 nonsmokers vs. 9 nonsmokers exposed to secondhand smoke, validated by plasma and urine cotinine; no effects of secondhand smoke on adducts were detected by ^{32}P-postlabeling	No	Daube et al. 1997
Unknown	NR	Significantly higher (63%) levels of 8-OH-dG in blood DNA of persons exposed to secondhand smoke in the workplace (n = 38) than in unexposed persons, verified by plasma cotinine (n = 36)	Yes	Howard et al. 1998b

Table 2.3 Continued

Carcinogen	Exposure data (if reported)	Biomarker levels	Exposed vs. unexposed: significant difference?	Study
Unknown	NR	No difference in 8-OH-dG levels in leukocytes of unexposed adults (n = 36), adults exposed 1–4 hours/day to secondhand smoke (n = 35), and adults exposed >4 hours/day (n = 21)	No	van Zeeland et al. 1999
Unknown	NR	Among 194 students in Athens and 77 persons in Halkida, Greece, ^{32}P-postlabeled DNA adducts in lymphocytes showed no relationship to secondhand smoke exposure in the entire group, but did correlate with secondhand smoke exposure measurements in winter in a subgroup living in the Halkida campus area	No/yes	Geordiadis et al. 2001

[*] $\mu g/m^3$ = Micrograms per cubic meter.
[†] tt-MA = *trans,trans*-Muconic acid.
[‡] NR = Data were not reported.
[§] ng/μL = Nanograms per microliter.
[Δ] mL = Milliliter.
[¶] NNK = 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone, a tobacco-specific *N*-nitrosamine.
[**] NNAL = 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol.
[††] NNAL-Gluc = A mixture of 4-(methylnitrosamino)-1-(3-pyridyl)-1-(*O*-β-D-glucopyranuronosyl) butane and 4-(methylnitrosamino)-1-(3-pyridyl-*N*-β-D-glucopyranuronosyl)-1-butanolonium inner salt.
[‡‡] 1-HOP = 1-Hydroxypyrene.
[§§] fmol/mg = Femtomoles per milligram.
[ΔΔ] pg/g = Picograms per gram.
[¶¶] 8-OH-dG = 8-Hydroxydeoxyguanosine.

secondhand smoke exposure significantly increases human uptake of PAHs is inconsistent.

Aromatic amines such as 4-aminobiphenyl form adducts with hemoglobin that GC–MS can quantify, but studies of the effects of secondhand smoke on 4-aminobiphenyl–hemoglobin adducts have provided mixed results. Hammond and colleagues (1993) demonstrated that adduct levels were elevated in pregnant women exposed to secondhand smoke. Maclure and colleagues (1989) observed slightly higher levels of 4-aminobiphenyl– and 3-aminobiphenyl–hemoglobin adducts in persons with confirmed secondhand smoke exposures compared with unexposed persons. 4-Aminobiphenyl–hemoglobin adducts were also elevated in children exposed to secondhand smoke (Tang et al. 1999). However, two other studies, including one of pregnant women, showed no consistent relationship between adduct levels and secondhand smoke exposures (Bartsch et al. 1990; Branner et al. 1998). A recent study of German children also showed no significant increase in aromatic amine–hemoglobin adduct levels with increased secondhand smoke exposures; in fact, there was a significant decrease in ortho- and meta-toluidine adducts (Richter et al. 2001). There is a background level of aromatic amine–hemoglobin adducts in apparently unexposed humans. The origin of this background is unknown, but it could be due in part to the uptake of corresponding nitro compounds from sources such as diesel emissions. Levels of aromatic amines in urine were unaffected by exposures to secondhand smoke in a study of nonsmokers (Grimmer et al. 2000).

Because tobacco-specific nitrosamines are found only in tobacco products or in related

Table 2.4 Relationship of specific biomarkers of carcinogen uptake to secondhand smoke exposure

Carcinogens in secondhand smoke	Biomarker	Association with secondhand smoke exposure	Study
Aromatic amines	Hemoglobin adducts	Mixed results	Maclure et al. 1989; Bartsch et al. 1990; Hammond et al. 1993; Branner et al. 1998; Tang et al. 1999; Richter et al. 2001
Benzene	*trans*,*trans*-Muconic acid in urine	Mixed results	Scherer et al. 1995, 1999; Weaver et al. 1996; Yu and Weisel 1996; Ruppert et al. 1997; Carrer et al. 2000
NNK*	NNAL† and NNAL-Gluc‡ in urine	Consistently increased	Hecht et al. 1993, 2001; Parsons et al. 1998; Meger et al. 2000; Anderson et al. 2001
NNK/NNN§	Hemoglobin adducts	None	Branner et al. 1998
PAHs∆	1-Hydroxypyrene in urine Hydroxyphenanthrenes in urine Albumin adducts Hemoglobin adducts	None in most studies	Scherer et al. 1992, 2000; Crawford et al. 1994; Van Rooij et al. 1994; Autrup et al. 1995; Nielsen et al. 1996; Siwińska et al. 1999; Tang et al. 1999

*NNK = 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone, a tobacco-specific *N*-nitrosamine.
†NNAL = 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol.
‡NNAL-Gluc = A mixture of 4-(methylnitrosamino)-1-(3-pyridyl)-1-(*O*-*β*-D-glucopyranuronosyl) butane and 4-(methylnitrosamino)-1-(3-pyridyl-*N*-*β*-D-glucopyranuronosyl)-1-butanolonium inner salt.
§NNN = *N*′-Nitrosonornicotine.
∆PAHs = Polycyclic aromatic hydrocarbons.
Source: Adapted from Scherer and Richter 1997.

nicotine-containing materials, their adducts or metabolites should be specific biomarkers of tobacco exposure. NNK- and NNN-hemoglobin adducts can be hydrolyzed to release 4-hydroxy-1-(3-pyridyl)-1-butanone (HPB), which GC–MS can then quantify. In smokers, levels of HPB-releasing hemoglobin adducts of NNK and NNN are low compared with hemoglobin adducts of several other carcinogens, possibly attributable to the high reactivity of the alkylating intermediate (Carmella et al. 1990; Hecht et al. 1994). Considering the relatively low levels of these adducts in smokers, nonsmokers exposed to secondhand smoke should not have significantly elevated amounts (Branner et al. 1998). However, urinary metabolites of NNK are readily measured in the urine of persons exposed to secondhand smoke. The metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronide conjugate (NNAL-Gluc) can be quantified using GC with thermal energy analyzer (TEA) nitrosamine-selective detection (GC-TEA) (Hecht et al. 1993, 2001; Parsons et al. 1998; Meger et al. 2000; Anderson et al. 2001). All studies reported to date show significantly higher amounts of NNAL plus NNAL-Gluc, or NNAL-Gluc alone, in the urine of secondhand smoke-exposed participants than in the urine of unexposed controls (Tables 2.3–2.5). In one study, the uptake of NNK was more than six times higher in women who lived with smokers compared with women who lived with nonsmokers (Anderson et al. 2001). The amount of NNAL plus NNAL-Gluc in these secondhand smoke-exposed women was about 5 percent as great as in their male partners who smoked. Another study found an uptake of NNK in a group of economically disadvantaged schoolchildren, and the range of levels varied approximately 90-fold (Hecht et al. 2001). Most of the studies demonstrate a correlation between levels of cotinine and NNAL plus NNAL-Gluc in urine (Figure 2.1). Cotinine is a

valid biomarker for nicotine uptake in nonsmokers exposed to secondhand smoke. Therefore, NNAL plus NNAL-Gluc is a biomarker for the uptake of the tobacco-specific lung carcinogen NNK in nonsmokers exposed to secondhand smoke. The NNAL plus NNAL-Gluc biomarker is more directly related to cancer risk than cotinine is because NNK (but not nicotine) is carcinogenic. The uptake of NNK by nonsmokers exposed to secondhand smoke thus provides a biochemical link between secondhand smoke exposure and lung cancer risk.

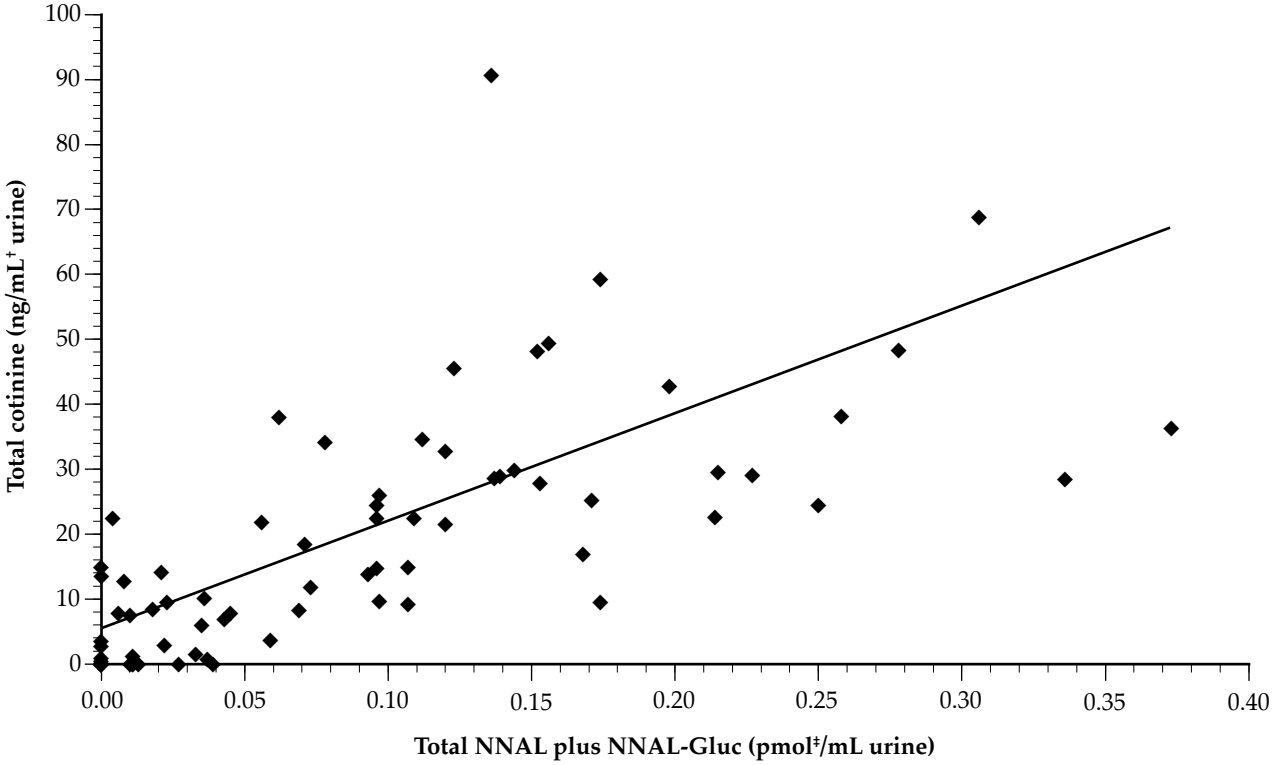
Studies of secondhand smoke exposure have also explored several other less specific markers. 8-Hydroxydeoxyguanosine (8-OH-dG) is a widely used biomarker of oxidative damage to DNA. Two studies observed no increase in 8-OH-dG levels in placentas and leukocytes of persons exposed to secondhand smoke compared with unexposed persons (Daube et al. 1997; van Zeeland et al. 1999). However, in a study of occupational exposure in Reno, Nevada, the average 8-OH-dG level in whole blood DNA of secondhand smoke-exposed workers was 63 percent higher than in unexposed persons; this finding represents a significant difference (Howard et al. 1998b). Urinary 3-ethyladenine is a biomarker of ethylating agents. In one study, exposure to secondhand smoke did not increase urinary concentrations of 3-ethyladenine (Kopplin et al. 1995). ^{32}P-postlabeling is a technique that can estimate levels of hydrophobic DNA adducts. Four investigations did not find effects of secondhand smoke exposure on levels of ^{32}P-postlabeled DNA (Holz et al. 1990; Scherer et al. 1992; Binková et al. 1995; Daube et al. 1997). However, a recent study conducted in Greece did find a relationship between secondhand smoke exposure and ^{32}P-postlabeled DNA adducts in lymphocytes from a subgroup (Georgiadis et al. 2001). Urinary thioethers are conjugates of carbonyl-containing mutagens. Thioethers did not significantly increase as a result of secondhand smoke exposure (Scherer et al. 1992, 1996). 3-Hydroxypropyl mercapturic acid, possibly from acrolein exposure, was identified as a possible secondhand smoke-related product in urine (Scherer et al. 1992). Studies investigating the effects

Table 2.5 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and NNAL-glucuronide (NNAL-Gluc*) in the urine of nonsmokers exposed to secondhand smoke

Study	Population	Analyte	Correlation with cotinine	Mean ± standard deviation pmol/mL[†] (number of samples analyzed)	Range[‡] (fold)
Hecht et al. 1993	Men exposed to secondhand smoke in a chamber	NNAL plus NNAL-Gluc	Yes	0.16 ± 0.10[§] (n = 7)	0.084–0.296 (4)
Parsons et al. 1998	Hospital workers	NNAL-Gluc	Yes	0.059 ± 0.028 (n = 27)	0.005–0.11 (22)
Meger et al. 2000	Nonsmokers exposed to secondhand smoke	NNAL plus NNAL-Gluc	Yes	0.043 ± 0.044[‡] (n = 16)	0.0038–0.148 (39)
Anderson et al. 2001	Women married to smokers	NNAL plus NNAL-Gluc	No	0.050 ± 0.068 (n = 23)	0.009–0.28 (31)
Hecht et al. 2001	Elementary school-age children	NNAL plus NNAL-Gluc	Yes	0.056 ± 0.076 (n = 74)	0.004–0.373 (93)

*NNAL-Gluc = A mixture of 4-(methylnitrosamino)-1-(3-pyridyl)-1-(*O*-*β*-D-glucopyranuronosyl) butane and 4-(methylnitrosamino)-1-(3-pyridyl-*N*-*β*-D-glucopyranuronosyl)-1-butanolonium inner salt.
[†]pmol/mL = Picomoles per milliliter.
[‡]Detected values only.
[§]Approximate, based on the assumption of 1,200 mL of urine excreted per day.
Source: Meger et al. 2000.

Figure 2.1 The correlation between levels of cotinine plus cotinine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) plus NNAL-glucuronide (NNAL-Gluc) conjugates in the urine of 74 school-age children exposed to secondhand smoke*



*r = 0.71; p <0.001.
†ng/mL = Nanograms per milliliter.
‡pmol = Picomoles.
Source: Hecht et al. 2001. Reprinted with permission.

of secondhand smoke on urinary mutagenicity have demonstrated conflicting results (Scherer et al. 1992; Scherer and Richter 1997). In general, there seem to be small and sometimes significant effects of secondhand smoke exposure on urinary mutagenicity when diet is controlled (Scherer et al. 1996; Smith et al. 2000a). In a recent study of 1,249 Italian women whose husbands smoked, there was an inverse dose-response relationship between the intensity of the secondhand smoke and concentrations of plasma beta-carotene and L-ascorbic acid found in the women. There also was a significant inverse association between urinary cotinine and plasma beta-carotene (Farchi et al. 2001).

Mechanisms of Carcinogenesis of Secondhand Smoke

Figure 2.2 presents a framework for considering mechanisms of secondhand smoke carcinogenesis. An analogous scheme proposes how cigarette smoke generally can induce lung cancer (Hecht 1999). The broad mechanisms of cancer induction from exposures to secondhand and mainstream cigarette smoke are probably similar because the same carcinogens are present in both, although in different concentrations. The major difference is the significantly lower carcinogenic dose from inhaling secondhand smoke compared with active smoking.

Exposure to secondhand smoke leads to a small but measurable uptake of NNK and perhaps other carcinogens, as discussed in the previous section. Carcinogens are enzymatically transformed into a series of metabolites as the exposed organism attempts to convert them into compounds that are easily excreted from the body (Miller 1994), a process called metabolic detoxification. An unintended consequence of this detoxification process is that the carcinogen sometimes converts to a form that is reactive with DNA and other cellular macromolecules. These reactive forms usually have an electron-deficient (or electrophilic) center that is reactive with the electron-rich (or nucleophilic) centers in DNA. This process, called metabolic activation, forms adducts in DNA, RNA, and protein.

Because most of the carcinogens in Table 2.1 require metabolic activation to induce cancer, the metabolism of a carcinogen is in most cases a key component of the mechanism of cancer induction. The balance between metabolic activation and detoxification will be important in determining individual risks for cancer upon exposure to carcinogens in secondhand smoke. The initial enzymatic steps are frequently catalyzed by cytochrome P-450 enzymes, which are encoded by the *CYP* family of genes (Guengerich 1997). These enzymes generally oxygenate the carcinogen. Other enzymes, such as cyclooxygenases, myeloperoxidases, lipoxygenases, and monoamine oxidases, may also be involved. The oxygenated intermediates formed in the initial reactions may undergo further transformations by glutathione *S*-transferases, uridine-5′-diphosphate-glucuronosyl-transferases, sulfatases, hydratases, and other enzymes (Armstrong 1997; Burchell et al. 1997; Duffel 1997). All of these enzymes occur in multiple forms with different substrate specificity. Some of the forms are polymorphic in humans (i.e., they occur in variants with different types of metabolic activation). For example, the glutathione *S*-transferase form M1 (GSTM1) is null in 50 percent of the population.

The complexity of carcinogen metabolism is illustrated for B[*a*]P and NNK in Figure 2.3 (Hecht 1999). The major metabolic activation pathway of B[*a*]P is its conversion to 7,8-diol-9,10-epoxide metabolites. One of the four enantiomers produced is highly carcinogenic and reacts with DNA to form an adduct with deoxyguanosine, BPDE-*N*2-dG. GSTM1 is one of the enzymes competing for the metabolically activated intermediates in this pathway. The major metabolic activation pathways of NNK and NNAL occur by hydroxylating the carbons adjacent to the *N*-nitroso group (α-hydroxylation), resulting in the formation of a variety of DNA adducts including 7-methylguanine, O^6-methylguanine, and pyridyloxobutyl adducts (Hecht 1998). No specific carcinogen–DNA adducts have been detected in nonsmokers exposed to secondhand smoke, probably because of the low carcinogenic dose. The characterization of such adducts in human tissues is difficult even in smokers, but has been accomplished for a number of different tobacco smoke carcinogens (Hecht 1999). The same adducts probably are present in nonsmokers exposed to secondhand smoke, but at considerably lower levels.

Two studies examined the role of GSTM1 and glutathione *S*-transferase form T1 (GSTT1) variants as modifiers of risk for lung cancer in nonsmokers exposed to secondhand smoke (Bennett et al. 1999; Malats et al. 2000). Neither study found an effect of GSTT1 variants, although opposing results were obtained for GSTM1 null. One study documented an increased risk for lung cancer in secondhand smoke-exposed nonsmoking women (Bennett et al. 1999); the other found no significant effect in secondhand smoke-exposed nonsmokers (Malats et al. 2000).

Figure 2.2 Scheme showing the steps linking secondhand smoke exposure and cancer via tobacco smoke carcinogens

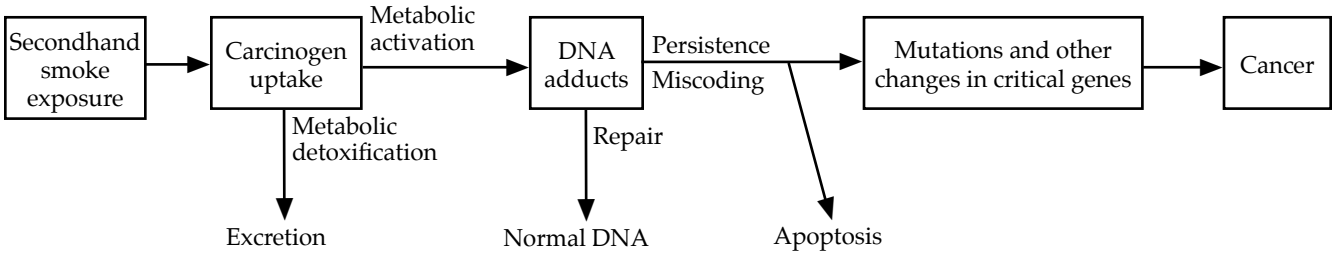
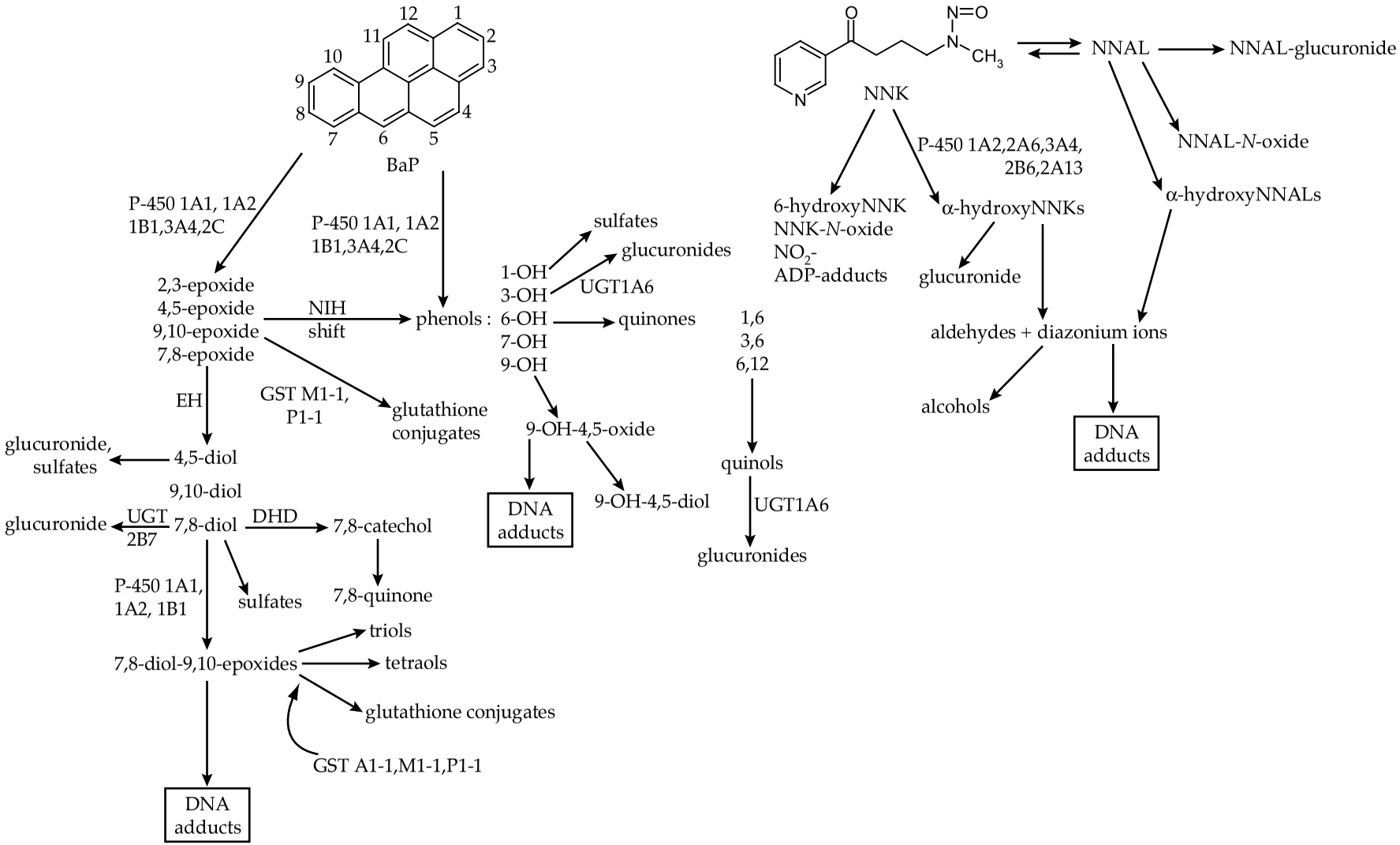


Figure 2.3 Metabolic pathways of benzo[*a*]pyrene (B[*a*]P) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)



Note: Metabolic pathways of B[*a*]P and NNK were modified from Cooper et al. 1983 and Hecht 1996, 1998. Some human enzymes involved in the various reactions are indicated (Gelboin 1980; Pelkonen and Nebert 1982; Cooper et al. 1983; Ketterer et al. 1992; Smith et al. 1992; Yamazaki et al. 1992; Yun et al. 1992; Tiano et al. 1993; Conney et al. 1994; Friedberg et al.
al. 1996; Baird and Ralston 1997; Staretz et al. 1997; Sundberg et al. 1997; Kim et al. 1998; Penning et al. 1999). ADP = adenosine diphosphate; DHD = 4 dihydrodiol dehydrogenase; EH = 4 epoxide hydrolase; GST = 4 glutathione *S*-transferase; NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NO_2 = nitrogen dioxide; P-450 = 4 cytochrome P-450; UGT = 4 UDP(uridine 5′-diphosphate)-glucuronosyl transferase; 1-OH, 3-OH: 4 1-hydroxy B[*a*]P, 3-hydroxy B[*a*]P; National Institutes of Health shift (where the shift [a biochemical process] was first identified) = intramolecular hydrogen migration, which can be observed in enzymatic and chemical hydroxylations of aromatic rings.

Source: Hecht 1999. Adapted with permission.

DNA adducts are critical for the induction of tumors by carcinogens. A great deal of mechanistic information is now available about the structures of DNA adducts and their potential to produce mutations (Hemminki et al. 1994; Geacintov et al. 1997). Cellular repair mechanisms exist to protect the DNA from persistent adduction. There are five main mechanisms of DNA repair: direct repair, base excision repair, nucleotide excision repair, mismatch repair, and double-strand break repair (Pegg et al. 1995; Sancar 1996; Singer and Hang 1997). If the adducts are not repaired, cells with damaged DNA may be removed by apoptosis (programmed cell death). When DNA adducts persist they may cause miscoding, resulting in a permanent mutation. Depending on the DNA polymerase involved, the sequence context, and other factors, DNA adducts will typically cause specific mutations. For example, O^6-methylguanine causes mainly G to A mutations, while BPDE-*N2*-dG frequently results in G to T mutations (Loechler et al. 1984; Shukla et al. 1997). If a permanent mutation occurs in a critical region of a growth control gene, it can lead to the loss of normal growth control mechanisms and ultimately to cancer. There are six proposed hallmarks of cancer: self-sufficiency in growth signals, evasion of apoptosis, insensitivity to antigrowth signals, sustained angiogenesis, tissue invasion and metastasis, and limitless replicative potential (Hanahan and Weinberg 2000). Virtually all of these processes are controlled by specific genes that can lose their normal function when miscoding occurs. The intricate circuitry of the cell, which involves multiple pathways of signal transduction, can be subverted by inappropriate carcinogen–DNA adduction and miscoding. Multiple events of this type lead to aberrant cells with the loss of normal growth control. For example, lung carcinogenesis involves changes that include the loss of heterozygosity at 3p, 5q, 8p, 9p, 9q, 11p, 11q, 13q, 17p, and 17q loci, which are known or possible sites of tumor suppressor genes such as *p53*, *p16*, and others (Sekido et al. 1998; Vähäkangas et al. 2001).

Although numerous studies describe mutations in the *p53* tumor suppressor gene and *K-ras* oncogene in lung tumors from smokers (Hecht 1999), few investigations include lung tumors from nonsmokers with documented exposures to secondhand smoke, mainly because lung cancer in nonsmokers is relatively uncommon. Two studies have addressed *p53* mutations in nonsmokers. In one study, the risk of mutation in the *p53* gene doubled (odds ratio = 2.0 [95 percent confidence interval (CI), 0.5–8.7]) with exposure to spousal secondhand smoke only compared with unexposed spouses (Husgafvel-Pursiainen et al. 2000). The risk was 1.5 (95 percent CI, 0.2–8.8) for those ever exposed to spousal or workplace secondhand smoke compared with those who were never exposed. These estimates are statistically unstable because of the small numbers of cases. The findings that G:C to A:T transversions were the most common among lifetime nonsmokers are in agreement with other studies. The second investigation reported a variety of mutations in the *p53* gene from tumors of lifetime nonsmokers exposed to secondhand smoke (Vähäkangas et al. 2001). Mutations in codons 12 and 13 of the *K-ras* gene were also observed. The observed *p53* and *K-ras* gene mutations are plausibly related to DNA adduct formation from carcinogens in secondhand smoke. It is difficult to specify which carcinogen may be responsible for a particular mutation, but the predominance of G mutations observed in these studies is consistent with the generally higher reactivity of G in DNA with metabolically activated carcinogens.

Summary

The evidence indicates that sidestream smoke, the principal component of secondhand smoke, contains carcinogens. Exposure to secondhand smoke results in the uptake by nonsmokers of many of these carcinogens. Although data are sparse on the specific elements in Figure 2.2 linking secondhand smoke exposure and tumor induction in humans via exposure to tobacco smoke carcinogens, substantial data from active smokers support this framework of biologic steps toward cancer. The most plausible mechanisms involved in lung cancer reflect the continuing exposure of the lungs to DNA-damaging material, which leads to multiple genetic changes that culminate in lung cancer. Available evidence points to these same mechanisms as the cause of lung cancer in persons exposed to carcinogens in secondhand smoke.

Conclusions

1. More than 50 carcinogens have been identified in sidestream and secondhand smoke.

2. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and its condensates and tumors in laboratory animals.

3. The evidence is sufficient to infer that exposure of nonsmokers to secondhand smoke causes a significant increase in urinary levels of metabolites of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). The presence of these metabolites links exposure to secondhand smoke with an increased risk for lung cancer.
4. The mechanisms by which secondhand smoke causes lung cancer are probably similar to those observed in smokers. The overall risk of secondhand smoke exposure, compared with active smoking, is diminished by a substantially lower carcinogenic dose.

Mechanisms of Respiratory Tract Injury and Disease Caused by Secondhand Smoke Exposure

Although attention has centered primarily on secondhand smoke and the risk for lung cancer and coronary heart disease (CHD), extensive epidemiologic data support a broader range of adverse effects, particularly related to respiratory health. Information on the underlying mechanisms of these effects is central to the interpretation of the epidemiologic data and in the understanding of the pathogenesis of the nonmalignant related disorders associated with secondhand smoke exposure. This review focuses primarily on pathogenetic mechanisms that likely contribute to secondhand smoke-induced respiratory diseases other than lung cancer. Respiratory effects of secondhand smoke exposure include a higher rate, an earlier onset, and an exacerbation of asthma (Wahlgren et al. 2000); spirometric indicators of lung impairment (Cook and Strachan 1999); an increased risk of lower respiratory tract illnesses in children (Strachan and Cook 1997); sudden infant death syndrome (SIDS) (Cook and Strachan 1999); and possibly chronic obstructive pulmonary disease (COPD) (Jaakkola 2002). This review also briefly discusses mechanisms of nonrespiratory disorders affected by secondhand smoke.

The respiratory system is the portal of entry for secondhand smoke and one of the key systems at risk for damage by secondhand smoke. Its structure and function are relevant to understanding the adverse effects of secondhand smoke. The respiratory tract includes the upper (nose, pharynx, and larynx) and lower (trachea, bronchi, and bronchioles) airways and the alveoli of the lung. Odor and irritant receptors are found primarily in the nose, but there are irritant receptors in the upper and lower airways as well. The airways conduct air to the alveoli where gas exchange occurs across the alveolar–capillary membrane, with oxygen taken up by red blood cells and carbon dioxide removed from the bloodstream. In addition, the upper and lower airways have defense mechanisms against inhaled particles and gases that impact or are adsorbed onto the airway walls. The upper airways, which clean and condition the inhaled air, prevent most large particles and water-soluble vapors from reaching the airways of the lower respiratory tract. The removal of small particles that reach the lower airways and alveoli is accomplished by mechanisms that include the mucociliary apparatus, macrophages, and epithelial cells. This anatomical framework of the respiratory tract provides a large area for deposition and adsorption of secondhand smoke components.

Secondhand Smoke and Asthma

Extensive data describe an association that connects secondhand smoke exposure, particularly from maternal smoking, with asthma in children (Strachan and Cook 1998) (Chapter 6, Respiratory Effects in Children from Exposure to Secondhand Smoke). Studies also link secondhand smoke exposure with asthma in adults (Dayal et al. 1994; Flodin et al. 1995; Hu et al. 1997; Larsson et al. 2001) (Chapter 9, Respiratory Effects in Adults from Exposure to Secondhand Smoke). This section considers biologic mechanisms that could underlie these associations as they reflect exposures during different points of the life span.

The biologic basis by which maternal smoking during pregnancy increases the risk of asthma is not fully understood, but a number of possible mechanisms have been identified. One mechanism is

the impairment of fetal airway development. A number of studies have reported that infants of mothers who had smoked during pregnancy had abnormal results on lung function tests, including decreased expiratory flow rates (Hanrahan et al. 1992; Cunningham et al. 1994; Tager et al. 1995) and increased airway resistance (Dezateux et al. 1999; Milner et al. 1999). These changes in lung mechanics that result from in utero tobacco smoke exposures persist through late childhood (Cunningham et al. 1994) and perhaps into adulthood (Upton et al. 1998). Also, diminished respiratory function in neonates precedes and is predictive of wheeze in early childhood (Martinez et al. 1988b; Dezateux et al. 1999; Young et al. 2000). Alterations in airway wall structure, particularly increased airway wall thickness, were found in infants exposed to maternal smoking (Elliot et al. 1998). This increased wall thickness could explain a major effect of maternal smoking on expiratory flow rates because it results in a smaller airway lumen, thereby increasing airway resistance. Supporting evidence comes from studies in rats that also indicated that exposure to smoking during pregnancy impaired fetal airway development and function (Collins et al. 1985).

A possible explanation for the impaired airway development, supported by recent data obtained in monkeys, is that the changes in airway structure are attributable to in utero effects of nicotine on extracellular matrix synthesis (Sekhon et al. 1999, 2002). Nicotine readily crosses the feto-placental barrier and attains concentrations in amniotic fluid that are equivalent to or higher than maternal serum nicotine levels (Luck and Nau 1984; Luck et al. 1985). At these concentrations, nicotine can exert profound biologic effects by targeting specific ionotropic channel receptors termed nicotinic acetylcholine receptors (nAChRs). These receptors are a family of ligand-gated, pentameric ion channels. In humans, 16 different subunits have been identified that form a large number of homopentameric and heteropentameric receptors with distinct structural and pharmacologic properties (Leonard and Bertrand 2001). Although the main focus on this receptor family has been to elucidate its role in transmitting signals for the neurotransmitter acetylcholine at neuromuscular junctions, recent interest has included its role in signaling events in nonneuronal cells. In the developing lung, α7 nAChRs are the most abundant form of nAChRs. Prenatal nicotine exposure strikingly increases α7 nAChR expression and binding. Acting through α7 nAChRs, nicotine markedly affects lung development. For example, prenatal exposure of primates to nicotine significantly alters lung structure (Sekhon et al. 1999). Specifically, paralleling the increase in α7 expression is a substantial increase in collagen expression surrounding large airways and vessels (Sekhon et al. 1999). Nicotine also increases collagen type I and type III mRNA expressions (i.e., copies of information carried by a gene on the DNA) in airways and alveolar walls (Sekhon et al. 2002). Collectively, these studies suggest that nicotine may be an important component of cigarette smoke responsible for increasing the airway wall thickness in infants of mothers who smoke during pregnancy.

A second mechanism that may cause a predisposition to asthma as a result of secondhand smoke exposure is the induction of bronchial hyperreactivity (BHR). Secondhand smoke exposure reportedly increases BHR in both children and adults. Martinez and colleagues (1988a) reported an increase in BHR following exposure to secondhand smoke in 70 percent of nine-year-old children whose mothers had smoked regularly during pregnancy. Young and colleagues (1991) reported a modest increase in BHR from inhaled histamine in infants (mean age four and one-half weeks) of parents who smoked compared with unexposed infants. That study was unable to separate the effects of prenatal and postnatal exposure to cigarette smoke. Recent results from the multicenter European Community Respiratory Health Survey demonstrated that secondhand smoke was also significantly associated with BHR in adults (Janson et al. 2001). This analysis included data from more than 7,800 adults who had never smoked. There were also significant dose-related trends between secondhand smoke and BHR. The increase in BHR caused by secondhand smoke may be attributable, in part, to cigarette smoke-induced increases of neuroendocrine cells in the lung. Located in the airway epithelium, neuroendocrine cells synthesize and release bronchoconstrictors, including serotonin, endothelin, and bombesin. Airways of persons with asthma also contained a higher number of neuroendocrine cells (Schuller at al. 2003). In rats, in utero and postnatal secondhand smoke exposure caused BHR and increased the number of neuroendocrine cells in the lungs (Joad et al. 1995). That study exposed pregnant rats to filtered air or to secondhand smoke under controlled conditions from day three of gestation until birth. The female rat pups were then exposed postnatally to either filtered air or secondhand smoke for 7 to 10 weeks. Exposure to prenatal and postnatal secondhand smoke resulted in lungs that were less compliant and more reactive to methacholine, with a 22-fold increase in the number of pulmonary neuroendocrine cells.

Nicotine may also be responsible for this increase in neuroendocrine cells. Sekhon and colleagues (1999) demonstrated that in utero nicotine exposure substantially increased neuroendocrine cells in the lungs of monkeys. Studies also suggest that nicotine may cause the release of bronchoconstrictors. Schuller and colleagues (2003) recently demonstrated that nicotine and its nitrosated carcinogenic derivative NNK bind to α7 nAChRs on pulmonary neuroendocrine cells. This results in the influx of calcium, the release of bronchoconstrictors, and the activation of (1) a mitogenic pathway mediated by protein kinase C, (2) the serine/threonine protein kinase Raf-1, (3) the mitogen-activated protein kinase, and (4) the proto-oncogene *c-myc*. These findings thus identify a possible effector cell for the increased BHR resulting from secondhand smoke exposure and indicate plausible mechanisms.

Researchers have also determined that secondhand smoke exposure affects the neural control of airways. In particular, there are extensive studies on the role of secondhand smoke exposure on the lung C-fiber central nervous system (CNS) reflex. The stimulation of sensory nonmyelinated bronchopulmonary C-fibers can trigger intense respiratory responses through local and CNS reflexes. Responses include bronchoconstriction, mucous secretion, and increased microvascular leakage, which are all hallmarks of asthma (Coleridge and Coleridge 1994). C-fibers are stimulated by components of secondhand smoke including nicotine (Saria et al. 1988), acrolein (Lee et al. 1992), and oxidants (Coleridge et al. 1993). In studies examining the role of secondhand smoke in neural control, Bonham and colleagues (2001) exposed one-week-old guinea pigs to filtered air or secondhand smoke for five weeks. Secondhand smoke exposure increased the excitability of afferent lung C-fibers and neurons in the CNS reflex pathway. This pathway could underline the increased risk for respiratory symptoms attributable to secondhand smoke exposure.

Altered immune responses may also play a role in the increased incidence of asthma in secondhand smoke-exposed children. Active smoking is associated with higher concentrations of total serum immunoglobulin E (IgE) (Sapigni et al. 1998; Oryszczyn et al. 2000). Magnusson (1986) extended these studies and demonstrated that cord blood IgE concentration was elevated significantly in infants whose mothers had smoked during pregnancy and that maternal smoking during pregnancy might predispose infants to subsequent sensitization and allergy. Studies have also associated high serum IgE levels with secondhand smoke exposure in children (Wjst et al. 1994) and in adults (Sapigni et al. 1998; Oryszczyn et al. 2000), although not all studies observed this association (Janson et al. 2001). Such enhanced IgE values might predict a later development of allergies (Marini et al. 1996).

Cigarette smoke exposure may also modify the balance of immune cells in airways. Studies on immune cells in airways have primarily addressed active smoking, and the effects of secondhand smoke exposure on airway immune cells remain unknown. Hagiwara and colleagues (2001) examined whether cigarette smoking could affect the distribution in the human airway of cells secreting T-helper 1 (Thl) or Th2 cytokines by identifying and quantifying the frequencies of cells spontaneously secreting cytokines in bronchoalveolar lavage fluid (BALF). The researchers collected BALF from nonsmokers or heavy cigarette smokers and performed cytokine assays to quantify cells secreting interleukin-2 (IL-2), IL-4, and interferon gamma (IFN-γ) with or without phorbol 12-myristate 13-acetate stimulation. No cells spontaneously secreting IL-2 were detected in BALF from smokers, whereas the BALF from most nonsmokers had detectable cells secreting IL-2. The number of cells secreting IFN-γ also decreased substantially in smokers compared with nonsmokers. Cells secreting IL-4 were not detected in samples from either group. There were also significant decreases in mitogen-stimulated Thl cytokine-secreting cells in the airways of smokers. The frequency of cells secreting IL-2 and the lymphocyte CD4/CD8 ratio in BALF had a weak positive correlation. These results indicate that cigarette smoking depletes Thl cytokine-secreting cells in the human airway and may explain the susceptibility of smokers to certain airway disorders, including allergic diseases.

Nicotine can impair antigen receptor-mediated signal transduction in lymphocytes, possibly contributing further to the asthma phenotype among the huge number of other sensitizing chemicals in tobacco smoke (Geng et al. 1995). Nicotine can inhibit both T cell-dependent and T cell-independent antibody forming cell responses and thus contribute to the immunosuppression that leads to an increased risk of respiratory infections, which are common triggers of BHR.

Nitric oxide (NO) plays an important role in the physiologic regulation of human airways. Changes in its production are implicated in the pathophysiology of airway diseases associated with cigarette smoking (Barnes and Belvisi 1993). Studies show that NO is a mild bronchodilator in persons with asthma when administered exogenously (Hogman et al. 1993). The inhibition of endogenous NO

synthesis by nitro-L-arginine methyl ester, a NO synthase (NOS) inhibitor, increases BHR in response to histamine in persons with asthma (Taylor et al. 1998). This reaction suggests that there are protective effects against bronchoconstriction by the NO that is released within the airways. Of note, inhalation of NG-monomethyl-L-arginine, another NOS inhibitor, increases BHR to bradykinin in patients with mild asthma (Ricciardolo et al. 1996), but not in those with more severe asthma (Ricciardolo et al. 1997), indicating a possible relationship between disease severity and the bronchodilatory role of endogenous NO. Several studies have demonstrated that exhaled NO levels, indicators of endogenous production, were lower in smokers than in nonsmokers (Persson et al. 1994; Schilling et al. 1994; Kharitonov et al. 1995). Those studies were more recently extended to secondhand smoke exposure. Yates and colleagues (2001) demonstrated a rapid (within 15 minutes) fall in exhaled NO levels during secondhand smoke exposure. The decreases in exhaled NO were observed at levels of secondhand smoke exposure frequently experienced in community settings (Yates et al. 1996). The inhibitory effect of cigarette smoke on exhaled NO has also been demonstrated in vitro, where cigarette smoke decreased NO production (Edwards et al. 1999). Thus, the decreased generation of NO in airways provides an additional mechanism for the increased BHR in persons exposed to secondhand smoke.

A number of plausible mechanisms could account for the decrease in exhaled NO associated with secondhand smoke exposure. Cigarette smoke contains high concentrations of oxides of nitrogen, and the reduction in exhaled NO may be attributable to the decreased production of NOS by a negative feedback mechanism (Kharitonov et al. 1995). Other possible mechanisms include an accelerated uptake of NO following tobacco smoke exposure, or an increased breakdown or modification of NO by oxidants in cigarette smoke. NO reacts rapidly with superoxide anion, yielding the harmful oxidant peroxynitrite. This mechanism would be similar to that observed in cystic fibrosis where nitrite levels, indicators of NO oxidative metabolism, are elevated in breath condensate of afflicted persons but exhaled NO is not (Ho et al. 1998).

The induction of BHR following exposure to secondhand smoke might also result from smoke-induced inflammation. Lee and colleagues (2002) demonstrated that airway inflammation markedly increased BHR. Saetta (1999) demonstrated that cigarette smoking caused a profound inflammatory response in airways and lung parenchyma. Cigarette smokers had increases in total inflammatory cell counts and polymorphonuclear leukocyte (PMN) counts (tested by BAL), and nonsmokers exposed to secondhand smoke for as little as three hours experienced an increase in circulating PMNs, enhanced PMN chemotaxis, and the augmented release of oxidants upon stimulation (Anderson et al. 1991). Airway epithelial cells are likely involved in producing this inflammatory reaction because they line the respiratory tract and interact directly with inhaled cigarette smoke to elaborate proinflammatory cytokines (Yu et al. 2002). Human bronchial epithelial cell cultures exposed to cigarette smoke extract exhibited significantly greater PMN chemotactic activity compared with the control cell cultures (Mio et al. 1997).

Secondhand Smoke and Infection

The topic of active smoking and host defenses against infectious agents has been covered in previous reports of the Surgeon General (USDHHS 1990, 2004). Epidemiologic studies show that secondhand smoke exposure enhances susceptibility to respiratory infections and/or worsens infections in both adults and children (Porro et al. 1992; Strachan and Cook 1997; Jaakkola 2002). Although mechanisms underlying the increased risk of infection associated with secondhand smoke exposure have not been fully evaluated, several studies have identified mechanisms that are likely to be involved. As reviewed earlier (Geng et al. 1995), secondhand smoke can inhibit antibody responses that are either T cell-dependent or T cell-independent, thus contributing to impaired immune responses. Secondhand smoke hinders macrophage responsiveness, further impairing the proper functioning of the immune system (Edwards et al. 1999). It also impairs mucociliary clearance (Wanner et al. 1996), enhances bacterial adherence, and disrupts the respiratory epithelium (Fainstein and Musher 1979; Dye and Adler 1994), a critical host defense barrier. Secondhand smoke exposure may also alter bacterial flora in pharyngeal mucosa of infants, thus providing an additional mechanism for enhanced susceptibility to infection (Kilian et al. 1995).

Secondhand Smoke and Chronic Obstructive Pulmonary Disease

As a slowly progressive condition, COPD is characterized by airflow limitation that is largely irreversible. Characteristic pathologic changes are the accumulation of inflammatory cells in airways and

lung parenchyma and the extensive derangement of the extracellular matrix, resulting in small distinct airspaces that coalesce into much larger abnormal ones (Niewoehner et al. 1974; Cosio et al. 1980; Jeffery 2001). The inflammatory cells are regarded as the source of enzymes (e.g., elastases) that cause the matrix destruction. Oxidative stress is also thought to play an important role in the development of COPD. A number of studies have shown an increased oxidant burden and consequently increased markers of oxidative stress in the airspaces, breath, blood, and urine of smokers and of patients with COPD (MacNee 2001). Sources of the increased oxidative burden in COPD patients include cigarette smoke, which contains abundant amounts of oxygen-based free radicals, peroxides, peroxynitrites, and phagocytes (Pryor 1992). Alveolar macrophages and PMN from smokers release increased amounts of reactive oxygen species under certain conditions when compared with the same cell types from nonsmokers (Hoidal et al. 1981; Ludwig and Hoidal 1982). The consequences of oxidative stress may include oxidative inactivation of antiproteinases, airspace epithelial injury, and expression of proinflammatory mediators (MacNee 2001), which are all elements of the inflammatory process underlying the development of COPD.

Although secondhand smoke clearly causes an increased oxidant burden in the lungs, only a few publications address secondhand smoke and COPD, and the magnitudes of the associations observed are modest. A few studies have suggested an increased risk of COPD with a high level of exposure (Coultas 1998). One approach investigators have taken to determine the potential risk of COPD from secondhand smoke exposure is to examine the relationship between lung function level and secondhand smoke. Although longitudinal data on the effects of active or involuntary smoking and the development of COPD are not available from childhood through adulthood, evidence suggests that COPD in adults may result from impaired lung development and growth, the premature onset of a decline in lung function, and/or an accelerated decline in lung function (Samet and Lange 1996; Kerstjens et al. 1997). As discussed earlier in this chapter (see "Secondhand Smoke and Asthma"), exposure to secondhand smoke in infancy and childhood and active smoking during childhood and adolescence contribute to impaired lung growth (Collins et al. 1985). In general, however, although studies have identified plausible mechanisms, there is a need for additional evidence on the relationship between secondhand smoke and COPD.

Secondhand Smoke and Sudden Infant Death Syndrome

Many epidemiologic studies document that maternal smoking during pregnancy and after birth is a major risk factor for SIDS (Haglund and Cnattingius 1990; Klonoff-Cohen et al. 1995; Taylor and Sanderson 1995). Earlier reports have concluded that maternal smoking during pregnancy causes SIDS (USDHHS 2001, 2004). Research has identified mechanisms in SIDS infants related to arousal failure, inadequate cardiorespiratory compensatory motor responses, and sleep apnea that are attributable to developmental abnormalities in the brainstem and autonomic nervous system (Avery and Frantz 1983; Harper 2000; Slotkin 2004; Spitzer 2005; Adgent 2006). Researchers have studied the potential mechanisms by which prenatal, perinatal, and postnatal exposures to secondhand smoke are related to neurodevelopmental abnormalities. The data suggest that the potent neurotoxic effects of nicotine are important (Slotkin et al. 1997; Önal et al. 2004; Slotkin 2004; Adgent 2006). Children who die from SIDS have higher concentrations of nicotine in their lungs compared with children who die of other causes (Milerad et al. 1998; McMartin et al. 2002). This association holds even when the parents report a nonsmoking environment. The specific role of nicotine and other tobacco smoke constituents in the pathogenesis of SIDS is not known. Research, however, particularly animal exposure models, suggests that many cardiorespiratory control deficiencies are associated with nicotinic receptors within the peripheral and central nervous systems (Neff et al. 1998; Adgent 2006). Animal studies have documented effects that can be related to several potential mechanisms that could cause SIDS, including the effects of perinatal exposure to secondhand smoke on increased nAChR production in brains of monkeys (Slotkin et al. 2002); the disruptions in brain development through cholinergic mechanisms (Slotkin 2004); and adverse effects on brain cell development, synaptic development and function, and neurobehavioral activity. Perinatal exposure to secondhand smoke also has adverse effects on neurobehavioral development (Makin et al. 1991), and recent studies indicate that perinatal exposure to secondhand smoke induces adenylyl cyclase (AC) activity and alters receptor-mediated cell signaling in brains of neonatal rats (Slotkin et al. 2001). In those studies, rats were exposed to secondhand smoke during gestation or during the early neonatal period or both. Brains were examined for alterations in AC activity and for changes in beta-adrenergic and

M2 muscarinic cholinergic receptors and their linkage to AC. Secondhand smoke exposure induced an increase in total AC activity, which was monitored with forskolin, the direct enzymatic stimulant. In the brain, the specific coupling of beta-adrenergic receptors to AC was inhibited in the groups exposed to secondhand smoke despite a normal complement of receptor-binding sites. Because alterations in AC signaling are known to affect cardiorespiratory function, the results provide a possible mechanistic link to the action of secondhand smoke, including postnatal secondhand smoke exposure, in disturbances culminating in SIDS. Secondhand smoke exposure causes the same changes in AC signaling seen previously with prenatal nicotine exposure: increases in AC production and the loss of specific receptor coupling to AC. In a recent independent analysis of perinatal and postnatal exposure to secondhand smoke in rhesus monkeys, researchers observed significant neural cellular effects from postnatal exposures alone, including specific damage in the occipital cortex, in the midbrain, and in temporal cortex cell development. These effects are similar to those previously observed in other animal models for either prenatal nicotine or perinatal secondhand smoke exposure, or for continuous prenatal and postnatal exposures (Slotkin et al. 2006).

A second possible mechanism for the increased incidence of SIDS following secondhand smoke exposure relates to earlier cited evidence from a guinea pig model of postnatal secondhand smoke exposure. That model demonstrated an increase in the production or release of lung C-fiber CNS reflex responses to secondhand smoke (Bonham et al. 2001). The responses invoked by the increased excitability of afferent lung C-fibers and nucleus tractus solitarius (NTS) neurons in the CNS reflex pathway include changes in breathing patterns, such as prolonged expiratory apnea. The findings suggest that an increase in secondhand smoke-induced excitability of NTS neurons augmenting C-fiber reflex output may contribute to SIDS.

Findings of a study that used a piglet model suggest that nicotine interferes with normal autoresuscitation (Frøen et al. 2000). The effect of nicotine was augmented by the additional administration of IL-1B, which is released during infections. Studies with a piglet model also suggest that early involuntary, postnatal nicotine exposure may be responsible for some neuropathologic changes in apoptotic markers that researchers have observed in SIDS infants (Machaalani et al. 2005).

Although investigators have not established a specific role for apnea as a potential cause of SIDS, one study of human newborns evaluated this theoretical potential of apnea in relation to SIDS (Chang et al. 2003). A controlled sleeping experiment included 10 infants either prenatally or postnatally exposed to tobacco smoke and 10 unexposed control infants. The researchers found that five of the exposed infants did not have a behavioral arousal response to a standard sequence of audiology stimuli, whereas all of the unexposed infants were aroused.

Secondhand Smoke and Nasal or Sinus Disease

Some studies indicate an association, particularly in children, between secondhand smoke exposure and acute or chronic nasal and sinus symptoms (Barr et al. 1992; Moyes et al. 1995; Benninger 1999). In children aged 4 through 11 years, frequent colds and general sinus symptoms were significantly associated with maternal smoking (Barr et al. 1992). Normal healthy persons have also developed nasal congestion, irritation, and increased rhinitis from exposure to moderate levels of secondhand smoke (Willes et al. 1998). Researchers have examined a number of potential mechanisms (Samet 2004). Tobacco smokers have abnormal nasal mucociliary clearance, and a study by Bascom and colleagues (1995) demonstrated differential nasal responsiveness to secondhand smoke. Using the clearance of ^{99m}Tc-sulfur colloid as an indicator of mucociliary function, decreased clearance occurred in 3 out of 12 persons following exposure. Persons with delayed clearances all had a history of secondhand smoke rhinitis (Bascom et al. 1995). In a follow-up study comparing persons who were not sensitive with persons who were sensitive to secondhand smoke, those who were sensitive had more rhinorrhea following the intranasal administration of capsaicin, thus suggesting a role for C-fiber stimulation (Bascom et al. 1991). The researchers observed no changes in nasal vascular permeability or inflammation following secondhand smoke exposure. Studies have also shown secondhand smoke-induced increases in epithelial permeability to environmental allergens, thus enhancing allergic reactions to inhaled allergens (Kjellman 1981; Zetterstrom et al. 1981).

Summary

Cellular, animal, and human studies indicate a number of mechanisms by which secondhand smoke injures the respiratory tract. There is extensive information on the harm from active smoking as well.

There are limitations to many of the cited studies. Most clinical studies base secondhand smoke exposure on self-reports and have not included objective measurements of exposure, such as salivary, serum, or urine cotinine concentrations. An additional limitation is that studies of secondhand smoke exposure frequently use a cross-sectional design and provide little data on the duration of the exposure. In addition, mechanistic studies frequently rely on animal models or in vitro studies. Both have limitations, particularly in relation to the level and duration of the exposures and difficulties in simulating human exposures. There is very little information about the concentrations of specific tobacco smoke constituents following secondhand smoke exposure in the alveolar milieu and limited information about the interactions among the various constituents.

Obviously, the closer a model mimics human exposure the more relevant this information will be. In addition to more closely simulating conditions of human exposure, future studies should focus on individual susceptibilities. This approach will lead to the recognition of genetic profiles that influence susceptibility to adverse effects of secondhand smoke and will provide insights into the underlying mechanisms of the health consequences.

Animal and human studies indicate several potential mechanisms by which exposure to secondhand smoke may affect the neuroregulation of breathing, apneic spells, and sudden infant death. The role of nicotine and other tobacco smoke constituents in the pathogenesis of SIDS is not known. However, the neurotoxicity of prenatal and neonatal exposures to nicotine and secondhand smoke in animal models can be related to several potential causal mechanisms, including adverse effects on brain cell development, synaptic development and function, and neurobehavioral activity.

Conclusions

1. The evidence indicates multiple mechanisms by which secondhand smoke exposure causes injury to the respiratory tract.

2. The evidence indicates mechanisms by which secondhand smoke exposure could increase the risk for sudden infant death syndrome.

Mechanisms of Secondhand Smoke Exposure and Heart Disease

When the association of CHD with secondhand smoke was first reported, its plausibility and the magnitude of the observed risk were questioned. The observed risk for involuntary smoking was thought to be relatively strong compared with the well-documented risk of active smoking. In addition, it was uncertain whether the mechanisms underlying the association of active smoking with CHD risk were relevant, considering the lower doses of smoke components associated with typical secondhand smoke exposures. Subsequently, an understanding of the potential mechanisms associating CHD with involuntary smoking has deepened, largely as a result of findings from human and animal experiments involving secondhand smoke exposure.

Clinical and experimental evidence continues to accumulate regarding the mechanisms by which active smoking causes CHD (USDHHS 1990, 1994, 1998, 2001, 2004). Active smoking promotes atherogenesis by unfavorably affecting many elements in the interface of the blood with the arterial wall and the cellular elements of the artery itself. Atherosclerosis is, in part, considered an inflammatory process (Ross 1993, 1999), and smoking results in a potent, systemic inflammatory stimulus (USDHHS 2004). Active smoking is associated with dysfunctional endothelial cells, the cells lining the inner arterial wall that are in contact with the circulating blood. This dysfunction leads to the secretion of inflammatory cytokines, the adhesion of monocytes and lymphocytes and their migration to the endothelium, the proliferation of smooth muscle cells, and the reduction of the normal antithrombotic properties of the endothelium. Compared with nonsmoking controls, smokers also have less endothelium-dependent vasodilatation (Celermajer et al. 1993).

The balance of the tightly regulated coagulation–fibrinolytic system is critical to the prevention of atherothrombotic events such as acute coronary syndromes, which include unstable angina and myocardial infarction (MI) (Corti et al. 2003). Smoking has a prothrombotic effect, tipping this system toward clot formation, which comes from a variety of actions of smoking including impaired endothelial cell functioning, increased platelet aggregation, and reduced fibrinolysis (USDHHS 2004).

Smoking is also associated with an adverse lipid profile (USDHHS 1990, 2004). Smokers tend to have higher concentrations of total low-density lipoprotein (LDL) and very low-density lipoprotein and decreased levels of high-density lipoprotein (HDL). Smoking also increases oxygen demand while reducing oxygen-delivering capacity.

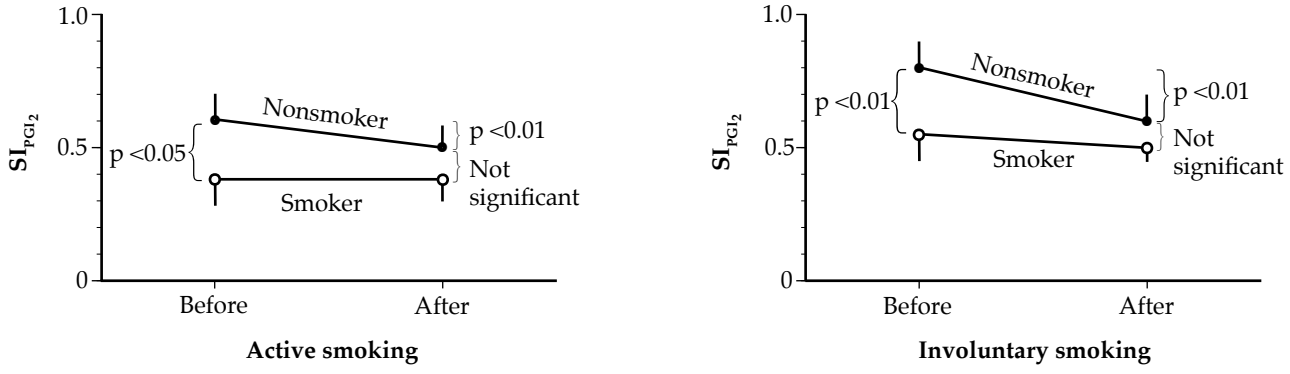
This section reviews mechanisms that are considered to be the basis of the association between exposure to secondhand smoke and CHD. The following section reviews the relevant body of research and covers each of the systems affected unfavorably by active smoking for which there is also research on secondhand smoke exposure. The discussion also provides a foundation for considering the observational evidence in Chapter 8, Cardiovascular Diseases from Exposure to Secondhand Smoke.

Platelets

Exposure to secondhand smoke activates blood platelets (i.e., makes them sticky), and thereby increases the likelihood of a thrombus. These activated platelets can damage the lining of the coronary arteries and may facilitate the development and progression of atherosclerotic lesions (Pittilo et al. 1982; Sinzinger and Kefalides 1982; Burghuber et al. 1986; Davis et al. 1989; Sinzinger and Virgolini 1989; Steinberg et al. 1989). Increased platelet activation is associated with an increased risk for ischemic heart disease (Elwood et al. 1991). Thus, increases in platelet activation observed in persons exposed to secondhand smoke would be expected to have acute adverse effects.

In one experiment, two groups each smoked two cigarettes: individuals who by history were nonsmokers and individuals who were reported smokers (Burghuber et al. 1986). At the beginning of the experiment, the platelets of the chronic smokers were less sensitive to stimulation by exogenous prostacyclin than those of the nonsmokers; platelet sensitivity did not significantly change in the smokers in response to smoking the two cigarettes (Figure 2.4). In contrast to these findings, nonsmokers who smoked just two cigarettes had a significantly ($p < 0.01$) decreased level of response to the same stimulus, reaching a level close

Figure 2.4 Effect of active and involuntary smoking on platelet aggregation in smokers and nonsmokers



Note: The sensitivity index, SI_{PGI_2}, is defined as the inverse of the concentration of prostaglandin I_2, which is necessary to inhibit adenosine disphosphate-induced platelet aggregation by 50 percent. Lower values of SI_{PGI_2} indicate greater platelet aggregation.
Source: Burghuber et al. 1986. Adapted with permission.

to that of the smokers. The findings indicate differing acute responses of platelets of nonsmokers and smokers to the toxins in cigarette smoke.

In an experiment more relevant to involuntary smoking, the same investigators used the same platelet assay in another group of smokers and nonsmokers before and after they sat in a room for 20 minutes where cigarettes had just been smoked (Figure 2.4) (Burghuber et al. 1986). The researchers again found no significant change among smokers, but a significant increase in platelet sensitivity to prostacyclin among nonsmokers brought them to a level similar to that of the smokers. These data, together with findings from other human experiments (Davis et al. 1989), indicate that nonsmokers are sensitive to secondhand smoke, and even very low levels of secondhand smoke exposure can have a major impact on platelet function in nonsmokers. Animal data also show an effect of secondhand smoke exposure. Bleeding time, another measure of platelet function, is significantly shortened by secondhand smoke exposure (meaning more activated platelet activity) in both rabbits (Zhu et al. 1993b; Sun et al. 1994) and rats (Zhu et al. 1994).

With regard to the mechanisms, studies of cigarette smoke extract on platelet function suggest that the toxins in cigarette smoke increase platelet function by interfering with and degrading platelet-activating factor acetylhydrolase (PAF-AH) (Miyaura et al. 1992). Exposure of serum to cigarette smoke extract reduces the effectiveness of PAF-AH and may thus increase the concentration of platelet-activating factor. The reduced efficacy of PAF-AH may explain the increased serum concentration of platelet-activating factor in smokers. Nicotine appears to be one of the active agents in tobacco smoke, but other specific compounds may also contribute to the effects of exposure on platelets (Davis et al. 1985; Miyaura et al. 1992). This in vitro finding complements results of clinical studies that compared the effects of smoking and transdermal nicotine on platelets and on hemostatic function. Benowitz and colleagues (1993) carried out a crossover trial that compared the effects of cigarette smoking and transdermal nicotine on eicosanoid formation and hemostatic function. Although both active smoking and transdermal nicotine produced similar nicotine levels, there was an increase in the urinary excretion of several markers of platelet function while smoking cigarettes that was not seen with transdermal therapy (Benowitz et al. 1993).

Some investigators have reported conflicting findings and have questioned whether platelet aggregation is an underlying mechanism of the association between CHD and secondhand smoke exposure (Smith et al. 2000b, 2001). Smith and colleagues (2001) conducted an observational study that compared secondhand smoke-exposed and unexposed adult nonsmokers and did not find differences in urinary metabolites of thromboxane and prostacyclin.

Endothelial Function and Vasodilation

Arteries are lined by a cell layer known as the vascular endothelium. The endothelium plays a critical role in controlling the ability of arteries to dilate and constrict as they regulate blood flow. In addition, damage to the vascular endothelium facilitates the development of atherosclerosis. Evidence in both animals (Hutchison et al. 1995, 1996, 1997a,b, 1998, 1999; Jorge et al. 1995; Zhu and Parmley 1995; Schwarzacher et al. 1998; Török et al. 2000) and humans (Celermajer et al. 1996; Sumida et al. 1998; Otsuka et al. 2001) shows that secondhand smoke interferes with endothelium-dependent vasodilation. Moreover, these effects can be attenuated by increasing the amount of L-arginine, an amino acid that is a precursor of NO, the mediator of endothelium-dependent vasodilation (Hutchison et al. 1996, 1997a, 1998, 1999; Schwarzacher et al. 1998). Studies in rats have also demonstrated that involuntary smoking reduces NOS in the penis (Xie et al. 1997), indicating that secondhand smoke specifically interferes with the production of NO.

Consistent with other results from animal studies, most human studies indicate that endothelium-dependent vasodilation in nonsmokers is sensitive to secondhand smoke following both chronic (Celermajer et al. 1996; Sumida et al. 1998) and acute (Otsuka et al. 2001) exposures. Indeed, the effects of secondhand smoke on endothelium-dependent vasodilation in human coronary circulation are comparable in magnitude to the effects observed in smokers when compared with nonsmokers (Sumida et al. 1998; Otsuka et al. 2001).

Celermajer and colleagues (1996) studied endothelium-dependent vasodilation in 78 healthy persons aged 15 to 30 years by measuring the extent of reactive hyperemia in the brachial artery after occluding it with a blood pressure cuff (with the flow increase determined by endothelium-dependent vasodilation) before and after administering nitroglycerine (an endothelium-independent vasodilator). Involuntary smokers were classified by self-reported levels of chronic exposure to secondhand smoke. Investigators found similar impairments in flow-mediated

dilation in both involuntary and active smokers when compared with unexposed nonsmoking controls (Figure 2.5). Among those exposed to secondhand smoke, there was an inverse relationship between the intensity of the exposure and flow-mediated dilation ($r = -0.67$, $p < 0.001$). Using similar methods, Woo and colleagues (1997) studied 72 rural Chinese persons and 72 White persons in Australia and England. These researchers did not find a smoking effect among adults living in rural China, but the analysis grouped active with involuntary smokers. An effect of exposure was observed in White participants, but results were also reported with active and involuntary smokers combined.

The adverse effects of chronic secondhand smoke exposure may be partially reversible. In a cross-sectional study of young adults, there was less evidence for arterial endothelial dysfunction in former involuntary smokers compared with current involuntary smokers (Raitakari et al. 1999). Kato and colleagues (1999) experimentally tested whether the reduction in endothelium-dependent vasodilation from secondhand smoke is an acute phenomenon in nonsmokers. The experiment included a brief, acute exposure to secondhand smoke (15 minutes). There were similar responses before and after exposure in the brachial artery flow to acetylcholine, which stimulates endothelium-dependent vasodilation, and to nitroprusside, which stimulates endothelium-independent vasodilation. The investigators concluded that the consequences of exposure to secondhand smoke were attributable to chronic rather than acute effects on the brachial artery.

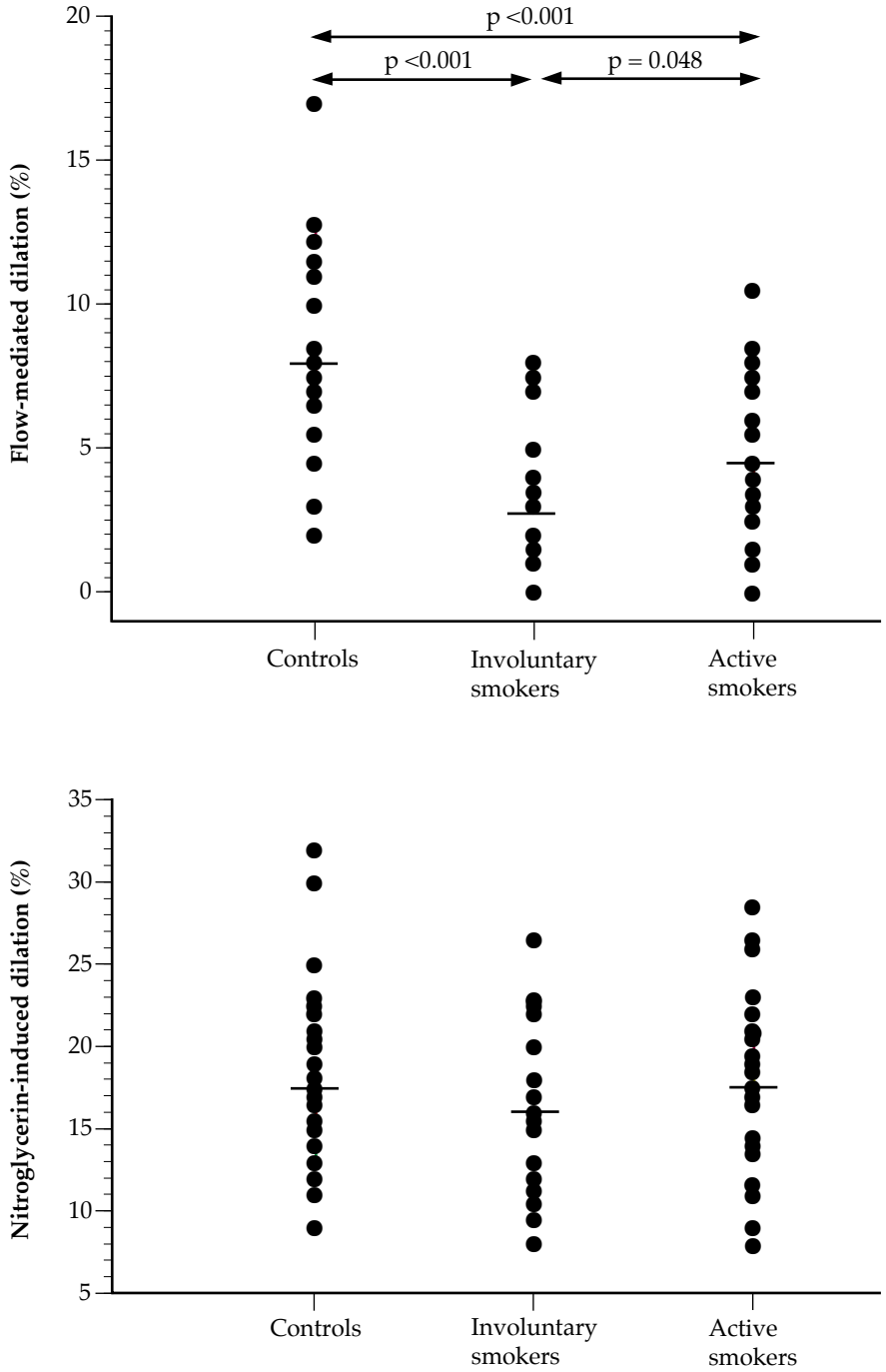
Two studies document the effects of secondhand smoke on human coronary arteries (Sumida et al. 1998; Otsuka et al. 2001). Sumida and colleagues (1998) studied 38 women aged 40 to 60 years with no known risk factors for CHD other than age and exposure to tobacco smoke. The participants included three groups: nonsmokers who had never smoked and had never been regularly exposed to secondhand smoke, nonsmokers with a self-reported history of exposure for at least an hour a day for at least 10 years, and active smokers. The study examined the changes in the diameter of the epicardial coronary artery (proximal and distal segments of the left anterior descending and left circumflex coronary arteries) in response to an intracoronary injection of acetylcholine. Acetylcholine constricted most coronary arteries in both exposed nonsmokers and active smokers to a similar extent and dilated the coronary arteries in unexposed nonsmokers. This result suggests possibly similar levels of coronary endothelial dysfunction among involuntary and active smokers.

Otsuka and colleagues (2001) used ultrasound in healthy young adult nonsmokers and smokers to measure coronary flow velocity changes in response to acetylcholine as a measure of endothelium-dependent vasodilation (quantified as coronary flow velocity reserve). The measurements were made before and 30 minutes after breathing secondhand smoke for 30 minutes in a hospital smoking room in Japan. Before the exposure, nonsmokers had a significantly higher coronary flow velocity reserve compared with smokers (Figure 2.6). The 30 minutes of exposure had no effect on the coronary flow velocity reserve among smokers, but significantly reduced the reserve in nonsmokers to a level that almost equaled the level found in smokers (Figure 2.6). This substantial acute response is similar in magnitude to the effect observed with chronic exposures on brachial (Celermajer et al. 1996) and coronary (Sumida et al. 1998) arteries. However, the finding differs from the lack of effect seen for short-term (15 minutes) acute exposures on the brachial artery (Kato et al. 1999). The different findings in these two studies (Sumida et al. 1998; Otsuka et al. 2001) may be attributable to the duration of the exposure (30 versus 15 minutes) or to differences in the responses of the coronary arteries and the brachial arteries to secondhand smoke exposure.

An experiment in humans also showed that an acute exposure to secondhand smoke reduces the distensibility of the aorta (Stefanadis et al. 1998). In this study, the nonsmokers were exposed to secondhand smoke for five minutes at a mean carbon monoxide (CO) level of 30 parts per million; the smokers smoked one cigarette. The distensibility of the aorta in nonsmokers exposed to secondhand smoke for just five minutes was reduced significantly by 21 percent compared with a 27 percent reduction in the active smokers. There was no change in the sham-exposed patients.

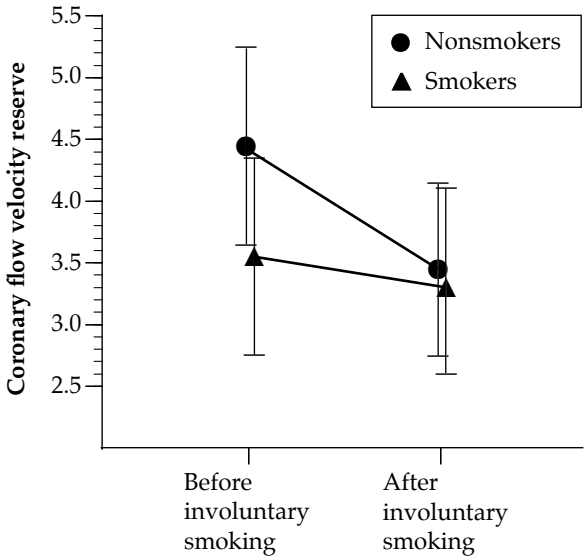
Human experiments have indicated that even short-term exposures to active smoking (Přerovský and Hladovec 1979) or to other tobacco product constituents significantly increase the number of nuclear endothelial cell carcasses in the blood (Davis et al. 1989). The presence of these cell carcasses suggests damage to the endothelium. The number of endothelial cell carcasses (i.e., remains of dead cells) in nonsmokers after they were exposed to secondhand smoke was almost as great as the number of carcasses observed in active smokers.

Figure 2.5 Flow-mediated (endothelium-dependent) and nitroglycerin-induced (endothelium-independent) vasodilation in human brachial arteries



Note: Flow-mediated (endothelium-dependent) vasodilation in human brachial arteries was significantly impaired in chronically exposed involuntary smokers and in active smokers to a similar degree, compared with the controls, whereas nitroglycerine-induced (endothelium-independent) vasodilation was similar in all three groups.
Source: Celermajer et al. 1996. Adapted with permission.

Figure 2.6 Coronary flow velocity changes before and after secondhand smoke exposure



Note: Data are mean (standard deviation). Coronary flow velocity reserve (CFVR) before involuntary smoking was significantly higher in nonsmokers than in smokers. However, CFVR after involuntary smoking was reduced significantly in nonsmokers, but only slightly among smokers. Source: Otsuka et al. 2001. Adapted with permission.

Atherosclerosis

Endothelial dysfunction may also contribute to the development of atherosclerosis. Normal endothelial cells promote vasodilation and inhibit atherosclerosis and thrombosis, in part through the release of NO (Harrison 1997). Dysfunctional cells, on the other hand, contribute to vasoconstriction, atherogenesis, and thrombosis. Risk factors contribute collectively to endothelial dysfunction. For example, active smoking interacts with LDL in a way that damages the endothelium (Heitzer et al. 1996). One unifying hypothesis for the effects of cardiovascular risk factors is a combined action to increase damaging oxidative stress (Oskarsson and Heistad 1997). Thus, reducing exposure to risk factors may improve endothelial function and lessen the risk for clinical coronary events. For example, lipid reduction improves endothelial function in patients with hyperlipidemia both acutely (Tamai et al. 1997) and chronically (Treasure et al. 1995).

Platelets are also relevant to the development of atherosclerosis (Ross 1986; Steinberg et al. 1989). Following damage to the arterial endothelium, platelets interact with or adhere to the subendothelial connective tissue and initiate a sequence that leads to the formation of atherosclerotic plaque. When platelets interact with or adhere to subendothelial connective tissue, they are stimulated to release their granule contents.

Endothelial cells normally prevent platelet adherence because of the nonthrombogenic character of their surface and their capacity to form antithrombotic substances such as prostacyclin (Corti et al. 2003). However, platelets can stick to damaged endothelial cells and release mitogens such as platelet-derived growth factor and chemoattractants, which encourage the migration and proliferation of smooth muscle cells in the region of the endothelial injury (Ross 1993). When platelet aggregation increases as a result of exposure to secondhand smoke, platelet accumulation at the injured site is also expected to increase. Tobacco smoke exposure has also been associated with the accumulation of glycosaminoglycans and glycoproteins in vascular tissues of rats, another early event in atherogenesis (Latha et al. 1991).

Effects on Children

Adverse cardiovascular effects of secondhand smoke exposure may begin in childhood. Adolescents and children whose parents smoked exhibited lower HDL levels than children who were not exposed to secondhand smoke (Moskowitz et al. 1990; Feldman et al. 1991). White and Froeb (1991) reported similar results among adults exposed at work. These findings indicate a less favorable lipid profile in persons exposed to secondhand smoke.

Cross-cultural comparisons suggest that genetic differences may influence how children are affected by secondhand smoke. There was a small exposure effect on HDL cholesterol in Japanese children (Misawa et al. 1989) and no effect in Turkish children (Işcan et al. 1996), but the LDL cholesterol level and the ratio of LDL to HDL cholesterol were adversely affected in Turkish children (Işcan et al. 1996). These effects were similar to those found in smokers and may be mediated by inhibiting the activity of the enzyme plasma lecithin: cholesterol acyltransferase in plasma and altered clearance of chylomicron remnants by the liver (Bielicki et al. 1995; Pan et al. 1997). In children with severe hypercholesterolemia, a lower HDL cholesterol level was associated with parental smoking (Neufeld et al. 1997).

Chemical Interactions with Low-Density Lipoprotein Cholesterol

Several animal studies (Albert et al. 1977; Penn et al. 1981, 1996; Majesky et al. 1983; Revis et al. 1984; Penn and Snyder 1993, 1996a,b) demonstrated that PAHs, in particular 7,12-dimethylbenz[*a*,*h*] anthracene and B[*a*]P, as well as 1,3 butadiene (Penn and Snyder 1996a,b), accelerate the development of atherosclerosis. PAHs, including B[*a*]P and 1,3 butadiene, are constituents of secondhand smoke. PAHs appear to bind preferentially to both LDL and HDL subfragments of cholesterol and may facilitate the incorporation of toxic compounds into the cells lining the coronary arteries. Thus, exposure to PAHs may contribute to both cell injury and hyperplasia in the atherosclerotic process. Adults who inhaled secondhand smoke for only five and one-half hours exhibited compromised antibiochemical defenses and an increased accumulation of LDL cholesterol in macrophages (Valkonen and Kuusi 1998).

Experimental Atherosclerosis

In addition to the studies of single tobacco smoke components, animal experiments have demonstrated that exposure to secondhand smoke for only a few weeks significantly speeds the atherosclerotic process (Table 2.6). These animal models provide an indication of the effect of exposure to more than one component of tobacco smoke.

Zhu and colleagues (1993b) exposed three groups of rabbits to a high-cholesterol diet. Two of the groups were also exposed to 10 weeks of secondhand smoke from Marlboro cigarettes for six hours a day, five days a week. One group was exposed to levels comparable to a smoky bar and the other group was exposed to much higher levels, with a nicotine level 30 times higher. The high-dose group experienced levels comparable to those observed in a car with the windows rolled up while four cigarettes per hour were smoked (Ott et al. 1992). With just 10 weeks of exposure (a total of 300 hours), the fraction of pulmonary artery and aorta covered with lipid deposits was nearly twice as high in the high-exposure group compared with the control animals. There was a smaller increase in the low-exposure group (Figure 2.7) (Zhu et al. 1993b).

This effect appears to be directly attributable to components in the cigarette smoke itself, rather than to an increase in adrenergic tone resulting from the discomfort associated with the forced breathing of secondhand smoke. Sun and colleagues (1994) exposed rabbits to secondhand smoke in an experiment similar to that of Zhu and colleagues (1993b) and gave half of the rabbits the beta-blocking drug metoprolol. As expected, the animals receiving metoprolol developed fewer lipid deposits than those receiving a placebo (saline), but this effect was independent of whether the rabbits were breathing secondhand smoke. Therefore, increased levels of catacholamines did not mediate the effect of secondhand smoke on the development of atherosclerotic-type lesions in the arteries.

Experiments exposing rabbits to secondhand smoke from standard (Marlboro) and nicotine-free cigarettes produced similar levels of lipid deposits. This finding suggests that nicotine is not the primary atherogenic agent, and there are other combustion products in cigarette smoke that may be responsible for the atherosclerosis (Sun et al. 2001).

Critics have questioned the findings of this rabbit model of atherosclerosis because the animals are fed a high-cholesterol diet in order to develop lesions within a reasonable time (Wu 1993). This experimental model of atherosclerosis has been used since 1908 (Zhu et al. 1993a). Supporting findings come from a different model of plaque development that used young cockerels between the ages of 6 and 22 weeks that were exposed to secondhand smoke for six hours a day, five days a week, for 12 weeks (Penn and Snyder 1993; Penn et al. 1994). The cockerels ate a normal, low-cholesterol diet and were exposed to lower secondhand smoke levels than the rabbits were. The incidence of plaque development was the same in the cockerels breathing secondhand smoke and those breathing clean air. However, the growth rate of the plaques was greater in the exposed animals.

Some specific components have been evaluated in that same model with effects that are not likely to be attributable to the CO in the smoke because exposure of cockerels to high doses of CO (Penn et al. 1992), to tobacco-specific nitrosamines (Penn and Snyder 1996b), or to the tar fraction of the smoke (Penn et al. 1996) did not produce similar effects. Thus, agents in the vapor phase of the smoke appear to be the atherogenic agents; 1,3 butadiene (Penn and Snyder 1996a,b) and 7,12-dimethylybenz[*a*]anthracene (Penn et al. 1981) did increase the amount of atherosclerotic plaque in this experimental model.

Gairola and colleagues (2001) studied the effects of secondhand smoke on apolipoprotein E -/- mice that were on a high-cholesterol diet, which is another model for human atherosclerosis. After exposure to secondhand smoke from University of Kentucky 1R4F research cigarettes for six hours a day, five days a week, for up to 14 weeks, there was a dose-dependent increase in the fraction of the aorta that was covered with atherosclerotic lesions. The exposed

mice had significant increases compared with control animals on the same diet who had breathed clean air for just seven days, with the effect increasing over time. The exposed mice had lesions that were about twice the size of those found in the clean-air controls; there were similar increases in the cholesterol content of the aortas in the exposed mice.

Elements in the smoke rapidly affect the process of incorporating LDL cholesterol into the linings of arteries. Roberts and colleagues (1996) used isolated perfused carotid arteries from rats exposed to secondhand smoke for two or four hours. The researchers demonstrated a synergistic effect between secondhand smoke and LDL that facilitated the binding of oxidized LDL to the vessel wall (Roberts et al. 1996). Rats exposed to secondhand smoke for just two hours had higher rates of incorporation of LDL cholesterol into their carotid arteries.

Secondhand smoke exposure induces atherosclerotic-like changes in four different species of experimental animals after only a few weeks of exposure to secondhand smoke at levels similar to those experienced by people in normal day-to-day life. These findings provide strong support for the epidemiologic evidence that exposure to secondhand smoke causes heart disease. The experimental studies on rabbits, cockerels, mice, and rats were not affected by potential confounding and support a causal conclusion by showing that atherosclerosis can be induced in experimental animals exposed to secondhand smoke.

Oxygen Delivery, Processing, and Exercise

Secondhand smoke reduces the ability of the blood to deliver oxygen to the myocardium. The CO in secondhand smoke competes with oxygen for binding sites on hemoglobin and thus displaces oxygen (USDHHS 1983, 1986; Leone et al. 1991; U.S. Environmental Protection Agency 1991). Children of smoking parents have elevated levels of 2,3-diphosphoglycerate, a compound that increases in red blood cells to compensate for reduced oxygen availability (Moskowitz et al. 1990, 1993) and is associated with serum thiocyanate levels, a measure of secondhand smoke exposure (Moskowitz et al. 1990).

Evidence from animal studies shows that in addition to reducing the ability of the blood to deliver oxygen to the heart, secondhand smoke may reduce the ability of the heart muscle to convert oxygen into the "energy molecule" adenosine triphosphate (ATP). In a rabbit model, there was an approximate 25 percent reduction in cytochrome oxidase activity after a single 30-minute exposure to secondhand smoke, and the activity continued to drop with a prolonged exposure; after eight weeks of exposure for 30 minutes per day, its activity was 50 percent of the level found in controls (Gvozdják et al. 1987). Thus, not only does secondhand smoke exposure reduce the ability of the blood to deliver oxygen to the myocardium, it may also reduce the ability of the myocardium to effectively use the oxygen it receives (Gvozdjáková et al. 1984, 1985, 1992; Gvozdják et al. 1987).

Secondhand smoke also significantly increases the amount of lactate in venous blood with an exercise challenge (McMurray et al. 1985). Eight women with and without exposure to tobacco smoke through a mouthpiece (concentration not given) engaged in exercises. Compared with the unexposed group, the exposed group documented a lower maximum oxygen uptake and a higher blood lactate. People with CHD cannot exercise as long or reach a level of exercise as high after breathing secondhand smoke, even relatively briefly, compared with breathing clean air (Aronow 1978; Khalfen and Klochkov 1987; Leone et al. 1991). Another study showed that 10 persons with a past MI were more likely to develop increased arrhythmias from exercise following secondhand smoke exposure (Leone et al. 1992).

Free Radicals and Ischemic Damage

Free radicals are highly reactive oxygen products (Church and Pryor 1985; Ferrari et al. 1991) that are destructive to the heart muscle cell membrane as well as to other processes within the cell. Tobacco smoke contains high levels of activated oxygen species, and the inflammatory consequences of tobacco smoke components in various organs are thought to be a critical path of injury. Antioxidants provide protection against the free radicals, but levels of antioxidants, such as beta-carotene and vitamin C, tend to be lower in active smokers (USDHHS 2004) and possibly in involuntary smokers (Farchi et al. 2001).

Experiments have demonstrated that exposure to secondhand smoke worsens the outcome of an ischemic event in the heart through the activity of free radicals during reperfusion injury. Animal studies indicate that low exposures to nicotine or to other cigarette smoke constituents significantly worsen reperfusion injury. Intravenous administration of the amount of nicotine delivered by just one cigarette doubled the reperfusion injury in a dog model of MI (Przyklenk 1994). This dose was low and had no effect on heart rate, blood pressure, regional myocardial shortening,

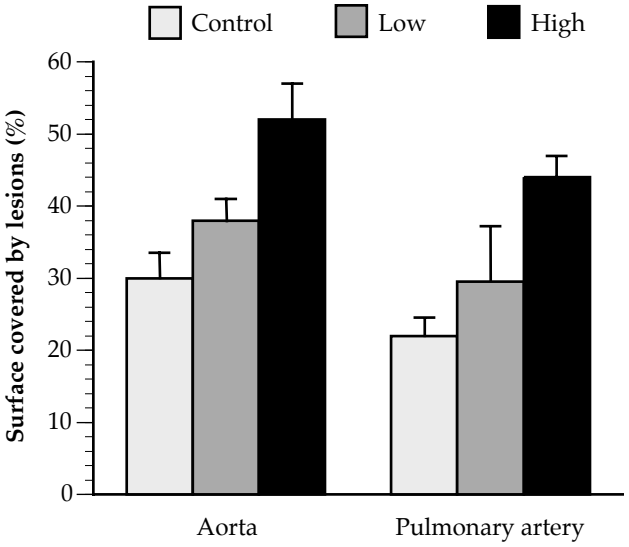
Table 2.6 Studies of experimental atherosclerosis in animals exposed to secondhand smoke

		Secondhand smoke exposure			
Study	**Species**	**Source**	**Duration**	**Measure**	
Penn and Snyder 1993	Cockerel	1R4F research cigarettes	6 hours/day, 5 days/ week for 16 weeks	Nicotine: CO[†]: Particulates:	365–414 μg/m^3* 35 ppm[‡] 8 mg[§]/m^3
Zhu et al. 1993a	Rabbit	Marlboro	6 hours/day, 5 days/ week for 10 weeks	Low exposure Air nicotine: CO: Particulates: High exposure Air nicotine: CO: Particulates:	 30 μg/m^3 19 ppm 4 mg/m^3 1,000 μg/m^3 60 ppm 33 mg/m^3
Penn et al. 1994	Cockerel	1R4F research cigarettes	1 cigarette/day, 5 days/week for 16 weeks	Nicotine: CO: Particulates:	90–130 μg/m^3 4 ppm 2.5 mg/m^3
Sun et al. 1994	Rabbit	Marlboro	6 hours/day, 5 days/ week for 10 weeks	Air nicotine: CO: Particulates:	1,100 μg/m^3 60–70 ppm 38 mg/m^3
Roberts et al. 1996	Rat	Data were not reported	2 or 4 hours	Nicotine: CO: Particulates:	615 μg/m^3 18 ± 2 ppm 3 μg/m^3
Gairola et al. 2001	Mouse	1R4F research cigarettes	6 hours/day, 5 days/ week for 7, 10, and 14 weeks	Blood CO hemoglobin: Particulates:	10% in secondhand smoke-exposed mice 25 mg/m^3
Sun et al. 2001	Rabbit	Standard or nicotine-free research cigarettes	6 hours/day, 5 days/ week for 10 weeks	CO: Particulates:	45–54 ppm 24–35 mg/m^3

*μg/m^3 = Micrograms per cubic meter.
[†]CO = Carbon monoxide.
[‡]ppm = Parts per million.
[§]mg = Milligram.
[Δ]LDL = Low-density lipoprotein.

End point	Findings
Number and size of plaques in aortic segments	• Exposure had no effect on the number of plaques • Plaques in exposed animals were significantly larger (median size about 1.5 times larger in each aortic segment) than in unexposed animals
Area of atherosclerotic lesions by planimetry in aorta and pulmonary artery; bleeding time (to measure platelet activity)	• High-exposure secondhand smoke group had dose-dependent lipid deposits with lesion size about 1.7 times larger than those in the low-exposure group • Low-exposure group was between the high-exposure and control groups • Bleeding times were shorter in rabbits that breathed secondhand smoke • No differences between high-dose and low-dose exposures for serum triglycerides, cholesterol, and high-lipoprotein cholesterol
Number and size of plaques in aortic segments	• Exposure had no effect on the number of plaques • Plaques in exposed animals were significantly larger (median size about 1.5 times larger in each aortic segment) than those in unexposed animals
Area of atherosclerotic lesions by planimetry in aorta and pulmonary artery; bleeding time (to measure platelet activity)	• Secondhand smoke exposure was associated with greater lipid deposits and shorter bleeding times • Metoprolol did not block these effects, indicating that they are not mediated by increased circulating catecholamines
Uptake of LDL$^{\Delta}$ cholesterol in isolated perfused carotid artery	• Rate of LDL uptake more than quadrupled
Area of atherosclerotic lesions at several places in aorta measured by planimetry; cholesterol content of aortic segments	• Increasing lesion size and cholesterol content over time in both groups • Secondhand smoke-exposed mice had approximately twice the level of atherosclerosis as controls at any given time
Area of atherosclerotic lesions by planimetry in aorta and pulmonary artery	• Secondhand smoke increased the area of arteries with lipid deposits by about 50% • There was no significant difference between nicotine and nicotine-free cigarette smoke

Figure 2.7 Secondhand smoke exposure and lipid deposits in rabbits



Note: Exposure to secondhand smoke increased lipid deposits in arteries of rabbits in a dose-dependent manner. Bars are for controls (clear air), and low doses and high doses of secondhand smoke exposures. Error bars represent standard error of the mean.
Source: Zhu et al. 1993b. Reprinted with permission.

or on other hemodynamic measures of cardiac function that are commonly affected by nicotine in active and involuntary smokers (Benowitz 1991). After an ischemic episode from ligation of the left anterior descending coronary artery for 15 minutes, the regional shortening during reperfusion was reduced by 50 percent of the pre-ischemic values. When the dog was exposed to nicotine from just a single cigarette, the regional shortening during reperfusion was reduced by 25 percent of control values. When the dog was given a free radical scavenger along with the nicotine, this effect was obliterated. Thus, exposure to a very low dose of nicotine doubled the impact of the reperfusion injury on the myocardium.

The effects of free radicals induced by secondhand smoke have been explored at the cellular level (van Jaarsveld et al. 1992a,b). Rats exposed to secondhand smoke from two cigarettes a day for two months exhibited severely damaged mitochondrial function during reperfusion injury. Thus, the ability of cardiac mitochondrial cells to convert oxygen into ATP was more compromised during reperfusion injury among rats exposed to these low doses than among control rats.

Secondhand smoke exposure is associated with lower levels of antioxidant vitamins in nonsmoking women (Farchi et al. 2001). Despite a similar dietary intake of beta-carotene, retinol, L-ascorbic acid, and alpha-tocopherol, women whose husbands smoked exhibited a dose-dependent relationship between the extent of exposure and plasma concentrations of beta-carotene and L-ascorbic acid. These associations persisted even after controlling for daily beta-carotene and vitamin C intake and for other potential confounders (vitamin supplementation, alcohol consumption, and body mass index). A similar dose-response relationship was observed when urinary cotinine was used as the measure of exposure.

In a mouse model, a 30-minute exposure to secondhand smoke also produced evidence of oxidative DNA damage in the myocardium assessed by increased levels of 8-OH-dG (Howard et al. 1998a). There are also parallel human data. In a cross-sectional study, persons exposed to secondhand smoke at work exhibited increased levels of 8-OH-dG (Howard et al. 1998b). The plasma cotinine levels were 65 percent higher in the exposed group compared with controls, and increases in 8-OH-dG levels were similar. In workers exposed to secondhand smoke, 8-OH-dG levels fell after 60 days of antioxidant supplementation (Howard et al. 1998c).

There is also evidence that smokers are less sensitive to free radical damage from cigarette smoke than nonsmokers are because of changes in the levels of enzymes that control free radicals (McCusker and Hoidal 1990). When hamsters were exposed to secondhand smoke from six cigarettes a day for eight weeks, the activity of antioxidant enzymes in their lungs nearly doubled. Similar changes found in the lungs of smokers compared with nonsmokers provide further evidence that secondhand cigarette smoke may affect smokers and nonsmokers differently. Chronic exposures to cigarette smoke appear to increase the capacity of free radical scavenging systems in smokers.

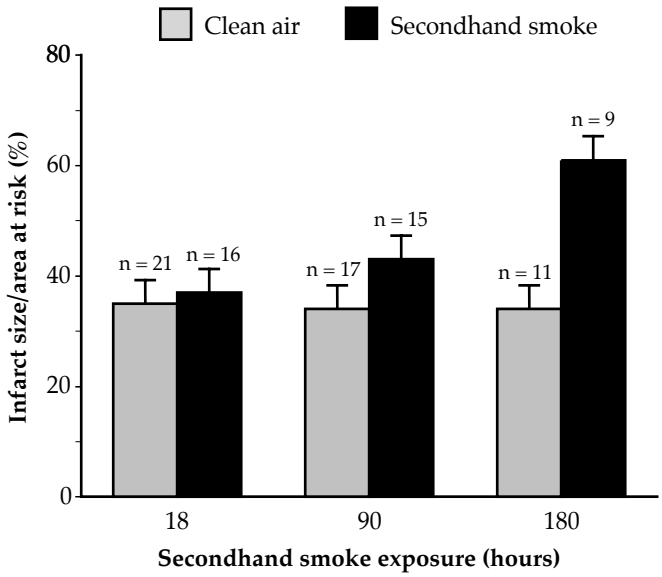
In addition, human exposures to secondhand smoke sensitize lung neutrophils (Anderson et al. 1991). As with platelets, neutrophils are an important element of the body's defenses against infection and damage. Inappropriately activated neutrophils, however, release oxidants that can play a role in tissue damage. In a group of nonsmokers exposed to three hours of sidestream smoke at relatively high levels

(respirable particles >2,000 micrograms/m^3), there were significant increases in circulating leukocyte counts, in stimulated neutrophil migration, and in the release of reactive oxidents by neutrophils.

Myocardial Infarction

Several of the effects discussed above would lead to the expectation that exposure to secondhand smoke would increase the severity of MIs. Direct animal data show that secondhand smoke increases tissue damage following a MI. Dogs exposed to secondhand smoke for one hour daily for 10 days and then subjected to a coronary artery blockage developed MIs that were twice as large as those found in controls breathing clean air (Prentice et al. 1989). This effect was not due to elevated circulating levels of nicotine or carboxyhemoglobin, because the infarcts were created the day after the last day of secondhand smoke exposure. Zhu and colleagues (1994) conducted an experiment in rats to investigate the effects of secondhand smoke exposure on infarct size. Rats were exposed to secondhand smoke six hours a day for three days, three weeks, or six weeks, and then subjected to a left coronary artery occlusion for 35 minutes followed by reperfusion. There was a dose-dependent increase in infarct size, with the longest exposure of 180 hours yielding infarcts nearly twice as large as in the control group that breathed clean air (Figure 2.8). This effect could be countered by feeding the animals L-arginine (Zhu et al. 1996). This finding suggests that the effect of secondhand smoke in producing an MI comes from interference with the vascular endothelium. There is no evidence indicating a threshold level of exposure that is needed to produce this effect.

Figure 2.8 Secondhand smoke exposure and infarct size in rats



Note: Exposure to secondhand smoke increased infarct size in rats subjected to a 35-minute occlusion of the left coronary artery in a dose-dependent manner. There is no evidence of a threshold effect.
Source: Zhu et al. 1994. Adapted with permission.

Heart Rate Variability

Alterations in heart rates are caused by the opposing effects of the sympathetic and parasympathetic nervous systems on the sino-atrial node (the pacemaker of the heart) through the elevation of catecholamines. The sympathetic nervous system tends to oppose the rate-slowing effects of the parasympathetic (vagus) nervous system, and sympathetic activation reduces heart rate variability. If sympathetic tone is reduced and vagal activity enhanced, heart rate variability increases. Clinically, decreased heart rate variability predicts a higher risk of cardiac death or arrhythmic events after an acute MI, presumably reflecting the adverse effects of increased sympathetic tone (Kleiger et al. 1987; Singh et al. 1996).

Activation of the sympathetic nervous system would tend to reduce heart rate variability. One experimental study has tested this hypothesis. Pope and colleagues (2001) measured heart rate variability in healthy young adults for two hours in the smoke-free areas of a U.S. airport, followed by two hours in the smoking area, and then repeated this protocol. When the experimental participants were in the smoking area, heart rate variability was 12 percent lower. The levels of secondhand smoke were not high enough to affect mean heart rate or blood pressure, but the secondhand smoke exposure was associated with altered cardiac autonomic function in a direction consistent with an increased risk of a cardiac event.

Summary

A source of uncertainty in interpreting evidence on secondhand smoke exposure and heart disease has been the apparently large size of the effect compared with active smoking. Active smoking delivers doses

of the toxins in secondhand smoke that are markedly greater than the doses received by a nonsmoker, and active smoking approximately doubles, depending on the amount smoked, the risk of heart disease (USDHHS 1983). Thus, the effect of secondhand smoke may appear large for the associated doses of cigarette smoke components, particularly since secondhand smoke exposure generally does not produce changes in systemic physiologic measures such as heart rate or blood pressure (Celermajer et al. 1996; Hausberg et al. 1997; Sumida et al. 1998; Otsuka et al. 2001). However, findings of a wide variety of clinical and experimental studies of various designs demonstrate that the effects of secondhand smoke on the cardiovascular system occur at low doses in nonsmokers, with some of the effects (on platelets and vascular function) similar to those in active smokers. For this reason, it is not appropriate to scale from the effects of active smoking in a linear, dose-dependent approach to estimate the effects of exposure to secondhand smoke based on comparative doses of smoke components (Howard and Thun 1999).

Secondhand smoke interferes with the normal functioning of the heart, blood, and vascular systems in ways that increase the risk of a cardiac event. For some of these effects (changes in platelet and vascular function), the immediate effects of even short exposures to secondhand smoke appear to be as large as those seen in association with active smoking of one pack of cigarettes a day. Some evidence indicates lower levels of circulating antioxidants associated with secondhand smoke exposure. The experimental and observational evidence reviewed in this chapter supports the plausibility of the findings of the epidemiologic studies reviewed in Chapter 8 (Cardiovascular Diseases from Exposure to Secondhand Smoke). The large body of evidence documenting that secondhand smoke produces substantial and rapid effects on the cardiovascular system demonstrates that even a brief exposure to secondhand smoke has adverse consequences for the heart, blood, and blood vessels (Glantz and Parmley 2001; Barnoya and Glantz 2005).

Conclusions

1. The evidence is sufficient to infer that exposure to secondhand smoke has a prothrombotic effect.

2. The evidence is sufficient to infer that exposure to secondhand smoke causes endothelial cell dysfunctions.

3. The evidence is sufficient to infer that exposure to secondhand smoke causes atherosclerosis in animal models.

Evidence Synthesis

This chapter reviews the substantial amount of data from cellular, animal, and human studies supporting the overall conclusion that exposure to secondhand smoke causes a broad range of adverse effects in both children and adult nonsmokers. These data provide a strong foundation for the biologic plausibility of causal conclusions related to specific diseases and other adverse health effects that are reviewed in Chapters 5 through 9. This chapter provides substantial additional evidence on the underlying pathogenic mechanisms for major adverse health outcomes associated with exposure to secondhand smoke.

Secondhand smoke is a complex mixture of thousands of chemicals emitted from burning tobacco. The toxicologic profiles of a large number of these specific chemicals and compounds are well established (http://www.atsdr.cdc.gov/toxpro2.html). This chemical mixture includes more than 50 carcinogens, and both IARC (2004) and the National Toxicology Program (USDHHS 2000) have classified this mixture as a known human carcinogen. Researchers have thus concluded that exposure to secondhand smoke can cause DNA damage and genetic mutations. For DNA-damaging carcinogens, the occurrence of permanent mutations implies that there is no level of exposure that does not pose a risk.

The complex mixture of chemicals in secondhand smoke also contains a large number of toxicants harmful to the respiratory and cardiovascular systems. Evidence from both animal and human studies indicates that exposures to secondhand smoke can produce substantial and rapid adverse effects on the

functioning of the heart, blood, and vascular systems in ways that increase the risk of a cardiac event. Furthermore, many of these acute and chronic changes in blood and vascular function appear to be as large as those seen in active smokers. The immediate effects in some measures of blood and vascular functioning among nonsmokers from even brief exposures (i.e., 30 minutes or less) to secondhand smoke are comparable in magnitude to the effects observed in active smokers. Thus, the evidence reviewed in this chapter supports the biologic plausibility of adverse cardiovascular health outcomes that are associated with exposure to secondhand smoke, which are reviewed in Chapter 8.

As the portal of entry for secondhand smoke, the respiratory system is the initial site of deposition for the particulate and gaseous compounds found in secondhand smoke. This chapter identifies the multiple mechanisms by which secondhand smoke exposure can induce both acute and chronic adverse health effects within the respiratory tract that affect infants, children, and adults. The evidence for underlying mechanisms of respiratory injury from exposure to secondhand smoke suggests that a safe level of exposure may not exist, thus implying that any exposure carries some risk. For infants, children, and adults with asthma or with more sensitive respiratory systems, even very brief exposures to secondhand smoke can trigger intense bronchopulmonary responses that could be life threatening in the most susceptible individuals.

Animal and human studies indicate that prenatal and postnatal exposure to nicotine and other toxicants in tobacco smoke may affect the neuroregulation of breathing, apneic spells, and sudden infant death. Experimental data on the neurotoxicity of prenatal and neonatal exposure to nicotine and secondhand smoke in animal models can be related to several potential causal mechanisms for SIDS, including adverse effects on brain cell development, synaptic development and function, and neurobehavioral activity. Finally, studies have documented that exposure to tobacco smoke from active smoking has a broad effect on immune function and host defenses against infectious agents. Evidence indicates that exposure to secondhand smoke appears to also impair immune function in both children and adult nonsmokers, which increases susceptibility to infection.

Conclusions

Evidence of Carcinogenic Effects from Secondhand Smoke Exposure

1. More than 50 carcinogens have been identified in sidestream and secondhand smoke.

2. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and its condensates and tumors in laboratory animals.

3. The evidence is sufficient to infer that exposure of nonsmokers to secondhand smoke causes a significant increase in urinary levels of metabolites of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). The presence of these metabolites links exposure to secondhand smoke with an increased risk for lung cancer.

4. The mechanisms by which secondhand smoke causes lung cancer are probably similar to those observed in smokers. The overall risk of secondhand smoke exposure, compared with active smoking, is diminished by a substantially lower carcinogenic dose.

Mechanisms of Respiratory Tract Injury and Disease Caused by Secondhand Smoke Exposure

5. The evidence indicates multiple mechanisms by which secondhand smoke exposure causes injury to the respiratory tract.

6. The evidence indicates mechanisms by which secondhand smoke exposure could increase the risk for sudden infant death syndrome.

Mechanisms of Secondhand Smoke Exposure and Heart Disease

7. The evidence is sufficient to infer that exposure to secondhand smoke has a prothrombotic effect.
8. The evidence is sufficient to infer that exposure to secondhand smoke causes endothelial cell dysfunctions.
9. The evidence is sufficient to infer that exposure to secondhand smoke causes atherosclerosis in animal models.

Overall Implications

The biologic mechanisms reviewed in this chapter underlie a wide range of acute and chronic adverse health effects in infants, children, and adults examined in Chapters 5 through 9. This broadly reaching body of evidence on the toxicology of secondhand smoke and on these biologic mechanisms indicates that any exposure to secondhand smoke will increase risk for adverse health outcomes.

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Chapter 3
Assessment of Exposure to Secondhand Smoke

Introduction

This chapter provides a review of key factors that determine exposures of people to secondhand smoke in indoor environments. The discussion describes (1) the dynamic movement of secondhand smoke throughout indoor environments, (2) the factors that determine secondhand smoke concentrations in these environments, (3) the atmospheric markers of secondhand smoke that are measured to assess concentrations, (4) the biomarkers that are measured to assess doses of tobacco smoke components, and (5) the models that can be used to describe patterns of human exposures. Chapter 4 (Prevalence of Exposure to Secondhand Smoke) reports on findings of studies on exposures to secondhand smoke that applied these methods with a focus on measurements of nicotine in the air and cotinine in biologic materials. The validity of nicotine as a marker for secondhand smoke concentrations supports the use of cotinine, a principal metabolite of nicotine, as an exposure biomarker.

As described earlier, the term secondhand smoke refers to a complex mixture of particulate (or solid) and gaseous components. The characteristics of secondhand smoke change over time, particularly the components of sidestream smoke that the smoldering cigarette releases. Sidestream smoke dilutes quickly and changes as the particles release volatile compounds and change in size and composition as they age. Although few studies have made measurements, available data indicate that the estimated median aerodynamic diameter of secondhand smoke particles is 0.4 micrometers (μm), a size range where particles tend to remain suspended in the air unless removed by diffusion to or impaction with a surface, or by air cleaning (Hiller et al. 1982; Jenkins et al. 2000).

The composition of secondhand smoke was addressed in the 1986 report of the Surgeon General, *The Health Consequences of Involuntary Smoking* (U.S. Department of Health and Human Services [USDHHS] 1986), and was the focus of a comprehensive monograph first published in 1992 and updated in 2000 (Guerin et al. 1992; Jenkins et al. 2000). The 1986 report commented on the richness of secondhand smoke as a mixture and its inherent variability over time and space as it moves through the air (USDHHS 1986). Nonetheless, the report concluded that secondhand smoke and mainstream smoke were qualitatively similar, a conclusion that subsequent research supports (U.S. Environmental Protection Agency [USEPA] 1992; Scientific Committee on Tobacco and Health 1998; International Agency for Research on Cancer [IARC] 2004).

People are exposed to secondhand smoke in multiple places where they spend varying amounts of time. The term "microenvironment" refers to places that have a fairly uniform concentration of a mixture of pollutants across the time that is spent there (National Research Council [NRC] 1991; Klepeis 1999a). In the microenvironmental model, total human exposure to an atmospheric contaminant, such as secondhand smoke, represents the time-integrated sum of the exposures in the multiple microenvironments where time is spent. The source of secondhand smoke—the burning cigarette—produces the resulting concentrations of secondhand smoke in the air of places where people spend time. The concentration depends on the intensity of smoking, dilution by ventilation, and other processes that remove smoke from the air. The consequent exposures lead ultimately to doses of secondhand smoke components that reach and harm target organs and manifest as adverse health effects. This conceptual framework, which is central to this chapter, makes clear distinctions between cigarette smoking as the source, secondhand smoke concentrations in the air (the amount of material present per unit volume), exposures to secondhand smoke (the time spent in contact with secondhand smoke at various concentrations), and the doses from secondhand smoke exposure (the amount of material entering the body). The strength of the source—cigarette smoking—depends on the number of smokers and the rate at which they are smoking. Total human exposure can be estimated by measuring secondhand smoke concentrations in key microenvironments and assessing the time spent in those environments. Concentrations are also determined by aspects of the design and operation of a building (NRC 1986, 1991).

The mass balance model is a conceptual approach that provides a framework for how the design and operation of a building may affect secondhand smoke concentrations within the building (Ott 1999). In this model, which is considered in more detail later in this chapter (see "Exposure Models"), the concentration of indoor air contaminants (such as secondhand smoke) is a function of the strength of the source(s) generating the contaminant, the dilution of the contaminant by the exchange of outdoor with indoor air, and the rate of removal of the contaminant by air cleaning and other processes.

Building Designs and Operations

Determinants of Secondhand Smoke Concentrations

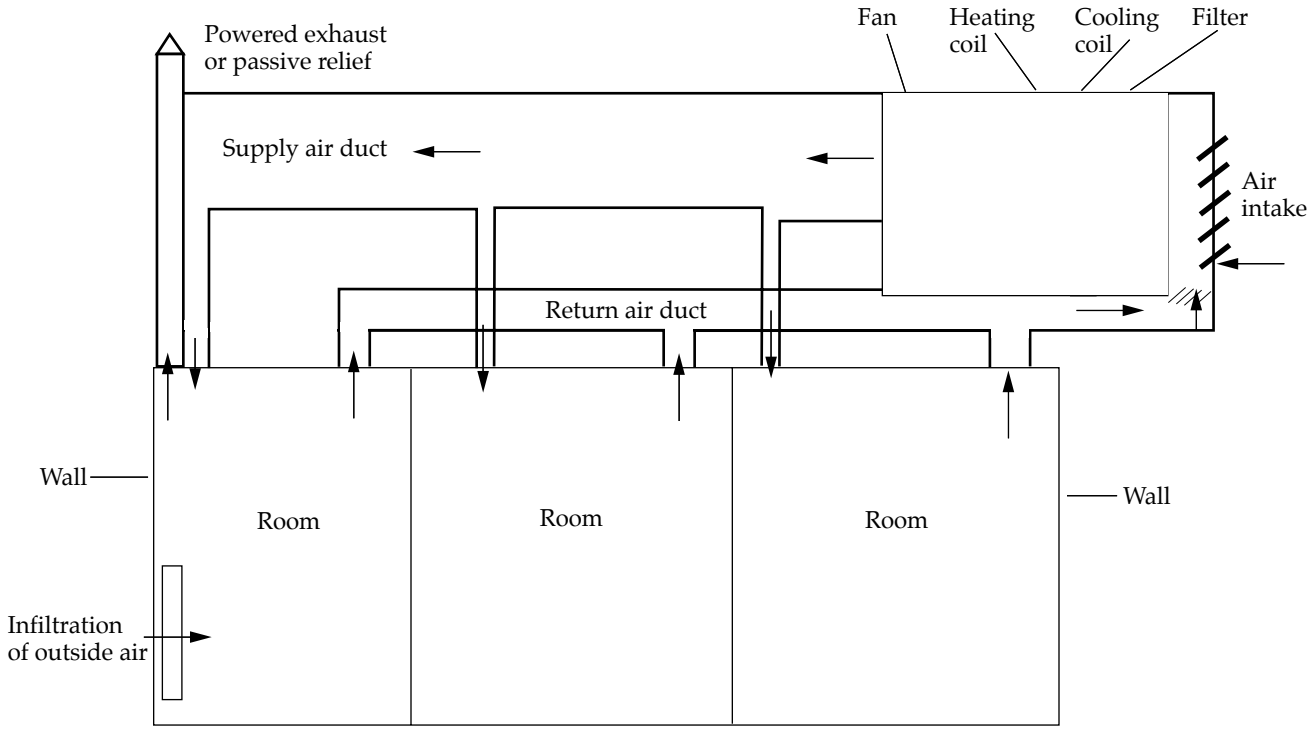
When people are exposed to secondhand smoke in indoor environments, the concentrations to which they are exposed depend not only on the number of cigarettes smoked, which determines the strength of the source, but on how air moves through buildings and at what rate indoor air is exchanged with outdoor air. The exchange of indoor with outdoor air is referred to as ventilation (American Society of Heating, Refrigerating and Air-Conditioning Engineers [ASHRAE] 1989). In general, the concentration of an indoor contaminant in a building or in a space within a building depends on the volume of the space and the rate at which the contaminant is generated and then removed. The removal may be by ventilation, air cleaning, or other processes such as chemical reactions or adsorption onto surfaces. This set of relationships is referred to as the mass balance model. It implies that concentrations of secondhand smoke components in a space (1) increase as the number of cigarettes smoked increases, (2) decrease with an increase in ventilation, and (3) decrease in proportion to the rate of cleaning or removal of secondhand smoke components from the air (Ott 1999). The cleaning or removal processes might include active air cleaning with a device, the naturally occurring passive deposition of particles onto surfaces, and the adsorption of gases onto materials.

The factors in the mass balance model vary across different kinds of buildings. Buildings can be ventilated using natural or mechanical methods. Air can be supplied naturally through windows, louvers, and leakages through building envelopes; air is supplied mechanically through a heating, ventilating, and air conditioning (HVAC) system that usually includes fans, duct work, and a system for delivering air in a controlled manner throughout a building (Figure 3.1). In most homes, ventilation occurs by a naturally occurring exchange of indoor with outdoor air. Commercial and public buildings generally have HVAC systems that move air through buildings to accomplish the exchange of indoor with outdoor air. Important considerations are variations in the range of surfaces and their characteristics across different kinds of buildings and microenvironments. For example, most HVAC systems incorporate a component for air cleaning that typically removes large particles but not the smaller particles or the gases found in secondhand smoke. The central air cleaning systems in homes and in many commercial buildings generally are not designed to remove smaller particles or gases (Spengler 1999).

Heating, Ventilating, and Air Conditioning Systems

For modern public and commercial buildings, often with sealed windows, air ventilation is required to provide a safe, functional, and comfortable environment for the occupants, and is defined as "outside air" delivered to or brought indoors. For many types of indoor environments, mechanical ventilation systems are used to control contaminant concentrations and to meet the comfort needs of occupants. Such systems are almost always used in hospitals, large office buildings, theaters, hospitality venues, schools, and many other larger buildings. This discussion addresses how these systems affect secondhand smoke concentrations in indoor environments and focuses on public and commercial buildings where HVAC units are generally in place. Mechanical systems are intended to provide thermally conditioned air, dissipate thermal loads, and dilute contaminants (Bearg 2001). These systems can also be used to maintain pressure differentials between areas when air is extracted and exhausted from specific spaces, or to clean and recirculate the air using filters, catalytic converters, and various sorbent beds. The efficiencies and costs for an entire ventilation system vary depending on specific requirements and settings (Liddament 2001). Although mechanical systems are widely used for general ventilation, their potential use as a control strategy for secondhand smoke requires a detailed understanding of the constituents to be controlled, the air distribution patterns within structures, the air cleaning or extraction techniques, and the requirements for ongoing operation and maintenance (Ludwig 2001). If not properly designed and maintained, mechanical systems can increase the risk of exposures by distributing pollutants (including secondhand smoke) throughout the building, by direct recirculation, or by poor pressure control.

Figure 3.1 Schematic of a typical air handling unit



Source: U.S. Environmental Protection Agency 1994, with modifications.

Complex and dynamic processes affect the characteristics and concentrations of secondhand smoke. As a foundation for considering ventilation systems commonly found in buildings, here is a description of the transport and fate of particles and gases released from a burning cigarette. In still air, the smoke plume from a cigarette is often observed rising intact as high as several meters above the burning tip. If plume gases remain concentrated, they are buoyant and have a temperature several degrees higher than the surrounding room air temperature. If the room air is not still, as in buildings with mechanical air handling systems, or if people move within the space, there will be some mixing that breaks up the plume and disperses "pockets" of smoke throughout the air space (Klepeis 1999b). Concentrations of secondhand smoke components are then reduced and, as the smoke spreads and ages, its components change as a result of condensation, evaporation, coagulation, and deposition to surfaces. The characteristics of secondhand smoke within a particular building thus depend, to an extent, on chemical and physical characteristics of spaces that vary among buildings. Volatile components such as nicotine are adsorbed and degassed by materials. As a consequence, the smell of cigarettes emanates from clothing, carpets, air conditioners, and other surfaces without the presence of active smoking, as previously deposited or adsorbed material is re-emitted by air currents (Klepeis 1999b).

Although interactions in the air and at surfaces modify the secondhand smoke mixture, under most circumstances concentrations within the original space will depend strongly on an exchange of air in the space with less contaminated air (Spengler 1999). Mechanically delivered air disperses secondhand smoke constituents through mixing (turbulence) and dilutes secondhand smoke by supplying less contaminated air. Generally, mechanical mixing is significantly more effective in reducing concentrations from a "point source" of pollution in a room, such as a burning cigarette, than is diffusion alone in still air. Air exchange and surface removal processes act together to lower secondhand smoke concentrations. Surface removal is enhanced if air is forced through

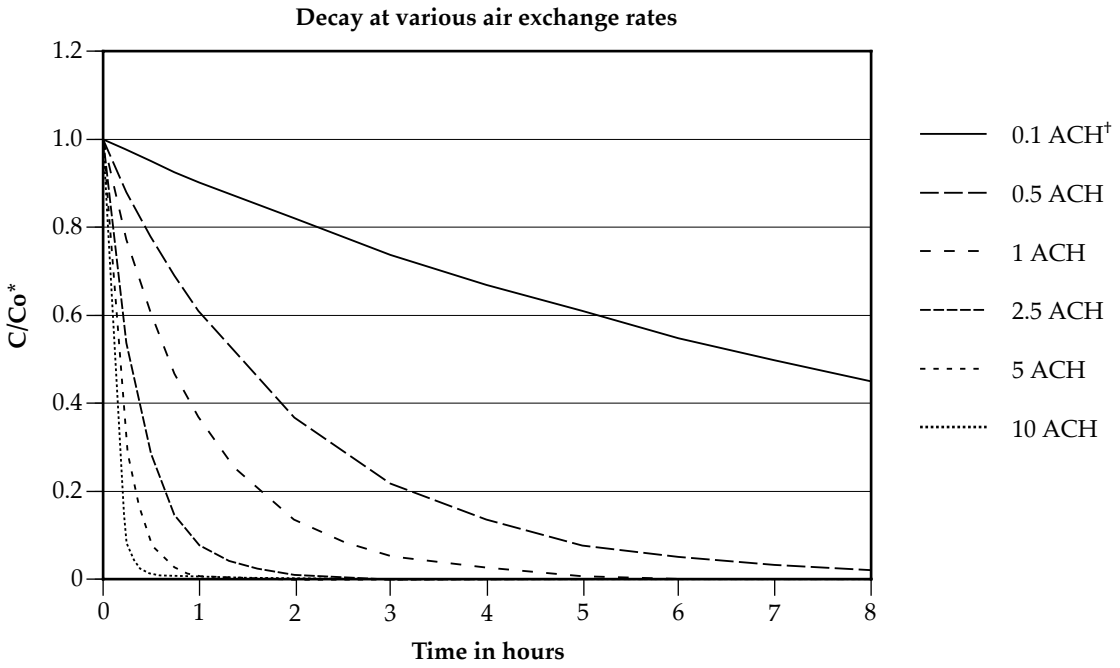
an air cleaning device and delivered back to the room with a reduced secondhand smoke concentration (McDonald and Ouyang 2001).

Building Ventilation Control

Mechanical HVAC systems that heat, ventilate, and air-condition indoor spaces achieve controlled building ventilation (Spengler 1999). The HVAC systems in buildings are composed of air handling units (AHUs) of various sizes and complexities that filter and condition air supplied to the building with varying degrees of effectiveness, depending upon need, design, and maintenance. Components of AHUs typically include fans, filters, cooling coils, and heat exchangers. Air ventilated by air conditioning (i.e., mechanical cooling) can be ducted to separate areas within a building and removed with an air return system that recirculates and/or exhausts the air. In Figure 3.1, a schematic demonstrates a typical AHU configured for general ventilation and pressure relationship control (USEPA 1994).

Three major categories are used for airborne contaminant control: general or dilution ventilation, displacement ventilation, and local exhaust ventilation. General or dilution ventilation requires mixing large volumes of outdoor air with room air. Although this ventilation system is the most commonly used method in buildings today for thermal comfort, it is not very efficient for controlling contaminant emissions from human activities such as smoking. Its effectiveness is highly dependent upon the number and location of emission sources (the smokers), the volume of air supply to the room, the capacity of materials and surfaces to remove various constituents of secondhand smoke, and the mixing efficiency of the room. Figure 3.2 demonstrates that the term "air exchange rate," when applied to dilution ventilation, is a misnomer. Mixing the supply air within the zone served by the AHU is often not uniform or complete. Even for a well-mixed space, one air change per hour (ACH) means that only 63.2 percent of the original air, including the corresponding airborne contaminants, is removed in one hour. So even though an amount

Figure 3.2 Anticipated changes in concentrations of airborne materials for various air exchange rates



*C/Co = Fraction of original concentration of contaminant at time t.
†ACH = Air changes per hour.

of air equivalent to the volume of the room is introduced during one hour, it does not completely replace all of the air occupying the space previously. Short-circuiting or moving air directly from inlets to the exhaust without mixing, obstructions to supply and exhaust air, and thermal gradients can reduce the mixing efficiency to much less than the theoretical limit. Thus, an air exchange rate greater than that made with simple calculations based on the volume of the space may be required to effect a meaningful reduction in airborne concentrations of various contaminants (Liddament 2001). Simple mass balance and volumetric calculations assume perfect mixing, no sink effects (the adsorption and possible re-emission of pollutants by materials acting as "sinks" [Sparks 2001]), and constant emission sources; these conditions generally are not met in real-world indoor environments. Any occupant of a space, particularly a space near a pollution source, may be exposed to much higher concentrations than estimated for the overall area.

Displacement ventilation, which is also referred to as piston or plug flow, conditions the space and removes contaminants by admitting air at one location and "sweeping" it across the space before exhausting it at the opposite "face." This design often uses low-velocity grills at or near floor level to admit cool supply air into the space that is then exhausted at ceiling level. For maximum effectiveness, displacement ventilation requires a more or less uniform and unidirectional flow. This flow structure might easily be disrupted by large numbers of people moving about a space, or through the use of ceiling fans or supplementary ventilation systems. Displacement ventilation often uses specific characteristics of the contaminant to aid in its capture. For example, a heated plume from a computer, copier, or cigarette develops convective (vertical) flows. If the displacement air is also moving vertically from floor to ceiling, pollutants and excess heat can be captured, treated, or exhausted from the ceiling. With this strategy, however, contaminants on their way to the exhaust stage can still pass through the breathing zones of both smokers and nonsmokers. Furthermore, vertical flows may be disrupted by furniture that is in the space, thus limiting the effectiveness of displacement ventilation.

Local exhaust ventilation extracts the air around a specific point source. It has been used for many decades to effectively control a variety of contaminants from specific activities or processes, often in industrial settings. Its effectiveness relies upon strict compliance with control measures that can include source enclosure, high air exhaust rates, and direct ducting to the outdoors that minimizes entrainment into outdoor air intakes. Restrictive compliance requirements limit its application to secondhand smoke in general indoor environments, except in separately exhausted smoking enclosures.

Operation of Ventilation Systems

Ventilation requirements for spaces such as office buildings, classrooms, and various hospitality venues are expressed as the volume of outside air per unit of time (e.g., liters per second, cubic feet per minute) per person, and/or volume flow rates of outdoor air per square foot of the area of the building. ASHRAE (1999) included the latter criterion in the revised Standard 62-1999 as a result of the recognition that air pollutants are also released by building sources—building materials, furnishings, and the HVAC equipment itself—and that to protect the occupants, ventilation standards should also apply to these sources as well as to the occupants. ASHRAE develops standards to guide building designs and operations that often become part of municipal codes (Chapter 10, Control of Secondhand Smoke Exposure). Consequently, ASHRAE standards are considered relevant to the control of secondhand smoke in the United States (Table 3.1). Building ventilation codes generally specify the total amount of air as well as a minimum percentage of outdoor air that should be supplied to occupied spaces. Minimum amounts between 10 and 20 percent are often specified, but in practice, outdoor air delivery into a building may vary from 0 to 100 percent over time. The variation depends on the design requirements of the space and operational characteristics of the ventilation system.

Ventilation systems are often quite complex and have multiple components. Controls are in place to modulate the air intake louvers, airflow, air temperature, and sometimes the humidity to meet specified thermal conditions (ASHRAE 1999). These control systems often consist of combinations of sensors, signal processors, computerized controllers, switches, dampers, valves, relays, and motors. The operating strategies for ventilation systems can have a major impact on the control of secondhand smoke within buildings. For example, many systems operate on economizer cycles that use the cooling or heating capacity of the outside air. During the economizer phase, the outside louvers open. Often, depending on the climate and season, a temperature range (generally between 50° and 65° F) will completely open the outside dampers (Spengler 1999; Bearg 2001). If ambient conditions become too warm and humid, the outside air vents

Table 3.1 Outdoor air requirements for ventilation*

Application	Estimated maximum† occupancy per 1,000 ft²‡ or 100 m²§	Outdoor air requirements		Comments
		cf/m/person△	cf/m/ft²	
Food and beverage services				
Dining rooms	70	20	NR¶	
Cafeteria, fast food	100	20	NR	
Bars, cocktail lounges	100	30	NR	Supplementary smoke-removal equipment may be required
Kitchen (cooking)	20	15	NR	Make-up air for hood exhaust may require more ventilating air; the sum of the outdoor air and transfer air of acceptable quality from adjacent spaces shall be sufficient to provide an exhaust rate of not less than 1.5 cf/m/ft² (7.5 liters/second/m²)
Hotels, motels, resorts, dormitories			cf/m/room	
Bedrooms	NR	NR	30	
Lobbies	30	15	NR	
Conference rooms	50	20	NR	
Casinos	120	30	NR	Supplementary smoke-removal equipment may be required
Offices				Some office equipment may
Office space	NR	20	NR	require local exhaust
Public spaces				Normally supplied by transfer
Smoking lounge	70	60	NR	air; local mechanical exhaust with no recirculation is recommended

*This table prescribes supply rates of acceptable outdoor air required for acceptable indoor air quality. These values have been chosen to dilute human bioeffluents and other contaminants with adequate margins of safety and to account for health variations and varied activity levels among people.
†Net occupiable space.
‡ft² = Square feet.
§m² = Square meters.
△cf/m/person = Cubic feet per minute per person.
¶NR = Data were not reported.
Source: American Society of Heating, Refrigerating and Air-Conditioning Engineers Standard 62-1999, Table 2.1 (1999).

will return to minimum or closed settings. To protect coils from freezing or to minimize heating, outside air vents might be closed or set at minimum openings during colder temperatures. Thus, contaminants such as secondhand smoke that are generated within a building are often subject to varying amounts of dilution air, and building occupants may face indoor air quality that varies during a day or over longer periods of time (Spengler 1999).

Most large, modern buildings use a building automation system (BAS) to provide direct digital control of ventilation through a central computer. Planned into the BAS is a sequence of operations for the HVAC system (USEPA 1998). Knowledge of routine activities related to building occupancy allow engineers to program HVAC systems through the central BAS to improve comfort and optimize energy efficiency.

However, a BAS is generally not programmed to control indoor air pollutants such as secondhand smoke.

Mechanical air handling systems exchange indoor air with outside air by pressure-driven flows through windows, doors, and cracks. Some buildings are not designed or constructed to be airtight; an estimated 40 percent of commercial buildings have operable windows, and natural ventilation is more common in older and smaller buildings (Liddament 2001). Pressure differentials across the building envelope are caused by wind and by indoor and outdoor temperature differences. The wind that flows around a building creates static positive pressures as well as negative pressures in the wake flow that is downstream of objects. Pressure differences across openings can force air into or out of a building. The HVAC system of pressurized ducts and building exhaust fans also creates an air exchange. Plumbing and electrical chases, elevator shafts, leaky air ducts, and cracks and openings between floors can become unplanned pathways for pressure-driven internal flows. Thus, contaminants such as secondhand smoke are not always controlled by HVAC airflows alone, and the HVAC ducts may transport and distribute secondhand smoke-contaminated air. Entrainment from doors, window cracks, or loading docks can bring tobacco smoke back into a building even when smokers are restricted to smoking outdoors. Even within buildings, secondhand smoke can move along unplanned or uncontrolled pathways to annoy and irritate occupants in other rooms or even on other floors far removed from the smoking areas.

Residential Ventilation

There are more than 100 million residential units in the United States. The most common types are single family (73 percent) followed by multifamily structures that include both low-rise and high-rise apartments (21 percent) and mobile homes (6 percent). The United States has a high rate of owner-occupied households (67 percent); 33 percent of households live in rental units (Diamond 2001).

The age and size of housing vary around the country. In general, older homes are smaller (<2,000 square feet of conditioned space) and are more common in the Northeast and Midwest. The average apartment unit is about half that size (approximately 1,000 square feet). Three million Americans live in public housing, most of which are two-bedroom units built in the 1950s and 1960s; the total size is typically 500 to 600 square feet (Diamond 2001). The south and southwestern regions of the United States continue to be the fastest growing areas and lead in new housing construction (Joint Center for Housing Studies of Harvard University 2002). Despite a decrease in the size of households, the size of single-family homes has increased with more square feet per person. Homes built in 1995 were 17 percent larger than those built just a decade earlier. During a 15-year period, new apartment units increased in average floor space by almost 10 percent (Diamond 2001).

Most houses and apartments have heating systems. Besides the size of the unit (i.e., volume), the type of heating, cooling, and exhaust system is an important factor in the dispersion, dilution, and removal of indoor-generated secondhand smoke across a room or throughout a residence. More than 50 percent of U.S. residences have central warm air furnaces. These systems include fan-forced directed air distributed to rooms with a gravity or ducted return back to the heat exchange unit of the furnace. Gravitational settling is not intended to remove the smaller particles found in secondhand smoke, nor is it efficient at removing them. Filters upstream of the blower serve to protect the mechanical parts from objects and large particles, but these filters also fail to remove the smaller secondhand smoke particles and gases.

Air conditioning can affect the distribution and concentration of secondhand smoke. Air conditioning systems are common in U.S. residences, including apartments. According to the Residential Energy Conservation Survey (U.S. Department of Energy 1999), 48 percent of residences were equipped with central air conditioning and 27 percent had window units. Forty-seven percent of the respondents with central systems versus only 18 percent with window units reported using their air conditioning "quite a bit" or "just about all summer." Similar to forced warm air mechanical systems, central air-cooling systems can rapidly mix secondhand smoke throughout the conditioned space. Doors and windows are generally closed when the air conditioner is in use and the system is usually set to recirculate the indoor air. These closed conditions tend to reduce the dilution of secondhand smoke.

Wallace (1996) comprehensively reviewed indoor air particle concentrations and sources and quantified the effect of air conditioning on the concentration of secondhand smoke. His review included studies that measured indoor and outdoor particulate matter 2.5 ($PM_{2.5}$) concentrations across six U.S. communities (Dockery and Spengler 1981; Spengler et al. 1981; Spengler and Thurston 1983; Letz et al. 1984; Neas et

al. 1994). Estimated concentrations of fine particles were 30 micrograms per cubic meter ($\mu g/m^3$) higher in homes with smokers than in homes without smokers. According to Wallace (1996), "A mass balance model was used to estimate the impact of cigarette smoking on indoor particles. Long-term mean infiltration of outdoor $PM_{2.5}$ was estimated to be 70% for homes without air conditioners, but only 30% for homes with air conditioners. An estimate of 0.88 $\mu g/m^3$ per cigarette (24-h average) was made for homes without air conditioning, while in homes with air conditioning the estimate increased to 1.23 $\mu g/m^3$ per cigarette" (p. 100). The greater estimate for air conditioning is consistent with lowered air exchange rates while the air conditioning is operating, and is supported by a 1994 study (Suh et al. 1994).

Air exchange rates in homes are usually determined by one of two methods: blower door pressurization or tracer gases. Blower door pressurization tests identify air leakage areas that are then used to estimate air exchange rates. Sherman and Matson (1997), who modeled the results of blower door tests, found that a typical single-family house constructed before 1990 has an estimated air exchange rate of 1.0 ACH. Homes built to meet more energy efficient building codes have estimated rates of 0.5 ACH.

Tracer gases are emitted into a home and measured over time to calculate short-term (decay rate) or long-term (mass balance method) air exchange rates. Murray and Burmaster (1995) examined the Brookhaven National Laboratory tracer gas data that included almost 3,000 households. The analysis derived best-fit, log-normal distributions from data classified by four regions or by heating degree days (a measurement used to relate a day's temperature to the demand for fuel to heat buildings: a 65° average daily temperature = the number of heating degree days), and by the four seasons. In general, air exchange rates are higher for homes that are in warmer climates. Air exchange rates across all regions are higher during the summer months followed by spring, fall, and winter. The summer mean air exchange rate is 1.5 h^{-1} (air changes per hour) versus 0.41 h^{-1} for the fall.

Other characteristics of air exchange rates derived from blower door and tracer gas methods indicate that apartment units and multifamily structures with shared interior walls have less external surface area, less unplanned air leakage, and typically lower air exchange rates compared with single-family detached houses.

Conclusions

1. Current heating, ventilating, and air conditioning systems alone cannot control exposure to secondhand smoke.

2. The operation of a heating, ventilating, and air conditioning system can distribute secondhand smoke throughout a building.

Implications

These conclusions suggest that control strategies for indoor exposure to secondhand smoke cannot use approaches based on HVAC system design and operation. The benefits from HVAC systems include a number of critical functions that help to maintain a healthful and comfortable indoor environment. This review of their functioning shows, however, that current HVAC systems cannot fully control exposures to secondhand smoke unless a complete smoking ban is enforced. Furthermore, unless carefully controlled, HVAC operations can distribute air that has been contaminated with secondhand smoke throughout a building. Simple predictions cannot be made about the consequences of these operations because they vary with the building and with the HVAC characteristics. However, to develop models that assess the effects of indoor secondhand tobacco smoke exposures, it is necessary to first develop an understanding of HVAC systems and their effectiveness in a particular structure. However, this review indicates that a complete ban on indoor smoking is the most efficient and effective approach to control exposures to secondhand smoke. Additional implications of these findings are considered in Chapter 10, Control of Secondhand Smoke Exposure.

Atmospheric Markers of Secondhand Smoke

Concepts and Interpretations of Exposure Markers

Secondhand smoke is a dynamic mixture that contains thousands of compounds in its vapor and particle phases. Some of these components are specific to secondhand smoke, such as nicotine, but others have additional sources and are not specific to secondhand smoke, as in the case of carbon monoxide (CO). Some of the more specific markers can be useful indicators of secondhand smoke concentrations, but no particular marker will be predictive of the full range of risks from exposures to secondhand smoke. Additionally, some components of particular interest for disease risk, such as the tobacco-specific nitrosamines, are not easily measured at typical indoor air concentrations (Hecht 1999). Nonetheless, some components of secondhand smoke can be quantified in indoor air. This quantification enables researchers to estimate exposures to secondhand smoke for research purposes and for tracking population exposures. In 1986, the NRC report on involuntary smoking proposed useful atmospheric markers that are believed to be unique to tobacco smoke or that are believed to have cigarette smoking as their primary source in most environments; the mass that is emitted is believed to be similar across cigarette brands (NRC 1986). Subsequent studies have evaluated some of the markers used to detect secondhand smoke in indoor environments (Guerin et al. 1992; Daisey 1999; Jenkins et al. 2000).

Researchers need sensitive and specific markers of secondhand smoke for exposure surveillance and potentially for enforcement of regulations. For research and for population risk assessments, measurements of marker compounds can be used with microenvironmental models to estimate exposures to secondhand smoke (Jaakkola and Samet 1999). Researchers can also estimate the relative contributions of different environments to these exposures and the potential consequences of exposure levels. Furthermore, the concentration of one marker may be used to predict concentrations of other constituents if the concentration ratios between the marker and the other constituents of interest are known.

Evaluation of Specific Markers

Concentrations of secondhand smoke components in indoor air have multiple determinants: the rate of smoking, the volume of the room or space, the air exchange rate, the exchange of volatile components between vapor and particle phases, deposition rates on surfaces, rates of re-emission from the surfaces, and chemical transformations (Daisey 1999). Although studies have measured concentrations of some of these chemicals in laboratory conditions, the behaviors of only a few of these compounds as tracers have been characterized in field settings. Studies document that each component under consideration has potential limitations as a marker. These limitations may be the result of photodegradation, variable partitioning between the particle and vapor phases, or adsorption/re-emission rates that differ from those of other compounds of concern. No single compound or component has been identified as a completely valid marker for every constituent found in secondhand smoke. On the other hand, several useful markers have a sufficient specificity for secondhand smoke and they can be used to characterize exposures of the public in general or of particular groups. Of these markers, nicotine is highly specific and is considered a valid marker of the PM component of secondhand smoke across a wide range of concentrations in indoor environments (Daisey 1999).

Researchers have studied secondhand smoke characteristics in chambers, with different cigarette brands as the source. In these studies, many different brands generated similar steady-state concentrations of both vapor phase nicotine and respirable particles, and the relationship between these two markers was similar among brands (Leaderer and Hammond 1991; Daisey et al. 1998). Sources other than smoking also contribute to background concentrations of particles found indoors, such as cooking and particles that have infiltrated from the outdoors (Leaderer and Hammond 1991). Thus, the models for estimating the relationship between nicotine and respirable particle concentrations involve regression approaches that estimate increases in nicotine concentrations

with increases in particle concentrations. In such linear regression models, the intercept estimates the background concentration of particles and the slope describes the relationship between concentrations of nicotine and secondhand smoke particles. In most environments where people spend time, secondhand smoke concentrations are usually much lower than in laboratory chambers, so background particles represent a significant fraction of the particle concentration. The relationship between concentrations of nicotine and respirable particles in indoor air has been consistent across field studies in 47 homes (Leaderer and Hammond 1991), in 44 office samples (Schenker et al. 1990), and in 14 other workplaces (Miesner et al. 1989). The range of slopes for the increase of respirable particulate matter (RPM) concentration with nicotine concentration is narrow: 8.6 to 9.8 μg of RPM per μg of nicotine. Daisey (1999) calculated a slope of 10.9 μg of RPM per μg of nicotine using personal sampling data that Jenkins and colleagues (1996) had compiled from more than 1,500 people in the United States. Thus, for each microgram of atmospheric nicotine in the various environments where people spend time, there is an estimated increase of about 10 μg in secondhand smoke particle concentrations.

Until recently, most studies incorporated either respirable particles or nicotine as markers for secondhand smoke, and they remain the most commonly used markers. The literature on the concentrations of these markers is now substantial. In an early study carried out in the late 1970s, Repace and Lowrey (1980) evaluated secondhand smoke levels by contrasting the concentration of particles measured during a bingo game in a church with the concentration measured during a church service with a similar number of people present who were not smoking. The particle levels were much higher during the bingo game (279 $\mu g/m^3$) compared with during the service (30 $\mu g/m^3$). Similarly, studies in the early 1980s of respirable particles in homes found that concentrations in the homes of smokers were substantially higher than concentrations in the homes of nonsmokers (approximately 74 $\mu g/m^3$ versus 28 $\mu g/m^3$, respectively) (Spengler et al. 1985). However, the high levels of respirable particles from other sources and the variability in the concentrations of these particles make it difficult to use the respirable particle concentration as an indicator of secondhand smoke, particularly if secondhand smoke concentrations are low.

In most environments where the public spends time, nicotine in the air comes only from tobacco smoke, so there is no background concentration to be considered. This very high specificity, in combination with the development of inexpensive, sensitive, and passive methods to measure nicotine concentrations in real-world environments, has led to the widespread use of nicotine as a marker for secondhand smoke (Jenkins et al. 2000). A 1999 review concluded that nicotine was a suitable marker for secondhand smoke (Daisey 1999).

Findings from initial secondhand smoke chamber studies that used nicotine as a marker provide evidence supporting its use (Hammond et al. 1987; Leaderer and Hammond 1991). The ambient concentrations of both nicotine and respirable particles were similar when human volunteers smoked 12 brands of cigarettes in separate tests. Nicotine and tar yields varied in mainstream smoke over an order of magnitude (0.1 milligram [mg] of nicotine per cigarette for ultra-low nicotine cigarettes to 1.3 mg per cigarette for regular cigarettes). Subsequent studies showed that nicotine decay in chambers did not follow first-order kinetics (where the speed of a chemical reaction is proportional to the concentrations of the reactants), and short-term measurements in chambers indicated varying ratios of nicotine when compared with other secondhand smoke constituents (Eatough et al. 1989a; Nelson et al. 1992; Van Loy et al. 1998). However, further investigations showed that these findings were artifacts of the chambers themselves. In real-world settings with longer sampling times, nicotine concentrations closely tracked levels of other secondhand smoke constituents (Van Loy et al. 1998; Daisey 1999; LaKind et al. 1999a).

Concentrations of eight possible tracers for secondhand smoke (nicotine, 3-ethenyl pyridine, myosmine, solanesol, scopoletin, RPM, ultraviolet-absorbing particulate matter [UVPM], and fluorescing particulate matter [FPM]) were measured in 469 personal samples collected in workplaces where smoking was allowed (LaKind et al. 1999a). The first three chemicals were in the gas phase, while the latter five were in the particle phase. Concentrations of the three gas phase markers (nicotine, 3-ethenyl pyridine, and myosmine) were highly correlated ($r^2 > 0.8$, where r^2 = the coefficient of determination describing the strength of the model), as were those for three of the particle phase markers (UVPM, FPM, and solanesol) (Table 3.2). Scopoletin was also correlated with UVPM, but only at higher concentrations. Respirable particle concentrations were not strongly correlated with concentrations of UVPM or of nicotine, probably because respirable particles were present in the workplaces from sources other than smoking. Nicotine concentrations in the gas phase correlated with concentrations of the particle phase marker UVPM and with the other particle phase markers that were correlated with UVPM: FPM, solanesol, and scopoletin.

Table 3.2 Correlations between various secondhand smoke constituents as selective markers of exposures

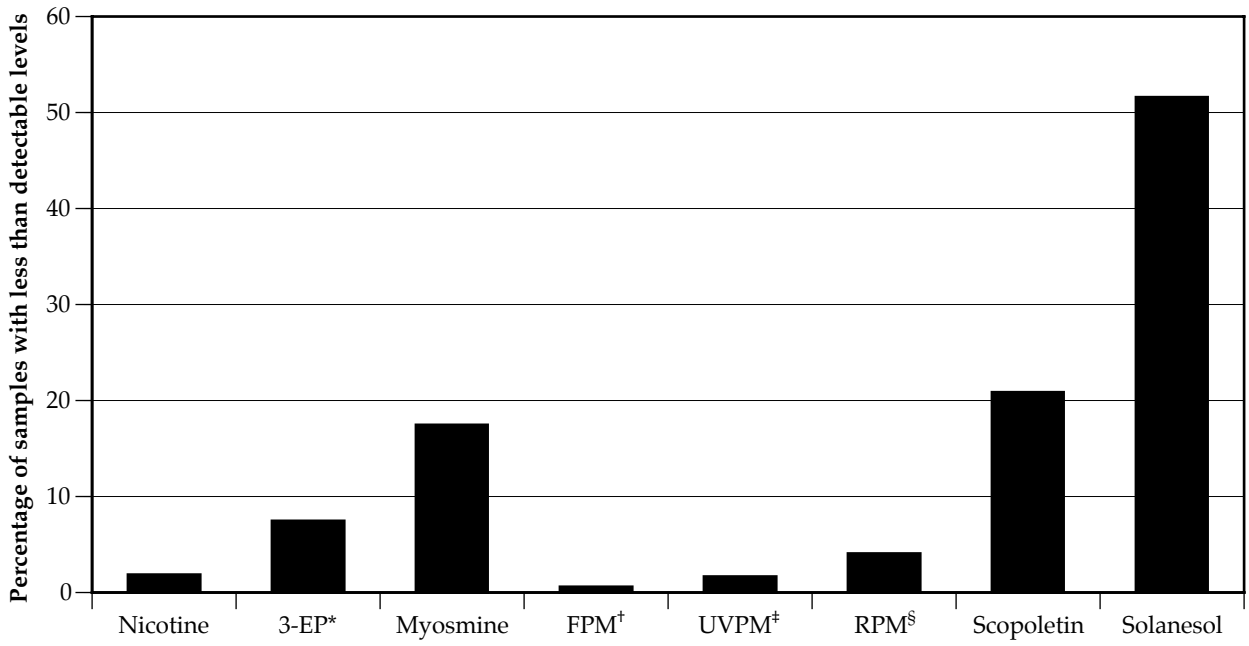
Secondhand smoke constituent	Secondhand smoke exposure marker	R^{2*}
Nicotine	3-EP[†]	.83
	Myosmine	.88
	UVPM[‡]	.63
UVPM	FPM[§]	.96
	Solanesol	.84
	Scopoletin >1	.73
	Scopoletin <1	.10

Note: 469 personal samples collected from workplaces that permitted smoking.
*R^2 = The coefficient of determination describing the strength of the model.
[†]EP = Ethenyl pyridine.
[‡]UVPM = Ultraviolet-absorbing particulate matter.
[§]FPM = Fluorescing particulate matter.
Source: LaKind et al. 1999b (from the 16 Cities Study).

Several studies examined concentrations of some of the toxic compounds that cigarette smoking emits into the air. Two studies found that different brands of cigarettes released very similar amounts of two nitrosamines, *N*-nitrosodimethylamine and *N*-nitrosopyrrolidine (Mahanama and Daisey 1996). Other toxic volatile organic compounds in secondhand smoke, including benzene, formaldehyde, 1,3-butadiene, and styrene, also exhibited little variation among brands (Daisey et al. 1998). This consistency in emissions among several different brands indicates that changes in the concentration of a particular marker imply proportional changes in the concentrations of other airborne toxic chemicals that are in secondhand smoke.

The level of sensitivity is another key characteristic of a potential marker for secondhand smoke. High sensitivity enables markers to detect low levels of secondhand smoke, which is a necessary quality for evaluating control programs and for surveillance. Some markers have this necessary degree of sensitivity. In the 16 Cities Study conducted by Jenkins and colleagues (1996), researchers collected 469 samples of these eight markers during one workday at worksites where smoking was allowed. Three markers were quite sensitive: nicotine, FPM, and UVPM; less than 2 percent of the samples had concentrations below the limit of detection. More than 10 percent of the samples fell below the limit of detection for myosmine, scopoletin, and solanesol (Figure 3.3). In fact, less than half of the samples collected in workplaces where smoking was allowed had detectable levels of solanesol.

Figure 3.3 Sensitivity of markers for secondhand smoke exposure



Note: 469 personal samples from workplaces that permitted smoking.
*EP = Ethenyl pyridine.
†FPM = Fluorescing particulate matter.
‡UVPM = Ultraviolet-absorbing particulate matter.
§RPM = Respirable particulate matter.
Source: Calculated from data in LaKind et al. 1999a.

Exposure Models

Models and mathematical representations can also be used to estimate human exposures to secondhand smoke (Ott 1999) because they are useful for predicting secondhand smoke concentrations with different patterns of cigarette smoking and for comparing control measures. The microenvironmental model is a tool that can estimate population exposures to secondhand smoke when there is information on the places where people spend time and whether people are smoking. Secondhand smoke concentrations can be inferred from models that characterize contamination of indoor spaces from smoking or from measurements made in the various microenvironments.

Standard techniques that are used to model concentrations of air contaminants indoors, based on the mass balance model, typically include terms that account for the volume of the room, the generation rate, and the removal rate. For secondhand smoke, the generation rate is the number of cigarettes smoked, and the removal rate may include terms such as the air exchange rate, the rate of deposition on surfaces, and

terms for chemical transformations. In some cases, the rate of re-emission from surfaces may also be important. Van Loy and colleagues (1998) have written one such equation:

$$\frac{dC_i}{dt} = \frac{E_i(t)}{V} - ACH * C_i - \frac{1}{V}\sum_{j=1}^{g} S_j \frac{dM_{ij}}{dt}$$

where C_i is the concentration of airborne chemical i, $E_i(t)$ is the emission rate of i, V is the volume of the room, ACH is the air exchange rate, S_j is the area of surface j, and M_{ij} is the mass of i deposited on surface j. The term

$$\frac{dC_i}{dt}$$

gives the rate of change of the concentration. The first term on the right is the emissions rate per volume, the second is the loss of concentration due to air exchange, and the third is the loss to surfaces.

Adapted to secondhand smoke, the model implies that secondhand smoke concentrations depend on the number of smokers and their rate of smoking corresponding to $E_i(t)$ and the space, air exchange rate, and surface deposition—the factors that determine the net removal of secondhand smoke. Ott (1999) has more specifically formulated this model for secondhand smoke, as have others (Daisey et al. 1998; Klepeis 1999a).

$$\frac{}{C(t)} = \frac{n_{ave}g_{cig}}{Q} - \frac{\Delta C}{(ACH)t}$$

The average secondhand smoke concentration at some time ($\overline{C}(t)$) depends on two terms. The first term

$$\frac{n_{ave}g_{cig}}{Q}$$

has the source strength as its numerator: n_{ave} is the number of smokers, and g_{cig} is the emission rate from the cigarette as mass multiplied by time. The denominator is the air flow rate, with higher air flows leading to lower concentrations. The second term

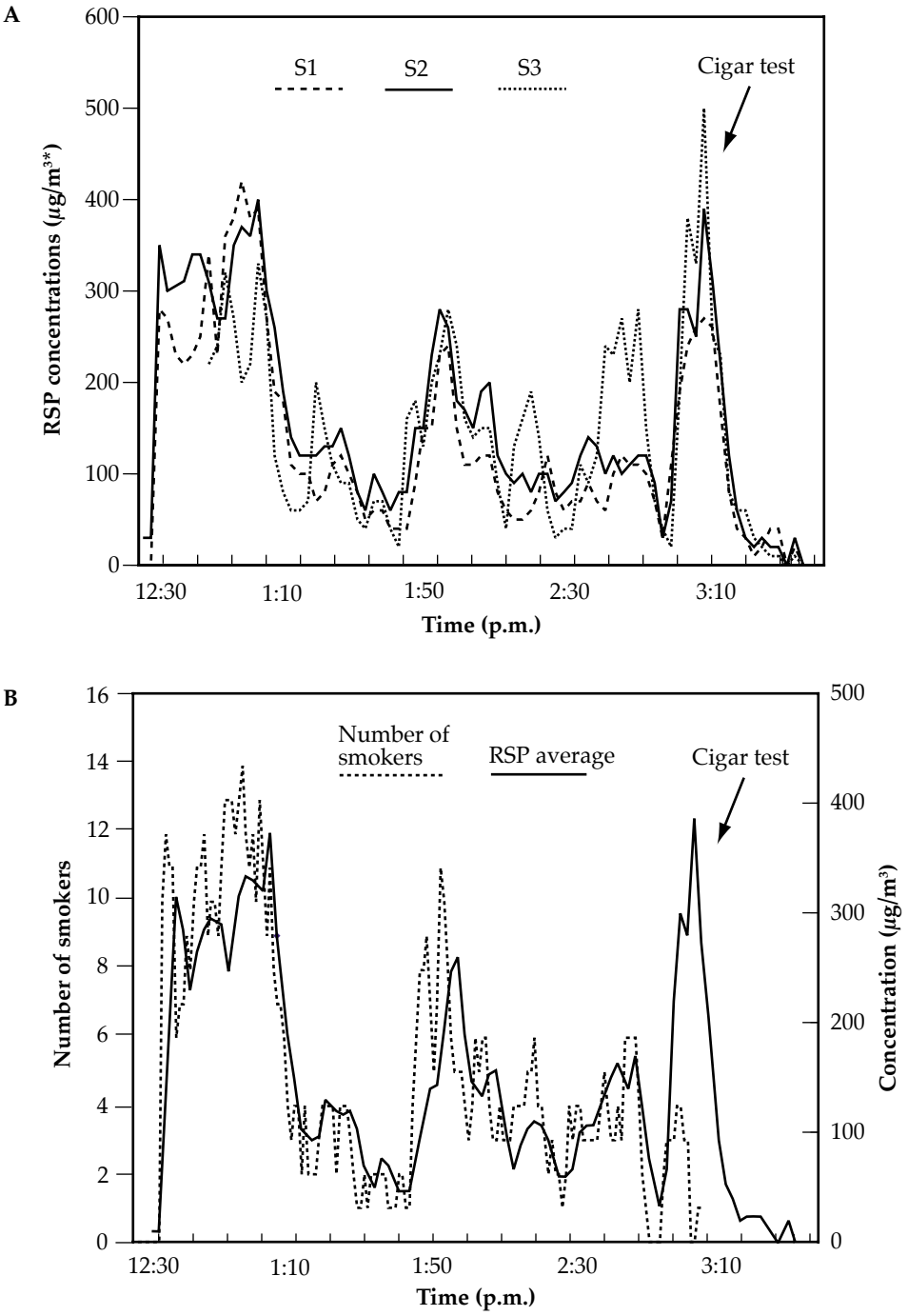
$$\frac{\Delta C}{(ACH)t}$$

captures changes in concentrations over the time of observation (ΔC), the air exchange rate (ACH), and the time of observation t. Thus, the average concentration is determined by source strength (the first term) and loss rate (the second term). If conditions are stable, then ΔC = 0, and the secondhand smoke concentration depends only on source strength ($n_{ave}g_{cig}$) and dilution rate (Q). This model assumes a uniform mixing of the smoke throughout the space.

Klepeis and colleagues (1996) applied this multismoker model to data collected from observations of respirable particle and CO measurements in smoking lounges in two airports. During 10 visits, the authors carefully tracked the number of cigarettes smoked and measured continuous particle and CO concentrations. A test with a cigar (several cigars at a time) generated substantial concentrations of CO and RPM that were then tracked as they decayed exponentially. Because CO does not react with surfaces, its decay rate was used to determine the mechanical air exchange rate. Calculating the difference between the CO and RPM decay rates provided estimates of the effective decay rate, which takes into account physical and chemical reactions that affect particle concentrations in addition to removal (dilution) by the mechanical ventilation system. The report documented that the removal of RPM by surface deposition and chemical reaction in both lounges was about 19 to 20 percent of the ventilatory removal. Air exchange rates for these airport smoking lounges were high, approximately 11 and 13 ACH. Mechanically induced turbulence will increase particle removal by surface deposition, but if the number of air changes is similar to that found in office buildings (1 to 3 ACH) and homes (0.3 to 3 ACH), the removal of RPM by deposition, evaporation, and agglomeration would be a more substantial fraction of the overall effective ventilation rate.

Surface adsorption also removes gaseous constituents of secondhand smoke. Because different physical and chemical processes are involved, different decay rates are expected for different components. Sorption, or the uptake and release of gaseous components of secondhand smoke, is a complex phenomenon involving physical and chemical processes on surfaces. Coverage of this topic is beyond the scope of this chapter. The model developed by Ott and colleagues (1992) and validated by Klepeis and colleagues (1996) provided realistic estimates of time-varying concentrations of respirable suspended particles associated with secondhand smoke (Figure 3.4) (Klepeis 1999a). The estimated RPM from cigarettes (11.4 mg per cigarette) was similar to the value derived independently by Özkaynak and colleagues (1996), who used a mass balance regression

Figure 3.4 Estimates of time-varying respirable suspended particle (RSP) concentrations associated with secondhand smoke



Note: Figure A shows RSP concentration time series measured by piezobalances (labeled S1, S2, and S3) at three widely spaced locations in the smoking lounge taken at the San Jose International Airport (SJC5) fifth study visit. The large decay c□

Figure B shows the cigarette count time series and the mean RSP concentration time series from the three piezobalances taken at the SJC5 study visit.

*$\mu g/m^3$ = Micrograms per cubic meter.

Source: Klepeis et al. 1996. Reprinted with permission.

model and indoor $PM_{2.5}$ data from the Particle Total Exposure Assessment Study. The model predicted CO emissions per cigarette similar to the values presented by Owens and Rosanno (1969).

The model for RPM exposures from secondhand smoke that Ott and colleagues (1992) developed is a useful tool for estimating short-term concentrations in settings where the smoking rates and ventilation rates are known. The model could also be used to advance exposure assessment studies and as a design aid for designated smoking areas within buildings. Mass-based models also successfully predict the concentration of nicotine. Repace and colleagues (1998) used a similar model to predict nicotine from secondhand smoke in office air and in salivary cotinine among office workers exposed only in the office; the agreement between the predicted concentrations and the levels observed in field studies was excellent: the mean-predicted concentration was 13.8 $\mu g/m^3$ and the observed mean of 61 samples in nine offices was 15.8 $\mu g/m^3$; the median-predicted salivary cotinine was 0.49 nanograms (ng)/m compared with an observed median of 0.5 ng/milliliter (mL) in 89 nonsmoking office workers who had not been exposed at home.

Both chamber and field studies have validated these models. Experimental chambers differ from many real-world environments such as homes, restaurants, and workplaces in several important aspects. For example, chambers typically have much greater surface to volume ratios, which increase the opportunity for adsorption onto those surfaces, and the air exchange rates are carefully controlled and often kept low to maintain high concentrations. Thus, adsorption onto and desorption from surfaces may have a greater impact in chamber studies than in the field. In fact, the adsorption and desorption of secondhand smoke chemicals onto surfaces have been studied in chambers, and concerns have been raised about the different rates of adsorption and desorption with different markers. However, this phenomenon was less important in field studies than in chamber studies. Thus, the concentrations of secondhand smoke marker chemicals measured in the workplace are well correlated with one another (Table 3.2).

Summary of Atmospheric Markers and Exposure Models

Researchers have suggested several markers for measuring the concentration of secondhand smoke (USDHHS 1986). Of the gas phase markers that researchers have most often used (nicotine, 3-ethenyl pyridine, and myosmine), concentrations were highly correlated in various real-world environments and were correlated with particle phase markers when these markers were detectable (Jenkins et al. 1996). Nicotine, FPM, and UVPM were the most sensitive of these gas and particle phase markers, detecting low levels of secondhand smoke when levels of other markers were below the limit of detection (LaKind et al. 1999b).

Conclusions

1. Atmospheric concentration of nicotine is a sensitive and specific indicator for secondhand smoke.

2. Smoking increases indoor particle concentrations.

3. Models can be used to estimate concentrations of secondhand smoke.

Implications

A set of approaches is available for documenting the exposures of people to secondhand smoke in indoor environments. The atmospheric concentration of nicotine can be readily measured, offering a valid quantitative indicator of the presence of secondhand smoke in the indoor air. Smoking increases levels of other contaminants, including particles. Measurements of nicotine can be used for both research and surveillance purposes. Models have also been developed to estimate concentrations of secondhand smoke in indoor spaces. These models can be used to assess the consequences of various scenarios of controlling for secondhand smoke.

Biomarkers of Exposure to Secondhand Smoke

A biomarker of exposure has been defined by the NRC (1989) as "…an exogenous substance or its metabolite or the product of an interaction between a xenobiotic agent (an external, biologically active agent) and some target molecule or cell that is measured in a compartment within an organism" (p. 12). Thus, measuring specific biomarkers in people can provide evidence that exposure of the individual to secondhand smoke has actually occurred. For some agents, measurements of biomarkers that have interacted with a target site in the body may indicate the biologically effective dose (Sampson et al. 1994; Perera 2000). However, biomarkers do not provide direct information on exposure microenvironments and are therefore complementary to environmental and personal monitoring (NRC 1991). In 1992, the EPA listed several criteria that a biomarker of exposure for a specific air contaminant should meet (USEPA 1992). Based on those criteria, the ideal biomarker of exposure to secondhand smoke should (1) be specific for involuntary smoking, (2) have an appropriate half-life in the body, (3) be measurable with high sensitivity and precision, (4) be measurable in samples collected by noninvasive techniques, (5) be inexpensive to assay, (6) be either an agent associated with health effects or strongly and consistently associated with such an agent, and (7) be related quantitatively to a prior exposure to secondhand smoke. Several biomarkers have been used to assess involuntary smoking, but each has had limitations when matched against these criteria. Nevertheless, these biomarkers have provided information for tracking population exposures to secondhand smoke. There are several published reviews of biomarkers of secondhand smoke exposure (Benowitz 1996, 1999; Jaakkola and Jaakkola 1997; Scherer and Richter 1997; National Cancer Institute 1999; Woodward and Al-Delaimy 1999).

Compounds that have been used as biomarkers for involuntary smoking include CO in exhaled air, carboxyhemoglobin (the complex form of CO found in the blood), thiocyanate, nicotine and its primary metabolite cotinine, polycyclic aromatic hydrocarbon (PAH) adducts in leukocyte DNA or plasma albumin, and hemoglobin (Hb) adducts of tobacco-related aromatic amines such as 3-aminobiphenyl (3AB) and 4AB. A relationship between urinary concentrations of hydroxyproline, an indicator of collagen degradation (a marker of effect), and exposure to secondhand smoke has been proposed (Yanagisawa et al. 1986) but has not been confirmed by other investigators (Adlkofer et al. 1984; Verplanke et al. 1987; Scherer and Richter 1997), and hydroxyproline analyses have not been used in more recent studies. The tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) may prove to be quite useful as an exposure marker in the future (Hecht et al. 1993b), although relatively few studies have been conducted of NNAL levels in nonsmokers (Hecht et al. 1993b, 2001; Parsons et al. 1998; Meger et al. 2000; Anderson et al. 2001). Levels of other compounds present in tobacco smoke such as benzene, 2,5-dimethylfuran, and benzo[*a*]pyrene (B[*a*]P) may be significantly higher among smokers compared with nonsmokers, but such compounds are of limited value as biomarkers of involuntary smoking because they are not specific to tobacco smoke. Thus, although some of these compounds may be of value in classifying active smokers and nonsmokers, only those compounds with the highest specificity and sensitivity are potentially useful for assessing variations in exposure to secondhand smoke. Feasibility and cost are additional considerations. The biomarkers most commonly proposed for this purpose have been CO, thiocyanate, and nicotine or its metabolites.

Carbon Monoxide and Thiocyanate

The compound CO is present in both mainstream and sidestream smoke and can be measured in people as either expired breath CO or as carboxyhemoglobin. Such measurements may be useful in confirming the absence of active smoking, but they are of limited value as markers of exposure to secondhand smoke because of a relatively short half-life and because of the nonspecificity of CO as a marker for exposure to tobacco smoke. In addition to tobacco combustion, CO has both indoor and outdoor sources, including vehicle exhaust and incomplete combustion in furnaces, space heaters, and other similar devices. The human body's own metabolic processes also produce CO, and nonsmokers have a typical carboxyhemoglobin concentration of about 1 percent. The half-life of CO in the body is about two to four hours (Castleden and Cole 1974). Therefore, although this time period varies with individual activity levels,

CO is only useful as an indicator of recent exposures. Both expired breath CO and blood level carboxyhemoglobin measurements have been used in studies of exposure to secondhand smoke. In general, however, a definite increase in these markers has only been noted immediately following substantial exposures (Table 3.3). Thus, levels of CO in exhaled breath or in carboxyhemoglobin in blood are of limited value as routine markers of involuntary smoking.

Cigarette smoke also contains significant amounts of hydrogen cyanide, which is detoxified in the body by conversion to thiocyanate. As a marker, thiocyanate is easily measured in serum, urine, or saliva by manual or automated colorimetric methods. Thiocyanate has an estimated half-life of about one week—a period of time that is a fairly long interval for the integration of an exposure (Junge 1985). However, thiocyanate lacks specificity as a marker of involuntary smoking primarily because of dietary contributions from cyanide-containing foods, such as almonds, or from the presence of thiocyanate itself in certain cruciferous vegetables such as cabbage, broccoli, and cauliflower. This lack of specificity restricts the usefulness of thiocyanate in assessing exposure to tobacco smoke. Although some studies have reported significantly increased levels of thiocyanate among nonsmokers exposed to secondhand smoke (Table 3.3), two rather large studies with more than 1,000 persons apiece found no significant difference in serum thiocyanate levels between nonsmokers with and those without reported exposure to secondhand smoke (Table 3.3) (Foss and Lund-Larsen 1986; Woodward et al. 1991). Both expired breath CO and serum thiocyanate levels may be useful as confirmatory markers in smoking cessation studies because no interference from nicotine replacement therapy occurs, but the lack of specificity of these markers limits their application in studies of involuntary smoking.

Nicotine and Cotinine

Nicotine is a highly tobacco-specific component of cigarette smoke that is present in abundant amounts (approximately 7 to 8 mg per cigarette) (IARC 2004). Nicotine can be readily measured in both active and involuntary smokers in a number of biologic materials including serum, urine, and saliva. Most of the nicotine emitted from a cigarette is found in sidestream smoke (NRC 1986), which is the major contributor to secondhand smoke. Nonsmokers inhale nicotine, which is present as a gas, during involuntary smoking. Some of the absorbed nicotine is excreted in urine, but on average, about 90 percent of the nicotine is further metabolized (Benowitz and Jacob 1994). Of this nicotine, about 70 to 80 percent is metabolized to cotinine (range: 60 to 90 percent). Cotinine is the major proximate metabolite of nicotine and the predominant nicotine metabolite present in the blood; cotinine is further metabolized to other chemicals, such as hydroxycotinine and cotinine glucuronide. Nicotine can be measured in physiologic fluids as an exposure biomarker, but its short half-life in the body of approximately one to three hours limits its utility as a marker of chronic exposure (Scherer et al. 1988; Benowitz et al. 1991). Consequently, cotinine, the primary metabolite of nicotine with a substantially longer half-life, is regarded as the biomarker of choice for exposure to secondhand smoke (Jarvis et al. 1987; Watts et al. 1990; Benowitz 1999). Participants in a workshop convened to discuss analytical approaches suitable for assessing involuntary smoking among people concluded with a general consensus "…that the nicotine metabolite, cotinine, has the prerequisites of specificity, retention time in the body, and detectable concentration levels that make it the analyte of choice for quantifying exposures" (Watts et al. 1990, p. 173).

The estimated half-life of cotinine in serum, urine, or saliva averages about 16 to 18 hours (Table 3.4) (Jarvis et al. 1988). Some investigators have reported that the cotinine half-life in nonsmokers may be significantly longer than in smokers, whereas other studies have found a similar half-life in both groups (Table 3.4). Kyerematen and colleagues (1982) used a relatively low dose of nicotine (less than 0.2 mg based on an assumed mean body weight of 70 kilograms) and found a statistical, but small, difference in the half-life of labeled cotinine between smokers and nonsmokers. However, Sepkovic and colleagues (1986) and Haley and colleagues (1989) reported a much longer half-life of cotinine in nonsmokers than in smokers. Both studies used a radioimmunoassay (RIA) for their analyses, and the cross-reactivity or limited sensitivity of their assays during the terminal elimination phase when cotinine concentrations would be low may have contributed to their results. Benowitz (1996) pointed out that more recent data indicate similar cotinine clearance rates for both smokers and nonsmokers. Benowitz (1996) suggested that any increase in the apparent half-life for nonsmokers at low nicotine concentrations may represent residual tissue storage of nicotine with continued release over time. This notion would be consistent with the finding that the mean half-life for the elimination of cotinine derived from labeled nicotine among nonsmokers was slightly

Table 3.3 Expired air carbon monoxide (CO), carboxyhemoglobin, and thiocyanate levels following exposure to secondhand smoke

			Findings		
Study	**Analysis**	**Method**	**Unexposed**	**Exposed**	**Difference**
Russell et al. 1973	Carboxy-hemoglobin	CO oximeter	1.6% ± 0.6	2.6% ± 0.7	p <0.001
Jarvis et al. 1983	Expired air CO	Data were not reported	4.7 ppm	10.6 ppm	p <0.001
Poulton et al. 1984	Serum thiocyanate	Colorimetric	54.2 ± 11.3 μmol/L[†] n = 10	97.3 ± 45.3 μmol/L n = 14	p <0.002
Foss and Lund-Larsen 1986	Serum thiocyanate	Colorimetric	Men 29.7 ± 14.2 μmol/L n = 248	30.9 ± 13.5 μmol/L n = 328	NS[‡]
			Women 30.2 ± 13.6 μmol/L n = 366	31.9 ± 15.8 μmol/L n = 229	NS
Husgafvel-Pursiainen et al. 1987	Carboxy-hemoglobin	CO oximeter	0.6% ± 0.2 n = 20	0.7% ± 0.3 n = 27	NS
	Plasma thiocyanate	Colorimetric	46 ± 16 μmol/L n = 20	58 ± 18 μmol/L n = 27	p <0.01
Robertson et al. 1987	Serum thiocyanate	Colorimetric	44.8 ± 21.2 μmol/L n = 57	Group A 44.1 ± 18.5 μmol/L n = 69	NS
				Group B 49.6 ± 27.3 μmol/L n = 21	NS
Chen et al. 1990	Serum thiocyanate	Colorimetric	26.9 (9.3–40.9) μmol/L n = 20	35.8 (14.8–78.2) μmol/L n = 26	p <0.05
Woodward et al. 1991	Expired air CO	Ecolyser	Men 2 ppm n = 519	3 ppm n = 259	NS
			Women 2 ppm n = 817	2 ppm n = 461	NS
	Serum thiocyanate	Colorimetric	Men 37 μmol/L n = 455	35 μmol/L n = 244	NS
			Women 40 μmol/L n = 702	39 μmol/L n = 401	NS
Otsuka et al. 2001	Carboxy-hemoglobin	Spectrophotometry	0.24% ± 0.18	1.57% ± 0.32	p <0.001

*ppm = Parts per million.
[†]μmol/L = Micromoles per liter.
[‡]NS = Not significant.

Comments
12 nonsmoking volunteers assayed before (unexposed) and immediately after remaining in a smoke-filled room for an average of 79 minutes; mean CO in the room was about 38 ppm*
7 nonsmokers assayed before (unexposed) and after 2 hours of exposure to secondhand smoke in a bar; peak ambient CO in the bar was 13 ppm
24 children or adolescents (mean age 7.6 years), with 14 living in homes with ≥1 smoker in the immediate family (exposed)
Nonsmokers in Norway with self-reported exposures to secondhand smoke at home or at work
Office workers with no reported exposure (unexposed) and restaurant employees exposed an average of 40 hours per week
Nonsmoking office workers who reported no exposure to secondhand smoke; exposure to secondhand smoke only at work (Group A); or exposure to secondhand smoke both at home and at work (Group B)
Median and range of serum levels among infants in the Chang-Ning Epidemiological Study who lived in nonsmoking homes (unexposed) or in homes where ≥20 cigarettes/day were smoked
Nonsmokers in the Scottish Heart Health Study self-reported either "none" or "a lot" of exposure to secondhand smoke
15 healthy nonsmokers assayed before (unexposed) and immediately after remaining in a room for 30 minutes with people who were smoking; the mean CO level in the room was approximately 6 ppm

longer (21 ± 4.6 hours) (Benowitz and Jacob 1993) than the mean half-life measured in nonsmokers (17 ± 3.9 hours) in a separate study that used labeled cotinine (Benowitz and Jacob 1994). Zevin and colleagues (1997) compared labeled nicotine with labeled cotinine and reported similar results. However, a small increase in the effective half-life resulting from tissue distribution effects would not be expected to influence estimates of secondhand smoke exposure based on cotinine measurements made under steady-state conditions. Collier and colleagues (1990) reported a significantly longer cotinine half-life in neonates and children, but a more recent evaluation found a similar half-life in both newborns and adults (Dempsey et al. 2000).

Besides possible differences in the effective half-life of cotinine among smokers and nonsmokers, research suggests that differences based on gender, race, and ethnicity may exist. Two studies found higher levels of serum cotinine per cigarette smoked in Black smokers than in White smokers—a finding that may reflect differences in nicotine metabolism or in the way that cigarettes are smoked (Wagenknecht et al. 1990; Caraballo et al. 1998). Total and nonrenal clearance of cotinine were significantly lower among Black smokers, and the metabolism of nicotine, cotinine, and *N*-glucuronidation activities were slower among Black smokers than among White smokers (Pérez-Stable et al. 1998; Benowitz et al. 1999). The mean half-life of cotinine among Black smokers (18 hours) was 12.5 percent longer than that found among White smokers (16 hours). One report also suggests that in comparisons with either Latinos or Whites, Chinese Americans metabolized nicotine more slowly; the mean increase in the cotinine half-life among Chinese American smokers was about 14 percent (Benowitz et al. 2002). Although Lynch (1984) found no gender differences in the cotinine half-life, Benowitz and colleagues (1999) found a significantly shorter cotinine half-life in women (14.5 hours) than in men (18.5 hours), a difference that the researchers attributed to a smaller volume of cotinine distribution in women. The same group reported higher metabolic clearance rates and a substantially shorter half-life (about nine hours) for cotinine in pregnant women (Dempsey et al. 2002), a finding that may require a slight revision of classification cutoff levels when assessing active smokers and women exposed to secondhand smoke during pregnancy.

Table 3.4 Half-life of cotinine in smokers and nonsmokers from several studies

Study	Exposure	Assay	Cotinine half-life in hours (mean ± SD*)	Comments
Kyerematen et al. 1982	Intravenous dose of ^{14}C-labeled nicotine at 2.7 μg/kg†	LC‡ separation; then measured radiolabeled metabolite	10.3 ± 2.3 n = 6	6 male smokers; overnight abstention before dosing and throughout the study; plasma assays
		Same	13.3 ± 2.2 n = 6	6 male nonsmokers
Benowitz et al. 1983	Intravenous cotinine infusion	GLC/NPD§	15.8 ± 4 n = 8	5 male and 3 female smokers; plasma assays
	Cotinine washout during 3 days of smoking abstention	GLC/NPD	19.7 ± 6.5 n = 12	8 male and 4 female smokers
Lynch 1984	Cotinine washout during 24 hours of smoking abstention	GLC/NPD	14.6 (men) 15.1 (women)	Averages from 47 male and 41 female smokers; cotinine half-life was calculated from 2-point data only; plasma assays
	Cotinine washout during 3 days of smoking abstention	GLC/NPD	15.4 (men) 15.7 (women)	8 male and 11 female smokers in a smoking cessation program; assayed once/day for 3 days
Sepkovic et al. 1986	Smokers abstained for 7 days	RIA∆	18.5 (plasma) 21.9 (urine)	10 smokers were followed during 7 days of smoking abstention
	Nonsmokers exposed to secondhand smoke in a chamber	RIA	49.7 (plasma) 32.7 (urine)	4 nonsmokers were exposed to secondhand smoke for 80 minutes/day for 4 days, then followed for an additional 7 days
De Schepper et al. 1987	Oral dose of cotinine at 10 and 20 mg¶ concentrations	GC–MS**	12.3 ± 2.6 n = 4	4 male nonsmokers; cotinine half-life was independent of dose, so both doses were averaged per person; the same results were obtained with infused cotinine; plasma assays
Jarvis et al. 1988	Oral dose of nicotine at 28 mg/day for 5 days before analysis	GLC/NPD 2 labs performed each assay	16.6 ± 3.4 n = 5	3 male and 2 female nonsmokers; plasma cotinine assays
			15.9 ± 3.1 n = 5	Salivary cotinine assays
			18.0 ± 4.0 n = 9	Urine cotinine assays

Table 3.4 Continued

Study	Exposure	Assay	Cotinine half-life in hours (mean ± SD*)	Comments
Scherer et al. 1988	Cotinine intravenous infusion	GLC/NPD	17.1 ± 4.4 n = 6	6 smokers; 5 days of smoking abstention before infusion; serum assays
Haley et al. 1989	Cotinine washout during 5 days of smoking abstention	RIA	16.6 ± 3.4 n = 9	9 smokers were followed for 5 days beginning with smoking cessation; urine assays
	Nonsmokers exposed to secondhand smoke in a chamber	RIA	27.3 ± 5.9 n = 10	10 nonsmokers were exposed to secondhand smoke for 8 minutes/day for 2 days, then followed for 4 additional days; urine assays
Curvall et al. 1990b	Oral dose of cotinine at indicated amount Followed for 4 days	GLC/NPD	14.9 ± 4.1 n = 3	7 male and 2 female nonsmokers; plasma cotinine assays following 5 mg dose
			15.6 ± 3.7 n = 9	Plasma cotinine assays following 10 mg dose
			14.9 ± 4.3 n = 9	Plasma cotinine assays following 20 mg dose
			16.3 ± 1.9 n = 3	Salivary cotinine assays following 5 mg dose
			15.7 ± 2.9 n = 9	Salivary cotinine assays following 10 mg dose
			14.9 ± 3.7 n = 9	Salivary cotinine assays following 20 mg dose
Benowitz and Jacob 1994	Native and isotopically labeled intravenous cotinine infusion	GC–MS	16.3 ± 4.4 n = 6	3 male and 3 female nonsmokers dosed with an average of 4.4 mg cotinine over 30 minutes (2 μg/minute/kg body weight); plasma half-life was measured for native cotinine
			16.9 ± 4.3 n = 6	Plasma half-life was measured for dideuterated cotinine
			17.2 ± 3.9 n = 6	Plasma half-life was measured for tetradeuterated cotinine

*SD = Standard deviation.
†μg/kg = Micrograms per kilogram.
‡LC = Liquid chromatography.
§GLC/NPD = Gas-liquid chromatography with nitrogen-phosphorus–specific detectors.
ΔRIA = Radioimmunoassay.
¶mg = Milligram.
**GC–MS = Gas chromatography with mass spectrometry.

Cotinine Analytical Procedures

Cotinine can be measured by a variety of techniques, but for application to studies of involuntary exposure, methods of high specificity and sensitivity are needed. The most commonly used methods have included RIAs and enzyme-linked immunoassays, gas-liquid chromatography (GLC) with nitrogen-phosphorus–specific detectors (NPD) or coupled to a mass spectrometer, and high-performance liquid chromatography (HPLC) using either ultraviolet (UV) or mass spectrometric detection. With the development of suitable antibodies (Langone et al. 1973; Knight et al. 1985), RIAs were made available for relatively sensitive and rapid analyses of nicotine and cotinine in biologic matrices. Enzyme-linked immunosorbent assays that use monoclonal antibodies have also been developed (Bjercke et al. 1986) that obviate radioactive reagents and provide a consistent antibody source. Immunoassays are well suited for screening large numbers of samples in epidemiologic investigations, but may be subject to cross-reactivity from other compounds that can limit the specificity. Even the more sensitive immunoassays for serum cotinine provide reliable results only for more heavily exposed nonsmokers who have serum cotinine concentrations of approximately 0.3 to 1 ng/mL or greater (Coultas et al. 1988; Emmons et al. 1996).

Chromatographic procedures for nicotine and cotinine measurements have commonly involved either HPLC with UV detection (Machacek and Jiang 1986; Hariharan et al. 1988; Oddoze et al. 1998), or capillary GLC/NPD (Jacob et al. 1981; Davis 1986; Teeuwen et al. 1989; Feyerabend and Russell 1990). The sensitive GLC/NPD methods of Feyerabend and Russell (1990) and of Jacob and colleagues (1981), with reported detection limits of about 0.1 ng/mL, have been used in support of several studies of exposure to secondhand smoke. There has been a more recent increase in the use of mass spectrometry for these analyses (Daenens et al. 1985; Norbury 1987; Jacob et al. 1991; McAdams and Cordeiro 1993; James et al. 1998). Gas chromatography (GC) with mass spectrometric detection provides a sensitive analytical method with inherently high specificity and enables the optimal use of stable isotopically labeled forms of the analyte as internal standards. This type of analysis is particularly well suited for sensitive cotinine measurements in complex biologic matrices. The recent availability of instrumentation combining HPLC with atmospheric pressure ionization tandem mass spectrometry has enabled the development of methods that provide high sensitivity and analytical specificity. These methods are also well suited for application to epidemiologic studies that analyze large numbers of samples (Bernert et al. 1997; Bentley et al. 1999; Tuomi et al. 1999). Benowitz (1996) has compared the relative sensitivity, specificity, and costs of these analytic procedures (Table 3.5).

Table 3.5 Analytical methods for measuring cotinine in nonsmokers

Study	Method	Sensitivity	Specificity	Cost
Langone et al. 1973; Haley et al. 1983; Knight et al. 1985	Radioimmunoassay	1–2 nanograms/milliliter (ng/mL)	Variable (poorest in urine)	Low
Jacob et al. 1981; Feyerabend et al. 1986	Gas chromatography	0.1–0.2 ng/mL	Good	Moderate
Hariharan and VanNoord 1991	High-performance liquid chromatography	±1 ng/mL	Good	Moderate
Jacob et al. 1991	Gas chromatography–mass spectrometry	0.1–0.2 ng/mL	Excellent	High
Bernert et al. 1997	Liquid chromatography/atmospheric pressure ionization tandem mass spectrometry	<0.05 ng/mL	Excellent	Extremely high

Source: Benowitz 1996.

Analytical Matrices for Cotinine Measurements

Nicotine and cotinine have been measured in a wide variety of physiologic matrices, including amniotic fluid (Lähdetie et al. 1993; Jauniaux et al. 1999), meconium (Ostrea et al. 1994; Dempsey et al. 1999; Nuesslein et al. 1999), cervical lavage (Jones et al. 1991), seminal plasma (Shen et al. 1997), breast milk (Luck and Nau 1984; Becker et al. 1999), sweat (Balabanova et al. 1992), and pericardial fluid (Milerad et al. 1994). However, most investigations of exposure to secondhand smoke have involved assays of cotinine in blood, urine, or saliva, or of nicotine or cotinine in hair. Nicotine is metabolized to cotinine mainly in the liver, but also in the lungs and kidneys; cotinine then enters the bloodstream. When an individual is subjected to involuntary smoking on a regular basis, a steady-state condition may be achieved in which blood cotinine levels remain fairly constant during the day (Benowitz 1996). Because of this stability in concentration levels, in conjunction with the reliable and well-defined composition of blood samples, blood serum or plasma has been considered the matrix of choice for quantitative cotinine assays (Watts et al. 1990; Benowitz 1996). Thus, in the past few years, plasma or serum cotinine measurements have been used in several large epidemiologic investigations of secondhand smoke exposure (Tunstall-Pedoe et al. 1991; Wagenknecht et al. 1993; Pirkle et al. 1996).

Despite a preference for blood plasma or serum as the matrix for cotinine assays, obtaining a blood sample is invasive, and collecting samples from younger children may be difficult. Consequently, saliva cotinine has been suggested as a useful alternative in many cases (Jarvis et al. 1987; Curvall et al. 1990a; Etzel 1990). Saliva is secreted into the oral cavity primarily by the parotid, sublingual, and submandibular glands. These glands typically produce between 18 and 30 mL of unstimulated saliva per hour (Sreebny and Broich 1987); the flow of stimulated saliva is three to six times greater. Oral fluids are a mixture derived from the individual salivary glandular secretions and oral mucosal transudates (gingival crevicular fluid), which are filtrates of plasma. Specific secretions may be recovered, but mixed or "whole" saliva is most commonly collected for cotinine analysis either by direct collection in an appropriate vessel or by adsorption onto commercially available collection pads (Sreebny and Broich 1987).

Many lipophilic drugs may pass from blood into saliva by simple diffusion through the lipid membranes of acinar cells. Because cotinine is a small, relatively lipophilic molecule with little protein binding (Benowitz et al. 1983), its concentration in saliva tends to closely parallel its concentration in blood. Several investigators have found a linear relationship between blood and saliva cotinine concentrations, with saliva levels typically about 1.1 to 1.5 times higher than the corresponding serum concentrations (Jarvis et al. 1988; Curvall et al. 1990a; Rose et al. 1993; Bernert et al. 2000). Schneider and colleagues (1997) compared cotinine levels in saliva samples that were obtained by using either sugar or paraffin wax to stimulate flow—unstimulated saliva samples were collected from the same persons. The researchers concluded that the significantly lower levels found in stimulated samples resulted from higher salivary flow rates. Other investigators, however, concluded that salivary flow rates did not influence cotinine concentrations in their samples (Van Vunakis et al. 1989; Curvall et al. 1990a), and the use of stimulated saliva with a somewhat higher and more uniform pH may reduce both the interindividual and intraindividual variability in the saliva-plasma ratio of a weak base such as cotinine (Knott 1989). Saliva cotinine assays have proven to be a quite useful noninvasive approach for assessing exposures to secondhand smoke, although a greater consistency in salivary collection methods among studies may facilitate subsequent comparisons of the results (Schneider et al. 1997).

Urine can also be readily obtained. Urine cotinine assays have several additional advantages over blood or saliva assays, such as the availability of the large volumes that can usually be collected, and typical cotinine concentration levels that average about five to six times higher than serum levels for unconjugated cotinine (Jarvis et al. 1984; Benowitz 1996). Besides nicotine and cotinine, urine samples may also contain significant amounts of the cotinine metabolite *trans*-3′-hydroxycotinine (Dagne and Castagnoli 1972; Neurath and Pein 1987) as well as several additional minor metabolites including nicotine-1′-*N*-oxide, cotinine-*N*-oxide, nornicotine, and norcotinine (Beckett et al. 1971; Jacob et al. 1986; Zhang et al. 1990; Benowitz et al. 1994). Two additional metabolites that were described more recently are 4-oxo-4-(3-pyridyl)butanoic acid and 4-hydroxy-4-(3-pyridyl)butanoic acid, which possibly arise from 2′-hydroxylation of nicotine and represent up to 14 percent of the nicotine dose (Hecht et al. 1999b, 2000). Nicotine, cotinine, and hydroxycotinine predominate in urine and are present in both an unconjugated form and as their glucuronides (Byrd et al. 1992), with nicotine and cotinine forming *N*-glucuronides and hydroxycotinine forming an O-glucuronide (Byrd et al. 1994; Benowitz et al. 1999).

Hydroxycotinine is often the most abundant nicotine metabolite present in urine, with a half-life of approximately six hours in adults when given alone, which is much shorter than that of cotinine (Scherer et al. 1988; Benowitz and Jacob 2001). In the presence of cotinine, however, the elimination half-life of 3'-hydroxycotinine is similar to that of continine (Dempsey et al. 2004). Consequently, cotinine is the most commonly used biomarker in urine samples. However, this half-life differential may not be present in newborns in whom the half-life is about the same for cotinine and 3'-hydroxycotinine (Dempsey et al. 2000). As with saliva, urine cotinine concentrations are also highly correlated ($r \pm 0.8$) with blood concentrations (Jarvis et al. 1984; Thompson et al. 1990; Benowitz 1996). Measuring a range of nicotine metabolites rather than cotinine alone may also be useful in some circumstances, and for such analyses, urine would often be the matrix of choice.

Higher cotinine concentrations present in urine can enhance sensitivity in an analysis of secondhand smoke exposure. However, urine assays have the disadvantage of being subject to variability that results from hydration differences among participants at the time of collection, because 24-hour urine samples are rarely available and random samples are most often used. Many investigators have attempted to circumvent this limitation by measuring both cotinine and creatinine in the sample and expressing the results as simple cotinine-creatinine ratios (NRC 1986), or by normalizing to a standardized creatinine concentration based on a regression between cotinine and creatinine in urine (Thompson et al. 1990). However, although daily urinary creatinine excretion is rather uniform within individuals, creatinine production is also directly related to muscle mass and varies by age and gender. Despite these potential limitations, creatinine adjustments of cotinine measurements are often used to provide an index of exposure to secondhand smoke from spot urine samples (NRC 1986).

Nicotine and Cotinine in Hair

One of the primary limitations of blood, urine, or saliva cotinine as a biomarker of exposure is the short exposure period that is represented. Assuming that substances such as nicotine are incorporated into the growing hair shaft over time, the use of hair as an analytical matrix has been suggested as an enhanced index of exposure to secondhand smoke covering a period of several months rather than just a few days. Ishiyama and colleagues (1983) first proposed using hair as a matrix for nicotine analyses, and several investigators have subsequently evaluated both nicotine and cotinine in hair. Unlike other matrices, the concentration of nicotine in hair is greater than that of cotinine (Haley and Hoffmann 1985; Kintz 1992; Koren et al. 1992). Because both concentrations are assumed to be stable once they have been deposited into the hair shaft, many hair analyses have included nicotine measurements or assays of both nicotine and cotinine. Studies of adult nonsmokers have reported a significant increase in hair nicotine concentrations with an increase in self-reported exposures to secondhand smoke (Eliopoulos et al. 1994; Dimich-Ward et al. 1997; Al-Delaimy et al. 2001; Jaakkola et al. 2001). Studies of infants and children have documented similar findings (Nafstad et al. 1995; Pichini et al. 1997; Al-Delaimy et al. 2000). Nafstad and colleagues (1998), however, found no significant differences in hair nicotine levels in a study of 68 nonsmoking women with no known exposure to secondhand smoke and 54 nonsmoking women with reported exposures. Some studies also found that hair nicotine levels for those most heavily exposed to secondhand smoke tended to overlap substantially with levels found in active smokers (Dimich-Ward et al. 1997; Al-Delaimy et al. 2001).

At this point, significant uncertainties remain concerning the use of hair analyses for either nicotine or cotinine to assess exposure to secondhand smoke, including the influence of variations in hair growth rates and in hair treatments such as bleaching or permanents. The mechanism of deposition and the influence of pigmentation are questions that also need to be addressed. The rate of hair growth, which varies among individuals, normally averages about one centimeter per month (Wennig 2000). Selecting nonrepresentative telogen stage (resting phase) hairs is a risk when only a few strands are selected for analysis (Uematsu 1993). Researchers believe that the systemic incorporation of nicotine or cotinine involves the passive diffusion of the substance from the blood into the hair follicle, and then into the growing hair shaft. Findings from studies that administered nicotine to animals are consistent with the systemic incorporation of both nicotine and cotinine into hair in this manner (Gerstenberg et al. 1995; Stout and Ruth 1999). In addition, Gwent and colleagues (1995) administered a single dose of nicotine (Nicorette Plus chewing gum) to six nonsmoking volunteers and demonstrated the incorporation of cotinine (but not nicotine) into beard hair. Cotinine levels peaked on the third day following the exposure. However, drugs may also be deposited

in the hair from contact with apocrine and sebaceous gland secretions, as well as directly into the hair shaft from the environment (Henderson 1993). Nicotine is present in apocrine and eccrine sweat (Balabanova et al. 1992), and studies have clearly demonstrated the adsorption of nicotine into hair from the environment (Nilsen et al. 1994; Zahlsen et al. 1996). Thus, multiple sources may contribute to the presence and levels of nicotine found in hair. Although each of these routes still reflects exposure of the nonsmoker to secondhand smoke, the proper interpretation of the results requires a better understanding of the relative contributions of these various factors. Direct environmental adsorption represents a form of personal air monitoring rather than a biomarker assessment. Because the adsorption of cotinine directly from the environment is expected to be quite low (Eatough et al. 1989b), the analysis of cotinine in hair would seem to provide an advantage in minimizing contributions directly from the environment. However, studies have found cotinine hair measurements to be generally less useful than nicotine hair measurements in assessing differences in exposure to secondhand smoke (Kintz 1992; Dimich-Ward et al. 1997; Al-Delaimy et al. 2000).

An additional concern with hair analyses is the influence of hair pigmentation on nicotine incorporation. Studies have documented a significantly greater systemic accumulation of nicotine in pigmented versus unpigmented hair in rodents (Gerstenberg et al. 1995; Stout and Ruth 1999), and in black hairs compared with white hairs from the same persons (Mizuno et al. 1993; Uematsu et al. 1995). This difference presumably reflects the strong binding of nicotine to melanin (Stout and Ruth 1999; Dehn et al. 2001), which is a relevant issue because differences in deposition as a function of either pigmentation or hair structure could lead to a differential sensitivity of detection or exposure classification among participants, including persons of differing ethnicity. This concern may be specific to nicotine deposition, however, because a similar differential response was not seen in a study of hair cotinine levels among children with either light or dark hair (Knight et al. 1996). Although the analysis of nicotine or cotinine in hair is potentially useful in assessing a longer-term exposure to secondhand smoke, this approach needs additional work.

Dietary Sources of Nicotine

Researchers consider the presence of nicotine or its metabolites in the body to be a specific indicator of prior exposures to tobacco smoke. This consideration thus provides an important rationale for the use of nicotine or its metabolites as biomarkers for secondhand smoke exposure. However, researchers have suggested that nicotine could be detected in some samples of tea and in certain vegetables, including potatoes and tomatoes, that belong to the same family (*Solanaceae*) as tobacco (Castro and Monji 1986; Sheen 1988). Idle (1990) subsequently referenced Sheen's (1988) results and suggested that cotinine measurements might be influenced by the ingestion of significant amounts of nicotine from these or other foodstuffs. Idle (1990) hypothesized that the uptake of dietary nicotine would be similar to the nicotine that is absorbed from the vapor phase in the lungs. However, Svensson (1987) proposed that at the acid pH of the stomach, nicotine would be protonated and not readily absorbed. Using direct measurements, Ivey and Triggs (1978) found essentially no absorption of nicotine from the human stomach at pH 1 and an approximate 8 percent absorption at pH 7.4. Even under moderately alkaline conditions (pH 9.8), the mean absorption was less than 20 percent. However, extensive intestinal absorption of nicotine does occur. Benowitz and colleagues (1991) found that the oral bioavailability of encapsulated nicotine administered to 10 smokers averaged about 44 percent. Bioavailability is low because of first-pass metabolism, which is when nicotine is converted to cotinine and other metabolites.

On the basis of their measurements and projections of dietary intake, Davis and colleagues (1991) proposed that from 9 μg to nearly 100 μg of nicotine per day might be ingested from food. However, this projection was based on maximum intakes of each of the foods of interest including large quantities of tea; actual intakes at that level would be unlikely (Benowitz 1999). In contrast, Repace (1994) used the food-nicotine concentrations reported by Domino and colleagues (1993) as well as a more realistic average consumption quantity of potatoes and tomatoes in the diet. The estimated daily nicotine intake from these foods was approximately 0.7 μg/day. Furthermore, more recent analyses of nicotine content in foodstuffs by specific mass spectrometric procedures found values that were somewhat lower than the earlier estimates. Siegmund and colleagues (1999a) developed a validated method for the extraction and recovery of nicotine from foods using capillary GC–mass spectrometry analysis. This method was subsequently applied to an analysis of a variety of foodstuffs including solanaceous vegetables and tea (Siegmund et al. 1999b). The estimated daily intake of nicotine from all

dietary sources for 14 countries, including the United States, was about 1.4 μg/day, with an estimated 2.25 μg/day at the 95th percentile. These values, which were derived from a Monte Carlo simulation that used mean daily consumption and measured nicotine contents of the foods, are well below the earlier estimates made by Davis and colleagues (1991) but are closer to those reported by Repace (1994).

Calculations of dietary nicotine contributions are necessarily imprecise. Direct evaluations of dietary intake should be more meaningful, and these measurements tended to produce lower results. For example, the dietary intake of nicotine estimated by Davis and colleagues (1991) included an important contribution from tea. Researchers assessed the contribution from tea in more than 1,800 nonsmokers, including many customary tea drinkers, in the Scottish Heart Health Study; no consistent relationship was found between serum cotinine levels and a daily tea intake of up to 10 cups (Tunstall-Pedoe et al. 1991). Those who consumed 10 or more cups per day had a slight increase in serum cotinine, but the effect of tea was noted to be inconsistent. In a large, national epidemiologic survey conducted in the United States, Pirkle and colleagues (1996) used a 24-hour food recall diary, which was completed by each study participant, to compare the dietary intake of potatoes, tomatoes, eggplants, cauliflowers, green peppers, and both instant and brewed tea with serum cotinine levels. Using regression models, these food items explained less than 2 percent of the variance in serum cotinine levels.

Benowitz and Jacob (1994) proposed a conversion factor between nicotine and serum cotinine and suggested that it can be used to estimate nicotine exposure under steady-state conditions. For example, using the most recent estimate from Siegmund and colleagues (1999b) of 1.4 μg of nicotine per day in the average diet, and assuming that 71.3 percent of the dietary nicotine is absorbed in the same manner as vapor phase nicotine from secondhand smoke (Iwase et al. 1991), applying this conversion factor would result in a predicted mean serum cotinine concentration of no more than 0.013 ng/mL; at the 95th percentile of dietary nicotine intake, the estimate would be 0.020 ng/mL. These estimates are consistent with the results of Pirkle and colleagues (1996) and indicate a minimal dietary contribution to serum cotinine measurements. Thus, trace amounts of nicotine may be consumed in the diet, but any contribution from this source is likely to be quite small for most people compared with the amount of nicotine absorbed from secondhand smoke exposure. Additionally, comparisons of cotinine within individuals over time, such as before and after an intervention, would probably be unaffected by diet.

Cotinine Measurements as an Index of Nicotine Exposure

Although the potential for overlap of levels always exists between nonsmokers with an extensive exposure to secondhand smoke and occasional or currently abstinent smokers, the use of cotinine measurements to separate smokers from nonsmokers provides a generally valid approach. Benowitz and colleagues (1983) originally proposed 10 ng/mL as a reasonable cutoff level for cotinine in serum to distinguish between smokers and nonsmokers. Consistent with that proposal, Repace and Lowrey (1993) estimated median serum cotinine levels to be about 1 ng/mL for U.S. adult nonsmokers and about 10 ng/mL for the most heavily exposed nonsmokers. In a study of 211 people in London, England, a plasma cutoff of 13.7 ng/mL provided an optimal classification with 94 percent sensitivity and 81 percent specificity based on self-reported exposure levels (Jarvis et al. 1987). The authors attributed the relatively poor specificity to "deception" in the self-reports of some participants with high serum cotinine levels. When the investigators reclassified those believed to be deceptive as smokers, sensitivities were 96 to 97 percent and specificities were 99 to 100 percent using plasma, saliva, or urine cotinine as the biomarker for comparison. The optimal cutoff values in this study were 14.2 ng/mL in saliva and 49.7 ng/mL in urine (Jarvis et al. 1987).

Pirkle and colleagues (1996) used a serum cotinine cutoff level of 15 ng/mL in a large U.S. epidemiologic study. They found a strong agreement with the self-reported nonsmoking status of the participants: those with serum cotinine levels above 15 ng/mL who claimed no tobacco use comprised only about 1.3 percent of the adult participants and 2.6 percent of the adolescents. Caraballo and colleagues (2001) examined the participants in this study aged 17 years and older in detail and used the same nominal cutoff of 15 ng/mL. There was a 92.5 percent agreement between serum cotinine concentrations and self-reported active smoking status and a 98.5 percent agreement among self-reported nonsmokers. The researchers regarded the infrequent or low rate of cigarette use as an explanation for the disagreement with serum cotinine levels among self-reported smokers in most cases. However, there may have been some deception in the 1.5 percent with discrepant results between their serum cotinine levels and self-reported

status as nonsmokers, particularly among those with relatively high concentrations of serum cotinine. Wagenknecht and colleagues (1992) found similar results in the Coronary Artery Risk Development in (Young) Adults Study, which had a serum cotinine cutoff value of 15 ng/mL that produced a sensitivity of 94.5 percent and a specificity of 96 percent. In general, self-reports of smoking status validated with biomarker assays were accurate in most studies (Patrick et al. 1994), although small adjustments to customary cutoff values between smokers and nonsmokers may be needed based on gender and race for both males and females and for pregnant women. The accuracy of questionnaire reports in determining the extent of exposure may be higher in population contexts than in clinical studies, particularly in investigations of smoking cessation.

The objective in many studies is not only to identify nonsmokers exposed to secondhand smoke, but also to estimate the relative extent of their exposure. If a quantitative relationship exists between exposure to nicotine in secondhand smoke and cotinine biomarker concentrations, then investigators should be able to estimate the average nicotine exposure of groups of individuals from their biomarker levels. Repace and Lowrey (1993) developed a model that related nicotine exposure to cotinine levels measured in both the plasma and urine of nonsmokers. Subsequent comparisons of the model predictions with data from 10 epidemiologic studies were consistent within 10 to 15 percent for median and peak levels of cotinine. Using the fractional conversion of nicotine to cotinine and estimated cotinine clearances in active smokers, Benowitz and Jacob (1994) proposed a factor (K = 0.08 with a coefficient of variation ±22 percent) that could be used to estimate daily nicotine intake (in milligrams of nicotine) from the steady-state plasma cotinine concentration in ng/mL. The validity of this factor is supported by the data from Galeazzi and colleagues (1985). They administered measured doses of nicotine intravenously to six volunteers on four consecutive days and assessed serum cotinine levels on the fourth day, when steady-state conditions had been reached. The results indicate that plasma cotinine concentrations could be directly and linearly related to daily nicotine intake. Predicted nicotine intake calculations, based on the factor proposed by Benowitz and Jacob (1994), demonstrated a close agreement in all cases with the actual exposures (Table 3.6).

Although Benowitz and Jacob (1994) had derived their factor from smokers, the clearance of cotinine was similar for smokers and nonsmokers (Zevin et al. 1997), and Benowitz (1996) noted that the factor for nicotine exposure among nonsmokers should also be similar. The results obtained by Curvall and colleagues (1990b) with short-term exposures and nonsteady-state correlations are in general agreement with that expectation. After administering various low doses of nicotine intravenously to nonsmokers, the researchers concluded that the average intake of nicotine among their participants could be estimated from the following relationship:

Cotinine concentration (ng/mL) ~ 0.5 * [nicotine infusion rate in μg/min] * [absorption time in hours]

where 0.5 represents the somewhat lower fraction of nicotine metabolized to cotinine among nonsmokers as Curvall and colleagues (1990b) had reported. A comparison of this expression with that of Benowitz and Jacob (1994) suggests that both should generate similar results, with the main difference between them reflecting the lower fractional conversion of nicotine to cotinine among nonsmokers as Curvall and colleagues (1990b) had estimated. Curvall and colleagues (1990b) noted that this conversion may represent a true difference, or may have resulted from differences in the experimental setups between the two studies. Zevin and colleagues (1997) reported that the mean conversion of nicotine to cotinine is approximately the same

Table 3.6 Calculation of nicotine dosage from plasma cotinine concentrations

Nicotine administered* (milligrams [mg]/day)	Mean plasma cotinine† (nanograms/milliliter)	Calculated dose† (mg/day)
7.3	92	7.4
14.6	185	14.8
22.0	278	22.2
29.3	381	30.5

*From the dosage and plasma cotinine concentrations given in Galeazzi et al. 1985 (Table 1). Doses were adjusted to mg/day based on the reported mean weight of the participants (61 kilograms, n = 6).
†Calculated from plasma cotinine multiplied by 0.08.
Sources: Galeazzi et al. 1985; Benowitz and Jacob 1994.

for nonsmokers as for smokers. If that conclusion is correct, then the factor derived by Benowitz and Jacob (1994) should be applicable to both groups.

These estimates are based on studies in which nicotine was infused into people, often at greater concentrations than would result from involuntary smoking. However, the estimates are consistent with a linear relationship between nicotine exposure and mean serum cotinine concentrations when measured under steady-state conditions. These findings suggest that at least an approximate quantitative estimate of nicotine exposures within population groups might be derived from their plasma cotinine concentrations. Because cotinine levels in an individual reflect not only exposure variations but also individual differences in metabolism and excretion, the value of a single measurement within an individual may be limited. However, the application of cotinine measurements in epidemiologic studies that involve large numbers of individuals may provide reliable estimates of average group exposures to nicotine in secondhand smoke (Benowitz 1999).

Protein and DNA Adducts

Measurements of DNA or protein adducts of carcinogens in secondhand smoke may indicate both the exposure (internal dose) and the interaction of the carcinogen or its metabolite with the host tissue, thus reflecting the biologically effective dose. Furthermore, if the adduct is stable, this approach can determine time-integrated exposures over the lifetime of the modified biopolymer. In the case of protein adducts, this exposure interval corresponds to the lifetime of the red cell (approximately 127 days) for Hb adducts and to the 21-day half-life of serum albumin adducts. Based on continuing daily exposures, this integration over time can lead to an approximate 60-fold amplification in Hb adduct levels and to a 30-fold amplification for serum albumin adduct levels (Skipper and Tannenbaum 1990). DNA adducts in human target tissue, such as the lung, are of particular interest because they may be directly relevant to carcinogenesis, but such tissue is available only by surgery or biopsy. Thus, many analyses have used white blood cell DNA adducts as surrogate markers. Many investigators prefer to analyze adducts in lymphocytes because of their significantly longer lifetimes (up to several years) than the lifetime of less than one day that monocytes and granulocytes have (Kriek et al. 1998). However, these assays are limited by the small amount of DNA that is available in peripheral blood, by the low rates of base modification typically observed, and by the removal of adducts through DNA repair mechanisms. Consequently, studies of adducts in response to the exposure of humans to secondhand smoke have largely focused on the use of protein adducts as surrogate markers because they are more abundant and are not subject to repair mechanisms.

Maclure and colleagues (1989) found that concentrations of both 4AB–Hb and 3AB–Hb adducts were significantly higher in nonsmokers with confirmed exposures to secondhand smoke (based on plasma cotinine concentrations) than in unexposed nonsmokers. The same investigators had previously demonstrated that concentrations of 4AB–Hb were significantly higher in smokers than in nonsmokers, and that the concentrations declined during smoking cessation to levels found in nonsmokers (Bryant et al. 1987; Skipper and Tannenbaum 1990). Hammond and colleagues (1993) found a dose-response relationship for 4AB–Hb concentrations in nonsmokers who were categorized into three levels of exposure to secondhand smoke based on their personal monitoring of nicotine exposure. These authors found that 4AB–Hb concentrations in nonsmokers exposed to secondhand smoke were about 14 percent of those found in smokers, whereas cotinine levels in nonsmokers were about 1 percent of those in smokers. These relative biomarker concentrations are consistent with the higher concentrations of 4AB–Hb and nicotine in sidestream versus mainstream smoke of about 31-fold and 2-fold, respectively (NRC 1986). These results implicate secondhand smoke exposure as a contributing factor to the amount of 4AB adducted to Hb. However, detectable background levels of 4AB–Hb adducts are commonly observed among nonsmokers with no known sources of exposure to secondhand smoke, although they were possibly exposed to other combustion emissions (Bryant et al. 1987; Maclure et al. 1990). As a consequence, the distributions of adduct levels in nonsmokers exposed to secondhand smoke and in those who have no known exposure may not be sharply separated. Additionally, at the time of these studies, secondhand smoke exposure may have been so ubiquitous that few persons were truly unexposed.

In a study of 109 children, 4AB–Hb and PAH–albumin adducts were higher in children whose mothers smoked and in children from households with a smoker other than the mother, compared with children unexposed to secondhand smoke (Crawford et al. 1994; Tang et al. 1999). Cotinine levels also increased with exposure and there were significant

differences among the groups for both biomarkers. After adjusting for the exposure group, the researchers found that these markers were higher among African American children than among Hispanic children. Conversely, in a study of 107 nonsmoking women, Autrup and colleagues (1995) found no significant difference in PAH–albumin levels of those exposed and those unexposed to secondhand smoke. Although serum cotinine measurements confirmed the status of the nonsmokers, the researchers did not compare cotinine and PAH–albumin levels of the participating smokers and nonsmokers. Scherer and colleagues (2000) also found no difference in B[*a*]P adducts of either Hb or albumin in a study of 19 nonsmokers exposed to secondhand smoke and 23 unexposed nonsmokers. This study measured nicotine from personal samplers on individual participants and cotinine levels in both plasma and urine. Cotinine levels were significantly higher among those exposed to secondhand smoke; this finding confirmed the differences in exposure. Additional work may be needed to resolve these findings for the PAH adducts.

Tobacco-Specific Nitrosamines

Tobacco-specific nitrosamines (TSNAs) are of considerable interest as biomarkers of exposure to secondhand smoke because they combine both high specificity for tobacco exposure and additional relevancy as presumed carcinogens. The formation, metabolism, and role of these nitrosamines as significant carcinogens in tobacco smoke were discussed in detail in Chapter 2 (Toxicology of Secondhand Smoke). Several recent studies demonstrated that NNAL and its glucuronide can be measured in the urine of nonsmokers exposed to secondhand smoke (Hecht et al. 1993b; Parsons et al. 1998; Meger et al. 2000; Anderson et al. 2001). There were significant correlations with urine cotinine levels (Hecht et al. 1993b; Parsons et al. 1998) and with nicotine exposures measured with personal samplers (Meger et al. 2000). An additional advantage of NNAL and NNAL-glucuronide as biomarkers is that they are reportedly eliminated more slowly than either nicotine or cotinine in smokers following smoking cessation (Hecht et al. 1999a). Hecht and colleagues (1999a) estimated that the elimination half-life of NNAL was 45 days compared with 40 days for NNAL-glucuronide. If a similar extended half-life can be confirmed in nonsmokers, then these markers may offer the promise of monitoring a longer period of exposure than is possible with either nicotine or cotinine. The main limitation of NNAL measurements is that the concentrations are quite low, even among active smokers, and relatively large urine sample volumes combined with extensive cleanup and sensitive analytical procedures are needed for assays of nonsmokers.

Besides forming urinary metabolites, both 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and another TSNA, *N*′-nitrosonornicotine, may also form adducts with Hb and DNA that release 4-hydroxy-1-(3-pyridyl)-1-butanone (HPB) on hydrolysis (Hecht et al. 1994). However, the HPB yield has been surprisingly low and was significantly elevated in only a minority of active smokers and in very few nonsmokers. There was also a substantial overlap in values from the samples of both groups. The reason for this finding is unclear; it may reflect individual metabolic differences in Hb alkylation (Hecht et al. 1993a) or limitations in the analytical procedures. If such limitations could be identified and resolved, the analysis of TSNA adducts might offer considerable promise. However, measurements of NNAL and NNAL-glucuronide in urine appear to be the best approach for monitoring exposures to NNK among people exposed to secondhand smoke.

Evidence Synthesis

Biomarkers are valuable for providing an objective index of the internal dose of a component or its metabolite from secondhand smoke following exposure. Biomarkers can be particularly useful in verifying self-reports of exposure to secondhand smoke because individuals may differ in their awareness of the extent and duration of such exposures. Thus, the use of sensitive biomarker measurements may permit the identification of previously unrecognized exposures within nominal control or unexposed groups, and thereby improve the reliability of classifications. However, biomarkers are also limited by interindividual and intraindividual variability, analytical constraints, and limitations on the exposure timeframe that can be monitored.

For example, as tobacco smoke ages and decays, the physical and chemical composition of secondhand smoke changes (NRC 1986), and the ratio of a marker compound such as nicotine to other components of interest may also change. Temporal variations in the ratio of a biomarker to other hazardous compounds in tobacco smoke could thus complicate the interpretation of exposure based on the measurement of that marker. However, as Benowitz (1999) noted, when ratios of nicotine to other constituents such as

respirable suspended particulates are averaged over exposure-time intervals of hours or days, as is typical of a human exposure, the ratios remain consistent. This consistency suggests that biomarkers such as nicotine or its cotinine metabolite should provide a valid assessment of exposure to other toxic constituents in secondhand smoke. Nevertheless, the continual changes in composition during aging will complicate the assessment of tobacco smoke exposure based on one specific marker such as nicotine.

Cotinine measurements in blood or other matrices provide the most useful biomarker for assessing exposure to secondhand smoke because these measurements combine high levels of specificity and sensitivity for exposure. However, as noted above, cotinine measurements reflect an exposure only to nicotine; they are limited to monitoring an exposure over the previous few days unless hair cotinine is measured, and are susceptible to short-term fluctuations that reflect metabolic variations. Even regular smokers may display diurnal variations in plasma cotinine that average 30 percent from peak to trough, with higher concentrations occurring later in the day (Benowitz and Jacob 1994); similar fluctuations may be expected in nonsmokers regularly exposed to secondhand smoke. Cotinine may also reflect an exposure to nicotine previously adsorbed onto dust or emitted from room surfaces rather than a direct exposure to secondhand smoke (Hein et al. 1991), although the extent of this indirect mode of exposure is believed to be trivial (Hein et al. 1991; Benowitz 1999). The interpretation of a result from a single cotinine measurement for an individual is difficult, but multiple measurements over time and mean values from groups within a population may provide useful indices of typical exposure levels. As Benowitz (1999) noted, current evidence "…indicates that cotinine levels provide valid and quantitative measures of average ongoing human ETS [environmental tobacco smoke] exposure over time" (p. 353).

Besides cotinine, other promising biomarkers of involuntary smoking include the tobacco-specific nitrosamine NNAL, the 4AB–Hb adduct, and perhaps hair analysis for nicotine. Each of these markers has the potential to provide an index of exposure over a period of at least several weeks rather than the few days afforded by cotinine, and both NNAL and Hb adducts of aromatic amines are directly relevant as indicators of potential adverse health risks.

Conclusions

1. Biomarkers suitable for assessing recent exposures to secondhand smoke are available.

2. At this time, cotinine, the primary proximate metabolite of nicotine, remains the biomarker of choice for assessing secondhand smoke exposure.

3. Individual biomarkers of exposure to secondhand smoke represent only one component of a complex mixture, and measurements of one marker may not wholly reflect an exposure to other components of concern as a result of involuntary smoking.

Implications

There is a need to refine the methodology used to measure biomarkers to increase their sensitivity and for research into their validity as predictors of population risk. There remains a need for a biomarker capable of reliably indicating past exposures over an extended time period. Until such a marker can be identified, long-term exposures to secondhand smoke can only be assessed through the use of questionnaires and similar approaches.

Conclusions

Building Designs and Operations

1. Current heating, ventilating, and air conditioning systems alone cannot control exposure to secondhand smoke.

2. The operation of a heating, ventilating, and air conditioning system can distribute secondhand smoke throughout a building.

Exposure Models

3. Atmospheric concentration of nicotine is a sensitive and specific indicator for secondhand smoke.

4. Smoking increases indoor particle concentrations.

5. Models can be used to estimate concentrations of secondhand smoke.

Biomarkers of Exposure to Secondhand Smoke

6. Biomarkers suitable for assessing recent exposures to secondhand smoke are available.

7. At this time, cotinine, the primary proximate metabolite of nicotine, remains the biomarker of choice for assessing secondhand smoke exposure.

8. Individual biomarkers of exposure to secondhand smoke represent only one component of a complex mixture, and measurements of one marker may not wholly reflect an exposure to other components of concern as a result of involuntary smoking.

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Chapter 4
Prevalence of Exposure to Secondhand Smoke

Introduction

The 1986 U.S. Surgeon General's report, *The Health Consequences of Involuntary Smoking*, outlined the need for valid and reliable methods to more accurately determine and assess the health consequences of exposure to secondhand smoke (U.S. Department of Health and Human Services [USDHHS] 1986). The report concluded that reliable methods were necessary to research the health effects and to characterize the public health impact of exposure to secondhand tobacco smoke in the home, at work, and in other environments. The report noted that without valid and reliable evidence, policymakers could not draft and implement effective policies to reduce and eliminate exposures: "Validated questionnaires are needed for the assessment of recent and remote exposure to environmental tobacco smoke in the home, workplace, and other environments" (USDHHS 1986, p. 14).

Since the publication of that report, public health investigators have made significant advances in the development and application of reliable and valid research methods to assess exposure to secondhand smoke (Jaakkola and Samet 1999; Samet and Wang 2000). Several investigators have recently developed new methods to measure tobacco smoke concentrations in indoor environments and have discovered sensitive biologic markers of active and involuntary exposures (Jaakkola and Samet 1999; Samet and Wang 2000). These advances have generated a substantial amount of data on exposure of nonsmokers to secondhand smoke and have improved the capability of researchers to measure a recent exposure. However, many public health investigators agree that more accurate tools are still needed to measure temporally remote exposures, which, by necessity, are still assessed using questionnaires (Jaakkola and Samet 1999).

The main methods researchers rely on to evaluate secondhand smoke exposure are questionnaires, measurements of concentrations of the airborne components of secondhand smoke, and measurements of biomarkers (Chapter 3, Assessment of Exposure to Secondhand Smoke). The discussion that follows on the prevalence of secondhand smoke exposure includes current metrics of exposure, changes in exposure over time, exposure of special populations such as children with asthma and persons in prisons, and international differences in exposure.

Methods

To identify research publications on biomarkers of secondhand smoke, the authors of this chapter reviewed the published literature for studies on population exposures to and concentrations of secondhand smoke in different environments by conducting a Medline search with the following terms: tobacco smoke pollution, environmental tobacco smoke, and secondhand smoke. These terms were then paired with the term population or survey. The authors then reviewed abstracts of articles to specifically identify studies that used representative surveys of the U.S. population for inclusion in this report.

To specifically identify articles on concentrations of secondhand smoke, the authors used Boolean logic to search Medline and Web of Science, pairing the selected terms for secondhand smoke (secondhand smoke, environmental tobacco smoke, passive smoking, and involuntary smoking) with terms indicative of a location that included home, work, workplace, occupation and restaurants, bars, public places, sports, transportation, buses, trains, cars, airplanes, casinos, bingo, nightclubs, prisons, correctional institutions, nursing homes, and mental institutions. The authors searched for these terms with and without other selected terms such as exposure, concentration, and level of exposure. The authors also included data from a review of studies on the composition and measurement of secondhand smoke (Jenkins et al. 2000).

This chapter focuses on measured concentrations of airborne nicotine—nicotine is a specific tracer for secondhand smoke and has therefore been widely used in many studies. This discussion also focuses on biomarker levels of cotinine, the metabolite of nicotine. Thus, the abstracts of articles identified through the literature search were further reviewed for data that contained measured values of nicotine in the air of selected environments.

Metrics of Secondhand Smoke Exposure

This chapter considers how researchers have used the techniques for assessing exposure to secondhand smoke to determine the extent of exposure among populations. The discussion includes the strengths and limitations of these techniques.

Questionnaires

A questionnaire-based assessment of exposure to secondhand smoke is the most widely used method to evaluate an exposure. Questionnaires have important advantages: they are relatively inexpensive; they can be feasibly administered in a variety of ways, including mail surveys, telephone surveys, or in person; and they are able to assess both current and past exposures (Jaakkola and Jaakkola 1997; Jaakkola and Samet 1999). The disadvantages include difficulties in validation, particularly of a past exposure, and the potential for misclassification. Misclassification may result from a respondent's lack of knowledge about a current or past exposure, the difficulty in characterizing an exposure in complex indoor environments, and biased recall, whether intentional or unintentional (USDHHS 1986).

Investigators have developed numerous questionnaires that assess exposures to secondhand smoke. The questionnaires address fundamental factors such as duration, source strength (the number of smokers or number of cigarettes smoked), room size, and distance from smokers, as well as the perception of an exposure such as observations of tobacco smoke, odor, and irritation. For example, the indirect index of being married to a smoker or of being in the presence of smokers has been widely used to examine the long-term effects of secondhand smoke exposure (Hirayama 1984; Sandler et al. 1989). However, a misclassification of total exposure may occur with indirect measures because they do not capture exposures outside of the home, and because some smokers may not smoke in the house. Nevertheless, compared with persons living in smoke-free homes, Hammond (1999) demonstrated that persons who are married to or living with smokers have higher exposures to secondhand smoke.

Several investigators have used questionnaires to quantitatively estimate exposures by ascertaining the number of hours per day of exposure and the number of cigarettes smoked in a specific location, such as in the home, at work, or in public places (Coghlin et al. 1989; Fontham et al. 1994; Pirkle et al. 1996). These estimates may be made either collectively or separately in each location where the respondents spend time. Although it may be necessary to ask many questions to cover all possible microenvironments of exposure, questionnaires that capture objective measures may provide more accurate estimates of an exposure, and measured concentrations of airborne components of secondhand smoke can be used to calculate summary measures across exposure locations.

Studies have assessed secondhand smoke exposure by asking respondents to rate their perceived level of exposure (e.g., none, slight, moderate, heavy) in various environments (Haley et al. 1989). However, this type of assessment cannot be readily standardized and could potentially result in both random and nonrandom misclassification. For example, persons with a respiratory disease such as asthma may be more likely to perceive exposures to secondhand smoke and to classify them toward the higher end of the scale.

Questionnaires are the only means of assessing remote past exposures to secondhand smoke, absent stored samples for biomarker measurements. For example, Sandler and colleagues (1989) used the smoking status of the spouse as a surrogate for determining household exposures to secondhand smoke. These researchers found that 30 percent of nonsmoking men and 64 percent of nonsmoking women in Washington County, Maryland, reported an exposure in 1963. This

information was used to assign an exposure in assessing subsequent disease risk. In a community-based study in California, 60 percent of nonsmoking participants reported secondhand smoke exposure during their lifetime, defined as at least one hour per day for at least one year (Berglund et al. 1999). However, biomarker data from other studies indicate higher percentages for secondhand smoke exposure. Data from the Third National Health and Nutrition Examination Survey (NHANES III) showed a detectable level of cotinine in 88 percent of nonsmoking adults (Pirkle et al. 1996).

Many investigators have validated questionnaire assessments of current exposures to secondhand smoke using biomarkers, specifically cotinine (Haley et al. 1989; Jarvis et al. 1991; Hammond et al. 1993; Pirkle et al. 1996; Al-Delaimy et al. 2000; Mannino et al. 2001). These studies have demonstrated that persons who were classified as having high levels of secondhand smoke exposure (often defined as living with a smoker) had higher levels of biomarkers in biologic samples of serum, urine, saliva, or hair when compared with persons who had low levels of exposure (often defined as not living with a smoker). Because there is no known biomarker that assesses long-term or temporally remote exposures, researchers still use questionnaires. For example, Coghlin and colleagues (1989) evaluated the reliability of a questionnaire and a personal diary by measuring the individual exposure of each study participant during a one-week period. The questionnaire and the personal diary were both used to collect information on the number of smokers the participants were exposed to, and the proximity and duration of exposure. The investigators found a high correlation (r^2 [prediction values] = 0.98) between the exposure score derived from data recorded in the personal diaries and the log of nicotine concentrations (r^2 measures the strength of the linear model that was used).

Airborne Concentrations

Measuring airborne concentrations of secondhand smoke constituents provides estimates of the level of an exposure and identifies the environments in which the exposure occurred. These measurements can be made using personal monitors, a form of assessing direct exposures (Hammond et al. 1987, 1988, 1993; Coghlin et al. 1989; Mattson et al. 1989; Kado et al. 1991; Emmons et al. 1994; Jenkins et al. 1996a), or monitors that evaluate the concentrations in various microenvironments, a form of assessing indirect exposures (Henderson et al. 1989; Leaderer and Hammond 1991; Marbury et al. 1993; Hammond 1999). Measurements of airborne contaminants can also evaluate the efficacy of various control measures (Vaughan and Hammond 1990; Hammond et al. 1995; Emmons et al. 2001; Hammond 2002). Concentrations are typically assessed by measuring specific components of secondhand smoke referred to as tracers.

Studies have used several airborne constituents of tobacco as tracers, and their advantages and disadvantages are reviewed in Chapter 3 (Assessment of Exposure to Secondhand Smoke) of this report. As noted in that chapter, the concentration of secondhand smoke in any given location will depend on the number of cigarettes smoked in that location, the size of the room, the exchange of air in that room with outdoor air (whether windows are open, or how much air is circulated by natural means and by mechanical systems), and the interaction of the tobacco smoke with surfaces in the room. Because each of these factors has a range of values across locations, the concentration of secondhand smoke varies across settings. This variation results in a distribution of secondhand smoke concentrations in each type of setting. For example, Rogge and colleagues (1994) found a wider range of concentrations in locations such as workplaces and restaurants than in the home because a wider range exists in the number of smokers, the size of the rooms, and the exchange rates of indoor with outdoor air.

Biomarkers

Biomarkers provide an indicator of the internal dose of secondhand smoke and reflect exposure (Chapter 3, Assessment of Exposure to Secondhand Smoke). Persons with comparable exposures to secondhand smoke can have different levels of a marker because of individual variations in factors that determine uptake, metabolism, and elimination of the biomarker (Pirkle et al. 1996; Jaakkola and Samet 1999). Cotinine is the biomarker most frequently used to measure tobacco smoke doses, including doses from secondhand smoke (Benowitz 1999). Cotinine has a half-life ranging from 7 to 40 hours in adults and 32 to 38 hours in children (Jaakkola and Jaakkola 1997) and can be measured in serum, urine, saliva, hair, and breast milk. Studies show that cotinine measurements separated current active smokers from current nonsmokers with a high degree of validity and were used to identify people with current and high levels of secondhand smoke exposure (Pirkle et al. 1996; Mannino et al. 2001). Given its half-life, investigators

have demonstrated that cotinine levels are generally not influenced by an exposure that occurred more than two to four days before the testing (Benowitz 1996). However, cotinine levels increased in people using nonsmoking-related sources of nicotine, such as nicotine patches or spit tobacco. Other biomarkers of tobacco smoke exposure, such as 4-aminobiphenyl adducts or nitrosamines, have not been widely used in population studies and are not discussed in this chapter (Jaakkola and Samet 1999).

Estimates of Exposure

National Trends in Biomarkers of Exposure

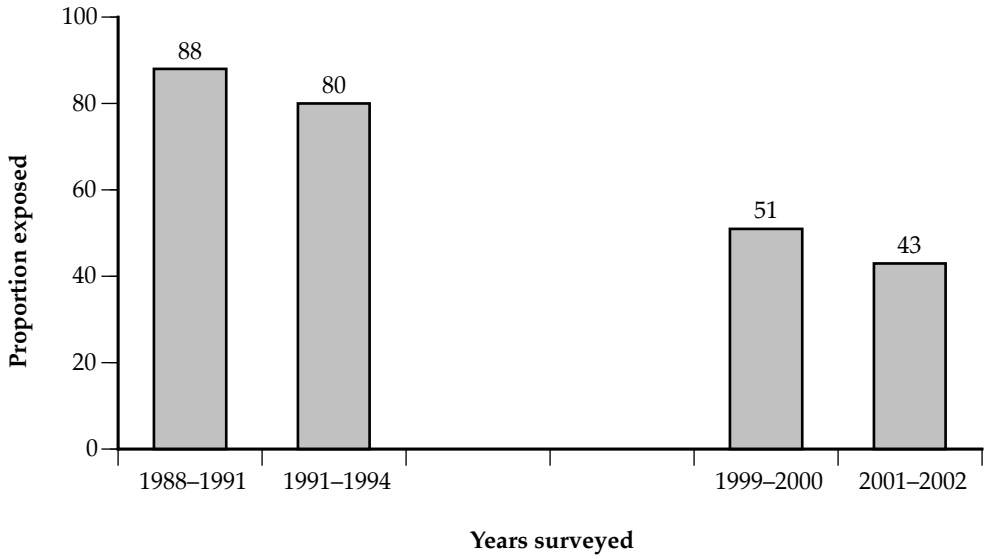
Beginning in 1988, researchers used serum cotinine measurements to assess exposures to secondhand smoke in the United States within the NHANES. The NHANES is conducted by the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC), and is designed to examine a nationally representative sample of the U.S. civilian (noninstitutionalized) population based upon a complex, stratified, multistage probability cluster sampling design (see http://www.cdc.gov/nchs/nhanes.htm). The protocols include a home interview followed by a physical examination in a mobile examination center, where blood samples are drawn for serum cotinine analysis. NHANES III, conducted from 1988 to 1994, was the first national survey of secondhand smoke exposure of the entire U.S. population aged 4 through 74 years. There were two phases: Phase I from 1988 to 1991, and Phase II from 1991 to 1994. There were no further studies between 1995 and 1998. In 1999, NCHS resumed NHANES on a continuous basis and completed a new nationally representative sample every two years. This more recent NHANES (1999) also began to draw blood samples for serum cotinine analyses from participants aged three years and older.

Researchers have reported serum cotinine levels in nonsmokers from the NHANES for four distinct intervals within the overall time period of 14 years, from 1988 through 2002: Phase I and Phase II of NHANES III, NHANES 1999–2000, and NHANES 2001–2002 (Pirkle et al. 1996, 2006). Researchers have reported additional data on serum cotinine levels in nonsmokers from NHANES 1999–2002 in the *National Report on Human Exposure to Environmental Chemicals* (CDC 2001a, 2003, 2005). To maintain comparability among survey intervals, trend data are only reported for participants aged four or more years in each study interval (Pirkle et al. 2006). Factors that affect nicotine metabolism, such as age, race, and the level of exposure to secondhand smoke, also influence cotinine levels (Caraballo et al. 1998; Mannino et al. 2001). Because cotinine levels reflect exposures that occurred within two to three days, they represent patterns of usual exposure (Jarvis et al. 1987; Benowitz 1996; Jaakkola and Jaakkola 1997).

Studies document NHANES serum cotinine levels in both children and adult nonsmokers (Pirkle et al. 1996, 2006; CDC 2001a, 2003, 2005). Nonsmoking adults were defined in these studies as persons whose serum cotinine concentrations were 10 nanograms per milliliter (ng/mL) or less, who reported no tobacco or nicotine use in the five days before the mobile examination center visit, and who were self-reported former smokers or lifetime nonsmokers. In NHANES III, the laboratory limit of detection was 0.050 ng/mL. However, the laboratory methods have continued to improve, and the detection limit was recently lowered to 0.015 ng/mL (CDC 2005; Pirkle et al. 2006). Additionally, researchers have categorized serum cotinine concentrations by age, race, and ethnicity. The racial and ethnic categories are non-Hispanic White, non-Hispanic Black, Mexican American, or "Other," and are self-reported. The category of "Other" was included in these reports in mean and percentile estimates for the total population but not in the geometric mean estimates because of small sample sizes (CDC 2005; Pirkle et al. 2006).

Figure 4.1 shows the overall proportion of all nonsmokers aged four or more years with serum cotinine levels of 0.050 ng/mL or greater for the four survey periods. Pirkle and colleagues (1996) reported detectable levels of serum cotinine among nearly all nonsmokers (87.9 percent) during Phase I (1988–1991) of NHANES III. Exposures among nonsmokers have declined significantly since that time

Figure 4.1 Trends in exposure* of nonsmokers† to secondhand smoke in the U.S. population, NHANES‡ 1988–2002



*Serum cotinine ≥0.05 nanograms per milliliter.
†Aged ≥4 years.
‡NHANES = National Health and Nutrition Examination Survey.
Source: Adapted from Pirkle et al. 2006.

(CDC 2005). The proportion of U.S. nonsmokers with cotinine concentrations of 0.050 ng/mL or greater fell to 43 percent in NHANES 2001–2002 (Pirkle et al. 2006).

Pirkle and colleagues (2006) provided additional data on the levels and distribution of serum cotinine concentrations in U.S. nonsmokers during 1988–2002. Trends in the adjusted geometric mean cotinine concentrations (adjusted for age, race, and gender) are in Table 4.1. Since Phase I of NHANES III, secondhand smoke exposures measured by serum cotinine concentrations in U.S. nonsmokers aged four or more years have declined by about 75 percent (from 0.247 ng/mL to 0.061 ng/mL). While declines among children aged 4 through 11 years and young persons aged 12 through 19 years also have been notable, the declines have been smaller than those among adults aged 20 through 74 years. Trends among racial and ethnic categories were also stratified by age: 4 through 11 years, 12 through 19 years, and 20 through 74 years. Pirkle and colleagues (2006) noted that serum cotinine levels in NHANES differed by race and ethnicity. Overall, in the order of the adjusted mean cotinine concentrations during each of the four time periods, concentrations among Mexican Americans were less than those of non-Hispanic Whites, which were less than those of non-Hispanic Blacks; the non-Hispanic Black mean cotinine concentrations were significantly higher during each of the four time periods (Pirkle et al. 2006).

Current patterns of secondhand smoke exposure are reflected in the NHANES 1999–2002 serum cotinine concentrations (Table 4.2). As noted in Figure 4.1, the proportion of U.S. nonsmokers with serum cotinine levels of 0.050 ng/mL or greater has declined since NHANES III to less than 45 percent. However, the proportion of children and nonsmoking adults with serum cotinine levels of 0.050 ng/mL or greater in NHANES 1999–2002 differs significantly by age, from 59.6 percent among children aged 3 through 11 years to 35.7 percent among nonsmoking adults aged 60 through 74 years. Additionally, the median cotinine concentration in the serum is significantly higher in children aged 3 through 11 years (0.09 ng/mL) than in older adults (0.035 ng/mL) (CDC 2005). Children aged 3 through 11 years and

Table 4.1 Trends in serum cotinine levels (nanograms per milliliter) of nonsmokers* stratified by age, gender, race, and ethnicity, United States, 1988–2002

Population		NHANES III, Phase I 1988–1991	NHANES III, Phase II 1991–1994	NHANES 1999–2000	NHANES 2001–2002	% decline from 1988–1991 to 2001–2002
Overall						
Aged ≥4 years	Geometric mean†	0.247	0.182	0.106	0.061	75.3
	95% CI‡	0.219–0.277	0.165–0.202	0.094–0.119	0.049–0.076	
Aged 4–11 years						
Male	Geometric mean	0.283	0.234	0.166	0.098	65.4
	95% CI	0.223–0.360	0.188–0.291	0.105–0.262	0.064–0.151	
Female	Geometric mean	0.328	0.285	0.172	0.115	64.9
	95% CI	0.240–0.449	0.235–0.345	0.113–0.262	0.075–0.177	
Race and ethnicity						
Non-Hispanic White	Geometric mean	0.295	0.255	0.171	0.100	
	95% CI	0.226–0.385	0.214–0.303	0.100–0.293	0.061–0.165	
Non-Hispanic Black	Geometric mean	0.534	0.460	0.284	0.261	
	95% CI	0.387–0.738	0.393–0.538	0.249–0.324	0.188–0.361	
Mexican American	Geometric mean	0.192	0.125	0.080	0.060	
	95% CI	0.148–0.250	0.107–0.145	0.066–0.097	0.042–0.086	
Aged 12–19 years						
Male	Geometric mean	0.346	0.239	0.189	0.090	74.0
	95% CI	0.255–0.470	0.190–0.300	0.138–0.258	0.061–0.132	
Female	Geometric mean	0.280	0.228	0.156	0.078	72.1
	95% CI	0.223–0.353	0.175–0.298	0.124–0.197	0.048–0.126	
Race and ethnicity						
Non-Hispanic White	Geometric mean	0.301	0.219	0.170	0.074	
	95% CI	0.228–0.396	0.174–0.276	0.139–0.210	0.044–0.123	
Non-Hispanic Black	Geometric mean	0.515	0.460	0.263	0.227	
	95% CI	0.392–0.677	0.374–0.567	0.229–0.303	0.191–0.270	
Mexican American	Geometric mean	0.179	0.143	0.095	0.063	
	95% CI	0.139–0.229	0.126–0.162	0.082–0.110	0.045–0.089	

Table 4.1 Continued

Population		NHANES III, Phase I 1988–1991	NHANES III, Phase II 1991–1994	NHANES 1999–2000	NHANES 2001–2002	% decline from 1988–1991 to 2001–2002
Aged ≥20 years						
Male	Geometric mean	0.293	0.199	0.106	0.067	77.1
	95% CI	0.259–0.332	0.178–0.222	0.092–0.122	0.054–0.082	
Female	Geometric mean	0.188	0.138	0.078	0.042	77.7
	95% CI	0.165–0.215	0.120–0.159	0.072–0.085	0.035–0.050	
Race and ethnicity						
Non-Hispanic White	Geometric mean	0.215	0.151	0.085	0.044	
	95% CI	0.189–0.244	0.133–0.172	0.077–0.095	0.036–0.055	
Non-Hispanic Black	Geometric mean	0.401	0.299	0.135	0.129	
	95% CI	0.325–0.494	0.271–0.330	0.116–0.157	0.101–0.163	
Mexican American	Geometric mean	0.204	0.138	0.078	0.058	
	95% CI	0.165–0.251	0.117–0.162	0.066–0.093	0.040–0.083	

*From four National Health and Nutrition Examination Survey (NHANES) study intervals.
†Individuals with serum cotinine levels below the laboratory limit of detection (LOD) were assigned a value of LOD/square root of 2.
‡CI = Confidence interval.
Source: Adapted from Pirkle et al. 2006.

youth aged 12 through 19 years are also significantly more likely than adults to live in a household with at least one smoker. Estimates of the number of secondhand smoke exposures nationwide in 2000 can be extrapolated from national estimates of the proportion of children and nonsmoking adults with measured serum cotinine concentrations of 0.05 ng/mL or greater. Overall, based upon serum cotinine measures, approximately 22 million children aged 3 through 11 years, 18 million nonsmoking youth aged 12 through 19 years, and 86 million nonsmoking adults aged 20 or more years in the United States were exposed to secondhand smoke in 2000 (Table 4.2).

Although the number of children and nonsmoking adults currently exposed to secondhand smoke in the United States remains very large, there have been significant declines in the proportion and mean concentrations of these exposures since 1988. In order to characterize these trends in exposure, data on the principal environments where children and nonsmoking adults are typically exposed to secondhand smoke are reviewed in the discussion that follows.

Environmental Sites of Exposure

The principal places where studies have measured exposures to secondhand smoke represent key microenvironments: homes, worksites, and public places such as restaurants, malls, and bars. The contributions of these different locations to total personal exposures vary across different groups. For example, the dominant site of exposure for children is the home, whereas worksites are typically important exposure locations for nonsmoking adults who may not be exposed at home.

People spend most of their time at home, which is potentially the most important location of secondhand smoke exposure for people who live with regular smokers (Klepeis 1999). Because the workplace is second only to the home as the location where adults spend most of their time, smoking in the workplace has been a major contributor to total secondhand smoke exposure. The National Human Activity Pattern

Table 4.2 Serum cotinine levels among nonsmokers aged 3 years and older, NHANES* 1999–2002

Age group	Median cotinine level (SE†) (95% CI‡)	% with levels ≥0.05 ng/mL§ (SE) (95% CI)	% with at least 1 smoker in the home (SE) (95% CI)	Total population (2000)	Estimated number of persons (in millions) with serum cotinine levels ≥0.05 ng/mL
≥3 years	**<LOD$^{\Delta}$ (<LOD–0.52)**	**47.0 (1.9) (43.0–50.9)**	**11.1 (0.45) (10.2–12.0)**	**270,005,230**	**126.9**
3–19 years	**0.08 (0.01) (0.06–0.11)**	**57.7 (2.8) (52.0–63.3)**	**22.6 (1.4) (19.9–25.6)**	**69,056,589**	**39.8**
3–11 years	0.09 (0.02) (0.06–0.12)	59.6 (2.9) (53.5–65.4)	24.9 (1.8) (21.5–28.7)	36,697,776	21.9
12–19 years	0.07 (0.01) (0.05–0.10)	55.6 (3.1) (49.1–61.9)	19.9 (1.3) (17.4–22.7)	32,358,813	18.0
≥20 years	**<LOD (<LOD–<LOD)**	**42.8 (1.9) (39.0–46.6)**	**6.56 (0.32) (5.93–7.25)**	**200,948,641**	**86.0**
20–39 years	<LOD (<LOD–0.066)	49.2 (2.9) (43.3–55.2)	6.85 (0.77) (5.43–8.61)	81,562,389	40.1
40–59 years	<LOD (<LOD–<LOD)	41.6 (2.2) (37.1–46.2)	7.3 (0.86) (5.73–9.26)	73,589,052	30.6
≥60 years	<LOD (<LOD–<LOD)	35.7 (1.7) (32.3–39.4)	5.12 (0.52) (4.15–6.3)	45,797,200	16.3

*NHANES = National Health and Nutrition Examination Survey.
†SE = Standard error.
‡CI = Confidence interval.
§ng/mL = Nanograms per milliliter.
$^{\Delta}$LOD = Limit of detection (0.05 ng/mL).
Sources: U.S. Bureau of the Census 2005; Centers for Disease Control and Prevention, National Center for Health Statistics, unpublished data.

Survey (NHAPS), conducted from 1992 to 1994, interviewed 9,386 randomly chosen U.S. residents about their activities and exposures to secondhand smoke (Klepeis 1999; Klepeis et al. 2001). For those persons reporting secondhand smoke exposure of at least one minute, the average daily duration of the exposure and the percentage of respondents who reported an exposure in each indoor locale were as follows:

- 305 minutes in the home (58 percent);
- 363 minutes in the office or factory (10 percent);
- 249 minutes in schools or public buildings (6 percent);
- 143 minutes in bars or restaurants (23 percent);
- 198 minutes in malls or stores (7 percent);
- 79 minutes in vehicles (33 percent); and
- 255 minutes in other indoor locations (6 percent) (Klepeis 1999).

Even for adults who live in homes where smoking routinely occurs, the workplace can add significantly to this exposure. Among NHANES III participants who lived in smoke-free homes, a workplace that permitted smoking was typically the major contributor to their total secondhand smoke exposure (Pirkle et al. 1996).

Studies have shown that restaurants can be important sites of exposures to children as well as adults (Maskarinec et al. 2000; McMillen et al. 2003; Skeer and Siegel 2003; Siegel et al. 2004), and other public places may also contribute substantially to exposures of selected segments of the population. Finally, persons who cannot move about freely, such as those who live in nursing homes, mental institutions, or correctional facilities, may find such exposures unavoidable.

Exposure in the Home

Secondhand smoke exposure at home can be substantial for both children and adults (Jenkins et al. 1996a; Pirkle et al. 1996; Klepeis 1999; Klepeis et al. 2001). This section considers children exposed to secondhand smoke at home separately from adults who are exposed at home because the patterns are different for the two groups (Mannino et al. 1996, 1997). The definition of "children" varies across the studies cited in this report. There are also separate data for special populations, including children with asthma, pregnant women, and persons living in the inner city.

Representative Surveys of Children

Researchers have conducted a number of local (Greenberg et al. 1989), state (King et al. 1998), and national (Mannino et al. 1996) surveys of childhood exposure to secondhand smoke. One of the best data sources available on children's secondhand smoke exposure in the home is the National Health Interview Survey (NHIS). This information can be derived from NHIS data by correlating data on smoking in the home with data on households with children. NHIS data shows that the proportion of children aged 6 years and younger who are regularly exposed to secondhand smoke in their homes fell from 27 percent in 1994 to 20 percent in 1998. Most surveys were primarily based on the indirect indicator of one or more smoking adults in a home; estimates of the percentages exposed in the home ranged from 54 to 75 percent of the children (Lebowitz and Burrows 1976; Schilling et al. 1977; Ferris et al. 1985). A 1988 survey using an indirect indicator estimated that 48.9 percent of the children studied had experienced postnatal exposures to secondhand smoke (Overpeck and Moss 1991). Exposure prevalence was higher for children in poverty (63.6 percent) or for those whose mothers had less than 12 years of education (66.7 percent). An analysis of National Health Interview Survey (NHIS) data for 1994 showed that 35 percent of U.S. children lived in homes where they had contact with a smoker at least one day per week (Schuster et al. 2002).

Use of the indirect approach assumes that the presence of a smoking adult in the household results in exposure of children to secondhand smoke. Over time, as more people recognized the health effects from exposure in the home and implemented in-home smoking policies, the presence of smoking adults in the home has become a less valid indicator of exposure. In a 1991 survey of U.S. adults, 11.8 percent of current smokers reported that because no smoking had occurred in their homes in the two weeks before the survey, their children had not been exposed to secondhand smoke in the home (Mannino et al. 1996). Using data from the California Tobacco Survey, Gilpin and colleagues (2001) found that the proportion of households prohibiting smoking increased from 50.9 percent in 1993 to 72.8 percent in 1999 (Gilpin et al. 2001). The increase was greater in homes with smokers, from 20.1 percent in 1993 to 47.2 percent in 1999 (Pierce et al. 1998; Gilpin et al. 2001). The survey did not capture data from nonfamily members who may have smoked in the home, nor would it have addressed the contamination of one dwelling from smokers in another within a multiresidence building.

Other analyses have used questionnaires that ask specifically about the number of cigarettes smoked in the home to determine whether children were exposed to secondhand smoke. A 1991 nationally representative survey estimated that 31.2 percent of U.S. children were exposed daily to secondhand smoke in their homes, with an additional 5.8 percent exposed at home at least one day in the previous two weeks (Mannino et al. 1996). This exposure varied significantly by socioeconomic status (SES) (46.5 percent for a lower SES versus 22.5 percent for a higher SES) and by region of the country, with the lowest exposure (24.3 percent) in the western part of the United States (Mannino et al. 1996). In Phase I of the NHANES III (collected from 1988 to 1991), 43 percent of children aged 2 months through 11 years lived in a home with at least one smoker (Pirkle et al. 1996). In NHANES 1999–2002, the proportion of children aged 3 through 11 years living with one or more smokers in the household was 24.9 percent (Table 4.2). However, 59.6 percent of children aged 3 through 11 years had a serum cotinine concentration of 0.05 ng/mL or higher. State and local surveys have documented higher levels of reported exposure. In a 1985 study from New Mexico, 60 to 70 percent of the children had been exposed to secondhand smoke (Coultas et al. 1987). In a 1986 study of North Carolina infants, 56 percent had been exposed (Margolis et al. 1997). On the basis of self-reported data on smoking among household residents, CDC estimated in 1996 that 21.9 percent of U.S. children had been exposed to secondhand smoke in their homes (CDC 1997). The prevalence of exposure varied by state, from a low of 11.7 percent in Utah to a high of 34.2 percent in Kentucky. However, the data on serum cotinine concentrations suggest that these estimates are low.

As noted above, since 1988 the NHANES has provided nationally representative measurements of serum cotinine levels in both children and adults (Pirkle et al. 1996, 2006; CDC 2001a, 2003, 2005). Figure 4.1 and Table 4.1 show overall U.S. trends in exposure measured by serum cotinine concentrations. Although exposures have declined among both children and adults since Phase I of NHANES III (1988–1991), the percentage of the decline was smaller among children aged 4 through 11 years. In the NHANES 2001–2002, mean cotinine levels were highest among children aged 4 through 11 years (non-Hispanic Black

children in particular) (Pirkle et al. 2006). Measured cotinine concentrations were more than twice as high among children aged 4 through 11 years than among nonsmoking adults aged 20 or more years, and the levels of non-Hispanic Black children were two to three times higher than those of non-Hispanic White and Mexican American children. While metabolic factors can also influence cotinine levels (Caraballo et al. 1998; Mannino et al. 2001), the racial and ethnic differences in serum cotinine concentrations overall, and particularly among children, presumably reflect greater exposures to secondhand smoke among non-Hispanic Black populations (Pirkle et al. 2006).

Table 4.2 compares current estimates of national exposure by age. In Phases I and II of NHANES III (1988–1994), 84.7 percent of children aged 4 through 11 years had a serum cotinine concentration of 0.05 ng/mL or greater; 99.1 percent of children with a reported exposure in the home and 75.6 percent of children without any reported exposure had measurable cotinine levels (Mannino et al. 2001). The strongest predictor of cotinine levels in children was the number of cigarettes smoked daily in the home, but other factors were also significant predictors, including race, ethnicity, age of the child, size of the home, and region of the country (Mannino et al. 2001). In the most recent estimates of exposure (Table 4.2), 59.6 percent of children aged 3 through 11 years had a serum cotinine concentration of 0.05 ng/mL or greater, and 24.9 percent reported living with at least one smoker in the household. Based upon this estimate of the proportion of children aged 3 through 11 years living with a smoker in the household, an estimated nine million children or more in this age range may be exposed to secondhand smoke. However, serum cotinine measurements indicate an even greater exposed population of almost 22 million children aged 3 through 11 years in the year 2000.

Trends in exposure of children to secondhand smoke indicate that levels of exposure have declined significantly since Phase I of NHANES III (Pirkle et al. 2006). The multiple factors related to this decline are still being studied. Several researchers have suggested that a major component of this decline is related to the decrease in parental smoking (Shopland et al. 1996) and to the increase in household smoking restrictions (Gilpin et al. 2001). Data from the 1992 and 2000 NHIS (Soliman et al. 2004) indicate that self-reported exposure of nonsmokers to secondhand smoke in homes with children declined significantly in the 1990s from 36 percent in 1992 to 25 percent in 2000. Because researchers have identified parental smoking in the home as a major source for exposure among younger children (Mannino et al. 2001), this decline in reported home exposures to secondhand smoke suggests that voluntary changes in home policies and smoking practices of adults in homes where children reside are a major contributing factor to the observed declines in serum cotinine concentrations among children since Phase I of NHANES III.

Protecting children from secondhand smoke exposure in homes has been the focus of the U.S. Environmental Protection Agency's parental outreach and educational programs to promote smoke-free home rules for the last decade. The potential for exposing children to secondhand smoke has dropped even further as more local and state governments restrict smoking in public areas (CDC 1999). Jarvis and colleagues (2000) documented similar findings in data from Great Britain. From 1988 to 1996, the proportion of homes without smokers increased from 48 to 55 percent. During this same period, the geometric mean salivary cotinine levels decreased from 0.47 to 0.28 ng/mL among children with nonsmoking parents, and from 3.08 to 2.25 ng/mL among children with two smoking parents (Jarvis et al. 2000).

Additional studies that document exposure of children in the United States to secondhand smoke in the home include three studies that reported the presence of some form of smoking ban at home in many households (Norman et al. 1999; Kegler and Malcoe 2002; McMillen et al. 2003). Norman and colleagues (1999) surveyed a representative sample of 6,985 California adults. Kegler and Malcoe (2002) studied 380 rural, low-income Native American and White parents from northeastern Oklahoma. McMillan and colleagues (2003) conducted a telephone survey of more than 4,500 eligible adults across the United States. Two other studies also focused on prevalence and patterns of childhood household secondhand smoke exposure in the United States: CDC (2001b) reported on the Behavioral Risk Factor Surveillance System (BRFSS) telephone interviews that took place in 20 states, and Schuster and colleagues (2002) reported on personal interviews with 45,335 respondents from around the country in the 1994 NHIS.

Representative Surveys of Adults

Representative surveys of adult household exposures to secondhand smoke in the United States were conducted at the national, state, and local levels to determine the prevalence of exposure in the home (Mannino et al. 1997; King et al. 1998). When analyzing these surveys, researchers need to consider that some current smokers may misclassify

themselves as lifetime nonsmokers or as former smokers (Haley et al. 1983; Coultas et al. 1988). Exposures at home were assessed using questionnaires and cotinine levels. In a California study that was conducted from 1979 to 1980, 24 percent of 37,881 adult lifetime nonsmokers and former smokers reported household exposures (Friedman et al. 1983). When data from Phase I of NHANES III (1988–1991) were analyzed, Pirkle and colleagues (1996) showed that 17.4 percent of nonsmokers reported exposures to secondhand smoke in the home. Mannino and colleagues (1997) reported similar findings when they analyzed data from another national survey that was conducted in 1991: 16.4 percent of lifetime nonsmokers and 19.2 percent of former smokers reported exposures in the home. In findings similar to those among children, there is also evidence that certain subgroups of adults are more likely to be exposed to secondhand smoke. For example, in a 1985–1986 study of 4,200 persons in Philadelphia, an industrialized and urban population, 60 percent reported household exposures (Dayal et al. 1994).

Table 4.1 shows trends in exposure among U.S. nonsmoking adults aged 20 or more years measured by serum cotinine levels. Among all adults in this age group, the geometric mean serum cotinine concentration declined more than 77 percent between Phase I of NHANES III (1988–1991) and NHANES 2001–2002: from 0.293 to 0.067 ng/mL among men and from 0.188 to 0.042 ng/mL among women. Analyses indicate that serum cotinine levels of adult nonsmokers were higher among adults who reported exposures at home or in the workplace (Pirkle et al. 1996). Recent data from NHANES 1999–2002 (CDC, NCHS, unpublished data) indicate that among younger nonsmoking adults aged 20 through 39 years, the proportion who reported living with at least one smoker is much lower (6.9 percent) compared with nonsmoking adults aged 20 through 39 years with a current job who reported that they could smell smoke at work (13.2 percent). However, among older nonsmoking adults aged 40 through 59 years, the proportion who reported living with a smoker (7.3 percent) was similar to the proportion of nonsmoking adults aged 40 through 59 years with a current job who reported smelling smoke at work (9.8 percent). Finally, while older nonsmoking adults reported a slightly lower portion of nonsmokers living with at least one smoker (5.1 percent), a significantly lower proportion of that age group with a current job reported smelling smoke at work (2.0 percent). Thus, particularly for adults aged 20 through 59 years, the worksite remains an important environment for exposure to secondhand smoke.

Susceptible Populations

Some populations may be particularly susceptible to secondhand smoke exposure. Examples include persons with asthma or other chronic respiratory diseases, and fetuses exposed to tobacco smoke components in utero either by maternal smoking or maternal exposure to secondhand smoke. In one 1994 community-based study in Seattle, 31 percent of children with asthma reported household exposures to secondhand smoke, but only 17 percent of children without asthma reported an exposure (Maier et al. 1997).

Studies have tracked smoking by pregnant women using several different data collection systems including natality surveys, NHIS, BRFSS, National Survey of Family Growth, and since 1989, birth certificates in nearly all states and the District of Columbia (CDC 2001a). The estimates from these different sources generally agree that the proportion of women who report smoking during pregnancy has decreased in recent years, from between 30 and 40 percent in the early 1980s to between 10 and 15 percent in the late 1990s. By 2003, only an estimated 10.7 percent of mothers of a live-born infant reported smoking during pregnancy. However, the prevalence of reported smoking was not uniform across all population groups or education levels. For example, a CDC report (CDC 2005) documented that 18 percent of American Indian or Alaska Native women reported smoking during pregnancy, but only 3 percent of Hispanic women reported smoking during pregnancy. And women with 9 to 11 years of education were far more likely to report smoking (25.5 percent) compared with women with 16 or more years of education (1.6 percent) (CDC 2005). Ebrahim and colleagues (2000) showed that the declining trend in smoking during pregnancy in recent years is primarily attributable to a decrease in smoking prevalence among women of childbearing age, rather than to an increase in smoking cessation during pregnancy. Of the women who reported smoking during pregnancy, most (68.6 percent) said that they had smoked 10 or fewer cigarettes daily.

Researchers have also found that pregnant women may conceal their smoking from clinicians (Windsor et al. 1993; Ford et al. 1997). Thus, smoking during pregnancy may be underestimated. Estimates of the prevalence of smoking during pregnancy are also sensitive to how smoking was defined in a study, which may range from any smoking at any time during pregnancy to smoking during the final three months of pregnancy.

Complicating the interpretation of findings on health effects of secondhand smoke exposure in very young children is evidence that a large proportion of children are exposed both prenatally and postnatally. Overpeck and Moss (1991) used CDC data to show that 96 percent of children with prenatal exposures also had postnatal exposures. The investigators found that 29 percent of the children had been exposed prenatally to maternal smoking and that an additional 21 percent had been exposed to secondhand smoke postnatally. A second source of involuntary smoking for a developing fetus is the exposure of a pregnant woman to secondhand smoke. The factors that predicted prenatal maternal exposure to secondhand smoke were similar to those associated with secondhand smoke exposure in general, such as low SES, low levels of education, and living in a small home (Overpeck and Moss 1991).

Although national surveys have not specifically asked about secondhand smoke exposure during pregnancy, they have provided estimates of exposure among women of childbearing age. In NHANES III, 18 percent of nonsmoking females aged 17 years and older reported exposures to secondhand smoke. However, the percentages of reported exposures were higher among women of childbearing age: 31 percent for 17- through 19-year-olds, 30 percent for 20- through 29-year-olds, and 26 percent for 30- through 39-year-olds (Pirkle et al. 1996). Of the nontobacco users surveyed in 1988–1991, 88 percent had detectable levels of serum cotinine (>0.050 ng/mL), a finding that suggests an unreported or unknown exposure. These findings are consistent with results from a 1985 study of 1,231 nonsmoking pregnant women in Maine, which found that 70 percent of the participants had cotinine levels above 0.5 ng/mL (Haddow et al. 1987).

Measurements of Airborne Tracers in Homes

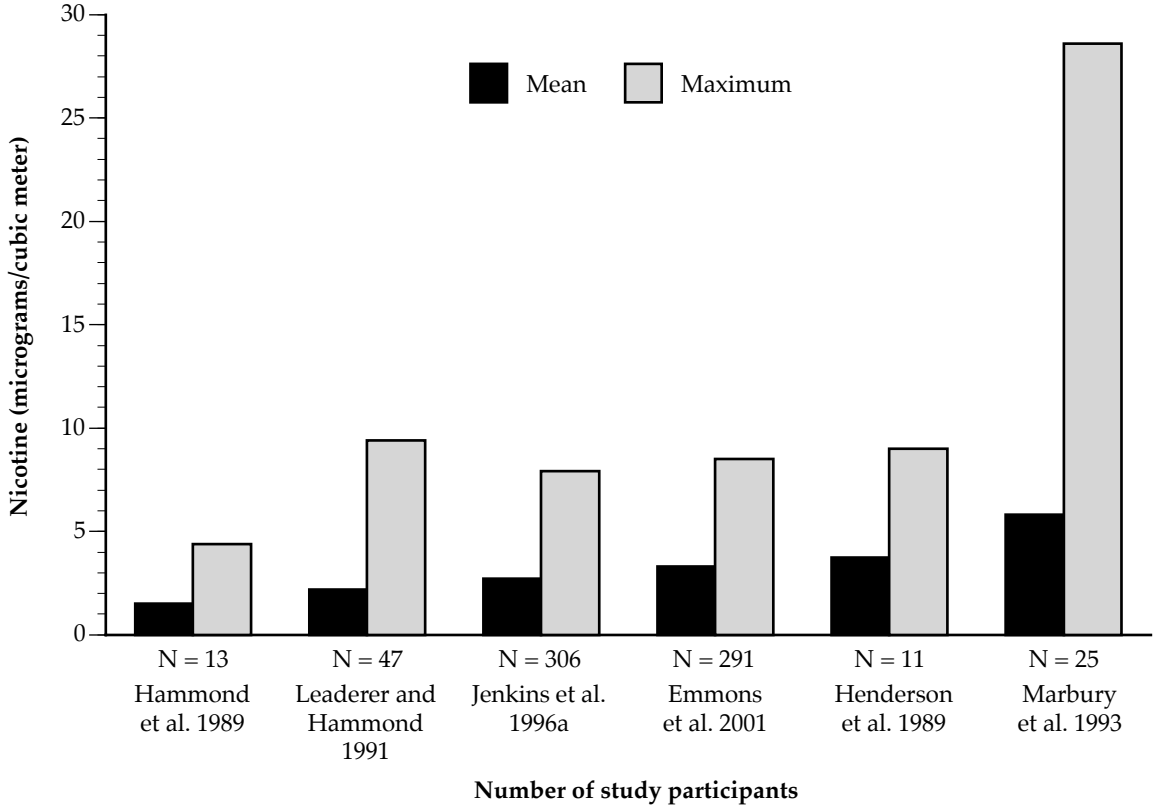
Numerous studies have measured secondhand smoke concentrations in homes (Leaderer and Hammond 1991; Hammond et al. 1993; Marbury et al. 1993; Manning et al. 1994; O'Connor et al. 1995; Jenkins et al. 1996a,b; Phillips et al. 1996, 1997a,b, 1998a–h, 1999a,b). Concentrations of secondhand smoke components are higher at the time that the cigarettes are smoked compared with a few hours later. Measurements taken only during periods of smoking document higher concentrations than samples measured during both smoking and nonsmoking periods. For example, Muramatsu and colleagues (1984) measured both nicotine and particulate matter sequentially for 10 hours in an office. They found that the 30-minute nicotine samples ranged from 2 to 26 micrograms per cubic meter ($\mu g/m^3$) during the workday; most values ranged between 5 and 15 $\mu g/m^3$. The 10-hour averaged concentration was 10 $\mu g/m^3$, which was based on a shorter time period than that used by other studies to obtain stable estimates. Most studies have measured concentrations averaged over longer periods of time, which include periods with and without smoking.

Studies have demonstrated a high correlation (Spearman rho correlation coefficient = 0.74, $p < 0.001$) between nicotine concentrations measured in the family activity rooms and in the kitchens (Emmons et al. 2001), as well as between concentrations in the activity rooms and in the bedrooms (Spearman correlation coefficient = 0.91; 0.90 for homes of smokers only) (Marbury et al. 1993).

The results of several studies that measured nicotine concentrations in the homes of smokers in the United States are presented in Figure 4.2 and Table 4.3. Median nicotine concentrations were generally between 1 and 3 $\mu g/m^3$ (averaged over 14 hours to several weeks), with nicotine concentrations ranging from <0.1 to 8 $\mu g/m^3$ across the span from minimum to the 95th percentile. An exception was a study of 291 low-income homes in New England that found 4 homes with concentrations above 18 $\mu g/m^3$ (Emmons et al. 2001). Homes where smoking was restricted to the basement or the outdoors had lower mean nicotine concentrations of 0.3 $\mu g/m^3$ (Marbury et al. 1993).

Personal sampling of secondhand smoke exposure has yielded similar results with measured home exposure. In a study of exposure away from work (predominantly at home, lasting 16 hours), 306 nonsmokers who reported secondhand smoke exposure had a mean nicotine exposure of 2.7 $\mu g/m^3$ (median 1.2 $\mu g/m^3$), with a 95th percentile value of 7.9 in 1993 and 1994 (Jenkins et al. 1996a). Personal sampling of 100 people in Massachusetts during 1987 and 1988 found the median of a weekly average of nicotine concentrations to be 1.0 $\mu g/m^3$ for nonsmokers married to nonsmokers and 3.5 $\mu g/m^3$ for those married to smokers; the respective maximum values were 9.5 and 14 $\mu g/m^3$. These values included all exposures throughout the week in homes, workplaces, and public places (Coghlin et al. 1989, 1991). To evaluate secondhand smoke exposure among pregnant women, participants in two studies wore passive samplers (small personal monitors that measure secondhand smoke exposure) for one week. Although the two studies had similar designs, the investigators reported quite different results. Among 36 low-income pregnant women in Massachusetts, 80 percent were exposed to

Figure 4.2 Concentrations of nicotine in homes of U.S. smokers



Note: Data are provided in detail in Table 4.3.

nicotine at 0.5 $\mu g/m^3$ or greater, and 25 percent were exposed at a concentration above 2.0 $\mu g/m^3$ (Hammond et al. 1993). The measured exposure was lower for 131 pregnant upper-middle-class women in Connecticut who reported secondhand smoke exposure, with a median of 0.1 $\mu g/m^3$ and a 90th percentile of 0.6 $\mu g/m^3$ (O'Connor et al. 1995).

International studies of secondhand smoke exposure sponsored by the tobacco industry (Jenkins et al. 1996a; Phillips et al. 1996, 1997a,b, 1998a–h, 1999a,b) followed a similar protocol where participants wore a sampling device for 16 to 24 hours. Figure 4.3 illustrates the median nicotine concentrations observed "away from work" (predominantly at home) in the United States compared with homes in Australia and in several European and Asian locations. U.S. homes had the second highest reported values after Beijing, which reported a median of 1.3 $\mu g/m^3$. Hong Kong homes reported 0.3 $\mu g/m^3$, which was consistent with a study of 300 Chinese homes in 18 provinces that reported a 0.1 $\mu g/m^3$ weekly average concentration of nicotine in the homes of smokers (Hammond 1999).

Exposure in the Workplace

This section reviews studies that measured secondhand smoke exposure in the workplace, an important source of secondhand smoke exposure for nonsmoking adults (Klepeis 1999; Klepeis et al. 2001). These studies include surveys, biomarkers (Pirkle et al. 1996), or (more commonly) measurements of airborne nicotine (Vaughan and Hammond 1990; Hammond et al. 1995; Jenkins et al. 1996a; Hammond 1999).

Surveys of Workplaces with Policies Regarding Smoking

Large representative surveys of secondhand smoke workplace exposure have looked at patterns of exposure and the impact of policies to reduce

Table 4.3 Concentrations of nicotine in homes of U.S. smokers

Study	Population Year sampled	Measurement duration	Number of study participants
Hammond et al. 1989	North Carolina 1988	Weekly	13
Henderson et al. 1989	Lower income North Carolina 1987	14 hours	11
Leaderer and Hammond 1991	Randomly chosen New York 1986	1 week (winter)	47
Marbury et al. 1993	Children aged <2 years Living room and bedroom Minnesota 1989	1 week†	25
Jenkins et al. 1996a	Adults Personal sampling 16 cities	16 hours	306
Emmons et al. 2001	Lower income Massachusetts 1997–1998	Weekly	291

*NR = Data were not reported.
† Following the initial measure of exposure, measures were taken weekly for 8 weeks.

exposure. Although not all workplaces are smoke-free, policies toward smoking in workplace settings have changed dramatically since the publication of the 1986 Surgeon General's report (USDHHS 1986). For example, using data from the California Tobacco Survey, Gilpin and colleagues (2001) showed that the percentage of indoor workers in California who reported smoke-free workplaces had increased from 35 percent in 1990 to 93 percent in 1999. Shopland and colleagues (2001) analyzed data from the national Current Population Survey (CPS), a monthly survey of about 50,000 households conducted by the Bureau of the Census for the Bureau of Labor Statistics, and found that the proportion of workers who reported a smoke-free workplace policy had increased from 46 percent in 1993 to 69 percent in 1999. The 1999 data documented a low of 49 percent in Nevada and a high of 84 percent in Utah (Shopland et al. 2001). In an analysis of the 1993 CPS data, Farrelly and colleagues (1999) noted that the proportion of workers in smoke-free worksites also varied by industry, from a low of 30 percent in wholesale or retail trades to 73 percent in medical services. A similar analysis of the 1996 CPS data showed that the proportion of smoke-free worksites ranged from a low of 44 percent in agriculture, forestry, fishing, mining, and construction to 82 percent in professional and related services (Sweeney et al. 2000).

However, having a smoke-free policy in the workplace does not assure workers that they will not be exposed to secondhand smoke. In a 1990 study from California, 9.3 percent of nonsmokers who worked in a "smoke-free" worksite reported at least one episode of exposure at work during the two weeks before the survey (Borland et al. 1992). This proportion was higher at 51 percent among nonsmokers working in sites without a smoking policy (Brancker 1990). In data from Phase I of NHANES III (1988–1991), 47.7 percent of adult nontobacco users who currently worked reported exposures at home or at the worksite (Pirkle et al. 1996). Nonsmoking workers who reported workplace exposures had higher geometric

Concentrations of nicotine (micrograms per cubic meter [$\mu g/m^3$])								
	Geometric mean	Standard deviation	Median	25th percentile	90th percentile	95th percentile	Minimum	Maximum
	1.5	1.1	1.4	NR*	NR	NR	1.1	4.4
	3.74	0.5	3.6	NR	NR	7.5	0.8	9.0
	2.2	2.4	1.0	0.2	8.0	8.5	<0.1	9.4
Living room	5.8	NR	3.0	NR	NR	9.0	0.1	28.6
Bedroom	2.7	NR	2.1	NR	NR	NR	NR	7.2
	2.7	NR	1.2	NR	NR	7.9	NR	NR
	3.3	5.0	1.6	0.3	8.5	10.4	0.3	45.1

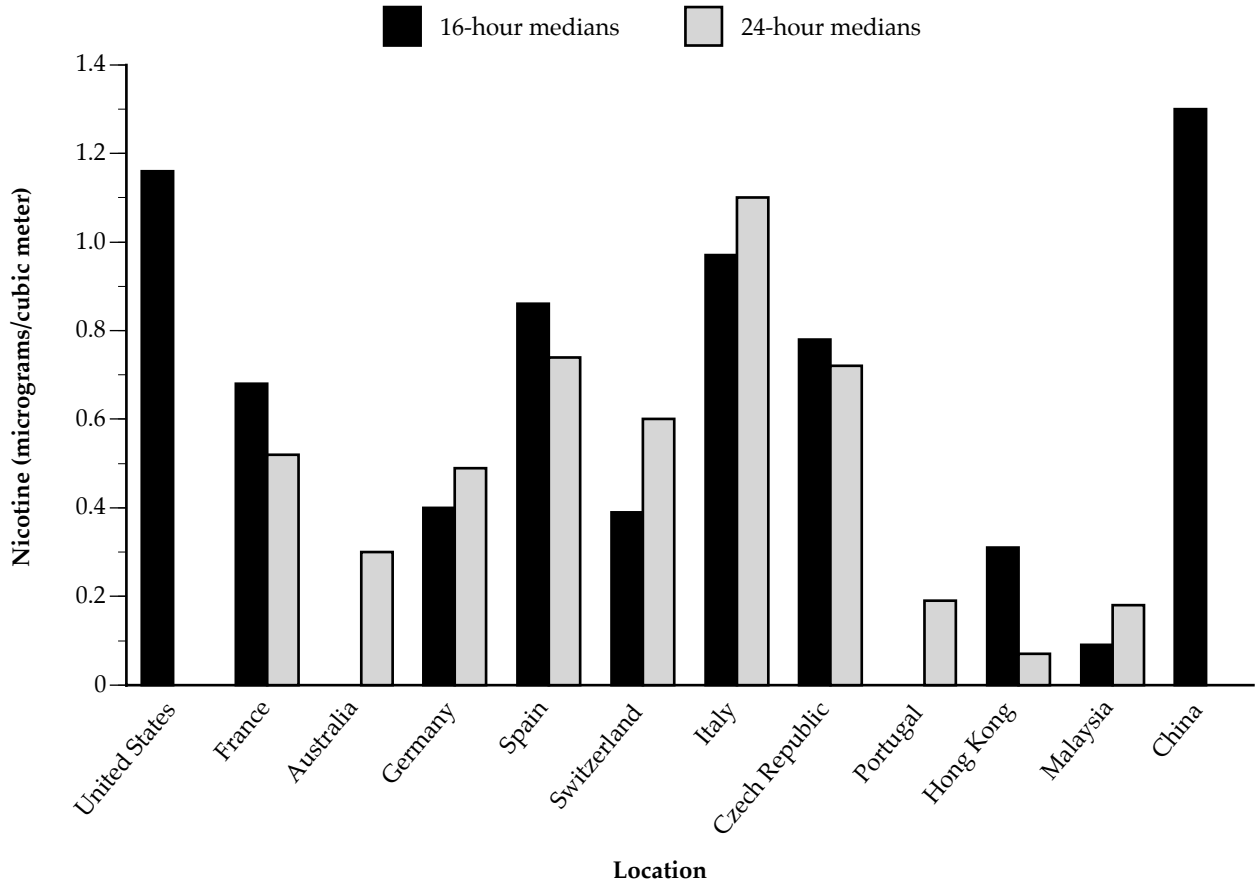
mean levels of cotinine (0.32 ng/mL) compared with workers who did not report workplace or home exposures (0.13 ng/mL) (Pirkle et al. 1996). Recent data suggest that worksite exposures may be declining significantly since Phase I of NHANES III (1988–1991). In NHANES 1999–2002, the proportion of adults aged 20 or more years with a current job who reported smelling smoke at work was 8.94 percent (95 percent CI, 7.84–10.10) (CDC, NCHS, unpublished data).

Workplace Surveys

Hammond (1999) reviewed studies of exposures to secondhand smoke among U.S. workers. The earliest personal sampling of workplace secondhand smoke exposure involved railroad workers studied between 1981 and 1984. Investigators collected more than 625 nicotine samples from participants wearing personal samplers at four railroad locations (Hammond et al. 1988; Schenker et al. 1990). In 1983 and 1984, 275 personal samples were collected and levels were analyzed by job type; 84 samples were collected from smokers and 191 from nonsmokers (Schenker et al. 1986, 1992; Hammond 1999). Among workers such as clerks and brakers who worked in small spaces, nonsmokers and smokers were exposed to similar levels of nicotine. For workers in other types of jobs (notably the repair shop workers), exposure was lower by more than an order of magnitude, possibly because of the large open space and ventilation of the shop. The range of nicotine exposure at work was notably greater among the nonsmoking railroad workers compared with exposures at home; minimum concentration values for all job categories were less than 0.1 $\mu g/m^3$ and maximum values ranged up to 38 $\mu g/m^3$. Half of the nonsmoking workers were exposed to more than 1 $\mu g/m^3$ on at least one sampling day.

Many investigators have studied offices in the United States. Where smoking was allowed, there was a wide range of nicotine concentrations, from less than

Figure 4.3 Concentrations of nicotine away from work in 12 locations



Sources: Jenkins et al. 1996a; Phillips et al. 1996, 1997a,b, 1998a–h, 1999a,b.

0.05 $\mu g/m^3$ to about 70 $\mu g/m^3$ (Table 4.4). For nearly half of the offices, the minimum value was more than 1 $\mu g/m^3$. For offices where five or more samples were collected, median values were between 1 and 17 $\mu g/m^3$, and average values were between 2 and 24.8 $\mu g/m^3$. Most worksites had at least one sample above 10 $\mu g/m^3$, and many studies reported concentrations greater than 40 $\mu g/m^3$.

Offices at worksites that restricted smoking to designated areas generally had much lower concentrations of nicotine (Table 4.4 and Figure 4.4). Half of these worksites had a median concentration of less than 1 $\mu g/m^3$, and only one site (Newspaper A) exceeded 2.5 $\mu g/m^3$. The maximum concentrations in five out of eight workplaces were 1 to 2 $\mu g/m^3$, but in the other three the maximum concentrations were 6.3, 13.7, and 16.7 $\mu g/m^3$. Workplaces with smoking bans had much lower concentrations, with the medians and averages at all worksites less than 1 $\mu g/m^3$, except for one worksite, the weapons systems worksite that had a mean of 2.8 $\mu g/m^3$. The maximum concentrations at three of these worksites were less than 1 $\mu g/m^3$; the maximum concentrations for the other three were 1.9, 2.4, and 8.5 $\mu g/m^3$. In one workplace, lower secondhand smoke concentrations were observed at the same location comparing measurements taken before and after smoking was restricted. Concentrations had declined by more than 90 percent as a result of restricting smoking (Vaughan and Hammond 1990). Thus, workplace policies decrease nicotine concentrations substantially but do not completely eliminate them. These results are consistent with questionnaire survey results cited above, where 9.3 percent of nonsmoking California workers in "smoke-free worksites" reported some secondhand smoke exposure.

A number of studies have measured the nicotine concentrations in a variety of other workplaces, including fire stations and manufacturing, printing, and medical facilities (Table 4.5). Although concentrations were lower in these settings than in offices, the results of the analyses showed that one-third of the workplaces that allowed smoking still had minimum values above 1 $\mu g/m^3$, and most workplaces had detectable levels of nicotine on all of the collected samples (Table 4.5). Two workplaces had maximum values above 50 $\mu g/m^3$, and most had at least one sample above 10 $\mu g/m^3$. Most of the median values were between 1 and 4 $\mu g/m^3$. Where smoking was restricted, the median dropped from 2.3 to 0.7 $\mu g/m^3$. Where smoking was banned, it dropped to 0.2 $\mu g/m^3$ (Hammond et al. 1995). Thus, smoking policies also effectively reduced secondhand smoke concentrations in these nonoffice settings (Figure 4.5).

Exposure in Public Places

Exposures to secondhand smoke in public places have been particular public health concerns for more than two decades. Although these sites are workplaces for some, they may now be the only source of secondhand smoke exposure for most of the U.S. population with no home or work exposures. Studies using biomarkers confirm that secondhand smoke exposure in public places continues to affect nonsmokers. Using NHANES III data, several investigators have shown that persons with no home or workplace exposures still had detectable levels of cotinine in their serum (Pirkle et al. 1996; Mannino et al. 2001). This finding suggests that many people are exposed to secondhand smoke in other locations.

Restaurants, Cafeterias, and Bars

Restaurants, cafeterias, and bars are worksites as well as public places where smoking is frequently unrestricted or restricted in a manner that does not effectively decrease exposure. Servers and bartenders working in environments where smoking is permitted may be exposed to high levels of secondhand smoke (Jarvis et al. 1992; Jenkins and Counts 1999). In a survey of 1,224 residents from Olmsted County, Minnesota, 57 percent of the respondents reported exposures to secondhand smoke: 44 percent reported exposures in restaurants, 21 percent reported exposures at work, and 19 percent reported exposures in bars (Kottke et al. 2001). A quarter of the respondents in the NHAPS study reported exposures in restaurants or bars on the previous day for an average of two and one-half hours (Klepeis 1999; Klepeis et al. 2001). Restaurants may be the principal point of secondhand smoke exposure for children from nonsmoking homes, and an exposure of even a short duration may be relevant to acute effects, such as inducing or exacerbating an asthma attack (Chapter 6, Respiratory Effects in Children from Exposure to Secondhand Smoke).

In eating establishments, a wide variability in factors determines the concentration of secondhand smoke, including the size of the room, ventilation rate, number of smokers, and smoking rate. Furthermore, these concentrations vary throughout the day and evening. Concentrations measured for one to two hours during lunch or dinner are likely to be much higher than the average concentrations measured during a full day or week. The nicotine concentrations measured in restaurants have ranged from less than detectable to values of 70 $\mu g/m^3$ (Table 4.6).

Tobacco smoke has long been considered a nuisance that interferes with the enjoyment of food. One approach to reducing exposures of nonsmokers has been to establish smoking and nonsmoking sections in restaurants. Nonsmoking sections generally do have lower concentrations of secondhand smoke (Lambert et al. 1993; Hammond 1999), but they neither eliminate secondhand smoke nor reduce secondhand smoke concentrations to insignificant levels. The concentrations of nicotine in nonsmoking sections of restaurants persist at high levels. For example, a study of seven restaurants in Albuquerque, New Mexico, found that half of them had concentrations above 1 $\mu g/m^3$ in the nonsmoking sections (Lambert et al. 1993). Similar results were noted in more than half of 71 restaurants surveyed in Indiana where nicotine concentrations were above 2 $\mu g/m^3$ in the nonsmoking sections (Hammond and Perrino 2002). In a study of waiters exposed to secondhand smoke, the average nicotine concentration was as high as 5.8 $\mu g/m^3$, with the upper end of the range at 68 $\mu g/m^3$ (Maskarinec et al. 2000).

Hammond (1999) reported that nicotine concentrations in cafeterias were somewhat higher than in restaurants; average values were between 6 and 14 $\mu g/m^3$. Out of the 37 samples from company cafeterias in Massachusetts that allowed or restricted workplace smoking, two-thirds had nicotine concentrations that were above 5 $\mu g/m^3$. Secondhand smoke concentrations measured during lunchtime at a medical center cafeteria revealed large gradients between the smoking and nonsmoking sections. The concentrations were generally 25 to 40 $\mu g/m^3$ in the smoking section, 2 to 5 $\mu g/m^3$ in a nonsmoking section that was

Table 4.4 Occupational exposures to nicotine among nonsmoking office workers stratified by the smoking policy in effect at the time of the measurements

Study	Worksite description	Year sampled	Number of samples
	Smoking permitted		
Schenker et al. 1986, 1990, 1992	Railroad clerks (personal)	1983–1984	31
Carson and Erikson 1988	Multiple worksites	Before 1988	28
Crouse and Carson 1989	Multiple worksites	Before 1989	32
Eatough et al. 1989	Multiple worksites	NR	28
Miesner et al. 1989	Two office buildings	1987–1988	3
Coultas et al. 1990	Social worker office (personal) Attorney office (personal) Stockbroker (personal) Multiple worksites (personal) Travel agent (personal)	1986–1987 1986–1987 1986–1987 1986–1987 1986–1987	1 1 1 5 2
Oldaker et al. 1990	Multiple worksites	Before 1990	156
Turner and Binnie 1990	Multiple worksites Multiple worksites (naturally ventilated)	Before 1990 Before 1990	33 17
Vaughan and Hammond 1990	Telephone company	1987	13
Guerin et al. 1992	Multiple worksites	Before 1990	194
Hammond et al. 1995; Hammond 1999	Labels and paper products Tool manufacturing Die manufacturer Textile finishing B Sintering metal Specialty chemicals Textile finishing A Newspaper B Union headquarters‡	1991–1992 1991–1992 1991–1992 1991–1992 1991–1992 1991–1992 1991–1992 1991–1992 1991–1992	7 7 4 2 7 7 3 19 15
Jenkins et al. 1996a	Multiple sites (personal)	1993–1994	<136
Sterling et al. 1996	Building 2 (personal) Building 1 (personal)	1994 1994	12 13
	Smoking restricted		
Miesner et al. 1989	Two office buildings	1987–1988	2
Vaughan and Hammond 1990	Telephone company	1988	19
Hammond et al. 1995; Hammond 1999	Filtration products Fiber optics Work clothing Film and imaging Valve manufacturer Newspaper A	1991–1992 1991–1992 1991–1992 1991–1992 1991–1992 1991–1992	6 4 4 7 8 7

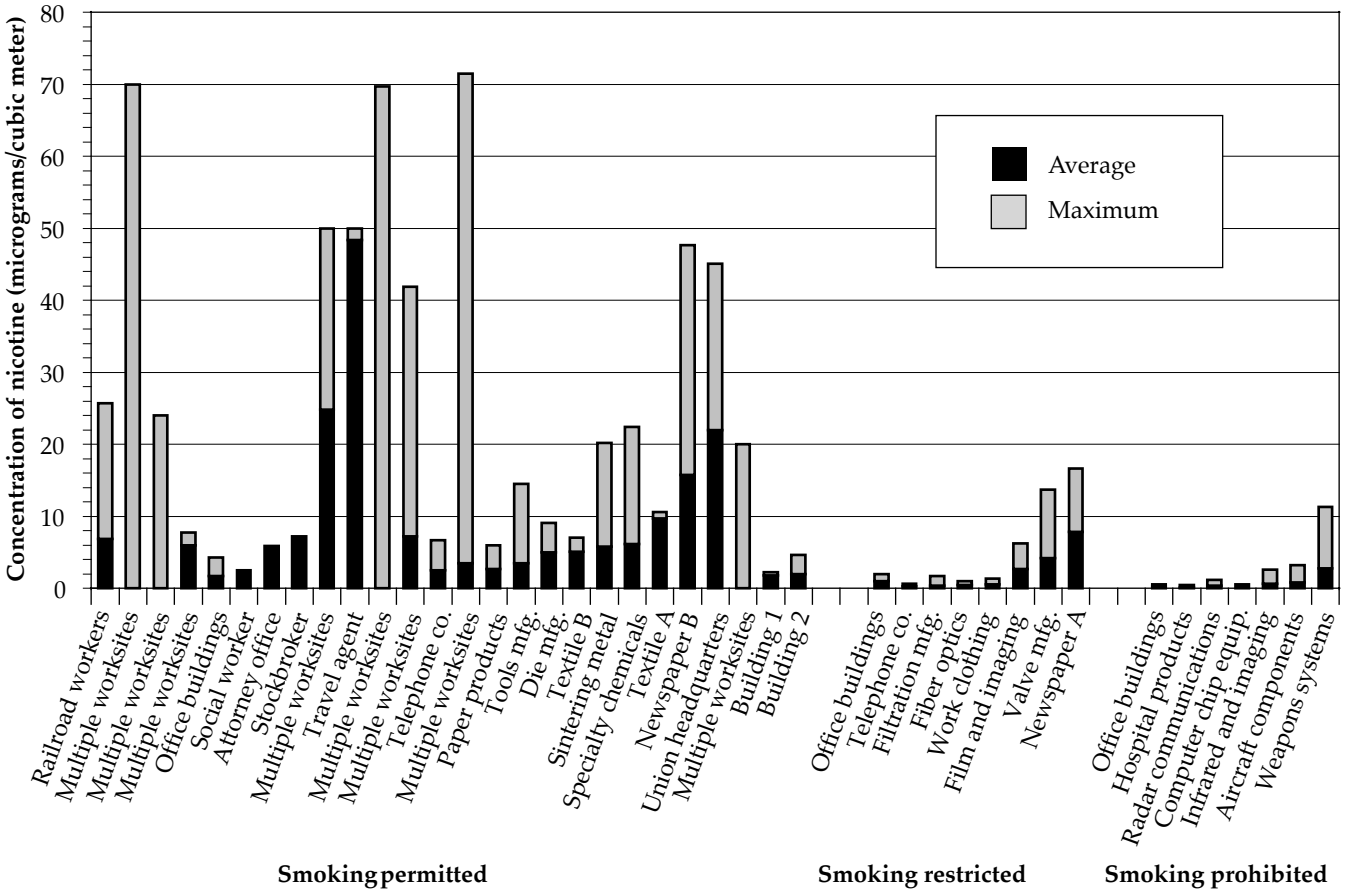
Concentrations of nicotine (micrograms per cubic meter [$\mu g/m^3$])					
Mean	**Standard deviation**	**Geometric mean**	**Minimum**	**Median**	**Maximum**
Smoking permitted					
6.9	6.7	3.2	<0.1	5.7	25.7
NR*	NR	7.2	LD†	NR	70.0
NR	NR	3.8	1.2	NR	24.0
6.0	NR	NR	4.1	NR	7.8
1.7	2.3	0.8	LD	0.6	4.3
2.5	NR	2.5	NR	2.5	NR
5.9	NR	5.9	NR	5.9	NR
7.2	NR	7.2	NR	7.2	NR
24.8	22.8	16.8	2.5	10.0	50.0
48.4	2.3	48.3	1.0	48.4	50.0
NR	NR	4.8	LD	NR	69.7
7.2	NR	NR	NR	LD	41.9
10.0	NR	NR	NR	LD	41.9
2.5	1.7	2.1	0.9	1.9	6.7
3.5	8.3	1.7	<1.6	NR	71.5
2.7	1.9	1.4	<0.05	2.6	6.0
3.5	4.9	3.5	0.8	1.4	14.5
5.0	4.2	3.2	0.7	5.1	9.1
5.1	2.8	4.7	3.1	5.1	7.1
5.8	8.9	1.6	0.3	0.9	20.2
6.2	7.8	2.0	<0.05	3.7	22.4
9.7	0.9	9.6	8.8	9.6	10.6
15.8	14.5	8.0	0.2	10.8	47.7
22.0	12.4	17.2	1.1	17.0	45.1§
NR	NR	NR	NR	1.9	>20.0§
1.8	NR	NR	1.1	1.7	2.3
2.0	NR	NR	0.3	1.6	4.7
Smoking restricted					
1.0	NR	NR	LD	1.0	2.0
0.3	0.2	0.2	<0.1	0.2	0.7
0.4	0.7	0.1	<0.05	0.1	1.7
0.5	0.4	0.4	0.2	0.4	1.0
0.6	0.5	0.5	0.3	0.4	1.4
2.7	2.2	2.0	0.6	1.8	6.3
4.2	4.5	2.5	0.5	2.5	13.7
7.9	5.9	5.2	0.6	7.6	16.7

Table 4.4 Continued

Study	Worksite description	Year sampled	Number of samples
	Smoking prohibited		
Miesner et al. 1989	Office building	1987–1988	2
Hammond et al. 1995; Hammond 1999	Hospital products	1991–1992	9
	Radar communications	1991–1992	4
	Computer chip equipment	1991–1992	1
	Infrared and imaging systems	1991–1992	8
	Aircraft components	1991–1992	5
	Weapons systems	1991–1992	3

*NR = Data were not reported.
†LD = Less than detectable.
‡Omits one data point, 130 $\mu g/m^3$.
§95th percentile, as given in paper.
Source: Hammond 1999.

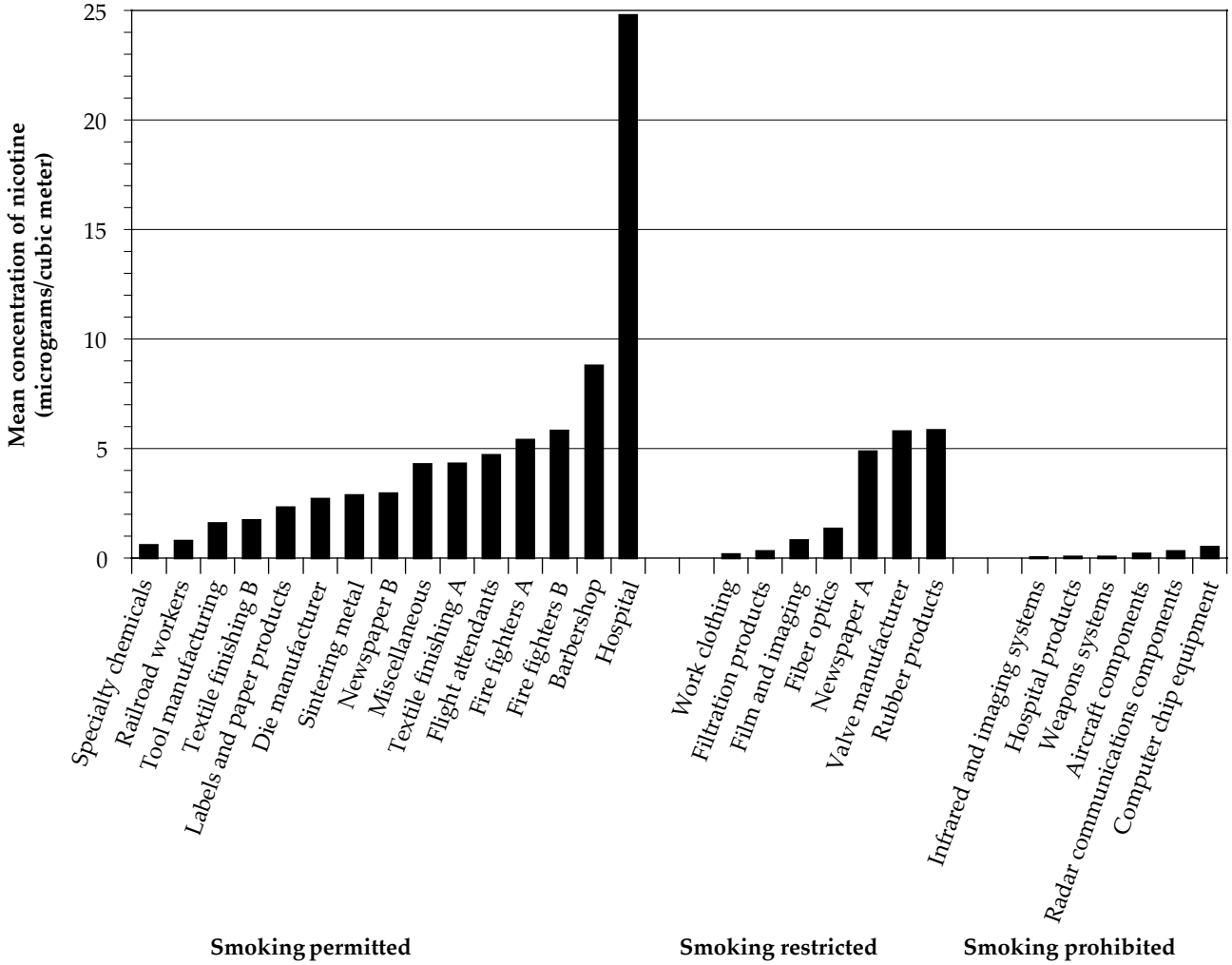
Figure 4.4 Occupational exposures to nicotine among groups of nonsmoking office workers



Note: Data are provided in detail in Table 4.4.

Concentrations of nicotine (micrograms per cubic meter [$\mu g/m^3$])					
Mean	**Standard deviation**	**Geometric mean**	**Minimum**	**Median**	**Maximum**
Smoking prohibited					
0.2	NR	NR	LD	0.2	0.4
0.1	0.2	0.1	<0.05	<0.05	0.4
0.4	0.3	0.2	<0.05	0.3	0.8
0.6	NR	NR	NR	0.6	NR
0.7	0.8	0.3	<0.05	0.4	1.9
0.8	1.0	0.4	<0.05	0.4	2.4
2.8	4.9	0.2	<0.05	<0.05	8.5

Figure 4.5 Mean concentrations of nicotine in nonoffice workplace settings with different smoking policies



Note: Data are provided in detail in Table 4.5.

Table 4.5 Occupational exposures to nicotine in nonoffice workplace settings among nonsmokers only, stratified by the smoking policy in effect at the time of the measurements

Study	Type of company	Year sampled	Number of samples
	Smoking permitted		
Schenker et al. 1986, 1990, 1992	Railroad workers (personal)	1983–1984	152
Mattson et al. 1989	Flight attendants (personal)	1988	16
Coultas et al. 1990	Barbershop (personal)	1986–1987	2
	Hospital (personal)	1986–1987	5
Guerin et al. 1992	Miscellaneous	Before 1990	282
Hammond et al. 1995; Hammond 1999	Specialty chemicals	1991–1992	8
	Tool manufacturing	1991–1992	13
	Textile finishing B	1991–1992	11
	Labels and paper products	1991–1992	1
	Die manufacturer	1991–1992	12
	Sintering metal	1991–1992	12
	Newspaper B	1991–1992	5
	Textile finishing A	1991–1992	11
	Firefighters A[†]	1991–1992	16
	Firefighters B	1991–1992	24
	Smoking restricted		
Hammond et al. 1995; Hammond 1999	Work clothing	1991–1992	9
	Filtration products	1991–1992	10
	Film and imaging	1991–1992	6
	Fiber optics	1991–1992	13
	Newspaper A	1991–1992	4
	Valve manufacturer	1991–1992	10
	Rubber products	1991–1992	2
	Smoking prohibited		
Hammond et al. 1995; Hammond 1999	Infrared and imaging systems	1991–1992	1
	Hospital products	1991–1992	5
	Weapons systems	1991–1992	12
	Aircraft components	1991–1992	12
	Radar communications components	1991–1992	13
	Computer chip equipment	1991–1992	10

Note: Concentrations were calculated by assuming that all smoking occurred during the workweek, although samplers were in place for 1 full week. Therefore, the nicotine was assumed to have been collected over 45 hours. The exceptions were the fire stations, where 112 hours were assumed.
*NR = Data were not reported.
[†]Omits one data point, 101 $\mu g/m^3$.
Source: Hammond 1999.

Concentrations of nicotine (micrograms per cubic meter [$\mu g/m^3$])					
Mean	**Standard deviation**	**Geometric mean**	**Minimum**	**Median**	**Maximum**
Smoking permitted					
0.8	3.3	0.2	<0.1	0.1	38.1
4.7	4.0	2.3	0.1	4.2	10.5
8.8	NR*	NR	4.0	NR	13.7
24.8	22.8	16.8	6.3	10.0	53.2
4.3	11.8	1.7	<1.6	<1.6	126.0
0.6	0.9	0.2	<0.05	0.5	2.8
1.6	1.0	1.2	0.2	1.8	3.4
1.7	1.7	1.1	0.3	0.9	5.1
2.3	NR	NR	NR	2.3	NR
2.7	1.3	2.5	1.2	2.4	5.4
2.9	2.6	2.1	0.6	2.2	9.7
3.0	1.4	2.7	1.2	2.8	4.6
4.3	8.8	1.8	0.5	1.4	30.7
5.4	3.8	4.1	1.2	4.8	13.4
5.8	6.8	3.8	0.7	3.6	27.5
Smoking restricted					
0.2	0.3	0.06	<0.05	<0.05	0.9
0.3	0.9	0.08	<0.05	<0.05	2.8
0.8	0.8	0.4	<0.05	0.7	2.2
1.3	2.8	0.6	0.2	0.6	10.6
4.9	6.6	2.6	0.9	1.8	14.8
5.8	7.8	3.6	1.2	3.3	27.3
5.8	5.4	4.2	2.1	5.8	9.6
Smoking prohibited					
<0.05	NR	NR	NR	<0.05	NR
0.08	0.17	<0.05	<0.05	<0.05	0.39
0.08	0.20	<0.05	<0.05	<0.05	0.63
0.20	0.18	0.13	<0.05	0.21	0.61
0.31	0.36	0.14	<0.05	0.26	1.08
0.51	0.33	0.41	0.15	0.39	1.08

Table 4.6 Concentrations of nicotine in restaurants

Study	Year sampled	State	Number of restaurants	Number of days	Number of samples
All sections					
Coghlin et al. 1989	1987	Massachusetts	6	NR*	NR
Crouse and Carson 1989	NR	NR	36	NR	NR
Miesner et al. 1989	1987–1988	NR	2	NR	NR
Thompson et al. 1989	NR	NR	34	NR	NR
Coultas et al. 1990	1986–1987	NR	1	NR	NR
Crouse and Oldaker 1990	NR	NR	21	NR	NR
	NR	NR	21	NR	NR
Oldaker et al. 1990	NR	NR	170	NR	NR
Jenkins et al. 1991	1991	NR	7	NR	NR
Lambert et al. 1993	1989	New Mexico	7	NR	NR
McFarling 1994	1994	Massachusetts	1	NR	NR
Maskarinec et al. 2000	1996–1997	Tennessee	NR	NR	32
	1996–1997 Waiters	Tennessee	NR	NR	83
Nonsmoking sections					
Lambert et al. 1993	1989	New Mexico	7	NR	NR
Moschandreas and Vuilleumier 1999	Before 1998	Illinois	1 theme restaurant	8	NR
	Before 1998	Illinois	1 gourmet restaurant	8	NR
Hammond and Perrino 2002	1998–1999	Indiana	71	NR	NR

*NR = Data were not reported.
†LD = Less than detectable.

Concentrations of nicotine (micrograms per cubic meter [$\mu g/m^3$])					
Mean	**Standard deviation**	**Geometric mean**	**Minimum**	**Median**	**Maximum**
			All sections		
NR	NR	NR	18.0	NR	70.0
NR	NR	4.1	1.0	NR	36.0
4.1	NR	NR	2.0	4.1	6.2
5.4	6.4	3.5	0.5	4.1	37.2
NR	NR	NR	NR	45.0	NR
4.3	NR	NR	LD[†]	2.9	24.0
6.3	NR	NR	0.3	4.2	24.8
NR	NR	5.1	LD	NR	23.8
3.4	NR	NR	LD	NR	16.1
NR	NR	NR	1.5	3.2	3.8
13.8	NR	NR	NR	NR	NR
6.0	11.9	NR	<0.24	0.8	49.3
5.8	11.9	NR	<0.24	1.2	67.9
			Nonsmoking sections		
NR	NR	NR	0.2	1.0	2.8
0.5	NR	NR	0.1	NR	1.2
1.1	NR	NR	0.1	NR	1.6
3.7	5.1	NR	0.02	2.2	26.7

within 25 feet of the smoking section, and less than 0.5 $\mu g/m^3$ in a nonsmoking section that was 30 feet from the smoking section (although on one day, the average in that section was 1.8 $\mu g/m^3$).

Among the highest concentrations of nicotine measured in public places were those found in bars and lounges, where reported values were generally greater than 50 $\mu g/m^3$ and occasionally were above 100 $\mu g/m^3$ (Table 4.7). Bartenders had higher exposures than waiters, at an average concentration of 14 $\mu g/m^3$ and a maximum exposure of more than 100 $\mu g/m^3$ (Maskarinec et al. 2000).

Other Locations

Casinos and bingo halls are other public locations where both nonsmoking workers and the public are exposed to high concentrations of secondhand smoke (Table 4.7). A 1986 study in California found a median nicotine concentration of 65.5 $\mu g/m^3$ (Kado et al. 1991). A study in Massachusetts the following year reported a median concentration of 56 $\mu g/m^3$ (Coghlin et al. 1989). In 1995, a study of casino workers in Atlantic City, New Jersey, showed increased levels of serum cotinine at baseline (geometric mean cotinine 1.34 ng/mL) that rose following a workshift (geometric mean cotinine 1.85 ng/mL) (Trout et al. 1998); nicotine levels in the personal breathing zone of casino workers ranged from 6 to 12 $\mu g/m^3$.

Reported nicotine concentrations in bowling alleys were between 10 and 23 $\mu g/m^3$ (Coghlin et al. 1989; Jenkins et al. 1996a) (Table 4.7). And although indoor exposures are expected to be higher than outdoor exposures, McFarling (1994) reported one nicotine sample at an outdoor baseball game that was at a concentration of 2.4 $\mu g/m^3$. Researchers have previously reported data for commercial aircraft, an environment now entirely smoke-free in the United States (Holm and Davis 2004).

Special Populations

Prisoners

Some of the highest concentrations of secondhand smoke in living quarters have been measured in correctional facilities (Hammond and Emmons 2005). Although most living and sleeping areas averaged 3 to 10 $\mu g/m^3$, Hammond and Emmons (2005) reported nicotine concentrations that averaged 25 $\mu g/m^3$ in a gym that was used as a bunkroom.

Evidence Synthesis

Since 1986, investigators have reported a substantial amount of new evidence on exposure to secondhand smoke. The more recent data provide insights into typical patterns of exposure, exposure in key microenvironments, and the consequences of various policies intended to reduce exposure. As noted in Figure 4.1 and Table 4.1, exposures of nonsmokers to secondhand smoke have declined significantly between 1988 and 2002. These declines have been observed in both children and nonsmoking adults, in both men and women, and in all racial and ethnic categories. However, significant levels of exposure persist for the U.S. population in general and for susceptible populations. Table 4.2 notes estimates for 2000; approximately 127 million children and nonsmoking adults were exposed to secondhand smoke. This estimated total includes almost 22 million children aged 3 through 11 years, and 18 million nonsmoking youth aged 12 through 19 years.

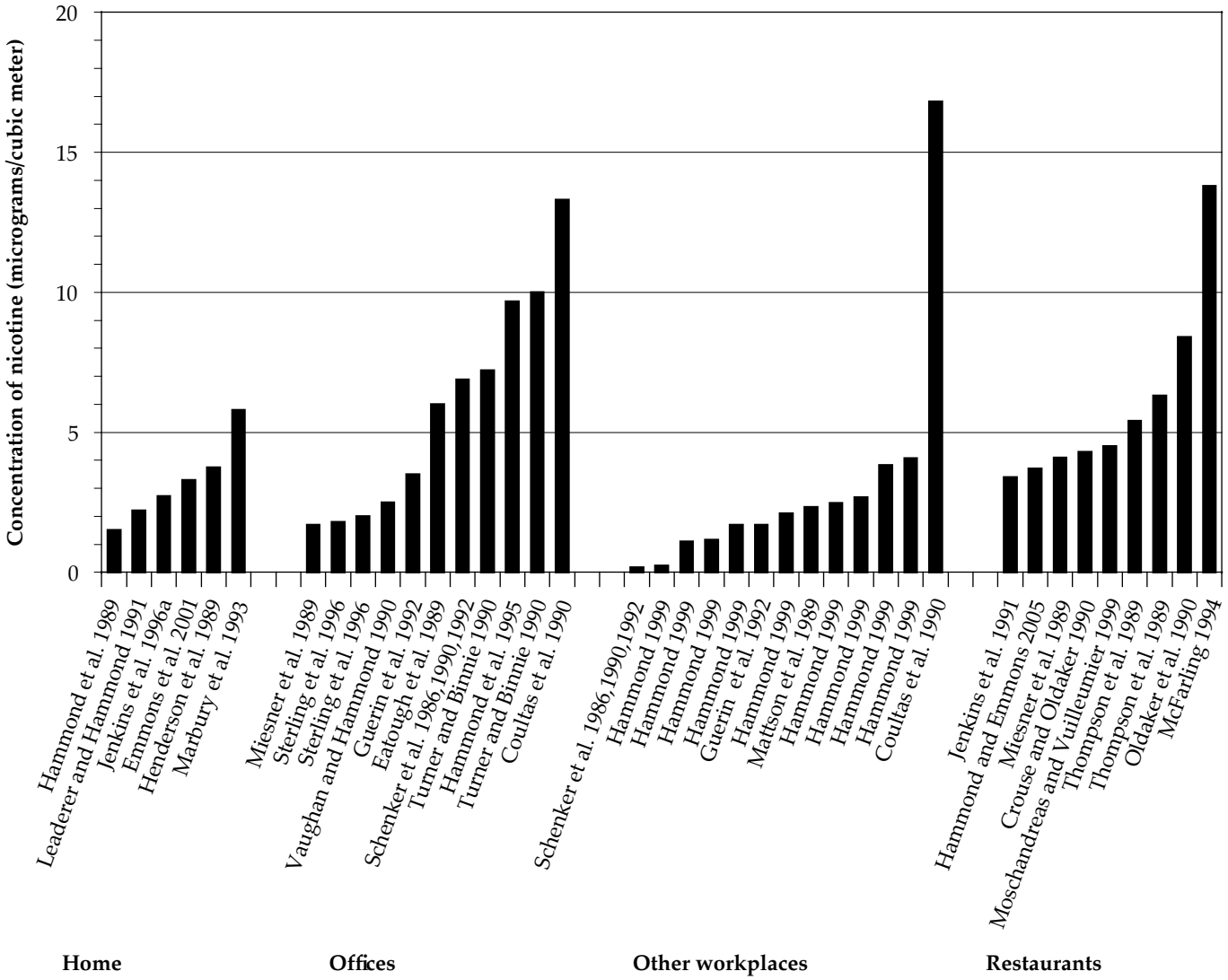
The findings consistently show the importance of two microenvironments as places for secondhand smoke exposure: the home and the workplace. Although microenvironments such as bars and restaurants may also be important for patrons, the home and the workplace are particularly significant because of the amount of time spent in these two locations. For the workplace, restrictions and smoking bans lead to much lower concentrations of secondhand smoke than in locations where smoking is allowed.

National surveys indicate that progress in reducing secondhand smoke exposure has been variable across the country. Certain states, such as California, Maryland, and Utah, have made significant advances in protecting nonsmokers, but others, such as Kentucky and Nevada, have not (Gilpin et al. 2001; Shopland et al. 2001). Even in locales with smoking restrictions in place, significant pockets of exposure remain, most notably in homes, some worksites such as restaurants and bars, and in automobiles. Exposures in some of these locations can be remedied by changing public policy. Exposures in other locations, particularly homes and automobiles, can perhaps only be addressed through education that alters lifestyle behaviors.

It is likely that geographic differences in secondhand smoke exposure are related to trends in tobacco use and policies that determine where tobacco use is permitted (Giovino et al. 1995; Gilpin et al. 2001). Wide regional differences exist within the United States

in secondhand smoke exposure and cotinine levels. In the NHANES III data, children with and without reported exposures had lower cotinine levels if they lived in the western part of the United States (Mannino et al. 2001)—a finding that may reflect lower community exposures to secondhand smoke. Where smoking is allowed, especially at worksites and in public places, concentrations are highly variable, so concentrations in individual locations may be significantly higher than average. Concentrations of secondhand smoke are also typically higher in the workplace and in restaurants than in the home (Figure 4.6). Policies that restrict smoking to particular areas reduce but do not eliminate secondhand smoke exposure. Smoke-free polices reduce secondhand smoke concentrations far more effectively.

Figure 4.6 Average concentrations of nicotine in homes, offices, other workplaces, and restaurants where smoking is permitted



Note: Data are provided in detail in Tables 4.3, 4.4, 4.5, and 4.6.

Table 4.7 Concentrations of nicotine in bars, lounges, and other public venues

Study	Year sampled	State	Number of venues	Number of days	Number of samples
		Bars			
Coghlin et al. 1989	1987	Massachusetts	11	NR*	NR
Loefroth et al. 1989	NR	North Carolina	1	2	NR
Miesner et al. 1989	1987–1988	NR	3	NR	5
Oldaker and Conrad 1989	NR	NR	NR	NR	NR
Jenkins et al. 1991	NR	NR	8	NR	NR
Guerin et al. 1992	NR	NR	2	NR	NR
Bergman et al. 1996	NR	NR	3	NR	17
Maskarinec et al. 2000	1996–1997	Tennessee	NR	NR	53
	1996–1997 Bartenders	NR	NR	NR	80
		Bingo halls			
Coghlin et al. 1989	1987	Massachusetts	NR	NR	2
Kado et al. 1991	1986	California	NR	NR	6
McFarling 1994	1994	NR	NR	NR	1
		Casinos and other betting establishments			
Jenkins et al. 1991	NR	NR	NR	NR	2
Kado et al. 1991	NR	NR	NR	NR	NR
Trout et al. 1998	1996	New Jersey	1	NR	1
		Bowling alleys			
Coghlin et al. 1989	1987	Massachusetts	NR	NR	2
Jenkins et al. 1991	NR	NR	NR	NR	4
		Professional baseball games			
McFarling 1994	1994	Massachusetts	NR	NR	1

*NR = Data were not reported.

Concentrations of nicotine (micrograms per cubic meter [$\mu g/m^3$])					
Mean	**Standard deviation**	**Geometric mean**	**Minimum**	**Median**	**Maximum**
			Bars		
NR	NR	NR	6.0	NR	82.0
65.5	NR	NR	60.0	NR	71.0
7.4	4.4	6.0	1.1	7.0	13.0
59.2	NR	NR	6.1	NR	109.0
17.6	NR	NR	1.8	NR	91.0
12.9	NR	NR	4.1	NR	21.6
37.1	6.9	36.0	28.0	34.9	50.0
14.4	16.9	NR	<0.2	5.8	61.1
14.1	20.9	NR	<0.2	4.4	116.0
			Bingo halls		
NR	NR	NR	53.0	56.0	60.0
NR	NR	NR	4.4	65.5	85.4
NR	NR	NR	NR	7.8	NR
			Casinos and other betting establishments		
10.7	NR	NR	NR	NR	NR
NR	NR	NR	NR	65.5	NR
10.0	NR	8.0	6.0	NR	12.0
			Bowling alleys		
18.0	NR	NR	13.0	18.0	23.0
10.7	NR	NR	NR	NR	NR
			Professional baseball games		
2.4	NR	NR	NR	NR	NR

Conclusions

1. The evidence is sufficient to infer that large numbers of nonsmokers are still exposed to secondhand smoke.

2. Exposure of nonsmokers to secondhand smoke has declined in the United States since the 1986 Surgeon General's report, *The Health Consequences of Involuntary Smoking*.

3. The evidence indicates that the extent of secondhand smoke exposure varies across the country.

4. Homes and workplaces are the predominant locations for exposure to secondhand smoke.

5. Exposure to secondhand smoke tends to be greater for persons with lower incomes.

6. Exposure to secondhand smoke continues in restaurants, bars, casinos, gaming halls, and vehicles.

Overall Implications

Exposure to secondhand smoke remains a serious public health problem in the United States, with exposure of almost 60 percent of children aged 3 through 11 years and more than 40 percent of nonsmoking adults. Since the publication of the 1986 Surgeon General's report, measured levels of exposure in the United States have declined significantly. However, the proportional decrease has been larger among adults than among children, and the most recent data suggest that children aged 3 through 11 years have serum cotinine concentrations that are more than twice as high as those among nonsmoking adults. Data suggest that the home remains the most important target for reducing exposures to secondhand smoke, particularly for children but also for middle-aged and older adults. Although progress has been made to protect nonsmoking workers, continuing efforts are needed to protect these workers, and particularly younger workers, in all occupational categories.

Research questions remain regarding exposure to secondhand smoke. As noted in the 1986 report, no indicator has been developed that can objectively estimate long-term exposure or early-life exposure. Secondhand smoke exposure from "shared air spaces" within a building is also of concern, as a significant proportion of the population lives in apartment buildings or condominiums where smoking in another part of the building might increase tobacco smoke exposure for households of nonsmokers.

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Chapter 5
Reproductive and Developmental Effects from Exposure to Secondhand Smoke

Introduction

This chapter concerns adverse effects on reproduction, infants, and child development from exposure to secondhand smoke. Previous Surgeon General's reports have not comprehensively addressed the relationship between secondhand smoke exposure and reproductive outcomes, infant mortality, or child development. The 2001 Surgeon General's report (*Women and Smoking*) did summarize the literature on developmental and reproductive outcomes in relation to secondhand smoke exposure, focusing on the specific outcomes of fertility and fecundity, fetal growth and birth weight, fetal loss and neonatal mortality, and congenital malformations (U.S. Department of Health and Human Services [USDHHS] 2001). The effects of active smoking by the mother during pregnancy were comprehensively reviewed in the 2004 report (USDHHS 2004). This new report reviews the possible effects of secondhand smoke exposure on reproductive and developmental outcomes, incorporates the substantial amount of evidence that has emerged since the 1986 Surgeon General's report (*The Health Consequences of Involuntary Smoking*, USDHHS 1986), and expands upon the 2001 report.

Conclusions of Previous Surgeon General's Reports and Other Relevant Reports

The early literature on secondhand smoke exposure and child health focused on adverse respiratory effects. Initial relevant reports were first published in the 1960s (Cameron et al. 1969), followed by larger studies in the 1970s (Colley 1974; Colley et al. 1974). The first summary report to comprehensively address reproductive and perinatal effects of secondhand smoke exposure was prepared by the California Environmental Protection Agency and released in 1997 (National Cancer Institute [NCI] 1999). These topics were also addressed by a number of other agencies and groups, including the United Kingdom Department of Health (1998), the World Health Organization (WHO 1999), and the University of Toronto (2001). Table 5.1 summarizes the conclusions for reproductive and perinatal outcomes from these reports.

Literature Search Methods

The authors identified most of the literature on secondhand smoke exposure and adverse reproductive and perinatal effects through a systematic search of the National Library of Medicine's indexed journals, which date back to 1966. The relevant Medical Subject Headings (MeSH) terms and text terms were used to search PubMed. Text terms were used because many of the relevant MeSH terms were not introduced into the PubMed key wording scheme until some time after 1966. For example, the MeSH term "Tobacco Smoke Pollution" was not introduced until 1982. The following text terms were also used in the search for articles: environmental, tobacco, smoke, secondhand smoke, paternal smoking, and passive smoking. By combining these text terms and MeSH terms using "or" as the Boolean connector, nearly 4,500 citations were identified. The authors also used this strategy to identify relevant research on outcomes. The results

Table 5.1 Findings on secondhand smoke exposure and reproductive and perinatal effects

Report	Outcome	Conclusion
Report of the Scientific Committee on Tobacco and Health (United Kingdom Department of Health 1998)	Sudden infant death syndrome	"Sudden infant death syndrome. . .is associated with exposure to environmental tobacco smoke. The association is judged to be one of cause and effect." (p. 10)
Health Effects of Exposure to Environmental Tobacco Smoke: The Report of the California Environmental Protection Agency (National Cancer Institute 1999)	Low birth weight/small for gestational age	"Taken together. . .[the studies] support a slight increase in LBW [low birth weight] or IUGR [intrauterine growth retardation] in association with ETS [environmental tobacco smoke, equivalent to secondhand smoke] exposure." (p. 102)
	Preterm delivery	"There was little evidence found for an association with preterm birth." (p. 102)
	Spontaneous abortion	". . .there is some epidemiologic evidence that ETS exposure may play a role in the etiology of spontaneous abortion. . . ." (p. 113)
	Congenital malformations	". . .it is not possible at this time to determine whether there is an association of ETS exposure with birth defects." (p. 119)
	Sudden infant death syndrome (SIDS)	There is "sufficient evidence that postnatal ETS exposure of the child is an independent risk factor for SIDS." (p. 139)
	Childhood cognition and behavior	"The evidence that ETS exposure of a nonsmoking pregnant woman can result in neuropsychologic deficits in the child. . .is inconclusive." (p. 154)
		"No conclusions regarding causality can be made on the basis of these studies, but they do provide suggestive evidence that [postnatal] ETS exposure may pose a neuropsychological developmental hazard." (p. 155)
	Postnatal physical development	". . .there is little to no epidemiological evidence that ETS exposure has a significant effect on height growth of children." (p. 162)
	Female fertility and fecundability	". . .the data are inadequate to determine whether there is an association of ETS exposure with effects on fertility or fecundability." (p. 178)
	Other female reproductive effects	". . .there is a paucity of data on the association of ETS exposure and lowered age at menopause or other measures of menstrual cycle dysfunction, and conclusions regarding causal associations cannot be reached." (p. 179)
	Male reproductive toxicity	". . .due to the paucity of data it is not possible to determine whether there is a causal association between ETS exposure and male reproductive dysfunction." (p. 180)
	Childhood cancers	". . .the evidence for a role of parental smoking and childhood cancers is inconclusive." (p. 282)

Table 5.1 Continued

Report	Outcome	Conclusion
International Consultation on Environmental Tobacco Smoke (ETS) and Child Health: Consultation Report (World Health Organization 1999)	Low birth weight	"ETS exposure among nonsmoking pregnant women can cause a decrease in birth weight…" (p. 4)
	SIDS	". . .infant exposure to ETS may contribute to the risk of SIDS." (p. 4)
	Neurodevelopment	". . .the effects of prenatal and postnatal ETS exposure on cognition and behaviour remain unclear." (p. 9)
	Childhood cancer	". . .there is suggestive evidence linking exposure to tobacco smoke and childhood cancer." (p. 10)
Women and Smoking: A Report of the Surgeon General (U.S. Department of Health and Human Services 2001)	Low birth weight/small for gestational age	". . .maternal exposure to ETS appears to be causally associated with detrimental effects on fetal growth." (p. 364)
	Fertility, spontaneous abortion, perinatal mortality	"Studies of ETS exposure and the risks for delay in conception, spontaneous abortion, and perinatal mortality are few, and the results are inconsistent." (p. 372)
Protection from Second-Hand Tobacco Smoke in Ontario: A Review of the Evidence Regarding Best Practices (University of Toronto 2001)	SIDS	"Exposure to second-hand smoke causes the following diseases and conditions. . . Sudden infant death syndrome. . ." (p. v)
	Low birth weight/ small for gestational age	"Exposure to second-hand smoke causes the following diseases and conditions… Fetal growth impairment including low birth-weight and small for gestational age. . ." (pp. v–vi)
	Spontaneous abortion	"Exposure to second-hand smoke has also been linked to other adverse health effects. The relationships may be causal. These include. . . Miscarriages. . ." (p. vi)

of each outcome-relevant search were then combined with the secondhand smoke-relevant search using "and" as the Boolean connector. These citations were imported into a database. Using title and abstract information, the authors selected the relevant articles for review. Finally, the references in the articles were reviewed for additional citations that were not identified through the PubMed searches.

Critical Exposure Periods for Reproductive and Developmental Effects

Assessing exposures to secondhand smoke in studies of fertility, fetal development, infant development, and child health and development is complex. For each of the three biologically relevant periods—preconception, pregnancy, and postdelivery—a number of potentially different biologic mechanisms of injury exist from exposure to secondhand smoke. Even within the nine months of pregnancy, vulnerability to the effects of secondhand smoke may change, reflecting differing mechanisms of injury as fetal

organs develop and the fetus grows. Moreover, there are multiple environments where the woman or child is exposed to secondhand smoke (e.g., workplace, home, and day care), as well as multiple sources of secondhand smoke exposure for each of these environments (e.g., household members, day care providers, and coworkers). Finally, because of the potential impact of active maternal smoking (USDHHS 2004), active smoking before and during pregnancy needs to be taken into account when assessing the potential independent effects of exposure to secondhand smoke. Maternal smoking has well-characterized adverse effects for several outcomes, such as fertility, sudden infant death syndrome (SIDS), and child growth and development. Thus, the effects of exposure to secondhand smoke may be confounded by those of maternal smoking.

Secondhand smoke exposure may have adverse effects potentially throughout the reproductive and developmental processes (Table 5.2). During the preconception period, maternal exposure to secondhand smoke can potentially affect female fertility by altering the balance of hormones that affect oocyte production, including growth hormone, cortisol, luteinizing hormones, and prolactin (Mattison 1982; Daling et al. 1987; Mattison and Thomford 1987), or by reducing motility in the female reproductive tract (Mattison 1982; Daling et al. 1987). However, separating the potential effect of secondhand smoke exposure on the mother's reproductive process and the effect of active paternal smoking on the father's reproductive process is very difficult. Although the evidence is mixed, active smoking has been shown to affect sperm morphology, motility, and concentration (Rosenberg 1987; USDHHS 2004). Cigarette smoke may also lead to infertility through a combined effect of decreased sperm motility with active paternal smoking and decreased tubal patency with active maternal smoking and secondhand smoke exposure.

During pregnancy, maternal exposure to secondhand smoke could potentially affect the pregnancy by increasing the risk for spontaneous abortion or by interfering with the developing fetus through growth restrictions or congenital malformations (NCI 1999; WHO 1999). During gestation, windows of susceptibility exist when the developing embryo or fetus is vulnerable to various intrauterine conditions or exposures. Organogenesis occurs mainly during the embryonic period (weeks three through eight of gestation), which is also the time when major malformations are most likely to develop. During weeks 9 through 38 of gestation, susceptibility decreases and insults are more likely to lead to minor malformations or functional defects (Sadler 1990).

Finally, secondhand smoke exposure in the postpartum period could affect the developing infant and child, resulting in a number of adverse health outcomes. Given the developmental processes in progress, infants and children are considered to be more vulnerable to the effects of environmental exposures than are adults (Goldman 1995; Dempsey et al. 2000). Mechanisms that could lead to compromised physical and cognitive development as a result of exposure to secondhand smoke may be similar to the processes that affect fetal development, such as hypoxia (USDHHS 1990; Lambers and Clark 1996). One review of the impact of prenatal exposure to nicotine summarized numerous animal studies that demonstrated the effects of nicotine on cognitive processes among exposed rats and guinea pigs, such as impeded learning abilities or increased attention or memory deficits (Ernst et al. 2001). In animal and human studies, prenatal nicotine exposure affected aspects of neural functioning such as the activation of neurotransmitter systems, which may lead to permanent alterations in the developing brain through changes in gene expression. The proposed consequences of altered gene expression included disturbances in neuronal pathfinding and in cell regulation and differentiation (Ernst et al. 2001). Other animal studies have shown that newborn rats exposed to sidestream smoke have reduced DNA and protein concentrations in the brain (Gospe et al. 1996). Ideally, researchers should have information on secondhand smoke exposures for all relevant periods that relate to the outcome under study, because different physiologic processes may be affected across developmental periods (Table 5.2). However, this information is frequently unavailable in a particular study.

Secondhand smoke exposures most commonly occur in the home or workplace, and exposures in public places tend to be more sporadic. Recent exposure assessment and monitoring studies have shown that the home tends to be a greater source of secondhand smoke exposure than the workplace (Emmons et al. 1994; Pirkle et al. 1996; Hammond 1999), particularly since workplace smoking bans have become more restrictive (Marcus et al. 1992) (Chapter 3, Assessment of Exposure to Secondhand Smoke, and Chapter 4, Prevalence of Exposure to Secondhand Smoke). In the home, the major sources of exposures to secondhand smoke have been smoking by the spouse or partner and other household members. Paternal smoking has been the most commonly

Table 5.2 Potentially relevant exposure periods for reproductive and perinatal outcomes

	Relevant exposure periods		
Outcome	**Preconception**	**Prenatal**	**Postnatal**
Fertility (female)	X		
Spontaneous abortion	X	X	
Low birth weight, small for gestational age, intrauterine growth retardation	X	X	
Congenital malformations	X	X	
Infant death (including sudden infant death syndrome)	X	X	X
Cognitive development	X	X	X
Childhood behavior	X	X	X
Height/growth	X	X	X
Childhood cancer	X	X	X

measured source of secondhand smoke in the home (USDHHS 1986), and paternal smoking status tends to be constant across the three developmental periods: preconception, prenatal, and postnatal (USDHHS 1986). Although many studies have not considered smoking in the home by other household members, some studies have documented that such smoking could be a significant source of secondhand smoke exposure for women (Pattishall et al. 1985; Rebagliato et al. 1995a; Pirkle et al. 1996; Ownby et al. 2000; Kaufman et al. 2002). Studies on workplace exposure have focused on whether or not the person was exposed, but less attention has been paid to quantifying the exposure (Misra and Nguyen 1999).

Fertility

Biologic Basis

Infertility is commonly defined as a failure to conceive after 12 months of unprotected intercourse. Infertility should not be confused with fecundability, which is defined as the probability of conception during one menstrual cycle and measured by time to pregnancy. Thus, low fecundability is delayed conception. The biologic plausibility that secondhand smoke exposure affects human fertility and fecundability is supported by both animal and human studies of active smoking, which include exposure to the same materials as involuntary smoking. In animal studies, numerous investigators have demonstrated the biologic effects of nicotine in disrupting oviduct function (Neri and Marcus 1972; Ruckebusch 1975) and in delaying blastocyst formation and implantation (Yoshinaga et al. 1979). Investigations of assisted reproduction among humans who actively smoke have also provided information on possible mechanisms of infertility and delayed conception from secondhand smoke exposure. Several studies of assisted reproductive techniques have suggested that active maternal smoking reduces the estradiol level in follicular fluid (Elenbogen et al. 1991; Van Voorhis et al. 1992), impedes ovulation induction (Van Voorhis

et al. 1992; Chung et al. 1997), reduces the fertilization rate (Elenbogen et al. 1991; Rosevear et al. 1992), and retards the embryo cleavage rate (dose-dependent) (Hughes et al. 1992). Metabolites of cigarette smoke have been measured in the follicular fluid of active smokers at assisted reproduction clinics (Trapp et al. 1986; Weiss and Eckert 1989; Rosevear et al. 1992) and in the cervical mucus of active smokers in a cervical cancer study (Sasson et al. 1985).

Together, the evidence from studies of biologic mechanisms and the findings of numerous epidemiologic studies have led to the conclusion that active maternal smoking causes reduced fertility. An early review by Stillman and colleagues (1986) of studies of natural reproduction in addition to the two most recent Surgeon General's reports (USDHHS 2001, 2004) support this conclusion of a causal association, and findings of meta-analyses have provided estimates of the magnitude of the effect of maternal smoking on fertility. Hughes and Brennan (1996) combined the results of seven studies on in vitro fertilization with gamete intrafallopian transfer. Comparing smokers and nonsmokers, the researchers obtained a combined odds ratio (OR) for conception of 0.57 (95 percent confidence interval [CI], 0.42–0.78). Similarly, Augood and colleagues (1998) pooled nine studies that compared smokers with nonsmokers and found a combined OR of 0.66 (95 percent CI, 0.49–0.88) for the number of pregnancies per cycle of in vitro fertilization. In their meta-analysis of 12 studies, Augood and colleagues (1998) compared smokers with nonsmokers and found that the overall OR for infertility was 1.60 (95 percent CI, 1.34–1.91). Several investigators found a dose-response trend between the level of active maternal smoking and decreased fertility (Baird and Wilcox 1985; Suonio et al. 1990; Laurent et al. 1992).

Although active paternal smoking could also play a role in infertility by affecting sperm quality, the 2004 Surgeon General's report found conflicting evidence on active smoking and sperm quality (USDHHS 2004). In another review, investigators performed a meta-analysis of 20 study populations (from 18 published papers) on cigarette smoking and sperm density and found a weighted estimated reduction of 13 percent in sperm density (95 percent CI, 8.0–17.1) among smokers compared with nonsmokers (Vine et al. 1994). The epidemiologic studies that have examined the effect of active paternal smoking on fertility are not as consistent in their findings as the studies that have investigated active maternal smoking and fertility (Underwood et al. 1967; Tokuhata 1968; Baird and Wilcox 1985; de Mouzon et al. 1988; Dunphy et al. 1991; Pattinson et al. 1991; Hughes et al. 1992; Rowlands et al. 1992; Bolumar et al. 1996; Hull et al. 2000). One review concluded that paternal smoking had no effect on fertility (Hughes and Brennan 1996).

Several studies that were conducted in reproductive clinics measured tobacco smoke biomarkers in nonsmoking men and women exposed to secondhand smoke. Cotinine was measurable in follicular fluid, with measurements related to dose (Zenzes et al. 1996), and benzo[*a*]pyrene adducts were found in ovarian cells (Zenzes et al. 1998). Both nicotine and cotinine were measured in semen of nonsmoking, secondhand smoke-exposed men attending a clinic specializing in infertility (Pacifici et al. 1995).

Epidemiologic Evidence

Although active maternal smoking has been causally associated with infertility (USDHHS 2004), less evidence is available on maternal exposure to secondhand smoke and fertility, and no data were found on paternal secondhand smoke exposure and fertility. Two studies specifically addressed maternal exposure to secondhand smoke in relation to infertility, although they examined different outcome measures (Chung et al. 1997; Hull et al. 2000). Chung and colleagues (1997) studied infertile patients undergoing a gamete intrafallopian transfer procedure (Table 5.3). The researchers found that a higher proportion of active smokers had anovulation and required significantly higher amounts of human menopausal gonadotropins (hMG) to stimulate ovulation than did nonsmokers. However, the investigators found no significant differences in these same parameters when they compared unexposed nonsmokers and secondhand smoke-exposed nonsmokers, defined as having at least one household member who smoked. Among the unexposed nonsmokers, 3.0 percent had anovulation and required an average of 26 vials of hMG. Among the exposed nonsmokers, 7.8 percent

had anovulation and required an average of 24 vials of hMG. The two groups also did not differ in pregnancy rates (45.5 percent in the unexposed group and 46.2 percent in the exposed group) or birth rates (33.3 percent versus 23.1 percent, respectively). This study included only 98 patients, of whom 13 were secondhand smoke-exposed only. Hull and colleagues (2000) assessed secondhand smoke exposures from the workplace and the home among more than 8,000 women with a planned pregnancy (Table 5.3). Nonsmoking women with any secondhand smoke exposure (n = 1,987) had an increased risk for conception delay of more than six months compared with unexposed nonsmoking women (n = 4,133) (adjusted OR = 1.17 [95 percent CI, 1.02–1.37]). In this study, the investigators also included an analysis of active paternal smoking (adjusted for active maternal smoking); they found that the fathers who smoked more than 20 cigarettes per day had an increased risk for conception delay of more than six months compared with nonsmoking fathers (OR = 1.39 [95 percent CI, 1.14–1.68]).

Two other studies examined maternal exposure to secondhand smoke in addition to active maternal smoking in relation to fertility (Table 5.3) (Baird and Wilcox 1985; Olsen 1991). Using regression analysis, Baird and Wilcox (1985) adjusted for active maternal smoking to examine the impact of active paternal smoking among 678 pregnant women. No effect was found after adjusting for active maternal smoking, although the data were not presented ($\chi^2 = 0.000$, $p = 0.953$). Olsen (1991) analyzed only nonsmoking women without a history of infertility treatments. Olsen's analysis categorized paternal smoking as 1 to 9, 10 to 19, and 20 or more cigarettes per day, and calculated the ORs for time to pregnancy of more than 6 and more than 12 months. There were increased risks for both time outcomes. The greatest risks were at exposures of 10 to 19 cigarettes per day for more than 6 months (OR = 1.32 [95 percent CI, 1.10–1.58]) and for more than 12 months (OR = 1.39 [95 percent CI, 1.10–1.75]).

The limited epidemiologic evidence on maternal secondhand smoke exposure and fertility does not warrant a meta-analysis of the relevant studies.

Evidence Synthesis

The observational evidence is quite limited. The four studies that directly address maternal secondhand smoke exposure and fertility differ substantially in study design and methods. For example, Chung and colleagues (1997) investigated patients who were attending a clinic for fertility-related problems and examined the success rate of assisted reproduction. Hull and colleagues (2000), on the other hand, included pregnant women and examined delayed natural conception. In the former study, the investigators did not account for potential confounders and obtained retrospective information about exposure to secondhand smoke from telephone interviews (Chung et al. 1997). Hull and colleagues (2000) relied on a self-administered questionnaire to ascertain exposure information during pregnancy, and used potential confounders in the analysis such as parental age, body mass index, and alcohol consumption. The evidence from this larger study on natural conception is consistent with the biologic framework established by the studies on active maternal smoking and fertility (Hull et al. 2000).

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal exposure to secondhand smoke and female fertility or fecundability. No data were found on paternal exposure to secondhand smoke and male fertility or fecundability.

Implications

As exposure of women of reproductive age to secondhand smoke continues, this topic needs further rigorous investigation. In particular, the frequency and extent of current exposures should be characterized. Further epidemiologic studies also merit consideration.

Table 5.3 Studies of secondhand smoke exposure and fertility

Study	Design/population	Source of exposure	Outcome	Exposure categories
Baird and Wilcox 1985	678 pregnant women who were not using contraceptives before conception, recruited through early pregnancy classes and obstetric practices	Husband	Time to pregnancy	Yes/no
Olsen 1991	Population-based survey conducted in Denmark between 1984 and 1987, completed by 10,866 women in their third trimester of pregnancy who had no history of infertility treatments	Father Father Father Father Father Father Father Father	Time to pregnancy	>6 months: 0 cigarettes/day 1–9 cigarettes/day 10–19 cigarettes/day ≥20 cigarettes/day >12 months: 0 cigarettes/day 1–9 cigarettes/day 10–19 cigarettes/day ≥20 cigarettes/day
Chung et al. 1997	98 infertile women undergoing a gamete intrafallopian transfer procedure	Home	Anovulation Pregnancy rate Birth rate	Data were not reported
Hull et al. 2000	12,106 pregnant women with due dates between April 1991 and December 1992	Work and home	Time to pregnancy	Yes/no

*OR = Odds ratio.
†CI = Confidence interval.

Findings	Comments
No effect (data were not presented) $\chi^2 = 0.000$, p = 0.953	Adjusted for maternal smoking and potential risk factors; paternal smoking did not affect fertility
>6 months: OR* = 1.16 (95% CI†, 0.95–1.41) OR = 1.32 (95% CI, 1.10–1.58) OR = 1.32 (95% CI, 0.96–1.80) >12 months: OR = 1.34 (95% CI, 1.05–1.72) OR = 1.39 (95% CI, 1.10–1.75) OR = 1.11 (95% CI, 0.72–1.71)	Results are for nonsmoking mothers
Anovulation: 3.0% in unexposed group 7.8% in exposed group Pregnancy rate: 45.5% in unexposed group 46.2% in exposed group Birth rate: 33.3% in unexposed group 23.1% in exposed group	13 were secondhand smoke-exposed only (nonsmokers); this study demonstrated that active, but not involuntary, cigarette smoking has an adverse impact on the pregnancy and live-birth rates in gamete intrafallopian transfer producers
Conceived after >6 months: OR = 1.17 (95% CI, 1.02–1.37) Conceived after >12 months: OR = 1.14 (95% CI, 0.92–1.42)	Findings are based on 4,133 unexposed and 1,987 secondhand smoke-exposed nonsmokers; trends by categories of cigarettes/day smoked by partners of nonsmoking women were not statistically significant; this study provides new evidence of delayed conception if a woman is exposed to secondhand smoke at home or in the workplace

Pregnancy (Spontaneous Abortion and Perinatal Death)

Biologic Basis

Fetal loss or spontaneous abortion is defined as the involuntary termination of an intrauterine pregnancy before 20 weeks of gestation (Anderson et al. 1998). Because most early fetal losses are underreported and unrecognized, spontaneous abortions are extremely difficult to study. Twenty to 40 percent of all pregnancies may terminate too early to be recognized or confirmed (Wilcox et al. 1988; Eskenazi et al. 1995). Furthermore, the etiology of spontaneous abortion is multifactorial and not fully understood. Some early miscarriages result from chromosomal abnormalities in the developing embryo; others are related to factors associated with maternal age, with the pregnancy itself, or to other types of exposures (e.g., occupational exposure, alcohol consumption, or fever). Moreover, relatively few animal studies have been conducted to gain an understanding of how exposure to sidestream smoke may affect the processes of spontaneous abortion (NCI 1999). In one study of sea urchins, investigators noted that exposure to nicotine prevented the cortical granule reaction, which typically prevents the entry of additional sperm into the egg once fertilization has occurred (Longo and

Table 5.4 Studies of secondhand smoke exposure and pregnancy loss

Study	Design/population	Exposure categories	Source of exposure
Koo et al. 1988	Cross-sectional 136 nonsmoking wives Hong Kong 1981–1983	• Unexposed • Secondhand smoke only • Light (1–20 cigarettes/day) • Heavy (>20 cigarettes/day)	• Husband • Some work exposure
Ahlborg and Bodin 1991	Prospective 4,701 pregnancies Sweden (Orebo County) 1980–1983	• Unexposed • Secondhand smoke only • Active smoking (1–9 cigarettes/day, 10–19 cigarettes/day, or ≥20 cigarettes/day)	• Maternal smoking • Secondhand smoke exposure
Windham et al. 1992	Case-control 626 cases and 1,300 controls United States (Santa Clara County, California) 1986–1987	• Exposure ≥1 hour in a room where someone else was smoking • No maternal smoking • Mother smoked 1–10 cigarettes/day • Mother smoked >10 cigarettes/day • Any smoking	• Smoking behavior 1 month before pregnancy • Any smoking changes during pregnancy • Paternal smoking

*RR = Relative risk.
†CI = Confidence interval.
‡OR = Odds ratio.

Anderson 1970). If this same process occurs in the human fertilized ovum as a result of nicotine exposure, this may be a mechanism by which abnormalities in the developing embryo result in spontaneous abortions (Longo and Anderson 1970; Mattison et al. 1989). Several tobacco components and metabolites are potentially toxic to the developing fetus, including lead, nicotine, cotinine, cyanide, cadmium, carbon monoxide (CO), and polycyclic aromatic hydrocarbons (Lambers and Clark 1996; Werler 1997). Finally, with regard to active smoking and spontaneous abortion, many studies have reported a greater increase in risk for smokers than for nonsmokers, and some studies have demonstrated dose-response relationships (USDHHS 2004).

Epidemiologic Evidence

Among five studies that reported on involuntary smoking and miscarriage or spontaneous abortion, three studies found an increased risk among exposed women compared with unexposed women. In a study conducted in Hong Kong, Koo and colleagues (1988) reported that if husbands were heavy smokers (>20 cigarettes per day), their wives were two times more likely to have a miscarriage or spontaneous abortion than were women whose husbands did not smoke. Windham and colleagues (1992) examined active and secondhand smoke exposures among 1,926 pregnant women and measured exposure to secondhand smoke two ways: the amount smoked by the "father of the unborn child," and maternal exposure to secondhand smoke for more than one hour per day (Table 5.4). After adjusting for maternal

Outcome	Findings	Comments
Miscarriage/abortion	Percentage with ≥1 miscarriage/abortion: Nonsmoking husband: 33% Husband was a light smoker: 43% Husband was a heavy smoker: 59% p value = 0.12 for wives with smoking husbands	Participants were interviewed in their homes by trained interviewers 44% of wives with nonsmoking husbands had been exposed to secondhand smoke at home or at work
Spontaneous abortion Preterm birth Low birth weight (LBW)	• Secondhand smoke exposure at work (RR* = 1.53 [95% CI†, 0.98–2.38]) for spontaneous abortion • Adjusted RR for active exposure from smoking 10–19 cigarettes/day = 2.18 (95% CI, 1.51–3.14) for preterm birth and 2.38 (95% CI, 1.22–4.65) for LBW • RR for active exposure from smoking ≥20 cigarettes/day = 2.30 (95% CI, 1.19–4.44) for preterm birth and 2.71 (95% CI, 0.86–8.53) for LBW	Source exposure data were self-reported (questionnaires)
Spontaneous abortion	• OR‡ = 1.31 (95% CI, 0.92–1.88) for mothers who smoked >10 cigarettes/day • OR = 1.5 (95% CI, 1.2–1.9) for mothers exposed to secondhand smoke for ≥1 hour/day • OR = 2.1 (95% CI, 0.8–6.0) for fathers who smoked 1–10 cigarettes/day • 40% of mothers smoked during pregnancy if fathers smoked (highly correlated)	Source exposure data were self-reported; there was no conclusive evidence of an association between active smoking and spontaneous abortion; a moderate association was observed with secondhand smoke exposure; findings were adjusted for maternal factors of age, race, education, marital status, prior fetal loss, tobacco use, alcohol consumption, bottled water intake, employment, insurance, and nausea

factors of age, race, education, marital status, prior fetal loss, tobacco use, alcohol consumption, bottled water intake, employment, insurance, and nausea, women exposed to secondhand smoke for one hour or more per day had an adjusted OR of 1.5 (95 percent CI, 1.2–1.9) for second trimester losses compared with nonsmokers. Windham and colleagues (1992), however, found no association for their second measure of involuntary smoking, which was paternal smoking (examined by dose). Ahlborg and Bodin (1991) examined involuntary smoking and spontaneous abortion among nonsmoking mothers in Sweden. Women who were exposed to secondhand smoke at work were at an increased risk for first trimester losses (relative risk [RR] = 2.16 [95 percent CI, 1.23–3.81]), but exposure to secondhand smoke at home was not associated with spontaneous abortion. In Finland, Lindbohm and colleagues (1991) examined paternal exposures to occupational lead and paternal smoking among 513 pregnancies (213 of which ended in spontaneous abortion). Without adjusting for potential confounding factors, the authors observed that paternal smoking did not increase the risk of spontaneous abortion (OR = 1.3 [95 percent CI, 0.9–1.9]). Windham and colleagues (1999b) conducted another prospective study that involved 5,000 women who resided in California from 1990 to 1991. The investigators examined exposure to secondhand smoke only among nonsmoking women and ascertained the number of hours per day that a woman was near others who smoked (including paternal smoking). There was little evidence for increased risks, and all ORs were an estimated 1.0.

Evidence Synthesis

The few studies that have examined the relationship between involuntary smoking and spontaneous abortion have inconsistent findings (Table 5.4). Although some studies reported an increased risk for spontaneous abortion among women exposed to secondhand smoke at work or at home, many found no association. However, for the studies that showed no associations, the study samples may have lacked adequate statistical power.

Three studies examined secondhand smoke exposures among women who were nonsmokers. Koo and colleagues (1988) examined rates of miscarriage among 136 nonsmoking wives who were part of a larger study on cancer. These 136 women were the controls in this study, which ascertained lifetime smoking histories of the husbands and reproductive histories of the wives. Social and demographic factors differed between families with smoking and nonsmoking husbands. The crude OR for more than two miscarriages among wives with husbands who smoked was 1.81 (95 percent CI, 0.85–3.85) (adjusted ORs were not reported). Ahlborg and Bodin (1991) reported on nonsmoking women who were exposed to secondhand smoke at home. Two estimates were provided, one for first trimester losses (OR = 0.96 [95 percent CI, 0.50–1.86]) and for one second or third trimester losses (OR = 1.06 [95 percent CI, 0.55–2.05]). Windham and colleagues (1999b) reported adjusted ORs for paternal smoking among women who were nonsmokers. When maternal age, prior spontaneous abortion, alcohol and caffeine consumption, and gestational age at initial interviews were taken into account, the investigators obtained an OR of 1.15 (95 percent CI, 0.86–1.55) for secondhand smoke exposure at home. The pooled estimate from these three studies (with the two estimates from Alborg and Bodin [1991] included separately) for secondhand smoke exposure in the home or from fathers who smoked and who were married to nonsmoking women was 1.18 (95 percent CI, 0.92–1.44).

Future studies not only need to ensure an adequate sample size, but they should give particular attention to the difficult issues of confounding and to accurate estimates of secondhand smoke exposures in the workplace and in the home.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal exposure to secondhand smoke during pregnancy and spontaneous abortion.

Implications

As for other outcomes that have very few studies, further research is warranted (see "Overall Implications" later in this chapter).

Infant Deaths

Infant mortality is defined as the death of a live-born infant within 364 days of birth. Many of the major causes of infant deaths, such as low birth weight (LBW), preterm delivery, and SIDS, are also associated with exposure to tobacco smoke during and after pregnancy. The biologic mechanisms by which secondhand smoke exposure leads to these particular outcomes are discussed in other parts of this chapter and will not be discussed here. In 2002, the infant mortality rate for infants of smokers (11.1 percent) was 68 percent higher than the rate for infants of nonsmokers (6.6 percent) (Mathews et al. 2004). For each race and Hispanic-origin group, the infant mortality rate among infants of smokers was higher compared with the rate among infants of nonsmokers.

Epidemiologic Evidence

Numerous studies have demonstrated associations of active maternal smoking with neonatal and perinatal mortality (Comstock and Lundin 1967; Rush and Kass 1972; Cnattingius 1988; Malloy et al. 1988; Schramm 1997). Even with modern neonatal intensive care, children of smokers are at an increased risk for neonatal mortality (death of a live-born infant within 28 days) (Cnattingius 1988; Malloy et al. 1988; Schramm 1997), with reported OR estimates of 1.2 for infants of smokers compared with infants of nonsmokers. Two studies have assessed neonatal mortality among infants exposed to secondhand smoke. Comstock and Lundin (1967) examined neonatal mortality among a sample of 448 live births, 234 stillbirths, and 431 infant deaths that occurred between 1950 and 1964 in Washington County, Maryland. When comparisons were made between families with paternal smokers only and families with two nonsmoking parents, neonatal mortality rates that were adjusted for gender and paternal education were higher: 17.2 (father smoked) versus 11.9 (neither parent smoked) neonatal deaths per 1,000 live births. Yerushalmy (1971) examined active and involuntary smoking and perinatal outcomes among an estimated 13,000 births in California. After examining crude rates for neonatal mortality, Yerushalmy (1971) found (without considering maternal smoking) that rates for both Blacks and Whites were elevated among infants whose fathers smoked compared with infants of nonsmoking fathers; there were no adjustments for any other confounding factors.

Evidence Synthesis

Only two studies examined the relationship of involuntary smoking with neonatal mortality. Both studies reported associations of secondhand smoke exposure from paternal smoking with neonatal mortality. There is significantly more literature on active smoking by the mother during pregnancy and neonatal outcome. Although the strength of the relationship in these two studies was strong, causality cannot be inferred because of the small number of studies and because of inadequate controls for potential confounders.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and neonatal mortality.

Implications

In addition to the consistent relationship demonstrated between exposure to secondhand smoke and neonatal mortality, numerous studies have reported significant associations between active maternal smoking during pregnancy and infant mortality. Thus, the association of secondhand smoke exposure during pregnancy and infant mortality warrants further investigation. Moreover, the data cited were from older studies, and smoking patterns and levels of secondhand smoke exposure may have changed since the time some of the studies were conducted. To clarify the association between maternal smoking and infant mortality, more evidence is needed.

Sudden Infant Death Syndrome

The sudden, unexplained, unexpected death of an infant before one year of age—referred to as SIDS—has been investigated in relation to exposure of the fetus and infant to smoking by mothers and others during the preconception, prenatal, and postpartum periods. The death rate attributable to SIDS has declined by more than half during the past two decades (Ponsonby et al. 2002; American Academy of Pediatrics [AAP] Task Force on SIDS 2005). SIDS has decreased dramatically because of interventions such as the "Back to Sleep" campaign implemented in the 1990s (Gibson et al. 2000; Malloy 2002; Malloy and Freeman 2004). Numerous studies have examined the association between active smoking among mothers during pregnancy and the subsequent risk of SIDS. The evidence for active smoking has demonstrated a causal association between maternal smoking during pregnancy and SIDS (Anderson and Cook 1997; United Kingdom Department of Health 1998; USDHHS 2001). The 2004 Surgeon General's report concluded that the evidence is sufficient to infer a causal relationship between SIDS and maternal smoking during and after pregnancy (USDHHS 2004). This new 2006 Surgeon General's report considers exposure of the infant to secondhand smoke from the mother, father, or others.

Biologic Basis

Although studies have identified social and behavioral risk factors for SIDS, the biologic mechanism or mechanisms underlying sudden, unexplained, unexpected death before one year of age are still unknown (Joad 2000; AAP Task Force on SIDS 2005). Chapter 2 (Toxicology of Secondhand Smoke) reviews the animal and human studies that provide evidence on how prenatal and postnatal exposure to nicotine and to other toxicants in tobacco smoke may affect the neuroregulation of breathing, apneic spells, and risk for sudden infant death. Experimental data from animal models on the neurotoxicity of prenatal and neonatal exposure to nicotine and secondhand smoke can be related to several potential causal mechanisms for SIDS, including adverse effects on brain cell development, synaptic development and function, and neurobehavioral activity (Slotkin 1998; Slotkin et al. 2001, 2006; Machaalani et al. 2005). Stick and colleagues (1996) observed newborns in the hospital and reported reductions in respiratory function among infants of smokers compared with infants of nonsmokers. Other proposed mechanisms for postpartum reductions in respiratory function have included irritation of the airways by tobacco smoke, susceptibility to respiratory infections that increases the risk of SIDS, and a change in the ventilatory responses to hypoxia attributable to nicotine (Anderson and Cook 1997).

A diagnosis of SIDS requires supporting evidence from an autopsy so as to exclude other causes. Thus, SIDS is a difficult outcome to study. Numerous studies have examined the association between active smoking among mothers during pregnancy and the subsequent risk of SIDS. The evidence for active smoking has demonstrated a causal association between maternal smoking during pregnancy and SIDS (Anderson and Cook 1997; United Kingdom Department of Health 1998; USDHHS 2001, 2004).

Epidemiologic Evidence

Anderson and Cook (1997) and the California Environmental Protection Agency (Cal/EPA 1997, 2005) have provided systematic reviews of the effects of secondhand smoke exposure on SIDS. The 1997 Cal/EPA review identified and selected 10 epidemiologic studies with the best data that examined the relationship between secondhand smoke and SIDS. On the basis of the the results from the quantitative meta-analysis and the qualitative review of results on paternal and other smokers in the household, Anderson and Cook (1997) concluded that the epidemiologic evidence points to a causal relationship between SIDS and postnatal exposure to tobacco smoke.

The discussion that follows includes a review of the epidemiologic studies that examined the association between household secondhand smoke exposure and SIDS among postpartum infants. Consideration was given to the most appropriate study design that controlled for the confounding factors that are critical

to delineating the independent risk related to secondhand smoke exposure and SIDS among postpartum infants. Because researchers have established the causal risk of maternal smoking during pregnancy (USDHHS 2001, 2004), there are epidemiologic studies that provide appropriate controls in the study design for the analysis of prenatal maternal smoking and other potentially important confounding factors (e.g., infant's sleeping position and birth weight, parental use of drugs or alcohol, and the potentially synergistic effect of maternal smoking and bed sharing) (Lahr et al. 2005). Although self-reported information on the smoking behaviors of adults living in the household is an indirect measure of the potential for exposing a newborn to secondhand smoke, researchers evaluate analyses of postnatal secondhand smoke exposure from the father or other smokers in the household because these studies have the potential to more fully control for the possible confounding of maternal smoking during pregnancy. Table 5.5 provides a summary of the design, methods, and findings of the Anderson and Cook (1997) meta-analysis and of the nine primary studies identified in that review, which evaluated the risks of postnatal maternal or paternal smoking. Table 5.5 also includes the four epidemiologic studies that were published subsequent to the review by Anderson and Cook (1997). The methodology varied across these studies; many used autopsies to determine that SIDS was the likely cause of death. The "Comments" column of Table 5.5 provides other important methodologic aspects of each study. Only one study evaluated maternal exposure to secondhand smoke during pregnancy (Klonoff-Cohen et al. 1995), and only one study used urinary cotinine levels to biochemically validate secondhand smoke exposures among newborns (Dwyer et al. 1999). Many studies controlled for potential confounders that included sleeping position, parental bed sharing, social class, parental use of drugs or alcohol, birth weight, gestational age, and prenatal maternal smoking.

Of the 13 individual studies in Table 5.5 that examined the association between household secondhand smoke exposure and SIDS among postpartum infants, 10 studies independently examined the effects of postpartum maternal smoking. Each study found a significant association between postnatal maternal smoking and SIDS (Bergman and Wiesner 1976; McGlashan 1989; Schoendorf and Kiely 1992; Mitchell et al. 1993, 1997; Klonoff-Cohen et al. 1995; Ponsonby et al. 1995; Blair et al. 1996; Brooke et al. 1997; Dwyer et al. 1999). Two of the studies did not consider potential confounders (Bergman and Wiesner 1976; McGlashan 1989), and three studies did not adjust for maternal smoking during pregnancy (Ponsonby et al. 1995; Brooke et al. 1997; Dwyer et al. 1999). Among the four studies (and five samples, including the separate analyses for Whites and Blacks within the Schoendorf and Kiely [1992] study) with more complete adjustments for important confounders such as prenatal maternal smoking, the adjusted ORs for postnatal maternal smoking were all statistically significant. The ORs ranged from 1.65 (95 percent CI, 1.20–2.28) (Mitchell et al. 1993) and 1.75 (95 percent CI, 1.04–2.95) for White infants and 2.33 (95 percent CI, 1.48–3.67) for Black infants (Schoendorf and Kiely 1992), to 2.28 (95 percent CI, 1.04–4.98) (Klonoff-Cohen et al. 1995) and 2.39 (95 percent CI, 1.01–6.00), respectively (Ponsonby et al. 1995). In one study that controlled for prenatal maternal smoking in addition to many other factors in a multivariate model, the effect for postnatal maternal smoking was no longer significant ($p = 0.16$), possibly because of the strong correlation between maternal smoking during pregnancy and postnatal smoking (Blair et al. 1996). However, this study observed a significant OR for the additive effect of postnatal maternal smoking to the risk of smoking during pregnancy (OR = 2.93 [95 percent CI, 1.56–5.48]). The remaining three studies in Table 5.5 (Mitchell et al. 1991; Nicholl and O'Cathain 1992; Alm et al. 1998) were included because they provide additional data on paternal and other smoking in the household or on dose-response relationships.

Two studies provided data that assessed exposure of the infant to secondhand smoke with greater precision than with classification by the postpartum smoking status of the mother alone (Klonoff-Cohen et al. 1995; Dwyer et al. 1999). Dwyer and colleagues (1999) assessed urinary cotinine levels in 100 infants as part of a prospective study of more than 10,000 births in the Tasmanian Infant Health Survey. Of the 53 mothers who reported postnatal smoking, only 32 reported smoking sometimes or always in the same room as the infant. Maternal smoking in the same room significantly increased infant urinary cotinine levels ($p < 0.0001$) and the OR of the risk of SIDS (1.96 [95 percent CI, 1.01–3.80]). Klonoff-Cohen and colleagues (1995) collected more extensive interview data on sources of infant exposure to tobacco smoke from the mother, father, and other live-in adults, including data on whether the person smoked in the

Table 5.5 Studies of secondhand smoke exposure and sudden infant death syndrome (SIDS)

Study	Design/population	Exposure categories	Source of exposure
Bergman and Wiesner 1976	Case-control (56 cases, 86 controls, matched for gender, race [all Caucasian], and date of birth) United States (King county, Washington state) 1970–1974	• Mother smoked after pregnancy • Father smoked	• Mother and father
McGlashan 1989	Case-control (167 cases, 334 controls, matched for gender, born in same hospital, and proximate date of birth) Australia (Tasmania) 1980–1986	• Smoking status of parents • Cigarettes/day smoked by mother (habitual, during pregnancy, and during the infant's first year)	• Mother and father
Mitchell et al. 1991	Case-control (128 cases, 503 controls randomly selected from all births) New Zealand 1987–1988	• Cigarettes/day smoked by mother during the 2 weeks before the interview	• Mother
Nicholl and O'Cathain 1992	Case-control (303 cases, 277 controls, matched for date and place of birth) United Kingdom 1976–1979	• Prenatal and postnatal smoking status of the mother's partner	• Mother's partner
Schoendorf and Kiely 1992	Case-control (435 cases ≥2,500 grams [g], 6,098 controls ≥2,500 g) All infant deaths were from causes other than SIDS Sample was stratified by race: Black infants (103 cases, 2,423 controls) White infants (89 cases, 1,987 controls) Data from the National Maternal and Infant Health Survey United States 1988	• None (no prenatal or postnatal maternal smoking), mother smoked after pregnancy (secondhand), and mother smoked during and after pregnancy (combined) • Secondhand smoke exposure from other household members (none vs. any)	• Mother (smoked prenatally and postpartum) • Other household members (smoking status at time of survey)

Outcome	Findings	Comments
SIDS	Maternal smoking OR* = 2.42 (95% CI†, 1.22–4.82) Paternal smoking OR = 1.53 (95% CI, 0.78–3.01) Unadjusted	Exposure data were self-reported (mailed questionnaire); all cases were autopsied; OR and CI were calculated from prevalence estimates provided in the paper; exposure to secondhand smoke appears to enhance the risk of SIDS; potential confounders were not assessed
SIDS	Father was habitual smoker RR‡ = 1.73 (p = 0.05) Mother smoked during infant's first year RR = 2.20 (p <0.01) During infant's first year, mother smoked >10 cigarettes/day: RR = 2.37 (p <0.05) >20 cigarettes/day: RR = 3.11 (p <0.05)	Exposure data were self-reported (interview); all cases were autopsied; RR was based on statistical analysis of case-2 matched control "triples"; dose-response for level of paternal smoking was noted but RR was not reported; parental smoking carries a high relative risk for SIDS
SIDS	In the past 2 weeks, mother smoked 1–9 cigarettes/day: OR = 1.87 (95% CI, 0.98–3.54) 10–19 cigarettes/day: OR = 2.64 (95% CI, 1.47–4.74) ≥20 cigarettes/day: OR = 5.06 (95% CI, 2.86–8.95) Unadjusted	Exposure data were self-reported (interview); all cases were autopsied; maternal smoking is an independent risk factor for SIDS
SIDS	Neither mother nor her partner smoked during pregnancy 1.0 (reference) Mother did not smoke during pregnancy, partner did smoke prenatally and postnatally RR = 1.63 (95% CI, 1.11–2.40)	Exposure data were self-reported (interview); all cases were autopsied; adjusted for birth weight, maternal age and gravidity, and condition of the family's housing; RR for paternal smoking increased over 4 age-at-death intervals; postnatal secondhand smoke exposure from the father plays a role in the risk of SIDS
SIDS	<u>From mothers</u> Black infants Secondhand: OR = 2.33 (95% CI, 1.48–3.67) Combined: OR = 3.06 (95% CI, 2.19–4.29) White infants Secondhand: OR = 1.75 (95% CI, 1.04–2.95) Combined: OR = 3.10 (95% CI, 2.27–4.24) Adjusted for marital status and maternal age and education <u>From other household members (none vs. any)</u> Black infants (by mother's smoking category) None: OR = 1.00 (95% CI, 0.62–1.58) Secondhand: OR = 1.03 (95% CI, 0.43–2.47) All infants: OR = 0.93 (95% CI, 0.68–1.27) White infants None: OR = 1.33 (95% CI, 0.77–2.27) Secondhand: OR = 1.63 (95% CI, 0.58–4.74) All infants: OR = 1.41 (95% CI, 1.04–1.90) Adjusted for marital status and maternal age and education	Race of infant defined as Black non-Hispanic and White non-Hispanic; control variables were selected from birth certificates; survey questionnaire was completed by the mother; possible bias in self-reported smoking behaviors of case and control mothers; 92% of cases were autopsied; both intrauterine and secondhand smoke exposures are associated with an increased risk of SIDS

Table 5.5 Continued

Study	Design/population	Exposure categories	Source of exposure
Mitchell et al. 1993	Case-control (485 cases, 1,800 controls randomly selected from all births) Data from the New Zealand Cot Death Study 1987–1990	• Mother smoked during pregnancy • Father smoked during the past 2 weeks • Other household members smoked during the past 2 weeks • Cigarettes/day smoked by mother during the past 2 weeks, stratified by father's smoking status	Smoking in the past 2 weeks by • Mother • Father • Other household members
Klonoff-Cohen et al. 1995	Case-control (200 cases, 200 controls) United States (southern California) 1989–1992	• Postpartum secondhand smoking status of household members was assessed using multiple methods including any smoking, quantity smoked, smoking in same rooom as the infant, number of hours spent smoking around the infant	• Mother • Father • Other adult live-in residents • Day care providers

Outcome	Findings	Comments
SIDS	Maternal smoking OR = 1.65 (95% CI, 1.20–2.28) Paternal smoking OR = 1.37 (95% CI, 1.02–1.84) Smoking by other household members OR = 1.17 (95% CI, 0.84–1.63) Adjusted for region, time of day, infant's age, maternal marital status, infant's gender, socioeconomic status, birth weight, infant's race, season, maternal age, sleeping position, bed sharing, breastfeeding, and maternal smoking during pregnancy; also adjusted for either maternal smoking during pregnancy, paternal smoking in the 2 weeks before the interview, or smoking by other household members in the past 2 weeks <u>Father did not smoke</u> In the past 2 weeks, mother smoked 0 cigarettes: 1.0 (reference) 1–19 cigarettes/day: OR = 2.56 (95% CI, 1.73–3.75) ≥20 cigarettes/day: OR = 3.43 (95% CI, 2.04–5.77) <u>Father smoked</u> In the past 2 weeks, mother smoked 0 cigarettes: OR = 1.0 (95% CI, 0.64–1.56) 1–19 cigarettes/day: OR = 4.40 (95% CI, 3.26–5.95) ≥20 cigarettes/day: OR = 7.40 (95% CI, 4.92–11.13) Unadjusted	Extended the Mitchell et al. 1991 study using similar methods; exposure data were from obstetric records and self-reports (interview); autopsies were carried out in 474/485 (97.7%) of SIDS cases; infants of smoking mothers who were breastfed had a lower risk than infants of mothers who were not; secondhand smoke exposure is causally related to SIDS
SIDS	Maternal smoking Any: OR = 2.28 (95% CI, 1.04–4.98) In same room as infant: OR = 4.62 (95% CI, 1.82–11.77) Paternal smoking Any: OR = 3.46 (95% CI, 1.91–6.28) In same room as infant: OR = 8.49 (95% CI, 3.33–21.63) Smoking by other live-in adults Any: OR = 2.18 (95% CI, 1.09–4.38) In same room as infant: OR = 4.99 (95% CI, 1.69–14.75) All combined household smoking Any: OR = 3.50 (95% CI, 1.81–6.75) In same room as infant: OR = 4.99 (95% CI, 2.35–10.99) <u>Exposure to cigarettes from all sources (mother, father, live-in adults, and day care providers</u> Total number of household smokers One: OR = 3.00 (95% CI, 1.51–5.97) Two: OR = 5.31 (95% CI, 1.94–14.54) Three–four: OR = 5.13 (95% CI, 0.72–36.61) Number smoking in same room as infant One: OR = 3.67 (95% CI, 1.66–8.13) Two–four: OR = 20.91 (95% CI, 4.02–108.7) Total daily cigarette exposure 1–10: OR = 2.40 (95% CI, 1.06–5.44) 11–20: OR = 3.62 (95% CI, 1.50–8.75) ≥20: OR = 22.67 (95% CI, 4.80–107.2)	Exposure data were self-reported (interview); all reported ORs were adjusted for birth weight (in grams), routine sleep position, medical conditions at birth, prenatal care, breastfeeding, and maternal smoking during pregnancy; breastfeeding was protective in nonsmokers but not in smokers; secondhand smoke exposure in the same room as an infant increases the risk for SIDS; risk of SIDS associated with secondhand smoke exposure was similar among different racial groups

Table 5.5 Continued

Study	Design/population	Exposure categories	Source of exposure
Ponsonby et al. 1995	Case-control (58 cases, 62 age- and region-matched controls, 58 age-, region-, and birth weight-matched controls) Australia (Tasmania) 1988–1991	• Postpartum smoking status of mother	• Mother
Blair et al. 1996	Case-control (195 cases, 780 controls, 4 per case matched for age) United Kingdom (Southwest, Yorkshire, and Trent) 1993–1995	• Smoking status of mother, father, and others in household • Number of smokers in household • Number of cigarettes smoked daily in household	Postpartum exposure from • Mother • Father • Other household members
Anderson and Cook 1997	Meta-analysis Systematic qualitative review of epidemiologic evidence (studies were identified by electronically searching EMBASE[§] and Medline) 39 relevant studies were assessed (43 papers)	• Maternal prenatal and postnatal smoking	• Mother

Outcome	Findings	Comments
SIDS	Mother smoked postnatally (full multivariate model) OR = 2.39 (95% CI, 1.01–6.00) Mother smoked postnatally (multivariate model excluding family history of asthma) OR = 3.10 (95% CI, 1.36–7.09)	Exposure data were self-reported (questionnaire); all cases were autopsied; adjusted for maternal age, usual sleeping position, employment status, and family history of asthma; postpartum maternal smoking is a predictor of SIDS
SIDS	<u>Parental smoking status</u> Only father smoked: OR = 3.41 (95% CI, 1.98–5.88) Only mother smoked: OR = 7.01 (95% CI, 3.91–12.56) Both parents smoked: OR = 8.41 (95% CI, 5.08–13.92) Adjusted for maternal smoking during pregnancy <u>Multivariate analysis</u> Postnatal paternal smoking, additive to maternal smoking OR = 2.50 (95% CI, 1.48–4.22) Adjusted for mother's age, mothers without partners, parity, multiple births, short gestation, socioeconomic status, sleeping position, maternal alcohol consumption, parental use of illegal drugs, parental bed sharing, breastfeeding, and birth weight Postnatal paternal smoking, additional adjustment for maternal smoking during pregnancy Nonsignificant (p = 0.1601) <u>Number of smokers at home</u> 1 smoker: OR = 2.44 (95% CI, 1.36–4.37) 2 smokers: OR = 5.15 (95% CI, 3.24–8.21) >2 smokers: OR = 10.43 (95% CI, 3.34–32.54) <u>Cigarettes/day smoked at home</u> 1–19 cigarettes/day: OR = 2.47 (95% CI, 1.29–4.73) 20–39 cigarettes/day: OR = 3.96 (95% CI, 2.40–6.55) >39 cigarettes/day: OR = 7.57 (95% CI, 4.00–14.32) <u>Infant's daily exposure to tobacco smoke (hours)</u> 1–2: OR = 1.99 (95% CI, 1.14–3.46) 3–5 : OR = 3.84 (95% CI, 1.97–7.48) 6–8: OR = 6.78 (95% CI, 3.17–14.49) >8: OR = 8.29 (95% CI, 4.28–16.05)	Exposure data were self-reported (questionnaire); multivariate analysis found nonsignificant effect for other smoking members of household; unclear if postnatal dose-response analyses adjusted for maternal prenatal smoking or other confounding factors; dose-response analyses were limited to households where smoking was allowed in the same room as the infant; exposure to secondhand smoke in the home has an independent effect on the risk of SIDS
SIDS	Prenatal maternal smoking OR = 2.08 (95% CI, 1.96–2.21) Postnatal maternal smoking OR = 1.94 (95% CI, 1.55–2.43)	Pooled adjusted ORs were calculated using a fixed effects model; calculated results are also available using a random effects model; results are also available for pooled unadjusted ORs; the relationship between maternal smoking and SIDS is almost certainly causal—maternal smoking doubled the risk

Table 5.5 Continued

Study	Design/population	Exposure categories	Source of exposure
Brooke et al. 1997	Case-control (147 cases, 276 controls, 2 controls per case from births immediately before and after index case, thus matched for age, season, and maternity unit) Scotland 1992–1995	• Smoking status of mother and father	• Mother and father
Mitchell et al. 1997	Case-control (232 cases, 1,200 population controls) New Zealand 1991–1993	• Maternal cigarettes/day and paternal smoking status when infant was 2 months old	• Mother and father
Alm et al. 1998	Case-control (244 cases, 869 controls, matched for gender, date of birth, and hospital) Denmark, Norway, and Sweden 1992–1995	• Postnatal household secondhand smoke exposure	• Mother • Father • Other household members

Outcome	Findings	Comments
SIDS	Only father smoked OR = 2.12 (95% CI, 0.99–4.55) Only mother smoked OR = 5.05 (95% CI, 1.85–13.77) Both parents smoked OR = 5.19 (95% CI, 2.26–11.91)	Exposure data were self-reported (questionnaire); all cases were autopsied; adjusted for sleeping position, old mattress, maternal age, deprivation score, moved under sheets, maternal marital status, social class, use of cot bumper, sleeping with parents, symptoms in previous week, gestational age, was usually swaddled in previous week, history of infant death in family, sweaty upon waking, warmth, maternal education, beastfeeding, parity, and birth weight; parental smoking is confirmed as a modifiable risk factor for SIDS
SIDS	Maternal smoking (at 2 months home visit) 0 cigarettes/day: 1.0 (reference) 1–19 cigarettes/day: OR = 4.90 (95% CI, 2.65–9.06) ≥20 cigarettes/day: OR = 21.42 (95% CI, 6.89–66.52) Paternal smoking (at 2 months home visit) No: 1.0 (reference) Yes: OR = 3.21 (95% CI, 1.81–5.71) Risks from maternal/paternal smoking combinations Nonsmoking mother Smoking father: OR = 1.54 (95% CI, 0.67–3.45) Smoking mother: Nonsmoking father: OR = 4.15 (95% CI, 2.05–8.38) Smoking father: OR = 10.09 (95% CI, 5.89–17.37) Adjusted OR (maternal smoking and bed sharing Nonsmoking/no bed sharing: 1.0 (reference) Nonsmoking/bed sharing: OR = 1.03 (95% CI, 0.21–5.06) Smoking/no bed sharing: OR = 1.43 (95% CI, 0.58–3.51) Smoking/bed sharing: OR = 5.02 (95% CI, 1.05–24.05) Adjusted for maternal age, marital status, age mother left school, number of previous pregnancies, infant's gender, ethnicity of infant, birth weight, sleep position, breasfeeding, and the combination of bed sharing and maternal smoking	Exposure data were self-reported (interviews conducted at postpartum and at 2 months postpartum); maternal smoking and bed sharing increase risk; maternal smoking is a significant risk factor for SIDS
SIDS	Maternal postnatal smoking OR = 3.7 (95% CI, 2.5–5.5) Paternal postnatal smoking OR = 1.2 (95% CI, 0.8–1.9) Smoking by other household members (after pregnancy) OR = 1.2 (95% CI, 0.6–2.2)	Exposure data were self-reported (questionnaire); all cases were autopsied; adjusted for age, maternal age, and maternal education; exposure to secondhand smoke is an independent risk factor for SIDS

Table 5.5 Continued

Study	Design/population	Exposure categories	Source of exposure
Dwyer et al. 1999	Nested case-control study with prospective cohort study (35 cases, 9,765 controls); urinary samples for cotinine analysis were collected from 105 infants (August–October 1995) Australia (Tasmania) 1988–1995	• Postnatal household secondhand smoke exposure	• Mother • Other household members

*OR = Odds ratio.
†CI = Confidence interval.
‡RR = Relative risk.
§EMBASE = Excerpta Medica Database.

same room as the infant and the number of hours the adult spent smoking in the presence of the infant. Although the researchers did not report the proportion of smoking mothers who smoked in the same room as the infant, the OR for any maternal postpartum smoking was 2.28 (95 percent CI, 1.04–4.98), adjusted for birth weight, routine sleeping position, medical conditions at birth, prenatal care, breastfeeding, and prenatal maternal smoking. The adjusted OR increased to 4.62 (95 percent CI, 1.82–11.77) when limited to mothers who reported smoking in the same room as the infant.

Of the 10 studies that independently evaluated postnatal maternal smoking, researchers observed a significant dose response in risk with the level of postnatal maternal smoking in the unadjusted ORs from 5 studies (Bergman and Wiesner 1976; McGlashan 1989; Mitchell et al. 1993, 1997; Dwyer et al. 1999), and in other measures of overall household postnatal smoking levels (maternal, paternal, and/or other) from 2 studies (Klonoff-Cohen et al. 1995; Blair et al. 1996). One study examined the risk of SIDS associated with increasing levels of postnatal exposure to cigarettes from all sources in three ways: total number of household smokers, total cigarette exposure per day, and the number of adults smoking in the same room as the infant (Klonoff-Cohen et al. 1995). Using these three approaches to classify increasing exposures of newborns to secondhand smoke, the investigators estimated unadjusted and adjusted ORs (controlling for birth weight, routine sleeping position, medical conditions at birth, prenatal care, breastfeeding, and maternal smoking during pregnancy). Although the OR was decreased slightly for one measure (total number of household smokers) by adjustment for other factors, the adjusted ORs for the other two measures were somewhat stronger than the unadjusted measures. The adjusted ORs were 3.67 (95 percent CI, 1.66–8.13) if one adult smoked in the same room as the infant, and 20.91 (95 percent CI, 4.02–108.7) if two to four adults smoked in the same room as the infant compared with infants from nonsmoking households. Using the total cigarette exposure per day as the measure of exposure, the OR for 1 to 10 cigarettes in comparison with nonsmoking households was 2.40 (95 percent CI, 1.06–5.44), which increased to 22.67 (95 percent CI, 4.80–107.2) for 21 or more cigarettes per day.

Nine studies examined paternal smoking as a source of exposure to secondhand smoke (Bergman and Wiesner 1976; McGlashan 1989; Nicholl and O'Cathain 1992; Mitchell et al. 1993, 1997; Klonoff-Cohen et al. 1995; Blair et al. 1996; Brooke et al. 1997; Alm et al. 1998). Three of the nine (McGlashan 1989;

Outcome	Findings	Comments
SIDS	Postnatal smoking Maternal postnatal smoking (breastfed infants) OR = 5.29 (95% CI, 1.16–24.11) Maternal postnatal smoking (bottle-fed infants) OR = 2.35 (95% CI, 0.73–7.62) Smoking by other household members OR = 0.69 (95% CI, 0.34–1.40) Dose-response of maternal postnatal smoking None (no maternal postnatal smoking): OR = 1.0 1–10 cigarettes/day: OR = 2.80 (95% CI, 1.08–7.27) 11–20 cigarettes/day: OR = 3.01 (95% CI, 1.22–7.42) ≥21 cigarettes/day: OR = 5.31 (95% CI, 2.04–13.81)	Exposure data are from self-reports (interview) and from urinary cotinine measures (results from n = 100); all cases were autopsied; adjusted for breastfeeding, birth weight, and smoking in same room as infant; analyses of postnatal smoking among 34 cases and 9,464 controls; cotinine data provide estimates of exposure levels by self-reported categories; there is a positive association between maternal smoking and SIDS, but cannot separate risks from prenatal and postnatal smoking

Mitchell et al. 1997; Alm et al. 1998) observed a significant risk for SIDS from paternal smoking without adjustment for several potential confounding factors, including maternal smoking during pregnancy. Four of the remaining six studies reported significantly higher risks of SIDS among infants whose fathers were smokers compared with infants whose fathers were nonsmokers (Nicholl and O'Cathain 1992; Mitchell et al 1993; Klonoff-Cohen et al. 1995; Blair et al. 1996). The fifth and sixth studies reported an association of borderline significance (OR = 1.76, $p < 0.20$) (Bergman and Wiesner 1976) and (OR = 2.12 [95 percent CI, 0.99–4.55]) (Brooke et al. 1997). Across the five studies with controls for maternal smoking, ORs ranged from 1.37 to 3.46, with the higher OR in the study with the stronger assessment of infant exposure to paternal smoking (Klonoff-Cohen et al. 1995). This study also reported an OR of 8.49 (95 percent CI, 3.33–21.63) for infants of fathers who smoked in the same room compared with infants of nonsmoking fathers, after adjustment for birth weight, routine sleeping position, medical conditions at birth, prenatal care, breastfeeding, and maternal smoking during pregnancy (Klonoff-Cohen et al. 1995). Five studies that measured paternal smoking provided the opportunity to examine secondhand smoke among families where the mothers were nonsmokers. Of the four studies that evaluated households with smoking fathers and nonsmoking mothers compared with nonsmoking households, two studies reported significant ORs and one study reported a borderline significance for the risk of SIDS. Blair and colleagues (1996) reported an OR of 3.41 (95 percent CI, 1.98–5.8); Nicholl and O'Cathain (1992) reported an OR of 1.63 (95 percent CI, 1.11–2.40); and Brooke and colleagues (1997) reported an adjusted OR of 2.12 (95 percent CI, 0.99–4.55). In the study with nonsignificant results for paternal smoking (OR = 1.54 [95 percent CI, 0.67–3.45]), smoking by both parents significantly increased the risk above maternal smoking only (OR = 10.09 [95 percent CI, 5.89–17.37] versus 4.15 [95 percent CI, 2.05–8.38]) (Mitchell et al. 1997). In a case-control study, Alm and colleagues (1998) reported that when the mother did not smoke during pregnancy but the father smoked after pregnancy, the OR was 1.2 (95 percent CI, 0.8–1.9) compared with nonsmoking parents. The results reported by Mitchell and colleagues (1997) and Alm and colleagues (1998) suggest that postnatal paternal exposure has a stronger effect if it augments the effect of prenatal maternal smoking. However, the significant effects for paternal smoking noted by

Mitchell and colleagues (1993), Klonoff-Cohen and colleagues (1995), and Blair and colleagues (1996), adjusting for prenatal maternal smoking and compared with households with nonsmoking mothers, indicate a likely effect from exposure to postnatal paternal smoking that is independent of prenatal maternal smoking. In addition, as noted above for maternal smoking, data from the two studies that provided more complete assessments of the infant's exposure (Klonoff-Cohen et al. 1995; Dwyer et al. 1999) suggest that using the smoking status of the father as an indirect indicator for exposure of the infant to tobacco smoke may result in a misclassification that would bias the estimated risk downward. Specifically, Klonoff-Cohen and colleagues (1995) reported that the adjusted OR for paternal smoking increased from 3.46 (95 percent CI, 1.91–6.28), based on the postpartum smoking status of the father, to 8.49 (95 percent CI, 3.33–21.63) when the father smoked in the same room as the infant.

Assessments of postnatal exposures from "other" smokers in the household are likely subject to more misclassification errors and may thus provide a weaker measure of exposure. In addition, sometimes these "other" exposures were reported for "other than maternal," thus including paternal smoking. Of the six studies that examined such "other" smoker estimates of postnatal exposure, two included smoking fathers in the "other" category and found nonsignificant overall effects (Schoendorf and Kiely 1992; Dwyer et al. 1999). But one of the studies that limited the "other" category to "mother's partner or other adult sometimes or always smokes while in the same room as infant" reported an OR of 1.96 (95 percent CI, 1.01–3.80) (Dwyer et al. 1999, p. 596). Four studies excluded postnatal parental smoking in the assessment of smoking by other adult residents (Klonoff-Cohen et al. 1995; Blair et al. 1996; Mitchell et al. 1997; Alm et al. 1998). Each of these studies observed a statistically significant effect without adjustment for other confounders; three of the studies provided adjusted ORs. The one study without adjustment found a weak dose-response effect for the amount smoked by others, but found an unadjusted OR of 4.12 (95 percent CI, 1.85–9.08) for 20 or more cigarettes per day smoked by other members of the household (excluding the parents) (Blair et al. 1996). Of the three studies with adjusted ORs, two were nonsignificant: 1.17 (95 percent CI, 0.84–1.63) (Mitchell et al. 1997) and 1.2 (95 percent CI, 0.6–2.2) (Alm et al. 1998); one remained significant: 2.18 (95 percent CI, 1.09–4.38) (Klonoff-Cohen et al. 1995). In this study by Klonoff-Cohen and colleagues (1995), the OR for other live-in adults who smoked in the same room as the infant was 4.99 (95 percent CI, 1.69–14.75), adjusted for birth weight, routine sleeping position, medical conditions at birth, prenatal care, breastfeeding, and maternal smoking during pregnancy.

A recent report by the European Concerted Action on SIDS (ECAS) provides additional supportive evidence (Carpenter et al. 2004). ECAS conducted a multicenter case-control study involving 745 SIDS cases (all with autopsies) and two or more live-birth controls per case (n = 2,411) matched by age and survey area. The multivariate analysis confirmed a significant increase in risk for SIDs after adjusting for sleeping position, older maternal age, more previous live births, and lower birth weight. The multivariate analysis of maternal smoking and household postnatal smoking (controlling for sleeping position, maternal age, number of previous live births, birth weight, and other variables) found no significant increase in risk for SIDs associated with bed sharing among mothers who did not smoke (OR = 1.56 [95 percent CI, 0.91–2.68]), but a highly significant risk associated with bed sharing among mothers who smoked (OR = 17.7 [95 percent CI, 10.3–30.3]). Among mothers who did not bed share, postnatal maternal smoking (unadjusted for prenatal smoking) significantly increased the risk of SIDs (<10 cigarettes per day, OR = 1.52 [95 percent CI, 1.10–2.09]; ≥10 cigarettes per day, OR = 2.43 [95 percent CI, 1.76–3.36]). In the multivariate analysis (adjusting for all of the above factors including maternal smoking but not prenatal smoking directly), researchers observed a risk associated with postnatal smoking by others in the household that increased from an OR of 1.07 (95 percent CI, 0.71–1.61) for 1 to 9 cigarettes per day to 1.54 (95 percent CI, 1.11–2.14) for 10 to 19 cigarettes per day, 1.73 (95 percent CI, 1.21–2.48) for 20 to 29 cigarettes per day, and 3.31 (95 percent CI, 1.84–5.96) for 30 or more cigarettes per day. These data provide additional evidence that postnatal smoking by other adults in the household independently increases the risk of SIDS.

Three studies used a case-control design to evaluate nicotine or cotinine as a biomarker of exposure at postmortem examinations in relation to the risk for SIDS. Rajs and colleagues (1997) measured nicotine and cotinine in pericardial fluid of SIDS and non-SIDS victims, all younger than one year of age at the time of their death. Mean values were similar in the two groups, but the children who died from SIDS included a greater proportion with cotinine values above 30 ng/mL. In a 1998 report based on a study with a similar design, Milerad and colleagues (1998) documented higher cotinine levels in children younger than seven years of age who had died suddenly compared with controls who had died of an infection. Because involuntary smoking increases the risk for childhood respiratory infection, the use of this control group may have underestimated the association of cotinine with a risk for sudden death. In addition, the inclusion of children up to seven years of age extends well beyond the traditional newborn period associated with SIDS. Finally, McMartin and colleagues (2002) compared lung tissue concentrations of nicotine and cotinine in deceased SIDS and non-SIDS infants who were younger than one year of age when they died. Both nicotine and cotinine concentrations were higher in the lungs of the SIDS victims.

Evidence Synthesis

The biologic evidence, especially from animal models, indicates multiple mechanisms by which exposure to secondhand smoke could cause SIDS (Chapter 2, Toxicology of Secondhand Smoke). The evidence for secondhand smoke exposure and the risk of SIDS consistently demonstrates an association between postpartum maternal smoking and SIDS (Table 5.5). The 1997 meta-analysis of 39 relevant studies produced an adjusted OR for postnatal maternal smoking of 1.94 (95 percent CI, 1.55–2.43), a level of risk that the authors concluded was almost certainly causal (Anderson and Cook 1997). Data from the four studies in Table 5.5 published since the 1997 meta-analysis add additional support for this conclusion. Nine of the thirteen studies in Table 5.5 more fully controlled for the major potential confounders (e.g., maternal smoking during pregnancy and routine sleeping position), and many controlled for a broad range of other relevant factors including maternal age, birth weight, and bed sharing. The nine studies all observed significant positive associations between postpartum maternal smoking and SIDS. Moreover, several studies demonstrated a dose-response relationship for secondhand smoke exposure attributable to postpartum maternal smoking, with increasing ORs for higher levels of postpartum maternal smoking. Finally, among the studies of postnatal maternal smoking with better adjustment for confounding, the adjusted ORs are sufficiently large, all greater than 1.5 and three of the five greater than 2.0. These ORs make it unlikely that this association is attributable to any residual confounding from unmeasured factors.

The epidemiologic evidence for secondhand smoke exposure from postpartum maternal smoking associated with the risk of SIDS is consistent and strong, and demonstrates a dose-response relationship. Evidence for secondhand smoke exposures from fathers and "other" smokers (as well as higher concentrations of nicotine and cotinine in children who die from SIDS compared with children who die of other causes) provides additional supporting evidence that secondhand smoke exposure increases the risk of SIDS. Although measures of paternal and "other" smokers in the household are not typically considered to be a comprehensive indicator of the infant's exposure to secondhand smoke, designs that can evaluate paternal smoking have the potential to more fully control for the possible confounding of maternal smoking during pregnancy. However, when considering evidence that supports an association between SIDS and paternal and "other" smokers, researchers also recognize the possible misclassification of actual infant exposures to tobacco smoke from these sources (Klonoff-Cohen et al. 1995; Dwyer et al. 1999). Despite this methodologic challenge, researchers observed an elevated OR in all nine studies of paternal smoking, ranging from 1.4 to 3.5, with many estimates around 2 or higher. Of these nine studies, five observed an elevated OR for households where the fathers smoked compared with households where neither parent smoked, and an OR of 8.5 for infants of fathers who smoked in the same room as the infant, adjusting for maternal smoking during pregnancy, routine sleeping position, and other factors. Also, out of the nine studies that examined paternal smoking, five found a statistically significant association between paternal smoking and SIDS after adjusting for maternal smoking during

pregnancy. Despite the potential for misclassification bias linking paternal smoking to an actual exposure of the infant to secondhand smoke, the pooled risk estimate was 1.9 (95 percent CI, 1.01–2.80) from the five studies of paternal smoking with stronger designs that used meta-analytic approaches and random effects modeling. Finally, all of the studies of "other" smokers in the household observed an elevated OR; however, the results that adjusted for maternal smoking during pregnancy and other important confounders were more mixed. The one study with the strongest assessment of infant exposures from "other" smoking residents (i.e., live-in adults smoking in the same room as the infant) reported an OR of 4.99 (95 percent CI, 1.69–14.75), with adjustment for multiple risk factors including maternal smoking during pregnancy and routine sleeping position (Klonoff-Cohen et al. 1995).

Researchers have established prenatal maternal smoking as a major preventable risk for SIDS (USDHHS 2001, 2004; AAP Task Force on SIDS 2005). Evidence indicates that exposure of infants to secondhand smoke from postpartum maternal smoking has a significant additive effect on risk if the mother smoked during pregnancy. In studies that accounted for maternal smoking during pregnancy, evidence indicates that postpartum maternal smoking, particularly in proximity to the infant, significantly increases the risk of SIDS. In addition, epidemiologic evidence indicates that postnatal exposure of infants to secondhand smoke from fathers or other live-in smokers can also increase the risk of SIDS. Thus, the full range of biologic and epidemiologic data are consistent and indicate that exposure of infants to secondhand smoke causes SIDS.

Conclusion

1. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and sudden infant death syndrome.

Implications

On the basis of the epidemiologic risk data, researchers have estimated that the population attributable risk of SIDS associated with postnatal exposure to secondhand smoke is about 10 percent (Cal/EPA 2005). Therefore, the evidence indicates that these exposures are one of the major preventable risk factors for SIDS, and all measures should be taken to protect infants from exposure to secondhand smoke.

There is a need for additional research to further characterize the risk of SIDS associated with prenatal and postnatal exposure to secondhand smoke, and to evaluate the relationship between maternal smoking and infant sleeping positions and bed sharing. Future research should also focus on better assessments of actual exposures of infants to secondhand smoke using biochemical assessments and/or more detailed interviews, rather than indirect assessments based on the smoking status of household adults. Because of the continuing and significant racial disparities in infant mortality from SIDS (Malloy and Freeman 2004), there is a need to study the preventable risks factors that could be involved.

Preterm Delivery

Biologic Basis

Pregnancy complications, including premature labor, placenta previa, abruptio placentae, and premature membrane rupture may lead to preterm delivery (<37 completed weeks of gestation). Although the underlying mechanisms are not yet fully characterized, maternal active smoking is associated with these pregnancy complications (U.S. Department of Health, Education, and Welfare [USDHEW] 1979b; USDHHS 1980, 2001; Andres and Day 2000). Preterm delivery is also associated with active maternal smoking (USDHEW 1979a; USDHHS 1980, 2001; van den Berg and Oechsli 1984; Andres and Day 2000). Smoking cessation during pregnancy appears to reduce the risk for preterm delivery (van den Berg and Oechsli

1984; Li et al. 1993; Mainous and Hueston 1994b; USDHHS 2001), placenta previa (Naeye 1980), abruptio placentae (Naeye 1980), and premature membrane rupture (Harger et al. 1990; Williams et al. 1992); but the risk remains high for those who continue to smoke throughout pregnancy. Tobacco-specific nitrosamines and cotinine have been measured in the cervical mucus of women who were active smokers and women who were nonsmokers (McCann et al. 1992; Prokopczyk et al. 1997). Given that active maternal smoking is associated with preterm delivery, this finding provided further support for the biologic plausibility that secondhand smoke has a role in the injurious processes leading to preterm delivery. Although the biologic pathway from active maternal smoking to preterm delivery is not clear, the evidence for this association is strong enough to infer that maternal secondhand smoke exposure may also lead to preterm delivery.

Epidemiologic Evidence

Few data are available on the effects of maternal secondhand smoke exposure on preterm delivery, and published findings are inconsistent across studies. Four studies did not find a statistically significant association between maternal secondhand smoke exposure and preterm delivery (Table 5.6) (Martin and Bracken 1986; Ahlborg and Bodin 1991; Mathai et al. 1992; Fortier et al. 1994), but several others did report significantly increased risks with exposure to secondhand smoke (Ahluwalia et al. 1997; Hanke et al. 1999; Windham et al. 2000; Jaakkola et al. 2001). Hanke and colleagues (1999) reported an adjusted OR of 1.86 (95 percent CI, 1.05–3.45) for preterm delivery among nonsmoking mothers who were exposed to secondhand smoke for at least seven hours per day compared with unexposed mothers. Using the same secondhand smoke exposure category—exposed for at least seven hours per day—Windham and colleagues (2000) found an adjusted OR of 1.6 (95 percent CI, 0.87–2.9) for exposed, nonsmoking mothers compared with unexposed mothers. The risk increased to 2.8 (95 percent CI, 1.2–6.6) among women aged 30 or more years. Similarly, Ahluwalia and colleagues (1997) classified secondhand smoke exposure dichotomously as yes/no and also found an increased risk among nonsmoking women aged 30 or more years for preterm delivery when exposed to secondhand smoke (OR = 1.88 [95 percent CI, 1.22–2.88]), but the risk was not observed among nonsmoking women younger than 30 years of age (OR = 0.92 [95 percent CI, 0.76–1.13]). Jaakkola and colleagues (2001) used the hair nicotine level, a biologic measure of exposure to secondhand smoke among nonsmoking women. Those with the highest hair concentrations of nicotine (≥4.0 μg/gram [g]) had an adjusted OR of 6.12 (95 percent CI, 1.31–28.7) for preterm delivery when compared with women with the lowest or undetectable concentrations of hair nicotine. The limited epidemiologic evidence on maternal secondhand smoke exposure and preterm delivery currently does not warrant a meta-analysis of the relevant studies.

Evidence Synthesis

The few studies that have evaluated the association between secondhand smoke exposure and preterm delivery have shown inconsistent findings. Of the four studies that found significant associations, two studies documented that the risk was significant only for women aged 30 years or older. Jaakkola and colleagues (2001) provided the strongest evidence for an association using hair nicotine measurements, which reduce the probability of exposure misclassification. There is a biologic basis for considering this association to be causal.

Conclusion

1. The evidence is suggestive but not sufficient to infer a causal relationship between maternal exposure to secondhand smoke during pregnancy and preterm delivery.

Implications

Further research should be carried out, although studies of substantial size will be needed.

Table 5.6 Studies of secondhand smoke exposure and preterm delivery

Study	Design/population	Source of exposure	Outcome	Exposure categories
Martin and Bracken 1986	3,891 antenatal women seen between 1980 and 1982	Home and work, ≥2 hours/day	Preterm delivery	Yes/no
Ahlborg and Bodin 1991	4,687 prenatal women between October 1980 and June 1983	Home only Work only Both	Preterm delivery	Yes/no
Mathai et al. 1992	994 nonsmoking women receiving obstetric care at a hospital between January and May 1990	Home	Preterm delivery	Yes/no
Fortier et al. 1994	Sample of 4,644 women delivering between January and October 1989	Home only Work only Both	Preterm delivery	Yes/no
Ahluwalia et al. 1997	17,412 low-income women who received services from public maternal and child health clinics	Household members	Preterm delivery	Yes/no
Hanke et al. 1999	1,751 nonsmoking women from a randomly selected group of women who gave birth between June 1996 and May 1997	Home Work Other	Preterm delivery	No exposure 0–1 hour/day 2–3 hours/day 4–6 hours/day ≥7 hours/day
Windham et al. 2000	4,454 pregnant women in their first trimester at their first prenatal appointment through a health plan	Home and work	Preterm delivery Very preterm (<35 weeks)	No exposure: 0 to <0.5 hour/day Moderate exposure: 0.5–6.5 hours/day N = 625 High exposure: ≥7 hours/day N = 134
Jaakkola et al. 2001	389 nonsmoking women who gave birth between May 1996 and April 1997	Home and work	Preterm delivery	Hair nicotine concentrations: <0.75 μg/g[Δ] 0.75 to <4.0 μg/g ≥4.0 μg/g

*RR = Relative risk.
†CI = Confidence interval.
‡OR = Odds ratio.
§AOR = Adjusted odds ratio.
Δμg/g = Micrograms per gram.

Findings	Comments
4.64% in unexposed nonsmokers 4.66% in exposed nonsmokers	No change in crude findings using regression analysis (data were not presented); secondhand smoke exposure showed no effect on preterm delivery
RR* = 0.49 (95% CI†, 0.23–1.06) RR = 1.86 (95% CI, 1.0–3.48) RR = 0.84 (95% CI, 0.53–1.33)	Adjusted; secondhand smoke exposure in the workplace was weakly associated with preterm birth
3.8% in unexposed nonsmokers 5.8% in exposed nonsmokers	Not statistically significant (data were not presented)
OR‡ = 0.93 (95% CI, 0.58–1.51) OR = 0.92 (95% CI, 0.64–1.31) OR = 0.98 (95% CI, 0.56–1.73)	Adjusted; secondhand smoke exposure was not related to preterm birth
Nonsmokers aged <30 years OR = 0.92 (95% CI, 0.76–1.13) Nonsmokers aged ≥30 years OR = 1.88 (95% CI, 1.22–2.88)	The association between secondhand smoke exposure and adverse pregnancy outcomes appears to be modified by maternal age
AOR§ = 0.54 (95% CI, 0.77–4.45) AOR = 1.24 (95% CI, 0.68–2.27) AOR = 1.73 (95% CI, 0.86–3.19) AOR = 1.86 (95% CI, 1.05–3.45)	Urine cotinine was measured in 71 women to verify nonsmoking status; maternal secondhand smoke exposure lasting ≥7 hours was a significant risk factor for preterm delivery; adjusted for maternal age, height, parity, employment, and marital status
Nonsmokers, high secondhand smoke exposure Preterm: AOR = 1.6 (95% CI, 0.87–2.9) Very preterm: AOR = 2.4 (95% CI, 1.0–5.3) Aged <30 years, high secondhand smoke exposure Preterm: AOR = 1.1 (95% CI, 0.46–2.6) Very preterm: AOR = 2.2 (95% CI, 0.75–6.6) Aged ≥30 years, high secondhand smoke exposure Preterm: AOR = 2.8 (95% CI, 1.2–6.6) Very preterm: AOR = 2.7 (95% CI, 0.74–9.7)	High secondhand smoke exposure was moderately associated with preterm birth and most strongly associated with very preterm birth; adjusted by logarithmic regression for prior pregnancy history, race, body mass index, life events, and education
AOR = 1.30 (95% CI, 0.30–5.58) AOR = 6.12 (95% CI, 1.31–28.7)	Adjusted for gender, birth order, maternal age, body mass index before pregnancy, marital status, socioeconomic status, alcohol consumption during pregnancy, and employment during pregnancy; results suggest an increase in the risk of preterm delivery

Low Birth Weight

Biologic Basis

Low birth weight (LBW), defined as less than 2,500 g or less than 5.5 pounds, can result from preterm delivery or intrauterine growth retardation (IUGR), which can occur simultaneously in a pregnancy. Reduced fetal physical growth during gestation, or IUGR, can lead to a small for gestational age (SGA) infant (≤10th percentile of expected birth weight for a given gestational age) that is either preterm or full term (≥37 weeks of gestation), and may or may not be LBW. The established link between active maternal smoking and LBW is known to occur mainly through IUGR rather than through premature birth (Chamberlain 1975; Coleman et al. 1979; Wilcox 1993). Fetal growth is greatest during the third trimester, and studies of active smoking during pregnancy demonstrate no reduction of infant birth weight if smoking ceases before the third trimester (USDHHS 1990, 2004). In 2003, 12.4 percent of births among smokers were LBW (Martin et al. 2005).

A number of researchers have postulated that the limitation of fetal growth from active maternal smoking comes from reduced oxygen to the fetus, which is directly attributable to CO exposure and nicotine-induced vasoconstriction leading to reduced uterine and umbilical blood flow (USDHHS 1990, 2004; Bruner and Forouzan 1991; Rajini et al. 1994; Lambers and Clark 1996; Werler 1997; Andres and Day 2000). Studies have shown elevated nucleated red blood cell counts, a marker of fetal hypoxia, among neonates of women who actively smoked during pregnancy (Yeruchimovich et al. 1999) and among women who were exposed to secondhand smoke (Dollberg et al. 2000). Several investigators have also found elevated erythropoietin, the protein that stimulates red blood cell production and another indicator of hypoxia, in cord blood of newborns whose mothers had smoked during pregnancy (Jazayeri et al. 1998; Gruslin et al. 2000). Because erythropoietin does not cross the placenta, it most likely originated from the fetus. A number of researchers have also reported that the concentration of erythropoietin is positively correlated with the concentration of cotinine measured in cord blood ($r = 0.41$, $p = 0.04$) (Gruslin et al. 2000), the number of cigarettes smoked per day by the mother ($r = 0.26$, $p < 0.0001$) (Jazayeri et al. 1998), and fetal growth retardation (r was not presented, $p < 0.01$) (Maier et al. 1993).

Studies have detected nicotine and its metabolites perinatally in umbilical cord serum in infants born to nonsmoking mothers, and in the cervical mucus of nonsmoking women; consequently, many researchers agree that the information on active maternal smoking is directly relevant to understanding the possible association of maternal secondhand smoke exposure and preterm delivery and LBW (USDHHS 2001). More direct evidence supports the hypothesis that maternal secondhand smoke exposure, specifically to nicotine, may lead to LBW through a pathway of fetal hypoxia (Çolak et al. 2002). One would expect attenuated physiologic effects from exposures to secondhand smoke than from active smoking based on relative dose levels, but the same biologic mechanisms of effect may apply.

Epidemiologic Evidence

A large body of literature is available on secondhand smoke exposure and LBW (Table 5.7). The first studies that reported an association were conducted in the 1960s (MacMahon et al. 1965; Comstock and Lundin 1967; Underwood et al. 1967; Terris and Gold 1969). These early studies found reductions in mean birth weight that ranged from 3 g (Underwood et al. 1967) to 42 g (Comstock and Lundin 1967) (CIs were not calculated) among infants with fathers who smoked compared with infants of nonsmoking fathers. A few relevant studies were published in the 1970s (Yerushalmy 1971; Mau and Netter 1974; Borlee et al. 1978), and one showed a statistically significant association. Borlee and colleagues (1978) found that the mean birth weight of infants of nonsmoking mothers and smoking fathers was 228 g less than the mean birth weight of infants with two nonsmoking parents. This study has been criticized, however, because the study population came from a case-control study of infants with malformations, and some evidence now indicates that both LBW (Xiao 1989; Xu 1992; Lin 1993; Samuelsen et al. 1998) and paternal smoking (Knorr 1979; Davis 1991; Savitz et al. 1991; Zhang et al. 1992; Fraga et al. 1996; Wasserman et al. 1996) are associated with birth defects.

Interest in the topic of LBW and secondhand smoke grew in the 1980s after the association between active maternal smoking during pregnancy and LBW had been established (USDHHS 1980; Stillman et al. 1986). Several investigators have reported RR estimates and adjusted OR estimates from studies published in the last two decades. These estimates have ranged from an OR of less than 1.0 (Sadler et al. 1999; Matsubara et al. 2000) to an OR of 2.31 (Mainous and Hueston 1994a) and, as a whole, have suggested that having a LBW infant is associated with maternal exposure to secondhand smoke. Some investigators have compared mean birth weights of infants whose mothers were exposed to secondhand smoke with infants of unexposed mothers. The results from these studies showed reductions in birth weights among the exposed groups that ranged from 1 g (Sadler et al. 1999; Haug et al. 2000) to 253 g (Luciano et al. 1998). In a 1998 meta-analysis of 11 studies, Peacock and colleagues (1998) found that the mean birth weight for infants of secondhand smoke-exposed mothers was 31 g less (95 percent CI, 19–44) than infants of unexposed mothers. Similarly, in a 1999 meta-analysis of secondhand smoke and LBW literature (19 studies), the summary estimates were an OR of 1.2 for LBW at term or SGA (95 percent CI, 1.1–1.3), and a difference in mean adjusted birth weights of -28 g (95 percent CI, -41 to -16) for infants of nonsmoking mothers exposed to secondhand smoke compared with infants of unexposed mothers (Windham et al. 1999a). The 1999 meta-analysis included most of the studies that were in the earlier 1998 analysis, plus a retrospective study of 992 nonsmoking pregnant women contacted by Windham and colleagues. The estimated reductions for the meta-analysis in mean birth weight were statistically significant in both meta-analyses, but a reduction of 30 g (approximately 1.24 ounces) would not be clinically significant to individual infants at low risk. On a population level, however, a slight shift in the birth weight distribution could put infants already at risk into greater risk for complications associated with LBW.

Some investigators have evaluated dose-response associations using cotinine or nicotine measures (Haddow et al. 1988; Nafstad et al. 1998), self-reported levels of exposure to secondhand smoke (Zhang and Ratcliffe 1993; Mainous and Hueston 1994a), or both (Rebagliato et al. 1995b). Of the five studies that examined these trends, findings in two studies (Haddow et al. 1988; Mainous and Hueston 1994a) suggested that a dose-response relationship exists between secondhand smoke exposure and birth weight. Haddow and colleagues (1988) measured maternal serum cotinine during the second trimester and found higher levels among nonsmoking mothers whose infants had lower mean birth weights. The adjusted mean birth weights were 3,535 g, 3,531 g, and 3,481 g for low, medium, and high cotinine levels, respectively. These results led Haddow and colleagues (1988) to "suggest that the linear model may not best reflect the true dose-response relationship" (p. 484). The difference in adjusted mean birth weights between the low- and high-exposure groups was statistically significant ($p < 0.001$). Mainous and Hueston (1994a) obtained secondhand smoke exposure information from the 1988 National Health Interview Survey and found statistically significant trends between increasing levels of maternal secondhand smoke exposure and an increase in proportions of LBW infants ($p = 0.01$) and a decrease in mean birth weights ($p = 0.007$).

Although the other three studies that evaluated dose-response relationships did not find any trends, two of those studies did find evidence of an association between maternal secondhand smoke exposure and reduced birth weight. Nafstad and colleagues (1998) measured hair nicotine levels and found that nonsmoking mothers whose nicotine levels were within the two middle quartiles were at an increased risk for having a SGA child compared with nonsmoking mothers whose nicotine levels were within the lowest quartile (OR = 3.4 [95 percent CI, 1.3–8.6]). For nonsmoking mothers with hair nicotine levels in the highest quartile, the estimated risk of having a SGA child was 2.1 (95 percent CI, 0.4–10.1). Zhang and Ratcliffe (1993) used paternal smoking as a measure of exposure to secondhand smoke and found that, compared with infants from the unexposed group, the exposed group had a mean birth weight that was 30 g lower. The mean birth weights did not decrease in a linear or monotonic manner with increasing exposure levels. Rebagliato and colleagues (1995b) also examined dose-response associations and did not find any significant trends with exposures at home, at work, from the partner, from all reported sources combined, or with measured cotinine levels. Increases in maternal exposures to secondhand smoke in public places, however, did show a significant dose-response trend with decreases in mean birth weights ($p = 0.028$).

Another means of looking for an exposure-response trend is by dividing exposure sources into home and work. One would expect that

Table 5.7 Summary of published literature on secondhand smoke and low birth weight (LBW)

Study Location	Design	Population size	Source of secondhand smoke	Cotinine measure	Findings
MacMahon et al. 1965 United States	Cohort	12,192	Husband	NR*	• Mean birth weight difference: -0.7 ounces (oz.) in boys • Mean birth weight difference: -0.8 oz. in girls • No association
Comstock and Lundin 1967 United States	Cohort	448	Husband	NR	• Mean birth weight difference: -42 g† • No association
Underwood et al. 1967 United States	Cohort	24,674	Husband	NR	• Mean birth weight difference: -3 g • No association
Terris and Gold 1969 United States	Case-control	197 197	Husband	NR	• No significant difference • No association
Yerushalmy 1971 United States	Cohort	13,000	Husband	NR	• Significant association with LBW among Whites but not among Blacks • Possible association
Mau and Netter 1974 Germany	Cohort	3,696	Husband	NR	• RR = 1.2 for IUGR‡ • RR = 1.4 for LBW • No significant association
Borlee et al. 1978 Belgium	Cohort	238	Husband	NR	• Mean birth weight difference: -228 g (statistically significant) • Significant association
Hauth et al. 1984 United States	Cohort	163	All (serum thiocyanate)	NR	• No difference in birth weights for infants of involuntary smokers compared with those of nonsmokers • No association
Magnus et al. 1984 Norway	Cohort	3,130	Husband	NR	• Mean birth weight difference: -4.9 (standard deviation = 9.3) per 10 cigarettes/day • No association
Karakostov 1985 Bulgaria	Cohort	NR	NR	NR	• Mean birth weight difference: -84 g • Mean height difference: -0.5 cm§ • No significant association
Martin and Bracken 1986 United States	Cohort	4,186	Both home and work	NR	• Mean birth weight difference: -23.5 g (95% CI△, -59.9–12.8) • RR¶ = 2.17 (95% CI, 1.05–4.50)
Rubin et al. 1986 Denmark	Cohort	500	Husband	NR	• Mean birth weight difference: -120 g/pack/day • Mean birth weight difference: -6.1 g/cigarette/day ($p < 0.03$) • RR = 2.17 (95% CI, 1.05–4.50)

Table 5.7 Continued

Study Location	Design	Population size	Source of secondhand smoke	Cotinine measure	Findings
MacArthur and Knox 1987 Britain	Cohort	180	Husband	NR	• Mean birth weight difference: 123 g ($p < 0.02$) • No association
Schwartz-Bickenbach et al. 1987 Germany	Cohort	38	Home	Breast milk and infant's urine	• Mean birth weight difference: -200 g • Association
Campbell et al. 1988 Britain	Cohort	518	Husband	NR	• Mean birth weight difference: -113 g (95% CI, -216 to -8), $p = 0.03$ • Significant association
Haddow et al. 1988 United States	Cohort	1,231	Both home and work	Serum	• Mean birth weight difference: -108 g ($p < 0.0001$) • 29% had LBW • Sufficient evidence for an association (possible nonlinear dose-response)
Brooke et al. 1989 Britain	Cohort	1,018	Home	NR	• -0.5% in birth weight ratio ($p = 0.56$) • Mean birth weight difference: -18 g • No association
Chen et al. 1989 China	Cohort	1,058	Home	NR	• Mean birth weight difference: -15 g ($p = 0.92$) • 0.7% had LBW ($p = 0.67$) • No association
Ueda et al. 1989 Japan	Cohort	259	Both home and work	Maternal urine, umbilical cord blood	• No specified findings • Significant association
Lazzaroni et al. 1990 Italy	Cohort	1,002	Both home and work	NR	• Mean birth weight difference: -16 g/hour/day of secondhand smoke exposure ($p < 0.07$); -38.16 g (95% CI, -106.9–30.7) overall birth weight • -0.26 cm (95% CI, -5.6–0.03) overall length • Possible association
Mathai et al. 1990 Britain	Cohort	300	Home	Urine	• Mean birth weight difference: -66 g (questionnaire) • Nonsignificant association
Ahlborg and Bodin 1991 Sweden	Cohort	4,687	Both home and work	NR	• RR = 0.99 (95% CI, 0.45–2.21) for both home and work • RR = 0.69 (95% CI, 0.21–2.27) for home only • RR = 1.09 (95% CI, 0.33–3.62) for work only • RR = 1.83 (95% CI, 0.53–6.28) for work in the third trimester • Nonsignificant association

Table 5.7 Continued

Study Location	Design	Population size	Source of secondhand smoke	Cotinine measure	Findings
Ogawa et al. 1991 Japan	Cohort	5,336	Both home and work	NR	• Mean birth weight difference: -24 g (95% CI, -5 to -54) • RR for IUGR = 1.0 (95% CI, 0.7–1.5) • No association
Saito 1991 Japan	Cohort	3,025	Husband	NR	• RR = 1.21 • Significant association
Mathai et al. 1992 India	Cohort	994	Both home and work	NR	• Mean birth weight difference: -63 g (95% CI, -114 to -12) • Significant association
Pan 1992 China	Cohort	253	Husband	NR	• Higher SGA** rate in the exposed group • No specified association
Zhang and Ratcliffe 1993 China	Cohort	1,785	Husband	NR	• Mean birth weight: -30 g (95% CI, -66–7) • LBW: 0.17% • SGA: 0.20% • Possible association
Fortier et al. 1994 Canada	Cohort	4,644	Both home and work	NR	• OR†† = 0.94 (95% CI, 0.60–1.49) for both home and work • OR = 0.98 (95% CI, 0.67–1.44) for home only • OR = 1.18 (95% CI, 0.90–1.56) for work only • Nonsignificant association/inconclusive
Mainous and Hueston 1994a United States	Cohort	3,253	Both home and work	NR	• Mean birth weight difference: -84 g • 3.6% had LBW • OR for LBW = 1.59 (95% CI, 0.92–2.73) • OR for LBW in non-Whites = 2.31 (95% CI, 1.06–4.99) • Association with high exposure (threshold effect)
Martinez et al. 1994 United States	Cohort	1,219	Husband	Cord serum	• Mean birth weight difference: -88 g • Significant association
Chen and Petitti 1995 United States	Case-control	111 124	Both home and work	NR	• OR = 0.50 (95% CI, 0.14–1.74) • No association
Eskenazi et al. 1995 United States	Cohort	3,896	NR	Serum	• Mean birth weight difference: -42 g • RR for LBW = 1.35 (95% CI, 0.60–3.03) • Nonsignificant association

Table 5.7 Continued

Study Location	Design	Population size	Source of secondhand smoke	Cotinine measure	Findings
Rebagliato et al. 1995b Spain	Cohort	710	Both home and work	Saliva	• Mean birth weight difference: -88 g (measured by cotinine); -41 g (questionnaire) • Nonsignificant association
Roquer et al. 1995 Spain	Cohort	76	Both home and work	NR	• Mean birth weight difference: -192 g • Association
Jedrychowski and Flak 1996 Poland	Cohort	1,165	NR	Serum	• Mean birth weight difference: -73.1 g • Significant association
Ahluwalia et al. 1997 United States	Cohort	17,412	Home	NR	• Mothers aged <30 years Mean birth weight difference: -8.8 g (95% CI, -43.7–26.1) • Mothers aged ≥30 years Mean birth weight difference: 90.0 g (95% CI, -0.8–180.9) • Inconclusive for SGA • Association for LBW in the group aged ≥30 years
Dejin-Karlsson et al. 1998 Sweden	Cohort	872	Both home and work	NR	• OR for SGA = 2.3 (95% CI, 1.1–4.6) • OR for LBW = 1.3 (95% CI, 0.7–2.5) • SGA crude OR in nonsmokers = 2.4 (95% CI, 1.02–5.8)
Luciano et al. 1998 Italy	Cohort	112	Both home and work	NR	• Mean birth weight difference: -253.5 g
Nafstad et al. 1998 Norway	Case-control	58 105	Both home and work	Hair	• OR in nonsmokers = 1.4 (95% CI, 0.4–4.4)
Hanke et al. 1999 Poland	Cohort	1,751	Both home and work	NR	NR
Sadler et al. 1999 United States	Cohort	2,283	Both home and work	NR	• OR for SGA = 0.82 (95% CI, 0.51–1.33) • Mean birth weight difference: -1.2 g (95% CI, -43.3–41.0)
Windham et al. 1999a United States	Cohort	992	Husband	NR	• OR for LBW = 1.8 (95% CI, 0.64–4.8) • OR for SGA = 1.4 (95% CI, 0.79–2.5)
Haug et al. 2000 Norway	Cohort	34,799	Husband	NR	• Mean birth weight difference: -1 g • No association
Matsubara et al. 2000 Japan	Cohort	7,411	Husband Both home and work	NR	Husband RR for LBW = 0.92 (95% CI, 0.71–1.20) RR for IUGR = 0.95 (95% CI, 0.72–1.26) Both home and work RR for LBW = 0.99 (95% CI, 0.77–1.30) RR for IUGR = 0.95 (95% CI, 0.71–1.26) No association

Table 5.7 Continued

Study Location	Design	Population size	Source of secondhand smoke	Cotinine measure	Findings
Windham et al. 2000 United States	Cohort	4,454	Both home and work	NR	• Adjusted OR for LBW = 1.8 (95% CI, 0.82–4.1) • Moderate association
Jaakkola et al. 2001 Finland	Cohort	389	Both home and work	Postpartum maternal hair nicotine	• OR for LBW = 1.06 (95% CI, 0.96–1.17) • OR for SGA = 1.04 (95% CI, 0.92–1.19) • Nonsignificant association

*NR = Data were not reported.
†g = Grams.
‡IUGR = Intrauterine growth retardation.
§cm = Centimeters.
ΔCI = Confidence interval.
¶RR = Relative risk.
**SGA = Small for gestational age.
††OR = Odds ratio.

combined exposures from both sources would lead to greater risks of LBW than would exposure from only one of the two sources, but Ahlborg and Bodin (1991) did not find this to be the case. The adjusted RR for LBW among nonsmokers with any secondhand smoke exposure either at home or at work was 0.99 (95 percent CI, 0.45–2.21), but the risks with exposure in the home only and in the workplace only were 0.69 (95 percent CI, 0.21–2.27) and 1.09 (95 percent CI, 0.33–3.62), respectively. Similarly, Fortier and colleagues (1994) did not find any exposure-response trend for SGA when risks were estimated for secondhand smoke exposure in the home only (OR = 0.98 [95 percent CI, 0.67–1.44]), at work only (OR = 1.18 [95 percent CI, 0.90–1.56]), and at both home and work (OR = 0.94 [95 percent CI, 0.60–1.49]). For any exposure either at home or at work, the estimated risk for SGA was 1.09 (95 percent CI, 0.85–1.39).

Evidence Synthesis

The risk estimates for secondhand smoke exposure and LBW have generally been small and have been consistent with the expectation that exposure to secondhand smoke should produce a smaller effect than exposure to active smoking. Most studies show a reduction in the mean birth weight and an increased risk for LBW among infants whose mothers were exposed to secondhand smoke. Across the studies, diverse potential confounding factors have been considered. Despite the lack of statistical significance in many of the studies, the consistencies seen in the literature have been summarized in several published reviews and have provided the strongest argument for an association between secondhand smoke and LBW. There are several plausible mechanisms by which secondhand smoke exposure could influence birth weight. Three comprehensive reviews of the literature on secondhand smoke and LBW that were published in the past decade all found a small increase in risk for LBW or SGA associated with secondhand smoke exposure (Misra and Nguyen 1999; Windham et al. 1999a; Lindbohm et al. 2002). Based on all of the studies that reported on LBW at term or SGA and secondhand smoke exposure, a meta-analysis provided a weighted pooled risk estimate of 1.2 (95 percent CI, 1.1–1.3) for this association (Windham et al. 1999a). Given the published review and meta-analysis by Windham and colleagues (1999a), an updated meta-analysis of the relevant studies on maternal secondhand smoke exposure and birth weight currently is not warranted.

Conclusion

1. The evidence is sufficient to infer a causal relationship between maternal exposure to secondhand smoke during pregnancy and a small reduction in birth weight.

Implications

Secondhand smoke exposure represents an avoidable contribution to birth weight reductions. Women, when pregnant, should not smoke or be exposed to secondhand smoke.

Congenital Malformations

Biologic Basis

Because of the direct fetal effects observed with exposure to tobacco smoke and because of the chemically complex and teratogenic nature of cigarette smoke, researchers have addressed the association between exposure to tobacco smoke and congenital malformations. Most of this literature has focused on active smoking during pregnancy by the mother, but a few studies have examined secondhand smoke exposure. The etiology of most congenital malformations is not fully elaborated (Werler 1997), and no studies have been conducted to identify the mechanisms by which exposure to secondhand smoke may result in congenital malformations in humans. The few studies that have assessed the effects of sidestream smoke in animals have produced little evidence to support an association of secondhand smoke exposure and malformations (NCI 1999). Some recent studies suggest that susceptibility to some malformations may depend in part on the presence of genes that increase susceptibility to tobacco smoke (Wyszynski et al. 1997). Other proposed mechanisms include teratogenic effects of high concentrations of carboxyhemoglobin and nicotine, or malformations that are the result of exposure to some yet unidentified component of the tobacco plant shown to be teratogenic if ingested by animals (Seidman and Mashiach 1991).

The evidence on the relationship between maternal smoking during pregnancy and congenital malformations is inconsistent. Most studies have reported no association between maternal smoking and congenital malformations as a whole. However, for selected malformations, particularly oral clefts, several studies have reported positive associations with active smoking during pregnancy by the mother (Little et al. 2004a,b; Meyer et al. 2004). In fact, recent studies on gene-environment interactions have furthered the etiologic understanding of oral clefts and the role of smoking (Hwang et al. 1995; Shaw et al. 1996; van Rooij et al. 2001, 2002; Lammer et al. 2004).

Epidemiologic Evidence

Of six studies that collected data on involuntary smoking and congenital malformations, two had very large sample sizes (Table 5.8). Holmberg and Nurminen (1980) examined occupational exposures among parents of infants born with congenital malformations and of control infants matched for date of birth and geographic area in Finland from 1976 to 1978. The researchers found that the distribution of paternal smoking around the time that the woman became pregnant was similar in the cases with CNS defects and their matched controls. Savitz and colleagues (1991) analyzed data collected between 1964 and 1967 on children five years of age from the Child Health and Development Studies (N = 14,685). The researchers examined 33 different malformations in relation to paternal smoking and 4 malformations—cleft lip with or without cleft palate, hydrocephalus, ventricular septal defect, and urethral stenosis—for dose-response relationships. Although prevalence ORs were 2.0 or greater for selected outcomes, the lower 95 percent confidence limits reached below 1.0 once adjustments for potential confounders were made for maternal smoking, maternal age, maternal race, and maternal education. These selected outcomes were hydrocephalus (OR = 2.4 [95 percent CI, 0.06–9.3]), ventricular septal defect (OR = 2.0 [95 percent CI, 0.9–4.3]), and urethral stenosis (OR = 2.0 [95 percent CI, 0.6–6.4]). Strabismus (OR = 0.7 [95 percent CI, 0.5–0.9]) and pyloric stenosis (OR = 0.2 [95 percent CI, 0.2–0.8]), however, occurred in significantly fewer infants with smoking fathers compared with infants of nonsmoking fathers.

Table 5.8 Studies of secondhand smoke exposure and congenital malformations

Study	Design/population	Exposure categories	Source of exposure
Holmberg and Nurminen 1980	Case-control (200) Children who were reported to the national birth defects registry and matched controls Finland	NR*	• Paternal secondhand smoke • Mothers were nonsmokers
Seidman et al. 1990	Retrospective cohort (17,152) Women on first or second postpartum day Israel	0 packs/day <1 pack/day ≥1 pack/day	• Maternal prenatal
Savitz et al. 1991	Prospective longitudinal (14,685) Children enrolled in Child Health and Development Studies between 1964 and 1967 in the San Francisco East Bay area of California United States	<20 cigarettes/day ≥20 cigarettes/day	• Paternal secondhand smoke
Zhang et al. 1992	Case-control (2,024) Birth defects were identified in the Shanghai Municipality during October 1986–September 1987 China	Nonsmokers 1–9 cigarettes/day 10–19 cigarettes/day ≥20 cigarettes/day	• Paternal
Shaw et al. 1996	Population-based case-control study Mothers of infants with orofacial cleft (731) and nonmalformed controls (734)	0 cigarettes/day 1–19 cigarettes/day ≥20 cigarettes/day	• Paternal periconceptional

Outcome	Findings	Comments
Congenital defects of the CNS[†]	• No significant association was found between smoking and CNS defects	All data were self-reported through maternal interviews; smoking was not the primary aim of the study; no adjustments were made except for maternal smoking status
Congenital anomalies	• No correlation was found between smoking behaviors and malformations of the cardiovascular, gastrointestinal, and CNS, or incidence of hypospadias • Slightly higher but not statistically significant incidence of cleft palate, cleft lip, spina bifida, and genitourinary system anomalies • Together with increased age (>35 years), smoking increased the risk of congenital malformations ($p < 0.002$) • Maternal age alone was associated with congenital malformations ($p < 0.005$)	Reproductive histories were self-reported through maternal interviews; maternal smoking may be a preventable risk factor for congenital anomalies among mothers aged ≥35 years
Congenital anomalies	• Urethral stenosis (POR[‡] = 2.4 [95% CI, 0.7–8.5]), cleft lip, and cleft palate (POR = 1.9 [95% CI, 0.5–7.3]) were more commonly seen in children of fathers who were heavy smokers	Source exposure data were reported through maternal intake interviews; assessment of paternal age, smoking, and alcohol consumption on fetal birth outcomes; outcomes were assessed independently by two physicians; this study does not strongly support the hypothesis that paternal smoking behavior is associated with birth defects
Congenital anomalies	• A modest relationship was detected between overall birth defects and paternal smoking behavior (OR[§] = 1.21 [95% CI, 1.01–1.45]) • Higher overall ORs (not broken down by the amount of exposure) for parental smoking and anencephalus (OR = 2.1), spina bifida (OR = 1.9), pigmentary anomalies of the skin (OR = 3.3), and varus/valgus deformities of the feet (OR = 1.8)	Source exposure data were reported through maternal interviews; a paternally mediated effect of smoking on birth defects is suggested and further research is encouraged
Orofacial cleft	• OR = 2.1 (95% CI, 1.3–3.6) for cleft lip with or without cleft palate and OR = 2.2 (95% CI, 1.1–4.5) for isolated cleft palate when mothers smoked ≥20 cigarettes/day • Clefting risks were even greater for infants with the transforming growth factor α (TGFα), ranging from 3-fold to 11-fold across phenotypic groups in White infants • Paternal smoking was not associated with clefting among the offspring of nonsmoking mothers • Secondhand smoke exposures were associated with slightly increased risks	Parental smoking information was obtained from telephone interviews with mothers; DNA was obtained from newborn screening blood spots and genotyped for the allelic variants of TGFα; controlling for the potential influence of other variables did not reveal substantially different results

Table 5.8 Continued

Study	Design/population	Exposure categories	Source of exposure
Wasserman et al. 1996	Case-control Mothers of infants with conotruncal heart defects (207), neural tube defects (264), limb deficiencies (178), and live-born controls (481)	0 cigarettes/day 1–19 cigarettes/day ≥20 cigarettes/day	• Maternal prenatal and postnatal • Paternal prenatal and postnatal • Home environment • Work environment • Any environment

*NR = Data were not reported.
†CNS = Central nervous system.
‡POR = Prevalence odds ratio.
§OR = Odds ratio.

Seidman and colleagues (1990) conducted immediate postpartum interviews with mothers of 17,152 infants from the three largest obstetrics units in Jerusalem; the data yielded crude ORs that showed no significant associations between paternal smoking and major anomalies (e.g., chromosomal anomalies, CNS anomalies, heart defects, cleft lip with or without cleft palate, omphalocele, diaphragmatic hernia, bowel atresias, hermaphroditism, and conjoined twins). Zhang and colleagues (1992) studied 1,012 infants with birth defects and 1,012 infants without birth defects (control group) from 10 urban districts and 29 hospitals in Shanghai. Mothers were interviewed while in the hospital. Although no adjustments were made for potential confounding variables, the investigators noted that the sample had very few families with characteristics pointing to potential confounders and that the two mothers who smoked were eliminated from the sample. In age-adjusted analyses, the investigators found that paternal smoking was associated with a slightly elevated risk among infants with birth defects (OR = 1.2 [95 percent CI, 1.01–1.45]). The researchers also investigated 25 types of malformations and observed that selected malformations were associated with paternal smoking when dose-response relationships were examined. Infants with pigmentary anomalies of the skin were more likely to have fathers who were moderate smokers (10 to 19 cigarettes per day, OR = 4.1 [95 percent CI, 1.2–14.7]); infants with spina bifida were more likely to have fathers who were heavy smokers (≥20 cigarettes per day, OR = 3.2 [95 percent CI, 1.1–9.2]); and infants with multiple defects were more likely to have fathers who smoked 1 to 9 cigarettes per day (OR = 1.74 [95 percent CI, 1.16–2.61]). Most malformations, however, were not associated with involuntary smoking.

Using maternal interviews, Shaw and colleagues (1996) assessed the association between secondhand smoke exposure during pregnancy and oral clefts. There were conflicting results for nonsmoking mothers exposed to secondhand smoke, with very few significant associations among seemingly small numbers of observations. Wasserman and colleagues (1996) examined associations between secondhand smoke exposure among nonsmoking women and risks for

Outcome	Findings	Comments
Conotruncal heart defects Neural tube defects Limb deficiencies	• OR = 1.9 (95% CI, 1.2–3.1) for conotruncal heart defects when both parents smoked compared with neither • OR = 1.7 (95% CI, 0.96–2.9) for limb deficiencies when both parents smoked compared with neither • No significant increase in risk was associated with maternal smoking in the absence of paternal smoking • An increased risk was associated with heavy paternal smoking in the absence of maternal smoking for limb deficiencies in offspring (OR = 2.1 [95% CI, 1.3–3.6]) • For conotruncal defects, the risks associated with parental smoking differed among racial and ethnic groups • Parental smoking was not associated with increased risks for neural tube defects (Father only, OR = 1.1 [95% CI, 0.76–1.7]; Mother only, OR = 0.56 [95% CI, 0.30–1.0]; Both parents, OR = 1.0 [95% CI, 0.62–1.7])	All data were self-reported through maternal interviews; observed risks did not change substantially when adjusted for maternal vitamin use, alcohol use, and gravidity

heart malformations, neural tube defects, and limb defects. With one exception, secondhand smoke exposure was not associated with these congenital malformations. For tetralogy of Fallot, nonsmoking women exposed at work (but not at home or at "any location") had an OR of 2.9 (95 percent CI, 1.3–6.5) for exposure to secondhand smoke compared with those who were not exposed. However, given the multiple associations examined in this study, and given the inconsistent results for this malformation and the other sources of secondhand smoke, this particular association may have resulted by chance alone.

Evidence Synthesis

The evidence regarding the relationship between involuntary smoking and congenital malformations is inconsistent. The few studies that have been conducted have reported no association between involuntary smoking and specific or all congenital malformations.

Investigating congenital malformations is challenging because of the sample size that is necessary to study specific malformations. To date, few clues are available regarding the hypothesized biologic mechanisms of tobacco smoke and congenital malformations. Although two studies have reported elevated rates of neural tube defects in association with involuntary smoking, this association should be examined further in future studies.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and congenital malformations.

Implications

The topic of tobacco smoke exposure and congenital malformations merits further investigation, particularly in part because of the teratogenic nature of tobacco smoke.

Cognitive, Behavioral, and Physical Development

Biologic Basis

In recent years, studies have suggested that exposure to tobacco smoke during pregnancy and childhood may affect the physical and cognitive development of the growing child. Researchers who examine the effects of these exposures on childhood outcomes need to account for potential confounding factors that reflect the various correlates of secondhand smoke exposure that also affect development. For example, factors that may affect physical and cognitive development include social class, parental education, the home environment as it relates to stimulation and developmentally appropriate exposures, and pregnancy-related factors such as voluntary and involuntary smoking and alcohol and substance use. Birth weight may also be a confounding factor because it is associated with both smoking (voluntary and involuntary) and physical and cognitive development. However, some researchers argue that adjusting for birth weight may overcontrol because it may be in the causal pathway from exposure to tobacco before birth to the time when childhood outcomes are assessed (Baghurst et al. 1992).

Another methodologic challenge lies in differentiating the effects of exposure to tobacco during and after pregnancy. This differentiation is often not possible because of the high correlation of tobacco smoke exposure for these two time periods. Studies with sufficient populations and detailed information on smoking status during both pregnancy and the postpartum period have been able to stratify participants into exposure groups: no prenatal or postpartum exposure, no prenatal but some postpartum exposure, and both prenatal and postpartum exposures. Other studies have examined the effects of secondhand smoke exposure from adults other than the mother among those children whose mothers did not smoke during pregnancy. These categories have served to partially address the timing of the exposures and, in particular, to control for exposures during pregnancy.

The mechanisms by which exposures to secondhand smoke may lead to compromised physical and cognitive development have not been fully explained and may be complex. Some of the mechanisms may be similar to those proposed for maternal smoking during pregnancy, such as hypoxia or the potentially teratogenic effects of tobacco smoke (USDHHS 1990; Bruner and Forouzan 1991; Lambers and Clark 1996; Werler 1997). Studies document that components of secondhand and mainstream smoke are qualitatively similar to those of sidestream smoke, but quantitative data for doses of tobacco smoke components that reach the fetus across the placenta from active and involuntary maternal smoking have not been available (Slotkin 1998). This consideration is particularly important for outcomes assessed after one year of age because the child's exposure will have occurred for a period of time longer than the exposure of the fetus during the nine months of pregnancy.

For cognitive development, investigators have proposed a number of effects on CNS development from smoking in general and nicotine in particular. First, the fetus may suffer from hypoxia as a result of reduced blood flow or reduced oxygen levels (USDHHS 1990; Lambers and Clark 1996). Alterations in the peripheral autonomic pathways may lead to an increased susceptibility to hypoxia-induced, short-term and long-term brain damage (Slotkin 1998). In one review of prenatal nicotine exposure, Ernst and colleagues (2001) summarized numerous animal studies that document the impact of nicotine on cognitive processes of exposed rats and guinea pigs, such as slowed learning or increased attention or memory deficits. These investigators identified animal as well as human studies that have demonstrated adverse effects of nicotine exposure on neural functioning. Exposure to nicotine alters enzyme activity and thus affects brain development, and alters molecular processes that affect neurotransmitter systems and lead to permanent neural abnormalities (Ernst et al. 2001).

Cognitive Development

Epidemiologic Evidence

Twelve studies have examined the effects of secondhand smoke exposure on cognitive development in children (Table 5.9) (Rantakallio 1983; Bauman et al. 1989, 1991; Makin et al. 1991; Baghurst et al. 1992; Roeleveld et al. 1992; Schulte-Hobein et al. 1992; Byrd and Weitzman 1994; McCartney et al. 1994; Olds et al. 1994; Fried et al. 1997, 1998). The age ranges of the children varied from infants to older

adolescents. Hence, the tools used to assess cognitive development also varied and included measures of intelligence, reading and language scores, school grade retention (staying in a grade for an additional year), and various standardized cognitive functioning tests. Four studies found no association between secondhand smoke exposure and cognitive outcomes among infants and children (Baghurst et al. 1992; Schulte-Hobein et al. 1992; McCartney et al. 1994; Fried et al. 1997); four other studies reported findings that varied across outcome measures (Bauman et al. 1991; Makin et al. 1991; Olds et al. 1994; Fried et al. 1998). For example, Makin and colleagues (1991) used standardized assessments to measure skills in the following areas: speech, language, intelligence, and visual and spatial processing. The authors examined involuntary smoking during pregnancy and controlled for potential confounders such as maternal education, maternal age, and family income. Results from 14 specific standardized tests indicated significant differences between exposed and unexposed groups in 11 of the tests. Similarly, Fried and colleagues (1997) examined the effects of prenatal and postpartum secondhand smoke exposures on 131 children aged 9 through 12 years who were given standardized reading and language assessments. For the prenatal period, the investigators considered only those mothers who were not smokers and found no association between prenatal or postpartum exposures and reading skills. For language skills, however, postpartum secondhand smoke exposures were associated with lower language levels among exposed versus the unexposed children (Fried et al. 1997). Several other investigators also reported associations with cognitive development (Rantakallio 1983; Bauman et al. 1989), mental retardation (Roeleveld et al. 1992), or school performance (Byrd and Weitzman 1994). Roeleveld and colleagues (1992) examined cigarette, pipe, and cigar smoking; only secondhand smoke exposures to pipe and cigar smoke during pregnancy and in the first six months of the infant's life were associated with an increased risk for mental retardation. Bauman and colleagues (1989) studied unexposed adolescents and adolescents who had been exposed to secondhand smoke from family members. The investigators examined overall and domain-specific California Achievement Test scores for math, language, reading, and spelling to identify differences between these two groups of adolescents. After considering several potential confounding factors, including active adolescent smoking, the investigators found that test performance decreased as smoking levels of the family increased.

Evidence Synthesis

The literature cited in this discussion examined the effects of involuntary smoking on children's cognitive development. However, it is difficult to synthesize the results of these studies because the ages of the children, the assessed exposures, and the outcomes vary across and even within studies. Moreover, some of the findings across and within studies are inconsistent. Eight of the 12 studies that examined associations between involuntary smoking and children's cognitive development reported associations between secondhand smoke exposures and reduced levels of cognitive development; these investigators had used a variety of assessments, such as performance on standardized tests, grade retention, or a diagnosis of mental retardation. The use of various cognitive measures across studies precludes an assessment of consistency with specific associations. Yet the finding that secondhand smoke exposure was associated with several different outcomes suggests that exposure may, indeed, impact the cognitive development of children. More studies are clearly needed; of the studies that have been conducted, there is a need for additional efforts to replicate findings.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and cognitive functioning among children.

Implications

Further research is needed but there are complex challenges to carrying out such studies, given the need for longitudinal design and consideration of the many factors affecting cognitive functioning.

Behavioral Development

Epidemiologic Evidence

Three studies examined associations between secondhand smoke exposures and behavioral problems among children (Table 5.10) (Makin et al. 1991; Weitzman et al. 1992; Fergusson et al. 1993). Weitzman and colleagues (1992) studied children aged 4 through 11 years and reported that after adjusting for several potential confounders, heavy maternal smoking after delivery was associated with greater behavioral problems reported by the parents.

Table 5.9 Studies of secondhand smoke exposure and cognitive development

Study	Design/population	Exposure categories	Source of exposure
Rantakallio 1983	Prospective cohort (3,392) Mothers who smoked during pregnancy and controls from two northernmost provinces in Finland	• Light smokers (<10 cigarettes/day) • Heavy smokers (≥10 cigarettes/day at end of second month of pregnancy) • Father never smoked • Father formerly smoked • Father currently smoked	• Prenatal and involuntary exposure to parental smoking
Bauman et al. 1989	Secondary data analysis (2,008) Eighth-grade students from Guilford County Public Schools in North Carolina United States	• None • 1 cigarette–1 pack/day • 1–2 packs/day • >2 packs/day • Adolescent CO* levels of ≥9 parts per million, an indication of smoking	• Secondhand smoke exposure to family smoking behaviors • Alveolar breath specimens • Adolescent reports of sibling smoking behaviors
Bauman et al. 1991	Longitudinal cohort (year 5 exam, n = 5,342; year 10 exam, n = 3,737; adolescent exam, n = 2,020) Pregnancies from 1960–1967 among women enrolled in the Kaiser Foundation Health Plan in the San Francisco East Bay area Children were all from the Child Health and Development Studies United States 1987	• Mother smoked at time of exam • Father smoked at time of exam • Average number of cigarettes smoked/day by mother and father	• Parental smoking and in utero exposure from maternal smoking during pregnancy
Makin et al. 1991	Cross-sectional (91 children) Aged 6–9 years Canada (Ottawa)	During pregnancy, mother was • Active smoker • Exposed to secondhand smoke • Nonsmoker, not exposed to secondhand smoke	• Mother • Others

Outcome	Findings	Comments
Respiratory disease School performance Retarded growth	• Children of smoking parents had the most frequent incidences of hospital admissions for respiratory illness ($p < 0.024$) • Significant height reduction among children of smokers at 6 months ($p < 0.001$), 12 months ($p < 0.004$), and 14 years of age ($p < 0.023$) • Controlling for height, children of maternal smokers had highly significantly reduced school performance ($p < 0.001$ by F-test) • Maternal and paternal sources of secondhand smoke exposures had similar associations with physiologic and performance outcomes	Source exposure data were from maternal self-reports (mailed questionnaires), school public health nurses, and hospital admission records from 5–10 years ago; these findings are a subset of overall characteristic studies within this birth cohort; school performance was based on school office reports; maternal smoking had an effect on children's physical and mental development, even when these factors were controlled with regression analysis
Test performance	• Stepwise regression identified 8 significant control variables • Pair-wise interactive analysis identified 6 interactive social and psychologic control variables • Controlling for all 14 variables, a statistically significant relationship remained overall between family smoking and CAT† scores ($p < 0.017$)	Source exposure data were from maternal self-reports; test performance was based on the CAT; CAT test scores significantly decreased as family smoking increased ($p < 0.001$); other potential variables accounting for an observed association may be active maternal smoking during pregnancy, tobacco smoke ingredients other than CO, and short-term exposures to secondhand tobacco smoke
Cognitive performance in 3 testing periods (aged 5, 9–11, and 15–17 years)	• PPVT‡ scores and RAVEN§ scores for children of nonsmoking parents were statistically significant, averaging 5.9% higher than for children of smokers ($p < 0.05$) • Analyses of covariance confirmed that parental smoking had a significant effect on PPVT and RAVEN scores at the 10-year exam • Following adjustments for covariates (e.g., age, low birth weight, race, parental education, and income), a linear dose-response relationship was observed between parental smoking and cognitive performance • No significant interactions were identified between maternal prenatal and current smoking status	Source exposure data were from maternal self-reports; cognitive measurements were made with Goodenough-Harris Drawing test, the Quick Test, PPVT, and RAVEN; husband's smoking status was not measured in one 5-year examination group and in adolescent measurements; child physiologic responses, such as middle-ear effusion and respiratory illness, were related to secondhand tobacco smoke and might influence cognitive performance; family cigarette smoking is associated with selected child cognitive performance skills, and some outcomes exhibited a dose-response relationship with exposure to smoking
Speech and language, intellectual, motor, visual/spatial, academic achievement, and behavior skills	• Children of nonsmoking, unexposed mothers performed better than children of smoking or secondhand smoke-exposed mothers on tests of speech and language skills, intelligence, visual/spatial abilities, and on mother's rating of behavior	Source exposure data were self-reported (interview); children of active and secondhand smoke-exposed mothers are at risk for a pattern of negative developmental outcomes

Table 5.9 Continued

Study	Design/population	Exposure categories	Source of exposure
Baghurst et al. 1992	Prospective cohort (548) Children enrolled in the Port Pine Cohort Study, aged birth to 4 years, whose mothers attended antenatal care between May 1979 and May 1982 Australia	• Nonsmokers (never smoked or smoked ≤5 cigarettes during pregnancy) • Smokers (>5 cigarettes ever)	• Prenatal and involuntary exposures to maternal smoking
Roeleveld et al. 1992	Epidemiologic (628) Cases and referent group were 0–15 years of age, selected from medical files of the Pediatric or Child Neurology Department of Nijmegen University Hospital, or from local rehabilitation centers between 1979 and 1987 Netherlands	• Average number of cigarettes/day reported by parents • Daily amount of paternal pipe or cigar smoking	• Prenatal and secondhand smoke exposures to parental smoking
Schulte-Hobein et al. 1992	Prospective longitudinal matched pair (69 cases, 69 controls) Mothers were selected soon after delivery from 3 maternity hospitals Germany (Berlin)	• Smoked >5 cigarettes/day during pregnancy • Never smoked	• Mother's milk and secondhand smoke exposures during first year of life
Byrd and Weitzman 1994	Cross-sectional data analyses (9,996) Children aged 0–17 years whose parents participated in the National Health Interview Survey, a nationally representative civilian population United States	• Household exposures to cigarette smoke at time of survey	• Maternal prenatal and involuntary exposures

Outcome	Findings	Comments
Neuropsychologic development	• Children with postnatal exposures had significantly lower scores on the MDI[Δ] ($p < 0.03$) and MSCA[¶] verbal ($p < 0.03$), perceptual performance ($p < 0.01$), and motor ($p < 0.01$) • A statistically significant inverse association was found between maternal smoking behavior and neuropsychologic development until other determinants of development were controlled (e.g., gender, mother's intelligence, birth weight, and socioeconomic status) • Children of smoking mothers performed significantly lower (2.4–4.1%) in testing sessions ($p < 0.03$) • There was no strong evidence that maternal smoking exerted an independent effect on neuropsychologic development in early childhood	Self-reports and interviews with trained nurse interviewers were used to assess postpartum secondhand smoke exposures; neuropsychologic development was measured by the BSID**, MSCA, and MDI; social and environmental factors are major confounders of the association between maternal smoking and neuropsychologic development in childhood; more precise measures of exposures to secondhand tobacco smoke and a comprehensive assessment of confounders are required for future studies
Mental and psychomotor retardation	• Paternal pipe or cigar smoking was associated with an OR[††] of 2.4 (95% CI[‡‡], 1.2–5.1) for cases to referents	Source exposure data were from parental reports obtained in a structured interview; paternal smoking before, during, and after pregnancy is a risk factor for mental retardation among offspring
Somatic development Mental development Infant cotinine levels	• 41% of children of smokers and 32% of children of nonsmoking mothers suffered from bronchitis and pneumonia • Cotinine levels present in infants of smokers were 3-fold to 10-fold higher than in infants of nonsmokers • No confirmation of mental/developmental retardation among exposed infants	Physiologic measurements (weight and head circumference) and secondhand smoke exposures were gathered through home interviews with mothers (self-reports) and from medical records (biologic markers); BSID measured development; to prevent health risks to infants, mothers should be encouraged to stop smoking during pregnancy and while nursing, and both parents should avoid smoking when children are present
History of repeating kindergarten or first grade	• OR = 1.4 (95% CI, 1.1–1.7) for children repeating kindergarten or first grade who had a history of exposures to household smoke	Source exposure data were from maternal self-reports (questionnaires); behavior problem assessments were dropped from the analyses because behavior interviews were conducted after the child had repeated kindergarten or first grade, an experience that may account for behavior; the survey was designed to assess a multitude of social and environmental exposures; smoking in the home may contribute to social and individual factors that influence the decision to retain a child in kindergarten or first grade

Table 5.9 Continued

Study	Design/population	Exposure categories	Source of exposure
McCartney et al. 1994	Longitudinal (quasi-experimental) (190) Children aged 6–10 years enrolled in the OPPS[§§] Canada	• Nonsmoking controls • Light (>0 mg[ΔΔ] nicotine/day to 16 mg nicotine/day) • Heavy (>16 mg nicotine/day)	• Prenatal and postnatal secondhand smoke exposures
Olds et al. 1994	Prospective follow-up (400) Children aged 1–4 years from a semirural county in New York state participating in a home nurse visitation program United States	• 0 cigarettes/day • 1–9 cigarettes/day • ≥10 cigarettes/day	• Prenatal exposure
Fried et al. 1997	Longitudinal (131) Children aged 9–12 years enrolled in OPPS Canada	• Nonsmoking controls • Light (>0 mg nicotine/day to 16 mg nicotine/day) • Heavy (>16 mg nicotine/day)	• Maternal prenatal exposure
Fried et al. 1998	Longitudinal (131) Children aged 9–12 years enrolled in OPPS Canada	• Nonsmoking controls • Light (>0 mg nicotine/day to 16 mg nicotine/day) • Heavy (>16 mg nicotine/day)	• Maternal prenatal exposure

*CO = Carbon monoxide.
[†]CAT = California Achievement Test.
[‡]PPVT = Peabody Picture Vocabulary Test.
[§]RAVEN = Raven Colored Progressive Matrices Test.
[Δ]MDI = Mental Development Index.
[¶]MSCA = McCarthy Scales of Children's Abilities.
**BSID = Bayley Scales of Infant Development.
[††]OR = Odds ratio.
[‡‡]CI = Confidence interval.
[§§]OPPS = Ottawa Prenatal Prospective Study.
[ΔΔ]mg = Milligrams.
[¶¶]WISC = Weschler Intelligence Scale for Children.

Outcome	Findings	Comments
Central auditory processing task (SCAN)	• Secondhand smoke exposures both during and after pregnancy were not significantly associated with SCAN results	Source exposure data were from maternal self-reports obtained through interviews with a woman interviewer; maternal smoking rates were averaged over the trimester interview recordings
Intellectual functioning during the first 4 years	• Children whose mothers reported smoking ≥10 cigarettes/day during pregnancy had reduced and adjusted Stanford-Binet scores by 4.35 points (95% CI, 0.02–8.68, $p < 0.049$)	Source exposure data were obtained from maternal self-reports; BSID, MDI, Cattell, and Stanford-Binet were used to measure intellectual functioning outcomes; smoking during pregnancy poses a unique risk of neurodevelopmental impairment for exposed children
Reading scores Language scores	• Maternal prenatal secondhand smoke exposure was not associated with language or reading outcomes • Postnatal exposure to secondhand smoke was associated with lower language scores • An association was observed between prenatal cigarette smoking and altered (reduced) auditory functioning among offspring	Source exposure data were obtained from maternal self-reports through interviews in the home of the participant; multiple measures used to assess reading and language abilities included the WISC[¶¶]-III, Wide Range Achievement Test—Revised, PPVT, Fluency Test, Woodcock Reading Mastery Test, Oral Cloze Task, Seashore Rhythm Test, and Regular and Exceptional Pseudoword Task; maternal smoking negatively impacts reading and language capabilities of exposed children
Cognitive performance	• After discriminant functional analysis and key covariate adjustments, a strong linear association persisted with prenatal exposures among the 3 smoking categories ($p < 0.01$) • After discriminant functional analysis and key covariate adjustments, a strong linear association persisted with postnatal secondhand smoke exposure and the 3 smoking categories ($p < 0.05$)	Source exposure data were from maternal self-reports obtained through interviews in the home of the participant; a battery of cognitive performance tests included WISC-III, Fluency Test, Auditory Working Memory, Tactual Performance Task, Category Test, Gordon Delay Task, and the Gordon Vigilance Task; there was a dose-response association between prenatal cigarette exposure and lower global intelligence scores

Table 5.10 Studies of secondhand smoke exposure and behavioral problems among children

Study	Design/population	Exposure categories	Source of exposure
Makin et al. 1991	Prospective longitudinal study (90) Children aged 6–9 years Subsample of Ottawa Prenatal Prospective Study Canada	• Nonsmokers • Involuntary smokers • Active smokers	• Maternal prenatal and postnatal secondhand smoke exposures
Weitzman et al. 1992	Longitudinal (2,256) Children aged 4–11 years participating in the National Longitudinal Survey of Youth United States	• <1 pack/day • ≥1 pack/day • Prenatal (mother smoked during pregnancy only) • Involuntary smoking (mother smoked only after pregnancy) • Prenatal and involuntary smoking (in utero and postnatal exposures to maternal smoking)	• Prenatal and involuntary exposures to parental smoking
Fergusson et al. 1993	Longitudinal (1,265) Children aged 8, 10, and 12 years born in Christchurch, New Zealand, enrolled in the Christchurch Health and Development Study	• Mean number of cigarettes smoked/day during pregnancy (reported during each trimester) • Annual questions regarding daily maternal smoking habits for the first 5 postnatal years and converted to a daily cigarette intake amount	• Maternal smoking during and after pregnancy

Outcome	Findings	Comments
Behavioral, language, and mental development	• The active smoking group demonstrated the poorest performance on the speech, language, intellectual, and behavioral battery of exams • Involuntary smokers had intermediate scores • Nonsmokers had the best scores of the 3 groups • Stepwise discriminant analysis was performed between the involuntary smoking and nonsmoking groups and identified a significant difference ($\chi^2 = 28.15$, $p < 0.001$) • Children in active and involuntary smoking groups rated higher in behavioral problems, with an apparent dose-response relationship	This study was designed to assess a spectrum of long-term consequences of active and involuntary smoking during pregnancy; secondhand smoke exposure was primarily based on the husband's smoking habits; source exposure data were obtained from maternal self-reports through controlled interviews; pregnant mothers, and other persons who may be sources of secondhand smoke, need education and factual information about the deleterious effects smoking can have on the developing fetus
Behavioral problems	• Increased rates of children's behavioral problems were independently associated with all categories of maternal smoking behaviors and with evidence of a dose-response relationship • Among children exposed during and after pregnancy, there were 1.17 additional problems associated with smoking <1 pack/day and 2.04 with ≥1 pack/day ($p < 0.001$) • Odds ratios for extreme behavioral problems = 1.41 for <1 pack/day ($p < 0.01$) and 1.54 for ≥1 pack/day ($p < 0.02$)	Source exposure data were obtained from maternal self-reports through interviews; behavioral problems were measured by the 32-item Child Behavior Problem Index and six subscales; this study suggests that increased behavioral problems among children should be added to the spectrum of adverse health conditions associated with children's prenatal and involuntary exposures to maternal smoking
Behavioral outcomes (disruptive)	• There was a consistent dose-response relationship between the amount smoked during pregnancy and mean problem behavior scores; all behavior assessment measures that compared exposures from 0 to >20 cigarettes/day were statistically significant ($p < 0.001$) • Postnatal exposures identified associations between maternal smoking during preschool years and child behavioral problems ($p < 0.01$) • Assessments of the independent influence of prenatal vs. postnatal exposures indicated that behavioral problems were typically associated with smoking during pregnancy	Source exposure data were from maternal self-reports; outcomes were adjusted for confounding factors potentially associated with maternal smoking and childhood behavioral problems; smoking during pregnancy is associated with a small but detectable increase in the risk of childhood behavioral problems; there was no association between behavioral problems and exposure to maternal postnatal smoking

Makin and colleagues (1991) also noted that compared with children of nonsmokers, children exposed to secondhand smoke had higher levels of maternal-reported behavioral problems even after considering potential confounders. Fergusson and colleagues (1993) studied behavioral problems reported by mothers and teachers of middle school children in New Zealand. After adjusting for confounders, the researchers found small but statistically detectable increases in rates of childhood problem behaviors associated with smoking during pregnancy, but did not observe any associations between exposures to maternal smoking after pregnancy and behavioral outcomes (Fergusson et al. 1993).

Evidence Synthesis

The evidence for an association between exposure to secondhand smoke and behavioral problems in children is inconsistent. Because so few studies have been carried out on this topic, more studies are clearly warranted.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and behavioral problems among children.

Implications

Further research is needed, but the same challenges remain that confront research on other effects such as cognitive functioning.

Height/Growth

Epidemiologic Evidence

Five studies examined the association between children's growth and secondhand smoke exposure (Table 5.11) (Rona et al. 1981, 1985; Rantakallio 1983; Chinn and Rona 1991; Eskenazi and Bergmann 1995). Two of the studies (Chinn and Rona 1991; Eskenazi and Bergmann 1995) reported no association for children aged 5 years and for children aged 5 through 11 years. Eskenazi and Bergmann (1995) used biochemical confirmation of secondhand smoke exposure and proposed that the height differences between exposed and unexposed children were attributable to the effect of tobacco smoke exposure on fetal growth. After adjusting for birth weight, however, any associations between secondhand smoke exposure and height were eliminated. Rona and colleagues (1981) found that differences in height remained among children of smokers even after adjusting for birth weight. Rantakallio (1983) examined secondhand smoke exposures from fathers during pregnancy and found that after adjusting for potential confounding factors, children exposed to paternal smoking during pregnancy were shorter than were children of nonsmoking fathers. Similarly, Rona and colleagues (1985) examined height among children aged 5 through 11 years and found small decreases among children exposed to secondhand smoke. Both of these studies found relatively small differences (1 centimeter or less) even among children exposed to heavy smokers.

Evidence Synthesis

The evidence for an association between secondhand smoke exposure and children's height/growth is mixed (Table 5.11). Those studies that do report associations find relatively consistent deficits associated with secondhand smoke exposure. However, the magnitude of the effect is small and could reflect residual confounding.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and children's height/growth.

Implications

The evidence suggests that any effect of secondhand smoke exposure on height is likely to be small and of little significance. Research on secondhand smoke exposure and height is complicated by the many potential confounding factors.

Childhood Cancer

Biologic Basis

Tobacco smoke contains numerous carcinogens and is a well-established cause of cancer (USDHEW 1964, 1974; USDHHS 1980, 1986; Smith et al. 1997, 2000a,b). Numerous animal studies elucidate evidence for, and mechanisms of, transplacental carcinogenesis (Rice 1979; Schuller 1984; Napalkov et al. 1989). For example, when the oncogenic compound ethylnitrosourea (ENU) was administered intravenously or intraperitoneally to pregnant rabbits, the offspring developed renal and neural cancers (Stavrou et al. 1984). Monkeys are also susceptible to transplacental carcinogenesis, with offspring developing vascular and a variety of other tumors following prenatal administration of ENU to the mother (Rice et al. 1989). The strongest human evidence that transplacental carcinogenesis is biologically plausible may be the occurrence of vaginal clear-cell adenocarcinoma among young women whose mothers were prescribed diethylstilbesterol during pregnancy (Vessey 1989).

Limited biologic evidence suggests that involuntary exposure to cigarette smoke may also lead to transplacental carcinogenesis. Maternal secondhand smoke exposure during pregnancy, as with maternal active smoking during pregnancy, can result in increased measurable metabolites of cigarette smoke in amniotic fluid (Andresen et al. 1982; Smith et al. 1982) and in fetal blood (Bottoms et al. 1982; Coghlin et al. 1991). For example, thiocyanate levels in fetal blood were less than 50 micromoles per liter (μmol/L) when the mother was not exposed to secondhand smoke during pregnancy (Bottoms et al. 1982). Among mothers who were prenatally exposed to secondhand smoke, fetal blood levels of thiocyanate were as high as 90 μmol/L, and among mothers who actively smoked, the measurements were about 170 μmol/L. Notably, however, two studies that measured thiocyanate levels in umbilical cord blood found no differences between secondhand smoke-exposed and unexposed nonsmoking women (Manchester and Jacoby 1981; Hauth et al. 1984). Hauth and colleagues (1984) found thiocyanate levels of 23 μmol/L in umbilical cord blood from unexposed infants of nonsmoking mothers and levels of 26 μmol/L in secondhand smoke-exposed infants of nonsmoking mothers (defined as living and/or working with someone who smoked at least 10 cigarettes per day). Manchester and Jacoby (1981) also found similar cord blood levels of thiocyanate in unexposed (34 ± 3 μmol/L) and secondhand smoke-exposed (35 ± 3 μmol/L) infants of nonsmoking mothers (exposure was defined as living with someone who smoked).

Studies of maternal smoking during pregnancy found enhanced transplacental enzyme activation (Nebert et al. 1969; Manchester and Jacoby 1981) and placental DNA adducts (Everson et al. 1986, 1988; Hansen et al. 1992), and several animal studies suggested that embryonic exposure to tobacco smoke components increased tumor rates (Mohr et al. 1975; Nicolov and Chernozemsky 1979). For example, diethylnitrosamine administered to female hamsters in the last days of pregnancy produced offspring that developed respiratory tract neoplasms in nearly 95 percent of the animals. Cigarette smoke condensate in olive oil that was used in another study of pregnant hamsters was injected intraperitoneally; it produced a variety of tumors in the offspring, including tumors of the pancreas, adrenal glands, liver, uterus, and lung (Nicolov and Chernozemsky 1979). Human studies document an increased frequency of genomic deletions in the *hypoxanthine-guanine phosphoribosyltransferase* gene found in the cord blood of newborns whose mothers were exposed to secondhand smoke (compared with newborns of unexposed mothers). This finding strongly supports a carcinogenic effect of prenatal secondhand smoke exposure, particularly since these mutations are characteristic of those found in childhood leukemia and lymphoma (Finette et al. 1998). Prenatal exposure to secondhand smoke may also play a role by enhancing any effect of postnatal exposure on the development of childhood cancer (Napalkov 1973), but the potential effects of prenatal and postnatal exposures are difficult to separate given the high correlation between prenatal and postnatal parental smoking. Several studies have assessed postnatal exposures by measuring cotinine and nicotine concentrations in the saliva and urine of infants. The investigators found that those infants with reported secondhand smoke exposures had significantly higher concentrations than those infants with no reported exposure in the 24 hours before measuring the concentrations (Greenberg et al. 1984; Crawford et al. 1994).

Table 5.11 Studies of secondhand smoke exposure and children's growth

Study	Design/population	Exposure categories	Source of exposure
Rona et al. 1981	Longitudinal (1,800) Children aged 5–11 years from England and Scotland who participated in the National Study of Health and Growth United Kingdom	• Children with no smokers in the home • One smoker in the home • Two or more smokers in the home	• Parental secondhand smoke exposure at home
Rantakallio 1983	Longitudinal (12,068) Finnish children (mothers enrolled during pregnancy and children followed until 14 years of age) Finland	• Maternal smoking • Paternal smoking (exposures were not clearly defined)	• Mother • Father
Rona et al. 1985	Editorial prospective (5,000–6,000) Primary school children (aged 5–11 years) from England and Scotland United Kingdom	NR*	• Prenatal and secondhand smoke exposures from parental smoking
Chinn and Rona 1991	Observational study (11,224) English and Scottish inner-city and representative children aged 5–11 years United Kingdom	• Number of cigarettes smoked by parents at home (recorded as a continuous variable) = 0, 1–4, 5–14, 15–24, 25–34, and ≥35	• Secondhand smoke
Eskenazi and Bergmann 1995	Longitudinal cohort (2,622) Children (aged 5 years ± 6 months) enrolled in Child Health and Development Studies between 1964 and 1967 in the San Francisco East Bay area United States	• Nonsmokers exposed to secondhand smoke (cotinine levels 2–10 ng/mL‡) • Unexposed nonsmokers • Serum cotinine levels of smokers: 0–79 ng/mL 80–163 ng/mL 164–569 ng/mL	• Maternal secondhand smoke exposure during pregnancy and prenatal maternal smoking • Serum cotinine sample during pregnancy

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

Outcome	Findings	Comments
Height	• There was a strong inverse association between height and the number of household smokers ($p < 0.001$ in England and $p < 0.01$ in Scotland) • After adjusting for confounding variables such as maternal smoking during pregnancy, paternal social class, maternal and paternal heights, and the number of siblings, a significant trend remained only in the English sample ($p < 0.01$)	Source exposure data were obtained from parental self-reports through questionnaires; children's heights were measured across all 28 study areas; persons identified regarding exposures smoked ≥5 cigarettes/day at home; secondhand smoke at home seems to affect the growth of children
Height at 14 years of age	• Children of smokers were shorter at 14 years of age compared with children of nonsmokers • Regression coefficient: -0.034 (maternal smoking, $p = 0.056$) -0.032 (paternal smoking, $p = 0.072$)	Source exposure data were self-reported (questionnaire); children of smokers were shorter than children of nonsmokers
Height (in mm[†])	• Children of mothers who smoked during pregnancy and whose parents smoked at home had significantly reduced ($p < 0.01$) heights by 2 mm for children aged 5–11 years	NR
Height, respiratory illness (wheeze)	• There were no regression coefficients of height standard deviation scores on involuntary smoking; controlling for confounders was significantly different from zero • Significant usual coughs were observed in English inner-city boys and girls ($p < 0.01$ and $p < 0.05$, respectively) • Persistent wheeze was significant for Scottish boys ($p < 0.05$)	Source exposure data were from maternal self-reports (questionnaires); heights were measured by Holtian stadiometer, and respiratory symptoms were gathered from maternal reports; overall risk of respiratory conditions resulting from secondhand smoke is small but not negligible
Height	• Children of smokers and those of nonsmokers in unadjusted analyses were 0.1, 0.2, and 0.5 centimeters shorter for each smoker's cotinine tertile, respectively • Only the adjusted heights of children of mothers who smoked prenatally and postnatally were significantly different from those of nonsmokers ($p < 0.05$), but when birth weight and gestational length were added to the model, the finding was no longer significant	Source exposure data were from maternal self-reports of smoking status; secondhand smoke exposure was measured using cotinine as a biomarker; self-reported smoking status and serum cotinine levels showed good agreement in height measurements collected by trained personnel; children whose mothers were heavy smokers during pregnancy were shorter at 5 years of age compared with children of nonsmokers; this effect appears to be attributable to in utero exposure rather than to postnatal secondhand smoke exposure

Epidemiologic Evidence

In the case of active maternal smoking during pregnancy, investigators who have reviewed the evidence have not found an association between maternal smoking and a transplacental effect on childhood cancer (Pershagen 1989; Tredaniel et al. 1994; Sasco and Vainio 1999). One meta-analysis found a 10 percent increase in risk (RR = 1.10 [95 percent CI, 1.03–1.19]) for all cancers based on 12 studies, but the quality of the available studies and the diversity of the cancer types considered precluded establishing a causal relationship (Boffetta et al. 2000). In a recent monograph on involuntary smoking, the International Agency for Research on Cancer (2004) concluded that the evidence regarding exposure to parental smoking and childhood cancer is inconsistent. Similarly, two other literature reviews of secondhand smoke exposure and childhood cancer also found no strong evidence of an association (Tredaniel et al. 1994; Sasco and Vainio 1999), but a pooled risk estimate that combined studies of specific cancer sites as well as all cancer sites was 1.23 (95 percent CI, 1.14–1.33) for paternal smoking (Sorahan et al. 1997a). Another meta-analysis of paternal smoking and risk of childhood cancer yielded a statistically significant increase in risk for non-Hodgkin's lymphoma based on 4 studies (RR = 2.0 [95 percent CI, 1.08–3.98]) and for brain tumors based on 10 studies (RR = 1.22 [95 percent CI, 1.05–1.40]) (Boffetta et al. 2000). The summary estimate from the meta-analysis for acute lymphocytic leukemia (ALL), the most common type of childhood leukemia, was not statistically significant (RR = 1.17 [95 percent CI, 0.96–1.42]). A separate review of the available studies on childhood brain tumors and tobacco smoke found mixed results for maternal exposure to secondhand smoke during pregnancy (Norman et al. 1996b).

Given the relative rarity of childhood cancer, the epidemiologic evidence on secondhand smoke exposure and childhood cancer comes almost exclusively from case-control studies (Table 5.12). One cohort study that addressed cancer outcomes among offspring (including adults) who had reported at least one parent with lung cancer assumed that these offspring had been exposed to secondhand smoke (Seersholm et al. 1997). Lung cancer patients were identified using the Danish Cancer Registry and their offspring were identified through the Danish Population Registry. Records of the offspring were then linked back to the cancer registry to obtain the overall cancer rate in this cohort, which was lower than the cancer rate for the general Danish population (standardized incidence ratio 0.9, 90 percent CI, 0.6–1.2). The cohort also did not have any statistically significant excesses for any specific cancer sites.

Seven of the case-control studies on secondhand smoke exposure evaluated all cancer types together as well as some specific types of cancers (Stjernfeldt et al. 1986; John et al. 1991; Sorahan et al. 1995, 1997a,b, 2001; Ji et al. 1997). Of another nine studies that examined only CNS tumors (Preston-Martin et al. 1982; Howe et al. 1989; Kuijten et al. 1990; Gold et al. 1993; Bunin et al. 1994; Filippini et al. 1994, 2000; McCredie et al. 1994; Norman et al. 1996a), four focused on leukemias (Magnani et al. 1990; Shu et al. 1996; Brondum et al. 1999; Infante-Rivard et al. 2000)—one included non-Hodgkin's lymphoma (Magnani et al. 1990)—and two other studies analyzed soft-tissue sarcomas (Grufferman et al. 1982; Magnani et al. 1989). Four of the seven studies that examined the overall cancer risk were conducted by the same primary investigator who studied cancer deaths in the United Kingdom during four time periods: 1953–1955 (Sorahan et al. 1997a), 1971–1976 (Sorahan et al. 1997b), 1977–1981 (Sorahan et al. 1995), and 1980–1983 (Sorahan et al. 2001). All four of these studies as well as a study from China (Ji et al. 1997) found positive exposure-response trends that were also statistically significant for the amount of paternal smoking and overall cancers, with ORs ranging from 1.08 (adjusted, 95 percent CI, 1.03–1.13) (Sorahan et al. 1995) to 1.9 (adjusted, 95 percent CI, 1.3–2.7) (Ji et al. 1997).

Because of the heterogeneity in the quality of the epidemiologic evidence on maternal secondhand smoke exposure and childhood cancers, a meta-analysis of the relevant studies is not currently warranted. In addition, the level of epidemiologic evidence on individual types of childhood cancers is limited.

Leukemia

The studies that focused on childhood leukemia (Magnani et al. 1990; Shu et al. 1996; Brondum et al. 1999; Infante-Rivard et al. 2000) did not find statistically significant associations with paternal smoking. Findings from one of these studies, which also investigated the modifying effect of three polymorphisms of the *CYP1A1* gene, showed no effect of paternal smoking on childhood leukemia (nonsignificant OR of 1.0 for all levels of reported paternal smoking), but

did suggest a protective effect with postnatal paternal smoking for children with the *CYP1A1*2B* allele but not for children without it (OR = 0.2 [95 percent CI, 0.04–0.9]) (Infante-Rivard et al. 2000). Two of the studies that examined overall and specific cancers did find significantly increased risks for ALL at the highest levels of paternal smoking, with ORs of 3.8 (95 percent CI, 1.3–12.3) for five or more pack-years[1] of smoking before conception (p for trend = 0.01) (Ji et al. 1997) and 5.29 (95 percent CI, 1.31–21.30) for 40 or more cigarettes per day before the pregnancy (p trend = 0.06) (Sorahan et al. 2001).

Lymphoma

Lymphoma was significantly associated with paternal smoking in three of the studies that analyzed multiple cancer sites (Ji et al. 1997; Sorahan et al. 1997b, 2001). The highest risk was associated with 10 or more pack-years of smoking (among nonsmoking mothers) before conception and postnatally (adjusted OR = 5.7 [95 percent CI, 1.3–26.0], p for trend = 0.03) (Ji et al. 1997). One study that was based on 17 cases of non-Hodgkin's lymphoma found large, increased risks with paternal smoking before the birth of the child (overall and by levels of smoking), although these estimates had lower confidence limits of 0.9 and 1.0, respectively (Magnani et al. 1990). Using the broader category of reticuloendothelial system neoplasms, Sorahan and colleagues (2001) also found a large increased risk (RR = 3.69 [95 percent CI, 1.49–9.15]) with paternal cigarette smoking of 20 to 29 cigarettes per day when cases were compared with controls identified from the general practitioners of the cases.

Central Nervous System

Four of the nine studies that analyzed only CNS tumors found statistically significant associations with maternal secondhand smoke exposure during pregnancy ranging from 1.5 (p = 0.03) (Preston-Martin et al. 1982) to 2.2 (95 percent CI, 1.1–4.6, p for trend = 0.02) (Filippini et al. 1994). One study of multiple cancer outcomes found significant associations for neuroblastoma and CNS cancers with paternal smoking after combining three study populations from different time periods (Sorahan et al. 1997b).

Evidence Synthesis

The strongest evidence for any childhood cancer risk from maternal secondhand smoke exposure is specific to leukemias, lymphomas, and brain tumors, although the causal pathway may actually be through DNA damage to the father's sperm from active smoking rather than through maternal secondhand smoke exposure during pregnancy. Some of the epidemiologic studies suggest a slightly increased risk in childhood cancers from prenatal and postnatal secondhand smoke exposures, but most of the studies were small and did not have the power to detect statistically significant associations. In addition, most of the studies lacked exposure assessments for relevant exposure periods (preconception, prenatal, and postnatal), which may also have reduced the risk estimates because of nondifferential misclassification of exposure status. Risk estimates may be inflated by recall bias, especially since interviews to assess exposures took place up to 15 years after birth. Parents of children with cancer may be more likely to think about possible causes for their child's illness, thereby improving their recall of exposure experiences around the time of the pregnancy and birth. Parents of healthy children, however, have no particular reason to think about their exposure experiences and their recall may not be as good. Differential recall is a potential problem common to all case-control studies. If differential positive recall between cases and controls is present, it will inflate the risk estimate for childhood cancer.

Researchers have observed exposure-response trends for overall cancers as well as for leukemia, lymphoma, and brain tumors in a number of studies. Most of the studies adjusted for potentially confounding factors such as the child's date of birth, age at diagnosis, parental education level, parental age at child's birth, socioeconomic status, residence, and race by multivariate adjustment or case-control matching. Only four studies, however, considered other cancer risk factors such as maternal x-rays, drug use, and consumption of foods containing sodium nitrite (Preston-Martin et al. 1982; Howe et al. 1989; Kuijten et al. 1990; Bunin et al. 1994). Although active maternal smoking during pregnancy does not appear to be related to childhood cancer, it was not clear in some studies whether mothers who actively smoked were excluded from the various analyses that estimated risks from

[1]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Table 5.12 Case-control studies of childhood cancer by cancer type

Study	Population	Exposure period	Source of exposure
		All cancers combined	
John et al. 1991	Children aged 0–14 years, diagnosed in Denver between 1976 and 1983; controls were selected by random-digit dialing	1 year before birth	Father smoked
		1 year before birth	Father smoked Father smoked 1–10 cigarettes/day Father smoked 11–20 cigarettes/day Father smoked ≥21 cigarettes/day
Sorahan et al. 1995	Cancer deaths among children in England, Wales, and Scotland between 1977 and 1981; included less than 50% of population cancer cases	Prenatal	Father smoked <10 cigarettes/day Father smoked 10–19 cigarettes/day Father smoked 20–29 cigarettes/day Father smoked 30–39 cigarettes/day Father smoked ≥40 cigarettes/day
		Prenatal	Father smoked <10 years Father smoked 10–19 years Father smoked ≥20 years
		Prenatal	Father smoked <10 cigarettes/day Father smoked 10–19 cigarettes/day Father smoked 20–29 cigarettes/day Father smoked 30–39 cigarettes/day Father smoked ≥40 cigarettes/day
		Prenatal	Father smoked

Risk (95% CI*)	Maternal smoking status	Confounding	Comments
		All cancers combined	
1.2 (0.8–2.1)	Nonsmokers	Matched for age, gender, and geographic area; adjusted for paternal education	None
1.3 (0.9–2.0) 1.9 (0.9–3.9) 1.3 (0.8–2.1) 1.0 (0.6–1.8)	Smokers and nonsmokers	Matched for age, gender, and geographic area; no adjustments	
1.20 (0.81–1.78) 1.24 (0.98–1.56) 1.26 (1.05–1.50) 1.35 (1.03–1.78) 1.47 (1.07–2.01), p trend <0.001	Smokers and nonsmokers	Matched for gender and date of birth; no adjustments	None
1.41 (1.16–1.72) 1.24 (1.04–1.47) 1.10 (0.81–1.50)	Smokers and nonsmokers	Matched for gender and date of birth; no adjustments	
1.23 (0.82–1.86) 1.17 (0.92–1.49) 1.24 (1.02–1.49) 1.30 (0.98–1.73) 1.39 (1.00–1.92), p trend = 0.003	Smokers and nonsmokers	Matched for gender, date of birth, and paternal alcohol consumption; adjusted for maternal smoking and alcohol consumption	
1.37 (1.12–1.68)	Nonsmokers	Matched for gender and date of birth; adjusted for alcohol consumption, SES†, and maternal age at child's birth	

Table 5.12 Continued

Study	Population	Exposure period	Source of exposure
		All cancers combined	
Ji et al. 1997	Children aged <15 years in Shanghai (China), diagnosed between 1985 and 1991; population-based controls were from household registry	NR‡	Father smoked <10 cigarettes/day Father smoked 10–14 cigarettes/day Father smoked ≥15 cigarettes/day
		NR	Father smoked <10 years Father smoke 10–14 years Father smoked ≥15 years
		Preconception	Father smoked <5 years: <10 cigarettes/day 10–14 cigarettes/day ≥15 cigarettes/day
		Preconception	Father smoked 5–9 years: <10 cigarettes/day 10–14 cigarettes/day ≥15 cigarettes/day
		Preconception	Father smoked ≥10 years: <10 cigarettes/day 10–14 cigarettes/day ≥15 cigarettes/day
		Preconception	Father smoked ≤2 pack-years§ Father smoked >2 to <5 pack-years Father smoked ≥5 pack-years
		Postnatal	Father smoked ≤2 pack-years Father smoked >2 to <5 pack-years Father smoked ≥5 pack-years
		Preconception	Father smoked

Risk (95% CI†)	Maternal smoking status	Confounding	Comments
		All cancers combined	
1.5 (1.1–2.3) 1.1 (0.8–1.6) 1.5 (1.0–2.3), p trend = 0.07	Nonsmokers	For all analyses: Matched for gender and birth year; adjusted for: birth weight; income; and paternal age, education, and alcohol consumption	Data were not collected on paternal smoking during mother's pregnancy; interviews took place ≥10 years after pregnancy
1.2 (0.7–1.8) 1.1 (0.8–1.7) 1.7 (1.2–2.5), p trend = 0.007	Nonsmokers		
1.2 (0.7–2.1) 0.9 (0.5–1.9) 0.7 (0.2–2.9)	Nonsmokers		
1.2 (0.7–2.0) 1.2 (0.8–1.9) 2.4 (1.3–4.4)	Nonsmokers		
1.5 (0.9–2.5) 1.3 (0.8–2.3) 2.0 (1.2–3.4)	Nonsmokers		
1.2 (0.8–1.8) 1.3 (0.9–2.0) 1.7 (1.2–2.5), p trend = 0.006	Nonsmokers		
1.2 (0.9–1.7) 1.4 (1.0–2.0) 1.1 (0.8–1.7), p trend = 0.57	Nonsmokers		
Diagnosis at 0–4 years of age 1.8 (1.2–2.6) Diagnosis at 5–9 years of age 0.9 (0.5–1.5) Diagnosis at 10–14 years of age 1.9 (0.5–1.8)	Nonsmokers		

Table 5.12 Continued

Study	Population	Exposure period	Source of exposure
		All cancers combined	
Sorahan et al. 1997a	Deaths of children in England, Wales, and Scotland between 1953 and 1955; included 79% of population cancer cases	Current	Father smoked 1–9 cigarettes/day Father smoked 10–20 cigarettes/day Father smoked >20 cigarettes/day
		Current	Father smoked
		Current	Father smoked
Sorahan et al. 1997b	Deaths of children in England, Wales, and Scotland between 1971 and 1976; included 51% of population cases	Current	Father smoked 1–9 cigarettes/day Father smoked 10–19 cigarettes/day Father smoked 20–29 cigarettes/day Father smoked 30–39 cigarettes/day Father smoked ≥40 cigarettes/day
		Current	Father smoked
		Current	Father smoked
Sorahan et al. 2001	Children aged <15 years in the United Kingdom, diagnosed between 1980 and 1983; hospital controls were acute surgical and accident patients; general practitioner controls were population based	Preconception	Father smoked <10 cigarettes/day Father smoked 10–19 cigarettes/day Father smoked 20–29 cigarettes/day Father smoked 30–39 cigarettes/day Father smoked ≥40 cigarettes/day
		Preconception	Father smoked (same as above)

Risk (95% CI	Maternal smoking status	Confounding	Comments
		All cancers combined	
1.03 (0.81–1.29) 1.31 (1.06–1.62) 1.42 (1.08–1.87), p trend <0.001	Smokers and nonsmokers	Matched for gender, date of birth, and residence; adjusted for SES, age of father and mother at child's birth, sibship position, obstetric radiography, and maternal smoking	Exposure assessment for current smoking only; time from birth to interviews was not reported
1.13 (1.05–1.23), p <0.01	Smokers and nonsmokers	Matched for gender, date of birth, and residence; adjusted for maternal smoking	
1.30 (1.10–1.53), p <0.01	Nonsmokers	Matched for gender, date of birth, and residence; adjusted for SES, age of father and mother at child's birth, sibship position, and obstetric radiography	
1.02 (0.78–1.34) 1.37 (1.13–1.65) 1.33 (1.13–1.55) 1.42 (1.09–1.84) 1.63 (1.23–2.15), p trend <0.001	Smokers and nonsmokers	Matched for gender, date of birth, and residence; adjusted for SES, age of father and mother at child's birth, sibship position, obstetric radiography, and maternal smoking	Exposure assessment for current smoking only; median time between birth and interviews for cases was 8.5 years, and 97% of cases were interviewed before the fourth anniversary of the child's death; nonsmokers included former smokers
1.29 (1.10–1.51), p <0.01	Nonsmokers	Matched for gender, date of birth, and residence; adjusted for SES, age of father and mother at child's birth, sibship position, and obstetric radiography	
1.09 (1.05–1.14), p <0.001	Smokers and nonsmokers	Matched for gender, date of birth, and residence; adjusted for maternal smoking	
General practitioner controls 0.94 (0.53–1.66) 1.63 (1.10–2.41) 1.46 (1.05–2.03) 0.95 (0.52–1.73) 1.77 (0.94–3.34), p trend = 0.02	Smokers and nonsmokers	No adjustments (nonsignificant in analysis: paternal age at child's birth, SES, and ethnic origin)	None
General practitioner controls p trend = 0.03 (risks were not reported)	Smokers and nonsmokers	Adjusted for maternal smoking	

Table 5.12 Continued

Study	Population	Exposure period	Source of exposure
		Acute lymphocytic leukemia	
Magnani et al. 1990	Pediatric hospital cases in Italy, diagnosed between 1974 and 1984 and still under observation (prevalent cases)	Preconception and prenatal (up to child's birth)	Father smoked Father smoked 1–15 cigarettes/day Father smoked ≥16 cigarettes/day
John et al. 1991	Children aged 0–14 years in Denver, diagnosed between 1976 and 1983; controls were selected by random-digit dialing	1 year before birth	Father smoked
		1 year before birth	Father smoked Father smoked 1–10 cigarettes/day Father smoked 11–20 cigarettes/day Father smoked ≥21 cigarettes/day
Sorahan et al. 1995	Deaths of children in England, Wales, and Scotland between 1977 and 1981; included less than 50% of population cancer cases	Prenatal	Father smoked
Shu et al. 1996	Cases aged ≤18 months, diagnosed between 1983 and 1988; identified through clinical trial registries in the United States, Canada, and Australia	1 month before conception	Father smoked
		Prenatal	Father smoked
		1 month before conception	Father smoked 1–10 cigarettes/day Father smoked 11–20 cigarettes/day Father smoked >20 cigarettes/day
Ji et al. 1997	Children aged <15 years in Shanghai (China), diagnosed between 1985 and 1991; population-based controls were from household registry	NR	Father smoked <10 cigarettes/day Father smoked 10–14 cigarettes/day Father smoked ≥15 cigarettes/day
		NR	Father smoked <10 years Father smoked 10–14 years Father smoked ≥15 years
		Preconception	Father smoked ≤2 pack-years Father smoked >2 to <5 pack-years Father smoked ≥5 pack-years
		Postnatal	Father smoked ≤2 pack-years Father smoked >2 to <5 pack-years Father smoked ≥5 pack-years
Sorahan et al. 1997a	Deaths among children in England, Wales, and Scotland between 1953 and 1955; included 79% of population cancer cases	Current	Father smoked

Risk (95% CI	Maternal smoking status	Confounding	Comments
		Acute lymphocytic leukemia	
0.9 (0.6–1.5) 0.9 (0.5–1.6) 0.9 (0.6–1.5)	Smokers and nonsmokers	No adjustments (nonsignificant in analysis: years of smoking, age at smoking initiation, and cumulative cigarette smoking)	Findings did not differ when considering paternal smoking from birth to diagnosis or during the year before birth
1.4 (0.6–3.1)	Nonsmokers	Matched for age, gender, and geographic area; adjusted for father's education	None
1.9 (1.0–3.7) 2.6 (0.9–7.9) 1.6 (0.7–3.7) 1.6 (0.7–4.0)	Smokers and nonsmokers	Matched for age, gender, and geographic area; no adjustments	
1.16 (1.06–1.27)	Smokers and nonsmokers	Matched for gender and date of birth	Risk is for 1 level increase in daily amount of cigarettes smoked (e.g., 6 levels from nonsmokers to ≥40 cigarettes/day)
1.56 (1.03–2.36)	Smokers and nonsmokers	Matched for telephone area code and exchange number; adjusted for gender, paternal age and education, and maternal alcohol consumption during pregnancy	None
1.45 (0.95–2.19)	Smokers and nonsmokers		
2.40 (1.00–5.72) 1.33 (0.79–2.34) 1.51 (0.82–2.77), p trend = 0.12	Smokers and nonsmokers		
1.5 (0.7–3.9) 0.9 (0.4–1.5) 1.9 (0.8–4.6), p trend = 0.27	Nonsmokers	For all analyses: Matched for gender and birth year; adjusted for: birth weight; income; and paternal age, education, and alcohol consumption	Data were not collected on paternal smoking during mother's pregnancy; interviews took place ≥10 years after pregnancy
0.9 (0.3–2.3) 1.0 (0.5–2.2) 1.7 (0.8–3.7), p trend = 0.23	Nonsmokers		
0.8 (0.2–2.5) 1.0 (0.4–2.7) 3.8 (1.3–12.3), p trend = 0.01	Nonsmokers		
1.1 (0.4–2.8) 1.8 (0.6–5.2) 1.8 (0.6–5.5), p trend = 0.33	Nonsmokers		
1.08 (0.91–1.27)	Smokers and nonsmokers	Matched for gender, date of birth, and residence; adjusted for maternal smoking	Exposure assessment for current smoking only; time from birth to interviews was not reported; risk is for 1 level increase in daily amount of cigarettes smoked (e.g., 4 levels from <1 cigarette/day to >20 cigarettes/day)

Table 5.12 Continued

Study	Population	Exposure period	Source of exposure
		Acute lymphocytic leukemia	
Sorahan et al. 1997b	Deaths among children in England, Wales, and Scotland between 1971 and 1976; included 51% of population cancer cases	Current	Father smoked
Brondum et al. 1999	Children aged <15 years, diagnosed between 1989 and 1993; identified through clinical trial registries in the United States	Ever	Father smoked
		Ever	Father smoked
		1 month before conception and prenatal	Father smoked
		Father's lifetime	Father smoked <10 cigarettes/day Father smoked 10 to <20 cigarettes/day Father smoked ≥20 cigarettes/day
		Father's lifetime	Father smoked <10 years Father smoked 10 to <20 years Father smoked ≥20 years
Infante-Rivard et al. 2000	Children aged 0–9 years in Quebec (Canada), diagnosed between 1980 and 1993; identified from tertiary care centers for childhood cancers	Postnatal up to diagnosis	Father smoked 1–20 cigarettes/day Father smoked >20 cigarettes/day
Sorahan et al. 2001	Children aged <15 years in the United Kingdom, diagnosed between 1980 and 1983; hospital controls were acute surgical and accident patients; general practitioner controls were population based	Preconception	Father smoked <10 cigarettes/day Father smoked 10–19 cigarettes/day Father smoked 20–29 cigarettes/day Father smoked 30–39 cigarettes/day Father smoked ≥40 cigarettes/day
		Lymphoma	
Magnani et al. 1990	Non-Hodgkin's lymphoma cases admitted to a pediatric hospital in Italy, diagnosed between 1974 and 1984 and still under observation (prevalent cases)	Preconception and prenatal (up to child's birth)	Father smoked Father smoked 1–15 cigarettes/day Father smoked ≥16 cigarettes/day

Risk (95% CI)	Maternal smoking status	Confounding	Comments
		Acute lymphocytic leukemia	
1.07 (0.99–1.16)	Smokers and nonsmokers	Matched for gender, date of birth, and residence; adjusted for maternal smoking	Exposure assessment for current smoking only; median time between birth and interviews for cases was 8.5 years, and 97% of cases were interviewed before the fourth anniversary of the child's death; nonsmokers included former smokers; risk is for 1 level increase in daily amount of cigarettes smoked (e.g., 6 levels from nonsmokers to ≥40 cigarettes/day)
1.04 (0.90–1.20)	Smokers and nonsmokers	Adjusted for income and paternal race and education	None
1.04 (0.86–1.26)	Nonsmokers	Adjusted for income and parental race and education	
1.07 (0.91–1.25)	Smokers and nonsmokers	Adjusted for income and paternal race and education	
1.16 (0.88–1.51) 1.04 (0.83–1.31) 1.06 (0.88–1.26), p trend = 0.56	Smokers and nonsmokers	Adjusted for income and paternal race and education	
1.12 (0.91–1.38) 1.22 (1.00–1.47) 0.91 (0.72–1.14), p trend = 0.79	Smokers and nonsmokers	Adjusted for income and paternal race and education	
1.0 (0.7–1.4) 1.0 (0.7–1.3)	Smokers and nonsmokers	Matched for age and gender; adjusted for maternal age and education	None
General practitioner controls: 0.99 (0.35–2.85) 1.34 (0.62–2.91) 1.32 (0.72–2.45) 2.33 (0.71–7.63) 5.29 (1.31–21.30), p trend = 0.06	Smokers and nonsmokers	No adjustments	None
		Lymphoma	
6.7 (1.0–43.4) 6.4 (1.0–45.5) 5.6 (0.9–37.5)	Smokers and nonsmokers	No adjustments	None

Table 5.12 Continued

Study	Population	Exposure period	Source of exposure
		Lymphoma	
Sorahan et al. 1995	Deaths among children in England, Wales, and Scotland between 1977 and 1981; included less than 50% of population cancer cases	Prenatal	Father smoked
Ji et al. 1997	Children aged <15 years in Shanghai (China), diagnosed with lymphoma between 1985 and 1991; population-based controls were from household registry	NR	Father smoked <10 cigarettes/day Father smoked 10–14 cigarettes/day Father smoked ≥15 cigarettes/day
		NR	Father smoked <10 years Father smoke 10–14 years Father smoked ≥15 years
		Preconception	Father smoked ≤2 pack-years Father smoked >2 to <5 pack-years Father smoked ≥5 pack-years
		Postnatal	Father smoked ≤2 pack-years Father smoked >2 to <5 pack-years Father smoked ≥5 pack-years
Sorahan et al. 1997a	Deaths among children in England, Wales, and Scotland between 1953 and 1955; included 79% of population cancer cases	Current	Father smoked
Sorahan et al. 1997b	Deaths among children in England, Wales, and Scotland between 1971 and 1976; included 51% of population cancer cases	Current	Father smoked
Sorahan et al. 2001	Children aged <15 years in the United Kingdom, diagnosed with cancer (other reticuloendothelial system cancers) between 1980 and 1983; hospital controls were acute surgical and accident patients; general practitioner controls were population based	Preconception	Father smoked <10 cigarettes/day Father smoked 10–19 cigarettes/day Father smoked 20–29 cigarettes/day Father smoked 30–39 cigarettes/day Father smoked ≥40 cigarettes/day

Risk (95% CI*)	Maternal smoking status	Confounding	Comments
		Lymphoma	
1.14 (0.99–1.31)	Smokers and nonsmokers	Matched for gender and date of birth	Risk is for 1 level increase in daily amount of cigarettes smoked (e.g., 6 levels from nonsmokers to ≥40 cigarettes/day)
3.4 (0.8–14.0) 1.1 (0.3–4.8) 3.8 (0.9–16.5), p trend = 0.09	Nonsmokers	For all analyses: Matched for gender and birth year; adjusted for: birth weight; income; and paternal age, education, and alcohol consumption	Data were not collected on paternal smoking during mother's pregnancy; interviews took place ≥10 years after pregnancy
1.3 (0.2–7.0) 3.4 (0.9–12.7) 3.5 (0.9–13.7), p trend = 0.05	Nonsmokers		
3.1 (0.8–11.4) 1.8 (0.4–7.8) 4.5 (1.2–16.8), p trend = 0.07	Nonsmokers		
3.9 (0.9–16.0) 2.7 (0.8–9.6) 5.0 (1.2–22.4), p trend = 0.08	Nonsmokers		
1.37 (1.02–1.83), p <0.05	Smokers and nonsmokers	Matched for gender, date of birth, and residence; adjusted for maternal smoking	Exposure assessment for current smoking only; time from birth to interviews was not reported; risk is for 1 level increase in daily amount of cigarettes smoked (e.g., 4 levels from <1 cigarette/day to >20 cigarettes/day)
1.07 (0.92–1.23)	Smokers and nonsmokers	Matched for gender, date of birth, and residence; adjusted for maternal smoking	Exposure assessment for current smoking only; median time between birth and interviews for cases was 8.5 years, and 97% of cases were interviewed before the fourth anniversary of the child's death; nonsmokers included former smokers; risk is for a 1 level increase in daily amount of cigarettes smoked (e.g., 6 levels from nonsmokers to ≥40 cigarettes/day)
General practitioner controls: 1.32 (0.32–5.51) 2.65 (0.83–8.46) 3.69 (1.49–9.15) 0.29 (0.03–2.56) 1.20 (0.29–5.05), p trend = 0.35	Smokers and nonsmokers	No adjustments	None

Table 5.12 Continued

Study	Population	Exposure period	Source of exposure
		Central nervous system (CNS) cancers	
Preston-Martin et al. 1982	Brain tumor cases aged <25 years, residents of Los Angeles County, diagnosed between 1972 and 1977; identified through the Los Angeles County Cancer Surveillance Program	Prenatal	Mother lived with a smoker
Howe et al. 1989	Brain tumor cases aged ≤19 years, diagnosed at two hospitals in Toronto between 1977 and 1983	Prenatal	Father smoked
Kuijten et al. 1990	Astrocytoma cases aged <15 years, diagnosed between 1980 and 1986; identified through tumor registries in 8 hospitals in Pennsylvania, New Jersey, and Delaware; controls were selected by random-digit dialing	Prenatal	Maternal exposure to secondhand smoke
Gold et al. 1993	Brain tumor cases aged <18 years, diagnosed between 1977 and 1981; identified through 8 SEER$^{\Delta}$ Program registries	During the year of child's birth 2 years before child's birth	Father smoked <1 pack/day Father smoked ≥1 pack/day Father smoked <1 pack/day Father smoked ≥1 pack/day
Bunin et al. 1994	Astrocytoma cases aged <6 years, diagnosed between 1986 and 1989; identified through clinical trial registries in the United States	Prenatal Prenatal	Maternal exposure to secondhand smoke Father smoked
Filippini et al. 1994	Brain tumor cases aged ≤15 years, diagnosed between 1985 and 1988; identified through 8 hospitals in northern Italy	3 months before conception Before mother was aware of pregnancy After mother was aware of pregnancy	Father smoked ≤2 hours/day secondhand smoke exposure >2 hours/day secondhand smoke exposure ≤2 hours/day secondhand smoke exposure >2 hours/day secondhand smoke exposure
McCredie et al. 1994	Brain tumor cases aged <15 years in New South Wales (Australia), diagnosed between 1985 and 1989; identified through the New South Wales Central Cancer Registry	Preconception Prenatal	Father ever smoked Father smoked

Risk (95% CI†)	Maternal smoking status	Confounding	Comments
		Central nervous system (CNS) cancers	
1.5 (p = 0.03)	Smokers and nonsmokers	Matched for gender, race, and birth year (within 3 years)	None
1.13 (0.615–2.09)	Smokers and nonsmokers	Matched for gender; adjusted for age at diagnosis	None
0.8 (0.5–1.3)	Smokers and nonsmokers	Matched for age, race, and telephone area code and exchange	None
0.68 (0.39–1.19) 1.07 (0.79–1.45) 0.90 (0.53–1.51) 1.15 (0.85–1.56)	Smokers and nonsmokers	Matched for age, gender, and maternal race	None
0.9 (0.6–1.5) 1.0 (0.6–1.7)	Smokers and nonsmokers	Matched for race, birth year, and telephone area code and prefix; adjusted for income	None
1.3 (0.8–2.2) 1.5 (0.7–3.5) 1.7 (0.8–3.7), p trend = 0.08 1.7 (0.8–3.8) 2.2 (1.1–4.6), p trend = 0.02	Smokers and nonsmokers Nonsmokers Nonsmokers	For all analyses: Matched for birth date, gender, and area of residence; adjusted for paternal education	Mean age at diagnosis was 8.5 years, so interviews took place more than 8 years after birth
2.0 (1.0–4.1) 2.2 (1.2–3.8)	Nonsmokers Smokers and nonsmokers	Matched for age and gender; adjusted for paternal education	None

Table 5.12 Continued

Study	Population	Exposure period	Source of exposure
		Central nervous system (CNS) cancers	
Norman et al. 1996a	Brain tumor cases aged ≤19 years, diagnosed between 1984 and 1991; identified through 19 U.S. West Coast SEER Program registries	Prenatal	Father smoked
Sorahan et al. 1997a	CNS cancer deaths among children in England, Wales, and Scotland between 1953 and 1955; included 79% of population cancer cases	Current	Father smoked
Sorahan et al. 1997b	CNS cancer deaths among children in England, Wales, and Scotland between 1971 and 1976; included 51% of population cancer cases	Current	Father smoked
Filippini et al. 2000	CNS tumor cases aged ≤15 years in northern Italy, diagnosed between 1988 and 1993; cases were identified through hospital records	5 years before conception	Father smoked
		Before mother was aware of pregnancy	≤2 hours/day secondhand smoke >2 hours/day secondhand smoke
		After mother was aware of pregnancy	≤2 hours/day secondhand smoke >2 hours/day secondhand smoke
		Before mother was aware of pregnancy	Secondhand smoke
		After mother was aware of pregnancy	Secondhand smoke

*CI = Confidence interval.
†SES = Socioeconomic status.
‡NR = Data were not reported.
§Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
ΔSEER = Surveillance, Epidemiology, and End Results.

Risk (95% CI	Maternal smoking status	Confounding	Comments
		Central nervous system (CNS) cancers	
1.2 (0.9–1.5)	Nonsmokers	Adjusted for gender, age at diagnosis or selection as control participant, birth year of child, and maternal race	None
CNS cancers 1.20 (0.96–1.51) Neuroblastoma 1.48 (1.09–2.02), p <0.05	Smokers and nonsmokers	Matched for gender, date of birth, and residence; adjusted for maternal smoking	Exposure assessment for current smoking only; time from birth to interviews was not reported; risk is for 1 level increase in daily amount of cigarettes smoked (e.g., 4 levels from <1 cigarette/day to >20 cigarettes/day)
CNS cancers 1.02 (0.93–1.11) Neuroblastoma 1.13 (0.99–1.29)	Smokers and nonsmokers	Matched for gender, date of birth, and residence; adjusted for SES, age of father and mother at child's birth, sibship position, obstetric radiography, and maternal smoking	Exposure assessment for current smoking only; median time between birth and interviews for cases was 8.5 years, and 97% of cases were interviewed before the fourth anniversary of the child's death; nonsmokers included former smokers; risk is for 1 level increase in daily amount of cigarettes smoked (e.g., 6 levels from nonsmokers to ≥40 cigarettes/day)
1.2 (0.9–1.7)	Smokers and nonsmokers	Adjusted for age, gender, and residence	Time from birth to interviews was ≤20 years
1.7 (1.1–2.7) 1.8 (1.1–2.9)	Nonsmokers		
1.7 (1.1–2.6) 1.7 (1.1–2.6)	Nonsmokers		
Astroglial: 2.0 (1.2–3.4)	Nonsmokers		
Astroglial: 1.8 (1.1–3.0)	Nonsmokers		

paternal smoking. Thus, some of the elevated risks for cancer in their offspring from paternal smoking may have been compounded by the child's postnatal exposure to active maternal smoking.

Conclusions

1. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood cancer.

2. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal exposure to secondhand smoke during pregnancy and childhood cancer.

3. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke during infancy and childhood cancer.

4. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood leukemias.

5. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood lymphomas.

6. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood brain tumors.

7. The evidence is inadequate to infer the presence or absence of a causal relationship between prenatal and postnatal exposure to secondhand smoke and other childhood cancer types.

Implications

Childhood cancers are diverse in their characteristics and etiology. Although the evidence is inadequate for some sources and periods of exposure, there is some evidence indicative of associations of childhood cancer risk with secondhand smoke exposure. Further research is needed to provide a better understanding of the potential causal relationships between types of exposures to secondhand smoke and childhood cancer risks.

Conclusions

Fertility

1. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal exposure to secondhand smoke and female fertility or fecundability. No data were found on paternal exposure to secondhand smoke and male fertility or fecundability.

Pregnancy (Spontaneous Abortion and Perinatal Death)

2. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal exposure to secondhand smoke during pregnancy and spontaneous abortion.

Infant Deaths

3. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and neonatal mortality.

Sudden Infant Death Syndrome

4. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and sudden infant death syndrome.

Preterm Delivery

5. The evidence is suggestive but not sufficient to infer a causal relationship between maternal exposure to secondhand smoke during pregnancy and preterm delivery.

Low Birth Weight

6. The evidence is sufficient to infer a causal relationship between maternal exposure to secondhand smoke during pregnancy and a small reduction in birth weight.

Congenital Malformations

7. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and congenital malformations.

Cognitive Development

8. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and cognitive functioning among children.

Behavioral Development

9. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and behavioral problems among children.

Height/Growth

10. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and children's height/growth.

Childhood Cancer

11. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood cancer.

12. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal exposure to secondhand smoke during pregnancy and childhood cancer.

13. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke during infancy and childhood cancer.

14. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood leukemias.

15. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood lymphomas.

16. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood brain tumors.

17. The evidence is inadequate to infer the presence or absence of a causal relationship between prenatal and postnatal exposure to secondhand smoke and other childhood cancer types.

Overall Implications

Because infant mortality for the United States is quite high compared with other industrialized countries, identifying strategies to reduce the number of infant deaths should receive high priority. The epidemiologic evidence for the association of secondhand smoke exposure and an increased risk of SIDS indicates that eliminating secondhand smoke exposures among newborns and young infants should be part of an overall strategy to reduce the high infant mortality rate in the United States.

The available evidence for five reproductive and childhood outcomes—childhood cancer, cognitive development, behaviors, LBW, and spontaneous abortion—calls for further research with improved methodologies. The methodologic challenges and issues that were discussed in relation to exposure assessment and reproductive outcomes might act as a guide for future research on these topics. There is a need for studies that examine exposure to secondhand smoke and childhood cancers to further evaluate the risks for specific cancer types. The evidence reviewed in this chapter points to germ-cell mutations among fathers who smoke as a possible pathway. Additional studies may be warranted that focus on childhood cancer and active paternal smoking, with improved controls for maternal secondhand smoke exposure and active smoking during pregnancy and the exposure of infants to secondhand smoke. For secondhand smoke and spontaneous abortions, studies using samples with adequate statistical power are needed. For all outcomes, investigations should include biochemical measures of exposures, and these measures should be used to determine the presence of dose-response relationships—determining dose-response relationships will greatly facilitate the assessment of causality.

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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

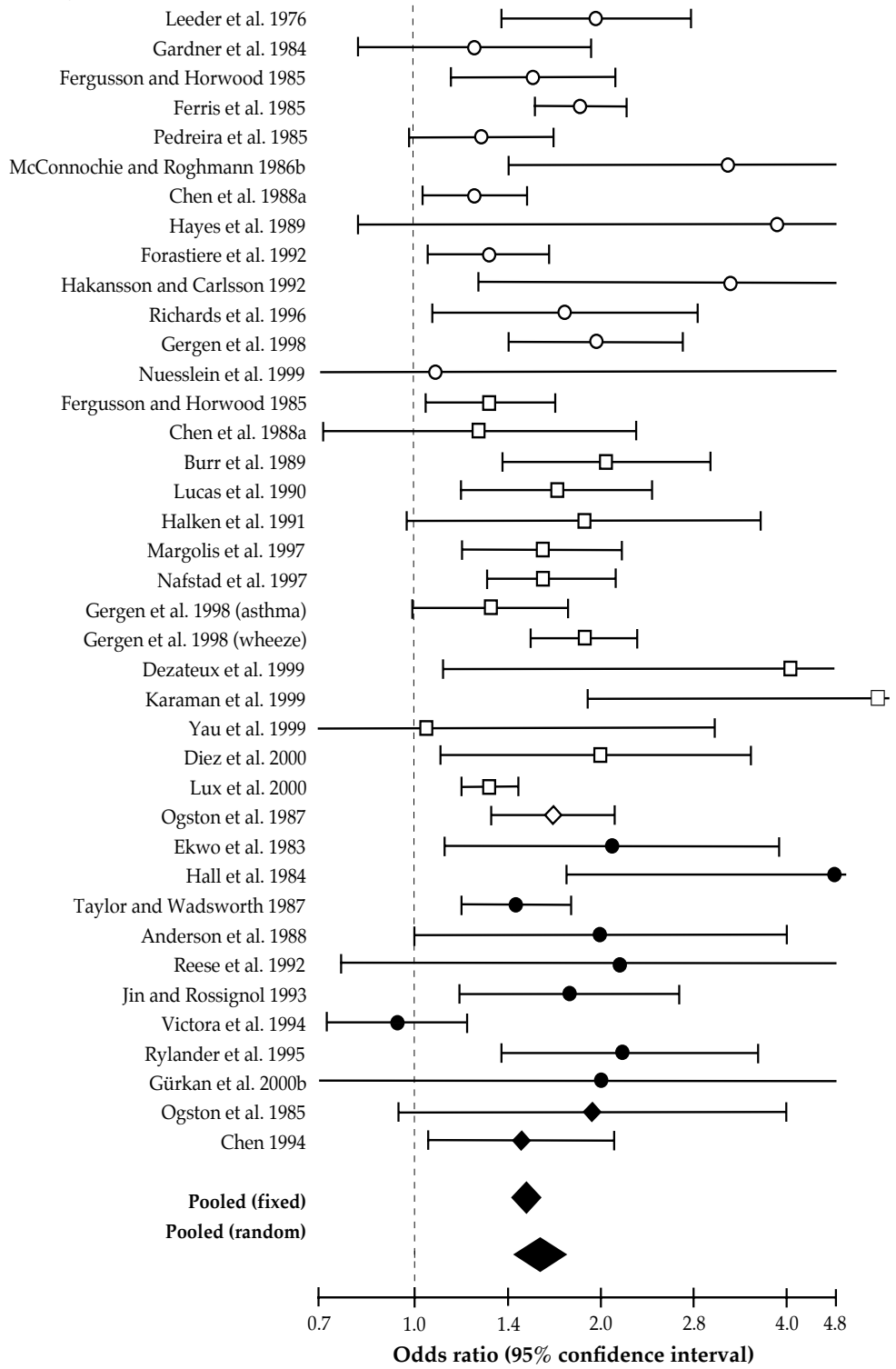
Study	Cases/ controls	Dose-response relationship	Outcome	Odds ratio for smoking (95% confidence interval)			
				Either parent	Mother	Father/other*	Both parents
Community studies of upper and lower respiratory illnesses (U/LRIs)							
Ogston et al. 1987	486/1,056	No; number of smokers	U/LRIs	1.68 (1.33–2.11)	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

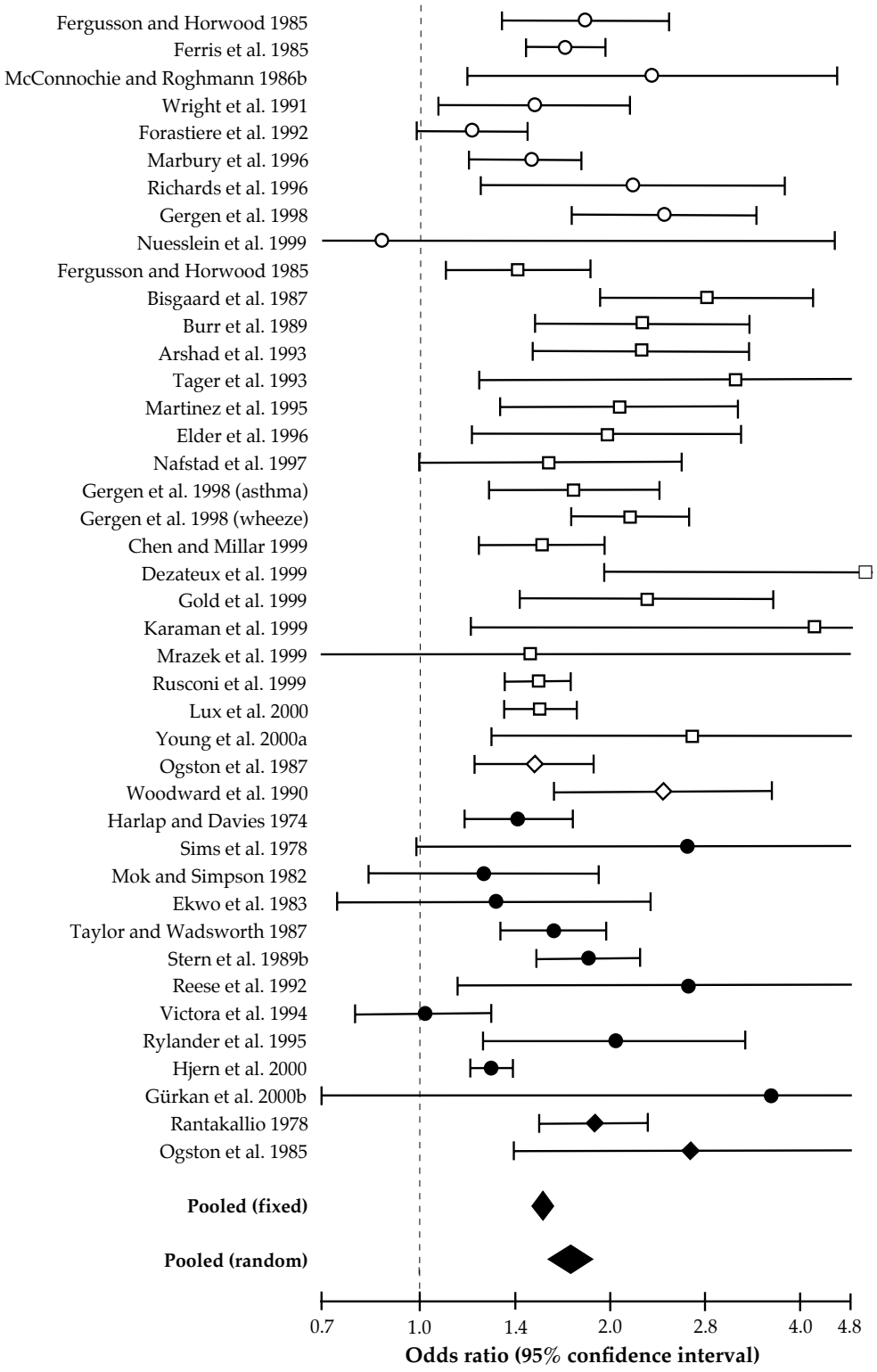
*In households where the mother did not smoke (compared with smoking by neither parent).
[†]NR = Data were not reported.
[‡]Results were published as person-time incidence rates; rate ratios, rather than odds ratios, are shown.
[§]Odds ratio or relative risk was cited in the paper without tabulated numerical 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



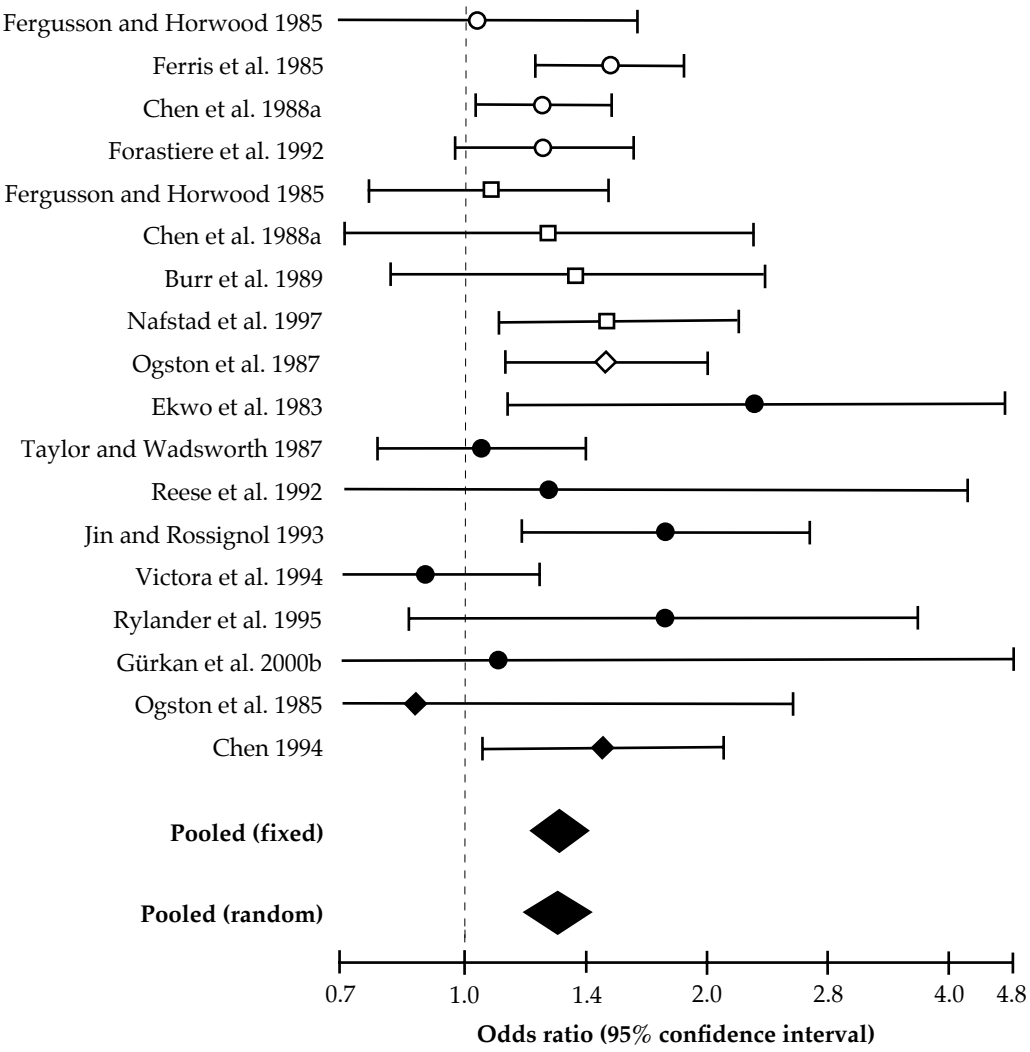
Note: Individual studies are denoted with the following symbols:
Circles = Studies of lower respiratory illnesses.
Squares = Studies of wheeze illnesses.
Diamonds = Studies of upper and lower respiratory illnesses.
Open symbols = Community studies.
Closed symbols = Studies of hospitalized illnesses.

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

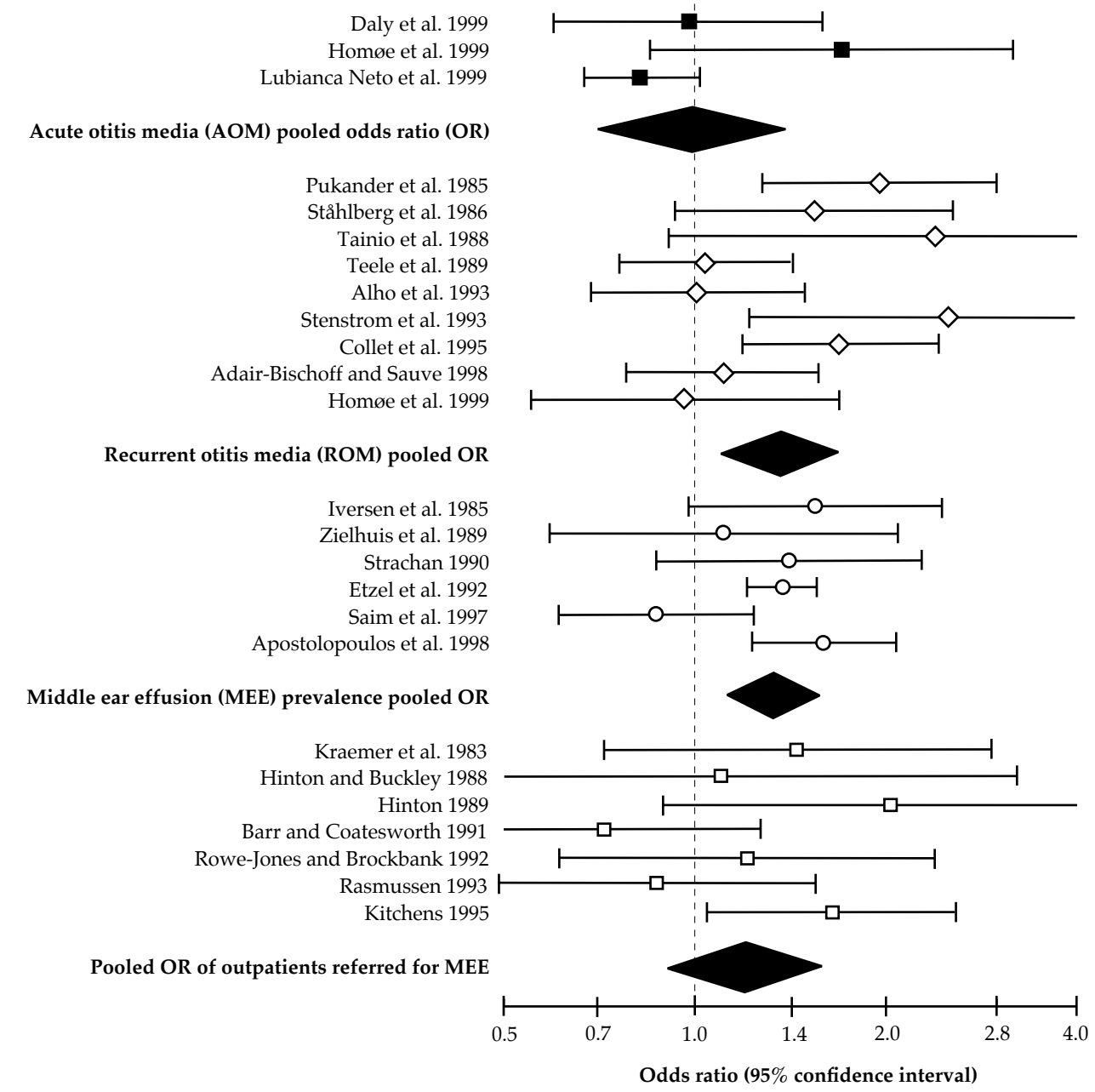
Study	Outcome	Odds ratio for smoking			Factors adjusted for or addressed in the text
		Exposure	Unadjusted	Adjusted	
		ROM			
Collet et al. 1995	ROM	Both parents	2.08	1.80	Gender, family history of OM, day care, SES
Ey et al. 1995	ROM	Mother smoked >20 cigarettes/day	2.10	1.78	Gender, siblings, day care, 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).

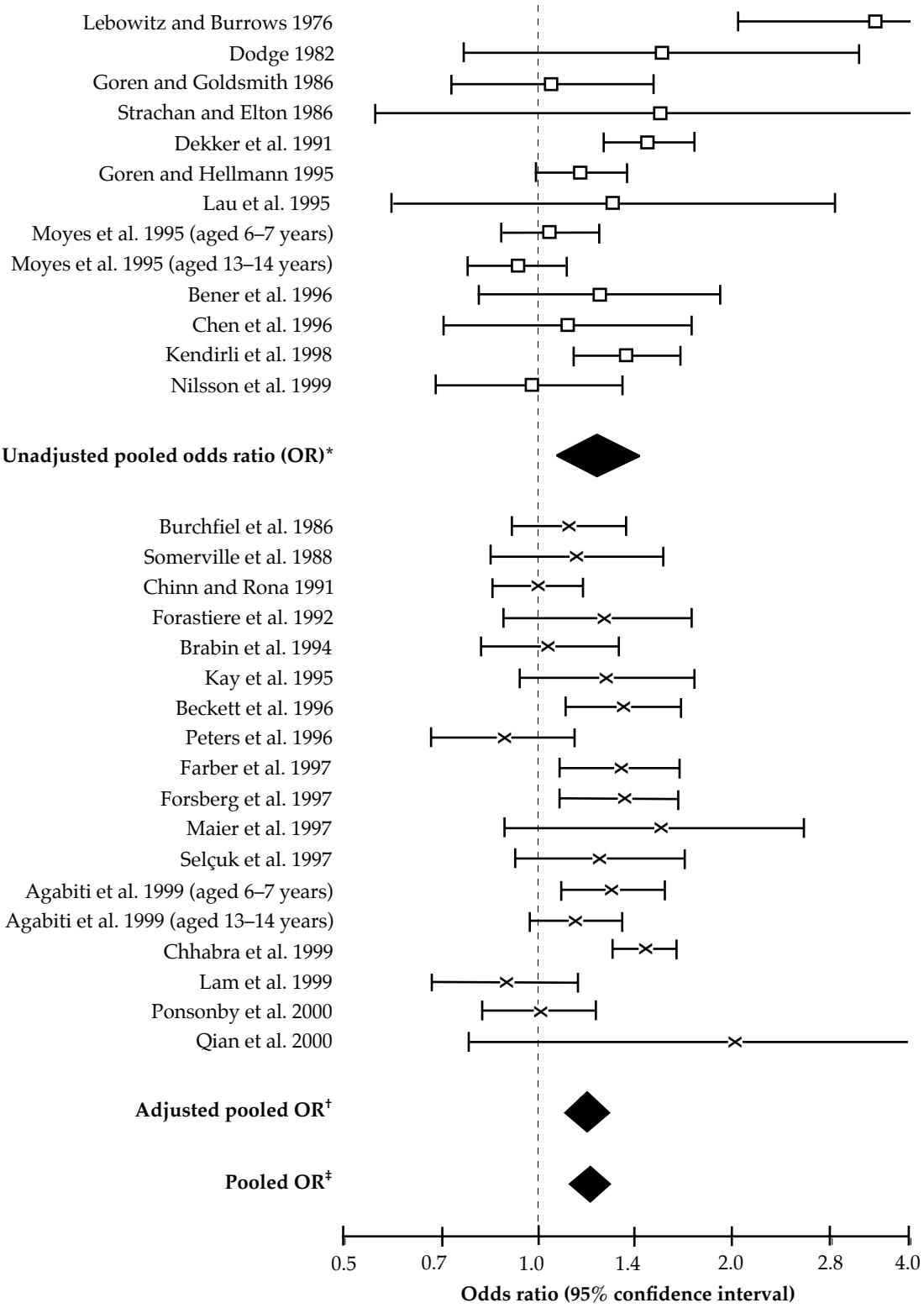
Pooled Odds Ratios

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

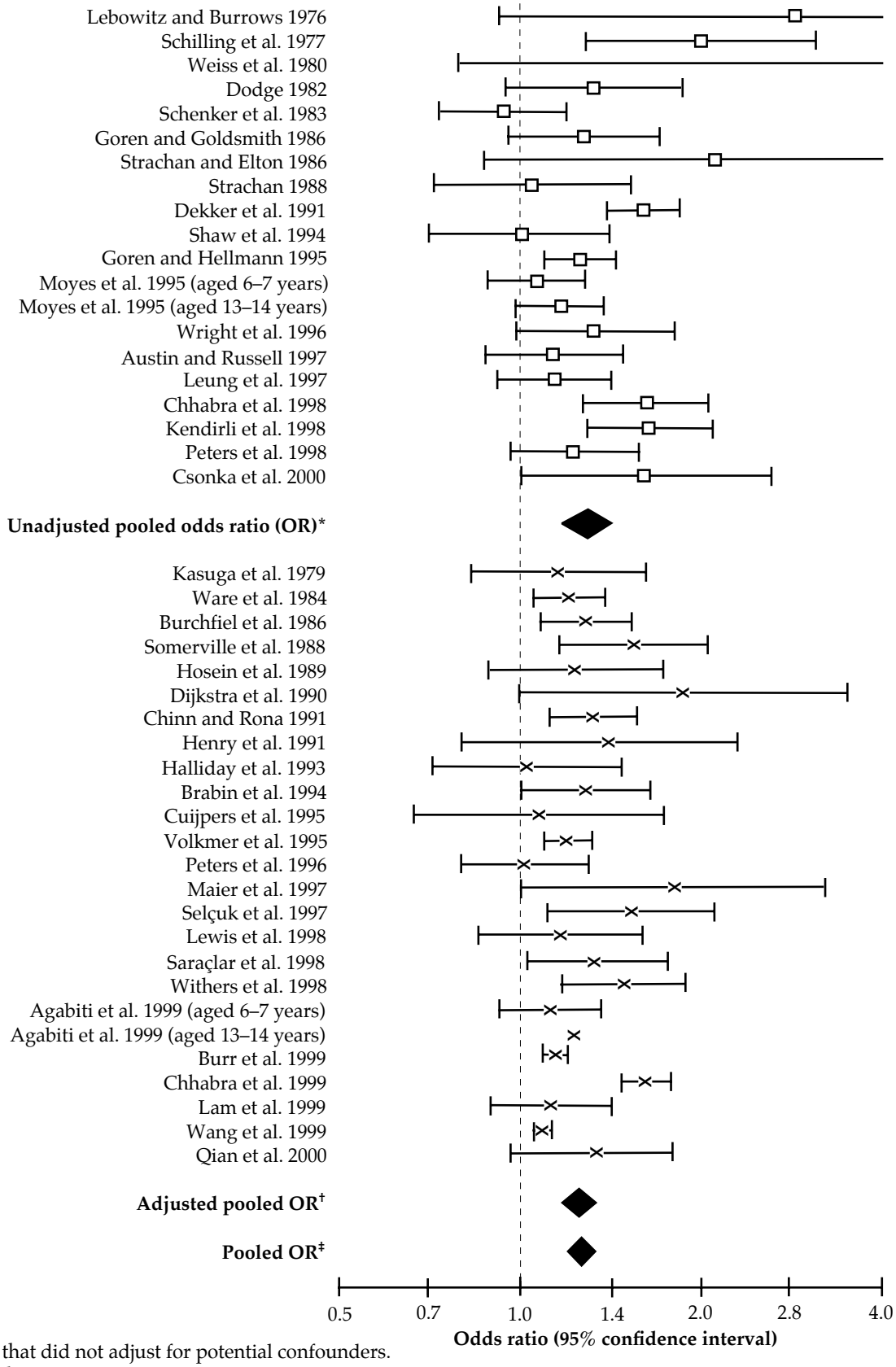
Table 6.11 Continued

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.

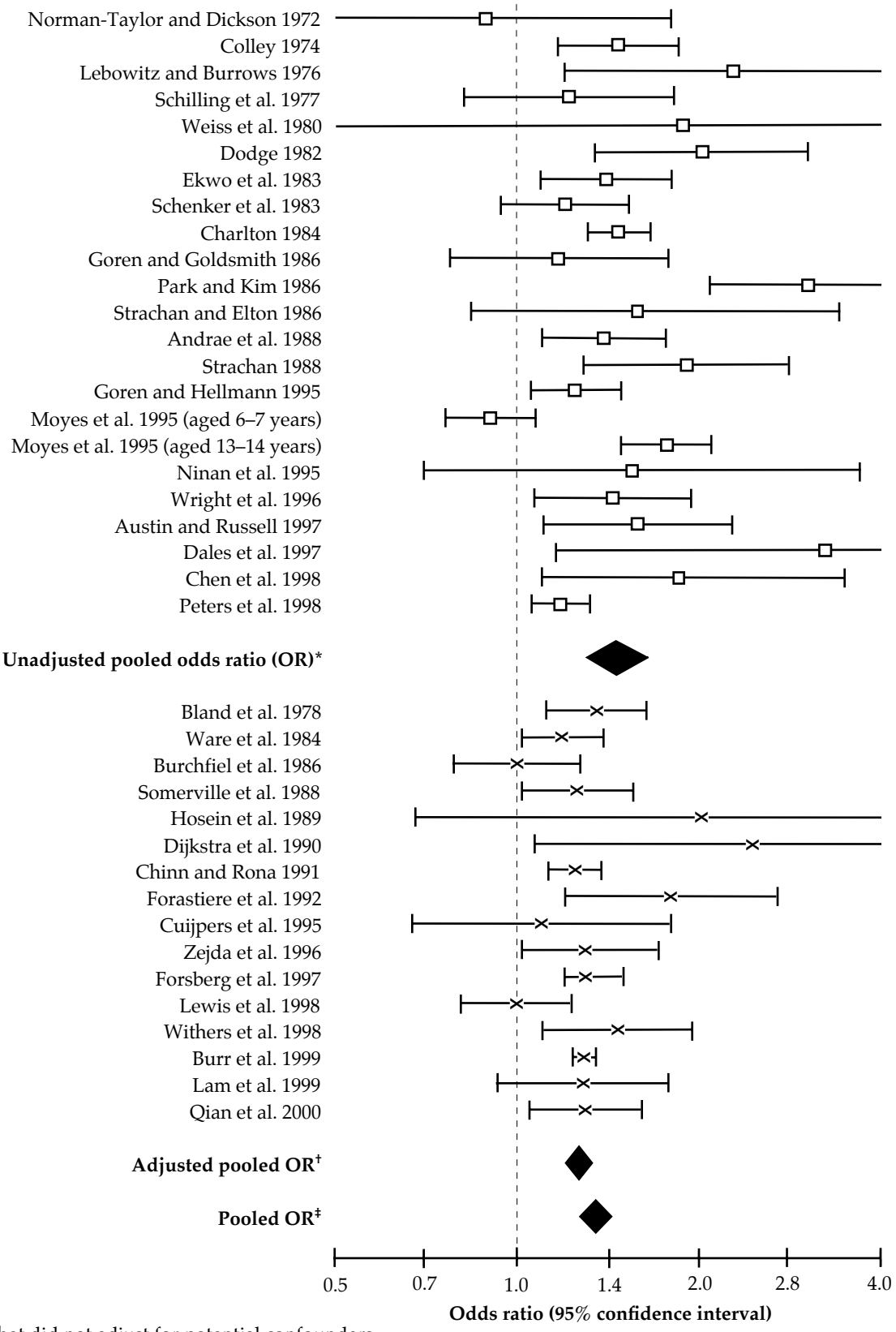
Odds ratio for smoking (95% confidence interval)				
One parent only vs. neither	**Both parents vs. neither**	**Mother only vs. neither**	**Father only vs. neither**	**Confounders adjusted for**
NR	NR	1.33† (1.2–1.5)	NR	Atopy, parental asthma, early life bronchitis
NR	NR	NR	NR	Gender, area, pets, cooking 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

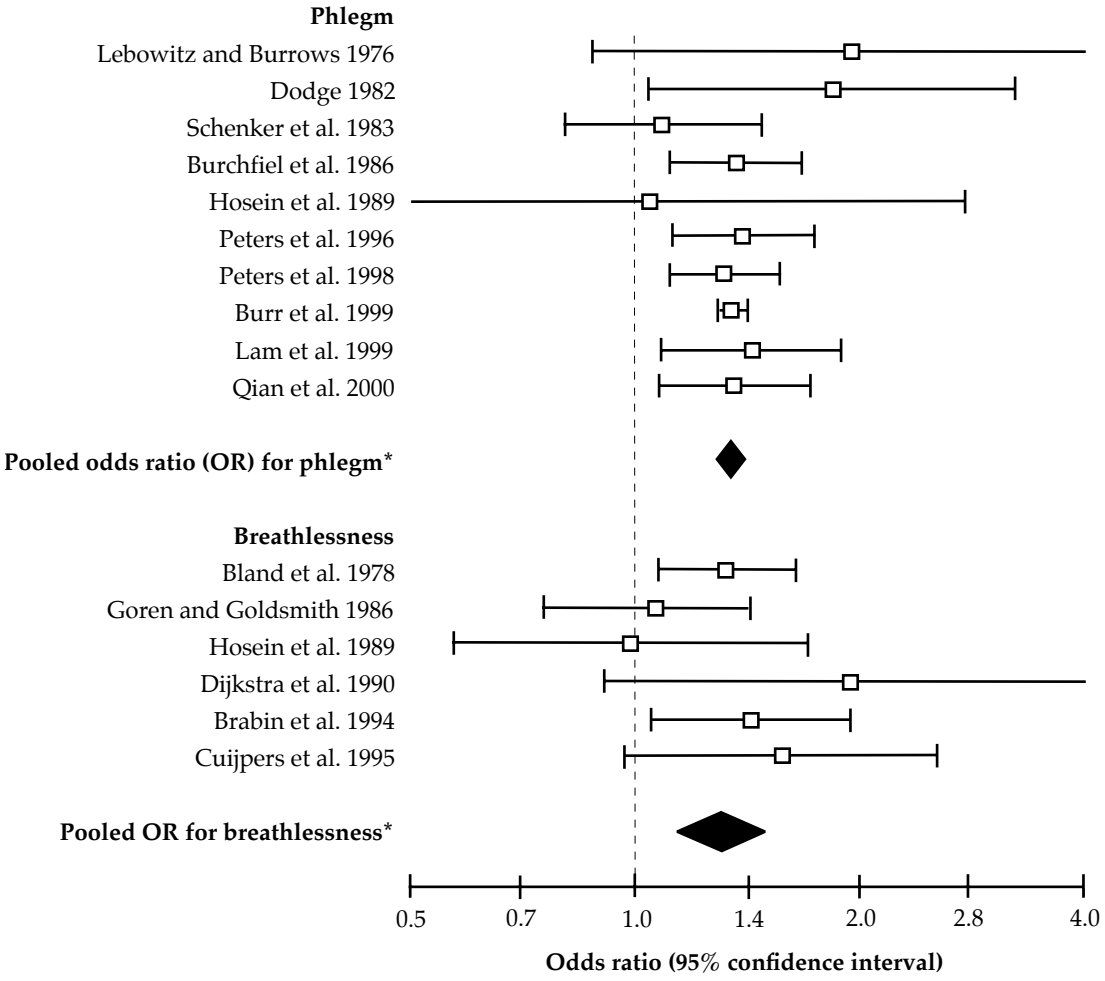
Table 6.13 Studies of phlegm and breathlessness associated with parental smoking

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

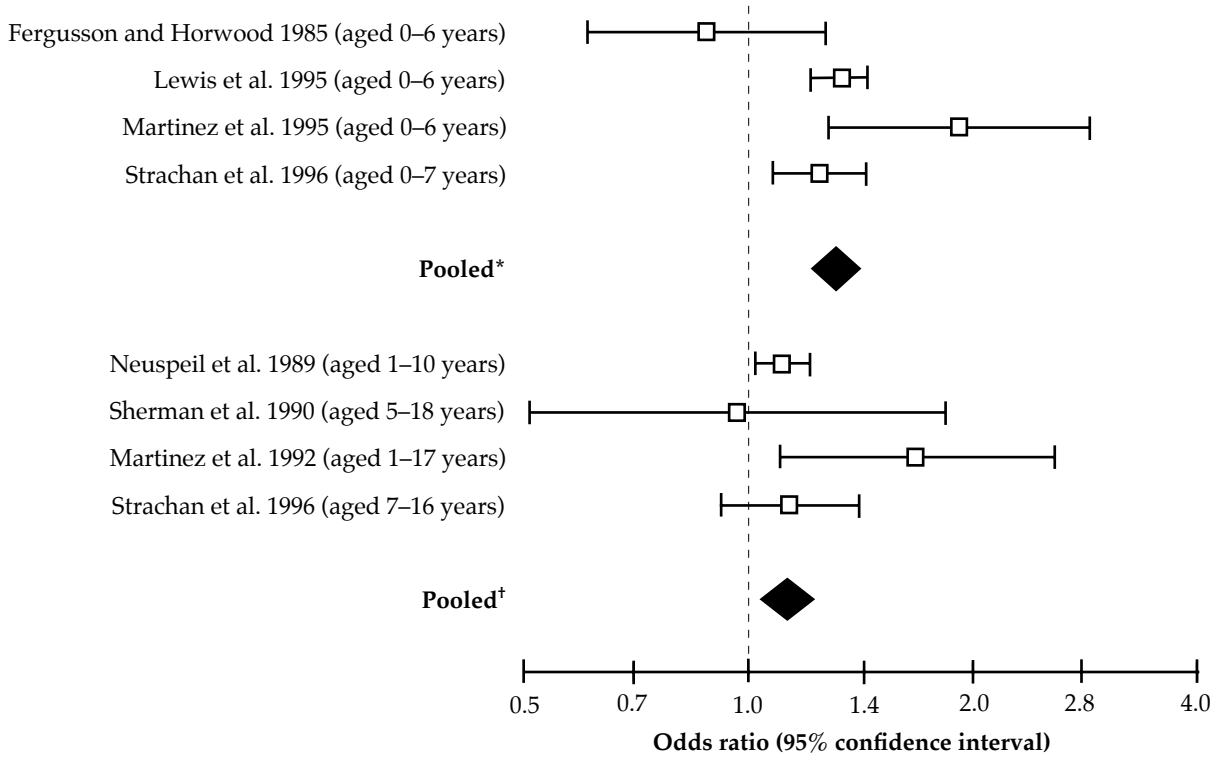
Study	Population		Age (years) at start/end (length of follow-up period)	Smoking exposure	Outcome	Odds ratio for smoking (95% confidence interval)
	Cases	Non-cases				
Incidence studies						
Fergusson and Horwood 1985	141	891	0/6	Mother smoked	Asthma	0.88* (0.61–1.27)
	141	891	0/6	Father smoked	Asthma	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.

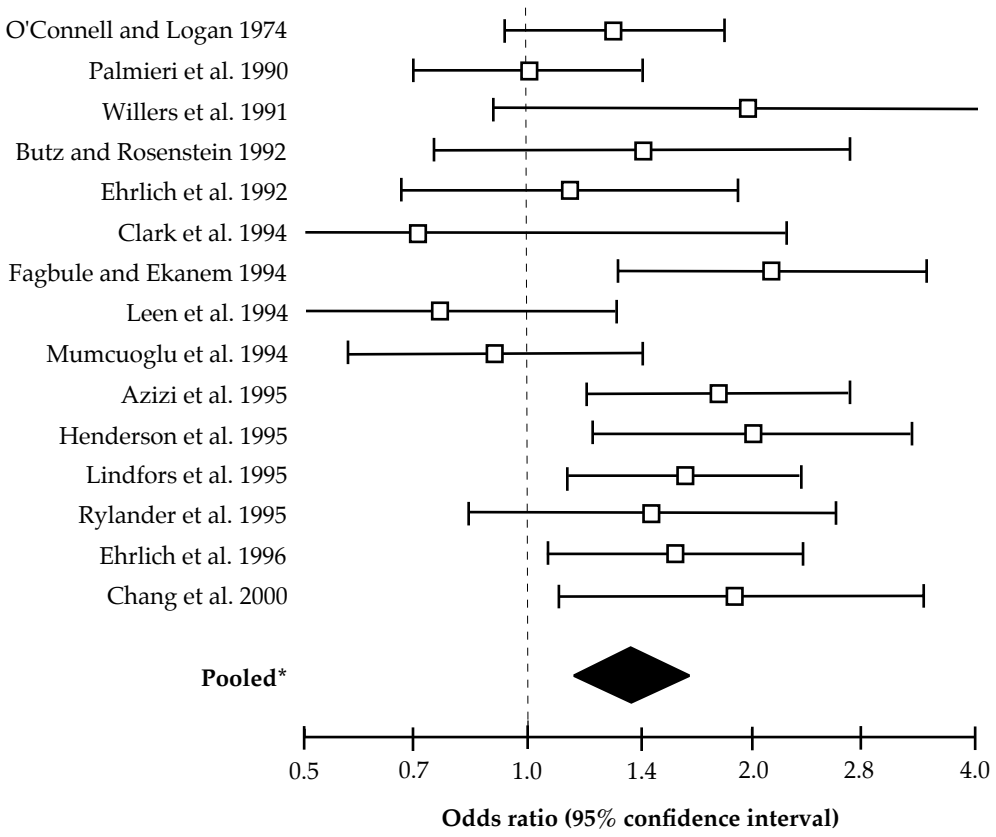
contrasts with prevalence surveys of asthma and wheeze among schoolchildren that found an effect of paternal smoking.

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.

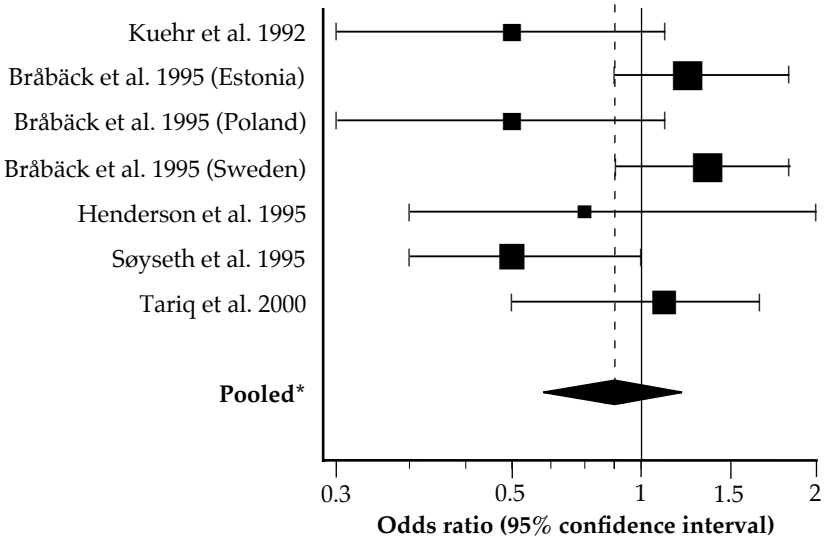
common in those with the highest levels smoked by the mother (current smoking OR = 0.78 [95 percent CI, 0.67–0.92]). A risk for eczema at 16 years of age was not associated with current maternal smoking.

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).

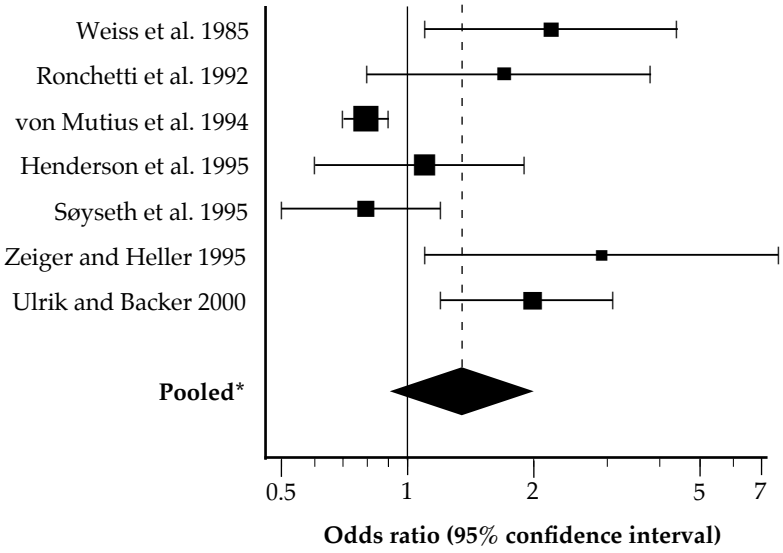
As part of ISAAC, parents answered a supplemental questionnaire regarding indoor environmental exposures and childhood symptoms of atopic rhinitis. For participants in Austria, there were questionnaire responses for 18,606 children aged six through nine years (Zacharasiewicz et al. 2000). Multiple indoor 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



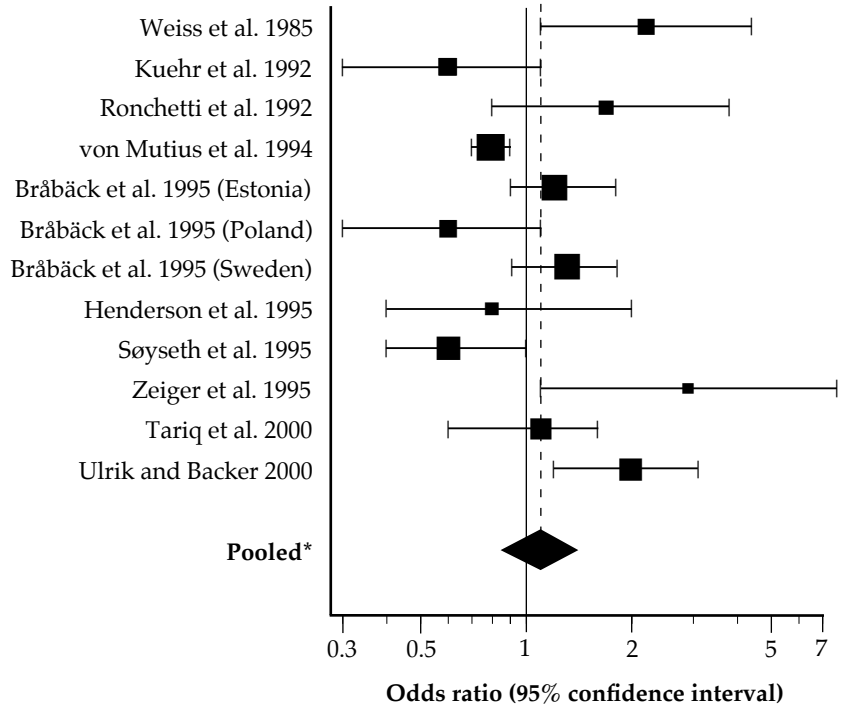
Note: Size of boxes is proportional to the weight of each study in the pooled odds ratio (OR). Solid line represents an OR of 1, dotted line is the combined result.
*From random effects meta-analysis.

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).

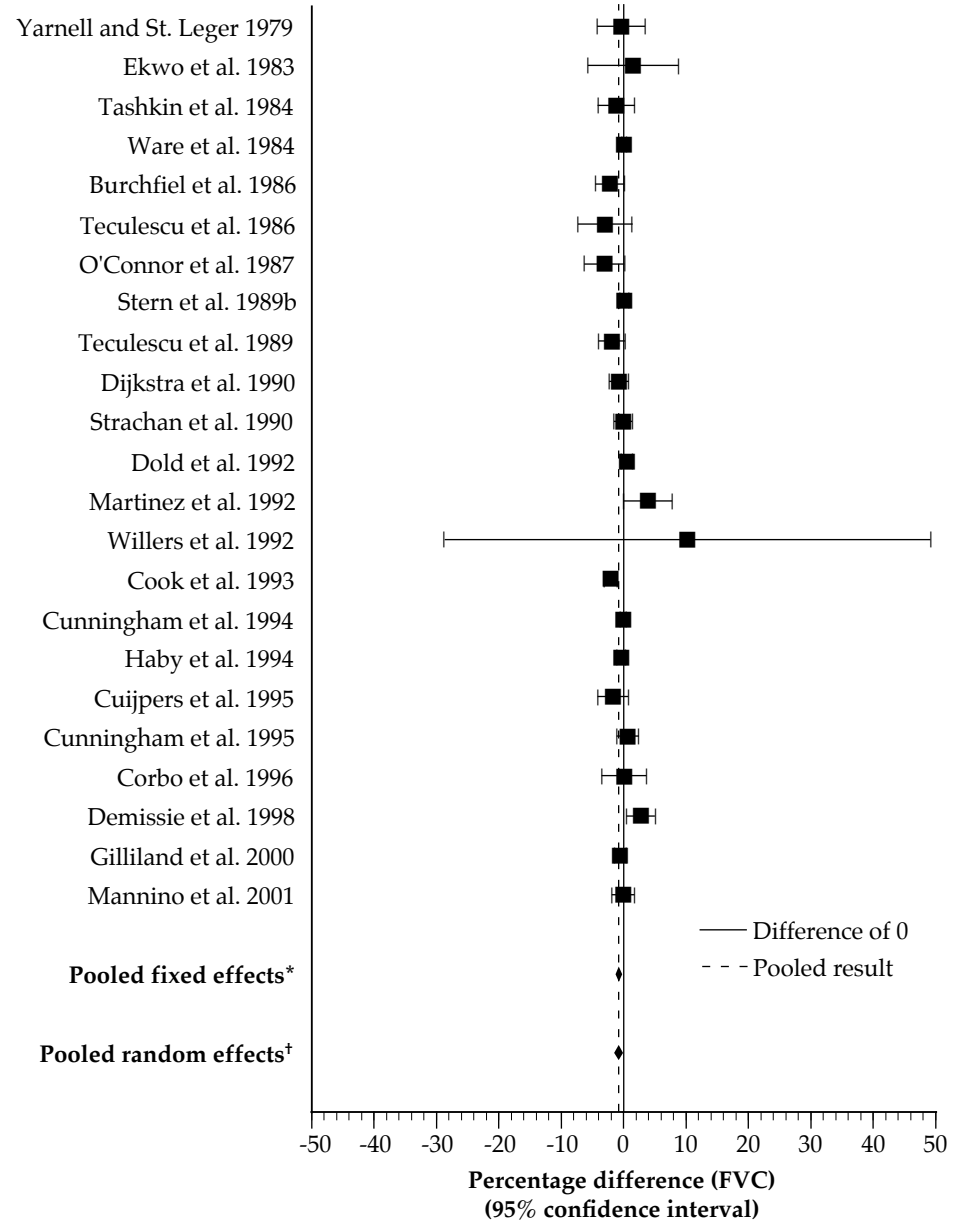
In a meta-analysis of the cross-sectional evidence relating parental smoking to spirometric indices in children (Cook et al. 1998), new cross-sectional studies (published from 1997 to 2000) were identified by using the same search strategy that the 1998 review had used (Cook et al. 1998). Six additional 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.

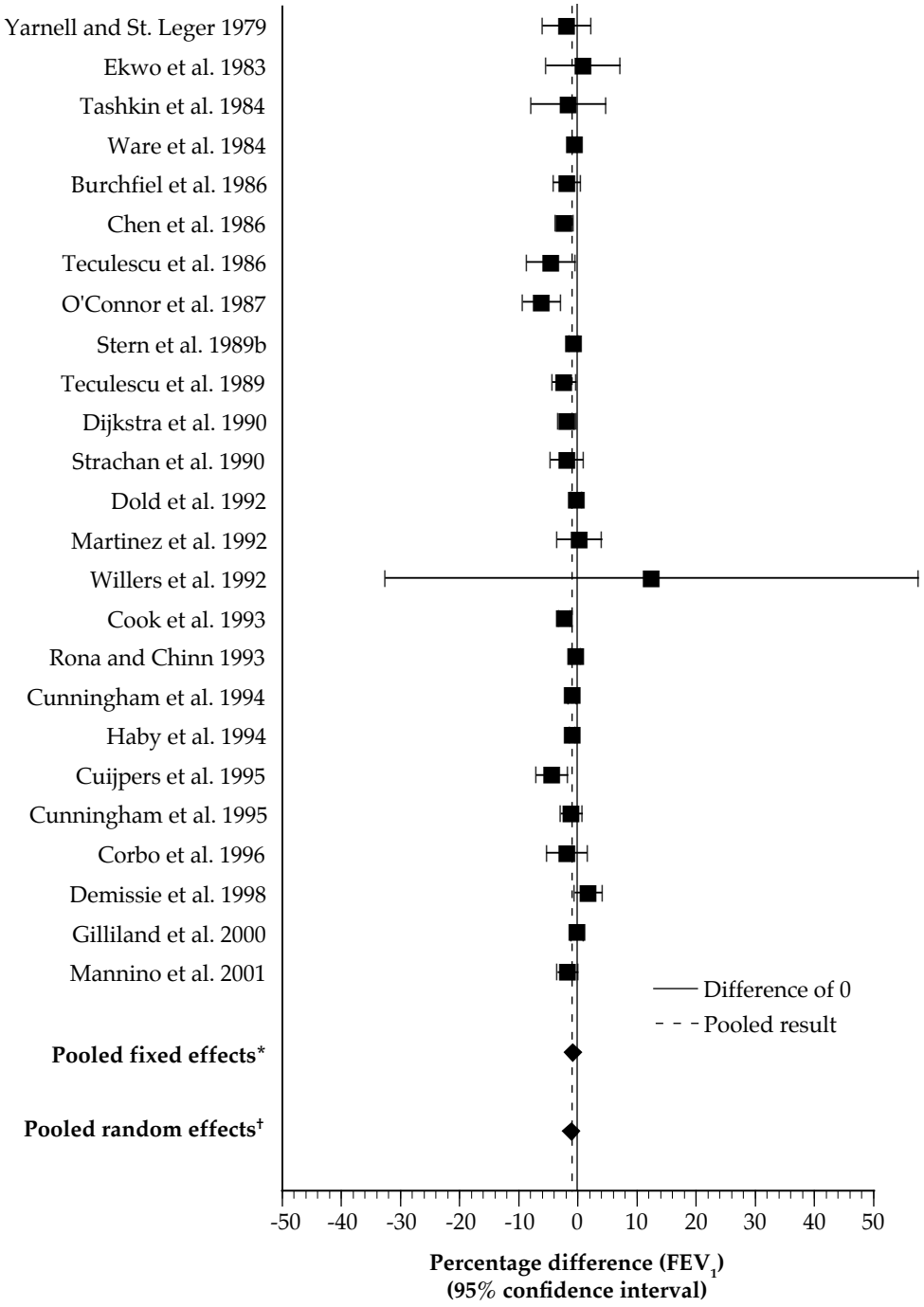
Of the 26 studies included in the updated quantitative synthesis, 4 were not in the 1998 analysis. There was significant variability among studies for all spirometric measures except the EEFR (Figures 6.14–6.17 and Table 6.25). Heterogeneity was

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



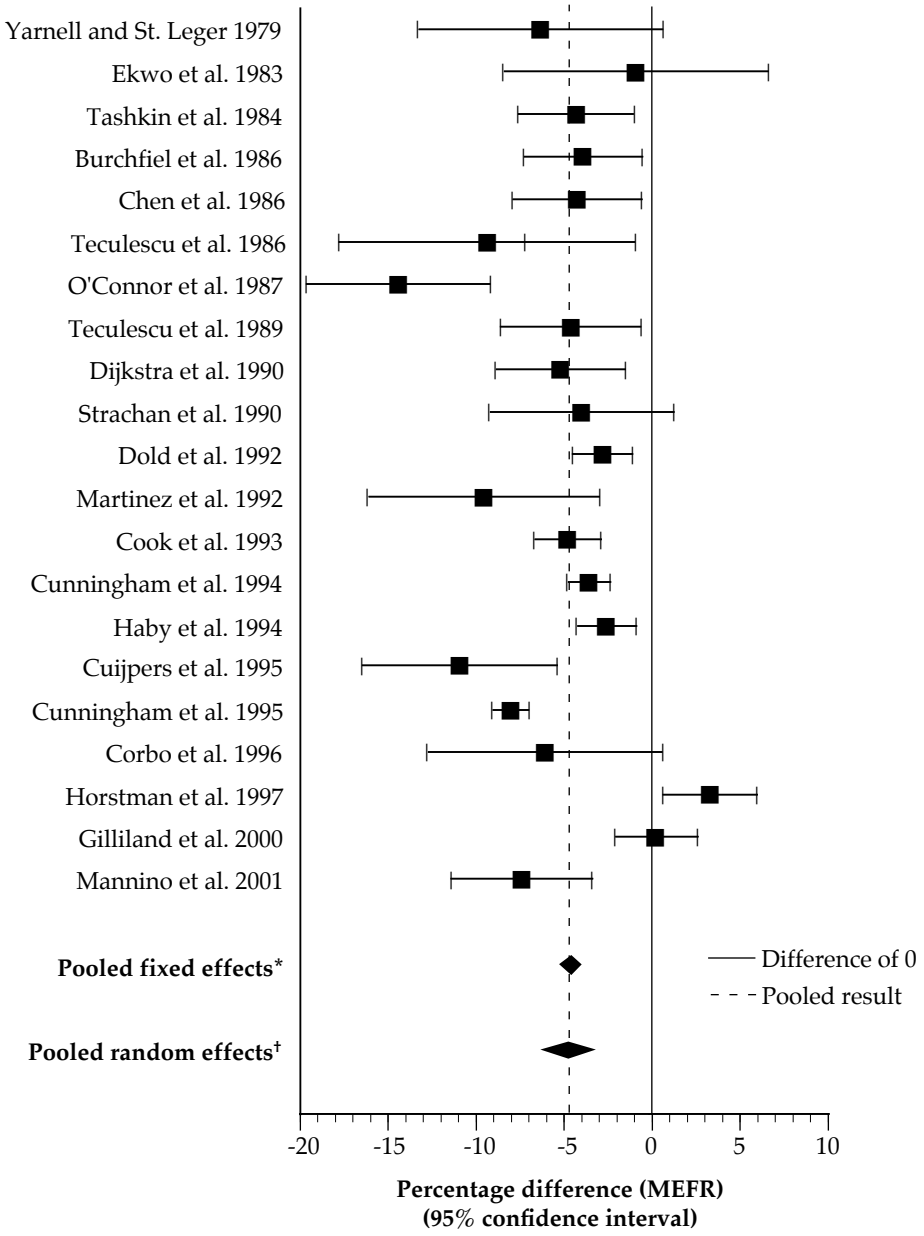
*Pooled difference is from the fixed effects meta-analysis.
†Pooled difference is from the random effects meta-analysis.

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



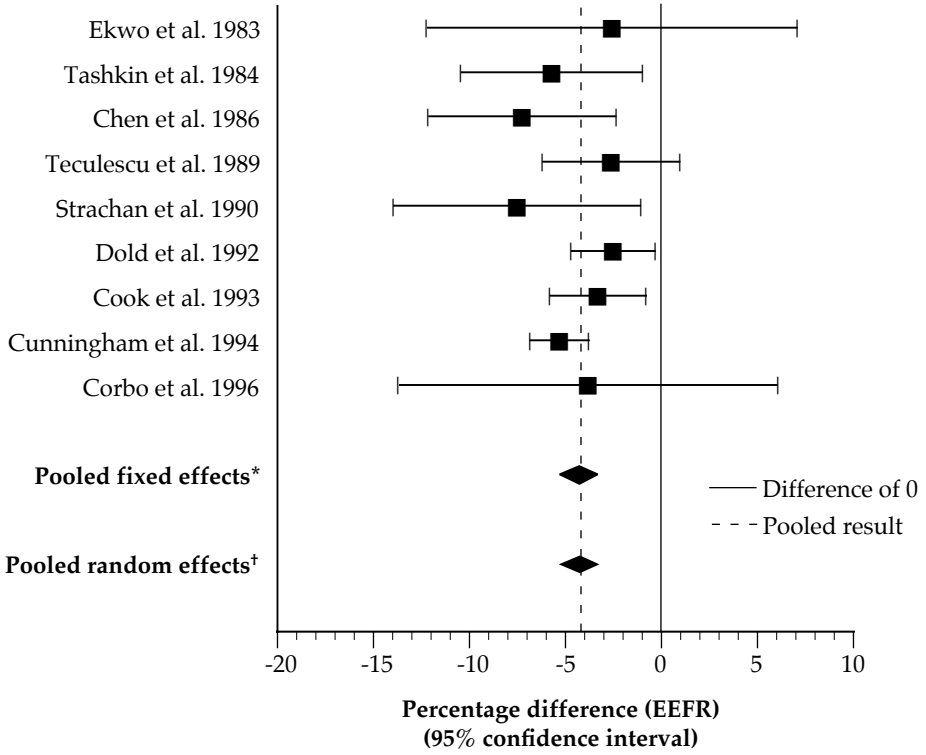
*Pooled difference is from the fixed effects meta-analysis.
†Pooled difference is from the random effects meta-analysis.

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.

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