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Epidemiology of Asthma and Allergic Airway Diseases

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CONTENTS

SUMMARY OF IMPORTANT CONCEPTS

- » Epidemiology is the study of the distribution of disease and, by extension, its causes and consequences, mostly in general populations.
- » The rates of allergic sensitization and allergic diseases have been increasing, although the increase in prevalence of allergic diseases has slowed among children.
- » Allergic disease is less common in rural parts of low-income countries, although allergic sensitization can be common in these areas.
- » There has been very little success in explaining the increased prevalence of allergic disease, although it has been linked to urbanization. The great changes observed in prevalence and distribution strongly suggest a major role for the environment.
- » Factors that initiate allergy and allergic diseases should be differentiated from factors that exacerbate them after they have been established.
- » Allergies are affected by environmental factors, including diet; exposure to a normal, diverse microflora; infections; exposure to air pollutants; and occupational exposures.
- » Allergy is not associated with higher mortality rates or loss of lung function, but asthma is associated with both.
- » Outcomes for asthma can be considerably improved by good management.

Introduction

Epidemiology is the study of the distribution of disease in populations. It is essential for assessing the spread and burden of disease. It is the appropriate method for understanding the cause and pathogenesis of disease.

Definitions and Methods of Measurement

ALLERGY

Definitions

Research into allergy has had a long history with many changes in direction, and the language that has been developed to describe what has been found has changed over time. This can lead to confusion. In this chapter, we use the term *sensitization* to indicate the production of immunoglobulin E (IgE) antibodies in response to allergens. We use the term *allergy* to refer to the presence of one or more diseases associated with IgE sensitization, the most common of which are asthma, eczema, and rhinitis. The term *atopy* was originally introduced to account for the observation that the main allergic diseases occurred in the same families and appeared to have a common origin. However, it is often used synonymously with the term *allergy*.

Tests

Test Standards. Good tests should possess reliability and validity.[1] A test is reliable if it always gives the same answer when applied under similar circumstances. Validity implies that the result of the test coincides well with the true condition of the person being tested. Validity has two components: sensitivity, which is the ability of the test to identify an existing condition, and specificity, which is the ability to identify as normal people who are free of the condition.

Measuring the validity of a test for a condition that is poorly defined, such as asthma, is a problem because it presupposes a gold standard test with which the proposed test can be compared. Although validity in an absolute sense may always be contested, what is as important in epidemiologic studies is standardization, meaning that the test is identical wherever and by whomever it is administered. Validity is essential to the measurement of absolute prevalence, but in many epidemiologic studies, we are as interested in relative prevalence, such as relative prevalence between age groups, countries, or districts, or differences between people exposed to various environmental or genetic risks. Standardization is essential for this, and considerable effort has been made to provide standardized measures, particularly for international studies.

Tests of Sensitization. Sensitization can be assessed directly by determining the presence of specific IgE to allergens in serum. In many places, mites, grass, and cat allergens are among the most common allergens, and most sensitized individuals can be identified by testing for relatively few allergens.[2,3] Some test kits can identify a mixture of several allergens. In the past, they have been used to test for the occurrence of sensitization, and this may be cost-effective, but it leaves unclear which allergens are

responsible for symptoms. Microchip technology and the development of recombinant and purified allergens have enabled testing for several allergens simultaneously and allowed more precise identification of the relevant allergens. The technology remains expensive and is not widely used in epidemiologic studies.

An alternative method of identifying sensitized individuals is to undertake skin-prick tests. They do not require a laboratory and do not involve taking blood. The technique involves introducing a small amount of allergen under the outer layers of the skin using a needle or lancet and reading the size of the wheal that appears in the 15 minutes after the test is applied.[4] This is compared with the wheal produced by a control solution (usually the diluent in which the allergens have been dissolved) and with a positive (usually histamine) control that tests whether the skin is able to respond to the release of mediators that the allergen induces. Skin tests have more operator-dependent variation than serologic tests, because they are influenced in part by the technique of the technician, but they typically are cheap and provide an immediate answer, which can be more satisfactory for the patient or participant. The criterion for a positive test result varies according to the purpose of testing. Using any test greater than the diluent control is more repeatable and less prone to observational error and reflects well the presence of allergen-specific IgE.[5] However, in a clinical context, small wheals are rarely associated with allergic disease that can be ascribed to that allergen, and in a clinical context, wheals less than 3 mm in diameter usually are discounted as irrelevant.

Defining the prevalence of sensitization in a population depends to some extent on which allergens are tested. In Western Europe and the United States, there is little change in overall prevalence after five or six allergens have been included in the panel.[2,3] Although less is known about other countries, mite allergens appear to be widespread in tropical and subtropical areas.

For the most part, skin tests and serologic tests for sensitization give similar results when technical failures and differences between allergens are taken into account. However, they are not equivalent. Skin tests also depend on the ability of mast cells to degranulate and for the skin to respond to histamine. When skin test results are negative, clinical allergy is unlikely even in the presence of specific IgE.[3]

ASTHMA

Definitions

Modern attempts to define asthma start with the CIBA Guest Symposium of 1958 on the terminology, definitions, and classification of chronic pulmonary emphysema and related conditions.[6] The symposium defined asthma as "the condition of subjects with widespread narrowing of the bronchial airways, which changes its severity over time spontaneously or under treatment, and is not due to cardiovascular disease". It further identified the clinical characteristics as "abnormal breathlessness, which may be paroxysmal or persistent, wheezing, and in most cases, relief by bronchodilator drugs (including corticosteroids)."

Soon after the publication of this report, Scadding, one of the contributors to the symposium, made two important points.[7] First, what had been described as a definition in the report was not a true definition in that it did not provide a clear test of whether someone had asthma. What had been provided was, in his view, no more than a description. Second, he pointed out that most diseases were concepts rather than "things" and that their definitions were therefore bound to be contested.

Since then, there have been many attempts to define asthma (Table 48-1), although most have paid little attention to the issues raised by Scadding.[7-14] This led to more complicated descriptions but not to any greater clarity. Some have introduced additional assumptions about mechanisms and causes. Despite these strictures, asthma has been an enduring and trusted concept clinically, but a separate question remains about how the condition can be identified in epidemiologic studies.

Tests

There are effectively three broad methods of identifying asthma in surveys: questionnaires asking about diagnosed asthma, questions about the symptoms of asthma, and physiologic tests of airway responsiveness. Questions asking whether someone has asthma, often qualified by asking whether a doctor has ever confirmed the diagnosis, are common. They are regarded as highly specific, meaning that there are few people who answer this question in the affirmative but do not have asthma, but there are many people who may be defined as asthmatic who deny that they have the condition. The worst characteristic of these questions is the lack of standardization. The answers to the questions depend on local medical practice and the terms used by health professionals when talking to patients. Variations in the use of the term *asthma* likely have influenced estimates of time trends and observed differences in mortality between countries.

Over the past 50 years, the prevalence of people with asthma has increased markedly, and there has been much debate about whether this can be explained by differences in the way the term has been used. This possibility is supported by the encouragement given to pediatricians, particularly from the 1980s onward, to diagnose all wheezy children as asthmatic because this would encourage the use of medication and was shown to enhance the quality of life of children regardless of the exact diagnosis.[15]

In the 1980s, Kelson and Heller sent scenarios of patients who had died to a representative group of physicians signing death certificates in several European countries.[16] One scenario (Box 48-1) described a person who had some symptoms of asthma but many of the features of chronic obstructive lung disease. Figure 48-1 shows the relationship between the proportion of the physicians in each country ascribing this death to asthma and the national mortality rate for asthma.[17] There is a strong suggestion that the way doctors in each country view such marginal cases may be influencing the national mortality data. Whether this is still the case is uncertain. Since then, there has been a major increase in international consensus documents.

Asking about symptoms rather than diagnosed disease avoids some of these problems, and efforts have been made to find suitable questionnaires and to standardize them across countries. The most commonly used questionnaire for children is that developed for the International Study of Asthma and Allergies in Childhood (ISAAC).[18] For adults, the questionnaire developed for the International Union against Tuberculosis and Lung Disease (IUATLD)[19,20] was subsequently adapted for use in the European Community Respiratory Health Survey (ECRHS)[21] and was further adapted for the World Health Survey.[22]

TABLE 48-1 Asthma Definitions

Source	Year	Definition
CIBA Foundation[6]	1959	Condition of subjects with widespread narrowing of the bronchial airways, which changes its severity over short periods spontaneously or during treatment
American Thoracic Society[8]	1962	Disease characterized by increased responsiveness of the trachea and bronchi to various stimuli and manifested by widespread narrowing of the airways that changes in severity spontaneously or as a result of therapy
World Health Organization (WHO)[9]	1975	Chronic condition characterized by recurrent bronchospasm resulting from a tendency to develop reversible narrowing of the airway lumina in response to stimuli of a level or intensity not inducing such narrowing in most individuals
American Thoracic Society[10]	1987	Clinical syndrome is characterized by increased responsiveness of the tracheobronchial tree to a variety of stimuli. Major symptoms are paroxysms of dyspnea, wheezing, and cough, which may vary from mild and almost undetectable to severe and unremitting (i.e., status asthmaticus). Primary physiologic manifestation of this hyperresponsiveness is variable airway obstruction, occurring in the form of fluctuations in the severity of obstruction after bronchodilator or corticosteroid use, or increased obstruction caused by drugs or other stimuli, as well as evidence of mucosal edema of bronchi, infiltration of bronchial mucosa or submucosa with inflammatory cells (especially eosinophils), shedding of epithelium, and obstruction of peripheral airways with mucus.
NHLBI/NIH[11]	1991	Lung disease with the following characteristics: (1) airway obstruction that is reversible (but not completely in some patients) spontaneously or with treatment, (2) airway inflammation, and (3) increased airway responsiveness to a variety of stimuli.
NHLBI/NIH[12,13]	1993 1995 1997	Chronic inflammatory disorder of the airways in which many cells play a role, particularly mast cells, eosinophils, and T lymphocytes. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough in early morning. Symptoms are usually associated with widespread but variable airflow limitation that is at least partly reversible spontaneously or with treatment. Inflammation also causes an increase in airway responsiveness that is associated with a variety of stimuli.
NIH/NHLBI[14]	2002	Chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible spontaneously or with treatment.

NHLBI/NIH, National Heart, Lung, and Blood Institute/National Institutes of Health.

BOX 48-1 CASE 8

Retired Cement Factory Worker Who Was a Smoker

- He had a regular cough and sputum production for many years.
- His breathing could become rapidly worse, and he awoke during the night with wheezing.
- During a trial of prednisolone, he improved to some degree with a maximum peak flow rate of 140 L/min.
- He was maintained on prednisolone but died after worsening of his breathlessness over several days with nighttime waking.

Adapted from Kelson MC, Heller RF. The effects of death certification and coding practices on observed differences in respiratory disease mortality in 8 E.E.C. countries. Rev Epidem Sante Publique 1983;31:423-32.

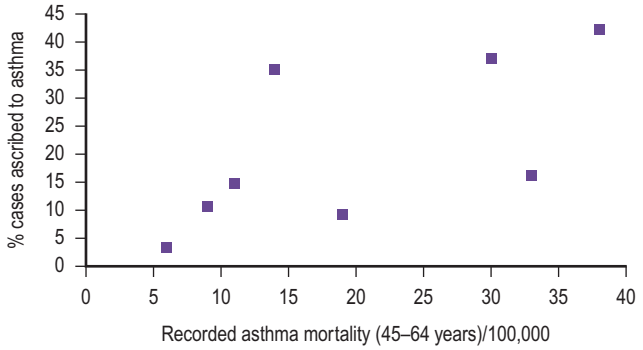

Figure 48-1 Death certification practices of physicians and asthma mortality by country. *(Data from Burney P. The effect of death certification practice on recorded national asthma mortality rates. Rev Epidem Sante Publique 1989;37:385-9.)*

Symptom questionnaires do not have the disadvantages of reported diagnoses, but they have problems of their own. First, used alone, symptoms are rarely diagnostic of a condition. This may not be a serious problem when there is no need for an accurate diagnosis in every case, but some symptoms are highly nonspecific. There may be considerable crossover of symptoms between different airway diseases such as asthma and bronchitis. Second, the interpretation of similar symptoms may vary among different people. This may become a serious problem when making comparisons in the settings of different cultures and languages. In translating asthma questionnaires, there may be particular problems in translating terms such as *wheeze* when there may not be an equivalent word, and even people who speak the same language may interpret *wheeze* differently.

Given the lack of a gold standard to test these questionnaires against, their validity cannot be fully assessed, because it depends in part on whether they are seen as plausible indicators of the presence of asthma and standardization against a plausible alternative indicator. In the IUATLD questionnaire, this indicator was the airway response to histamine, which usually increases

in patients with asthma. Although it is not diagnostic of asthma, it is reassuring to find that answers to the questionnaires can predict the results of the alternative test[19] and that they can do this in approximately the same way in different countries and different translations.[20] For the ISAAC questionnaires, a video was developed that demonstrated the symptoms of asthma, and it was used to help standardize comprehension of the questionnaire in different settings.[23] Although fully validated questionnaires for diagnosing asthma are not available, the current questionnaires do allow comparison of symptoms that plausibly represent conditions close to asthma in a standardized way. Although cautious interpretation is always advisable, they have enabled substantial advances in our knowledge of the relative distribution of the condition.

An objective test for asthma that did not depend on interpretation of questionnaires would be ideal, and several tests have been proposed. The lack of a gold standard for diagnosing asthma and the similarity of asthma to other conditions make a perfectly validated test unattainable, but tests do provide additional tools to check the findings of surveys that use questionnaires only.

The physiologic tests for asthma have been based on the definition of asthma as a condition of the airways that changes its severity over time spontaneously or after treatment (Box 48-2). Reversibility of airway obstruction after use of a bronchodilator (i.e., reversibility testing) has been used in clinical studies to distinguish between asthma and fixed airway obstruction, and some have used it as a test in surveys to identify asthma. The difficulty lies in interpreting the results. A positive test result indicates the likely presence of asthma, but a negative test result is uninformative. Because a patient with asthma who is receiving good treatment or in remission for some other reason does not respond to a bronchodilator, this approach has not found much use in surveys of the general population.

Spontaneous changes in airway caliber can be assessed using peak flow diaries, a clinical technique that has been commonly used in primary care in the United Kingdom. Although they can be difficult to use in large-scale studies, they do provide data comparable to that using more invasive bronchial challenge tests.[24] They have some of the same limitations as reversibility testing.

More promising has been the use of bronchial challenge tests, most of which use a direct bronchoconstrictor such as histamine or methacholine. Lung function is assessed before and after inhaling increasing doses of the agent. The decline in lung function (usually the forced expiratory volume in 1 second [FEV_1]) is regarded as a marker of asthma.[25,26] This may be expressed as the dose or concentration of agent that produces a given (often 20%) fall in lung function, in which case the result usually is dichotomized as those falling by at least that amount (i.e., hyperresponsive) and those that do not (i.e., normal). Alternatively, the slope of the dose-response curve has been used as a continuous measure of airway reactivity, a method that uses epidemiologic information more efficiently but may be clinically less intuitive.[27] Development of these tests for use in surveys has provided a tool for assessing a physiologic measure associated with asthma. There is little difference between the use of histamine and methacholine, but methacholine is more widely used because it has fewer side effects.

One disadvantage of nonspecific challenge tests is that they produce positive results for those with asthma and also with chronic obstructive pulmonary disease (COPD).[28,29] This has led to the use of alternative agents that act indirectly by releasing mediators from mast cells in the airway. Challenge agents include adenosine, hypertonic solutions (e.g., saline, mannitol), exercise, and cold, dry air. These alternatives have not been used as widely as methacholine. Exercise testing usually has been confined to studies of children. Its effects depend on weather conditions (e.g., cold, dry conditions produce a greater stimulus than warm, moist conditions), and it requires well-motivated groups of participants. Equipment to provide cold, dry air has not been widely available. Use of saline and mannitol has promise, but they have not been widely used in surveys. The theoretical advantage of using these methods is that they are less likely to provoke airway constriction in those with COPD.

BOX 48-2 TESTS FOR ASTHMA

QUESTIONNAIRES
- Questions about diagnosed asthma
- Questions about symptoms

TESTS OF REVERSIBILITY
- Response to bronchodilator
- Response to steroids

MEASURE OF AIRWAY VARIABILITY
- Peak flow diaries

CHALLENGE TESTS
- Directly acting constrictors
  - Histamine
  - Methacholine
- Indirect challenges
  - Adenosine 5′-monophosphate (AMP)
  - Exercise
  - Cold air
  - Hypertonic saline
  - Mannitol

RHINITIS

Allergic rhinitis has been investigated much less frequently than asthma using epidemiologic approaches. Population-based studies are made difficult by misclassification arising from reliance on questionnaires to establish the presence of allergic rhinitis. Typically, the questionnaires used by epidemiologists ascertain self-reports of responders having something they call *allergic rhinitis* or *hay fever*.

Nonetheless, studies show that allergic rhinitis is among the most common chronic diseases. Symptoms of individuals with rhinitis include sneezing, nasal irritation, rhinorrhea, and nasal blockage.[30] These symptoms can also involve the eyes, ears, and throat, including postnasal drainage.[31] Allergic rhinitis is most commonly classified as seasonal, perennial, or occupational,[30] but a recent guidelines statement advocated classifying allergic rhinitis as intermittent or persistent.[32] The symptoms of allergic rhinitis are associated with exposure to allergen sources such as pollens, pets, and house-dust mites (HDMs).[30] Symptoms result from inflammation induced by a specific IgE-mediated immune response to the allergens.[31]

Criteria for diagnosing chronic rhinosinusitis have been published.[33,34] A questionnaire based on the symptomatic part of this definition has been devised and tested for epidemiologic surveys.[35]

ECZEMA

Similar to allergic rhinitis, the epidemiology of eczema is less well understood than the epidemiology of asthma. Eczema, also known as atopic dermatitis, is a pruritic rash characterized by chronic, recurrent papular lesions typically affecting skin at the flexor surfaces, buttocks, and back of the neck. Infants frequently have involvement of the face. In its acute and subacute forms, eczema is characterized primarily by erythema and a papular eruption, but in its chronic form, it is characterized by lichenification of affected areas. Allergic sensitization plays an important role in provoking eczema flares, particularly in pediatric patients.[36]

Some studies have relied on physician diagnosis to define eczema, but standardized questions have been developed for identifying eczema cases with or without additional information from standardized examination.[37] These questions are included in the ISAAC questionnaire, and they focus on the chronic and recurrent nature of the rash, its location, and the presence of pruritus.

FOOD ALLERGY

During the past 10 years, food allergy has received increased attention, and there is a growing body of literature available regarding its epidemiology. Food allergy is an immune-mediated reaction to a food. It can produce a wide spectrum of clinical manifestations, including acute IgE-mediated reactions, mixed IgE-mediated and non–IgE-mediated reactions that are often characterized by insidious gastrointestinal symptoms, and non–IgE-mediated syndromes such as allergic colitis and food protein–induced enterocolitis syndrome. Even among patients with acute IgE-mediated types of food-allergic reactions, symptoms can vary and include one or many of the following: urticaria, angioedema, pruritus, cough, wheezing, hoarseness, vomiting, diarrhea, oral pruritus, hypotension, and rhinorrhea. Because the diagnosis is based on the clinical history and diagnostic test results, with the gold standard being a double-blind, placebo-controlled food challenge, conducting large epidemiologic surveys can be difficult because of reliance on questionnaire-based tools for identification of food allergy and evidence of IgE sensitization. Because there is no validated questionnaire for food allergy and many reported food allergies are not confirmed when a full diagnostic evaluation is completed, estimates obtained from questionnaires are likely to be inflated.[38]

Estimates of Prevalence

SENSITIZATION

The prevalence of sensitization depends on the selection of allergens. For this reason, the relative prevalence of responses to a standardized panel of allergens is more informative than an absolute prevalence.

The ECRHS estimated the prevalence of specific IgE (≥0.35 kU/L) to mites (*Dermatophagoides pteronyssinus*), cats, grass (Timothy grass), or *Cladosporium* among young adults between the ages of 20 and 44 years in 35 centers, mostly in Western Europe.[39] The prevalence of a positive response to any of the four common allergens ranged from 16.2% to 44.5% ,with a median prevalence of 33.1%. High prevalence rates were found in Australia, New Zealand, the United States, the United Kingdom, and the Netherlands. Low prevalence rates were found in Spain, Iceland, and Italy.

The second phase of the ISAAC study estimated the prevalence of positive skin-prick test responses to at least one of six allergens in children between the ages of 8 and 12 years living in 18 sites, mostly in Western Europe.[40,41] Estimated prevalence ranged from 11.6% in Tallin, Estonia, and 16.5% in Mumbai, India, to 39.5% in Rome, Italy, and 44.7% in Almeira, Spain.

Unlike in Western countries, the prevalence of sensitization in Africa heavily depends on the methods used to assess sensitization. In rural areas, the prevalence of positive skin-prick test results is very low, whereas the prevalence of allergen-specific IgE is high. The high prevalence of allergen-specific IgE in poor rural areas was first shown in Zimbabwe (formerly called Southern Rhodesia) by Merrett and associates,[42] but the dissociation in these environments between specific IgE levels and skin test results also has been shown in Kenya[43] and South Africa.[44] Where skin test results are negative, even in the presence of specific IgE to aeroallergens, clinical allergy is rare.[3]

ASTHMA

Asthma is a global problem. It is estimated that approximately 300 million people worldwide have asthma.[45]

Childhood Asthma

Prevalence rates for children and adults are substantially different in countries around the world. The first phase of the ISAAC study provides the most extensive information on variation in childhood asthma prevalence. In 1998, the ISAAC Steering Committee reported findings for 463,801 13- to 14-year-old children (155 centers in 56 countries) and 257,800 6- to 7-year-old children (91 centers in 38 countries).[46] For the younger and older children, the prevalence of asthma symptoms was based on a positive response to this question: Have you had wheezing or whistling in the chest in the past 12 months? Across countries, there was an approximately twentyfold range of prevalence, with the highest rates usually found in more developed countries (Figs. 48-2 and 48-3). The countries with the highest prevalence rates (>20%) were the Isle of Man, the United Kingdom, New Zealand, Ireland, Australia, Peru, Panama, Costa Rica, the United States, and Brazil.

Adult Asthma

The ECRHS assessed geographic variation in asthma among 140,000 adults from 22 countries. A sixfold variation in the prevalence of current asthma was found among the countries.[21] A high (>7%) prevalence of asthma was found in Australia, New Zealand, the United States, Ireland, and the United Kingdom. Asthma prevalence of less than 4% was found in Iceland, parts of Spain, Germany, Italy, Algeria, and India. *Current asthma* was defined in the ECRHS as "having an attack of asthma in the past 12 months or currently taking medicine for asthma."

The ECRHS did not examine many sites outside the developed market economies, but the World Health Survey interviewed adults older than 18 years of age in six continents using questions derived from the ECRHS on wheezing and diagnosed asthma.[22] The prevalence of diagnosed asthma ranged from 1.8% in Vietnam to 32.8% in Australia (Fig. 48-4). A very wide variation in the prevalence of diagnosed asthma (and wheezing) was found in all countries, regardless of gross national income per capita adjusted for purchasing power parity. In countries

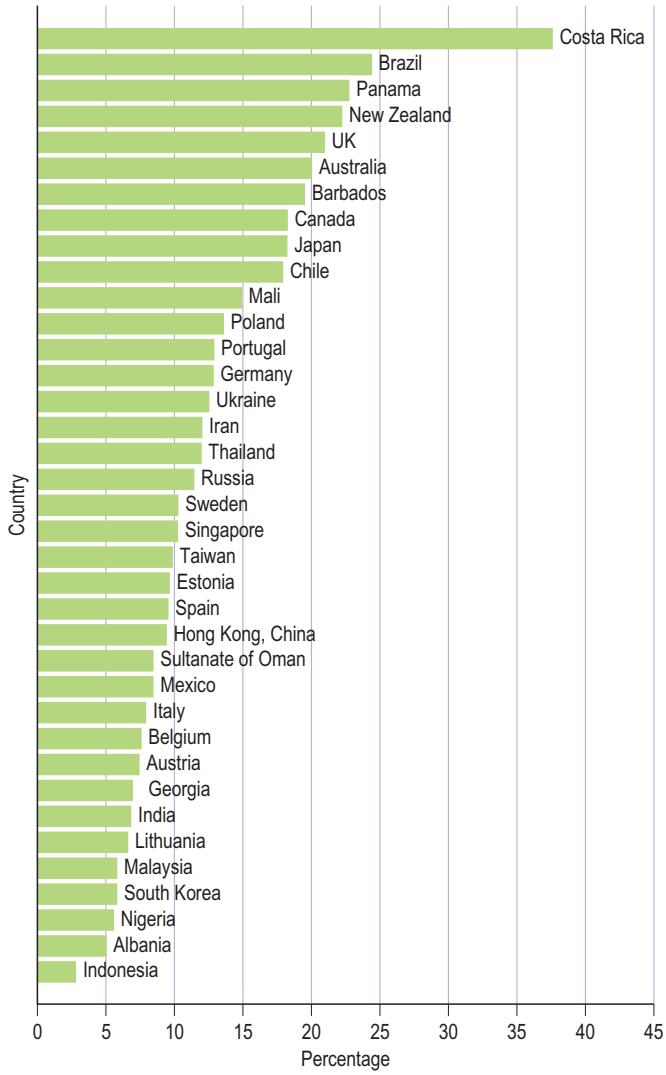

Figure 48-2 Prevalence of asthma symptoms by country among children 6 to 7 years of age according to the 1999-2004 International Study of Asthma and Allergies in Childhood (ISAAC) III study. *(From Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 2006;368:733-43.)*

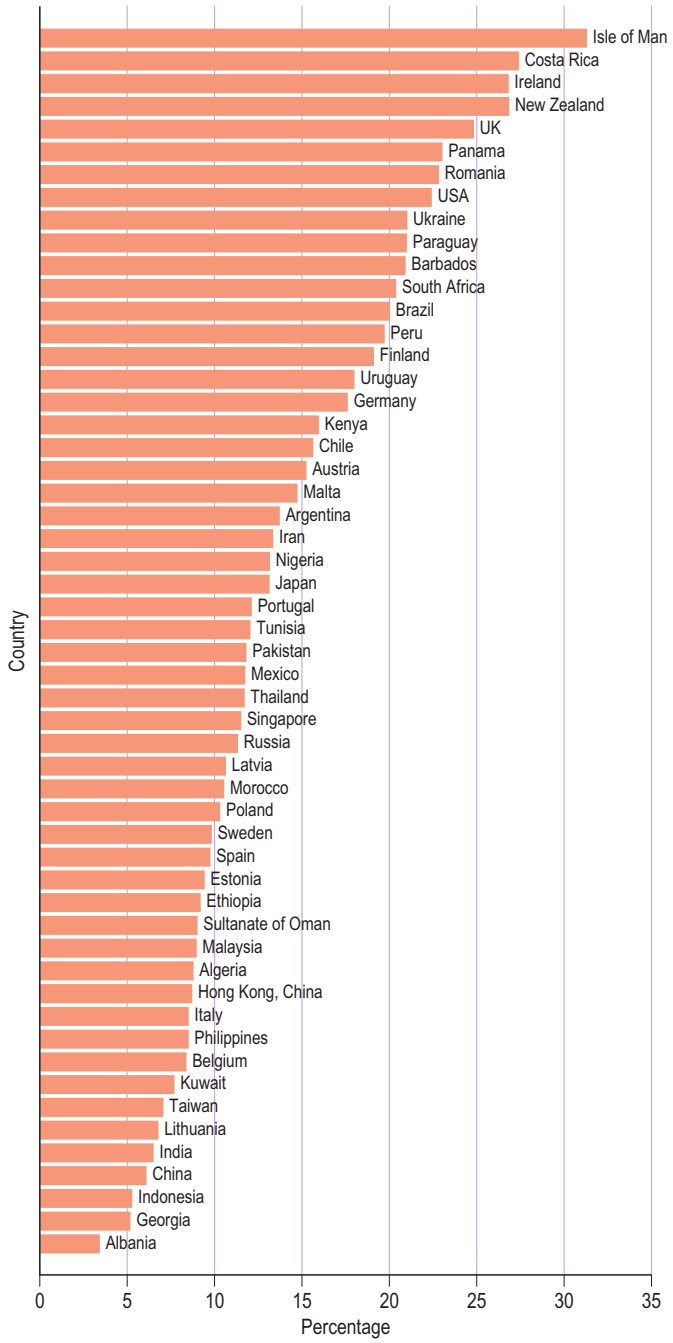

Figure 48-3 Prevalence of asthma symptoms by country among children 13 to 14 years of age according to the 1999-2004 International Study of Asthma and Allergies in Childhood (ISAAC) III study. *(From Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 2006;368:733-43.)*

with the lowest incomes (<US$3000), none of 20 sites had a prevalence of diagnosed asthma of more than 10%; among countries with intermediate incomes, 3 (19%) of 16 countries had a prevalence higher than 10%; and among counties with the highest incomes (<US$8000), 7 (26%) of 27 countries had a prevalence above 10%.

United States Prevalence Rate

The National Health Interview Survey (NHIS) and the National Health and Nutrition Examination Survey (NHANES) include random samples of the whole U.S. population. Both also provide periodic prevalence estimates.

Standardization of the methods of prevalence surveys is essential because the wording of questions on asthma or other aspects of data collection may affect estimates based on the questionnaires. For example, Table 48-2 provides prevalence rates for different questionnaire-based indicators of asthma: physician report, current disease, and the symptom of wheezing used in the National Health and Nutrition Survey of the United States from 1976 through 1980.[47] Questions that ask about asthma or wheeze provide estimates that are almost twice those of questions asking about either alone, and this difference varies with age. For those between the ages of 3 and 17 years,

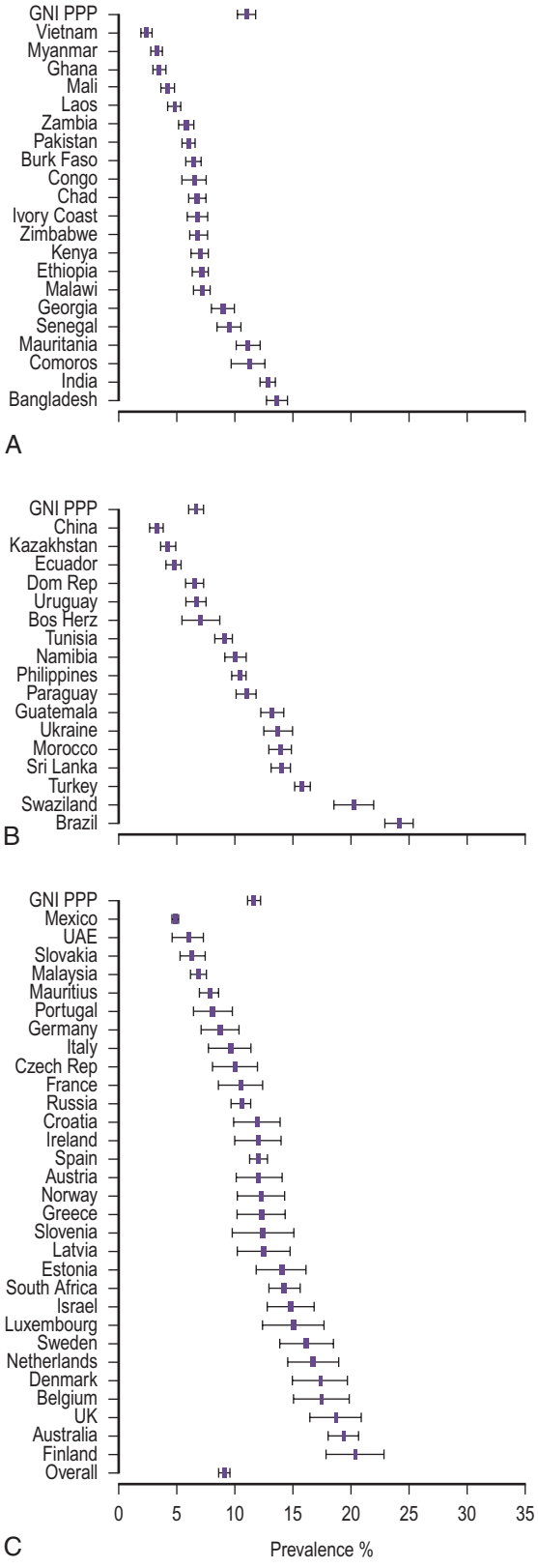

Figure 48-4 **A-C**, Estimates of adult asthma prevalence from the World Health Survey by country and gross national income. *Bos Herz*, Bosnia Herzegovina; *Burk Faso*, Burkina Faso; *Dom Rep*, Dominican Republic; *GNI PPP*, gross national income per capita at purchasing power parity rates; *Rep*, Republic; *UAE*, United Arab Emirates; *UK*, United Kingdom. *(From Sembajwe G, Cifuentes M, Tak SW, et al. National income, self-reported wheezing and asthma diagnosis from the World Health Survey. Eur Respir J 2010;35:279-86.)*

wheeze is much more likely to be associated with a diagnosis of asthma.

State-specific asthma prevalence data for adults are available from the 2010 Behavioral Risk Factor Surveillance System (BRFSS), a state-based, random-digit-dialed survey of noninstitutionalized U.S. adults age 18 years or older. It was conducted by the Centers for Disease Control and Prevention (CDC) and the state or territorial departments of health. Information was gathered from all 50 states, Puerto Rico, the Virgin Islands, and the District of Columbia. The definition for current asthma was based on providing positive answers to two questions: Have you ever been told by a doctor, nurse, or other health professional that you had asthma? Do you still have asthma? The overall current asthma prevalence rate was 8.6%, ranging on the mainland from 6% in Tennesee to 11.1% in Vermont (Fig. 48-5).[48]

Asthma prevalence rates in the United States vary with demographic and social conditions. Figure 48-6 gives prevalence rates from the NHIS for 2008 through 2010. Children have more reported asthma than adults, women have more than men, those in poverty have more asthma than those not in poverty, Asian respondents reported less asthma than any other group, and all other racial groups have more asthma than white respondents.[49]

ALLERGIC RHINITIS

Estimating incidence and prevalence of allergic rhinitis is as challenging as for asthma. The diagnosis is symptom based, and there is no consensus for measurement. Some attempts have been made to estimate the incidence of allergic rhinitis using cohort or longitudinal data. In a birth cohort study from Germany that followed 587 children for 7 years,[50] 15% of them developed seasonal allergies, defined as a combination of exposure-related symptoms and sensitization. A 23% cumulative incidence rate was determined in a 23-year longitudinal study of 738 college students.[51] The researchers also observed that regression of hay fever symptoms was inversely related to age of onset. Almost 85% of those with hay fever onset before 5 years of age had improvement of their symptoms.

The ISAAC researchers collected data on 12-month prevalence of allergic rhinoconjunctivitis for children 13 to 14 years old from 56 countries.[46] Allergic rhinoconjucntivitis was defined as having a problem with sneezing or a runny or a blocked nose without a cold or flu and accompanied by itchy, watery eyes. There was a thirtyfold variation in the prevalence rate among the sites, from 1.4% to 39.7%.

Estimates for adults obtained in the ECRHS ranged from 9.5% in Algeria to 40.9% in Australia.[21] The median prevalence of nasal allergies in the ECRHS was about 21%. Countries with significantly high prevalence rates were the Netherlands, Belgium, Switzerland, France, the United Kingdom, New Zealand, Australia, and the United States.

Chronic rhinosinusitis is an inflammation of the nose and paranasal sinuses lasting over 12 weeks. Another multicenter European study estimated the prevalence of chronic rhinosinusitis using a questionnaire based on the European Position Paper on Rhinosinusitis and Nasal Polyps (EP^3OS) on symptom criteria[35] to be about 11% among adults, ranging from 7% in Helsinki, Finland, to 27% in Coimbra, Portugal. The condition was more common in women, in younger participants, and in smokers.[52]

TABLE 48-2 Estimated Prevalence of Asthma by Age from the Second National Health and Nutrition Examination Survey of the United States, 1976-1980

Question	Total	6 mo-2 yr	3-5 yr	6-11 yr	12-17 yr	18-44 yr	45-64 yr	65-74 yr
Did a doctor ever tell you that you had asthma?	6.2	4.0	6.5	7.6	6.6	6.2	5.7	5.9
Do you still have asthma?	3.0	2.3	3.9	3.9	3.2	2.5	3.2	3.5
During the past 12 months, not counting colds or flu, have you often had trouble with wheezing?	6.5	7.2	6.2	5.9	4.5	5.7	8.3	9.1
Have you ever been told you have asthma and/or wheezing?	10.5	8.8	9.8	10.4	8.7	10.3	11.8	12.4
Do you still have asthma and/or wheezing?	7.7	7.8	7.6	7.4	5.7	6.9	9.6	10.4

From Evans R, Mullally DI, Wilson RW, et al. National trends in the morbidity and mortality of asthma in the US: prevalence, hospitalization and death from asthma over two decades: 1965-1984. Chest 1987;91(Suppl):65S.

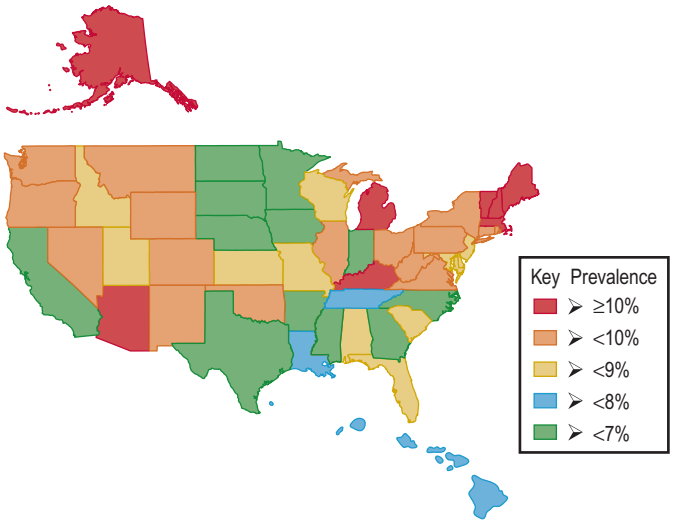

Figure 48-5 State-specific asthma prevalence data for adults from the 2008 Behavioral Risk Factor Surveillance System (BRFSS). *(Adapted from Centers for Disease Control and Prevention (CDC). Behavioral risk factor surveillance system survey: current asthma prevalence data. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2010. Available at http://www.cdc.gov/asthma/brfss/2010/current/tableC1.htm [accessed May 15, 2012].)*

ECZEMA

The worldwide prevalence of eczema was best documented in ISAAC Phase Three, in which the prevalence for 6- to 7-year-old children ranged from 0.9% in India to 22.5% in Ecuador.[53,54] The worldwide prevalence of eczema in children 6 to 7 years of age has increased in most regions of the world and has remained stable only in Western, Northern, and Eastern Europe. For this younger age group, the prevalence in ISAAC Phase Three was 7.9%, an increase from the prevalence in Phase One of 6.1%. The overall prevalence among 13- to 14-year-old adolescents declined to 7.3% in ISAAC Phase Three from 8.8% in Phase One. The regions with the most striking increases in eczema prevalence were Asia and Latin America.

FOOD ALLERGY

A growing number of population-based studies have estimated food allergy prevalence and incidence. The prevalence of food allergy and the foods that are most commonly implicated in food allergy vary widely across the world. For example, a meta-analysis found that the self-reported prevalence of food allergy ranged from 3% to 35%.[55] Although some of the heterogeneity observed is attributable to study methodology, other studies that have focused on specific geographic regions and populations support the notion that there is marked worldwide heterogeneity in food allergy prevalence. For example, in the United States, the estimated prevalence of food allergy is 4% to 8% among children,[56,57] and in Australia, a prevalence of more than 10% among 1-year-old children has been reported.[58] In contrast, findings from a population-based birth cohort from the United Kingdom indicate that between 2.2% and 5.5% of infants have food allergy in the first year of life,[59] and in other U.K. studies, the estimated prevalence of food allergy among 6-year-old children is 1.6% to 2.5%,[60] and among adolescents, it is 2.3%.[61] An international study that used allergen-specific IgE data for young adults confirmed the heterogeneity of food allergy prevalence observed in the questionnaire-based studies.[62] In this study, prevalence of sensitization to any 1 of 24 foods ranged from 7.7% in Iceland to 24.6% in the United States. However, sensitization to the major foods, such as fish, egg, and milk, was uncommon (<1%).

The incidence and prevalence of allergy to specific foods have been studied. A random telephone survey administered in 2002 to estimate the prevalence of seafood allergy in the United States found that 2.3% of the general population reported allergy to fish or shellfish.[63] Another telephone survey was conducted in 1997 and repeated in 2002 and 2010 to estimate the prevalence and incidence of peanut and tree nut allergies.[64,65] The prevalence rate of peanut or tree nut allergy was stable at 1.4% among adults, but it increased from 0.6% to 1.2% to 2.1% among children during this period. In contrast, data from U.K. general practices were used to estimate a prevalence rate of peanut allergy of 0.05%, and a school-based survey in Singapore and the Philippines estimated a prevalence rate of peanut and tree nut allergy of less than 1%.[66] In Australia, the prevalence of peanut allergy may be higher than that observed in the United States or United Kingdom, because the prevalence of peanut allergy among 1-year-old children was estimated to be 3%.[58]

There is limited information about the epidemiology of allergic gastrointestinal diseases. However, the incidence and prevalence of eosinophilic esophagitis appear to have increased over the past decade. A range of gastrointestinal symptoms and mucosal eosinophilia characterizes eosinophilic esophagitis. Approximately one half of cases demonstrate IgE sensitivity to foods.[67] What was once thought to be a rare disease was found

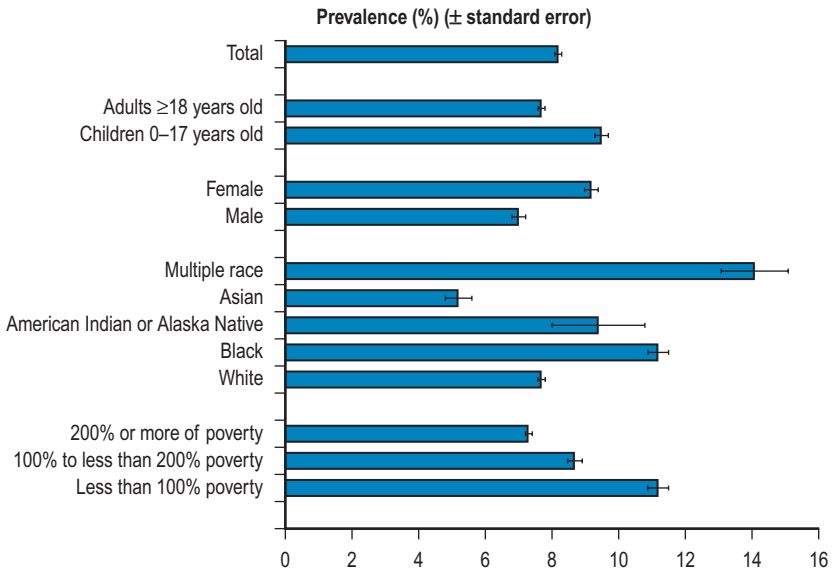

Figure 48-6 Average annual asthma prevalence (± standard error) per 100 people according to different socioeconomic characteristics in the United States for 2008 through 2010. *(From Akinbami LJ, Moorman LE, Bailey, C, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. NCHS Data Brief 2012;94:1-8.)*

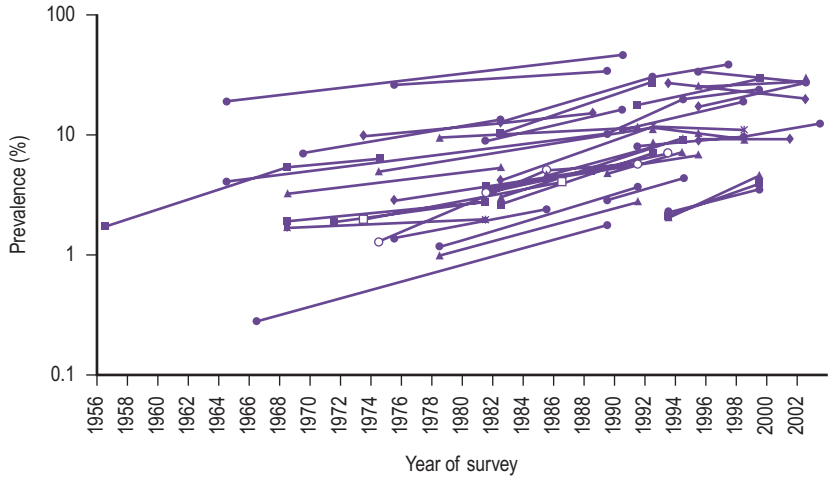

Figure 48-7 Changes in the prevalence of asthma and wheeze in repeated cross-sectional surveys from 1957 through 2002.

by one study based in Switzerland to have increased in incidence from 1.2 to 7.4 per 100,000 adults from 1989 to 2009.[68,69] In another study in Hamilton County, Ohio, the incidence in children younger than 19 years old has increased from 0.009 to 0.013% per year, and the prevalence has increased from 0.01% to 0.04% from 2000 to 2003.[67]

TRENDS IN PREVALENCE

Sensitization

A few studies have made serial assessments of the levels of IgE specific to common allergens in the same populations over many years. These studies have shown a fairly consistent increase in the prevalence of sensitization over time.

Analysis of the data from the Tucson[70] and the first and second ECRHS surveys[71] found that the apparent decline in the prevalence of sensitization with age was more easily explained as a birth cohort effect. The apparent effect of age results from people born later in the century having a higher prevalence of disease throughout their lives. In cross-sectional surveys, this pattern of disease is indistinguishable from a decline in disease with age. In the ECRHS, there was almost no net change in the prevalence of sensitization over the 8 years between the surveys within any birth cohort, but succeeding birth cohorts had increasingly high prevalence rates. A subsequent analysis of some British data showed that this phenomenon was apparent in successive birth cohorts since at least the 1930s.[72]

Asthma

To evaluate changes in prevalence, repeated surveys are required for the same populations and using the same instruments for assessment. In the 1950s and 1960s, Smith in Birmingham, England, first observed that the prevalence of asthma was rising among schoolchildren undergoing school medical examinations.[73] Since then, many studies have assessed changes in prevalence. These studies are summarized in Figure 48-7, which

shows the changes in prevalence over time plotted on a logarithmic scale. Most of the studies surveyed children, although a few looked at military conscripts in countries with compulsory military service. The very large variations in the absolute prevalence estimates reflect differences in the definitions used and the populations examined. From the late 1950s to the mid-1990s, the values rose uniformly at a rate that represented a doubling of prevalence approximately every 14 years, and this occurred regardless of the definition used and the starting prevalence. Only in the mid-1990s did reports begin to suggest that this increase had slowed down.

A much smaller number of studies have assessed changes in the prevalence of airway responsiveness (Fig. 48-8). During the 1980s, a small number of studies showed increases in prevalence over time.[74-77] The study of Dubois, which showed a yearly increase in prevalence among Belgian conscripts over 14 years, is particularly persuasive given the difficulties of standardizing the tests. Since the 1980s, most studies have shown a flattening of or a decline in prevalence,[76-78] although increases were seen in a study from Ghana,[79] and a large increase was observed in Germany in two surveys made very close together in time and seem unlikely to represent a long-term trend.[80]

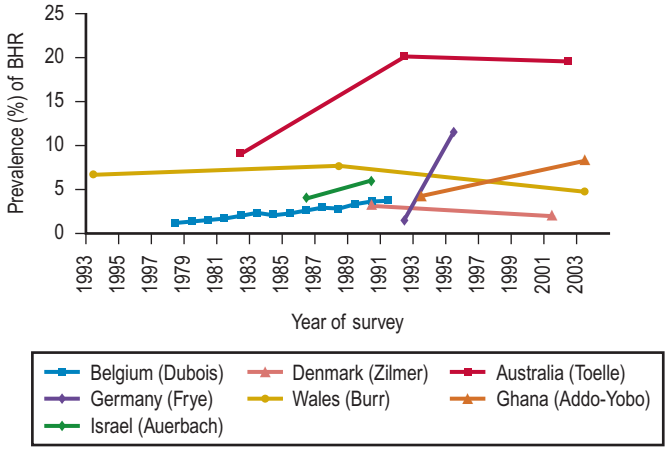

Figure 48-8 Changes in the prevalence of bronchial hyperresponsiveness in repeated cross-sectional surveys from 1993 through 2003.

The ISAAC reassessed prevalence of asthma and other allergic diseases by questionnaire for 6- to 7-year-old children in 66 centers in 37 countries and for 13- to 14-year-old children in 106 centers in 56 countries.[45] The results for asthma prevalence are given in Figure 48-9. Among the younger children, rates were more commonly rising than declining, whereas among the older children, the rising and declining rates were more evenly balanced. Among the older children in centers with a high prevalence, the rates were more likely to be declining.

In the United States, the NHIS, a population-based interview survey of U.S. households, is a key source of information on trends in the prevalence of asthma.[81] Before 1997, prevalence estimates were based on a positive response to one question: During the past 12 months, did you have asthma? In 1997, the NCHS redesigned the NHIS questionnaire. Consequently, answers to the NHIS questionnaire after 1996 cannot be compared with those in previous surveys because the new questions assess asthma morbidity differently.[82] Lifetime incidence is measured by this question: Have you ever been told by a doctor or other health professional that you had asthma?

The prevalence of asthma attacks is obtained by a positive response to another question: During the past 12 months, have you had an episode of asthma or asthma attack? The asthma attack prevalence in 2009 was 4.2% for all age groups. In 2001, NCHS added a question (Do you still have asthma?) after the lifetime incidence question to provide estimates of current asthma prevalence (Table 48-3). The 2009 estimates indicate that 8.2% of U.S. residents currently have asthma that has been diagnosed by a doctor or other health professional.[49] Table 48-3 provides the estimates for asthma prevalence before and after the revisions of the NHIS questionnaire.[83]

Figures 48-10 and 48-11 show data from the NHIS with different estimates of prevalence of asthma over time for children and adults and by race or ethnic group. For children and adults, the 12-month and lifetime prevalence rates increased over time. Current and attack prevalence rates have not shown a marked trend since the use of these outcomes began. Prevalence rates also vary among racial and ethnic groups; this variation likely reflects differences in genetic, environmental, social,

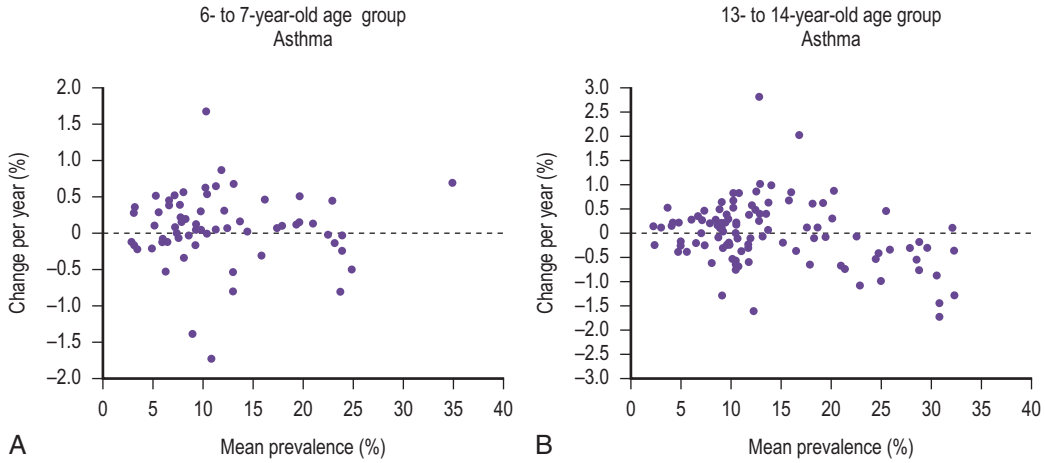

Figure 48-9 A and B, Changes in asthma prevalence between International Study of Asthma and Allergies in Childhood (ISAAC) I and II are plotted against the mean prevalence for both surveys by age group.

TABLE 48-3 Estimated Prevalence of Asthma by Age from the National Health Interview Surveys of the United States, 1996, 1997, and 2001

Question	Total	<18 yr	18-44 yr	45-64 yr	>65 yr
1996 NHIS: During the past 12 months did you have asthma? (12-month prevalence)	5.5	6.2	5.6	4.8	4.5
1997 NHIS: Have you ever been told by a doctor or other health professional that you had asthma? (lifetime prevalence)	9.6	11.3	9.5	8.7	7.6
1997 NHIS: During the past 12 months, have you had an episode of asthma or asthma attack? (attack prevalence)	4.1	5.4	4.0	3.6	2.7
2001 NHIS: Have you ever been told by a doctor or other health professional that you had asthma? (lifetime prevalence)	11.3	12.6	11.8	10.4	8.7
2001 NHIS: Do you still have asthma? (current prevalence)	7.3	8.7	7.2	6.7	6.0
2001 NHIS: During the past 12 months, have you had an episode of asthma or asthma attack? (attack prevalence)	4.3	5.7	4.3	3.8	2.6

NHIS, National Health Interview Survey.

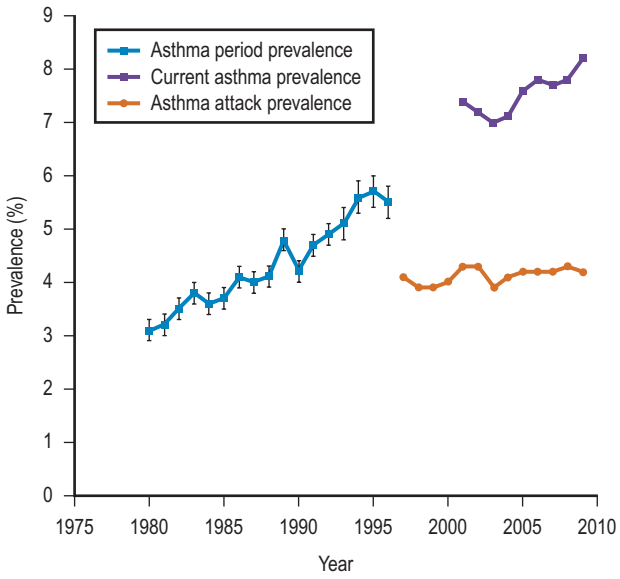

Figure 48-10 Asthma prevalence per 100 adults and children in the United States, 1980-2005. *(From Akinbami LJ. Asthma prevalence, health care use and mortality: United States, 2003-05. 12-12-0006. Hyattsville, Md.: National Center for Health Statistics; 2006.)*

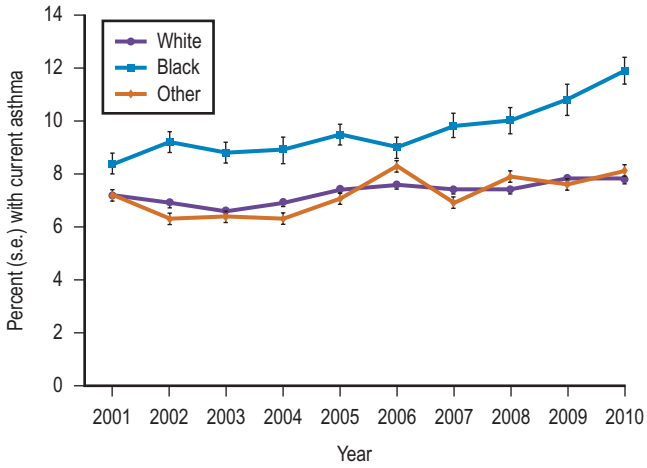

Figure 48-11 Asthma prevalence per 100 people in the United States by race or ethnicity for 2001 through 2009. *s.e.*, Standard error. *(From Akinbami LJ. Asthma prevalence, health care use and mortality: United States, 2003-05, 12-12-0006. Hyattsville, Md.: National Center for Health Statistics; 2006.)*

and cultural influences among population groups.[84] Between 1980 and 1996, the prevalence of asthma had increased from 3.1% to 5.4% among whites and from 3.3% to 6.5% among blacks, representing cumulative increases of approximately 4% per annum.[85] Between 2001 and 2009, rates of current asthma had increased from 7.2 % to 7.8% among whites, a cumulative increase of approximately 0.8% per annum, and from 8.4% to 11.9% among blacks, a further increase of approximately 4% per annum (see Fig. 48-11).[86]

Allergic Diseases

Many of the studies that reported changes in the prevalence of asthma and wheeze also found increased reporting of other allergic diseases, most notably allergic rhinitis and eczema in children. As for asthma, almost all studies reporting before the mid-1990s found increases in other atopic conditions with time. Since then, results have been more mixed, and the ISAAC has provided a more representative spread of data than is possible from individual studies. (Fig. 48-12)[53] For the 6- to 7-year-old children, most sites showed an increase in prevalence of allergic rhinoconjunctivitis and eczema in the 5 years after the baseline surveys of ISAAC Phase One. For the 13- to 14-year-old children, the changes were more evenly distributed between increases and decreases, and the size of the annual percentage change (positive and negative) appeared to be proportional to the initial value.

A follow-up of the ECRHS sample approximately 9 years later estimated an incidence rate of rhinitis of 7.5 cases per thousand people per year. Males had a greater risk in childhood and a lower risk in adulthood of incident rhinitis compared with females. Atopic subjects had the highest incidence of rhinitis, at more than 22 cases per thousand people per year.[87]

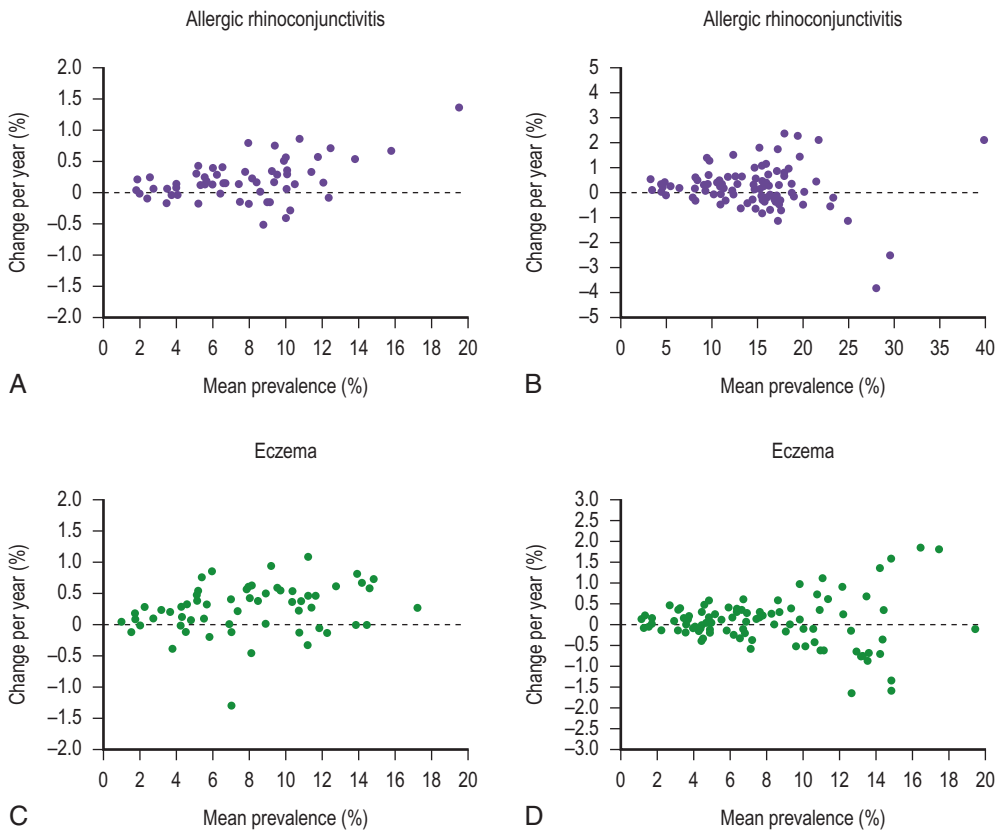

Figure 48-12 Changes in the prevalence of allergic rhinoconjunctivitis (**A** and **B**) and eczema (**C** and **D**) between International Study of Asthma and Allergies in Childhood (ISAAC) I and II are plotted against the mean prevalence for both surveys for 6-7 year olds (**A** and **C**) and 13-14 year olds (**B** and **D**).

The prevalence of allergic rhinitis has increased over time in the United States. The 2004 NHIS estimated a seasonal allergic rhinitis prevalence of 9%,[88,89] an increase of 66% from the prevalence estimate of 5.4% based on the 1970 NHIS.[90] The 2004 NHIS estimated that about 25.3 million Americans, 6.7 million of them younger than age 18 years, have allergic rhinitis.[88,89] The survey also showed geographic variation in the prevalence of seasonal allergic rhinitis, with the highest estimated prevalence for the Western United States (10.8%), followed by the Northeast (9.5%), South (8.0%), and Midwest (7.2%). Studies in other countries have also documented an increase in the prevalence of allergic rhinitis over time. Von Mutius and colleagues[91] observed a significant increase in hay fever prevalence among schoolchildren from Leipzig, Germany. The hay fever prevalence rate in the 1991-1992 survey was 2.3%; in the 1995-1996 survey, the prevalence had increased to 5.1%. An Italian retrospective study compared data on allergic rhinitis prevalence among Italian recruits observed in 1983 and from 1993 to 1995.[92] The investigators found a significant increase in allergic rhinitis prevalence, from 1.5% in 1983 to 2.2% in the 1993-1995 period.

Results from surveys conducted in 1989 and 1997 of an adult Danish population showed a significant increase of 61% in the prevalence of allergic rhinitis after adjustment by age and gender.[93] A Scottish study observed a threefold increase in the age-adjusted prevalence rate of hay fever between 1972 and 76 and 1996 in middle-age adults.[94] The hay fever prevalence rates were compared for fathers (5.4%) and sons (15.4%) and for mothers (5.8%) and daughters (20%). Later findings from a U.K. study suggested that the prevalence of hay fever had been stable in the latter half of the 2000s.[95]

Eczema

The worldwide prevalence of eczema among 6- to 7-year-old children has increased in most regions of the world and has remained stable only in Western, Northern, and Eastern Europe. For this younger age group, the prevalence found in the ISAAC Phase Three was 7.9%, an increase from the prevalence in Phase One of 6.1%. The overall prevalence among 13- to 14-year-old children declined to 7.3% in the ISAAC Phase Three from 8.8% in the ISAAC Phase One. The regions with the most striking increases in eczema prevalence were Asia and Latin America.

Food Allergy

Two cross-sectional Chinese studies from Chongqing showed a statistically significant increase in food allergy prevalence, from 3.5% in 1999 to 7.7% in 2009, among young children between the ages of 0 and 24 months.[96] These studies also showed that sensitization to food allergens assessed by positive skin-prick test results had almost doubled, rising from 9.9% to 18% during the same 10-year period. Other than these studies, there is little evidence on time trends using food challenge tests in general populations, although there is more circumstantial evidence for an increase over time.

During the 14-year period from 1990 to 2004, hospital admissions for food allergy showed continuing increases of 5 to 26 cases per million people overall and 16 to 107 cases per million children, particularly in the 14-year-old age group. Hospital admissions attributed to "dermatitis due to food" increased in England and Wales from 5 cases per million people in 1990 to 26 cases per million people in 2004, an increase of almost 13% per annum.[97,98] Apart from true changes in the epidemiology of food allergy, alternative explanations for this dramatic increase in health care use for presumed food allergy include changes in the coding behavior of doctors, changes in the awareness and behavior of patients, and changes in the health care system.

In the United States, the NHIS recorded much smaller increases in parent-reported food allergy,[99] although such reports are usually regarded as unreliable. Increasing reports of more specific complaints of peanut allergy have been made for children in the United States[56] and the United Kingdom.[100]

Risk Factors

ASTHMA

Genetic and Familial Factors

A genetic component of asthma has long been recognized, based initially on the observation that asthma tends to cluster in families. Familial aggregation, twin, genetic linkage, and association studies subsequently provided evidence to support this hypothesis. Detailed descriptions of the molecular genetics of asthma and atopic disease are provided in Chapter 22.

Family aggregation studies compare disease occurrences between family members. Disease aggregation between siblings and between parents and children supports a hereditary component, whereas increased aggregation between spouses suggests that environment is more important. However, aggregation among related individuals may represent shared genes or a common household environment. Evidence of a hereditary component of asthma has been demonstrated in numerous family-based studies.[101-104] Population-based studies also have shown an increased prevalence of asthma among first-degree relatives of index cases.[105-109]

Twin studies compared disease frequency in monozygotic (MZ) twins, who share 100% of their genes, with dizygotic (DZ) twins, who share on average 50% of their genes. This is another method to determine the relative contribution of genetic and environmental factors. A greater occurrence of disease in MZ than in DZ twins is evidence for a genetic component to the disease because both types of twins are assumed to share environmental factors similarly. Significantly higher concordance rates for MZ twins have been observed in some small studies.[110] Larger studies of twin registries also suggest a significant genetic contribution to asthma. In 6996 twin pairs from the Swedish Twin Registry, Edfors-Lubs found the prevalence of asthma to be 3.8%.[111] The higher concordance of asthma in MZ (19.8%) over DZ (4.8%) pairs suggests that genetic factors contribute to asthma. Similarly, Duffy and associates observed a 30% concordance in MZ twins and 12% in DZ twins in a total of 2902 Australian pairs.[112]

Whole-genome association studies have identified specific loci associated with clinical asthma. The genes associated with total IgE levels were not strongly associated with asthma, and some genotypes were specifically associated with childhood-onset asthma.[113]

Gender

Data from epidemiologic studies consistently reveal male gender to be a risk factor for asthma among young children, whereas studies of adolescents and adults show females to be at greater risk. A review of prospective studies showed that male children were at greater risk for incident asthma or wheeze, and studies of adolescents or adults showed females to be at greater risk.[114,115]

One hypothesis explaining the excess of asthma seen in boys during childhood is the different airway geometry in boys and girls. Boys have smaller airways for a given lung size than girls. Lower flow rates were found for boys 4 to 6 years of age,[116] and they have higher airway resistance compared with girls of the same age.[117] This difference in airway anatomy predisposes boys to more wheezing, and they have a higher incidence of lower respiratory tract infections.[118,119] Martinez and coworkers[120] suggested that reduced lung function was a key determinant of wheezing in boys and girls. In the Tucson study, lung function was measured within weeks of birth in 124 healthy infants. The subsequent incidence of wheezing illness over the first 6 years of life was increased in boys with high respiratory resistance and in girls with low functional residual capacity. One hypothesis for females being at higher risk of developing asthma or wheeze during adolescence or adulthood is the smaller relative airway caliber in women compared with men after puberty.[121]

Atopy

Epidemiologic studies consistently show an association between atopy and asthma, although the strength of the association varies with the index used and the study population. Part of the problem lies in the ambivalent nature of the term *asthma*.The symptoms of asthma in older adults also can indicate COPD, and the differential diagnosis may be difficult even in a clinic. A distinction used to be made between asthma and other wheezy syndromes in children. However, the management is very similar, the distinction has fallen largely into disuse, and use of the term *nonatopic asthma* has become common for children, whereas it was prviously reserved for a condition associated with eosinophilic inflammation but negative skin test results that predominantly presented in middle age, often among women, and had a relatively poor prognosis. The idea that atopic and airway components of asthma are distinct[101,109] has been confirmed by genetic studies thatidentified gene polymorphisms associated with asthma but not obviously related to the regulation of IgE or associated immunologic responses.

ISAAC found little variation in the prevalence of nonatopic asthma that could be explained by the local gross income, but prevalence of asthma associated with sensitization became less common in low-income settings.[41,122] The distinction is important, because atopic asthma in children apears to have a less benign course than nonatopic disease.[123] Burrows and colleagues[124] assessed this association in a random sample selected from Tucson, Arizona, using skin tests with local antigens as an index of atopic status. In children 3 to 14 years old, atopy was strongly associated with attacks of wheezing and dyspnea, regardless of whether asthma had been diagnosed. Later analyses of the Tucson population indicated that the total serum IgE level was more strongly associated with the prevalence of asthma,[125] an association that was also found in an NHANES analysis (discussed later). Another study using self-reported

diagnosis of hay fever in a population sample from western Pennsylvania showed atopy to be more common in asthmatic than nonasthmatic children.[126] Two other studies demonstrated parental atopy and asthma as risk factors for asthma in their children.[127,128] The results also demonstrated a complex interaction between these factors and the gender of the child. A study of 525 New Zealand children assessed the relationship of total serum IgE levels at the age 11 years and asthma, and investigators found that the prevalence of diagnosed asthma was strongly related to the serum IgE level (P trend < .0001).[129,130] Asthma was not reported for children with IgE levels of less than 32 IU/mL, whereas 36% of children with IgE levels of 1000 IU/mL or higher had asthma. Asthma and atopy are closely linked, and the causal nature of the factors seems to be complex and require more investigation. Nonetheless, atopy in parents and children does increase the risk of asthma and can be used as an empiric predictor.[131]

Diet

Diet, including breastfeeding, food intolerance and sensitivity, and intake levels of specific micronutrients, has been investigated as a potential risk factor for asthma for over 2 decades. In 1987, Burney[132] was among the first to propose diet as a potential explanation for the rising frequency of asthma, suggesting the possibility that increasing salt intake might have a role.

The rationale for investigating diet as a possible risk factor for asthma and allergic disease is that diet has changed in recent decades and biologically plausible mechanisms exist. Many dietary constituents have been investigated for potential involvement in the pathogenesis of asthma and allergic disease, including antioxidants (e.g., vitamin E, vitamin C, carotenoids, flavonoids), polyunsaturated fatty acids, vitamin D, folate,[122,133] foods (e.g., fruits, vegetables), metals or trace minerals (e.g., sodium, magnesium, selenium, zinc, copper), and components of the Mediterranean diet (Table 48-4).

TABLE 48-4 Nutrients Implicated in Asthma

Nutrients	Activity and Potential Mechanisms of Effect
Vitamins A, C, E	Antioxidant; protection against endogenous and exogenous oxidant inflammation
Vitamin C	Prostaglandin inhibition
Vitamin E	Membrane stabilization, inhibition of immunoglobulin E production
Flavones and flavonoids	Antioxidant; mast cell stabilization
Magnesium	Smooth muscle relaxation, mast cell stabilization
Selenium	Antioxidant cofactor in glutathione peroxidase
Copper, zinc	Antioxidant cofactors in superoxide dismutase
n-3 fatty acids	Leukotriene substitution, stabilization of inflammatory cell membranes
n-6 polyunsaturated/*trans*-isomer fatty acids	Increased eicosanoid production
Sodium	Increased smooth muscle contraction

From McKeever TM, Britton J. Diet and asthma. Am J Respir Crit Care Med 2004;170:725-7.

Many related methodologic issues complicate the study of diet and disease.[134] Obtaining unbiased exposure estimates is difficult because of recall problems, difficulties in measuring intake, and limited range of variation in the Western diet.[135] Diet is fundamental to existence and is closely associated with many lifestyle, social, cultural, and environmental factors that may influence the development of disease. Although many studies adjust for potential confounders, it has been argued that this is insufficient and that many or all of the reported associations between diet and disease are likely to be confounded by social and behavioral factors acting across the life course.[136,137] Several reviews on the topic of diet and asthma and allergic disease are available.[138-144]

Observational and randomized studies have directly correlated dietary sodium levels with increased bronchial responsiveness to histamine challenge.[145-147] One study showed this response occurred in males but not in females.[146] Ecologic data from England and Wales support these experimental findings; the purchases of table salt correlated with the regions of increased asthma mortality for men and children.[131] Other population-based studies, however, have not shown a relationship between urinary sodium levels and methacholine airway responsiveness,[148-150] although two did show an association with higher levels of potassium excretion.[148,150] Britton and associates[151] found that increased magnesium intake was associated with a reduced risk of bronchial hyperresponsiveness and wheeze. Because of the relationships among sodium, potassium, and magnesium, these investigators suggest the possibility that low levels of dietary magnesium may confound the association of sodium and potassium with bronchial hyperresponsiveness or asthma.[151] A systematic review of the clinical trials of dietary sodium reduction in persons with asthma concluded that dietary sodium reduction does not significantly improve asthma control.[152] Dietary sodium reduction was associated with some improvement in lung function in people with exercise-induced asthma, but because extremely large reductions in sodium intake were required, the clinical utility, as distinct from the potential public health relevance of this finding, is likely to be small.

A systematic review of the studies correlating asthma and allergic disease in children with dietary intake or status of vitamin A, vitamin C, vitamin E, selenium, zinc, copper, iron, fruits, vegetables, and components of the Mediterranean diet identified 62 eligible reports.[138] There were no randomized, controlled trials, and all studies were judged to be at moderate to substantial risk of bias. Meta-analyses demonstrated that serum vitamin A was lower in children with asthma compared with controls (odds ratio [OR] = 0.25; 95% confidence interval [CI], 0.10 to 0.40). The meta-analyses also showed that high maternal dietary vitamin E intake during pregnancy was protective against development of childhood wheezing (OR = 0.68; 95% CI, 0.52 to 0.88) and that maternal adherence to a Mediterranean diet during pregnancy was protective against persistent wheeze (OR = 0.22; 95% CI, 0.08 to 0.58) and atopy (OR = 0.55; 95% CI, 0.31 to 0.97) in children. Seventeen of 22 fruit and vegetable studies reported beneficial associations with asthma and allergic outcomes. Although weak, the available epidemiologic evidence supports dietary intake of vitamin A, vitamin D, vitamin E, zinc, fruits, vegetables, and a Mediterranean diet for the prevention of asthma.[138]

The fatty acid composition of the diet, particularly the relative amounts of n-3 (ω-3) and n-6 (ω-6) polyunsaturated fatty

acids (PUFAs) found in fish and vegetable oils, respectively,[153] affects cell functioning. Fatty acids appear to have specific roles in inflammatory and immune responses, and changes in fatty acid consumption are a postulated cause of the rising incidence of asthma and other allergic diseases.[154,155]

Conflicting observational data relating n-3 and n-6 PUFA intake or status during pregnancy, childhood, and adulthood to asthma and allergic disease have been surpassed by intervention trials. A 2008 systematic review with meta-analysis evaluated the interventional studies of n-3 and n-6 PUFA supplementation in the context of primary prevention of asthma and allergic disease.[143] Ten reports from six double-blind, randomized, controlled trials were identified. Four studies compared n-3 PUFA supplements with placebo, and two studies compared n-6 PUFA supplements with placebo. The meta-analyses failed to identify any consistent or clear benefits associated with n-3 PUFA supplementation during pregnancy or infancy for atopic dermatitis (relative risk [RR] = 1.10; 95% CI, 0.78 to 1.54), asthma (RR = 0.81; 95% CI, 0.53 to 1.25), allergic rhinitis (RR = 0.80; 95% CI, 0.34 to 1.89), or food allergy (RR = 0.51; 95% CI, 0.10 to 2.55). Similarly, n-6 PUFA supplementation in early life was not associated with any clinical benefit for atopic dermatitis (RR = 0.80; 95% CI, 0.56 to 1.16).

Two subsequent trials reported the consequences of n-3 PUFA supplementation during pregnancy. In the first, high-dose n-3 PUFA supplementation of 117 pregnant women from 25 weeks' gestation and during breastfeeding reduced the incidence of food allergy and IgE-associated atopic dermatitis in children in the first year of life compared with placebo (2% versus 15% [$P < .05$] and 8% versus 24% [$P < .05$], respectively).[156] In the second, larger study of 368 pregnant women, high-dose n-3 PUFA supplementation from 21 weeks' gestation until delivery did not reduce the incidence of IgE-associated disease or atopic dermatitis during the first year of life compared with placebo (RR = 0.70 [95% CI, 0.45 to 1.09] and RR = 0.64 [95% CI, 0.40 to 1.02], respectively).[157] There is insufficient evidence to recommend PUFA supplementation in any period of life as a means of reducing the burden of asthma and allergic disease.

The role of vitamin D in the cause asthma and allergic disease remains unclear. The increase in asthma and allergic disease in developed countries has been attributed to early-life vitamin D supplementation as rickets prophylaxis,[158] and widespread vitamin D deficiency is thought to be a consequence of more time being spent indoors and the active promotion of sun avoidance.[159] Cross-sectional, observational studies have reported vitamin D status to be no different[160] or increased in adults[161] with asthma but decreased in children with asthma.[162,163] Blood levels of 25-hydroxyvitamin D (25-OH-D) concentrations were found to be lower in adults with atopic dermatitis and allergic rhinitis.[164,165] In two studies using NHANES data, blood levels of 25-OH-D have been no different in adults with evidence of atopic sensitization; however, atopic sensitization was associated with reduced blood 25-OH-D levels in children and adolescents in one study[166] but not in adolescents in the other.[167] The effect of blood 25-OH-D levels on current wheeze depended on age and atopic status in another study using NHANES data, with nonatopic individuals and adults 50 years of age or older having a greater risk of wheeze if they had lower 25-OH-D levels.[168]

In children with asthma, lower blood levels of 25-OH-D have been associated with increased asthma severity, including increased IgE levels, eosinophilia, methacholine responsiveness, asthma-related hospitalization, exacerbations, use of antiinflammatory medication, and use of oral corticosteroids and with reduced asthma control scores.[169] Analogous findings have been reported for adults with asthma.[170] Similarly, for children with atopic dermatitis, lower serum 25-OH-D concentrations have been associated with increased severity of atopic dermatitis.[171]

Longitudinal cohort studies quantifying vitamin D status before the development of disease are not subject to many of the limitations of cross-sectional studies, such as reverse causation, whereby the vitamin D status of an individual is influenced by the presence of disease (e.g., children with asthma may spend more time indoors). A systematic review and meta-analysis of the longitudinal studies relating maternal vitamin D status during pregnancy to childhood outcomes concluded that high maternal dietary vitamin D intake is associated with a reduced risk of children wheezing up to the age of 5 years (OR = 0.56; 95% CI, 0.42 to 0.73).[138] However, maternal dietary vitamin D intake during pregnancy is not indicative of total body vitamin D status, because 90% of vitamin D is derived from cutaneous exposure to ultraviolet light. In contrast to maternal dietary vitamin D intake, high (>75 nmol/L) maternal serum 25-OH-D levels in late pregnancy have been associated with an increased likelihood of childhood eczema at age 9 months and asthma at age 9 years.[172]

During infancy, increased vitamin D intake has been associated with an increased risk of atopic dermatitis at age 6 years and an increased likelihood of allergic rhinitis and atopic sensitization at the age of 31 years.[173,174] In later childhood, an increased serum 25-OH-D concentration at 4 years of age has been associated with a reduced likelihood of asthma at 8 years of age,[175] and an increased serum 25-OH-D concentration at 6 years of age has been associated with a reduced likelihood of asthma, rhinoconjunctivitis, and atopic sensitization at 14 years of age.[176] The epidemiologic data support the hypotheses that vitamin D may have beneficial and adverse influences on the development of asthma and allergic disease. Ongoing clinical trials are clarifying the potential clinical role of vitamin D in modifying the risk of developing asthma and as an adjunct to asthma and atopic dermatitis therapy.

Although breastfeeding of infants is recommended because of well-documented benefits for mother and child, the effects of breastfeeding on the subsequent development of atopic dermatitis, wheezing disease, and asthma are not clear.[177,178] Conceptually, the advantageous consequences of breastfeeding for the infant include acquisition of maternal antibodies and immune-competent cells such as macrophages and leukocytes and protection against early occurrence of lower respiratory tract infections. However, breastfeeding may also be a route of exposure to a variety of immunologically active substances from the mother, such as tobacco smoke, cow's milk, eggs, wheat, maternal IgE, and sensitized lymphocytes.[135] Many studies have investigated the association between breastfeeding, asthma, wheezing illness, and atopic disease, and they have been subject to several systematic reviews, most of which highlight the limitations and difficulties in conducting and interpreting such studies (e.g., confounding, recruitment bias, reporting bias, reverse causation, variation in breastfeeding patterns, inability to randomize and blind). The systematic reviews have themselves been reviewed in consensus documents, which conclude that the exclusive breastfeeding for 3 to 4 months of

infants at high risk for atopic disease reduces the likelihood of atopic dermatitis and that breastfeeding beyond 3 to 4 months appears to confer no additional benefit.[179,180]

The available evidence also suggests that the breastfeeding of infants at low risk for atopic disease does not reduce the incidence of atopic dermatitis. The evidence for a protective effect of breastfeeding against respiratory disease is controversial. Although breastfeeding appears to reduce the incidence of virus-associated wheezing episodes in young children (<4 years), the evidence of an effect on breastfeeding on the development of asthma is inconsistent. Systematic reviews suggest that exclusive breastfeeding for 3 to 4 months is associated with a reduced risk of asthma in children 2 to 5 years old, but this beneficial effect is limited to infants at high risk for atopic disease.

Some systematic reviews have revisited the literature relating breastfeeding to childhood atopic dermatitis, asthma, and wheezing. A systematic review examining the association between exclusive breastfeeding for 3months or longer and the development of childhood atopic dermatitis identified 21 reports from 27 study populations and concluded that there was no strong evidence that exclusive breastfeeding confers a beneficial effect on the development of childhood atopic dermatitis (summary OR = 0.89; 95% CI, 0.76 to 1.04), even in children at high familial risk (OR = 0.78; 95% CI, 0.58 to 1.05).[181] Another systematic review clarified the association between breastfeeding and childhood asthma and wheezing after 5 years of age.[182] It examined 31 publications and concluded that breastfeeding for 3months or longer did not confer any beneficial effect on the incidence of asthma and wheezing illness after the age of 5 years. The summary odds ratio for any breastfeeding and wheezing was 0.97 (95% CI, 0.90 to 1.04), and for exclusive breastfeeding and wheezing, it was 0.96 (95% CI, 0.86 to 1.06).

Obesity

The prevalence of obesity increased dramatically in many countries, particularly Western and other developed countries in the latter decades of the twentieth century. In the United States, for example, the prevalence of overweight and obesity among adults rose sharply across the 1990s, such that most adults are now overweight.[183] The prevalence of childhood overweight is also rising rapidly.[183] The rise in obesity parallels the rise of asthma, and a hypothesis has been advanced that obesity could be a risk factor for asthma.[184] Several mechanisms have been postulated for the association, including the mechanical effects of obesity, a higher frequency of gastric esophageal reflux, upregulation of immunologic and inflammatory correlates of obesity, and a shared genetic basis for both conditions.[185,186]

The association of obesity with asthma has been investigated in children and adults. Camargo and colleagues offered one of the first reports in their 1999 paper based on the Nurses' Health Study II.[187] The body mass index (BMI) in 1991 was positively and strongly associated with asthma risk over the next few years (Fig. 48-13).[188] Similar studies have addressed obesity and asthma in children. In a cross-sectional study using NHANES III data, von Mutius and colleagues[188] found a positive association between BMI and asthma risk (OR = 1.77; 95% CI, 1.44 to 2.19) by comparing the highest and lowest quartiles of BMI. In the Tucson study, girls becoming overweight or obese between the ages of 6 and 11 years had a sevenfold increased risk for asthma.[189] Although many cross-sectional observational studies

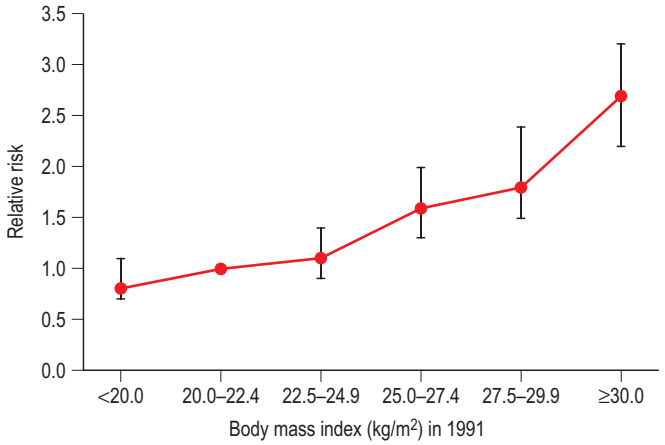

Figure 48-13 Relative risk of adult-onset asthma from 1991 through 1995 according to body mass index among 61,324 women who reported undergoing a recent health screening examination (n = 1061 cases). *(From Camargo CA Jr, Weiss ST, Zhang S, et al. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. Arch Intern Med 1999;159:2582-8.)*

have reported associations between the prevalence of asthma and obesity, it is not possible to exclude reverse causation, whereby asthma may contribute to obesity through inactivity and use of oral corticosteroids.

The most relevant data come from prospective cohort studies that have assessed risk for incident asthma in relation to initial weight or BMI. Beuther and Sutherland systematically reviewed prospective studies evaluating the association between BMI and incident asthma among adults.[190] Meta-analysis of the data from 333,102 subjects participating in the seven identified studies demonstrated that being overweight or obese (BMI ≥ 25) was associated with an increase in the rate of 1-year incident asthma (OR = 1.51; 95% CI, 1.27 to 1.80), with evidence of a dose effect for being overweight (OR = 1.38; 95% CI, 1.17 to 1.62) or obese (OR = 1.92; 95% CI, 1.43 to 2.59). There was no difference between sexes. A systematic review of similar literature for children and adolescents concluded that obesity precedes and is associated with the persistence and intensity of asthma symptoms.[191] In observational designs, a potential methodologic concern is that nonspecific respiratory symptoms resulting from cardiorespiratory loading and deconditioning may be misclassified as asthma. Careful studies of children and adults suggest that asthma is not inappropriately overdiagnosed in the obese.[192,193]

Observational studies have also reported adverse associations for BMI, obesity and overweight, and atopic dermatitis and atopic sensitization in children and adults.[194-197] A retrospective case-control study of children with a mean age of 7.0 years confirmed an association between obesity and atopic dermatitis and reported that early-life and prolonged obesity was associated with atopic dermatitis. Atopic dermatitis was more prevalent among children who were obese before 2 years of age (OR = 15.1; 95% CI, 1.51 to 151) and between 2 and 5 years of age (OR = 2.58; 95% CI, 1.24 to 5.41). Obesity after the age of 5 years was not associated with atopic dermatitis. Children who were obese for 2.5 to 5.0 years (OR = 2.64; 95% CI, 1.13 to 6.18) and for more than 5 years (OR = 3.40; 95% CI, 1.34 to 8.63) were more likely to be diagnosed with atopic dermatitis.[197]

These findings are provocative and indicate another potential risk factor for asthma and allergic disease, one that is increasingly prevalent and amenable to intervention. A better understanding of the mechanisms and potential role of intervention in the primary and secondary prevention of disease is needed.

Respiratory Infection

Respiratory infections are common in the first years of life, and they provoke wheezing in children with or without asthma. Less certain is whether viral or other respiratory infections have a direct role in the pathogenesis of asthma or they merely reveal that a child is predisposed to asthma. Investigation of the association of viral infection and asthma has been limited by available technology, with culture, serology, and antigen detection having 30% to 50% detection rates. The newer molecular technologies have improved the rates of viral detection up to about 90% and have revealed the importance of previously unknown viruses, such as human rhinovirus C (HRV-C).

Lower respiratory tract infections in children, which are caused by HRVs, respiratory syncytial virus (RSV), parainfluenza viruses, and other pathogens, are universal in childhood. A community-based study in Tecumseh, Michigan, estimated that children experience, on average, 2.1 lower respiratory tract infections in the first year of life and 1.5 such infections between 1 and 2 years of age.[119] Another cohort study of respiratory illnesses from birth through 18 months in Albuquerque, New Mexico, adapted a surveillance system similar to the one used in Tecumseh and found comparable incidence rates from 1988 through 1992.[198] The incidence of severe episodes of viral respiratory infections was captured in another study using surveillance through a pediatric group practice.[118] This study showed that 25% of children were affected in the first year of life, that 12% had annual occurrences by age 5 years, and that 8% of children 6 to 8 years old experienced annual episodes of infection.

Follow-up studies of children with a history of hospitalization for respiratory infections suggest that these illnesses may predispose to the development of asthma. In several studies, children with past hospitalizations tended to have abnormal lung function that was indicative of airflow obstruction, including hyperinflation, increased respiratory resistance, and reduced spirometric flow rates.[199-206] In children with past hospitalizations, increased airway reactivity occurred after assessment by exercise, cold air inhalation, methacholine, or histamine inhalation challenge.[201-203]

Infants hospitalized with RSV-associated bronchiolitis are more likely to wheeze and develop asthma later in childhood. A study of Swedish children found that those who were hospitalized with RSV bronchiolitis in infancy were almost nine times more likely to have physician-diagnosed asthma at age 13 years than those without infection.[207] Being hospitalized with RSV bronchiolitis in infancy was an independent risk factor for current asthma and recurring wheezing (OR = 9.3; 95% CI, 3.6 to 24.5).

Henderson and colleagues[208] described the relationship of hospitalization for RSV bronchiolitis in infancy and asthma in a population-based birth cohort study of more than 8000 children from the United Kingdom. Hospitalization for RSV bronchiolitis was associated with physician-diagnosed asthma at age 7 years (OR = 2.5; 95% CI, 1.4 to 4.3) only among nonatopic children. No association was observed for children with atopy at 7 years. Because most children are not hospitalized for lower respiratory tract disease, these results apply only to the more severe infections. A population-based study of children in East Boston, Massachusetts, however, found that a history of bronchiolitis or croup was a predictor of increased airway responsiveness.[209] In another Boston area study, children from a birth cohort with lower respiratory tract infection (i.e., croup, bronchitis, bronchiolitis, or pneumonia) in the first year of life were twice as likely to report two or more episodes of wheeze than children with no lower respiratory tract infection.[210]

The Tucson Children's Respiratory Study provides relevant data on follow-up from birth to age 13 years.[158,211] Results from this longitudinal study show that RSV infection was associated with an increased risk of infrequent and frequent wheeze by age 6 years.[211] The relative risk for wheeze after 3 years of age for children with RSV infection compared with children with no RSV infection decreased over time. The relative risk decreased with age from 3.2 and 4.3 at age 6 years to no risk at age 13 years for infrequent wheeze and frequent wheeze, respectively.[198] Support for the idea that severe RSV-associated respiratory disease probably does not contribute to the development of asthma has been provided by a large (8280 pairs) Danish Twin Registry study that applied genetic variance and direction of causation models to data on RSV-associated hospitalization and the development of asthma.[212] A model in which asthma caused RSV-related hospitalization fit the data significantly better than a model in which RSV-related hospitalization caused asthma, suggesting that RSV infection does not cause asthma but reflects an underlying predisposition to asthma.

The role of viruses in the natural history of asthma has been highlighted by several longitudinal cohort studies. The Wisconsin Childhood Origins of Asthma (COAST) study prospectively evaluated the timing, frequency, severity, and cause of symptomatic viral infection in the first 3 years of life in relation to later wheezing illness in a cohort of 289 neonates at high familial risk for asthma.[213] By using molecular technologies to identify viral infections in nasal lavage samples collected routinely and when symptomatic, this study highlighted the prognostic importance of HRV. Having one or more HRV-associated wheezing episodes during the first 3 years of life was more strongly associated with wheezing in the third year (OR = 10.0; 95% CI, 4.7 to 23.0) than having one or more RSV-associated wheezing episodes during the first 3 years of life (OR = 3.0; 95% CI, 1.6 to 5.8). First-year wheezing associated with HRV was the strongest predictor for third-year wheeze (OR = 6.6).[213] The pattern of viral respiratory tract infection in the first 3 years was different for children with or without asthma at the age of 6 years (Fig. 48-14).[214] Asthma at 6 years of age was strongly associated with HRV-associated wheeze in the first 3 years of life (OR = 9.8; 95% CI, 4.3 to 22.0). The frequency of HRV-induced wheezing episodes increased in the first 3 years of life for children diagnosed with asthma by age 6, whereas for children without asthma, HRV-associated wheezing episodes declined in the first 3 years (see Fig. 48-14). Almost 90% of children with HRV-associated wheezing episodes in year 3 had been diagnosed with asthma by the age of 6 years, and HRV-associated wheeze was a more robust predictor for subsequent asthma than atopic sensitization to aeroallergens. Asthma at 6 years of age was also associated with RSV-associated wheezing episodes in the first 3 years (OR = 2.6; 95% CI, 1.0 to 6.3). The likelihood of asthma by age 6 years being associated with RSV-induced wheeze in the first 2 years of life was increased

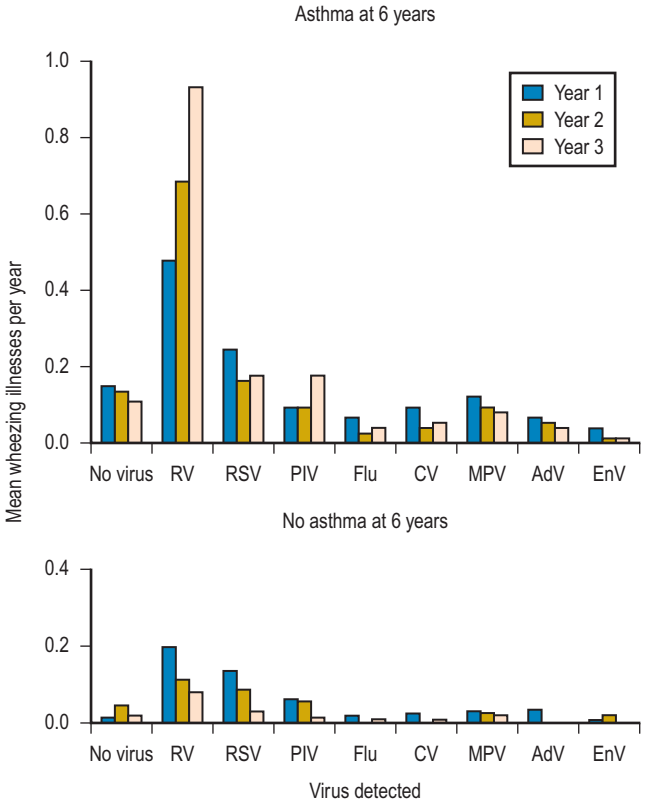

Figure 48-14 The Childhood Origins of Asthma (COAST) study evaluated the viral causes of wheezing illnesses in the first 3 years of life of children with or without asthma at 6 years of age. *AdV*, Adenovirus; *CV*, coronaviruses (OC143, NL63, and 0229); *EnV*, enteroviruses; *Flu*, influenza types A and B; *MPV*, metapneumoviruses; *PIV*, parainfluenza virus types 1 through 4; *RSV*, respiratory syncytial virus. *RV*; rhinovirus. *(From Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. Am J Respir Crit Care Med 2008;178:667-72.)*

only for children who had also had HRV-associated wheezing episodes.

Measurement of lung function in the COAST cohort at age 8 years demonstrated that HRV-associated wheezing episodes in the first 3 years of life were associated with reduced lung function: FEV_1 of 96% of predicted for those with HRV-associated wheeze versus 102% for no HRV-associated wheeze ($P < .03$). Similar differences were found for absolute FEV_1, forced expiratory volume in 0.5 second ($FEV_{0.5}$), and forced expiratory flow determined over the middle 50% of a patient's expired volume (FEF_{25-75}).[215] Lung function at age 8 was not associated with the frequency of HRV-associated wheeze nor with RSV-associated wheeze.

Although studies such as COAST demonstrate that HRV respiratory infection is prognostically more important than RSV infection for subsequent asthma, whether virus-associated wheezing episodes (particularly HRV) contribute to the pathogenesis of asthma or are merely manifestations of infection in children predisposed to asthma remains an unanswered question. There is evidence supporting the concept that children predisposed to asthma have lung function and airway epithelial abnormalities from very early in life that increase the likelihood of virus-associated wheezing episodes.[216-218] Human rhinovirus type 16 (HRV-16) replicates more readily in the airway epithelial cells of people with asthma, and the airway epithelial cells are more likely to lyse and have greatly impaired interferon-λ (IFN-λ) and IFN-β responses. Van der Zalm and coworkers reported that increased neonatal airway resistance was related to an increased likelihood of HRV-associated wheeze in the first year of life (OR = 1.77; 95% CI, 1.16 to 2.69).[218]

HRV was originally classified as serotypes HRV-A and HRV-B, but in 2007, a novel HRV designated HRV-C was identified using reverse transcription-polymerase chain reaction (RT-PCR).[219] HRV-C has been implicated in the natural history of wheezing disease and asthma, and it appears to have prognostic importance. In a prospective, population-based study of 1052 children younger than 5 years of age who were hospitalized in two U.S. counties with acute respiratory illness or fever, HRV was detected in 16%, and HRV-C was isolated slightly more than 50% of them. Children from whom HRV-C was isolated were significantly more likely than those with HRV-A or HRV-B to have underlying high-risk conditions such as asthma (OR = 2.32; 95% CI, 1.05 to 5.23).[220]

In Australia, HRV serotypes were isolated from 88% of 128 children 2 to 16 years old who presented to the hospital with acute asthma. HRV-C was isolated from 59% of the children, and these children had higher asthma severity scores than those infected with HRV-A or HRV-B.[221] In a study of children hospitalized in Hong Kong, HRVs were isolated from 85% of 128 children admitted because of acute asthma and from 33% of 192 control, nonatopic children hospitalized with nonasthma respiratory conditions.[222] HRV-C was isolated from 70% of the children with acute asthma and 19% of the controls, and children with HRV-C were more likely to require supplemental oxygen. These studies implicate HRV-C in most episodes of acute asthma requiring hospital attention. HRV-C appears to be more virulent than other HRV serotypes, particularly in children with atopic sensitization.[223]

Although the major focus has been on viral respiratory tract infection, asymptomatic early-life bacterial airway colonization has also been associated with childhood wheeze and asthma.[224] In the Copenhagen prospective Study of Asthma in Childhood, 321 neonates at high familial risk for asthma had their hypopharyngeal regions sampled at 1 month of age, and the children were then followed up to 5 years of age. Neonatal colonization of the hypopharyngeal region by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* (but not *Staphylococcus aureus*) in isolation or in combination was associated with increased likelihood of subsequent wheeze, hospitalization with wheeze, and asthma. Hypopharyngeal colonization at 1 year of age was not associated with neonatal colonization or the development of wheeze or asthma. Although has been postulated that early-life bacterial colonization induced neutrophilic airway inflammation with consequent wheeze and asthma, it also has been suggested that neonatal airway colonization by these bacteria reflects defective early-life innate immune responses that predispose to asthma.[225]

Asthma-like symptoms, especially in young children, often are treated with antibiotics, and an association has been observed between the use of these drugs and the risk of asthma. The simultaneously increased use of antibiotics in children and the increasing prevalence of asthma in developed countries has led to the hypothesis (consistent with the hygiene hypothesis) that antibiotic use may contribute to asthma by altering the normal colonization of gut flora in infants and increasing the

atopic, helper T cell type 2 (Th2) immune responses.[226,227] In support of this hypothesis, humans exposed to stable and farm environments, which are rich in microbes, show significantly reduced levels of asthma and atopic disease compared with those in other rural or nonrural environments.[227] Other studies have shown that the different proportion of aerobic and anaerobic gut flora in children from Sweden compared with Estonia parallels the difference in atopy incidence between these populations.[227,228] Animal studies also support the hypothesis. Mice given oral antibiotics had altered intestinal flora and impaired helper T cell type 1 (Th1) immune responses.[229]

Epidemiologic studies of asthma and allergic disease in relation to antibiotic use are beset by biases, including reverse causality (i.e., asthma leads to more common prescription of antibiotics)[230] and confounding by indication (i.e. respiratory infections leading to antibiotic use may be implicated in the development of asthma). To illustrate this problem, in a carefully conducted Tucson birth cohort study, information on illness, antibiotic use, and physician visits was ascertained on seven occasions in the first 9 months of life and correlated with the development of asthma and allergic disease up to the age of 5 years.[231] A significant association between the number of early-life courses of antibiotics and asthma was reported. The number of physician visits was associated with the number of antibiotic courses and with asthma. However, after adjustment for the number of physician visits, antibiotic use was not associated with asthma, and it was concluded that any association between early-life antibiotic use and asthma was an artifact of the number of physician visits for illness, which was strongly associated with antibiotic use and risk of asthma.

Two systematic reviews have provided insight into the possible causative association between early-life antibiotic use and asthma and allergic disease. A systematic review of studies that have related antibiotic exposure during pregnancy or in the first year of life with risk of childhood asthma identified relevant 22 studies.[232] Antibiotic use in the first year of life was associated with an increased likelihood of childhood asthma (OR = 1.52; 95% CI, 1.30 to 1.77). Stratified analysis indicated that retrospective studies reported the strongest associations (OR = 2.04; 95% CI, 1.83 to 2.27) compared with database and prospective studies (OR = 1.25; 95% CI, 1.08 to 1.45). Studies that addressed potential biases by adjusting for respiratory infections reported the weakest associations (OR = 1.16; 95% CI, 1.08 to 1.25). A second systematic review focusing on longitudinal studies identified 18 studies, and a meta-analysis indicated that antibiotic use was associated with subsequent wheeze or asthma (OR = 1.27; 95% CI, 1.12 to 1.43).[233] However, after eliminating nine studies with a high risk of bias, the magnitude of the association was reduced (OR = 1.12; 95% CI, 0.98 to 1.26). Both systematic reviews concluded that there might be a weak link between antibiotic use and subsequent asthma and that biases had exaggerated the strength of any association that might exist.

Prematurity

Premature birth has been associated with the development of symptoms consistent with asthma and other long-term pulmonary sequelae in a number of studies. The cause of the sequelae is uncertain. The pulmonary injury may be acquired during mechanical ventilation of preterm infants with respiratory distress syndrome (RDS), from the RDS itself, or from some other facet of prematurity. Prematurity has been examined as a risk factor for asthma in cohort studies of affected children and in cross-sectional studies. In one of the earliest reports, Northway and coworkers[234] considered the first possibility—that asthma is a long-term consequence of bronchopulmonary dysplasia (BPD). BPD is a syndrome of chronic lung disease in premature infants who are mechanically ventilated for at least 1 week as a treatment for RDS. The clinical diagnosis requires the symptoms of persistent respiratory distress during infancy, dependence on supplemental oxygen, and abnormal chest radiographs. Northway and colleagues[235] then studied adolescents and young adults born between 1964 and 1973 who had BPD in infancy and compared their long-term pulmonary outcomes with those of two control groups. They found that most subjects with a history of BPD in infancy had pulmonary dysfunction. Moreover, the increase in airway reactivity was not associated with a more frequent family history of asthma in this sample or with an increased prevalence of atopy. These findings suggest that lung injury resulting from mechanical ventilation of premature infants has a role in the pathogenesis of persistent pulmonary dysfunction that is similar to asthma.

Bertrand and associates[236] investigated the role of RDS in prematurity in the pathogenesis of airway hyperresponsiveness (AHR) in subjects who did not have BPD as infants. The group with a history of RDS had evidence of more hyperinflation and airway obstruction compared with controls. However, results from the histamine challenge to determine AHR and familial aggregation of AHR were inconclusive. The incidence of airway reactivity was elevated among cases and controls and among the mothers and siblings of cases and controls. The investigators suggest that the elevated incidence of AHR among mothers of both groups supports the hypothesis that there may be an association between the onset of premature labor and airway reactivity. Because no comparison group was established for mothers of term children, however, this assertion cannot be affirmed from the study.

Some researchers have investigated the effect of very low birth weight (VLBW < 1501 g) and BPD on asthma development in birth cohorts.[235-241] Children with VLBW were followed for 8 years as part of the Newborn Lung Project conducted in Wisconsin and Iowa.[237,238] Results at age 5 years did not show a consistent association between asthma and BPD.[237] Children with diagnosed BPD and children with radiographically identified BPD had about a threefold and twofold increase, respectively, in the risk of bronchodilator use up to age 2 years, adjusted for birth weight, gestational age, gender, race, and neonatal center. Among children with BPD, the prevalence of ever having asthma at age 8 years did not show a difference by the period of birth.[238] However, the prevalence of wheezing in the last year at 8 years of age decreased from 50% to 16% over time. As the researchers observed, this finding could have resulted from the introduction of surfactant therapy as a BPD treatment.

Prematurity as a risk factor for asthma has been explored in cross-sectional studies.[242-247] A significant association between current asthma prevalence and premature girls was observed in a study of 5000 schoolchildren.[243] Significantly more premature children had a family history of asthma than did term children, and this association was stronger among children who required mechanical ventilation as premature infants. Another German study of schoolchildren did not show an association between former or current asthma and low birth weight (LBW < 2500 g) among premature children.[244] However, bronchial hyperresponsiveness was significantly increased in children born at

term with LBW compared with children born with normal birth weight, with values adjusted for height, gender, and age.

A study conducted as part of the ECRHS examined birth characteristics and asthma symptoms in young adults from Norway.[245] The researchers observed a significant decrease in asthma symptoms per 500-g increase in birth weight, adjusted for gestational age, length at birth, parity, maternal age, gender, adult height, hay fever, and current smoking habits.

Race and socioeconomic status may be determinants of prematurity and asthma. To test the hypothesis that prematurity was a risk factor for asthma independent of race or socioeconomic status, Oliveti and colleagues[248] performed a case-control study using a population restricted to African-American children from impoverished inner-city census tracts in Cleveland, Ohio. Their findings confirmed previous findings with regard to prematurity and LBW. Asthmatic children had significantly lower birth weights and gestational ages than nonasthmatic children and were more likely to have required positive-pressure ventilation (PPV) after birth. The risk of asthma was increased more than three times for children receiving PPV after birth. However, the increased risk of asthma due to LBW and prematurity was not significant when maternal history of asthma, bronchiolitis, lack of prenatal care, low maternal weight gain, and PPV were considered simultaneously.[248] This suggests that lung injury and perhaps mechanical ventilation lead to an asthma-like syndrome, rather than LBW and prematurity directly.

Researchers have examined the lung function of preterm children over time. Koumbourlis and associates[249] followed 17 preterm children with chronic lung disease, including BPD, from 8 to 15 years of age. The investigators observed improvements in the lung volumes of these patients throughout childhood and into adolescence, and these improvements were experienced by all children, regardless of the severity of the neonatal chronic lung disease. If patients had airway obstruction, it was primarily localized to the smaller airways, associated with AHR, and relatively fixed over time.

Two systematic reviews have investigated the association between prematurity and childhood asthma and wheezing outcomes. Patelarou and colleagues identified nine studies that had reported on the association between adverse birth outcomes (e.g., premature, LBW, VLBW, fetal growth retardation) and early (0 to 2 years) childhood wheeze.[250] They concluded that adverse birth outcomes were associated with wheezing in early life. Similarly, a systematic review that identified 19 studies reported that preterm (<37 weeks' gestation) was associated with an increased likelihood of childhood asthma (OR = 1.074; 95% CI, 1.072 to 1.075).[251] These results suggest that premature infants with or without neonatal respiratory disease may be at higher risk for asthma or a syndrome similar to asthma than term infants. However, the mechanistic pathways involved and the potential interactions with other asthma risk factors, such as viral respiratory infections and susceptibility genes, remain uncertain.

Occupational Asthma

Occupational asthma is defined as variable airflow limitation or bronchial hyperresponsiveness due to exposure to a specific agent or conditions in a particular occupational setting but not to stimuli encountered outside the workplace.[252] Several hundred agents have been identified as causes of occupational asthma.[253,254] They include animal allergens (e.g., urine, dander), plants (e.g., grain dust, flour, latex, castor bean, green coffee bean), enzymes (e.g., subtilisin from *Bacillus subtilis*, papain, fungal amylase), wood dust or barks (e.g., Western red cedar, oak, reactive dyes), drugs (e.g., penicillin, methyldopa), metals (e.g., halogenated platinum salts, cobalt), and others such as oil mists. They have been classified according to possible pathogenetic mechanisms: high-molecular-weight agents that induce specific IgE antibodies; low-molecular-weight substances, such as isocyanates, for which underlying mechanisms are largely unknown; and irritant gases, fumes, and chemicals that induce occupational asthma by nonimmunologic mechanisms.[255] More extensive coverage of these agents and the topic is available elsewhere.[256,257]

Other causes of occupational asthma have been identified through clinical reports, epidemiologic investigations, and population studies. Jaakkola and colleagues[258] conducted a case-control study in Finland. Risk for asthma was found to be increased for several occupational groups, including some for which occupational asthma had not been previously reported, such as being a male or female waiter. Le Moual and coworkers[259] explored associations for occupation and occupational exposures with asthma in 14,000 participants in a French survey conducted in 1975. Several jobs were associated with an increased risk of asthma of about 50%. A similar analysis was reported for the United States based on the NHANES III.[260]

Several studies provide estimates of the overall importance of occupational asthma. Kogevinas and colleagues[261] analyzed data from more than 15,000 young adults participating in the ECRHS. An estimated 6.9% of asthma was attributed to occupation, with asthma defined by asthma symptoms or use of medication and assessed by questionnaire. When asthma was defined by questionnaire responses and bronchial hyperresponsiveness, the attributable risk estimated for occupation increased to 9.9%. Among members of a U.S. health maintenance organization, one third of persons identified as having new or recurrent asthma were classified as having a potential association with work as the basis for asthma.[262]

Blanc and Toren[263] conducted a meta-analysis of studies on occupational asthma from 1966 to mid-1999. The median attributable risk estimate for occupational asthma was 9% for all studies identified. When the study quality was taken into account and analyses were limited to those of higher quality, the estimate was 15%. These estimates included new-onset asthma and reactivation of preexisting asthma.

Outdoor Air Pollution

Outdoor air pollutants can be classified by origin as natural or manmade. Among the naturally occurring air pollutants are particulate matter (including bioaerosols), volatile organic compounds, and ozone. For asthma, the key manmade pollutants result from combustion of fossil fuels in cars, power plants, heating devices, and industrial point sources and from emissions of chemicals from manufacturing facilities, storage tanks, and accidental releases. In the United States, air pollutants have been categorized on the basis of their regulation under the Clean Air Act as criteria pollutants (e.g., lead, nitrogen dioxide [NO_2], sulfur dioxide [SO_2], particulate matter [PM], ozone [O_3], carbon monoxide [CO]) and as air toxics, a specified listing of 189 chemicals that includes some irritants relevant to asthma.[264]

These pollutants are a concern throughout the world's polluted cities and regions. Many cities and smaller towns and

villages in the developing world have the problem of smoke from biomass fuel use for indoor cooking and heating that is emitted outdoors.[265] Although it is accepted that exposure to outdoor air pollution can exacerbate existing asthma,[266-269] the role of outdoor air pollution in the development of childhood asthma is less well established. However, there is increasing evidence, especially from studies with a focus on exposure related to traffic within urban areas, that implicates outdoor air pollution in the development of childhood asthma[270-272] and lung function.[273]

The outbreaks of acute asthma in Barcelona illustrate the consequences of exposure to an airborne contaminant and the need to investigate asthma epidemics. During the 1980s, a remarkable series of epidemics of asthma occurred in Barcelona, a port city. Careful analysis of one outbreak showed spatial clustering near the harbor, and an epidemiologic investigation showed a very strong association between unloading of soybeans at the harbor and occurrence of the epidemics.[274] An antigen was identified in the soybeans that proved to be responsible for the outbreaks.[275] The outbreaks were traced to releases of dust at a particular silo, and control measures were enacted.[276] Subsequently, a review of the historical record showed that there had been similar outbreaks of soybean asthma in New Orleans.[277]

A large body of experimental and observational evidence links outdoor air pollution to exacerbation of asthma.[266-269,278-283] Compilations of the evidence can be found in the criteria documents prepared by the U.S. Environmental Protection Agency (EPA) for particulate matter and ozone.[282,283] Human experimental studies have provided some insights, showing for example, that the oxidant pollutants nitrogen dioxide and ozone may enhance the effects of allergens, possibly by increasing the permeability of airways.[284,285] Epidemiologic data, primarily coming from studies of panels of persons with asthma or of medical morbidity, have shown that the adverse effects of air pollution on asthma are relevant clinically and are significant from a public health perspective. There is uncertainty about the relative effects of specific pollutants compared with the overall toxicity of the air pollution mixture.[286] Gent and colleagues investigated the effect of exposure to ozone and particulate matter of 2.5 μm in diameter ($PM_{2.5}$) in a U.S. cohort study of 271 asthmatic children.[287] Among children using maintenance medication, the level of ozone, but not $PM_{2.5}$, was significantly associated with worsening of respiratory symptoms and an increase in rescue medication use. Significant associations were not found for children not using maintenance medication. These findings suggest that children with asthma using maintenance medication are especially vulnerable to ozone, even after adjusting for exposure to $PM_{2.5}$ and at air pollution levels below the EPA air quality standards.

Various lines of epidemiologic evidence continue to indicate a potential role of air pollution in the cause of asthma. Cross-sectional studies have investigated asthma prevalence and air pollution. After the unification of East and West Germany, studies were conducted to compare respiratory diseases among children who had a relatively homogenous genetic background but had experienced exposures to air pollution at very different concentrations.[288-291] In a study conducted between 1989 and 1992, children 9 to 11 years old from Munich (West) had a higher prevalence of physician-diagnosed asthma than those from Leipzig and Halle (East).[288] Current asthma prevalence among children living in West Germany, an area with a greater amount of heavy road traffic, was 5.9%, compared with 3.9% for children from East Germany, where pollution originated from burning brown coal and industrial emissions.[290] However, living in West Germany was not an independent risk factor for asthma after adjustment for sensitivity to pollen, HDMs, and cat allergens.

Another German study conducted from 1995 through 1996 obtained similar results.[289] Current asthma prevalence for children from Munich was 5.1%, compared with the prevalence for their counterparts from Dresden of 4.0%. Significant differences in physician-diagnosed asthma prevalence were observed by comparing children in Munich (10.3%) and those in Dresden, former East Germany (5.8%).[289]

A study enrolling children 8 to 12 years of age who were living in Hong Kong compared physician-diagnosed asthma prevalence in a high-pollution district and a low-pollution district.[291] The researchers found that asthma prevalence was almost doubled in the high-pollution area compared with the low-pollution area.

Some studies have investigated the possible role of specific air pollutants in the development of asthma. In a cross-sectional study that was conducted as part of the ISAAC Phase Two and enrolled the same German children from Dresden, an increase in estimated traffic-related exposure to benzene was associated with an increased prevalence in physician-diagnosed asthma after adjusting for potential confounders.[292] However, this association reached statistical significance only when the home and school addresses used as the exposure indicators were combined. The prevalence of asthma was not associated with concentrations of SO_2, NO_2, and CO. An increase in the exposure to air pollutants (except ozone) was associated with an increased prevalence of physician-diagnosed asthma in 5421 nonatopic children (5 to 7 years and 9 to 11 years old). This relationship was not observed in atopic children.

Another cross-sectional study evaluating the effects of general air pollution was conducted among 165,173 high school students in Taiwan as part of the ISAAC.[293] The researchers investigated the role of long-term exposure (i.e., annual average concentration) to air pollution and the prevalence of asthma. Long-term exposure to total suspended particles, NO_2, CO, ozone, and airborne dust was associated with increased prevalence of asthma after adjusting for exercise, smoking, alcohol consumption, incense use, and environmental tobacco exposure. A similar study of 331,686 middle school students living in 24 counties and cities in Taiwan found a positive association between physician-diagnosed asthma prevalence and exposure to CO and nitrogen oxides (NO_x) when adjusted for age, history of atopic eczema, and parental education.[294]

Baldi and coworkers[295] reanalyzed data from a survey of 3193 children and 20,310 adults from seven French towns between 1974 and 1976. They estimated a significant increase (OR = 1.24; 95% CI, 1.08 to 1.44) in asthma prevalence per 50 $\mu g/m^3$ in the SO_2 3-year-period annual mean after adjusting for age, education, and smoking status. The association remained significant when they restricted the analysis to adults reporting their first attack after moving to the study areas. They did not observe this relationship for children. These cross-sectional studies address the prevalence of asthma, which reflects the incidence and duration of the disease. If air pollution increases the duration of asthma, the prevalence would be increased, even without an effect on incidence.

The clearest evidence of a causal association between outdoor air pollution and childhood asthma comes from cohort studies.

The Traffic-Related Air Pollution and Childhood Asthma (TRAPCA) study is a birth cohort study of children from the Netherlands, Germany, and Sweden that is funded by the European Union.[296] Preliminary results from the 1756 German children followed for their first 2 years of life showed a 23% (95% CI, 1.00 to 1.51) increase in the risk of asthmatic, spastic, or obstructive bronchitis for those living close to major roads (<50 m) compared with children farther away.

A cohort study of almost 5000 children between the ages of 5 and 7 years, who lived in nine communities surveyed in the California Children's Health Study and four other communities, was started in 2003 to evaluate characteristics that might increase children's susceptibilities to the effects of traffic-related pollution.[297] Preliminary results showed that living within 75 m of a major road was associated with an increased risk of physician-diagnosed asthma (OR 1.29; 95% CI, 1.01 to 1.86), prevalent asthma (OR = 1.50; 95% CI, 1.16 to 1.95), and wheeze (OR = 1.40; 95% CI, 1.09 to 1.78). Among long-term residents (i.e., living in the same home since the child was 2 years old or younger) with no parental history of asthma, an increased risk of physician-diagnosed asthma (OR = 1.85; 95% CI, 1.11 to 3.09), prevalent asthma (OR = 2.46; 95% CI, 1.48 to 4.09), and wheeze (OR = 2.74; 95% CI, 1.71 to 4.39) was associated with living within 75 m of a major road. Increased risk was not associated with the exposure for children with a parental history of asthma and for short-term residents.

The Adventist Health Study on Smog (AHSMOG) is a prospective cohort study that enrolled more than 3000 nonsmoking adults (27 to 87 years old) living in California in 1977.[298] In the first 10 years of follow-up, Abbey and colleagues[298] examined 79 incident asthma cases in relation to PM and found a 30% increased risk of asthma for a 1000 hr/yr exposure to concentrations of PM_{10} that exceeded 100 $\mu g/m^3$. A later report on the AHSMOG participants used the 1973-1992 8-hour mean ozone concentration as the exposure and found that the risk of developing asthma doubled per 27 parts per billion increase for males but not in females after adjusting for age, education, respiratory infection before age 16 years, and smoking status.[299]

A systematic review commissioned by the U.K. Committee on the Medical Effects of Air Pollution (COMEAP) was established to investigate whether outdoor air pollution causes asthma.[300] This 2010 review identified 14 cross-sectional studies relating asthma prevalence in more than four cities to quantitative pollution measures; the number of cities ranged from 6 to 62 and covered Europe, North America, and Asia. A meta-analysis revealed no significant associations between NO_2, PM_{10}, or SO_2 and period prevalence of wheeze and lifetime prevalence of asthma. The review also identified 14 studies of 10 birth cohorts and 11 studies of cohorts recruited during child or adulthood. In these studies, exposures were individualized by modeling, usually to the individual's home address. In contrast to the cross-sectional studies, meta-analysis revealed associations between NO_2 and the incidence of asthma (OR = 1.07; 95% CI, 1.01 to 1.14; 11 studies) and between $PM_{2.5}$ and the incidence of asthma (OR = 1.43; 95% CI, 1.01 to 2.02; 5 studies). The COMEAP systematic review concluded that the evidence from the cohort studies is consistent with a significant increase in the incidence of asthma associated with NO_2 and PM from traffic sources. The possibilities of air pollution aggravating existing subclinical asthma and residual confounding by factors associated with asthma and residential proximity to traffic were also raised. The disparity between cross-sectional and prospective studies suggests that although the incidence of asthma among those living close to traffic is increased, it is not evident at a population level because of the small effect size and the lack of variation in the distance between home and traffic.

Cohort studies published since the COMEAP are consistent with its findings, but they also highlight a possible early-life effect and the importance of exposure while at school. The Dutch Prevention and Incidence of Asthma and Mite allergy (PIAMA) birth cohort study related symptom data prospectively collected annually from 3863 children up to the age of 8 years to land-use regression estimates of individual NO_2, $PM_{2.5}$, and soot exposures at their birth addresses.[271] $PM_{2.5}$ was associated with an increased annual incidence of asthma (OR 1.28; 95% CI, 1.10 to 1.49), prevalence of asthma (OR = 1.26; 95% CI, 1.04 to 1.51), and asthma symptoms (OR = 1.15; 95% CI, 1.02 to 1.28). The associations between outcomes and NO_2 and soot exposures were similar, but there was a high correlation ($r > 0.9$) for $PM_{2.5}$, NO_2, and soot exposures. Only 48% of the cohort were still living at the birth address at age 8 years, and the associations between pollutants and outcomes were evident only in those who had not moved house; for the children who had moved from the birth addresses, the only significant association was between $PM_{2.5}$ and the prevalence of wheezing symptoms (OR = 1.15; 95% CI, 1.00 to 1.32).

The Southern Californian Health Study evaluated 2497 symptom-free children recruited in kindergarten or the first grade (≤6 years old) from 13 communities, each with continuous ambient ozone, NO_2, $PM_{2.5}$, and PM_{10} measurement.[272] The incidence of asthma in the subsequent 3 years was determined by annual questionnaires and correlated with individualized estimates of traffic-related pollution at home and at school. The incidence of asthma was increased by nonfreeway traffic–related pollution at home (hazard ratio [HR] = 1.51; 95% CI, 1.25 to 1.81) and at school (HR = 1.45; 95% CI, 1.06 to 1.98).

Although the balance of evidence suggests an association between outdoor air pollution and the development of asthma in some individuals who live near busy roads, there does not appear to be an association between air pollution and the development of asthma at the population level. Moreover, the well-documented increase in asthma prevalence in the latter decades of the twentieth century cannot be readily explained by changes in levels of the major combustion pollutants. The emerging association between traffic-related emissions and asthma requires further investigation.

Indoor Air Pollution

In the home and other indoor environments, children and adults inhale diverse pollutants that may be associated with the risk for asthma.[279,301] They include combustion-source emissions from cooking stoves and ovens, space heaters fueled by gas or kerosene, wood-burning stoves or fireplaces, and tobacco smoking; volatile and semivolatile organic compounds released from household products, furnishings, and other sources; and allergens from insects, molds, mites, rodents, and pets.[279,301] Many of these pollutants can be present in higher concentrations indoors than outdoors, providing a rationale for studies that have examined indoor pollutants as factors that may cause or exacerbate asthma. For example, in a prospective cohort study of inner-city U.S. children with asthma, indoor NO_2[302] and PM[303] were associated with asthma symptoms. The associations were independent of each other and of outdoor

concentrations of the pollutant. A full examination of this literature is beyond the scope of this chapter, but reviews of indoor air pollution are available.[279]

Whether these exposures by themselves, in the absence of underlying genetic susceptibility, can cause asthma is uncertain.[301] However, mounting evidence indicates that maternal smoking is associated with an increased risk for asthma in offspring and later exacerbations of asthma (see "Involuntary or Passive Smoking") and that levels of allergen exposure are associated with the incidence of asthma and wheezing. However, there have been only limited investigations of indoor air pollution and the incidence of asthma linked to risk factors other than passive exposure to tobacco smoke. An Institute of Medicine committee reviewed the evidence on indoor air pollution and childhood asthma and derived conclusions regarding causation and exacerbation.[301] This topic also has been reviewed elsewhere.[304,305]

Several investigations have addressed the prevalence of asthma and exposure to nitrogen oxides from cooking stoves. Homes with natural gas–fueled or propane-fueled cooking stoves tend to have NO_2 levels substantially above those of homes with electric stoves.[306] Some investigations indicate a general increased risk of respiratory symptoms, including wheezing, in households with gas stoves, but the data are inconsistent and not indicative of increased asthma incidence caused by nitrogen oxides.[31,307]

The myriad exposures to volatile and semivolatile organic compounds that can occur in homes and other locales have been investigated as risk factors for childhood asthma. Although many cross-sectional studies report an association between volatile organic compound exposure and asthma in children[308,309] and adults,[310,311] these studies cannot establish causality and are beset by the problem of reverse causality, whereby parents modify their houses (e.g., laminate flooring) as a consequence of their children developing asthma.[312] Cohort studies suggest that maternal volatile organic compound exposure during pregnancy can influence the development of childhood allergic disease.[313] This is an area of ongoing research because of the potential for intervention by behavioral modification and low volatile organic compound technology.

Studies of indoor allergens have largely focused on the status of children with asthma in relation to levels of allergen rather than considering the levels of allergens as predictors of asthma.[314] A prospective cohort study conducted in the United Kingdom found levels of HDMs in the home to predict later development of asthma, and children with higher levels of HDM antigen in their homes tended to wheeze at a younger age.[315] The German Multicentre Allergy Study followed 1314 children from birth to 13 years of age and found that sensitization to perennial allergens such as HDMs, cat hair, and dog hair that developed before 3 years of age was associated with a loss of lung function at school age.[316] A U.S. study of 474 children indicated that exposure to two or more dogs or cats in the first year of life might reduce subsequent allergic sensitization risk to multiple allergens during childhood.[317]

Not all studies support the conclusion that allergen exposure causes asthma. A British cohort study did not find a significant association between levels of HDM exposure and sensitization or wheeze.[318] Results from a German birth cohort of 939 children followed until age 7 years showed a strong association between sensitivity to HDM allergens or cat allergens and wheezing from 3 years of age.[319] However, the investigators also assessed early indoor allergen exposure and physician-diagnosed asthma or wheeze and did not find an association. They concluded that their results did not support the hypothesis that allergen exposure causes asthma.

Prospective cohort studies have studied the relationship between exposure to mold and the risk of asthma. A study of 1916 Finnish children 1 to 7 years old used parents' reports of mold and dampness as a surrogate for exposure to aeroallergens in the home.[320] After 6 years of follow-up, exposure to mold was found to be an independent risk factor for asthma among Finnish children. The incidence of physician-diagnosed asthma was double for children in homes with reported mold odor compared with those that did not. Jaakkola and Jaakkola reviewed the literature on indoor molds and asthma, and they concluded that exposure to molds at home increases the risk of asthma among adults and that exposure to molds at work increases the risk of wheezing.[321] They observed that exposure to indoor molds increases the severity of asthma and that removing the source relieves or eliminates symptoms and signs of asthma. Sensitization to mold has been linked to the presence, persistence, and severity of asthma.[322,323] A review of housing interventions designed to improve outcomes concluded that asthma symptoms could be reduced by removing moldy items and eliminating leaks and other moisture sources in homes.[324]

Intervention studies with avoidance of aeroallergens and food allergens have not consistently found a reduction of asthma risk among children. The Canadian Childhood Asthma Primary Prevention study included 545 high-risk children who were randomized to intervention (i.e., avoidance of HDM by use of mattress covers and acaricides, pets, and passive smoking and encouragement of breastfeeding with delayed introduction of solid foods) or to control groups before birth.[325] For 380 children at 7 years of age, the prevalence of physician-diagnosed asthma was significantly lower for the intervention group (15%) than for the control group (23%).

Another intervention study of a birth cohort of 110 high-risk children living on the Isle of Wight assessed asthma (i.e., wheeze and bronchial hyperresponsiveness) prevalence at age 8 years and found that the asthma risk was ninefold higher for the control group than the intervention group.[326] Intervention included breastfeeding by a mother on a low-allergen diet or giving a hydrolyzed formula and reducing HDM exposure with an acaricide and mattress covers. However, the Australian Childhood Asthma Prevention Study, which included 516 high-risk children randomized to an HDM avoidance intervention group or control group, did not find a significant reduction in the prevalence of current asthma at age 8 years for the intervention group compared with the control group.[327]

A systematic review and meta-analysis of prospective birth cohort studies evaluating the effects of allergen (i.e., HDM or dietary) avoidance during pregnancy concluded that early-life allergen avoidance in isolation does not reduce the likelihood of asthma in children at age 5 years (OR = 1.22; 95% CI, 0.83 to 1.78). However, multifaceted antenatal intervention that combines breastfeeding with allergen avoidance and maternal smoking cessation does reduce the likelihood of asthma in children at age 5 years (OR = 0.73; 95% CI, 0.55 to 0.97).[328]

Tobacco Smoke

Exposure to tobacco smoke has serious adverse effects on the respiratory tract. Perhaps because of the sensitivity of the

asthmatic lung to cigarette smoke, young smokers tend to have somewhat greater lung function and less underlying airway responsiveness than nonsmokers—a phenomenon sometimes referred to as the *healthy smoker effect*.[329] Nonetheless, substantial data show that active smoking increases nonspecific responsiveness of the airways, perhaps by inducing inflammation[329] or by narrowing baseline airway caliber in older people.[28] Smokers also tend to report wheezing more frequently than nonsmokers, and wheezing tends to decline after cessation of smoking. Increased airway responsiveness in active smokers also tends to abate after smoking cessation.[329,330]

A systematic review of studies exploring the temporal association between active smoking and asthma reported that most studies indicated that people who smoked were at increased risk for asthma.[331] These studies evaluated diverse sample populations and used different methods, and the review highlighted the potential for residual confounding by health behaviors (e.g., physical exercise). The review concluded that although active smoking might be a risk factor for asthma, the evidence was insufficient to conclusively state whether smoking was a causal or proxy risk factor for asthma.

Involuntary or Passive Smoking

The nonsmoking child is exposed to *second-hand smoke*, a name given to the mixture of sidestream smoke released by a burning cigarette and the mainstream smoke exhaled into the air by the smoker. This mixture has also been called *environmental tobacco smoke*. Smoking adds respirable particles and irritant gases to indoor air, and it represents one of the major sources of fine particles in the air of U.S. homes.[332] Exposure of children to particles and gases in tobacco smoke has been documented by measuring personal exposures and using biomarkers that indicate the levels of tobacco smoke components absorbed into the body.[333] Cotinine, a major metabolite of nicotine, has been extensively investigated in children in relation to parental smoking. Compared with children living in households in which there is no smoking, children living with smokers tend to have substantially higher cotinine levels.[332,333] In the past, exposure to second-hand smoke was widespread. Almost all participants, including nonsmokers, in the 1988-1990 NHANES III had detectable serum cotinine levels.[334] Ten years later, NHANES IV showed a dramatic reduction in cotinine levels,[335] a trend that has continued.[331]

Exposure to second-hand smoke contributes to both the causation and the exacerbation of asthma. First, passive smoking may increase the risk of more severe lower respiratory tract infections during the early years of life.[336] Second, the direct toxic effects of second-hand smoke may induce and maintain the heightened nonspecific responsiveness of airways found in asthmatic children. Third, many children have second-hand smoke exposure during gestation and after birth. Substantial evidence suggests that in utero exposure to tobacco smoke components affects fetal airway and immune system development.

Young and associates assessed nonspecific airway responsiveness using a histamine challenge for 63 normal infants at a mean age of 4.5 weeks.[337] Even at this young age, parental smoking and a family history of asthma were associated with an increased level of airway responsiveness. In a similar prospective investigation, Hanrahan and colleagues found that children whose mothers smoked during pregnancy had a lower level of airway function soon after birth.[338] Maternal smoking during pregnancy has also been associated with increased in vitro cord blood mononuclear cell proliferative and cytokine responses after stimulation with allergens.[339,340]

There is extensive literature on the relationship between passive smoking and childhood wheeze and asthma. A systematic review identified 79 relevant prospective cohort studies.[341] Exposure to maternal (prenatal and postnatal), paternal, and household sources of cigarette smoke was associated with an increased likelihood of children wheezing up to the age of 18 years. The strongest associations for childhood wheeze were for postnatal exposure to maternal cigarette smoking: wheeze at 2 years or younger (OR = 1.70; 95% CI, 1.24 to 2.35), 3 to 4 years (OR = 1.65; 95% CI, 1.20 to 2.68), and 5 to 18 years (OR = 1.18; 95% CI, 0.99 to 1.40). The associations between exposure to maternal, paternal and household cigarette smoke and childhood asthma were not as strong as for wheeze, but they were most noticeable for maternal smoking during pregnancy: childhood asthma at 2 years or younger (OR = 1.85; 95% CI, 1.35 to 2.53) and 5 to 18 years (OR = 1.23; 95% CI, 1.12 to 1.36). Paternal smoking was associated with an increase in childhood asthma between 3 and 4 years, and household smoking was associated with an increase in childhood asthma after the age of 3 years.

The Children's Health Study based in California reported a transgenerational association, suggesting that exposure to cigarette smoke in utero may have epigenetic effects.[329] In a nested case-control study of children at 5 years of age (279 with asthma and 412 controls), the likelihood of childhood asthma was increased if the mother (OR = 1.5; 95% CI, 1.0 to 2.3) or the maternal grandmother (OR = 2.1; 95% CI, 1.4 to 3.2) smoked during pregnancy.[342] If the mother and grandmother smoked during pregnancy, the likelihood of childhood asthma was increased further (OR = 2.6; 95% CI, 1.6 to 4.5).

ALLERGIC DISEASE

Allergic Rhinitis

Although allergic rhinitis is common, few epidemiologic studies have focused on this disease. The most frequently cited risk factors include increasing age, atopy, and high socioeconomic status.[343] Parental history is positively associated with the development of allergic rhinitis in offspring. In the Tucson birth cohort study, a maternal history of physician-diagnosed allergy was significantly associated with a diagnosis of rhinitis by age 6 years (OR = 2.2; 95% CI, 1.35 to 3.54).[344]

Perinatal and infant risk factors have been examined. For example, younger gestational age at birth has been associated with a decreased risk of allergic rhinitis.[345,346] Some researchers have postulated that early-life exposures to microbes may modulate risk of allergic rhinitis, and this hypothesis has been supported by the observations that birth by cesarean section is a risk factor for allergic rhinitis,[347] as is reduced diversity of the intestinal microbiota in infancy.[348] Other risk factors under investigation include genetics,[349] early-life exposure to infections, acetaminophen use,[350] oral contraceptive use,[351] and indoor and outdoor air pollution exposure.[352]

Eczema

Risk factors for eczema include gender, race or ethnicity, family history, early-life antibiotic use, environmental exposures, and dietary factors, including breastfeeding, timing of the introduction of solids, and inclusion of probiotics. Family history of

eczema has been identified as a risk factor for eczema in several studies,[353] pointing to genetic determinants of eczema. Loss-of-function mutations in the filaggrin gene (*FLG*), which encodes a protein critical to skin barrier function, have been directly linked to eczema, and approximately 42% of people heterozygous for these mutations develop eczema.[354]

Black and Asian race or ethnicity is a risk factor, along with male gender,[353,355] although ISAAC Phase Three found that worldwide, boys were less likely to have eczema than girls. Early-life exposure to endotoxin appears to protect against the development of eczema, as reported in several studies.[356,357] Dietary factors, including breastfeeding, infant formulas, timing of solid food introduction, and supplementation with probiotics, have been studied. Neither breastfeeding nor timing of solid food introduction has been associated with protection against eczema.[358-363] Evidence suggests that hydrolyzed infant formulas and supplementation with probiotics may afford some protection against eczema,[364,365] but study results are mixed, and infection by the probiotic organism has been reported in infants receiving probiotic supplementation.

Food Allergy

Established risk factors for food allergy include male gender for children, eczema, and an atopic family history.[366-368] Other possible risk factors are diet and feeding practices during early childhood. Controversy exists about whether early allergen introduction or allergen avoidance may predispose to the development of food allergy.

Natural History and Course of Asthma

The natural history of asthma is a concern for affected children, their parents, the clinicians providing care, and researchers. Parents ask whether the child will outgrow asthma, and clinicians should be able to answer this question. Researchers have studied the natural history of asthma and searched for factors that determine prognosis. During adulthood, the former asthmatic child may be exposed to environmental agents, including cigarette smoke, which may adversely affect respiratory health. Childhood asthma has been postulated to increase the likely adverse effects of these exposures and other long-term consequences, such as persistent physiologic impairment from airway remodeling.[369,370]

Initial information on the natural history of childhood asthma largely came from cohort studies of children attending general practices or clinics.[140,371] These studies, some dating to the 1930s, were a principal source of data on the natural history of asthma until population-based investigations were implemented beginning in the 1960s. These early studies provided evidence of waning of clinical symptoms over time in a substantial proportion of children with asthma. However, most children tended to remain symptomatic. Interpretation of these data is constrained by differences between past and current therapeutic approaches, possible lack of representativeness of children receiving care at a particular clinical facility, and by diversity of the research methods.[140] These studies drew the participants from general practices and clinics, and presumably, more severe asthma was represented. Nevertheless, they provide evidence that the prognosis is favorable for some children with asthma, even in an era antedating contemporary therapeutic approaches.

Later epidemiologic studies provided a deeper understanding of the physiologic consequences of having childhood asthma and indicated that the lungs of these children might already have heightened airway responsiveness at birth. Birth cohort studies that include indices of ventilatory function and airway responsiveness during the first weeks of life indicate that infants at risk for asthma because of a parental history of asthma and atopy already have heightened responsiveness to a challenge.[337]

The Tucson study clarified the early natural history of wheezing.[120,372] Martinez and colleagues described the natural history of wheezing beginning before 3 years of age and found that some children had only transient early wheezing. Children who continued to wheeze up to 6 years of age were more likely to have mothers with a history of asthma and to have an elevated serum IgE levels, suggesting that the early wheezing represented asthma. Children whose wheezing did not persist had diminished airway function in early life but did not tend to have mothers with asthma or elevated IgE levels. The pattern of persistence of wheezing during childhood and into adulthood was similar in a smaller cohort study of 100 children in England, who were followed from birth to age 22 years.[373] In this high-risk cohort, early wheezing was not likely to persist, but wheezing at 11 years of age did tend to persist. The results of these studies imply that clinicians should be cautious in labeling all early childhood illnesses with wheezing as asthma, because some children are predisposed to wheeze with respiratory infections because of reduced airway function.

Population-based groups of children have been followed over time in prospective cohort studies (Table 48-5). Because most of these studies have drawn participants from defined populations, there is less potential for bias by the selection process, and the children with asthma are more likely to be representative. Information collected from childhood to early adulthood is available from several investigations, including two particularly large studies involving lengthy follow-up: the cohort study in Australia and the 1958 birth cohort study in the United Kingdom.[374,375] Findings of a number of smaller studies have been similar (see Table 48-5).

One of the first studies using a birth cohort design was conducted in Australia, initially by Williams and McNicol.[374,376-378] On enrollment in 1964, the children were 7 years of age, and after 35 years of follow-up, they were 42 years old.[376-378] Wheezing tended to track over time, but 43% were no longer wheezing at 28 years of age, and only 32% had wheezing at least weekly. Those with more severe wheezing at age 28 years tended to have a lower level of lung function tested by spirometry and to have a higher degree of airway responsiveness to a methacholine challenge. Over time, some improved, but an approximately equal proportion worsened. At age 42 years, 60% of the group with wheezy bronchitis at baseline was free of wheeze, and only 5% of this group had persistent asthma.[378] Symptoms continued in 70% of the original asthma group and in 90% of the severe asthma group. Almost one half of the severe asthma group continued to have persistent asthma at age 42 years. Those with severe asthma had suffered a loss in lung function by 14 years of age, but this loss did not progress in adulthood. Children with milder symptoms did not have a significant loss of lung function.

In another large, long-term study, members of the 1958 birth cohort in the United Kingdom were followed up to age 33 years.[375,379,380] Parents were interviewed when the participants

TABLE 48-5 Studies of the Natural History of Childhood Asthma

Population	Follow-up	Findings
401 Australian children; age 7 yr at enrollment[377,378,414-416]	Follow-up on five occasions up to age 28 yr	Wheezing tended to abate in those with less severe wheezing on enrollment and to persist in those with more wheezing initially. At age 28 yr, lung function tended to be lower in those with more severe wheezing.
11,486 children in a U.K. birth sample in 1970[417]	Questionnaire at ages 5 and 10 yr	80% of 2345 children with wheezing before age 5 were wheeze free at age 10, and 50% of 238 children with asthma diagnosed at age 5 yr did not have this diagnosis at age 10.
121 children with asthma, 167 with wheeze, and 167 controls enrolled at age 9 to 15 yr in Scotland[411]	Evaluation after 25-year follow-up	Former asthmatics more likely to wheeze, had lower lung function, and greater airway reactivity
283 participants from above Scottish population[418]	Evaluation in 2001 after 12 yr of follow-up	Asthma: FEV_1 = 2.45 (95% CI, 2.20 to 2.62) Wheeze: FEV_1 = 2.78 (95% CI, 2.64 to 2.91) Control: FEV_1 = 2.96 (95% CI, 2.83 to 3.10) Cases showed a significantly greater decline in asthma and wheeze than controls.
67 infants in the United Kingdom at risk for atopic disorder[408]	Annual evaluation through age 5 yr and then at age 11 yr	Of 21 children with wheezing when younger than 2 yr, 76% were wheeze free and 61% did not have bronchial hyperresponsiveness at age 11 yr. Of 21 with wheezing when older than 2 yr, 17 were wheezing and 12 were hyperresponsive at age 11 yr.
63 children followed from UK study above[373]	Evaluated at year 22 from birth	25% showed both wheeze and bronchial hyperresponsiveness. Remission of wheeze common in subjects younger than 5 yr if wheezing occurred only once or twice; wheeze at age 1 yr was likely to persist.
1335 children in a U.K. birth sample (1958)[375,380]	Periodic evaluation up to age 35 yr	Of the 302 with wheezing by age 16 yr , about 40% still had asthma or wheezing in the last year at age 34 to 35 yr.
108 children in Finland with a diagnosis of asthma by age 15 yr[419]	Evaluation at age 20 to 24 yr	28% were symptom free, and 22% had symptoms at least weekly; 48% had bronchial hyperresponsiveness.
406 children, age 8 to 12 yr on enrollment, referred to a clinic in the Netherlands[381]	Follow-up for mean of 14.8 yr to mean age of 24.7 yr	Decreased level of airways responsiveness over time and increasing percent of predicted FEV_1
13 children in Dunedin, New Zealand, born April 1972 to March 1973[382]	Assessed up to 9 mo from age 9 to 26 yr	51.2% reported more than one wheezing episode by age 26 yr; 14.5% had wheezing that persisted to age 26 yr; 15% were in remission at age 26 yr; 27.4% never reported wheezing.

FEV_1, Forced expiratory volume in 1 second.

were 7, 11, and 16 years of age, and the participants themselves were interviewed at age 23 and 33 years. Asthma tended to remit over time; of the children with a report of asthma or wheezy bronchitis before 7 years of age, only 10% had wheezing in the last year at age 23 years, although this figure increased to 27% at age 33 years.[375] Lung function was evaluated in a sample of 1060 of the participants with a history of asthma or wheezy bronchitis and 275 controls.[380] For those not reporting wheezing at age 33 years, lung function was only slightly reduced compared with controls. For those with wheezing, FEV_1 was reduced by approximately 10% compared with controls. Similar results were found in a 1994 follow-up study of 181 Dutch individuals.[381] Subjects were extensively tested as children 25 years earlier and reexamined as adults. The data revealed that 11% of persons were no longer considered asthmatic, 25% had an FEV_1 greater than 90% of predicted, 21% were no longer bronchial hyperresponsive, and 40% did not report asthmatic symptoms. Results of these studies support the hypothesis that early intervention in mild asthma may lead to improved outcomes.

In a longitudinal, population-based, cohort study carried out in Dunedin, New Zealand,[382] 1139 children were enrolled, and a substantial proportion was followed to age 26 years with repeated assessment by questionnaires, lung function testing, bronchial challenge testing, and allergy testing. Of the 613 participants with complete data for the follow-up period, 14.5% had persistent wheezing into adulthood, and only 27.4% never reported wheezing. The remainder had various patterns of intermittent wheezing. Predictors of persistent wheezing included sensitization to HDMs, female sex, and smoking at age 21 years. Pulmonary function was reduced in those with persistent wheezing.

Evaluation of the natural history of asthma in adults is complicated by the occurrence of COPD and the potential difficulty of separating COPD from asthma. In adults, asthma includes disease originating in childhood and following its natural course into adulthood and asthma developing during the adult years. These natural histories have not been carefully delineated, although the lengthier studies of childhood asthma can provide information on its course into adulthood.

There is less information on asthma in adulthood that is comparable to that on childhood asthma, such as the longitudinal picture of symptoms and clinical status. However, the effect of having asthma on the decline of lung function has been assessed, and there is limited information on the development of irreversible airflow obstruction in persons with asthma (Table 48-6). The evidence on asthma and change in lung function over time is inconsistent with some studies showing

TABLE 48-6 Annual Decline in FEV_1 in Adult Asthmatics

Study Location	Population	Follow-up	FEV_1 Decline
Lebanon, Connecticut[384]	73 asthmatics, 278 persons with wheezing from a general population sample	6 yr (2 observ)	Asthma: 24.0-24.3 mL/yr Nonasthma: 6.0-6.3 mL/yr
Tucson, Arizona[389]	27 asthmatics (group 1), 45 mixed (group 2), 45 COPD (group 3), age 40 to 74 yr from a general population sample	10 yr (2 observ)	Group 1 (asthma: 5 mL/yr Group 2 (mixed): 20 mL/yr Group 3 (emphysema): 70 mL/yr
Busselton, West Australia[383]	92 asthmatics and 186 controls, age 22 to 69 yr from a general population sample	18 yr (4-7 observ)	Asthma: 50 mL/yr Controls: 35 mL/yr
Busselton, West Australia[420]	9317 subjects who participated in the Busselton Health Survey (as above)	Up to 7 surveys, 1966 to 1995	*In never smokers* Asthma/female: 28.35 mL/yr Asthma/male: 39.71 mL/yr No asthma/female: 24.51 mL/yr No asthma/male: 36.02 mL/yr
Netherlands[387]	71 asthmatics recruited from family physicians	2 yr (7 observ)	Asthma: 94 mL/yr (PC_{20} < 2 mg/mL) Controls: 21 mL/yr (PC_{20} ≥ 2 mg/mL)
Copenhagen[412]	343 urban adult outpatients with bronchial asthma history	7 yr (2 observ)	51-57 mL/yr (values after bronchodilator use)
Denmark[422]	213 asthmatics age 18 to 80 yr from chest clinic, 170 age 13 to 69 yr from allergy clinic; 117 with intrinsic asthma, and 53 with extrinsic asthma	10 yr (2 observ)	Intrinsic asthma: 50 mL/yr Extrinsic asthma: 23 mL/yr
Copenhagen[385]	396 asthmatics age 20 to 90 yr from a general population sample of 10,952	5 yr (2 observ)	*New asthma* ΔFEV_1 = 39 mL/yr in men ΔFEV_1 = 11 mL/yr in women
Copenhagen[388]	1095 asthmatics from a sample of 17,506 adults	15 yr (3 observ)	Asthma: 38 mL/yr Controls: 23 mL/yr
Quebec, Canada[413]	391 participants age 15 to 40 yr, recruited from high schools, one college, and two banks	8 yr (2 observ)	Asthma: 42.6 mL/yr New wheeze: 12.3 mL/yr New dyspnea: 16.2 mL/yr

COPD, Chronic obstructive pulmonary disease; *FEV_1*, forced expiratory volume in 1 second; *observ*, observations; *PC_{20}*, provocative concentration that induces a 20% fall in FEV_1.

increased decline in persons with asthma compared with controls and others showing no difference between asthmatics and controls. Peat and Woolcock followed 92 persons with asthma, who were 22 to 69 years old on enrollment, and 186 control participants from Busselton, Australia.[383] The asthmatic individuals had lower lung function values at enrollment and the FEV_1 declined at 15 mL/yr more in the persons with asthma compared with the controls. Schachter and colleagues[384] followed the lung function of 73 persons with asthma and 278 with wheezing. Over a 6-year interval, there was a similar excess loss of FEV_1 in the persons with asthma. Ulrik and Lange[385] followed subjects over a 5-year period and found that asthmatic subjects had lower baseline lung function values and an excess annual decline in FEV_1 compared with nonasthmatics; the excess annual decline was 39 mL in asthmatic men and 11 mL in asthmatic women. Some individuals with asthma appear to eventually develop irreversible airflow obstruction, which has been related to duration and severity of asthma.[356,387] A continuing effect of asthma was found when follow-up was extended to 15 years.[388]

Other studies have not shown increased loss of function associated with having a diagnosis of asthma. Burrows and colleagues[389] examined the course of asthma over 10 years in 27 asthmatics from the general population and compared them with two other groups: 45 COPD subjects and 45 subjects who did not fit clearly into either group. The asthmatic subjects had a 5 mL/yr decline in FEV_1, compared with a 70-mL decline in the COPD group and a 20-mL loss in the intermediate group.

The balance of the evidence indicates that a diagnosis of asthma is associated with an increased rate of FEV_1 decline (see Table 48-6). Perhaps reflecting this excess decline, many elderly persons with asthma have fixed airflow obstruction.[389] There are few studies on the clinical course of asthma in adults (Table 48-7), and as airway obstruction becomes fixed with advancing age, separating asthma from COPD becomes increasingly difficult. In the study by Schachter and coworkers,[384] of the male participants age 18 years or older with asthma, 75% improved and only 1% worsened during follow-up. Among female participants, 58% improved and none worsened during follow-up.

Bronniman and Burrows[390] followed 136 asthmatics, who were drawn from the general population sample in Tucson, Arizona, of 2300 persons, over a 9-year period. Participants were classified as in remission if they had active disease at baseline and on follow-up denied medication use, asthma attacks, and frequent attacks of shortness of breath with wheezing during the preceding year. After 9 years of follow-up, 22% were in remission, with the highest rate found among those between 10 and 19 years of age at enrollment (65%) and the lowest rate found for those between 40 and 49 years of age (6%). Remission was more common in those with less frequent wheezing, less frequent asthma attacks, and less frequent attacks of shortness of breath with wheezing. Remission was significantly less likely

TABLE 48-7 Remission and Relapse Rates for Adult Asthma

Location	Population	Follow-up Time	Outcome
Lebanon, Connecticut[384]	73 asthmatics, 278 with wheeze, age ≥7 yr, from a general population sample	6 yr	*Age ≥18 yr* Asthma Remission: 75% (M), 58% (F) Worsening: 1% (M), 0% (F) Wheezing Remission: 81% (M), 80% (F) Worsening: 5% (M), 5% (F)
Tucson, Arizona[390]	136 asthmatics from a general population sample of 2300	9.4 yr	Overall remission: 22%
Israel[421]	1609 asthmatics from population of 107,636; those age >18 yr in the armed forces	5-7 yr	Overall relapse: 38% Unchanged: 83.2%
Copenhagen[385]	396 asthmatics age 20 to 90 yr from a general population sample of 10,952	5 yr (2 observations)	Improved
Rhode Island[393]	84 asthmatics from population of 1601 college students	23 yr	Asthma was inactive in half of asthmatics at follow-up.
Netherlands[104]	181 asthmatics age 13 to 44 yr (mean age, 24 yr)	25 yr	Asthma was inactive in 11% of participants at follow-up.

F, Female; *M*, male.

in those with chronic productive cough or a coexisting diagnosis of chronic bronchitis or emphysema. A normal level of percent predicted FEV_1 at baseline was the most powerful predictor of remission. Persons 30 to 60 years old with active symptoms had only a 10% remission rate over 9 years.

Broder and colleagues[391] reported similar findings, with a remission rate of 16.7% for patients between 16 and 44 years of age and 21% in those 45 years of age or older. All relapse rates increased with age. Braman and coworkers[392] investigated the outcomes of 25 nonsmoking asthmatics older than 70 years of age. All had moderately severe asthma requiring daily bronchodilators, and 22 of the 25 needed daily glucocorticoids. Over 7 years, dependency on those drugs and complications of therapy were common. No patients died of acute asthma, but two died of chronic respiratory failure. Mortality was not related to the level of pulmonary function or duration of asthma in years. This was a highly selected group with many comorbidities, which probably influenced the eventual outcome. Unfortunately, little is known about the outcome of elderly asthmatics that are not as ill.

Panhuysen and colleagues[104] followed 181 persons with asthma over 25 years. The participants had been comprehensively evaluated in an asthma clinic in the Netherlands between 1962 and 1970 at the ages of 13 to 44 years (mean, 24 years). On retesting, 38% no longer showed bronchial hyperresponsiveness on histamine challenge, and based on a lack of bronchial hyperresponsiveness, symptoms, and lung function level, 11% were considered to no longer have asthma. Settipane and colleagues[393] followed a group of college students over 23 years. Half of those with asthma on follow-up reported the disease as inactive, although about 50% of the new cases occurred during follow-up.

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