INTRODUCTION

In a 2001 clinically oriented review, Busse and Lemanske defined asthma as “a complex syndrome with many clinical phenotypes in both adults and children. Its major characteristics include a variable degree of airflow obstruction, bronchial hyperresponsiveness, and airway inflammation” (1, p. 350). They concluded that, for many people, the disease begins in infancy and that a genetic propensity to be allergic, combined with environmental exposures, contributes to disease development. Symptoms of asthma are exacerbated by exercise, strong emotions, viral infection, airborne allergen exposure, airborne pollutants, and change in the weather (2).

The first studies of allergy appeared in print in the 1870s, and recognition of asthma is evident from ancient writings, but population studies of these conditions have become common just since the 1970s (3–5). Thus, the epidemiologic study of asthma and allergies, relative to other major chronic conditions, is in its infancy. The challenges posed are somewhat unique compared with the more extensively studied chronic illnesses, such as cardiovascular disease and cancer. The most significant and as-yet unsolved methodological issue is one fundamental to the conduct of epidemiology: arriving at a definition of disease.

As defined in the 1991 National Heart, Lung, and Blood Institute Expert Panel Report on Asthma, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells all play a role in this condition (6). Production of immunoglobulin (Ig)E is central to the pathophysiology of pediatric allergic diseases such as allergic rhinitis, atopic dermatitis, and atopic asthma. After IgE binds to high-affinity mast cell surface FcεRI receptors and is cross-linked by antigen, mast cell activation occurs and sets in motion a cascade of events resulting in the clinical manifestations of allergic disease (7). The interaction of IgE and antigen results in an immediate hypersensitivity reaction that can be responsible for the classic asthma symptoms exhibited during acute exacerbation, for example, mucosal edema, mucus production, and smooth-muscle constriction. Eventually, these and other reaction cascades can induce the production of cells responsible for the airway inflammation that underlies asthma and is observed even in the absence of symptoms (8, 9).

The most commonly used biomarkers for allergy, positive blood tests for allergen-specific serum IgE and positive allergen-specific skin-prick tests, unfortunately are not always correlated and are not synonymous with clinical disease (10–12). Case definition is even more problematic for asthma because there are no consistent or generally accepted criteria or biomarkers. Although a number of markers are associated with asthma, such as high serum total IgE, positive allergen-specific IgE or skin-prick tests to common allergens, and bronchial hyperreactivity, none of these surrogates has both high sensitivity and high specificity (13–16).

Over the years, many studies have demonstrated that pediatric asthma is strongly associated with atopy (at least one
positive skin-prick test or allergen-specific serum IgE detected among a battery of common allergens), albeit with a substantial variation in estimated proportions (8, 17, 18). Many pediatric asthma patients will have some evidence of atopy, whether clinical or serological; however, not all persons with atopy will develop asthma (19, 20). In a recent meta-analysis, Pearce et al. estimated the role of atopy in asthma (17). Defining skin-prick test positivity as atopy, they estimated that, in children, the proportion of asthma cases attributable to atopy varied from 25 percent to 63 percent (weighted mean, 38 percent). In adults, the attributable risk varied from 8 percent to 55 percent (weighted mean, 37 percent). These estimates have challenged the widely held perception that pediatric asthma is nearly always atopic in origin and suggest that previous risk factor research has been muddied by inappropriately combining diseases with distinct etiologies into one category. The wide range in the association between atopy and pediatric asthma across studies may reflect the fact that the proportion of pediatric asthma attributable to atopy varies substantially by location.

In the Western Australia Pregnancy Cohort Study, current asthma at age 6 years, as defined by previous physician diagnosis of wheeze or cough without cold in the previous 12 months and use of asthma medications, was found in 18 percent (n = 387) of the children born from 1989 to 1992 (21). At this age, 41.4 percent of the children were atopic with at least one positive skin-prick test; 55.5 percent of the asthmatics were atopic, whereas 44.5 percent were not atopic (odds ratio (OR) = 2.01 for being asthmatic and atopic vs. neither, 95 percent confidence interval (CI): 1.55, 2.60; p < 0.0005). In 1989, Burrows et al. reported on a community sample from Tucson, Arizona, that asthma was related to total serum IgE levels in children aged 11 years (10). After the findings were expressed as standardized z scores and were adjusted for age and gender, none of the children whose z scores corresponded to the lowest levels of serum IgE (z less than 1.46 standard deviations below the mean) were found to have asthma. This relation to IgE was stronger than that to skin test reactivity to a battery of common allergens. A few years later, Burrows et al., this time using data from the Dunedin, New Zealand, birth cohort, as well as Sears et al. in their study of this same population, reported a positive relation between bronchial hyperreactivity and total serum IgE levels (19, 22). Bronchial hyperreactivity was associated with serum IgE level (p < 0.0001), regardless of asthma status. Prevalence of diagnosed asthma was strongly related to serum IgE (p for trend <0.001), and no asthma was reported in children whose serum IgE levels were <32 IU/ml. However, only 36 percent of the children whose serum IgE levels were >1,000 IU/ml reported a diagnosis of asthma.

Similar findings were reported by Sunyer et al., who conducted a study in more than 1,600 adults aged 20–44 years (23). Compared with persons whose serum IgE levels were less than 100 IU/ml, persons whose total serum IgE levels were more than 100 IU/ml were 4.7 times more likely to have asthma (23). The Isle of Wight Whole Population Birth Cohort Study data showed that atopy, as defined by one or more positive skin-prick tests to a battery of common allergens, was closely related to asthma, rhinitis, and eczema in a direct, linear fashion (24). This study estimated that 30–40 percent of these diseases in early childhood are attributable to atopy. Among the 1,046 children in the British National Child Development Study who had a history of asthma or wheezy bronchitis by the age of 7 years, the strongest risk factors were a history of hay fever, eczema, and pneumonia (25).

Asthma is best defined through clinical observations and medical history and by assessing response to medications over a period of time. Allergy and asthma symptoms may wax and wane both in occurrence and severity by season and over time, and they sometimes disappear for very prolonged periods or perhaps permanently, making the distinction between the use of incident versus prevalent cases both problematic and important. Among the 59 children ever reporting asthma symptoms who were followed up clinically through age 14 years in the Swedish Birth Cohort (n = 1,701), 86 percent had a history of other atopic diseases, 16 (27 percent) no longer had prevalent asthma, and 68 percent had exercise-induced asthma (26). Children with more severe prevalent asthma (11/59) were found to have had asthma before 18 months of age more often than children with less severe asthma. However, early onset of asthma did not always imply a negative prognosis; for 22 percent of children with no prevalent asthma and 30 percent who had mild asthma, asthma onset occurred before 18 months of age.

In a small, English, hospital-based, high risk (based on family history) birth cohort established in 1976–1977, the prevalence of bronchial hyperreactivity was 29 percent at age 11 years and 40 percent at age 22 years; 15 (25 percent) of the subjects had a current asthma diagnosis as young adults (27). There was a strong association between wheezing persisting or beginning when subjects were older than age 5 years, early allergic sensitization, and bronchial hyperreactivity. Subjects younger than age 2 years who had wheeze were no more likely to become adult asthmatics than those without wheeze. Allergic sensitization and bronchial hyperreactivity at age 11 years were unlikely to remit before adulthood (27). British National Child Development Study cohort subjects with a history of wheezing illness in childhood retained a risk of later wheezing above that of their healthy peers, even after a disease-free interval of 7 years or more (25). Relapse at 33 years of age after prolonged remission of childhood wheezing was more common among adult smokers and atopic subjects.

Another small birth cohort study (n = 253) from Perth, Australia, was designed to determine whether the pattern of wheezing during the first 2 years of life was important and predictive of an asthma diagnosis and whether lung function abnormalities in children at an older age were present in early life (28, 29). Of the 81 who reported wheeze, 28 (35 percent) experienced it during the first year of life only, 21 (26 percent) experienced it in the second year of life only, and 32 (39 percent) wheezed in both the first and second years of life. Associations between lung function and wheeze varied by gender, with males having a lower airflow than females among nonwheezers and wheezers alike. The authors suggested that wheezing during the first 12 months of life is often a transient condition due to reduced small airway caliber in infancy, which improves with time. They
proposed that wheezing beginning or persisting into the second year of life is related to continuing abnormality of the airways and more likely leads to clinical asthma (29).

Much is yet to be learned regarding the natural history of these conditions. The current consensus is that what has been called “asthma” in children is likely a syndrome of several different conditions, each with varying etiologies. Investigators from the Tucson Children’s Respiratory Study of a health maintenance organization–based birth cohort were among the first to clearly demonstrate that most infants who wheeze in the first 3 years of life have transient symptoms associated with diminished airway function and do not have an increased risk of asthma or allergies later in life (30). These investigators postulated that early wheezing episodes are probably related to a predisposition to asthma in only a minority of infants. In their cohort, such children already had elevated serum IgE levels during the first months of life and at age 6 years, had substantial deficits in lung function by the age of 6 years, and were more likely to have a family history of disease (30). They proposed the existence of at least three distinct pediatric phenotypes: transient wheezing (generally occurring under 1 year of age and resolving by age 3 years), nonatopic wheezing (perhaps related to a lower respiratory tract infection with onset before age 3 years and often resolving by age 13 years), and atopy-associated asthma (progressive disease with usual onset before 6 years of age) (31). Investigators from the Avon Longitudinal Study of Parents and Children, a birth cohort of more than 14,000 English children born from 1991 to 1992, recently observed a number of different patterns of wheezing syndromes, with early and transient wheezers evincing a different risk factor pattern than persistent and later-onset wheezers (32). Indeed, even within the classification of atopic asthma, it may be that airway diseases associated with sensitivity to different allergens have different natural histories (33, 34).

This lack of ability to readily define and classify these diseases has had a number of ramifications. From the epidemiologic perspective, the most pressing issue is clearly to identify and develop criteria to differentiate these syndromes so that cogent risk factor studies can be conducted. A major consequence of this enigma is that there are no geographically based “registries” or routine surveillance mechanisms to ascertain incident cases, thus making it difficult to obtain even basic descriptive epidemiologic statistics, not to mention the impact on identifying cases for etiologic studies. Neither asthma nor allergy is a reportable disease. Most national and international measures of asthma and allergy are based on cross-sectional surveys and data from hospitalization and mortality databases. The latter are less useful compared with other chronic illnesses; these diseases, although associated with a very high morbidity burden, have low case-fatality rates, and mild disease rarely requires hospitalization. The most generally used definition of pediatric asthma in epidemiologic studies worldwide is “parental report of a history of a physician diagnosis of asthma,” a measure that would be unthinkably crude to epidemiologists investigating other major chronic and infectious diseases.

A second fundamental issue in the conduct of etiologic studies of these conditions is again related to disease definition: difficulty in distinguishing factors related to incidence versus persistence (prevalence) versus severity. Most studies have used prevalent cases, and factors that have been associated with increased risk of symptoms generally have been assumed to be causal as well. Only recently has there been a growing recognition that the factors that exacerbate these diseases may not be associated with primary etiology (35, 36).

There are some methodological advantages to the epidemiologic study of these conditions. One is that the majority of cases begin in childhood. Therefore, the time period during which potentially important exposures occur is limited. In fact, most investigators are currently focusing on very early life and even the prenatal period as most critical. A second advantage is that these conditions are relatively common. Accordingly, cohort rather than case-control methodology has been often implemented. A number of birth cohorts have been developed worldwide to prospectively examine risk factors for pediatric asthma and allergy, while other investigators have capitalized retrospectively on birth cohorts designed for other purposes.

This paper provides an update of the descriptive epidemiology of pediatric asthma and allergy, presents current immunologically based etiologic hypotheses, and summarizes the risk and preventive factors currently considered to play a role in these disorders, with a focus on findings generated from the major birth cohort studies. Compelling evidence exists to support the idea that atopy, bronchial hyperreactivity, and asthma are under extensive genetic influence, and a review of the genetics related to these conditions is presented in another paper in this issue of Epidemiologic Reviews (37). Although inherited factors related to susceptibility most certainly contribute to disease risk, it has been hypothesized, on the basis of the striking increases in prevalence over just the past two decades, that changes in environmental exposures are mostly responsible for the apparent epidemic of asthma and allergies among children.

DESCRIPTIVE EPIDEMIOLOGY

In a 2000 review of the trends in asthma and allergy worldwide, Beasley et al. concluded, on the basis of sequential cross-sectional surveys in the same geographic locations, that the prevalence of these conditions is increasing substantially (38). In 1990, the International Study of Asthma and Allergies in Childhood (ISAAC) began prevalence studies of children aged 6–7 and 13–14 years across 120 centers in 50 countries, which revealed striking variations (38). The prevalence of asthma symptoms ranged from 1.6 percent to 27.2 percent among the children aged 6–7 years and 1.9 percent to 35.3 percent among those aged 13–14 years. Beasley et al. concluded that the prevalence of asthma, allergic rhinitis, and atopic eczema is increasing worldwide (38). They also concluded that pediatric asthma is more common in western countries, with the highest prevalence in English-speaking countries, and that prevalence increases as developing countries become more urbanized and westernized.

Another 2000 review article estimated that asthma prevalence has been increasing worldwide by 5–6 percent per year (39). In a school-based study in Scotland, the prevalence of physician-diagnosed asthma increased from 4.1 percent in
1964 to 10.2 percent in 1989 (40). Prevalence continued to rise and was 19.6 percent in a 1994 follow-up (41). In a United Kingdom birth cohort, the British Cohort Study, the prevalence of current asthma at age 16 years in 1986 was measured at 6.5 percent compared with 3.8 percent measured at this age in the earlier British National Child Development Study; the prevalence ratio was 1.71 (95 percent CI: 1.52, 1.93) (42). Hay fever and eczema prevalence doubled between the two studies. The largest increases in asthma prevalence have been among children and adolescents. According to the Centers for Disease Control and Prevention (Atlanta, Georgia), the self-reported prevalence of asthma in the United States increased 75 percent from 1980 to 1994 for all ages (43). The report also stated, ‘The most substantial increase occurred among children aged 0–4 years (160 percent, from 22.2 per 1,000 to 57.8 per 1,000) and persons aged 5–14 years (74 percent, from 42.8 per 1,000 to 74.4 per 1,000)” (43, p. 5).

According to a National Health Interview Survey, asthma prevalence between 1990 and 1992, estimated at 46.2 per 1,000 persons, was highest among people less than age 19 years (61.2/1,000), more common among boys than girls (72.3 vs. 49.7 per 1,000), and more prevalent among African Americans than Caucasian Americans (53.3 vs. 45.7 per 1,000) (44). One geographically population-based incidence study was conducted at the Mayo Clinic (Rochester, Minnesota) and showed an asthma incidence rate of nearly 6 per 100 among children less than age 1 year, 1.8 per 100 for those aged 1–4 years, and 0.64 per 100 for those aged 5–9 years (45). When incidence was measured between 1964 and 1983, a steady rise was noted beginning in the 1970s, which was attributed to the age groups between 1 and 14 years.

On the basis of data collected from the 1995 National Health Interview Survey, the Centers for Disease Control and Prevention estimated that, in 1998, more than 17 million Americans suffered from asthma (44). At least 5.3 million were under the age of 18 years, making asthma the leading serious chronic illness in children (46). Although asthma, as mentioned above, is usually not a cause of mortality, it is a major cause of morbidity among children and adolescents. In 1998, 166,000 discharges from short-stay hospitalizations were attributed to pediatric asthma (less than age 15 years), 39 percent of all short-stay asthma admissions (47). For the same year, the estimated cost of school days lost because of asthma was $1.2 billion (48). Nocturnal awakening, or sleep disruption due to asthma symptoms, is a common problem for persons suffering from asthma (49). Nocturnal asthma may be caused by one of several mechanisms including, but not limited to, airway cooling and drying, mucus retention due to impaired mucociliary clearance, increased vagal tone, and circadian variations in airway caliber and in plasma levels of histamine and various hormones (50). In a cross-sectional survey of the parents of 438 children with asthma enrolled in one of three managed care organizations during 1997–1998, Diette et al. reported that 40 percent of the targeted children (aged 5–17 years) had been awakened at least once a night with asthma symptoms in the last 4 weeks, that nocturnal symptoms were associated with missing at least 1 day of school in the past 4 weeks (OR = 3.7, 95 percent CI: 2.1, 6.2), and that a parent had to miss work or other activity at least 1 day during the same time period (OR = 4.0, 95 percent CI: 2.2, 7.1) (51).

While generally less severe, the other forms of allergic disease are very common. These conditions affect approximately 20 percent of children and produce significant morbidity in terms of lost school days and frequent visits for medical care (52, 53).

A number of birth cohort studies have reported incidence and prevalence statistics. The Tucson Children’s Respiratory Study estimated that 33.6 percent of the children born between 1980 and 1984 had a wheezing-related illness during the ages of 0–3 years (30). By age 6 years, 47 percent of the children in the study had either transient early, persistent, or late-onset wheezing. As calculated by Sears, the mean incidence of asthma among this cohort was 5 percent per year (54). Croner and Kjellman followed a cohort of Swedish children from birth to the time they reached age 11 years (n = 1,654) in the mid-1980s (55). The cumulative incidence of allergic rhinitis and asthma in this population was 15 percent and 5.3 percent, respectively. Thirty-three percent of those developing asthma did so before reaching age 1.5 years, and 50 percent developed asthma before the age of 3 years (55). In a northern Finland birth cohort, the overall prevalences of atopy and ever having been diagnosed by a physician as having asthma at age 31 years were 30.7 percent and 8 percent, respectively (56). The Detroit, Michigan, area Childhood Allergy Study measured a cumulative incidence of physician-diagnosed asthma of 11.0 percent among predominantly Caucasian children followed from birth to 7 years of age in the mid-1990s (57). The German Multicenter Allergy Study birth cohort determined that at age 7 years, the prevalences of “wheezing ever” and of “asthma ever diagnosed by a doctor” were 17.4 percent and 6.1 percent, respectively, in a cohort of 1,314 children born in 1990 (18). In the Odense University Hospital Birth Cohort of more than 3,000 Danish children born in 1992–1994 who were linked to administrative national databases, the prevalence of asthma at age 4–5 years, based on medication use, was 3.4 percent (58).

The British National Child Development Study found 1,046 children who had a history of asthma or wheezy bronchitis by the age of 7 years, equal to a cumulative incidence of 18 percent (25). This study is an example of data that have clearly demonstrated the reversal at puberty in the consistently higher male-to-female ratio of childhood, with female cases becoming more prevalent at age 20 years and beyond (59). In the Christchurch Health and Development Study in New Zealand, wheeze and lower respiratory tract infections during infancy as well as parental asthma history varied by sex in their relation to later asthma prevalence, generally seeming to be more important in boys (60). The Detroit Childhood Allergy Study indicated that the pattern of development of total IgE differed between boys and girls, with boys showing a more rapid increase between birth and 2 years of age (61). Girls showed more variation in their level of allergen-specific IgE.
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MAJOR BIRTH COHORT STUDIES

Table 1 summarizes the relevant birth cohort studies conducted worldwide, in order of year of cohort establishment, that included subjects who were actively enrolled, had relatively large sample sizes and long follow-up periods, or were notable for their impact in contributing to epidemiologic hypotheses (18, 21, 24, 25, 27–30, 32, 34, 42, 55, 56, 58, 60–87). Some were designed specifically to study atopy or asthma; others studied pediatric health in general and included analyses related to allergic conditions. Those designed solely to study interventions have not been not included. To our knowledge, five other ongoing, large birth cohorts in the United States are focusing on asthma and allergy etiology, but limited methods and results have been published in manuscript form to date. Included are the Yale study centered in Connecticut and south-central Massachusetts (88, 89); the COAST (Childhood Origins of Asthma) high-risk birth cohort in Wisconsin; the Infant Immune Study birth cohort in Tucson, Arizona; the Mothers and Newborns Study in New York City, New York (90); and the WHEALS (Wayne County Health, Environment, and Atopy Longitudinal Study) cohort in metropolitan Detroit, Michigan.

ETIOLOGY

The next sections review the major mechanisms and factors considered to contribute to the natural history of pediatric asthma and allergies. Topics include factors related to immunology, environment, and lifestyle.

Immunologic factors

Currently, two overlapping, but competing theories have linked changes in environmental factors to observed trends in asthma and allergy epidemiology over the last several decades. The first theory, the “hygiene hypothesis,” was introduced in 1989 by Strachan and postulates that environmental exposures that promote a generalized suppression of Th2 cytokines and trigger strong Th1 responses are becoming increasingly less common (91–96). The recently proposed “immunotolerance hypothesis” (97) is a challenge to the widely held belief that allergen exposure relates to allergic disease incidence in a linear fashion, suggesting that early high levels of exposure to allergens reduce risk by potentiating the regulatory capacity of the immune system.

Immune balance: Th1 versus Th2. Immune recognition of “nonself” antigenic proteins by the immune system is central to the development of atopy. The predominant immune response to antigens in humans not predisposed to atopy includes production of antigen-specific IgG antibodies and proliferation of Th1-type lymphocytes (those T cells that secrete interferon gamma). In contrast, in humans who are predisposed to atopy, immune recognition results in production of an “allergic response” typified by proliferation of Th2-type T lymphocytes that secrete interleukin (IL)-4, IL-5, and IL-13. These Th2 cytokines promote allergen-specific IgE antibody and also induce eosinophil-dominated inflammatory tissue responses. This Th2-driven process is the
defining immunopathologic characteristic of atopic diseases including atopic asthma, atopic dermatitis, and allergic rhinitis. A schematic representation of the Th1-Th2 paradigm for the etiology of allergic disease is shown in figure 1.

A Th2-skewed immune response is normal in newborns. However, recent evidence suggests that early-life environmental exposures may influence whether the Th2 response persists and whether atopy develops. A landmark study by Prescott et al. reported a Th2-polarized response in infants regardless of whether they were at high genetic risk of atopy based on family history (98). The authors concluded that the key etiologic factor in atopic disease may not be the initial acquisition of allergy-specific, Th2-skewed immunity but instead the efficiency of immune deviation that, in normal, nonatopic persons, redirects the response toward the Th1 phenotype in the first year of life.

In fact, a Th2-like profile of cytokines may be more pronounced in children at low risk of atopic disease when evaluated at birth (98–100). Another study by Prescott et al. supports the hypothesis that immune deviation toward the Th1 (nonatopic) phenotype after birth is defective in atopic children (101). Children at low risk of atopy exhibit suppressed Th2-like cytokine responses and increased interferon-gamma secretion in response to antigen during the first year of life. In contrast, children who develop clinical atopic disease consolidate a Th2-skewed immune response. Several studies demonstrate that persistent Th2-polarized systemic immune responses are associated with the atopic phenotype and often persist into later childhood and adulthood (102–104).

Inhibition of the atopic phenotype by children showing strong Th1-biased immune responses was demonstrated in a seminal article by Shirakawa et al. (105). In this study, 867 Japanese children vaccinated against tuberculosis (Bacillus Calmette-Guérin vaccine or BCG) were evaluated at ages 6 and 12 years. Those who exhibited a persistent, strong, delayed skin response to tuberculin protein at ages 6 and 12 years (an indicator of a strong Th1 response) or those who converted from negative to positive between ages 6 to 12 years, had lower total and allergen-specific IgE levels, fewer allergy symptoms, lower Th2 serum cytokine levels, and increased serum interferon gamma levels. The size of the cutaneous response was inversely correlated with total IgE. This paper further supports a dichotomous relation between the Th1/Th2 systemic immune response and the atopic phenotype. Associations between clinical asthma and persistently Th2-biased cytokine profiles have also been shown among older children and adults (106–111).

**Immunotolerance.** In spite of a substantial body of bench-based research and recent epidemiologic studies suggesting that atopic persons have Th2-skewed cytokine profiles (112), it appears that the Th1-versus-Th2 paradigm of risk for atopic disease is an oversimplification. Some persons develop allergen exposure tolerance in spite of specific T-cell recognition and may produce a predominant IgG response. Recent investigations suggest that a set of regulatory T cells (Treg cells) that secrete the cytokine IL-10 provide a natural mechanism for inducing allergen exposure tolerance and also suppression of Th2 (as well as Th1) cytokines. This set of T cells appears to be activated when high levels of allergen are encountered. In addition, these Treg cells appear to be activated by natural allergen exposure in a dose-dependent manner whereby relatively high-level exposure to certain airborne allergens results in allergen-specific IgG production without IgE production in what has been described as a “modified Th2 response.” The schematic representation in figure 2 illustrates how high-level allergen exposure may induce a “second-level” immune response typified by IL-10 suppression of the Th2 atopic response.

It has become clear that the intensity of exposure to allergen can influence cytokine profiles. The Th1/Th2 pattern of cytokine response in murine T cells is determined by the antigenic dose such that low levels of antigen induce maximal IL-4 secretion, but increasing doses of antigen induce suppression of IL-4 and increased interferon-gamma production (113). However, even after a Th2 response to antigen is established, exposure to high levels of the protein can induce a shift in the Th1/Th2 balance. In humans, the subcutaneous injection of high levels of antigen in sensitized patients modifies an established T-cell response by inducing a pattern of decreased IL-4 and increased interferon-gamma production (114). Such an immunomodulatory approach is used during administration of allergy desensitization injections (also called allergen-specific immunotherapy), a proven treatment modality for allergic patients. Allergen-specific immunotherapy involves the injection of allergenic proteins into allergen-sensitized patients suffering from allergic rhinitis,
asthma, and hymenoptera (bee, wasp, hornet, etc.) venom anaphylaxis. This method of treatment, if a high-level antigenic dose is achieved, induces an immune transformation from an “allergic” immune response to clinical tolerance of allergen exposure (115). Immunologic correlates of successful allergen-specific immunotherapy include production of “allergen-blocking” IgG antibodies, suppressed T-cell proliferation, and decreased Th2 cytokine release upon allergen exposure (116). It appears that IL-10 secretion by T<sub>R</sub> cells is central to the suppressed T-cell proliferation and altered cytokine response seen in allergen-specific immunotherapy. In bee-venom allergen-specific immunotherapy, enhanced production of IL-10 causes specific anergy in peripheral T cells while suppressing antigen-specific IgE and enhancing specific IgG4 production. In addition, neutralization of IL-10 fully reconstitutes specific T-cell proliferative and cytokine responses (117).

Natural exposure to high levels of allergens has also been shown to have allergen-specific, immunotherapy-like suppressive effects. Subjects who have had multiple bee stings exhibit a specific T-cell anergy similar to that in those receiving allergen-specific immunotherapy (118). However, it is clear that the route of exposure to high-dose allergen does not need to be percutaneous. The route of allergen exposure inducing a tolerant state may be the respiratory tract. Intranasal administration of pollen allergen has been shown to be effective in controlling allergic rhinitis and is associated with elevated IL-10 levels in nasal lavage obtained during subsequent exposure to natural pollen (119). It also appears that natural exposure to high levels of cat allergen, presumably through inhalation, is protective against allergic sensitization to cat and may induce an immune response that promotes tolerance and is typified by a high specific IgG and IgG4 response with little specific IgE production. In a recent cross-sectional study reported in The Lancet, the effect of high-level cat exposure (>8 µg/g of dust) was specific for protection against cat sensitization (97). Furthermore, a role for IL-10 in mediating this cat-specific response has also been suggested (120).

In contrast to the allergen-specific T-cell effects described above, the hygiene hypothesis is related to a more generalized protective effect from putative environmental exposures. The mechanism for such a protective effect is unknown. Although a down-regulation of Th2 responses by IL-10 mechanisms can be theorized, it is not clear whether this immune mechanism can result in generalized protection or whether the effect is antigen specific. To our knowledge, whether high-level allergen exposure during a critical period of immune development (early life) can result in a generalized state of tolerance to allergens, mediated by T<sub>R</sub> cells and IL-10, has not been studied. Finally, as reported in a 2002 review, the observation that many Th1-associated diseases such as type 1 diabetes, multiple sclerosis, and Crohn’s disease have been increasing in prevalence concordant with atopic conditions suggests that changes in environmental factors are negatively impacting immune regulation overall (121).

Environmental and lifestyle factors

Early exposure to infectious agents. Ecologic and cross-sectional international studies by Crane et al. (122), von Mutius et al. (123), and Bjorksten (124) provided evidence to support the importance of early infection in preventing the development of atopic disease. These studies evaluating migrants to New Zealand; populations from East versus West Germany; and populations from Estonia, Poland, and Sweden, respectively, suggested that children from affluent and presumably more “hygienic” environments were more likely to develop atopic diseases than children raised in economically disadvantaged environments. Figure 3 portrays this hypothesis and the relation between genetic susceptibility, environmental factors, a Th2 profile, and atopic asthma.

It is well accepted that, following a person’s birth, the intestinal flora is colonized by commensal microbes that affect oral tolerance and development of the systemic immune system. It has been suggested that the particular makeup of the microbial intestinal flora could exert pressure on the immune system’s deviation. In 1997, Sepp et al. (125) found differences in the intestinal flora of Estonian and Swedish infants. Estonian infants had more eubacteria and lactobacilli and less clostridia, in particular Clostridium difficile. The same group of researchers conducted a subsequent study to examine intestinal microflora differences in allergic Estonian and Swedish children aged 2 years (126). They found that “allergic children were less often colonized with lactobacilli and bifidobacteria, as compared with the non-allergic children. … In contrast, the allergic children harbored higher counts of aerobic micro-organisms, particularly coliforms in the Estonian and S. aureus in the Swedish children” (126, p. 344). The differences in microbial intestinal flora between allergic and nonallergic children were attributed to the extent and duration of breastfeeding, antibiotic use, and cleanliness of the birth environment.

After a decade of research, Strachan reported in a 2000 review article that “infections remain the most promising candidates” to explain the ecologic differences observed in atopic diseases (127, p. S9). In 2001, Matricardi and Rochetti concluded that the protective effect might be due to the turnover of the microenvironment of the intestinal flora (128).

A number of studies have consistently demonstrated that factors that are surrogates or are indirectly related to early childhood infections are associated with the prevalence of atopy, atopic asthma, and asthma in general. These factors include family size, breastfeeding, immunizations, day-care use, antibiotic use, exposure to household pets, and farm living.

Increased family size and day care attendance as surrogates for increased exposure to infectious agents are two areas of child-to-child contact that have been investigated extensively in relation to the development of asthma and allergy. Several studies have shown a larger family size to be protective against asthma and allergic sensitization (38, 129–134). A recent review of 53 studies strongly supports this relation (135), although the authors concluded that the sibling effect is more likely a result of in utero programming.
or endocrine mechanisms rather than the hygiene hypothesis theory. In the British National Child Development Study, Strachan demonstrated a dose-response relation in which the prevalence of hay fever was 10 percent in first-borns, 8 percent in second-borns, 5 percent in third-borns, 4 percent in fourth-borns, and 2.6 percent in children with four or more older siblings (129). The Tucson Children’s Respiratory Study found a similar trend for asthma, with corresponding prevalence figures of 21 percent, 19 percent, 14 percent, and 13 percent for children with three or more older siblings (130). An increased ratio of residents per home has been shown to be protective for allergic sensitization in the diverse settings of Estonia, Poland, and Sweden (adjusted OR = 0.58, 95 percent CI: 0.43, 0.77) (136). Results from the Detroit Childhood Allergy Study demonstrated that first-borns were at a higher risk of allergen-specific IgE (OR = 1.92, 95 percent CI: 1.16, 3.18) and positive skin-prick tests at 6 years of age (OR = 1.68, 95 percent CI: 1.02, 2.75) (137).

Ponsonby et al., in a study of the Tasmanian cohort (138), demonstrated that increased household size was associated with a higher risk of early upper respiratory tract infections (adjusted OR = 1.77, 95 percent CI: 1.07, 2.94) but not lower respiratory tract infections. They also found that resident density during infancy was associated with protection against hay fever at age 7 years (adjusted OR = 0.67, 95 percent CI: 0.45, 0.98) but not asthma (adjusted OR = 1.26, 95 percent CI: 0.93, 1.71), and that early upper and lower respiratory tract infections increased the risk of asthma. It may be that viral infections are not the primary means of early immunologic deviation and that some viral infections, such as early exposure to respiratory syncitial virus, increase risk, but that such infections are often correlated with increased exposure to bacteria.

The site of viral infection may be important. In the Western Australia Pregnancy Cohort Study, lower respiratory tract infections in the first year of life, especially those involving wheeze, were associated with an increased risk of current asthma (adjusted OR = 3.84, 95 percent CI: 2.82, 5.24 for two or more illnesses) but not atopy (21). This association was evident for both nonatopic and atopic asthmatics. The Boston, Massachusetts, cohort demonstrated that wheezing during the first year of life was associated with lower respiratory tract illness (relative risk = 2.25, 95 percent CI: 1.58, 3.19) (86). Results from the German Multicenter Allergy Study cohort showed that repeated lower respiratory tract infections early in life were positively associated with subsequent development of asthma, wheeze, and bronchial hyperreactivity, but that early episodes of runny nose and herpes-type viral infections were inversely related to development of asthma and respiratory symptoms (83). Compared with children who had one or fewer episodes of runny nose before the age of 1 year, those who had two or more episodes were less likely to have a physician’s diagnosis of asthma at age 7 years (adjusted OR = 0.52, 95 percent CI: 0.29, 0.92). Having one or more herpes-type viral infections in the first 3 years of life was inversely associated with asthma at age 7 years (adjusted OR = 0.48, 95 percent CI: 0.26, 0.89). However, in the Swedish Birth Cohort, asthma was reported more often in children born during August through October, suggested to be a consequence of more time spent indoors and more viral infections in the first 6 months of life (55).

Another setting that promotes increased child-to-child contact is day-care centers. In westernized cultures, the number of working mothers has increased dramatically in recent decades, resulting in more children attending day care (139). Day-care attendance has been associated with increased risk of respiratory infections (139–141). As stated

FIGURE 3. Diagram of factors and markers potentially associated with the development of persistent pediatric atopic asthma. Th, T-helper cell; Ig, immunoglobulin; IL, interleukin; IFN-γ, interferon gamma; BHR, bronchial hyperreactivity.
above, respiratory infections have been associated with asthma risk and exacerbation, but, in the Tucson cohort study, which sorted out incident from prevalent diagnoses, day-care attendance was shown to be protective against asthma and frequent wheezing later in childhood (130). Again, it appears to be important to sort out “types” of wheezing. Infections may play a different role in atopic versus nonatopic asthma. It is also likely important to consider types of infectious agents and lower versus upper respiratory tract infections as specific exposures. Data from the Detroit birth cohort indicated that day-care use in the first 12 months of life was protective for allergen-specific IgE at the age of 6–7 years (OR = 0.57, 95 percent CI: 0.34, 0.96) (137).

Several studies, including the Western Australia Pregnancy Cohort Study, have shown that breastfeeding is protective against atopy, wheezing, and asthma (141–144), although data from several of the other birth cohorts have not found this association (42, 145) and even suggest that breastfeeding is a risk factor if the mother is allergic (145). In most of the former studies, 4–6 months of breastfeeding was required to achieve the protective effect. However, a recent report from the Dunedin, New Zealand, cohort suggests that breastfeeding 4 weeks or longer increases the risk of atopy and asthma, regardless of parental history of hay fever or asthma (146). Risk was increased for atopy at age 13 years (adjusted OR = 1.94, 95 percent CI: 1.42, 2.65) and for current asthma at age 9–26 years (adjusted OR = 1.83, 95 percent CI: 1.35, 2.47).

A possible mechanism related to the hygiene hypothesis through which effects of breastfeeding, if preventive, may operate is the establishment of normal intestinal flora. A study by Harmsen et al. found that the components of the fecal samples from breastfed infants were mainly lactobacilli and streptococci, whereas samples from formula-fed infants often contained staphylococci, Escherichia coli, and clostridia (147). Prevention of disease by normal intestinal flora is the result of metabolites that make the environment less favorable for pathogenic colonization and the pressure that the microbial environment exerts on immune deviation.

Recent studies in the industrialized world have found that use of antibiotics in infancy is associated with increased risk of asthma and atopic disease (96, 148–152). These studies have been mainly cross-sectional or retrospective, relying on a report of a physician diagnosis of asthma and parental recall of their child’s antibiotic use, sometimes years earlier. A recent study showed that antibiotic use alters gastrointestinal function by promoting colonization of the gut with pathogenic bacteria (153). In addition, Oyama et al. showed in a mouse model that administration of antibiotics increased serum levels of total IgG1 and IgE, increased in vitro IL-4 secretion, and reduced in vitro interferon gamma secretion (154). This finding is suggestive of the positive role that nonpathogenic bacteria, such as lactobacilli, may play in immunologic functioning.

Immunizations, either by stimulating the immune system or preventing a natural infection, have been suggested as a risk factor for atopic conditions. It has been difficult to study the relation of childhood immunizations to development of asthma. US children who are not immunized often have other risk factors for asthma and are likely to possess characteristics that distinguish them in many other ways from the general population (155, 156). During the 1970s, Europe experienced a decline in the acceptance of immunizations, creating a less-biased environment for the study of this issue (157, 158). Infections, vaccinations, and repeated exposure to other allergens can tip the balance in the stimulation of T-cell responses (101, 159–162). The vaccine receiving the most attention as being a potential risk factor for asthma development is the diphtheria-tetanus-pertussis vaccine, given in five doses between the ages of 2 months and 6 years (155, 156). Kemp et al., using the Christchurch cohort, found that allergy and asthma were extremely uncommon in unvaccinated children, although the number of such children was exceedingly small (23 of 1,265 subjects) (157). Two other cross-sectional surveys, one conducted in London and one using US Third National Health and Nutrition Examination Survey data, also reported an association (163, 164). In addition, some laboratory results have supported increased levels of IgE in subjects exposed to diphtheria, pertussis, and tetanus antigens (101, 165, 166). The Avon Longitudinal Study of Parents and Children (ALSPAC) cohort found no increased risk associated with pertussis vaccination for wheezing illnesses in young English children (84).

In the United States, the largest and most recent known study to date on this issue was conducted by using 167,240 children enrolled in four large health maintenance organizations during 1991–1997 (167). Follow-up was available from birth through age 6 years. Information on immunizations and asthma was obtained by using available automated databases. The incidence of asthma in the study population was 11 percent. The percentage of children for whom no record existed of pertussis-tetanus-pertussis, oral polio, or Haemophilus influenzae type b vaccines was 3.6 percent, 2.6 percent, and 2.2 percent, respectively. Percentages were higher for children who, according to automated data, did not receive the measles-mumps-rubella (7.4 percent) or recombinant hepatitis B (11.1 percent) vaccines. The researchers did not find an association between diphtheria-tetanus-pertussis, oral polio, or measles-mumps-rubella vaccine and the risk of asthma. Weak associations were observed for H. influenzae type b (18 percent increase in risk) and hepatitis B (20 percent increase in risk) vaccines, which seemed to be explained by use or information bias.

As mentioned above, one vaccine with published reports of being protective against asthma and allergy is the attenuated bovine Mycobacterium tuberculosis vaccine (Bacillus Calmette-Guérin) (105). Despite strong evidence from this Japanese study, this relation has not been confirmed (168).

A significant body of literature has been generated regarding the role of common household allergens, particularly dust mite, cockroach, and pet allergens. In a recent review article by Platts-Mills et al., a clear dose-response relation between dust mite exposure and sensitization was supported by studies of different communities and climates (169). A high level of Aeroallergen exposure was initially demonstrated, using the Poole England birth cohort, to be related to the development of sensitization and subsequent asthma, with a statistically significant, although unadjusted relative risk of 4.8 for asthma at age 11 years associated with
high household levels of dust mite allergen at 1–2 years of age (69). Positive skin reactions to egg and milk tended to be early and transient, whereas those for airborne allergens tended to be permanent. In the Boston cohort study, two or more episodes of wheeze in the first year of life were associated with a cockroach allergen level in the home’s family room of >0.05 U/g in dust (relative risk = 1.76, 95 percent CI: 1.20, 2.57), an association that remained significant after further adjustment for socioeconomic factors including race and income (86). Recent results from the Yale Birth Cohort presented at the 2002 American Thoracic Society meeting indicated that airborne mold measurements were associated with wheeze and persistent cough before 1 year of age (89).

However, several papers have reported no association between allergic sensitization to cat and level of exposure to cat allergen (69, 170–173). No association was observed between early indoor allergen exposure to house dust mites or cat dander during infancy and wheezing, bronchial hyper-reactivity, or asthma at age 7 years in the German Multicenter Allergy Study, although mite exposure was associated with mite sensitization (18). Lau et al. suggested that induction of specific IgE responses and development of childhood asthma are determined by independent factors (18).

The low level of allergen reported in the German homes led to criticism of these findings (174). These observations, along with other studies, have also led to the proposal that a "threshold" dose of allergen exposure might be necessary to trigger either allergic sensitization or symptomatic disease. However, data regarding the presence of a strict threshold level of exposure for any particular allergen are lacking. In the German cohort, the likelihood of persistent sensitization to allergen was largely dependent on family history of atopy, with maternal history being most predictive. Other genetically linked markers such as elevated cord IgE levels were also linked to likelihood of sensitization (175). From such observations, one can conclude that genetic factors, in contrast to a fixed threshold level of exposure, may significantly influence the level of exposure necessary to induce sensitization within a given person. However, the measurement of allergen exposure has been limited in nearly all epidemiologic studies to one or several in dust samples obtained from carpets or mattresses. Thus, "allergen exposure" has tended to be a crude measurement that, depending on the allergen’s size and seasonality characteristics, may not be a particularly satisfactory surrogate for inhaled dose.

Data from the Detroit Childhood Allergy Study have shown that exposure to two or more cats or dogs during infancy was associated with a lower probability of subsequent allergic sensitivity to common allergens and with lower serum IgE levels in both boys and girls and with less methacholine responsiveness and better lung function in boys (73). A recent systematic review and analysis of the literature found a consistent protective effect of pet ownership for pediatric asthma in young children, although the authors state that this finding could also be explained by selection bias in relation to pet keeping (176). One recent article not included in the review found that early life pet exposure was associated with decreased risk of atopic disease (asthma, allergic rhinitis, and atopic eczema) (177). Another article from the Tucson birth cohort reported that early pet exposure was preventive for the risk of frequent wheeze but not skin test positivity (178).

It has been suggested that the effect of dogs and cats is not related to the household allergen levels to which they contribute but instead to the bacterial products associated with their presence. Gereda et al. found in metropolitan home environments that the strongest positive association with household endotoxin levels was the number of animals in the home (179). Recent studies showed that household endotoxin levels were higher in farming than in nonfarming households (92, 180–182). In a cross-sectional study of 812 school-aged children residing in rural areas of Germany, Austria, and Switzerland, current mattress endotoxin levels have been found to be inversely associated with hay fever, atopic sensitization, and atopic asthma as well as cytokine levels in stimulated leucocytes (183).

Bacterial endotoxins activate a Th1-type immune response, suppressing the expression of a Th2-type, or allergic, immune response. Animals therefore may play a crucial role during early life by serving as the bacterial exposure vehicle necessary for the immune system’s deviation to a mature nonallergic Th1-type response. Studies have shown that children from farm environments, in which endotoxin levels are higher (180), have a significantly decreased risk of developing atopy and asthma (56, 92–94, 181, 182). This finding is consistent with the research on pet ownership (184). Work by Gereda et al. published in 2000 has provided possibly the first in vivo evidence that indoor endotoxin exposure is inversely related to allergen sensitization and cytokine profiles (95). Specifically, they showed that, among infants at high risk of developing asthma, there was a statistically significant correlation between house-dust endotoxin concentrations and proportions of interferon-gamma-producing CD4 T cells. However, in the Boston birth cohort of children who had at least one atopic parent, Gold’s group found that increased endotoxin in household dust was associated with repeated wheeze, although this association was limited to the first year of life (185). Douwes et al. reported that, for a group of children aged 7–11 years, of whom 50 percent had self- or parent-reported chronic respiratory symptoms, adjusted analyses showed an association of peak expiratory flow variability with fungal (1→3)-β-D-glucan but not endotoxin levels, particularly for atopic children with asthma symptoms (186).

As mentioned by Kay, one nagging contradiction to the hygiene hypothesis is the apparently higher asthma prevalence in the US urban minority population (187). The living conditions of this population may at first glance be expected to be more comparable to those of other economically disadvantaged populations, which, under the hygiene hypothesis, would predict a lower burden of atopic disease. The difference in the expected and the observed asthma prevalence among the US minority urban population may be related to a number of factors, including lower birth weight, increased exposure to some allergens, less pet keeping, diet, physical activity, diesel pollution, diagnostic bias, and genetic or biologic characteristics (16, 188). In the Yale cohort, after adjustment for symptom frequency and medication use in the first 2 years of life, African-American children were found to be more likely than Hispanics or Caucasians to receive an...
asthma diagnosis (189). Data from a population of middle-class African-American children indicated that they were more reactive to methacholine and had higher total IgE levels than their Caucasian counterparts in the Detroit Childhood Allergy Study, and these two characteristics were related in the Caucasian but not the African-American children (16). Furthermore, the increased prevalence in this population may be attributable to the contribution of these factors as well as to lifestyle and medical care patterns, which worsen and prolong asthma severity, possibly resulting in a seemingly increased prevalence despite a similar incidence of disease.

Pre- and perinatal factors. A number of recent epidemiologic studies have attempted to measure the association of perinatal factors with the risk of asthma and allergic rhinitis by using patient or parental reporting. In the largest known series to date, data from the enrollment of 149,378 Swedish military conscripts (aged 17–20 years) were linked to the Swedish Birth Register (190). A self-reported history of recurrent wheezing or breathlessness was classified as asthma, and nasal or ocular symptoms induced by allergens were classified as allergic rhinitis. For those born at less than 33 weeks of gestation versus those born between 37 and 41 weeks of gestation, the adjusted odds ratio was 0.82 (95 percent CI: 0.68, 0.98) for allergic rhinitis. As is consistently shown, a greater number of older siblings was protective for allergic rhinitis, with an adjusted odds ratio of 0.63 for those with four or more older siblings compared with being the first-born. The risk of allergic rhinitis also increased with increasing maternal age at birth; the adjusted odds ratio was 0.68 for a maternal age of less than 20 years compared with more than 29 years. Interestingly, the association for many of the risk factors for asthma was in the opposite direction of those for allergic rhinitis. Lower birth weight and younger maternal age were both independent risk factors for asthma, even in the subset of asthmatics with allergic rhinitis. Allergic rhinitis was an independent risk factor for asthma (adjusted OR = 4.37, 95 percent CI: 4.17, 4.57), again demonstrating that atopy is an important risk factor for asthma.

In 1997, Olesen et al. reported the results of a record linkage study of the birth records of 7,862 infants born between January 1984 and December 1986 in the Danish municipality of Aarhus (191). Medical record data were used, and the adjusted odds ratio for children born at 41 or more weeks of gestation was 1.32 (95 percent CI: 1.06, 1.63) for atopic dermatitis when compared with children born at 39–40 weeks. Similarly, by parental report, the adjusted odds ratio for children born at 41 weeks or more was 1.35 (95 percent CI: 0.96, 1.89); the test for trend between 36 weeks and 41 or more weeks of gestation was statistically significant (p = 0.03). Again, parity (i.e., the number of older siblings) was statistically significant when medical record data were used; the adjusted odds ratio was 0.26 (95 percent CI: 0.10, 0.73) for four or more older siblings compared with being first-born. In a Danish hospital-based cohort study of children born from 1993 to 1994, gestational age of less than 37 weeks (OR = 2.2, 95 percent CI: 1.2, 4.2), low maternal educational level (OR = 1.7, 95 percent CI: 1.1, 2.5), and maternal allergic disease (OR = 2.6, 95 percent CI: 1.7, 4.2) were associated with asthma medication use (58).

Although birth order may be a surrogate for exposure to infections, this association may also reflect the relation between successful expression of the Th2 phenotype in utero and fetal survival (i.e., parity). In a study to examine whether the “sibling effect” had its origin in utero, Karmaus et al. studied the relation between birth order and cord blood IgE levels by using data from the Isle of Wight cohort (192). They found that IgE levels were reduced with increasing birth order (first child, OR = 1 (referent); second child, OR = 0.78 (95 percent CI: 0.57, 1.05); third child, OR = 0.59 (95 percent CI: 0.41, 0.83)). Cord blood IgE was a significant predictor of skin-prick test positivity at age 4 years. The authors concluded that the association found between birth order and atopy may reflect a different in utero environment in successive pregnancies.

The investigators from the Dunedin Multidisciplinary Child Development Study recently contributed to the theory that the prenatal period is important, with the finding that increased fetal growth is related to risk of asthma and atopy in childhood, consistent with the theory of intrauterine programming of the developing respiratory and immune systems (66). Intrauterine programming is the concept that an early stimulus at a specific time during prenatal development can lead to changes in the structure or function of an organ system. Large head circumference at birth (237 cm) was associated with elevated IgE levels at age 11 years (adjusted OR = 3.4 (95 percent CI: 1.4, 7.9)) but was protective for a past or current history of asthma. Increased birth length (≥56 cm) was associated with a history of asthma (adjusted OR = 6.4 (95 percent CI: 2.0, 19.8)) but not atopy. Birth weight was analyzed as a risk factor for atopy in this cohort, and the relation was not statistically significant (193). This study did not find an association between being first-born and atopy (p = 0.21). In fact, a lower birth weight (<3 kg) was protective for asthma (adjusted OR = 0.2, 95 percent CI: 0.0, 0.6); however, 76 percent of the infants whose birth weight was less than 3 kg weighed more than 2.5 kg, placing them in normal weight range (66).

In the northern Finland cohort, a significant association was found between atopy and longer gestation (56, 194). The effect appeared linear, with children born at 41 weeks or more at the highest risk (adjusted OR = 1.65, 95 percent CI: 1.16, 2.34) (values for 39–40 weeks: adjusted OR = 1.42, 95 percent CI: 1.02, 1.98; 36–38 weeks: adjusted OR = 1.22, 95 percent CI: 0.87, 1.70; ≤35 weeks, referent). Although birth weight was not significantly associated with atopy, parity was. The odds of being atopic were higher for first-born children compared with children born later. The effect appeared linear; the adjusted odds ratio for first-born children was 1.83 (95 percent CI: 1.42, 2.35) when compared with those born fifth or later. Unlike atopy, asthma was not associated with increasing gestational age nor was it correlated with parity. No association with gestational age was noted even after asthma was partitioned into those with atopy and those without. In the Boston Home Study of high-risk infants, two or more episodes of wheeze in the first year of life was associated with low birth weight (relative risk = 1.28; 95 percent CI: 1.04, 1.58) (86).
Increased gestational age appears to be a risk factor for later atopy, but its association with asthma is less clear. A number of studies have shown that low birth weight and premature birth are more important risk factors for subsequent asthma (190, 195–198). This conundrum likely is a reflection of the multifactorial nature of asthma. In premature and very low birth weight babies, the etiology for reversible airway obstruction may be more a function of smooth muscle hypertrophy than atopy (196).

In a study of 280 men and women born at a single hospital in Lancashire, England, head circumference at birth was statistically associated with elevated serum IgE concentrations (≥80 IU/ml) in adulthood (average age, 51 years; range, 47–55 years) (199). Thirty-seven percent of subjects whose head circumference at birth was more than 14 inches (35.6 cm) had an elevated IgE concentration compared with 14 percent of those whose head circumference at birth was 13 inches (33.0 cm) or less. These findings have been confirmed by other studies, including the Dunedin cohort, as mentioned earlier (66). Depending on the definition of asthma used, Ferguson et al., using the Christchurch birth cohort, found that the odds of asthma by age 16 years was 1.8–3.0 times greater for children whose head circumference at birth was 37 cm or more compared with other children (60). Finally, in a cross-sectional study by Gregory et al., 239 children were tested for atopy by skin-prick test and for serum IgE levels (200). The relative risk for having an elevated serum IgE (>150 IU/liter) concentration in children whose head circumference was 37 cm or more at birth was 3.2 (95 percent CI: 1.0, 10.4) compared with other children. The mean age of the children when they were tested was 13 years (range, 6–23 years). No consistent relation was found between head circumference at birth and either skin test positivity or clinical asthma.

Air pollution. Although a number of studies have investigated air pollution and asthma, the majority do not support a major role for air pollution as a determinant of asthma incidence or prevalence (5). It is notable that pediatric asthma prevalence is substantially lower in relatively highly polluted European countries such as the former East Germany, Poland, and Estonia (123, 124). Some studies have demonstrated that close proximity of the residence to areas with a high density of traffic increases asthma risk (5, 201). Other reports have indicated that poor air quality in infancy, reflected by exposure to environmental tobacco smoke and gas appliance use, is related to subsequent wheeze or asthma (76). In the Epidemiology of Home Allergens and Asthma Birth Cohort in Boston, investigators using multivariable analyses reported that predictors of two or more wheeze episodes in the first year of life included maternal smoking during pregnancy (relative risk = 1.83, 95 percent CI: 1.12, 3.00) (86), although the Childhood Allergy Study investigators in Detroit found that, although decreased birth weight and length were associated with maternal smoking, neither maternal nor paternal smoking was associated with IgE level in cord blood (73). Analyses from the Tasmanian Infant Health Survey revealed that exposure to home gas appliances during infancy was related to atopy, as measured by skin-prick test to major inhalant allergens, with statistically significant crude odds ratios ranging from 2.0 to 4.6 (34). McConnell et al. published results from southern California suggesting that asthma incidence can be associated with heavy exercise in communities with high ozone concentrations (202). Even though factors related to poor air quality have generally not been shown to increase the risk of development of pediatric asthma or allergy (203), the methodological challenges associated with studying these conditions epidemiologically render such studies especially difficult to conduct.

Obesity and physical activity. The possible contribution of obesity and physical activity to the asthma epidemic has been given more attention in the last few years, but it is still relatively unexplored. Obesity is another chronic condition affecting young people in the United States, with nearly 25 percent of US children and adolescents considered obese (204). Similar to asthma and allergy, childhood obesity prevalence continues to rise. In the past decade, there has been a reported 45.2 percent increase in obesity among boys aged 6–17 years and an increase of 42.2 percent among girls of the same age (204). The parallel increases in asthma and obesity in US children beg further investigation to determine whether any association exists between the two chronic conditions and, if so, what that relation may be.

In a pro/con editorial recently published in the American Journal of Respiratory and Critical Care Medicine, von Mutius and Platts-Mills argued the validity of the hygiene hypothesis but noted the potential contribution of obesity and physical inactivity to the observed worldwide asthma epidemic (205). Varner et al. provided evidence for a convergence of the hygiene hypothesis and obesity (206–208). The biologic activity of adipose tissue, according to Varner et al., includes production of Th2-type cytokines including IL-4, IL-5, and IL-13, which are associated with asthmatic inflammation. Thus, the contribution of obesity to the asthma epidemic may be twofold, as a mechanical inhibitor of the development of normal lung function and as a contributor to asthmatic inflammation.

It has been shown that obesity in children is related to a lack of physical activity (209). In recent years, US children have been leading a more sedentary lifestyle in which physical activity and recreation time have been replaced by nonactive activities such as watching television (210–212). A positive association between lack of physical activity, obesity, and asthma could be postulated to partly explain the puzzling paradox that urban African-American children seem to have a higher prevalence of asthma than US White children. A 1998 case-control study conducted by Gennuso et al. (213) examined the relation between obesity and asthma in urban minority children aged 4–16 years. A significant difference in asthma status was found between those at or above the 85th percentile of body mass index (BMI) (p < 0.04). The association between asthma and obesity was strongest among children whose BMI was in the 95th percentile, the cutoff used to indicate severe obesity. Nearly one third (30.6 percent) of the asthmatic children had a BMI greater than the 95th percentile, but only 12 percent of controls were this obese (p < 0.002). Similar results were found in a cross-sectional study of inner-city children aged 2–18 years (214). Among children with asthma, 21.5 percent had a BMI in the 95th percentile or above compared with
only 15.3 percent of the controls \((p = 0.03)\). However, two studies did not find a relation between BMI and asthma (197, 215). The study populations used in these investigations were quite different (inner city vs. national and international) and may explain the apparent contradiction in results.

Von Kries et al. showed a positive trend in the lifetime prevalence of physician-diagnosed asthma for normal-weight (3.5 percent, 95 percent CI: 2.9 percent, 4.1 percent), overweight (5.8 percent, 95 percent CI: 3.2 percent, 8.4 percent), and obese (10.3 percent, 95 percent CI: 5.3 percent, 15.2 percent) girls but not boys (216). A cross-sectional study in the United Kingdom showed that levels of obesity were associated with asthma symptoms (217). The Tucson birth cohort showed evidence of a relation between obesity and the incidence of asthma-like symptoms and bronchial responsiveness in girls (218).

A positive relation between obesity and asthma prevalence has also been shown in adult studies. Results from the 1970 British Cohort Study indicated that the prevalence of asthma and wheezing increases with increasing adult BMI; the strongest effect was evident among women (219). Results from three additional national health surveys, the US Nurses’ Health Study, the Netherlands Health Interview Survey, and Canada’s National Population Health Survey, confirm the association between weight and asthma among women (220–222). Additional data from Canada’s National Population Health Survey were highlighted in the February 1, 2002, issue of the American Journal of Epidemiology. Chen et al. showed a relation between obesity and the incidence of asthma in women but not in men (223). Several additional recently published articles have also reported a relation between obesity and asthma in adults (224–226).

Few studies have examined the relation between physical activity and asthma. The European Respiratory Journal recently published results of a prospective study of physical activity and asthma among 757 asymptomatic children followed from an average age of 9.7 years for 10.5 years (227). This study showed that a high level of physical fitness was associated with a reduced risk of the development of asthma. Two studies found no difference between activity levels of children with and without asthma (228, 229). This finding is surprising considering that research has shown that exercise stimulates an asthmatic response in children diagnosed with asthma but not in children without a diagnosis (230). The contradiction could be due to the design approach (cross-sectional) used in these two studies. Studies of physical exercise must be interpreted in light of the fact that the most common trigger of asthma symptoms is exercise, which likely leads to earlier diagnosis in active children and perhaps underascertainment in sedentary youngsters.

**CONCLUSIONS**

The cohort studies described above, as well as several cross-sectional studies, have elicited a number of epidemiologic features consistently associated with pediatric asthma and allergies. Although measurement of the prevalence and incidence of these illnesses is difficult, most studies across the world indicate an increasing presence of these conditions. The prevalence of both allergy and asthma has historically been higher in areas with a higher standard of living. Hay fever and asthma are less common in geographic areas with lower air quality and less of a western lifestyle. The enigma of the higher severity, and perhaps prevalence or incidence, of asthma among US inner-city African-American children awaits explanation.

These conditions tend to run in families. The specific role that inherited characteristics play in disease causation requires further studies. The pattern of a higher male-to-female ratio that reverses during the second decade is an intriguing epidemiologic feature, and risk factors often vary by gender. Being a first-born child has been shown repeatedly and in different settings to increase risk. Exposure to animals, either livestock or pets, while well known to exacerbate allergic and asthmatic symptoms, appears to decrease the incidence of disease.

The relation between early infections and asthma is complex and only beginning to be unraveled. The recent theories that asthma in children consists of at least three different syndromes, not all tending to persist throughout life, suggest that future risk factor analyses should routinely attempt to distinguish these case groups. Very large birth cohorts will therefore be necessary to elucidate the natural history of the differing asthma, and perhaps allergic, phenotypes that have heretofore been collapsed into one disease category. The development of noninvasive sensitive and specific validated criteria or biologic markers for the various asthma phenotypes would revolutionize the field. Epidemiologists, clinicians, immunologists, and molecular geneticists are working together in many settings and starting to narrow down the factors related to causation and exacerbation of allergic conditions and asthma, with every indication that substantial advances in this field will occur in the not-too-distant future.

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