



Trends in the Prevalence of Asthma

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The asthma epidemic of the last few decades may have peaked; studies suggest that the incidence and prevalence of asthma has decreased in some countries in the last few years, although other studies suggest continuing small increases in prevalence. Increasing awareness and changing diagnostic habits make precise evaluation of epidemiologic trends difficult in the absence of a gold-standard test for asthma, and on a global basis uncertainty persists. Trends in prevalence in some populations (eg, immigrants, farming communities) suggest both adverse and beneficial effects of specific environmental factors. Although the effects of indoor allergens, dampness, and mold and of outdoor air pollutants, especially traffic related, have traditionally dominated risk-factor research, more recent epidemiologic and clinical studies have focused on metabolic and nutritional factors, including maternal obesity and vitamin D levels, mode of delivery and its effect on the infant microbiome, fetal and infant growth, the psychosocial environment, and medication use by mother and infant. It is likely that changes in incidence and prevalence are due to multiple factors, each contributing a relatively small effect. Longitudinal studies from pregnancy through childhood to adulthood will yield greater insights into the complex pathways leading to asthma.

CHEST 2014; 145(2):219–225

Abbreviations: AHR = airway hyperresponsiveness; ISAAC = International Study of Asthma and Allergies in Childhood

The substantial upward trend in the reported prevalence of asthma in the latter part of the 20th century has been termed the “asthma epidemic.” Compared with 50 years ago, when only 2% to 4% of the population reported asthma,^{1,2} recent data suggest 15% to 20% or more of the general population in many countries suffer from asthma,^{3–5} clearly a cause for concern.

There are many questions to be addressed in reviewing this modern-day epidemic. Has the prevalence of asthma really increased? Is prevalence still increasing, has it reached a plateau, or is it even decreasing? Are the changes in prevalence global or population spe-

cific? Are the changes in prevalence evident across all levels of severity? What factors may underlie these changes? And finally, what further studies are needed to understand recent trends in the prevalence of asthma?

In 2006, Eder et al⁴ highlighted substantial increases in the prevalence of asthma in children and young adults in almost every country where repeated population-based surveys of the prevalence of asthma had been undertaken. The most striking increases were in westernized countries such as Australia, Canada, and the United Kingdom, which already had substantial rates of reported asthma, but significant increases were also noted in Asia and eastern Europe, which had a much lower baseline prevalence. That the changes were not simply reflective of diagnostic habits was suggested by the similar changes in reporting of the prevalence of asthma symptoms, irrespective of an asthma diagnosis.

Also in 2006, Asher et al⁵ reported on global time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood, using cross-sectional data from the International Study of Asthma and Allergies in Childhood (ISAAC), which was repeated in many countries with at least

Manuscript received August 30, 2013; revision accepted September 21, 2013.

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DOI: 10.1378/chest.13-2059

5 years between surveys. For asthma ever, most countries reported an increase. However, for current wheezing, there was a trend toward a decrease in prevalence in those countries with initially higher prevalence and no consistent change in countries with modest or low prevalence. While there was an increase in the overall prevalence of asthma ever across the repeated surveys, the frequency of reporting four or more episodes in the last 12 months in several of the countries with higher prevalence (such as the United Kingdom and New Zealand) was lower in phase 3 than in phase 1 of the ISAAC,⁶ suggesting that the overall increase in asthma mainly reflected milder disease. In countries with lower baseline prevalence, this differentiation of severity judged by frequency of episodes was less evident.

DIFFICULTIES IN STUDYING THE EPIDEMIOLOGY OF ASTHMA

There are a number of specific difficulties in studying the epidemiology of asthma. There is no standardized definition of the disease, and, increasingly, the heterogeneity of the “asthmias” is being recognized. There is no gold-standard diagnostic test, as symptoms, although still the best indicator of the presence of asthma, are nonspecific and have a significant differential diagnosis.^{7,8} Airway hyperresponsiveness (AHR) can be increased in a proportion of children who have never had symptoms of asthma^{9,10} and likewise can be absent on the day of testing despite a clear history of symptoms over time that are fully consistent with asthma.¹¹ There is increasing community awareness of asthma, leading to changing diagnostic habits, and international classification systems have also changed over time, all leading to difficulties determining the reality and accuracy of reported trends. There is some evidence for overdiagnosis of asthma. Aaron et al¹² studied adults with physician-diagnosed asthma, using objective testing of AHR and withdrawal of therapy to confirm or negate the diagnosis, and reported that one-third of the adults assessed did not have sufficient evidence on these objective measurements to validate the diagnosis.

Illustrating the difficulties inherent because of increased community awareness is a study by Kälvesten and Bråbäck,¹³ who examined time trends for the prevalence of asthma among schoolchildren in a Swedish district. Repeated cross-sectional surveys with identical study design were conducted among schoolchildren aged 7 to 16 years in 1985, 1995, and 2005 (response rates were 91%, 94%, and 81%, respectively). There was an increased positive response to screening questions on asthma between 1985 and 1995 (10.0% to 14.5%) but no increase in 2005 (14.2%).

The prevalence of three or more asthma-like symptoms decreased, yet the prevalence of doctor-diagnosed asthma increased steadily since 1985, suggesting a component of community awareness and changing diagnostic habit.

The prevalence of asthma in a population is related not only to the incidence of the disease but also to its duration, which reflects persistence. In a national study of 333,294 patients with a recorded diagnosis of asthma, drawn from the health database of 422 British practices, the incidence of asthma decreased in all patients from the period of 2001 to 2005, from 6.9 to 5.2 per 1,000 people.¹⁴ Among children there was a 38% reduction in incidence and a 34% reduction in lifetime prevalence of asthma, whereas among adults there was an age-dependent increase in lifetime prevalence ranging from 22% to 28%, reflecting the persistence of disease despite a lower incidence.

IS THE PREVALENCE OF ASTHMA STILL INCREASING?

Repeated use of identical screening questionnaires in serial cross-sectional studies in Italy between 1990 and 2010 revealed an increase in the prevalence of asthma from 4.1% to 6.6%; wheezing increased from 10.1% to 13.9%, and allergic rhinitis from 16.8% to 25.8%.¹⁵ Other studies reported increases in some communities but not others with similar genetic background; for example, Finnish Karelia showed an increase in asthma (5.5% to 8.1%) and hay fever (8.1% to 13.2%), but no such increases occurred in adjacent Russian Karelia, where there has been no evidence of an asthma epidemic.¹⁶ In Ontario, Canada, age- and sex-standardized asthma prevalence increased from 8.5% in 1996 to 13.3% in 2005, a relative increase of 55%.¹⁷ Asthma incidence increased in children by 30% but was relatively stable in adults.

In contrast to the reported increases, asthma prevalence in some populations appears to have reached a plateau or even decreased. In Greece, population surveys in 1978, 1991, 1998, 2003, and 2008 yielded prevalences of 1.5%, 4.6%, 6.0%, 6.9%, and 6.9%, respectively (ie, no change in the last 5 years).¹⁸ In Turkey, surveys in 1992, 1997, 2002, and 2007 yielded prevalences for asthma of 8.3%, 9.8%, 6.4%, and 3.3%, respectively, with similar downward trends in hay fever and eczema.¹⁹ The Aberdeen school survey, which was one of the first to report increased prevalences in repeated surveys,²⁰ noted decreasing rates of wheezing in the last three surveys, which were conducted in 1999, 2004, and 2009 (27.9%, 25.2%, and 22.2%, respectively; $P < .001$) with a greater reduction seen in girls than boys.²¹ In Merseyside children, doctor-diagnosed asthma increased from 1991 to 1998,

but in 2006 had decreased substantially (29.8% to 19.4%, $P < .001$).²² However, paternal and maternal asthma prevalence increased during that latter period (8.6% to 10.7% and 11.2% to 13.4%, respectively).

Anandan et al²³ undertook a systematic review of epidemiologic studies to assess the trends in prevalence of asthma. This review, which included cohort studies, repeat cross-sectional studies, and health-care datasets, identified 48 studies satisfying inclusion criteria. They concluded that overall, there were no signs of declining prevalence, and prevalence was still increasing in many parts of the world. Reductions in emergency health-care use were considered to reflect better quality of care rather than a decrease in prevalence.

Studies of the prevalence of asthma are generally conducted in specific areas within countries and do not necessarily reflect data from the entire population; even with multiple cities and areas participating within a country, as in the ISAAC study,⁵ results are still only applicable in the regions studied. The best evidence of changes in prevalence comes from repeated studies using the same questionnaires or investigations in the same population at sufficient intervals of time.

ARE CHANGES IN PREVALENCE MORE EVIDENT IN CERTAIN POPULATIONS OR ENVIRONMENTS?

Studies in immigrants have consistently indicated that those coming from a country of low asthma prevalence to one of higher prevalence develop an increased prevalence proportional to the duration of residence in the new country. Wang et al²⁴ compared prevalence data from ISAAC phase 3 studies conducted among 13- to 14-year-old Chinese adolescents living in China and in Canada. Asthma prevalence was lowest in those born and still resident in China, with somewhat higher rates in those born in China but living in Canada for < 7 years and even higher rates in those born in China but living in Canada for 7 to 14 years. The highest rates were found in Chinese children born in Canada and living their whole life in Canada.

Motika et al²⁵ studied a communal farming community of Hutterites living in South Dakota. Repeated surveys, conducted from 1996 to 1997 and from 2006 to 2009, using questionnaires, lung function measurements, methacholine AHR measurements, and measures of atopy, found an increase in asthma from 7.5% to 11.1% ($P = .049$) but no change in atopy (45.0% and 44.8%, respectively; $P = .95$). The increase in asthma was almost exclusively seen in female patients, with a prevalence of 5.8% increasing to 11.2% ($P = .02$), whereas among male patients, the change in prevalence was insignificant (9.4% to 10.9%, $P = .57$). In contrast, a recent systematic review and meta-analysis of 39 studies of effects of exposure

to farming environments (largely in childhood) confirmed an approximately 25% lower asthma prevalence among farm-exposed subjects compared with unexposed subjects; there was substantial heterogeneity across studies.²⁶

WHAT FACTORS MAY UNDERLIE CHANGES IN PREVALENCE?

The last 2 decades have seen an explosion of research into the epidemiology of asthma, examining many risk factors from environmental to dietary to psychosocial to medications, and associated gene-environment interactions and epigenetic effects. A comprehensive literature review and meta-analysis of these studies is outside the scope of this article. Rather than review all possible risk factors for asthma, this article highlights some putative risk factors in which trends in the frequency or intensity of particular exposures could possibly explain observed changes in prevalence.

Physical Environment

For decades, studies of risk factors for asthma have focused on indoor environmental exposures such as mold, dampness, indoor allergens (especially house dust mites and pet allergens), oxides of nitrogen associated with gas cooking and heating, volatile organic compounds, and environmental tobacco smoke,^{27,28} and on outdoor air pollutants, including diesel particles, other petrochemicals, and particulates.^{29,30} The question is whether any of these effects have become more evident in recent decades. Perhaps the main contender for consideration is traffic-related air pollution. The effects of this complex mixture (particulate matter, nitrogen oxides, carbon monoxide, and organic compounds) on asthma likely also depend on interactions with multiple endogenous or exogenous factors, such as genetics,³¹⁻³³ co-exposures such as allergens and environmental tobacco smoke,³⁴ and psychosocial stress.^{35,36}

Metabolic and Nutritional Factors

More recently, epidemiologic and clinical studies have explored other parental and infant exposures and characteristics potentially impacting the risk of developing asthma. Rates of obesity in many populations are increasing, including in pregnant women.³⁷ Maternal overweight during pregnancy has been associated with childhood asthma, based on data from a Swedish registry study, with a clear dose-response relationship; if causal, this might explain 11% to 13% of childhood asthma.³⁸ Recent analyses from the ISAAC study found an association between consumption of fast food three or more times per week with

severe asthma in adolescents and children, while fruit consumption three or more times per week appeared protective.³⁹

Fetal and infant growth may impact asthma symptoms in preschool children. The Generation R study, a population-based cohort study in Rotterdam, examined fetal growth estimated by second and third trimester ultrasonography and measured infant growth at 3, 6, and 12 months.⁴⁰ Outcomes of asthma were assessed by annual parental questionnaire to age 4 years. Accelerated infant growth from birth to 3 months after normal fetal growth was associated with wheezing (OR, 1.44), dyspnea (OR, 1.32), dry cough (OR, 1.16), and persistent phlegm (OR, 1.30). However, there was no association with eczema (OR, 0.95).

In 2007, Litonjua and Weiss⁴¹ suggested that the epidemiologic patterns seen in the asthma epidemic, including the increased risks associated with obesity, African American race, and recent immigrants to westernized countries, may be explained by vitamin D deficiency, due to more prosperous populations now spending more time indoors with less exposure to sunlight. This hypothesis, and evidence supporting it, was recently reviewed by Paul et al.⁴² There are several observational studies suggesting this linkage. Japanese children whose mothers had higher consumption of vitamin D during pregnancy (>25th percentile) had a significantly reduced risk of wheeze at 16 months to 24 months of age (adjusted OR, 0.64; 95% CI, 0.43-0.97).⁴³ Similarly, in Finland, maternal intake of vitamin D from food was negatively related to the risk of asthma (hazard ratio, 0.80; 95% CI, 0.64-0.99) and allergic rhinitis (hazard ratio, 0.85; 95% CI, 0.75-0.97).⁴⁴ In a New Zealand cohort, cord blood 25(OH)D levels were inversely associated with the risk of wheezing by 15 months, 3 years, and 5 years of age (all $P < .05$), but there was no association with incident asthma at 5 years.⁴⁵ Even later in childhood, serum vitamin D levels at age 6 years in an Australian cohort predicted subsequent atopy/asthma-associated phenotypes at age 14 years, especially in boys.⁴⁶ However, not all studies support this hypothesis; for example, in a Spanish birth cohort, higher maternal 25(OH)D at 12 weeks' gestation was not associated with wheezing at 1 year or 4 years or asthma at age 4 to 6 years, although there were fewer respiratory tract infections in the children.⁴⁷

Stress

Parental stress, especially maternal prenatal stress, has been implicated as a risk factor for asthma. Is stress now more prevalent? An exposure-response relationship between higher levels of stress and childhood wheeze was documented in a Boston cohort in which

prenatal stress in nonsensitized mothers, but not in sensitized mothers, was associated with childhood wheezing.⁴⁸ Pittman et al⁴⁹ examined the association of community stressors with childhood asthma prevalence in Winnipeg, Canada, using a birth-cohort study. After adjusting for individual risk factors, children living in birth homes in a neighborhood with a high rate of theft were twice as likely to have asthma; this marker of community stress explained more than one-half of the observed neighborhood variation in asthma prevalence.

Medications

Acetaminophen, commonly used for pain and fever in children over the last few decades since the risks associated with acetylsalicylic acid in children were recognized, may influence development of asthma through depletion of glutathione, a major antioxidant in the airways. Several studies suggest an association of acetaminophen use in pregnancy and early infancy with asthma in later childhood, but confounding by indication is difficult to exclude.⁵⁰ Respiratory viral infections leading to use of acetaminophen may induce changes in the airways leading to later asthma, or the apparent "infection" may in fact be a manifestation of asthma not yet diagnosed.⁵¹⁻⁵³ Increasing prenatal exposure to acid-suppressive drugs may also be a risk factor for childhood asthma. A study using data from Danish medical registries to follow 197,600 singletons born between 1996 and 2008 found the relative risk of asthma following prenatal use of proton-pump inhibitors was 1.41 (95% CI, 1.27-1.56).⁵⁴ There was a similar risk associated with histamine-2-receptor antagonists, suggesting a class effect of gastric acid-suppressive drugs or, alternatively, confounding by indication related to maternal gastroesophageal reflux disease as a risk factor for childhood asthma. The effects of antibiotics on the risk of developing asthma remain controversial, with several studies reporting associations,⁵⁵⁻⁵⁹ but reverse causation or confounding by indication is difficult to exclude.⁶⁰

Delivery by Cesarean Section

Several studies have shown differences in asthma outcomes according to mode of delivery, with a 10% to 20% higher rate of subsequent asthma associated with cesarean section.^{61,62} Rates of cesarean section have increased, especially in Western countries.⁶³ The lack of exposure to the vaginal microbiome may lead to altered immune development in the infant. Fecal microbiota profiles differ in infants delivered by cesarean section and persist to 6 weeks of age.⁶⁴⁻⁶⁶ Changing trends in antibiotic use by newborns may also alter infant microbiota profiles.⁶⁷

WHAT FURTHER STUDIES ARE NEEDED TO UNDERSTAND THE EPIDEMIOLOGY OF ASTHMA?

While cross-sectional studies may provide clues to mechanisms underlying the changing epidemiology of asthma, longitudinal studies from pregnancy through childhood are more likely to yield insights into the complex pathways leading to asthma, although, unfortunately, more slowly and at substantially greater cost.⁶⁸ Numerous cohort studies are currently in progress, ranging from very early studies in the United Kingdom^{69,70} and those established in 1970s and 1980s in Australia⁷¹ and New Zealand³ to more recent studies in Europe,⁷²⁻⁷⁴ the United States,⁷⁵ and elsewhere. These studies with longitudinal outcome data allow a better understanding of the importance of risk factors for persistent disease.⁶⁸ For example, it has been suggested, based on cross-sectional studies, that atopy is related to less than one-half of the cases of asthma,^{76,77} whereas recent analyses from the Dunedin study³ show that a very high proportion of those with asthma persisting from childhood into adulthood and showing more severe disease manifested by both AHR and incompletely reversible airflow obstruction are atopic.⁷⁸ We are currently engaged in another wide-ranging longitudinal birth cohort study, the Canadian Healthy Infant Longitudinal Development Study, which is examining many facets of environmental exposure (broadly defined) in relation to host characteristics, including genetics and epigenetics,²⁷ and examining not only the indoor and outdoor environment, but also maternal diet in pregnancy and infant diet from birth, viral and other infections in the first year of life, immune and inflammatory responses to pathogens and allergens, markers of innate immune function, assessment of lung function in infancy and early childhood, and family health and stress. Collaboration and data sharing among cohorts should provide greater power to address the many unanswered questions regarding the complex etiology of asthma.⁷⁹ Eventually, such research should result in identifying testable interventions that may reduce the prevalence of this disease.

CONCLUSIONS

There has been, and in some countries continues to be, a real increase in the prevalence of asthma, although this is more likely to be mild than severe, and the incidence and prevalence of asthma appear to be decreasing in some countries. There is some evidence of overdiagnosis of asthma. The changes in prevalence of asthma, whether increasing or decreasing, are likely due to many factors, each contributing a relatively small individual effect. Variations in prevalence reflect both the incidence and the persistence of the disease. Studies including the impact of mode of

delivery, use of antibiotics in early life, and maternal and early infant nutrition may shed new light on aspects of the “hygiene hypothesis” in terms of understanding and tracking the development of the infant microbiome and its influence on developing immunologic responses. Although cross-sectional studies have suggested many possible factors related to observed changes in the epidemiology of asthma, comprehensive multifaceted longitudinal studies are also needed to prospectively assess the complex gene-environment interactions underlying its development.

ACKNOWLEDGMENTS

Financial/nonfinancial disclosures: The author has reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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