

REVIEW ARTICLE

CURRENT CONCEPTS

The Asthma Epidemic

Waltraud Eder, M.D., Markus J. Ege, M.D., M.P.H., and Erika von Mutius, M.D.

From University Children's Hospital, Munich, Germany. Address reprint requests to Dr. von Mutius at University Children's Hospital, Lindwurmstr. 4, D-80337 Munich, Germany, or at erika.von.mutius@med.uni-muenchen.de.

N Engl J Med 2006;355:2226-35.
Copyright © 2006 Massachusetts Medical Society.

THE PREVALENCE AND INCIDENCE OF ASTHMA ARE VERY HIGH IN THE Western world. There is widespread concern that the prevalence of asthma is still rising in developed countries, but the economic and humanitarian effects of asthma are probably greater in the developing world, where the prevalence is also rising. Primary prevention strategies to combat the asthma epidemic are therefore urgently sought, but they must be based on a sound understanding of the various determinants of the onset of asthma. In this synopsis of the temporal trends and determinants of asthma and associated features such as atopy, we seek to provide insight into the complex nature of this illness.

TIME TRENDS

DIAGNOSIS OF ASTHMA

According to the Centers for Disease Control and Prevention, the prevalence of asthma among U.S. children increased from 3.6% in 1980 to 5.8% in 2003. Asthma is the third leading cause of hospitalization among persons under 18 years of age in the United States, exceeded only by pneumonia and injuries.¹ Increases in the prevalence of asthma of similar or even greater magnitude were reported from other countries during the second half of the 20th century (Fig. 1A). For example, in 1964, 19% of Australian children were reported by their parents to have had asthma or wheezing at some time during their first 7 years of life; in 1990, such symptoms were reported for 46% of children.⁵² For many countries, there are no data on temporal changes in the prevalence of asthma before the 1990s (Fig. 1A). After the 1990s, estimates of temporal trends in the prevalence of asthma in several European and Asian countries are conflicting. In some populations, the prevalence of diagnosed asthma is still rising, whereas in others it appears to be stable or decreasing slightly (Fig. 1A). There are no clear differences in trends in prevalence between children and adults, between severe and mild asthma, or between developed and developing countries; however, there are few studies from developing countries.

SYMPTOMS OF ASTHMA

Trends in the prevalence of symptoms suggestive of asthma show greater variation than trends in the prevalence of diagnosed asthma (Fig. 1B). The prevalence of asthma symptoms increased in most countries up to the 1990s, but since then there has been no clear temporal pattern. The variability among countries may in part be attributable to differences in definitions of asthma symptoms, such as wheezing, shortness of breath, and asthma attacks. Recent data from the International Study of Asthma and Allergies in Childhood (ISAAC) phase 3 showed that in the mid-1990s, the prevalence of wheezing increased in most centers where the prevalence had been low and decreased or remained unchanged in most centers where the prevalence had been high.⁵³

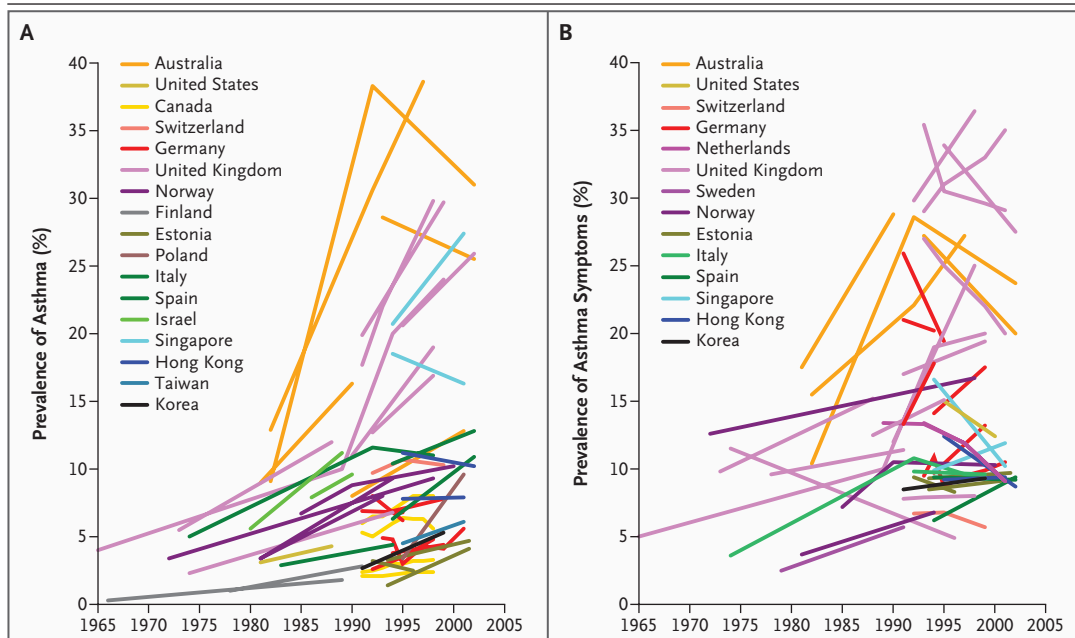


Figure 1. Changes in the Prevalence of Diagnosed Asthma and Asthma Symptoms over Time in Children and Young Adults.

Data in Panel A are from Australia,²⁻⁶ the United States,⁷ Canada,^{8,9} Switzerland,¹⁰ Germany,¹¹⁻¹⁵ the United Kingdom,¹⁶⁻²³ Norway,²⁴⁻²⁷ Finland,^{28,29} Estonia,^{30,31} Poland,³² Italy,^{33,34} Spain,³⁵ Israel,^{36,37} Singapore,³⁸ Hong Kong,^{39,40} Taiwan,⁴¹ and Korea.⁴² Data in Panel B are from Australia,²⁻⁵ the United States,⁴³ Switzerland,¹⁰ Germany,^{11,13,15,44} the Netherlands,⁴⁵ the United Kingdom,^{16-23,46-49} Sweden,⁵⁰ Norway,²⁵⁻²⁷ Estonia,^{30,31} Italy,^{33,51} Spain,³⁵ Singapore,³⁸ Hong Kong,^{39,40} and Korea.⁴²

ASSESSMENT OF ASTHMA IN EPIDEMIOLOGIC STUDIES

No single instrument can be used to identify asthma with certainty. Asthma is a clinical diagnosis made by physicians on the basis of a patient's medical history, physical examination, assessment of the reversibility of airway obstruction, and exclusion of alternative diagnoses that mimic asthma. In epidemiologic studies, questionnaires are used to ascertain whether subjects have had symptoms of asthma or have ever received a diagnosis of asthma from a physician. The prevalence rates of both symptoms and diagnoses of asthma are heavily dependent on an awareness of asthma in the population studied. In recent decades, asthma has received widespread publicity, education of the public about asthma has increased, and new medications for asthma have been introduced. These measures may have increased public awareness of asthma and the rates of reporting of the disease.^{8,17,18,54} In Scotland,²⁰ the proportion of children reporting asthma symptoms who received a diagnosis of asthma increased

from 28% in 1964 to 64% in 1999, a result suggesting that part of the increase in the prevalence of asthma is attributable to changes in diagnostic labeling. The magnitude of the resulting bias in different populations is, however, difficult to appraise.

AIRWAY HYPERRESPONSIVENESS

Airway hyperresponsiveness, the exaggerated narrowing of the airways after the inhalation of various stimuli, is a key feature of asthma. The difficulties with the diagnosis of asthma discussed above have prompted researchers to include airway challenges as an objective measure of asthma in their studies. The results are inconclusive, and no clear time trends in the prevalence of airway hyperresponsiveness have been seen in children or adults (Fig. 2). The variability in the results may be due in part to the different types of challenge tests used (pharmacologic and physiological), the low sensitivity of the tests, the difficulty of standardizing the tests conducted at different times and in different locations, and the variable nature of asthma and of airway re-

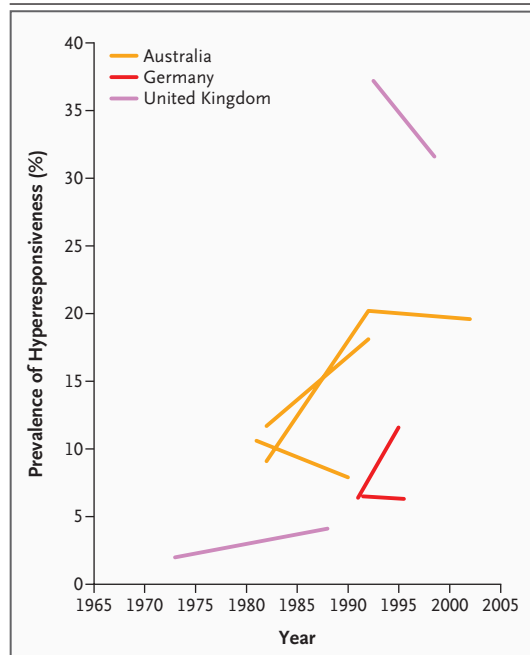


Figure 2. Changes in the Prevalence of Airway Hyperresponsiveness over Time in Children and Young Adults.

The data are from studies that also investigated changes in the prevalence of asthma over time. Studies in Australia measured the response to histamine,^{2,3,55} studies in Germany measured the response to cold air,^{11,12} and studies in the United Kingdom measured the response to methacholine¹⁸ and to exercise.¹⁶

sponsiveness. Measurements of airway responsiveness appear to reflect the activity and severity of asthma at the time of measurement rather than to define the prevalence of the illness over a lifetime or over a specific period; data on long-term prevalence may be better obtained by questionnaires.

ATOPY

Atopy, which can be detected by specific serum IgE or skin-test reactivity to environmental allergens, is often associated with asthma. The prevalence of atopy has increased over time in some populations, whereas in others there has been a decrease or a plateau in prevalence since 1990 (Fig. 3). Asthma and atopy can occur either independently or jointly in patients, in populations, and over time. In the United Kingdom¹⁸ and Australia,⁴ the prevalence of both asthma and skin-test reactivity has increased, whereas in Hong Kong,³⁹ Germany,^{11,12} and Italy,⁵¹ the prevalence of atopy but not of asthma

has increased. In some populations, the prevalence of asthma associated with allergies has increased more than that of nonatopic asthma,⁵⁹ whereas in others the prevalence of the two types of asthma has increased to a similar degree.^{19,24,25} Today it is still not known what factors cause asthma in a person with atopy or what factors cause atopy in a person with asthma.⁶⁰

ENVIRONMENTAL DETERMINANTS OF ASTHMA

Several factors have been proposed to account for the increasing prevalence of asthma. It is agreed that genetic changes in populations would be too slow to account for such a rapid change in prevalence. Most information on the effects of environmental exposures on the risk of asthma comes from cross-sectional studies that do not take temporal changes into account. Robust data linking changes in the environment to changes in the prevalence and incidence of asthma over time are still lacking. Changing environmental exposures may not affect disease prevalence immediately. If exposures exert their effect in utero or early in life, changes in the prevalence of asthma may take more than a generation to become apparent.

EXPOSURE TO TOBACCO SMOKE

Some environmental exposures have rather consistently been shown to influence the incidence of asthma. The most consistent association is that with passive or active exposure to tobacco smoke. A thorough meta-analysis has concluded that parental smoking is very likely to be causally related to acute lower respiratory tract illnesses in infancy and to childhood asthma and wheezing.⁶¹ A number of studies have also shown that active smoking is associated with the onset of asthma in adolescents and adults.⁶²⁻⁶⁴

EXPOSURE TO AIR POLLUTION

There is sufficient evidence to suggest that air pollutants, such as ozone and particulate matter, decrease lung function, trigger exacerbations of asthma, and increase rates of hospitalization for asthma.⁶⁵ Whether air pollution also contributes to the initial development of asthma remains unclear. Because the rates of asthma and atopy in areas of Germany with a high level of exposure to products of coal combustion have been found to be

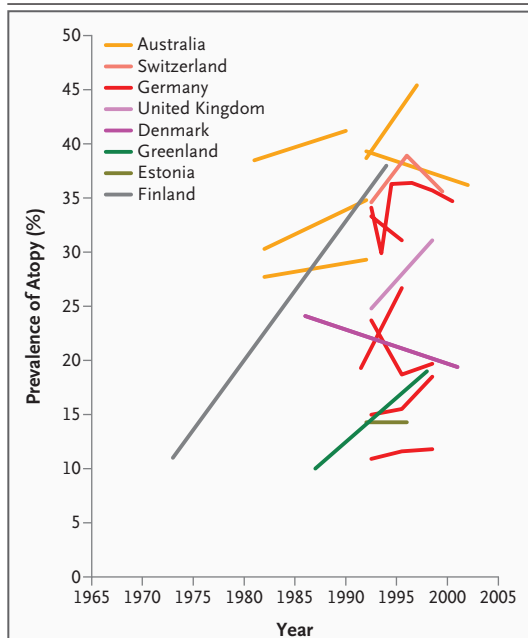


Figure 3. Changes in the Prevalence of Atopy over Time in Children and Young Adults.

The data are from skin-test studies in Australia,^{2-4,55} Germany,¹¹ the United Kingdom,¹⁸ Denmark,⁵⁶ and Estonia³⁰ and from IgE tests in Switzerland,¹⁰ Germany,^{12,14,15} Greenland,⁵⁷ and Finland (in serum samples collected in 1973 and analyzed in 1998).⁵⁸

much lower than those in less polluted areas,⁶⁶ the focus of research has shifted toward pollution from motor vehicles. Children living within 100 to 400 m of motorways^{67,68} or within 50 to 90 m of major roads^{69,70} are at risk for wheezing but not airway hyperresponsiveness.⁷⁰⁻⁷² The proportion of children living in such high-exposure areas, however, is rather small. The overall evidence that exposure to pollution from motor vehicles is a risk factor for asthma is thus relatively weak.

EXPOSURE TO ALLERGENS

Exposure to environmental allergens has been analyzed in numerous studies over the past few decades. It seems likely that the level of exposure to allergens such as house-dust mites and cat dander affects a person's risk for the development of IgE antibodies against these allergens.⁷³ There is, however, more recent evidence to suggest that exposure to house-dust mites early in life is unlikely to be an important risk factor for the onset

of asthma. Several prospective birth-cohort studies have found no association between increased levels of exposure to house-dust mites early in life and various phenotypes of childhood asthma.^{73,74} Furthermore, intervention studies have failed to find convincing evidence of a reduction in the risk of asthma among children 1 to 8 years of age after the implementation of allergen- and food-avoidance strategies.⁷⁵ Some studies have found that exposure to pets early in life actually decreases the risk of asthma, but consistency among studies is lacking.^{76,77} Indoor exposure to allergens may, however, contribute to the persistence of symptoms among children with allergic asthma.⁷⁸

OBESITY AND DIET

Obesity is a major cause of morbidity that has been increasing in prevalence over the past few decades. The parallel trends in the increase of asthma and obesity may indicate a potential link between the conditions. There is increasing evidence relating body-mass index to the prevalence and incidence of asthma in both children and adults, although most consistently in adolescent girls.⁷⁹ It is unlikely that the association is attributable to reverse causation — that is, that people with asthma exercise less because exercise induces symptoms of asthma. Rather, weight gain can antedate the development of asthma. Weight loss by patients with asthma tends to improve lung function.⁷⁹ Potential explanations for the association of obesity and asthma are that the development of both conditions is determined in early life, that mechanical factors promote symptoms of asthma, or that gastroesophageal reflux resulting from obesity induces asthma. Physical inactivity may promote both obesity and asthma. A British study found that trends in overweight and obesity did not explain the increase in the incidence of asthma from 1982 to 1994.⁸⁰ The association between asthma and obesity may therefore be of recent origin, suggesting that recent changes in lifestyle and diet are now associated with both asthma and overweight.⁸⁰

Studies have examined dietary intakes of fruits, vegetables, cereals and starches, various fatty acids, vitamin A, vitamin C, vitamin E, minerals (sodium, magnesium, copper, zinc, and selenium), and antioxidants for possible associations with asthma.⁸¹ Diet is complex and difficult to measure, and standardized tools are still lacking. Variation

in methods of determining the frequency of intake, which individual foods are consumed, eating habits, and serum nutrient levels can introduce substantial misclassification, and the close correlations among the intakes of different nutrients make it difficult to identify independent effects. In cross-sectional surveys, a wide range of nutrients appear to have an effect on asthma outcomes. The evidence from prospective studies and randomized clinical trials, however, is far less consistent and conclusive.⁸² Maternal nutrition during pregnancy may have a role, but data on this subject remain scarce. Intervention studies promoting avoidance of cow's milk and eggs during pregnancy have failed to protect the infants from asthma,⁸³ and breast-feeding also does not protect children from asthma.⁸⁴ Recent studies showing a positive association between breast-feeding and asthma⁸⁴ may reflect adherence to recommendations for children at risk for asthma rather than breast-feeding's being a causal factor for asthma.

EXPOSURE TO INFECTIONS

Over the past decade, the so-called hygiene hypothesis has received much attention. According to this hypothesis, the development of asthma is due in part to a lack of exposure to infections and microbial products early in life. There is widespread evidence that the number of older siblings affects the risk of hay fever and eczema: the risk decreases as the number of older siblings increases.⁸⁵ Whether this effect is attributable to an increase in the number of infections transmitted by unhygienic contact with older siblings remains a matter of debate. Other, unknown factors associated with an increased number of pregnancies may also have a role in the development of atopy, supporting the importance of prenatal exposure for the inception of this condition.

The role of viral infections early in life in the development of asthma has been fiercely debated.⁸⁶ Viruses are potent triggers of exacerbations of asthma, and the inability to restrict the symptoms of rhinovirus infections to the upper respiratory tract may be considered a hallmark of asthma at all ages.⁸⁷ Moreover, infection with respiratory syncytial virus can result in bronchiolitis in infancy, which, if severe, further increases the risk of subsequent wheezing episodes up to school age. Host factors such as reduced lung function and immature immune responses at birth

may contribute to the expression of asthma induced by viral infections. Population-based studies assessing infectious exposure either indirectly, by recording whether a child has attended day care, or directly, by performing serologic tests for viruses (hepatitis A virus and herpes simplex virus) and other microorganisms (*Helicobacter pylori* and *Toxoplasma gondii*), have found that exposure to infectious agents protects against asthma. Chronic infestation with helminths may also confer protection, but short-lived episodes of infestation may exacerbate atopic disorders.⁸⁸ Much of the inverse association between infections and asthma may be attributable to atopy.

EXPOSURE TO MICROBIAL SUBSTANCES IN THE ENVIRONMENT

Microbial exposure may occur primarily in the gut, and antibiotic use may contribute to the inception of asthma by altering the gut microflora. Because asthma-like illnesses, particularly in young children, are still treated with antibiotics in many countries, there is an association between the use of these drugs and the risk of asthma. Only studies taking into account the indication for prescribing antibiotics and the use of antibiotics before the onset of asthma can adequately address the question of the association between antibiotic use and asthma, and studies conducted in this manner have not found such an association.⁸⁶ Likewise, there is no evidence to suggest that vaccination appreciably affects the onset of asthma.⁸⁶ The use of acetaminophen has also been linked to the onset of asthma,⁸⁹ but the effects appear to be small and so far do not justify avoiding exposure to this drug.

Exposure to microbes can occur in the absence of overt infection. Viable germs and nonviable parts of microbial organisms are found in various concentrations in most indoor and outdoor environments. Exposure to environments rich in these substances, such as stables and barns of traditional dairy farms, has consistently been shown to significantly reduce the risk of asthma and atopy.⁹⁰

Differences in the level of microbial exposure may also in part contribute to differences in the prevalence of asthma between urban and rural areas, particularly in developing countries.⁹¹ Furthermore, objective measures of bacterial and fungal exposure have documented inverse asso-

ciations with asthma and wheezing.^{92,93} Endotoxin, which is found in the cell walls of gram-negative bacteria, has two opposing effects: it protects against atopy but is a risk factor for nonatopic asthma and wheezing.⁹³

SYNOPSIS OF FINDINGS

The disparity and heterogeneity of findings in the asthma literature are daunting, reflecting the complex nature of the illness. A basic requirement for the demonstration of a causal relation between a given exposure and a disease is knowledge of the temporal sequence of events. Only exposures occurring before the first symptoms of an illness can influence its inception. In a large proportion of patients, asthma starts in the first years of life. New-onset asthma also occurs during puberty and later in adulthood, but many cases of asthma in adults represent the reappearance of symptoms in persons who were transiently free of problems during adolescence and young adulthood. The environmental exposure causing asthma is likely to be important during fetal life and the early years and during the period before the onset of asthma in adults and adolescents.

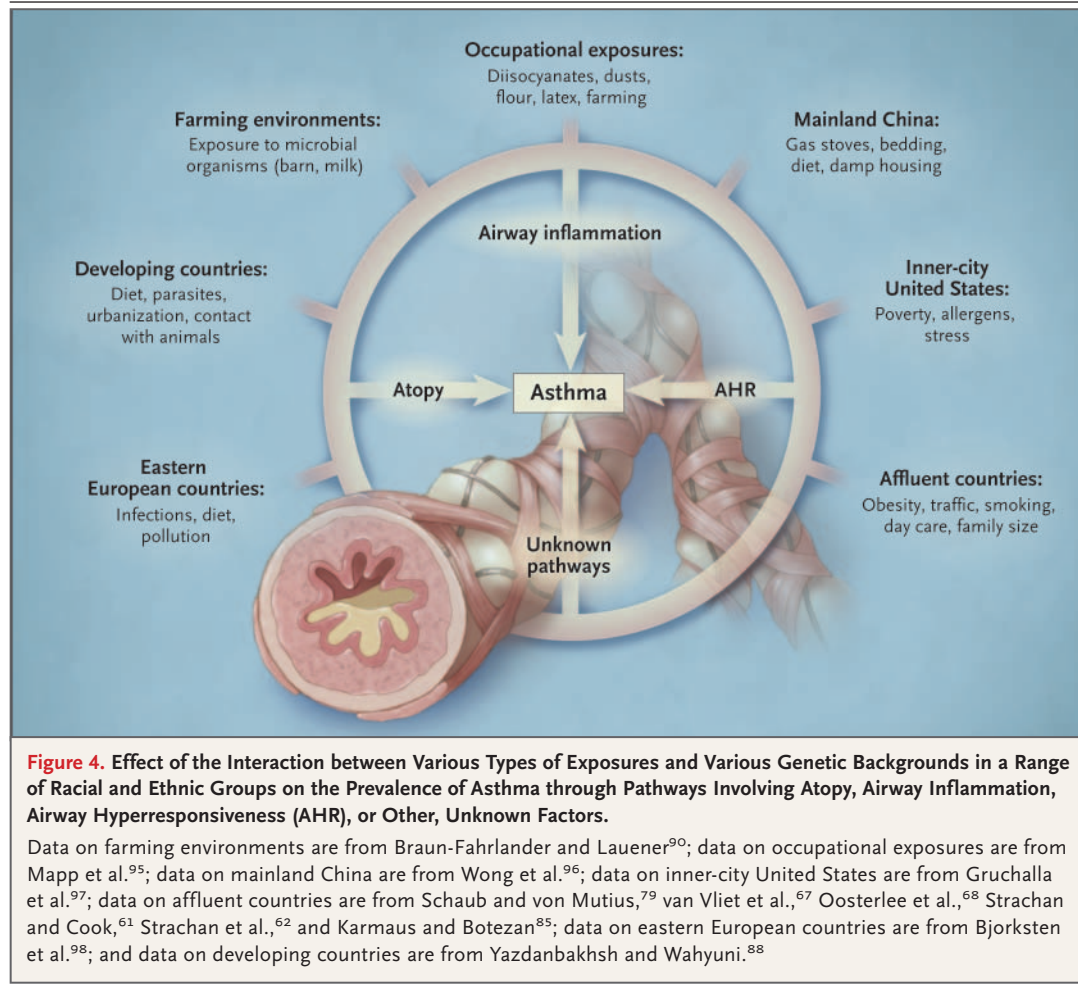
Any potential risk factor must eventually interact with an underlying, genetically determined pathway to result in the manifestation of disease. We do not fully understand the underlying mechanisms of asthma; they are likely to involve both inflammation and control of airway tone and reactivity. Asthma is probably not one illness, but a syndrome. The disease has different phenotypes with respect to its course and prognosis and its association with atopy.⁹⁴ In infants with transient wheezing and in toddlers with nonatopic wheezing, self-limited airway obstruction develops after viral infection, whereas chronic, persistent asthma is more likely to develop in those with IgE-mediated wheezing. Asthma in adults includes phenotypes not seen in childhood, such as aspirin-induced and occupational asthma. However, these different phenotypes cannot readily be distinguished clinically. The disease is analogous to anemia, in which a number of different pathways related to congenital defects, dietary deficiencies, chronic infections, cancers, and autoimmune reactions all result in pallor and fatigue in affected patients.

Another aspect of the causation of asthma is

the context in which exposures occur and interact with a subject's individual pathophysiological pathways. Variation in these pathways is determined by genes. Environmental exposures interact with these pathways, and these interactions can be detected through interactions between genes and the environment. However, these interactions do not occur in isolation. Pathways have more than one component, and the function of each component is determined by the gene or genes contributing to and regulating the processes. Not one but several genes involved in the construction and regulation of pathways are likely to contribute to the expression of a disease. If in fact more than one pathway leads to the development of asthma (as is the case with anemia), then not only many genes with small individual contributions, but also many environmental factors and gene-environment interactions will eventually be found to contribute to disease manifestation. Hence, different contexts in which a number of different exposures interact with various genetic backgrounds in a range of racial or ethnic groups will eventually result in changes in the incidence of asthma as a result of changes in pathways involving atopy, airway inflammation, airway hyperresponsiveness, or other still unknown factors (Fig. 4). The challenge in the years to come will be to integrate complex interactions between multiple exposures and numerous genetic variants to achieve an understanding of the causation of asthma.

CONCLUSIONS AND PRACTICAL IMPLICATIONS

There is evidence that, in some areas of the Western world, the prevalence of asthma may have plateaued. The environmental factors causally driving the temporal changes remain largely unknown. Therefore, there are few truly justified recommendations for the prevention of asthma. Avoidance of passive and active exposure to smoke is warranted for many other health reasons and also for asthma prevention, because the epidemiologic evidence strongly suggests a causal link between exposure to smoke and the onset of asthma. By contrast, many other proposed avoidance strategies, such as reducing allergen levels, implementing changes in diet, withholding vaccinations or treatment with antibiotic and antipyretic agents, administering probiotics, or even exposing



children to pets early in life, are either ineffective or unverified as primary prevention measures. Our view, however, is that the rapid progress in the identification of protective microbial substances has great potential for the development

of prevention strategies to combat the asthma epidemic.

Dr. von Mutius reports receiving consulting or lecture fees from AstraZeneca, DPC Biemann, GlaxoSmithKline, UCB, Merck Sharp & Dohme, and Novartis. No other potential conflict of interest relevant to this article was reported.

REFERENCES

1. Health, United States, 2005. Hyattsville, MD: National Center for Health Statistics, December 8, 2005:63. (Accessed October 30, 2006, at <http://www.cdc.gov/nchs/data/hus/05.pdf>) (page 345.)
2. Peat JK, Haby M, Spijker J, Berry G, Woolcock AJ. Prevalence of asthma in adults in Busselton, Western Australia. *BMJ* 1992;305:1326-9.
3. Toelle BG, Ng K, Belousova E, Salome CM, Peat JK, Marks GB. Prevalence of asthma and allergy in schoolchildren in Belmont, Australia: three cross sectional surveys over 20 years. *BMJ* 2004;328:386-7.
4. Downs SH, Marks GB, Sporik R, Belousova EG, Car NG, Peat JK. Continued increase in the prevalence of asthma and atopy. *Arch Dis Child* 2001;84:20-3.
5. Robertson CF, Roberts MF, Kappers JH. Asthma prevalence in Melbourne schoolchildren: have we reached the peak? *Med J Aust* 2004;180:273-6.
6. Wilson DH, Adams RJ, Appleton SL, et al. Prevalence of asthma and asthma action plans in South Australia: population surveys from 1990 to 2001. *Med J Aust* 2003;178:483-5.
7. Weitzman M, Gortmaker SL, Sobol AM, Perrin JM. Recent trends in the prevalence and severity of childhood asthma. *JAMA* 1992;268:2673-7.
8. Senthilselvan A. Prevalence of physician-diagnosed asthma in Saskatchewan, 1981 to 1990. *Chest* 1998;114:388-92.
9. Senthilselvan A, Lawson J, Rennie DC, Dosman JA. Stabilization of an increasing trend in physician-diagnosed asthma prevalence in Saskatchewan, 1991 to 1998. *Chest* 2003;124:438-48.
10. Braun-Fahrlander C, Gassner M, Grize L, et al. No further increase in asthma, hay fever and atopic sensitisation in ado-

- lescents living in Switzerland. *Eur Respir J* 2004;23:407-13.
11. von Mutius E, Weiland SK, Fritzsche C, Duhme H, Keil U. Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. *Lancet* 1998;351:862-6.
 12. Frye C, Heinrich J, Wjst M, Wichmann HE. Increasing prevalence of bronchial hyperresponsiveness in three selected areas in East Germany. *Eur Respir J* 2001;18:451-8.
 13. Maziak W, Behrens T, Brasky TM, et al. Are asthma and allergies in children and adolescents increasing? Results from ISAAC phase I and phase III surveys in Munster, Germany. *Allergy* 2003;58:572-9.
 14. Heinrich J, Hoelscher B, Frye C, Meyer I, Wjst M, Wichmann HE. Trends in prevalence of atopic diseases and allergic sensitization in children in Eastern Germany. *Eur Respir J* 2002;19:1040-6.
 15. Zollner IK, Weiland SK, Piechotowski I, et al. No increase in the prevalence of asthma, allergies, and atopic sensitization among children in Germany: 1992-2001. *Thorax* 2005;60:545-8. [Erratum, *Thorax* 2006;61:274.]
 16. Burr ML, Butland BK, King S, Vaughan-Williams E. Changes in asthma prevalence: two surveys 15 years apart. *Arch Dis Child* 1989;64:1452-6.
 17. Anderson HR, Ruggles R, Strachan DP, et al. Trends in prevalence of symptoms of asthma, hay fever, and eczema in 12-14 year olds in the British Isles, 1995-2002: questionnaire survey. *BMJ* 2004;328:1052-3.
 18. Barraclough R, Devereux G, Hendrick DJ, Stenton SC. Apparent but not real increase in asthma prevalence during the 1990s. *Eur Respir J* 2002;20:826-33.
 19. Kuehni CE, Davis A, Brooke AM, Silverman M. Are all wheezing disorders in very young (preschool) children increasing in prevalence? *Lancet* 2001;357:1821-5. [Erratum, *Lancet* 2001;358:846.]
 20. Devenny A, Wassall H, Ninan T, Omran M, Khan SD, Russell G. Respiratory symptoms and atopy in children in Aberdeen: questionnaire studies of a defined school population repeated over 35 years. *BMJ* 2004;329:489-90.
 21. Upton MN, McConnachie A, McSharry C, et al. Intergenerational 20 year trends in the prevalence of asthma and hay fever in adults: the Midspan family study surveys of parents and offspring. *BMJ* 2000;321:88-92.
 22. Ng Man Kwong G, Proctor A, Billings C, et al. Increasing prevalence of asthma diagnosis and symptoms in children is confined to mild symptoms. *Thorax* 2001;56:312-4.
 23. Rizwan S, Reid J, Kelly Y, Bundred PE, Pearson M, Brabin BJ. Trends in childhood and parental asthma prevalence in Merseyside, 1991-1998. *J Public Health (Oxf)* 2004;26:337-42.
 24. Skjongsberg OH, Clench-Aas J, Leegaard J, et al. Prevalence of bronchial asthma in schoolchildren in Oslo, Norway: comparison of data obtained in 1993 and 1981. *Allergy* 1995;50:806-10.
 25. Nystad W, Magnus P, Gulsvik A, Skarpaas JJ, Carlsen KH. Changing prevalence of asthma in school children: evidence for diagnostic changes in asthma in two surveys 13 yrs apart. *Eur Respir J* 1997;10:1046-51.
 26. Selnes A, Nystad W, Bolle R, Lund E. Diverging prevalence trends of atopic disorders in Norwegian children: results from three cross-sectional studies. *Allergy* 2005;60:894-9.
 27. Brogger J, Bakke P, Eide GE, Johansen B, Andersen A, Gulsvik A. Long-term changes in adult asthma prevalence. *Eur Respir J* 2003;21:468-72.
 28. Haahtela T, Lindholm H, Bjorksten F, Koskenvuo K, Laitinen LA. Prevalence of asthma in Finnish young men. *BMJ* 1990;301:266-8.
 29. Rimpela AH, Savonius B, Rimpela MK, Haahtela T. Asthma and allergic rhinitis among Finnish adolescents in 1977-1991. *Scand J Soc Med* 1995;23:60-5.
 30. Riikjarv MA, Annus T, Braback L, Rahu K, Bjorksten B. Similar prevalence of respiratory symptoms and atopy in Estonian schoolchildren with changing lifestyle over 4 yrs. *Eur Respir J* 2000;16:86-90.
 31. Annus T, Riikjarv MA, Rahu K, Bjorksten B. Modest increase in seasonal allergic rhinitis and eczema over 8 years among Estonian schoolchildren. *Pediatr Allergy Immunol* 2005;16:315-20.
 32. Emeryk A, Chojna E, Bartkowiak-Emeryk M, Postepski J. Prevalence of asthma and some respiratory symptoms in the years 1995 and 2001 in schoolchildren from rural regions of Poland. *Ann Agric Environ Med* 2004;11:63-6.
 33. Ronchetti R, Villa MP, Barreto M, et al. Is the increase in childhood asthma coming to an end? Findings from three surveys of schoolchildren in Rome, Italy. *Eur Respir J* 2001;17:881-6.
 34. Ciprandi G, Vizzaccaro A, Cirillo I, Crimi P, Canonica GW. Increase of asthma and allergic rhinitis prevalence in young Italian men. *Int Arch Allergy Immunol* 1996;111:278-83.
 35. Garcia-Marcos L, Quiros AB, Hernandez GG, et al. Stabilization of asthma prevalence among adolescents and increase among schoolchildren (ISAAC phases I and III) in Spain. *Allergy* 2004;59:1301-7.
 36. Goren AI, Hellmann S. Changing prevalence of asthma among schoolchildren in Israel. *Eur Respir J* 1997;10:2279-84.
 37. Auerbach I, Springer C, Godfrey S. Total population survey of the frequency and severity of asthma in 17 year old boys in an urban area in Israel. *Thorax* 1993;48:139-41.
 38. Wang XS, Tan TN, Shek LP, et al. The prevalence of asthma and allergies in Singapore: data from two ISAAC surveys seven years apart. *Arch Dis Child* 2004;89:423-6.
 39. Lee SL, Wong W, Lau YL. Increasing prevalence of allergic rhinitis but not asthma among children in Hong Kong from 1995 to 2001 (Phase 3 International Study of Asthma and Allergies in Childhood). *Pediatr Allergy Immunol* 2004;15:72-8.
 40. Wong GW, Leung TF, Ko FW, et al. Declining asthma prevalence in Hong Kong Chinese schoolchildren. *Clin Exp Allergy* 2004;34:1550-5.
 41. Lee YL, Lin YC, Hwang BF, Guo YL. Changing prevalence of asthma in Taiwanese adolescents: two surveys 6 years apart. *Pediatr Allergy Immunol* 2005;16:157-64.
 42. Hong SJ, Lee MS, Sohn MH, et al. Self-reported prevalence and risk factors of asthma among Korean adolescents: 5-year follow-up study, 1995-2000. *Clin Exp Allergy* 2004;34:1556-62.
 43. Carter ER, Debley JS, Redding GJ. Changes in asthma prevalence and impact on health and function in Seattle middle-school children: 1995 vs 2003. *Ann Allergy Asthma Immunol* 2005;94:634-9.
 44. Heinrich J, Richter K, Magnussen H, Wichmann HE. Is the prevalence of atopic diseases in East and West Germany already converging? *Eur J Epidemiol* 1998;14:239-45.
 45. Mommers M, Gielkens-Sijstermans C, Swaen GM, van Schayck CP. Trends in the prevalence of respiratory symptoms and treatment in Dutch children over a 12 year period: results of the fourth consecutive survey. *Thorax* 2005;60:97-9.
 46. Anderson HR, Butland BK, Strachan DP. Trends in prevalence and severity of childhood asthma. *BMJ* 1994;308:1600-4.
 47. Venn A, Lewis S, Cooper M, Hill J, Britton J. Increasing prevalence of wheeze and asthma in Nottingham primary schoolchildren 1988-1995. *Eur Respir J* 1998;11:1324-8.
 48. Frank PI, Wicks PD, Hazell ML, et al. Temporal change in the prevalence of respiratory symptoms and obstructive airways disease 1993-2001. *Br J Gen Pract* 2005;55:596-602.
 49. Linehan MF, Hazell ML, Frank TL, Frank PI. Prevalence of respiratory symptoms in under 5s: 1993 to 2001. *Arch Dis Child* 2005;90:516-9.
 50. Aberg N, Hesselmar B, Aberg B, Eriksson B. Increase of asthma, allergic rhinitis and eczema in Swedish schoolchildren between 1979 and 1991. *Clin Exp Allergy* 1995;25:815-9.

51. Verlato G, Corsico A, Villani S, et al. Is the prevalence of adult asthma and allergic rhinitis still increasing? Results of an Italian study. *J Allergy Clin Immunol* 2003;111:1232-8.
52. Robertson CF, Heycock E, Bishop J, Nolan T, Olinsky A, Phelan PD. Prevalence of asthma in Melbourne schoolchildren: changes over 26 years. *BMJ* 1991;302:1116-8.
53. Asher M, Montefort S, Björkstén B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733-43.
54. van Schayck CP, van Der Heijden FM, van Den Boom G, Tirimanna PR, van Herwaarden CL. Underdiagnosis of asthma: is the doctor or the patient to blame? The DIMCA project. *Thorax* 2000;55:562-5.
55. Peat JK, van den Berg RH, Green WF, Mellis CM, Leeder SR, Woolcock AJ. Changing prevalence of asthma in Australian children. *BMJ* 1994;308:1591-6.
56. Thomsen SF, Ulrik CS, Larsen K, Backer V. Change in prevalence of asthma in Danish children and adolescents. *Ann Allergy Asthma Immunol* 2004;92:506-11.
57. Krause T, Koch A, Friborg J, Poulsen LK, Kristensen B, Melbye M. Frequency of atopy in the Arctic in 1987 and 1998. *Lancet* 2002;360:691-2.
58. Kosunen TU, Hook-Nikanne J, Salomaa A, Sarna S, Aromaa A, Haahtela T. Increase of allergen-specific immunoglobulin E antibodies from 1973 to 1994 in a Finnish population and a possible relationship to *Helicobacter pylori* infections. *Clin Exp Allergy* 2002;32:373-8.
59. Russell G, Helms PJ. Trend in occurrence of asthma among children and young adults: reporting of common respiratory and atopic symptoms has increased. *BMJ* 1997;315:1014-5.
60. Priftanji A, Strachan D, Burr M, et al. Asthma and allergy in Albania and the UK. *Lancet* 2001;358:1426-7.
61. Strachan DP, Cook DG. Health effects of passive smoking. 6. Parental smoking and childhood asthma: longitudinal and case-control studies. *Thorax* 1998;53:204-12.
62. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ* 1996;312:1195-9.
63. Larsson L. Incidence of asthma in Swedish teenagers: relation to sex and smoking habits. *Thorax* 1995;50:260-4.
64. Withers NJ, Low L, Holgate ST, Clough JB. The natural history of respiratory symptoms in a cohort of adolescents. *Am J Respir Crit Care Med* 1998;158:352-7.
65. Tatum AJ, Shapiro GG. The effects of outdoor air pollution and tobacco smoke on asthma. *Immunol Allergy Clin North Am* 2005;25:15-30.
66. von Mutius E, Martinez FD, Fritzsche C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994;149:358-64.
67. van Vliet P, Knape M, de Hartog J, Janssen N, Harssema H, Brunekreef B. Motor vehicle exhaust and chronic respiratory symptoms in children living near freeways. *Environ Res* 1997;74:122-32.
68. Oosterlee A, Drijver M, Lebrecht E, Brunekreef B. Chronic respiratory symptoms in children and adults living along streets with high traffic density. *Occup Environ Med* 1996;53:241-7.
69. Venn AJ, Lewis SA, Cooper M, Hubbard R, Britton J. Living near a main road and the risk of wheezing illness in children. *Am J Respir Crit Care Med* 2001;164:2177-80.
70. Nicolai T, Carr D, Weiland SK, et al. Urban traffic and pollutant exposure related to respiratory outcomes and atopy in a large sample of children. *Eur Respir J* 2003;21:956-63.
71. Janssen NA, Brunekreef B, van Vliet P, et al. The relationship between air pollution from heavy traffic and allergic sensitization, bronchial hyperresponsiveness, and respiratory symptoms in Dutch schoolchildren. *Environ Health Perspect* 2003;111:1512-8.
72. Hirsch T, Weiland SK, von Mutius E, et al. Inner city air pollution and respiratory health and atopy in children. *Eur Respir J* 1999;14:669-77.
73. Lau S, Illi S, Sommerfeld C, et al. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. *Lancet* 2000;356:1392-7.
74. Cullinan P, MacNeill SJ, Harris JM, et al. Early allergen exposure, skin prick responses, and atopic wheeze at age 5 in English children: a cohort study. *Thorax* 2004;59:855-61.
75. Simpson A, Custovic A. Allergen avoidance in the primary prevention of asthma. *Curr Opin Allergy Clin Immunol* 2004;4:45-51.
76. Remes ST, Castro-Rodriguez JA, Holberg CJ, Martinez FD, Wright AL. Dog exposure in infancy decreases the subsequent risk of frequent wheeze but not of atopy. *J Allergy Clin Immunol* 2001;108:509-15.
77. Ownby DR, Johnson CC. Does exposure to dogs and cats in the first year of life influence the development of allergic sensitization? *Curr Opin Allergy Clin Immunol* 2003;3:517-22.
78. Illi S, von Mutius E, Lau S, Niggemann B, Grüber C, Wahn U. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. *Lancet* 2006;368:763-70.
79. Schaub B, von Mutius E. Obesity and asthma, what are the links? *Curr Opin Allergy Clin Immunol* 2005;5:185-93.
80. Chinn S, Rona RJ. Can the increase in body mass index explain the rising trend in asthma in children? *Thorax* 2001;56:845-50.
81. Ellwood P, Asher MI, Björkstén B, Burr M, Pearce N, Robertson CF. Diet and asthma, allergic rhinoconjunctivitis and atopic eczema symptom prevalence: an ecological analysis of the International Study of Asthma and Allergies in Childhood (ISAAC) data. *Eur Respir J* 2001;17:436-43.
82. McKeever TM, Britton J. Diet and asthma. *Am J Respir Crit Care Med* 2004;170:725-9.
83. Falth-Magnusson K, Kjellman NI. Allergy prevention by maternal elimination diet during late pregnancy — a 5-year follow-up of a randomized study. *J Allergy Clin Immunol* 1992;89:709-13.
84. Friedman NJ, Zeiger RS. The role of breast-feeding in the development of allergies and asthma. *J Allergy Clin Immunol* 2005;115:1238-48.
85. Karmaus W, Botezan C. Does a higher number of siblings protect against the development of allergy and asthma? A review. *J Epidemiol Community Health* 2002;56:209-17.
86. von Mutius E. Infection: friend or foe in the development of atopy and asthma? The epidemiological evidence. *Eur Respir J* 2001;18:872-81.
87. Corne JM, Marshall C, Smith S, et al. Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. *Lancet* 2002;359:831-4.
88. Yazdanbakhsh M, Wahyuni S. The role of helminth infections in protection from atopic disorders. *Curr Opin Allergy Clin Immunol* 2005;5:386-91.
89. Allmers H. Frequent acetaminophen use and allergic diseases: is the association clear? *J Allergy Clin Immunol* 2005;116:859-62.
90. Braun-Fahrlander C, Lauener R. Farming and protective agents against allergy and asthma. *Clin Exp Allergy* 2003;33:409-11.
91. Keeley DJ, Neill P, Gallivan S. Comparison of the prevalence of reversible airways obstruction in rural and urban Zimbabwean children. *Thorax* 1991;46:549-53.
92. van Strien RT, Engel R, Holst O, et al. Microbial exposure of rural school children, as assessed by levels of N-acetylmuramic acid in mattress dust, and its

association with respiratory health. *J Allergy Clin Immunol* 2004;113:860-7.

93. Eder W, von Mutius E. Hygiene hypothesis and endotoxin: what is the evidence? *Curr Opin Allergy Clin Immunol* 2004;4:113-7.

94. Martinez FD. Links between pediatric and adult asthma. *J Allergy Clin Immunol* 2001;107:Suppl 5:S449-S455.

95. Mapp CE, Boschetto P, Maestrelli P, Fabbri LM. Occupational asthma. *Am J Respir Crit Care Med* 2005;172:280-305.

96. Wong GW, Ko FW, Hui DS, et al. Factors associated with difference in prevalence of asthma in children from three cities in China: multicentre epidemiological survey. *BMJ* 2004;329:486.

97. Gruchalla RS, Pongracic J, Plaut M, et

al. Inner City Asthma Study: relationships among sensitivity, allergen exposure, and asthma morbidity. *J Allergy Clin Immunol* 2005;115:478-85.

98. Bjorksten B, Dumitrescu D, Foucard T, et al. Prevalence of childhood asthma, rhinitis and eczema in Scandinavia and eastern Europe. *Eur Respir J* 1998;12:432-7.

Copyright © 2006 Massachusetts Medical Society.