

Searching for the cause of the increase in asthma

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The prevalence of asthma has increased dramatically over the last 30 years, and the clearest evidence for the increase has come from population-based studies of school-aged children and young adults. The strongest established risk factors for asthma are family history and sensitization to one or more indoor allergens. Some studies suggest that the increase in asthma has been part of an overall increase in atopic disease. The American data, however, suggest that hay fever was already common in 1960. Thus the primary increase has been in wheezing among allergic children. It seems unlikely that increases in mite, cockroach, and domestic animal allergens have been sufficient to explain the scale or the consistency of the increase in asthma prevalence. The challenge is to identify a change that could have increased inflammation of the lungs or lowered the threshold for wheezing.

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Abbreviations

ISAAC International Study of Asthma and Allergies in Childhood

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The increase in the prevalence of asthma over the last half of the 20th century is striking in both its magnitude and its consistency [1]. Increases have been documented in many countries, including Europe, Australia, Japan, and the United States, and where reliable figures are available it appears that the prevalence has increased steadily from 1960 to 1995. Despite intensive investigation, there is no consensus about the cause or causes of the increase. Investigations into the effects of air pollution, childhood immunization, increasing antibiotic use, and dietary changes have not provided convincing explanations for such an increase. All population-based studies of children of school age have found a strong association between sensitization to indoor allergens and asthma [2-5,6•]. Therefore, it is likely that most of the increase in asthma is among atopic individuals. However, there are major differences in the perception of whether this is part of a general increase in atopy or a specific increase in asthma. In keeping with this, many of the hypotheses have assumed that the primary phenomenon has been a change in immune responsiveness. Other investigators suggest that the increase is primarily in wheezing. This could be explained either by a progressive increase in exposure to those perennial indoor allergens that cause asthma or by progressive loss of some as yet undefined factor that protects the lungs from wheezing, even in the presence of atopy.

Data supporting an increase

The earliest evidence for an increase in the prevalence of asthma was reported in 1971, based on observations of school children in Birmingham, England, first in 1956 and again in 1968 [7]. Similar increases have been reported in the United States, and more recent work has suggested that the increase is persisting into the 1990s [8-12]. The scale of the increase is too large to be explained by increased sensitivity to the diagnosis either by patients or physicians. In Finland, for instance, records have been kept since the 1920s on all 19-year-old men entering compulsory military service, and these records show a 20-fold increase in asthma since 1960 [13]. Despite the uniformity of the evidence about increasing prevalence, a recent paper in the *British Medical Journal* sheds doubt on the evidence that there has been an increase. Magnus and Jaakkola [14] analyzed 16 studies published from 1983 through 1996. All 16 studies showed increases in lifetime asthma, current asthma, current wheezing, or all three conditions. Despite these results, the authors concluded that the measures used in these studies were "susceptible to systematic errors" [14]. They argued that the increases could be attributed to changes in labeling, public percep-

tion, and awareness of the disease among professionals. However, they excluded from their analysis the Finnish army studies [13], those by Peat and her colleagues in Australia [5], and analyses of hospital admission data [15]. They also ignored the evidence that asthma remains very rare in "rural" areas of Africa, Australia, and Papua New Guinea. Overall there is very strong evidence that asthma has become a common disease in Western society and considerable evidence that the increase has occurred between 1960 and the present. We believe the increase in asthma is real and that data to support the belief will continue to accumulate.

The International Study of Asthma and Allergies in Childhood (ISAAC) has published its initial data on the worldwide prevalence of asthma, allergic rhinoconjunctivitis, and eczema [16•]. The group found wide variation in the prevalence of these disorders. Asthma was most common in the United Kingdom, New Zealand, Australia, and Ireland. Asthma was least prevalent in Eastern Europe, China, Taiwan, and India. Overall, asthma correlated strongly with allergic rhinoconjunctivitis ($r=0.75$, $P<0.0001$) and atopic eczema ($r=0.74$, $P<0.0001$), confirming that an allergic diathesis is associated with asthma. Though the ISAAC study provides a useful baseline for future analyses of increasing asthma prevalence, it tells us little about the increase in asthma that has already taken place. Furthermore, it provides no evidence to show that allergic rhinoconjunctivitis or eczema has risen in parallel with asthma, only that the two conditions are associated at a single point in time.

Butland *et al.* [17•] recently reported that the prevalence of hay fever and eczema doubled in the United Kingdom between 1974 and 1986. In the United States, hay fever prevalence was documented at 10% to 20% in the 1960s [18], whereas a recent national survey found that the prevalence of hay fever is still around 10% [19]. Clearly, hay fever is not a new problem in the United States, but epidemic asthma is.

What factors in Western society could explain both the wide difference in prevalence between developed and underdeveloped countries and the increase in asthma prevalence in the West from 1960 onwards? Diet has been heavily scrutinized, with blame placed on diets consisting mainly of processed foods that are high in sodium, high in fat, and low in antioxidants. Early studies in adults found a correlation between salt intake and both bronchial reactivity and asthma symptoms [20]. A subsequent, larger, case-control study in children showed an association between salt intake and airway reactivity, although there was no association with clinical asthma [21]. Still other studies have shown increased bronchial reactivity in subjects with low dietary intake of antioxidants as well as in subjects who consumed a more traditional Western diet compared with an Asian diet [22,23]. While diet may

influence bronchial reactivity, the effects of diet on clinical asthma are not as clear. In addition, changes in diet over the last 40 years have not been the same in the different parts of the world where asthma incidence has increased.

To the lay observer, air pollution is the most obvious factor that could influence asthma, but analyses of air pollution as a factor in the increase have shown little or no correlation [24,25]. In fact, air quality has improved in both the United States and Great Britain since the 1960s, while asthma prevalence and severity have increased [26,27]. Similarly, studies examining direct exposure to automobile exhaust and asthma prevalence have failed to find a relationship [28]. The most persuasive evidence against air pollution as a factor in the increase comes from analyses of asthma prevalence in Western Europe as compared with Eastern Europe. Asthma prevalence is lower in the polluted cities of Eastern Europe than in their Western counterparts [29]. A recent large study of 10 cities in Switzerland with different degrees of industrialization and air pollution also failed to find any relationship between reported asthma and residence in places with more polluted air [30•]. On the other hand, there are several reports of allergic rhinitis associated with living near heavily trafficked streets [31,32]. Moreover, recent report from Taiwan suggested that there was increased asthma prevalence in a polluted industrial area [33•]. However, a closer analysis of the data suggests that wheezing was not more common [34]. Overall, it seems that air pollution may contribute to respiratory symptoms, but there is very little evidence connecting objective evidence of asthma or bronchial hyperreactivity with increases in air pollution.

Relevance of indoor allergens to the increase in asthma

The first reports of an increase in asthma came from countries such as Holland and England, where dust mites were the dominant allergen associated with asthma [7]. Evaluating the reported increases in 1980, it was obvious that many of the changes in houses that had occurred over the period between 1950 and 1975 would have improved conditions for mite growth. This led logically to the view that increases in asthma could be a direct consequence of increased allergens inside houses and more time spent indoors. It is very important to recognize that there were two parts to this argument: the first was the evidence that exposure to dust mite or other allergens could be an important cause of asthma; the second is the argument that increasing exposure to dust mite allergens was an important cause of the *increase* in asthma. Several recent developments have strengthened the evidence that indoor allergens are an important cause of asthma, but these same observations also suggest that increasing exposure to allergens may not be the primary cause of the increase in asthma prevalence.

Following the first reports of an increase in asthma, similar changes were reported from other areas where mites were important, such as Australia, New Zealand, and Japan. However, in these areas where houses had become tighter, warmer, and more heavily furnished, the increases in prevalence have continued for almost 20 years after the changes in houses were "completed" (*ie*, 1975–1995). High levels of mite and mite allergens were present in houses in England as early as 1978, and it is not clear that further increases in allergen levels have occurred since then [35,36].

During the 1980s, a high prevalence of asthma, or documented increases in the disease, was reported from areas of the world where housing is too dry for dust mite growth. In these areas, such as Northern Scandinavia and the mountain states of the United States, the dominant allergens associated with asthma are those derived from domestic animals [4,37].

The high prevalence and severity of asthma among black children in the United States has become very obvious in the last 20 years, although it is not clear when the increase began. Hospitalization rates and mortality rates in this minority group are among the highest in the world, with evidence coming from national figures and also from individual cities, such as Philadelphia, Chicago, Atlanta, and New York [26,38]. These areas have strikingly different housing conditions and climates and, in keeping with that, the relevant allergens are different. In Atlanta, both mite and cockroach allergens are significant [39]. In the Northern cities, cockroach appears to be the single most important allergen, judged by the combination of exposure and sensitization [40,41•].

Considering the evidence in 1998, it is clear that the increase in asthma among school-aged children is predominantly among children who are allergic to indoor allergens. However, at least three sources of allergens are involved: dust mites, the German cockroach, and domestic animals. Although exposure to all indoor allergens may have increased because children spend more time indoors, it is very difficult to argue that several different sources of indoor allergens have increased in parallel over more than 30 years.

What has really happened

The current status of our understanding of the asthma epidemic is truly enigmatic. Most of the changes that have been considered as causes of the increase are unconvincing. Thus evidence about changes in diet, air pollution, viral infections, vaccination, family size, or antibiotic use cannot explain changes of the magnitude that have been observed and are not supported by clear mechanistic evidence about their contribution to asthma. By contrast, exposure to indoor allergens is a very convincing cause of asthma [42]. While it is always difficult to evaluate the

independent role of genetics and environment, a large twin study from Australia concluded that indoor allergens are likely to be direct environmental causes of asthma [43•]. Despite the consistency of the data about indoor allergens, it is not likely that progressive increases in mite, cat, and cockroach allergen exposure have occurred in so many different countries over this time period. Thus it is essential to step back and ask what other changes in Western society could be relevant. For this argument, it is clearly essential to decide whether we are looking for the cause of an increase in atopy in general or the cause of a specific increase in wheezing.

We have chosen to focus on the increase in asthma because this disease leads to the most obvious and severe clinical results, including emergency room visits, hospitalization, and mortality, because asthma, rather than any other allergic disease, has increased among black children, and because we are not convinced by the evidence that immune responsiveness has changed over this period of time. The question is, are there other changes in Western society that could have an impact on the lungs?

Recently, the pediatric literature has been dominated by reports of decreasing physical activity and increasing body mass among American children and adolescents [44–48]. The question is whether decreased physical activity, for which obesity is a surrogate measure, could directly influence asthma. There is abundant pulmonary literature establishing that full expansion of the lungs can decrease lung resistance. There is also experimental evidence that exercise is good for asthmatics. In general, it is very difficult to separate the epidemiologic evidence about obesity, diet, and exercise. However, the Surgeon General's report in 1996 concluded that increasing obesity among teenagers had occurred over a 10-year period when caloric intake had decreased [49]. In addition, several studies have demonstrated a direct correlation between obesity and hours spent in passive, visual entertainment [45].

If asthma has increased in developed countries over the period when physical activity has declined, what has happened to communities where physical activity has not changed? The data show that in villages where walking remains the normal form of transport, asthma is still rare. In Papua New Guinea, rural Africa, Aboriginal Australia, and among Inuit Eskimos, asthma is uncommon [50–52,53•,54•]. By contrast, the ISAAC study found evidence of epidemic asthma in all developed, urbanized communities. If, as we believe, the dietary changes are unconvincing and the air pollution data both weak and mechanistically unconvincing, then changes in physical exercise may be the most obvious change that could have affected the lungs. The recent study comparing rural villagers in Ethiopia with residents of the city of Jimma provides very striking evidence for a different relationship between atopy and

wheezing in these two areas [54•]. The investigators found that the prevalence of atopy (as judged by positive skin tests) was significant in both rural and urban areas, but none of the mite-allergic individuals in the rural areas reported having asthma or wheezing. It could be inferred from this study that one of the consequences of westernization is that allergy becomes a risk factor for asthma. Put another way, we would suggest that much of the change that has occurred in Europe and the United States since 1960, or is occurring today, as nations move from a traditional lifestyle to modern urban life, can be seen as the progressive loss of a lung-specific protective effect against asthma. In any analysis of this kind, it is important to distinguish between routine physical activities such as walking or playing and "exercise" designed to achieve fitness. Aggressive exercise, such as wind sprints, is the surest way to trigger exercise-induced asthma. By contrast, gradual or repeated activity (associated with spontaneous play among children) is similar to the regimens that can help to minimize exercise-induced asthma [55,56].

Prior to 1980, the image of a typical asthmatic child was middle-class, studious, and thin. In the United States today, asthma is more common and more severe among low-income families, and an increasing number of these children are overweight. Luder *et al.* [57•] found that children in New York who had a body mass index greater than the 85th percentile were significantly more likely to have a peak expiratory flow rate less than 60% predicted and to have been prescribed asthma medicines. Given that body mass index is related to both diet and exercise, it is now reasonable to ask whether the progressive decline in physical exercise, which is particularly severe among inner-city children, has played a role in the rise in asthma. In most areas of the world, asthma is not more common among poor children. But poor areas of cities in the United States are among the most violent in the world, with the consequence that parents encourage their children to stay indoors. The result is both an increase in exposure to indoor allergens and a further decrease in routine physical activity. It is our view that the rise in indoor entertainment characterizes the life of children in American cities more than any other change in the last 40 years. The fact that most of these children spend 3 or 4 hours per day sitting, when previously they were playing outdoors, should be considered in any analysis of the asthma epidemic.

References and recommended reading

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Using the protocol that has previously been applied to a middle school in New Mexico (see Sporik *et al.* [4]), the authors surveyed 1054 children and identified 135 with symptoms of asthma. Detailed study of these children identified 48 who had bronchial reactivity. The study confirmed the significance of sensitization to mite, cat, or cockroach, or any combination, in an area where these allergens were commonly present in houses. Using multiple regression analysis, it was found that total serum IgE, sensitization to pollens, passive smoke, and social class did not contribute to the risk of asthma or symptoms.

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The ISAAC survey used written and video questionnaires to study 463,801 children aged 13 to 14 years in 155 centers in 56 countries. The investigators found wide variation, both between different countries and within countries. In the United Kingdom, for example, asthma prevalence ranged from 20% to 37%, depending on the center. Wide variation in asthma prevalence in countries with multiple study centers speaks to the difficulty of collecting such data and to probable regional variations. Unfortunately, in countries with a single study center, that center was used to represent data for the entire country, which may not reflect country-wide prevalence.

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