

The environmental influence on childhood asthma

Authors' affiliations:

B. Björkstén, University Hospital, Linköping, Sweden

Correspondence to:

Professor B. Björkstén
Division of Paediatrics
Department of Health and Environment
University Hospital
S-581 85 Linköping
Sweden
Fax: +46-13 14 82 65

The pathogenesis of allergy depends on the interaction between the time and amount of allergen exposure and the presence of nonspecific "adjuvant" factors in genetically susceptible individuals. There seems to be a period in early life during which the individual is particularly susceptible to sensitization, and there are variations in susceptibility over time. Allergens are almost ubiquitous, but the relative importance of the individual allergens varies between regions. In many temperate regions, house-dust mites used to be absent but are now more common. This may be due to modern methods of building houses. Differences in the prevalence of a particular allergy cannot explain variations in the prevalence of allergy in general. Various environmental factors that may enhance sensitization include tobacco smoke, NO₂, SO₂, ozone, and diesel particles. Passive smoking is by far the best established risk factor, particularly in early childhood. The indoor environment probably plays a larger role than outdoor air pollution in the development of allergic disease. The mother is not only a source of genetic information, but also an "environmental factor", as there is a close immunologic interaction between the mother and her offspring, mediated through the placenta and the breast milk, which may affect the likelihood of allergic disease. The concepts of "lifestyle" and "environment" should be expanded to include, for example, dietary changes, the microbial environment, and extensive traveling, as all the currently suspected risk factors taken together can only explain a small proportion of the geographic differences in and increasing prevalence of allergy. The future search for significant environmental factors should be interdisciplinary and be directed toward areas that have not yet been explored, thus giving "lifestyle" a broader interpretation.

There is now an almost universal consensus that the prevalence of allergic diseases has increased considerably

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in the Western industrialized countries, particularly since World War II (1, 2). The reasons for this increase have obviously to be looked for in the environment, and several potential risk factors have been identified. However, even if all factors that are known to affect the incidence of allergic manifestations are combined, this would only partly explain the increase.

The pathogenesis of allergy is multifactorial, and depends on the interaction between the time and amount of allergen exposure and the presence of nonspecific "adjuvant" factors, including air pollution, in genetically susceptible individuals. Environmental factors that influence the development of allergic disease are either specific or nonspecific. It is also common knowledge that psychological factors may trigger, or at least aggravate, clinical manifestations of allergic disease; whether they could also enhance sensitization to allergens is not known.

Experimental, epidemiologic, and clinical observations strongly support the concept that the conditions under which the primary encounter with an allergen takes place influence the immune response; i.e., whether tolerance or sensitization is triggered (3). Thus, the conditions under which an allergen is encountered in infancy may have consequences for many years, and perhaps even for life. If this is true, the prevalence in adults would continue to increase for many years, even after the institution of effective allergy-preventive measures in childhood.

Political changes in Europe have opened the formerly socialist countries of Central and Eastern Europe to epidemiologic studies. The prevalence of allergic diseases among children and young adults is low in these countries (4, 5). As the lifestyle is similar in many respects to that prevailing in Western Europe 30–40 years ago, comparative studies between Eastern and Western Europe may reveal new insights into the recent changes in the environment that have caused the increased prevalence in the West.

This review discusses some environmental factors that may affect the incidence of sensitization to allergens with an emphasis on factors encountered in early childhood.

Variations in susceptibility

The likelihood of developing allergic disease in an individual is not constant over time, even if the general propensity is genetically determined. Thus, the risk of sensitization is affected by the duration of exposure to allergens and the conditions under which exposure takes place. There seems to be a period in early life during which an infant is

particularly susceptible to sensitization (1, 3). A higher incidence of allergy to birch and grass pollen has been reported in children born in the spring (6); similar increases have been reported in the prevalence of grass allergy in British children born in the spring (7) and of ragweed allergy in North Americans born in the late summer (8).

This relationship between season of birth and development of allergy seems to be limited to children with a congenital propensity to develop allergic disease (9). Similarly, early feeding with foreign proteins is associated with an increased risk of allergic disease, but mainly in genetically susceptible individuals (1).

Animal studies and clinical observations have indicated that stress alters the immune response, as measured by various laboratory tests of inflammatory responses, immunoglobulin production, and cell-mediated immunity (10). It is well established that psychological factors influence the severity of asthmatic symptoms and allergic reactions in affected patients, but little is known regarding a possible adjuvant effect on the sensitization process.

Variations in individual susceptibility to sensitization over time may also partly be explained by the presence and absence of respiratory tract infection. However, the role of infections in the respiratory tract as risk factors for the development of childhood allergic disease and asthma is complex. While it is well established that infections may trigger and aggravate asthma in already sensitized individuals, and that infections increase bronchial hyperreactivity, they may also possibly downregulate Th2-like immune responses early in life, as discussed more in detail elsewhere in this supplement by Holt *et al.*

Allergens

In order to develop an allergy, the individual has obviously to be exposed to the allergen. Allergens are present in almost every part of the world, but the relative importance of individual allergens varies, depending on climatic conditions. In temperate and subarctic regions, such as the Scandinavian countries, house-dust mites used to be absent, but there is now evidence of their increasing prevalence (11, 12). This may, at least partly, be due to the modern technology used to build houses and energy-conservation measures. Such differences and geographic differences may explain why certain allergies are common in a region, but they may not explain the large differences in the prevalence of allergy in general.

Table 1. Some examples of changes in "lifestyle" and environment after World War II in industrialized countries with market economy that may possibly have affected incidence of sensitization to allergens

Urbanization:	Major changes in habits, exposure to air pollution
Diet:	Foods that are new to area, wider range of foods, food additives, foods processed by industry, altered intestinal microbial flora
Buildings:	New building materials, more efficient insulation, altered methods for construction, construction all year round even in temperate climates, leading to increased humidity
Homes:	Larger dwellings, many new chemical compounds in home environment, increased indoor humidity in temperate and cold climates
Lifestyle:	Most time spent indoors, extensive traveling and exposure to new environments

As already indicated, there is a period in early childhood during which exposure to inhalant allergens may result in the development of allergy several years later. Thus, early contact with pollen, pets, and house-dust mites and early feeding with foreign proteins all appear to be associated with an increased risk of the development of allergic disease (13). A high concentration of allergens in the home of a neonate, particularly if there is a family history of allergy, may thus increase the risk of clinical manifestations of allergy to that allergen several years later.

The fact that exposure to high levels of allergens early in life appears to be a risk factor for sensitization and allergic manifestations later in life has prompted studies of the possible effects of allergy prevention (for review, see reference 14). Such approaches have included the supplementation of cow's milk-based formulas with extensively hydrolyzed products and extensive measures to avoid exposure to certain inhalant allergens such as pets and house-dust mites. The results of these studies indicate only a modestly reduced incidence of sensitization to the particular allergens that were avoided. From current knowledge of the kinetics of the primary immune responses, it is not reasonable to expect a general preventive effect by the avoidance of certain allergens, but merely a possibly delayed sensitization to that particular allergen. Thus, the level of allergen exposure early in life does not seem to be a major risk factor, and certainly cannot explain the increasing prevalence of these diseases.

Pre- and perinatal risk factors

The mother is not only a source of genetic information but also a major environmental factor for her offspring during gestation. For example, administration of the β -receptor blocking agent propranolol during the first trimester of pregnancy may be associated with an increased risk of allergy in the children (15). This observation is interesting since β -receptor blockade may enhance IgE antibody formation in animals (16). Furthermore, there is a close immunologic interaction between the mother and her offspring, through the placenta and the breast milk. Relatively little is known

about the exchange of immunologic information. There are indications, however, that allergen-specific immune responses may be present already at birth; i.e., that the immune responses were induced during fetal life (17). It is not known to what extent these responses are protective or may indicate sensitization and future allergy.

Human milk is another source of immunologic information that may be transferred from the mother to her offspring. Besides numerous components providing protection against infection, human milk contains components that enhance the maturation of the immune system of the neonate (18). Observations include an early stimulation of IgA-antibody synthesis in breast-fed infants and transfer of cell-mediated immunity and cytokines. Thus, human milk not only provides passive protection against infections, but also actively stimulates infant immunity. There are considerable individual variations in the composition of human milk, however, a fact which suggests that maternal immunity may represent an environmental factor influencing the risk of allergic manifestations in the child, possibly even several years later (19).

Nonspecific, environmental factors ("adjuvants")

The results of some epidemiologic studies lend support to a relationship between air pollution and an increased incidence of sensitization to inhalant allergens. Compounds shown to enhance sensitization in animal models include tobacco smoke, NO₂, SO₂, and ozone, as well as diesel particles (10). It is not entirely clear exactly how the adjuvants act. Possibly, an inflammatory reaction is induced in the airways, facilitating the penetration of allergens and enhancing antigen presentation.

While the relationship between air pollution (with the exception of tobacco smoke in early childhood) and sensitization is still, to some extent, open to debate, it is well known that various air pollutants may trigger clinical symptoms in an individual who is already sensitized and hyperreactive. It is also well established that allergic asthma is more easily triggered when allergen exposure is combined with air pollution.

Table 2. Epidemiologic observations related to allergic diseases of confirmed or probable significance for understanding risk factors in environment*General*

Sensitization often triggered early in life.

Industrialized countries with market economy

Prevalence higher in urban than in rural areas.

Prevalence higher in northern than in southern Scandinavia.

Increasing prevalence over 20th century, particularly last 40 years.

Increase first observed in privileged socioeconomic groups.

Increase most obvious in children and young adults.

Regional differences can only to a small extent be explained by air pollution, respiratory infections, and breast-feeding practice.

Developing countries

Highest prevalence among privileged socioeconomic groups.

Increasing prevalence with increasing industrialization.

Tobacco smoke

Passive smoking is by far the best identified risk factor for the development of allergic disease. This is particularly true in early childhood and is independent of how allergy is defined. There is now convincing evidence that daily exposure to tobacco smoke results in an increased risk of developing wheezy bronchitis, asthma, and bronchial hyperreactivity in children (20). An association between passive smoking and an increased risk of sensitization to environmental allergens has also been demonstrated in many clinical studies, as well as in animal experiments (20). Moreover, passive smoking results in increased morbidity, increased need for medical treatment, and increased use of asthma medication in asthmatic children. Exposure to maternal smoking seems to have the largest effects, possibly because the mother is the parent more often at home with the child. The long-term effects of childhood exposure to tobacco smoke are unknown. As the number of cigarette-smoking young women has steadily increased in the Western industrialized countries over the last 40 years, passive smoking early in life may be one of the factors behind the increasing prevalence of allergy. Exposure to tobacco smoke is also a risk factor for respiratory symptoms in children living in Eastern Europe, but it cannot explain the differences between Eastern and Western Europe.

Indoor environment

It has conventionally been assumed that air pollution primarily occurs outdoors. A number of studies have shown, however, that indoor concentrations of some pollutants may be far in excess of the outdoor concentrations (21). There is probably no air outdoors that is as polluted as that in a room where people are smoking. In many countries, outdoor air pollution has decreased over the past decades. Furthermore, there is no clear relation between air pollution and the

prevalence of allergy. On the contrary, Swedish studies have reported a higher prevalence of allergy in the northern, less polluted part of the country than in the southern, more industrialized parts (22). Similar results have been reported from Finland and Norway. Therefore, the indoor environment probably plays an equally large, or even larger, role in the development of allergic sensitization and the appearance of allergic disease in the sensitized individual.

Modern, well-insulated houses have been associated with an increased risk of the development of allergic manifestations, as well as with sensitization. In temperate climates, where house-dust mites used to be scarce, the increased humidity in modern energy-saving homes has resulted in an increased prevalence of mite allergy. In a large epidemiologic study, comprising 5300 children living in a defined geographic area, it was found that living near an air-polluting paper-pulp plant, living in damp homes, and having smoking parents were all strong risk factors for allergic disease (23). This relationship was particularly pronounced in children with a family history of allergy. Children living in a damp home and having smoking parents had an increased prevalence of asthma compared with children not exposed to these risk factors. This was particularly obvious in children with a family history of allergy, of whom 22 % had manifest asthma if exposed to the two risk factors.

Psychological factors

The family interaction is often disturbed in the families of asthmatic children, and family therapy can improve the asthma. A prospective study investigated whether the disturbed family interaction is a primary finding or a consequence of disease (24). The study included the families of 100 infants with a strong family history of allergy. When the children were 3 and 18 months old, the entire family participated in a standardized family test assessing the ability to adapt to changing circumstances (adaptability) and the balance between emotional closeness and distance (cohesion). An unbalanced family interplay was common at 3 months (37%), but it was not predictive of respiratory illness. At 18 months, a dysfunctional interaction was significantly more common in families of children with eczema and obstructive symptoms than in families of healthy children. The study indicates that a dysfunctional family interaction is the result rather than a cause of recurrent wheezing in infancy.

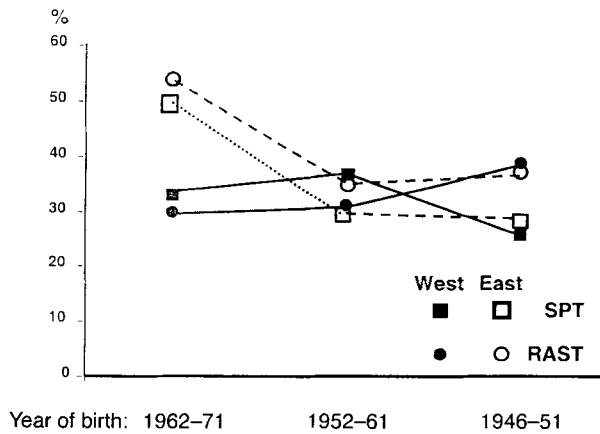


Figure 1. Prevalence of positive skin prick tests and circulating IgE antibodies to allergens among adults in former East and West Germany in relation to year of birth (29).

Recent changes in the environment

The environment has undergone major changes. The discussion on the possible impact of the various environmental changes on the incidence of asthma and other allergies has mostly been limited to the possible effects of deteriorating air quality, poorly ventilated houses, and increased exposure to certain allergens, notably house-dust mites. "Environment" is much more than emissions from traffic and exposure to mites, however. The concept of "lifestyle" should therefore be expanded considerably (Table 1), since an altered lifestyle also includes dietary changes, the microbial environment, extensive traveling to new environments, stress, and much more.

Any hypothesis to explain a decisive connection between a certain environmental factor and manifestations of atopy should accommodate a number of certain or probable facts from previous research (Table 2). It is also necessary to define precisely the relationship, e.g., *when*, and on *whom* the factor is exerting its effect, and to define *which* outcome variables are studied, e.g., obstruction or asthma, according to certain defined criteria, clinical symptoms, or the appearance of IgE antibodies. Does the relationship include primary sensitization or only manifestations of disease? Is the relationship similar in rural and urban areas, in all social classes, and independently of other lifestyle factors? Is there an interaction between several environmental factors?

Geographic differences

Several studies of individuals belonging to the same ethnic group, but living under different conditions, clearly demon-

strate that the prevalence of allergic disease is higher in industrialized countries than in rural areas or developing countries. There are considerable differences in the prevalence of allergy within industrialized countries; i.e., between urban and rural areas. For example, the relative risk of a positive skin prick test is 70% higher among 11-year-old children living in a moderately polluted town in northern Sweden than among children living in the neighboring countryside (4, 25).

Studies comparing the prevalence of atopy in different environments are complicated by the lack of uniform diagnostic criteria and standardized procedures. Recently, however, international questionnaire surveys have provided comparative prevalence figures in adults and in children. The International Study of Asthma and Allergy in Children (ISAAC) confirmed that the prevalence of symptoms related to allergy, e.g., wheezing, rhinoconjunctivitis in the absence of an infection, and flexural dermatitis, were all much more common in Western Europe, even in rural regions with very little air pollution such as Finnish Lapland, than in the formerly socialist countries of Central and Eastern Europe, including heavily industrialized cities in Poland, Estonia, Latvia, and Russia (26).

The reported differences between populations are not genetically determined. Instead, they seem to be explained by differences in living conditions. The results of migrant studies demonstrate a higher prevalence of allergic disease in developing countries in people living under privileged conditions than among the poor. Thus, a low prevalence of asthma was observed in children migrating to the UK from the West Indies with their parents, while the prevalence of asthma in the younger children in these families, who were born in the UK, was similar to that of native British children (27). A South African study yielded similar results, in that children of the Xhosa tribe who were born in a rural area had much less asthma and allergy than Xhosa children raised in Cape Town (28).

The hypothesis that early childhood is a period of particular susceptibility to environmental influences, and the onset of the "atopic march" is supported by studies showing that the large differences between East and West Germany in the prevalence of sensitization to inhalant allergens are limited to the age groups born after 1961 (Fig. 1) (29), and the increase in Sweden seems largely to have occurred in people born from 1960 onward (1). These findings are supported by similar observations comparing Estonia and Sweden and by a Swedish study indicating that the major increase in the prevalence of atopy-related

diseases (but not contact dermatitis) among Swedish conscripts has occurred among those born after 1960 [30].

In addition to the introduction of many new chemicals into the environment, there have been many changes in lifestyle in industrialized countries over the past decades. The type of foods eaten has changed dramatically with the introduction of new industrial products with numerous additives. Even fresh foods differ in many respects from those available only a few decades ago. For example, the storage time of food has been much prolonged by genetic manipulation and the use of various chemical compounds. Virtually nothing is known regarding the possible influence on childhood allergy of such changes in dietary components.

Concluding remarks

The prevalence of allergies is increasing in many countries and the increase appears mostly to be a consequence of the

lifestyle characteristic of Western industrialized countries. The major lifestyle and environmental factors probably exert much of their influence during the first few years of life. Numerous risk factors have been identified which can all influence the likelihood of sensitization and trigger symptoms in already sensitized individuals. Even if they are all taken together, however, they cannot explain the large geographic differences in the prevalence of allergy. The conclusion from a broad compilation of what is known regarding triggers of allergy is that we cannot identify the environmental factors that are primarily responsible for the large increase in prevalence in recent years. However, we can make a list of various conditions that are *not* of major significance. The future search for significant environmental factors should be directed toward other areas that have not yet been explored. Future research should be truly interdisciplinary, and "lifestyle" should be given a broad interpretation.

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