

Food allergy: what can be done to prevent progression to asthma?

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Objectives: The primary objective of this review is to discuss risk factors for asthma development in food allergen-sensitized children. In the paper we discuss the possible measures to prevent progression to asthma by allergen and other adjuvant factor avoidance.

Data Sources: A review from literature of articles on these topics was performed.

Study Selection: Relevant publications on asthma risk factors and implementation of protective factors were critically evaluated.

Results: Children with familiar history of atopy and sensitization to food proteins in early infancy are at high risk of subsequent respiratory allergic diseases and require specific prevention. Because early allergic sensitization is a significant risk factor for later development of asthma, prevention of asthma by early allergen avoidance is mandatory in high-risk children. Adjuvant factors such as tobacco smoke and mold exposure may act as nonspecific triggers for the development of atopy. The role of protective factors such as infections in early life, breast-feeding, a "healthy" diet needs to be evaluated in prospective studies. Pharmacologic intervention with antihistamines led to significant reduction in incidence of asthma in high-risk children, but confirmatory longitudinal studies in large populations are necessary.

Conclusions: There is now accumulating evidence that preventing exposure to house-dust mite may significantly reduce the prevalence of childhood asthma. However, allergen avoidance can not be recommended as the only strategy. Avoidance of adjuvant factors and implementation of potential protective factors aimed to reduce the risk to progression to asthma need to be evaluated in prospective studies.

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INTRODUCTION

There has been a dramatic increase in the prevalence of asthma over the last few decades, particularly in industrialized countries.^{1,2} This increase in prevalence has been reported in children^{3,4} and in young adults,^{5,6} but not in adults.⁷ Further, asthma shows its peak of incidence in the first 1 to 4 years of life.⁸ This points toward the importance of childhood years for the development of asthma and, consequently, for the implementation of strategies aimed at its prevention early in life.

Two major factors are critical to the development of asthma: the individual's genetic background and the environment. The genes for asthma have not been completely identified. Thus, environmental factors seem to be the critical factors that can be controlled. Potentially preventable environmental factors for childhood asthma include exposure to allergens,^{9,10} parental smoking,¹¹ and lack of breast-feeding^{12,13} and several dietary factors including antioxidants and omega fatty acids.¹⁴⁻¹⁶

There are different levels of prevention: *primary prevention*, which is aimed at a population that is still healthy but at risk of the disease and *secondary prevention* aimed at children who have not yet had a definite phenotype (allergic

airway manifestation), but have markers indicating a high risk of subsequent disease manifestation such as children with sensitization to food protein in infancy or atopic dermatitis.

RISK FACTORS FOR ASTHMA DEVELOPMENT

Identification of young children at high risk of developing the disease is an important public health priority. Parental history of asthma and the presence of eczema and food allergy have been demonstrated to be major risks for the development of asthma.¹⁷ Sensitization to food allergens develops first and is followed by development of sensitivity to inhalant allergens, which is a strong determinant of asthma.^{18,19} In children followed up from birth, risk factors for sensitization to indoor and/or outdoor allergens at the age of 3 years were 1) a positive family history and 2) the presence of hen's egg-specific immunoglobulin (Ig)E antibodies (≥ 0.35 kU/L) at the age of 12 months.¹⁹ Egg-specific IgE >2 kU/L in combination with a positive family history of atopy were highly specific (specificity 99%) and predictive (positive predictor value, 78%) markers for sensitization to inhalant allergens at 3 years of age.¹⁹ In the same cohort twice as many children who, at the age of 7 years, presented bronchial hyperresponsiveness (BHR) and asthma were sensitive to food allergens at the age of 1 year compared with nonasthmatic children.²⁰ Further, the children persistently sensitized for more than 1 year to food allergens had a 5.5-fold higher risk for developing asthma than infants who were only transiently food sensitized.²¹ It has been confirmed very recently in another birth

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cohort, that sensitization to dietary allergens occurred in infancy and waned after early childhood, but it predicted the early sensitization to inhalant allergens and persistence of asthma up to the age of 22 years.²²

Thus, sensitization to food allergens during early childhood is related to development of IgE-mediated hypersensitivity to inhalant allergens and development of allergic asthma in children and adults. Therefore, persistent milk and egg sensitivity has to be regarded as a high risk factor for subsequent development of respiratory symptoms.

In addition to parental family history of asthma and food sensitization, other risk factors are wheezing without colds and allergic rhinitis¹⁷ and eosinophilia or normal eosinophil count during viral infection.²³ During viral infections, in fact, there is usually a decrease of the number of circulating eosinophils.²³ All these young infants are in a high-risk group and should be considered for preventive measures against respiratory atopy.

EARLY SENSITIZATION TO INHALANT ALLERGENS AND ASTHMA

Considering risk factors the relevance of the variable considered may be expressed as relative risk (RR) or odds ratio (OR). The RR estimates the risk of the variable considered in comparison to normals. The OR indicates significant evidence of a relationship between variables.

In Australian schoolchildren it has been shown that early onset (before the age of 8 years) of atopy is an important risk factor for BHR, diagnosed asthma, and continuing symptoms of wheeze, and it is a particularly important risk factor for BHR with current wheeze in later childhood years.²⁴ This was confirmed in other studies. In children enrolled in the Tucson epidemiology study of obstructive diseases, it has been documented that sensitization to any allergen before age 8 years was significantly more likely associated with shortness of breath with wheeze (OR = 4.1), wheeze apart from colds (OR = 3.88), and wheeze most days (OR = 2.83).²⁵ Further, the German Multicenter Allergy Study demonstrated that only those children sensitized to any allergen early in life and sensitized to inhalant allergens by the age of 7 years were at a significantly increased risk of being asthmatic patients at this age (OR = 10.12).²⁶ In a randomized followup study in infants less than 2 years of age who had been hospitalized for infection associated with wheezing and followed up for 3 years, it has been observed that skin prick test positivity at the age of 16 months significantly predicted asthma (RR = 9.5) 3 years after wheezing in infancy.²⁷ In a cohort of asthmatic children studied at 7-year intervals up to the age of 35 years, it has been documented that the presence of an atopic condition in childhood increases the odds for more severe asthma also in adult life.²⁸

The results of these studies clearly indicate that early allergic sensitization is a significant risk factor for later development of asthma. For these reasons it is important to start inhalant allergen avoidance early in life with the aim to prevent or at least delay sensitization. Avoidance measures

comprising mite-proof covers for parental bed, high-filtration vacuum cleaner, vinyl flooring in infant's bedroom, new crib, and portable crib mattresses encased in mite-proof material have been demonstrated to achieve and maintain a low mite allergen environment during pregnancy and in the first year of life in homes of infants at risk of atopy.²⁹

ALLERGEN AVOIDANCE

The aim to alter the natural incidence of atopic illness and the progression of the allergic march from food allergy to respiratory allergy and asthma by avoiding specific foods during early life did not prove to be effective.^{30,31} However, the principal foods included in prevention studies were milk, eggs, and nuts, foods that do not show cross-reactivity with inhalant allergens responsible for asthma. In a recent cross-sectional and case-control analysis, it was shown that the introduction of cereals in the diet of children, especially wheat before 4 months of age, is a risk factor for subsequent development of grass-pollen asthma (OR = 5.95).³² The percentage of asthmatic patients sensitized to grass-pollen among these fed with an early cereal diet was 84.4% and among the patients who were breast-fed was only 15.2%.³² An intake of cereals in diet during early life might cause IgE sensitization to cereals, which cross-react with grass pollen. Of course, prospective studies are necessary to evaluate the effects of different cereals such as rice and wheat. A delayed introduction of solid foods is however recommended also for the prevention of atopic dermatitis.³³

Only the early avoidance of specific indoor allergens has been demonstrated to be effective in reducing specific sensitization and development of wheezing (primary prevention).³⁴⁻³⁶ A prospective study performed in the Isle of Wight demonstrated that avoidance of inhaled allergens in infancy protects against the development of allergic disorders and wheezing at the age of 12 months.³⁴ The preventive effect on asthma development declined at ages of 2 and 8 years, and it was no longer significant in this group of 120 high-risk children.^{35,37} At the age of 8 years, wheezing was present in 27% of children in the control group compared with 14% of the children in the active group ($P = 0.07$).³⁷ However, if these data are extrapolated from this small sample to population levels, the result remains extremely important.³⁸ Further, environmental manipulation, aimed at reducing allergen exposure during pregnancy and during the first year of life, significantly reduced the risk of severe wheeze with shortness of breath (RR = 0.44), wheezing after vigorous playing, crying, or exertion (RR = 0.18) and reduced the prescribed medication for the treatment of wheezy attacks (RR = 0.58) in the active treated group in comparison to placebo-treated subjects.³⁶ The preventive effect of indoor allergen avoidance on development of mite sensitivity and wheezing has been demonstrated in infants with atopic dermatitis and food allergy (secondary prevention).^{39,40} In a study mite-blocking bedding encasing made from microfine fibers significantly reduced mite allergen exposure in the active group compared with placebo group (0.77 $\mu\text{g/g}$ dust vs 3.0 $\mu\text{g/g}$ dust, $P <$

0.001). In the 1-year followup, this prevented this high-risk group of children from becoming sensitized to mites (positive skin prick tests to mites in 31% vs 63%, $P < 0.02$) and from consequent wheezing (11% vs 37%, $P < 0.05$).³⁹

In another study of children, a reduction of indoor allergen exposure by introducing mattress encasings, eliminating wall-to-wall carpets, avoiding damp housing conditions by increasing ventilation, and avoiding furred pets at home has been demonstrated to be a meaningful intervention for secondary prevention.⁴⁰ Of course, primary and secondary prevention is difficult and can not be limited to inhaled allergen avoidance.⁴¹ It must be implemented with other strategies aimed at avoiding concomitant adjuvant risk factors and increasing exposure to potential protective factors.⁴²

AVOIDANCE OF ADJUVANT FACTORS

Environmental Tobacco Smoke (ETS)

Parental smoking either before or immediately after birth is unlikely to increase the risk of allergic sensitization in children.⁴³ However, childhood asthma associated with ETS exposure very likely differs from asthma associated with atopy.⁴⁴ Recent studies indicated some adverse effects of ETS exposure during the first few years of life on repeated wheeze during the first year of life⁴⁵ and asthma development in school-aged children.^{46,47} Childhood exposure to ETS is associated with an increased prevalence of asthma among adult never-smokers, especially in nonatopic subjects.⁴⁸ Further, ETS may potentiate the effect of allergen exposure in subjects already sensitized. Children with a history of atopic dermatitis were much more likely to have asthma if their mother was a smoker than if she was a nonsmoker (79% vs 52%; $P = 0.001$).⁴⁹

Independently of all these considerations, because children exposed to ETS are more likely to become smokers and because tobacco use kills 2.5 times as many people each year as alcohol and drug abuse combined, it is imperative that pediatricians play an active role in preventing both exposure to tobacco and tobacco use.⁵⁰

Mold Exposure

Exposure to molds during childhood may be a significant etiologic factor in allergic respiratory diseases in general.⁵¹ In a study performed in locations in former West and East Germany, dampness and visible molds were reported significantly more often for East German apartments (10.3%) versus West German (1.9%, OR = 5.85).⁵² Dampness and visible molds were associated with a higher frequency of both general sensitizations (40.6% vs 27.6% in unaffected homes) and specific sensitization to house-dust mites (OR = 3.7), to cat (OR = 3.19), and to mugwort pollen (OR = 2.86).⁵² Similar evidence has shown that the occurrence of sensitization to common environmental allergens (atopy) and new allergic diseases significantly increased among schoolchildren after starting school in a water-damaged school building compared with those attending a nondamaged school.⁵³

Exposure to molds may have complex immunogenetic effects that may act as a nonspecific trigger for allergic sensitization leading to the development of atopy (Fig 1).⁵⁴ A polymerase compound (1→3)- β -D-glucan presents in the cell wall structure of fungi may block the beneficial effect of endotoxin on the maturation of the immune system interfering with the link between endotoxin and its receptor CD-14 on macrophages.⁵⁴

Vaccinations

The role of vaccinations in the development of atopic disorders is particularly important and must be treated on scientific grounds and with a rational approach to avoid possible manipulations by groups operating outside the scientific community. A recent study showed that positive tuberculin responses in schoolchildren correlated with a lower prevalence of atopic disorders.⁵⁵ This was, however, not confirmed by other studies.^{56,57} Further, Bacille Calmette-Guerin (BCG) vaccination in early infancy is not associated with a subsequently decreased risk of atopic sensitization or allergy.^{58,59} Thus, BCG vaccination can not be recommended as a potential strategy to prevent asthma development even if intranasal administration of *Mycobacterium bovis* BCG has been demonstrated to suppress airway eosinophilia and BHR in an animal model of atopic asthma, and therefore, other studies are necessary.⁶⁰

Transient production of IgE antibodies to pertussis toxin has been demonstrated after pertussis immunization; however, randomized clinical trials involving both whole cell and acellular pertussis vaccines have failed to show any enhancement of atopic manifestations in children.⁶¹⁻⁶³ Further, in a case-control study of children aged 7 to 9 years there was no significant association between having polio vaccination, hepatitis B vaccination, or measles/mumps/rubella vaccination and asthma.⁶⁴ Therefore, there seems to be no reason for withholding scheduled vaccinations from infants, irrespective of family history of allergy.

IMPLEMENTATION OF PROTECTIVE FACTORS

The lack of protective factors which may enhance the development of tolerance toward environmental allergens early in life might also increase the risk for asthma.

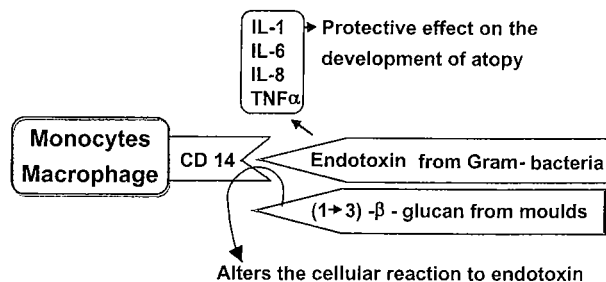


Figure 1. The effect of endotoxins and molds on the maturation of immune system.

Infections

Several cross-sectional studies support the notion of a potential protective effect of early-life infections on the development of atopy and asthma later in childhood.⁶⁵ In this context, particularly interesting is the preventive effect of daycare exposure early in life on the development of atopy and asthma, as it has the potential to be used as a preventive strategy. We can not prescribe an older sibling, but we can suggest early admission to daycare centers. In a cross-sectional study of children ranging in age between 5 and 14 years, it has been shown that entering day nursery in the first year of life was associated with a lower risk of positive skin prick test, but children attending daycare after the second year of life did not similarly benefit.⁶⁶ Another cross-sectional study in a large number of children 6 to 7 years old having attended a daycare center was a risk factor for transient early wheezing, but resulted to be a protective factor for late-onset wheezing.⁶⁷ These results have been confirmed in a prospective study: attendance in daycare in the first 6 months of life was associated with a significant lower risk of atopy and asthma over the 13-year followup period.⁶⁸

Thus, daycare exposure before 1 year of age mimics the presence of older siblings with consequent multiple infections. Further, it is very likely that daycare attendance is associated with increased physical activity, which is another potentially protective factor.⁶⁹ Of course, the protective effect of early daycare needs to be prospectively evaluated in children who have already developed food allergy. In this case, training of nursery and school staff needs to be implemented to prevent the potential risk of anaphylaxis⁷⁰ and deal with it appropriately in an emergency.^{71,72}

Diet

Consumption of vegetables and fresh fruits had declined in the United Kingdom as atopic diseases have risen.¹⁴ At the same time in many western countries there has been an increase in the consumption of omega-6, linoleic acid-containing foods, such as margarine, whereas the consumption of omega-3 fatty acids, that are present in high amounts in fish oil, has diminished.⁷³ There is now some evidence that eating a diet poor in antioxidants (ie, fresh fruits and vegetables) and rich in fats increase the risk of wheeze and BHR.⁷⁴

In relation to fish oil consumption, it is noteworthy that the prevalence of asthma is very low among the Inuit who have a high intake of fish oils,⁷⁵ and that diagnosed asthma is less common in Australian children who ate salmon, tuna, and sardines than children eating other types of food.⁷⁶ On the contrary, high dietary intake of polyunsaturated omega-6 fats is associated with increased risk (OR = 2.03) of asthma in preschool children.⁷⁷ Polyunsaturated fatty acids and antioxidants may have complementary roles in the pathogenesis of asthma. A diet low in vegetables and in vitamin E has been shown to increase the risk of asthmatic symptoms in Saudi Arabian school children.⁷⁸ In a study of 2,650 children aged 8 to 11 years from the United Kingdom, it has been shown that consuming fresh fruit more than once a day is associated

with a forced expiratory volume in 1 second of 88 mL greater than that of children who never ate fresh fruit.⁷⁹ Further, in a cross-sectional population study comparing subjects with BHR and those without, the lowest tertile of intake of vitamin C was associated with a sevenfold increase in risk of having increased reactivity.⁸⁰ In a longitudinal study the risk of adult onset asthma increased almost fivefold in subjects with the lowest tertile of intake of vitamin E and doubled in relation to low vitamin C intake.⁸¹ The explanation for these relationships is the following (Fig 2). Linoleic acid is a precursor of arachidonic acid, which, in turn, is a precursor of prostaglandin E₂, which presents inhibitory effect on the production of interferon- γ and a tendency to increase the production of interleukin (IL)-4. Omega-3 fatty acids compete with omega-6 as a substrate for several enzymes thus reducing the production of prostaglandin E₂.⁸² Throughout their effects on glutathione/glutathione peroxidase metabolic pathway, antioxidants may decrease the secretion of IL-4 by human T cell clones and the secretion of IgE by human peripheral blood mononuclear cells co-cultured with IL-4.⁸³

Of course, prospective studies evaluating food supplementation with omega-3 fatty acids and with antioxidants are needed to evaluate their potential preventive effect in children who have already developed food-specific sensitivity. This is particularly important as there is no evidence of any effect of fish oil when asthma is already established.⁸⁴ Thus, we need to know what happens when the allergic march has already started. Further, the effect of a healthy diet rich in fresh fruits and vegetables means more than a simple supplementation with different vitamins and this may explain the conflicting results of intervention studies of vitamin supplementation.⁸⁵ Also, the effect of omega-3 fish-derived oil might be different from that of an omega-3 plant-derived oil. Omega-3 fatty acids derived from fish oil have been proven to be more effective in improving IL-2 production from monkey T cells in response to mitogens than plant-derived omega-3 polyunsaturated fatty acids.⁸⁶ This clearly expresses the complexity

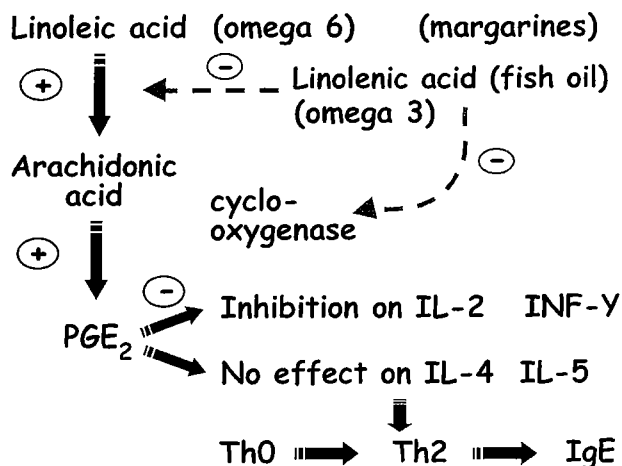


Figure 2. Polyunsaturated fatty acids and atopy.

of issues linked to asthma development and prevention. Further, the potential contamination of fish oils with toxic chlorine must be evaluated before starting fish oil supplementation in the infant diet.

Breast-feeding

In a long-term prospective followup study until 17 years of age, breast-feeding was prophylactic against atopic diseases, including atopic eczema, food allergy, and respiratory allergy throughout childhood and adolescence.⁸⁷ A recent meta-analysis of 12 prospective studies that evaluated the association between exclusive breast-feeding during the first 3 months after birth confirmed the protective effect of breast feeding (summary OR = 0.70) on the development of asthma during childhood.⁸⁸ However, it was reported that the relationship between breast-feeding and asthma or recurrent wheeze varies with the age of the child and the presence or absence of maternal asthma and atopy in the child.⁸⁹ Although associated with protection against recurrent wheeze early in life (OR = 0.45), breast-feeding is associated with an increased risk of asthma and recurrent wheeze beginning at the age of 6 years, but only for atopic children with asthmatic mothers (OR = 5.7).⁸⁹ This effect was less evident for breast-feeding under 4 months. Breast milk of atopic mothers appears to have a higher omega-6/omega-3 ratio than milk of nonatopic mothers.⁹⁰ Further atopic mothers have higher levels of IL-4, IL-5, IL-8, IL-13, and RANTES.⁹¹ Because of the different composition of the breast milk of atopic and nonatopic mothers, it seems possible that children who have inherited their atopic predisposition from the mother will not benefit from the possible allergy-protecting effect of the breast milk, whereas, by contrast, children whose fathers are atopic might be protected.⁹²

Prospective studies are needed in breast-fed infants with food allergy and with an atopic mother on the opportunity to continue with breast milk or to switch to an appropriate formula feeding. This, of course, is not the case with a nonatopic mother.

THE USE OF DRUGS

Prevention of adult asthma by early intervention during childhood may potentially be attempted by the use of drugs capable of blocking the progression from trivial allergy to persistent asthma.⁹² There is limited information in this regard and this only in the case of antihistamines which may have additive anti-inflammatory effects in addition to the H₁-receptor blocking activity. In a 1-year followup study of 121 infants with atopic dermatitis without history of asthma (cough and/or wheezing), ketotifen or placebo has been administered. Asthma was observed in 13.1% of the ketotifen group and in 41.6% of the placebo group ($P < 0.001$).⁹³ In another study, 100 infants with a family history of major allergy and elevated serum IgE levels (but with no history of bronchial obstruction) were treated with either ketotifen or placebo over a 3-year period. At the end of 3 years, 9% of the infants who received ketotifen had developed asthma. This was the case in 35% of the children receiving placebo ($P = 0.003$).⁹⁴

More recently and in a larger cohort of young children with atopic dermatitis and positive family history for atopy, cetirizine led to a significant reduction in the incidence of asthma in a subgroup that had early sensitization to grass pollen or house-dust mites.^{95,96} Further, the treatment was not associated with any side effects. Cetirizine has been shown to inhibit eosinophil trafficking in the skin, nose, lungs, and conjunctiva,⁹⁷ and to inhibit upregulation of adhesion molecule 1⁹⁸ and release of IL-8 from proinflammatory cytokine-stimulated human epithelial cells.⁹⁹ Thus, it is possible that the mechanism of action of cetirizine is through prevention of eosinophil and neutrophil trafficking into the airway as a key component of the inflammation that is associated with asthma and infantile wheezing.⁹⁶ Confirmatory studies are necessary¹⁰⁰ before this type of intervention can be generally recommended.

CONCLUSION

We have now accumulated evidence that preventing exposure to house-dust mites has the potential to significantly reduce the prevalence of childhood asthma. The apparently small effects observed in prospective avoidance trials make a large difference to the total burden of asthma in the community.³⁸ However, allergen avoidance can not be recommended as the only strategy, as large-scale epidemiologic studies have provided evidence about other environmental risk or potentially protective factors. Interventional studies aimed to implementing the protective factors as well as reducing exposure to risk factors will help clarify the interrelationship of different environmental conditions.

It is reasonable that all parents should be advised to avoid smoking during pregnancy and to avoid ETS after childbirth and to provide their child with a healthy diet rich in fresh fruits and vegetables, as well as omega-3 fatty acids. Further, parents of a child with food sensitivities should be instructed to avoid regionally specific perennial allergens.^{101,102} The effect of potential protective factors such as early admission to daycare and consequent exposure to infections, as well as the use of drugs, needs to be evaluated in prospective studies.

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