

Allergen avoidance and prevention of atopy

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Purpose of review

Recent increases in the prevalence of atopic disease argue strongly that environmental factors operating primarily in early life play a significant role. Exposure to food and inhalant allergens early in life may constitute a risk factor amenable to manipulation.

Recent findings

Recent observational and interventional studies have produced conflicting data regarding the effectiveness of allergen avoidance in primary and secondary prevention of atopic diseases.

Summary

Exclusive breast feeding for 4–6 months may protect against the development of allergic diseases in early childhood and remains good advice. Convincing proof for the preventive effects of the delayed introduction of solid foods and hydrolyzed formula in formula-fed infants is lacking. There is some evidence to support a preventive effect of house dust mite allergen avoidance before sensitization occurs. The effect of exposure to animal allergen is uncertain, with some studies showing an increase in sensitization while others suggest a protective effect. Therefore, no evidence-based advice can be given at this stage regarding allergen avoidance measures to be adopted by families with infants at high risk of atopy, except perhaps to breast feed exclusively for at least 4 months. Data regarding the secondary prevention of allergic disease by allergen avoidance were more secure until the publication this year of two randomized controlled trials which suggest that mattress impermeable covers, the main dust mite allergen avoidance measure, may not work. Allergen avoidance, however, should remain an essential part of the management of allergic diseases, even if the benefit of mattress covers is in doubt.

Keywords

allergen, atopy, asthma, prevention

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Abbreviation

RCT randomized controlled trial

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Introduction

Atopy is defined as the genetic propensity to develop IgE following allergen exposure (sensitization) and manifests clinically as allergic asthma, allergic rhinitis, atopic dermatitis and IgE-mediated food allergy. The exponential rise in the prevalence of asthma and related allergic disorders in the last few decades has put an enormous burden on health care resources and adversely affected the quality of life of millions of children and adults. A recent population-based study showed that nearly 14% of children suffer from asthma and 20% from rhinitis at the age of 10 years [1–3]. This emphasizes the need for devising effective methods for primary prevention in children at high risk of atopy. Allergen avoidance, both food and aeroallergens (particularly house dust mite), has been the subject of several recent studies. This review focuses on the role of allergen avoidance in the primary and secondary prevention of atopic disorders.

Primary prevention

Development of atopic disease depends on an interaction between genetic and environmental factors. Hence manipulation of environmental risk factors may lead to a reversal of this trend. Exposure to allergen is one such factor that has received considerable attention in recent years.

Allergen exposure and development of atopy

A dose-dependent relationship between allergen exposure and sensitization [4,5] and between sensitization and the development of allergic disease [6] is well established. There is also some evidence to support the fact that early exposure to cow's milk and house dust mite may be risk factors for the development of asthma [7,8]. Some investigators, however, have not found a direct relationship between allergen exposure and the development of asthma [9]. Overall, the evidence weighs in favour of early allergen exposure and sensitization as a significant risk factor for later development of asthma and thus prevention of atopy by early allergen avoidance seems a logical step in high-risk children.

Allergens

Food allergens are important in early life and include, among others, cow's milk, egg and peanut. Aeroallergens may differ according to the geographical location. For example, house dust mite is critical in humid climates, whereas in some arid climates in the USA and Australia, the fungus *Alternaria* assumes primary importance, and in inner city areas the most significant allergen may be

cockroach. The role of allergen dose involved in the onset of atopy is controversial. For food allergens, the minimal sensitization and provocation doses have not been determined. For house dust mite allergen, the minimal sensitization and provocation doses have been suggested at 2 and 10 $\mu\text{g/g}$ dust. This presumes, however, that higher doses are more harmful. Indeed, some investigators suggest that smaller doses are more likely to lead to sensitization and higher doses may induce tolerance, particularly so for allergens of animal origin [10]. This challenges the very basis of the strategy to prevent atopy by avoidance of allergens.

Time of contact with allergen

The significance of in-utero exposure to allergens is not entirely clear [11–13], primarily because of the lack of prospective studies. There is evidence, however, that exposure to dust mite allergen during infancy is important for the development of asthma in later childhood [14]. Animal experiments provide further support for this hypothesis. In an elaborate experiment, Schiessl *et al.* [15•] showed that early sensitized dogs developed significantly higher OVA-specific serum IgE levels than late sensitized dogs. Moreover, in early sensitized dogs, allergic responses, in terms of production of IgE antibodies, were more intense when a new allergen was injected later in life for the first time. Dynamic pulmonary compliance and resistance, both parameters for bronchoconstriction induced by OVA aerosol challenge, were also significantly higher in early sensitized dogs. This study clearly shows that, at least in dogs, early sensitization results in a higher level of IgE production, influences the direction of immune responses such that response to allergen exposure later in life is also more intense and leads to bronchial hyperreactivity—a common manifestation of asthma.

Food allergens avoidance

Maternal dietary allergen avoidance during pregnancy does not prevent atopic disease in children and may even be harmful to the foetus [16]. A recent World Health Organization report [17•] states that exclusive breast feeding and avoidance of solid food for 4 months seems to be effective for allergy prevention. However, the debate regarding the preventive effect of breast feeding on the development of atopy and allergic diseases continues. Observational studies have consistently shown a preventive effect on infantile wheeze but a less consistent effect on other allergic disorders during the first few years of life and later development of asthma [18–20]. The inconsistent results of observational studies and the presence of confounders differentiating breast-fed from formula-fed infants make it difficult to assess the true preventive effect of breast feeding. This is partly due to the lack of randomized controlled trials (RCTs), which would be considered unethical today.

Two recent large observational studies support the view that breast feeding protects against allergic diseases in early childhood. Kull *et al.* [21] followed a birth cohort up to the age of 2 years and reported less wheeze, atopic dermatitis and rhinitis in those who were exclusively breast fed. Data from the third National Health and Nutrition Examination Survey in the USA indicate that ever breast-fed children, compared with never breast-fed, had less asthma diagnosis during the first 2 years of life and in children who were exposed to tobacco smoke the protective effect can be shown up to the age of 6 years [22]. It should be kept in mind that the effect of breast feeding is more than the simple avoidance of allergenic food proteins during early infancy, as food, including cow's milk, protein can be shown to be present in breast milk. Maternal dietary avoidance of food allergens during lactation may have an added protective effect [23]. A recent study claims that there is a differential effect of breast feeding on the development of atopy, such that, in children (aged 4 years) with atopic heredity, breast feeding reduced the risk of atopy (allergic rhinoconjunctivitis and sensitization to furred pets) while it increased the risk in those without atopic heredity. A significant interaction was found between heredity and breast feeding [24]. This is interesting and may help to explain why large unselected cohorts have failed to find a significant protective effect of exclusive breast feeding on atopy.

Cow's milk protein is an important food allergen in early life. In children with atopic heredity who are not breast fed, hypoallergenic formulas are often recommended in an attempt to avoid early exposure to cow's milk protein [25]. The benefit has not been conclusively demonstrated, however, and there is also controversy regarding the use of extensively versus partially hydrolyzed formulas in this context. A recent large RCT (German Infant Nutritional Intervention Study) [26•] compared the preventive effect of differently hydrolyzed formulas with cow's milk formula. Three hypoallergenic formulas (partially hydrolyzed whey formula, extensively hydrolyzed whey formula, and extensively hydrolyzed casein formula) were compared for their preventive effect. The incidence of allergic manifestations, such as atopic dermatitis, food allergy or allergic urticaria, was significantly reduced by using an extensively hydrolyzed casein formula compared with a cow's milk formula. Use of partially hydrolyzed whey formula reduced the incidence of atopic dermatitis.

Avoidance of aeroallergens

To prevent the development of atopy (primary prevention), allergen avoidance has to be instituted before sensitization occurs. Keeping in mind the importance of allergen exposure in early life and allergic diseases being common in infancy, it was presumed that allergen

avoidance measures would have to be applied from birth (or even during pregnancy). A large multicentre study (Study on the Prevention of Allergy in Children in Europe) took an innovative approach of using three childhood cohorts (newborns, toddlers and school children) at high risk of developing sensitization to dust mite, and assessed the role of dust mite allergen avoidance in prevention of sensitization to house dust mite and the development of allergic diseases. The primary prevention measure was dust mite impermeable covers with an educational package as the main intervention measure. Three reports have appeared in the last 2 years from each of the three cohorts, 1 year after preventive measures were instituted [27,28*,29]. In each cohort, sensitization to dust mite was significantly reduced, but reduction in clinical allergic manifestations was modest and nonsignificant. It would be interesting to ascertain if atopy and asthma can be prevented with these relatively simple measures with further follow-up of these children.

In a recent RCT [30*] house dust mite avoidance (use of impermeable mattress covers and an acaricide) during pregnancy and infancy did not reduce the development of atopy or clinical manifestations such as wheeze. Interestingly, supplementation with $\omega 3$ fatty acids did have an effect, by the age of 18 months, in reducing the prevalence of wheeze, although not atopy (skin prick test and serum IgE) or asthma.

In the Prevention and Incidence of Asthma and Mite Allergy study [31], allergen-impermeable and placebo mattress encasings were applied to the beds of children and parents before birth. House dust mite allergen levels were modestly reduced in those with allergen-impermeable mattress encasings. However, this reduction does not seem to have had a beneficial effect on the development of atopy, at least in early childhood [32].

The effect of exposure to animal allergen during early life on the development of atopy and asthma remains controversial. A large survey revealed a differential effect of pet keeping in early childhood on the risk of allergic diseases [33]. Having a cat in the household during early childhood increased the risk of allergic asthma in adult life in those communities where exposure to cat outside the house was low. Keeping a dog in childhood reduced the risk of hay fever in adult life but increased that of nonallergic asthma. This was a retrospective survey, however, and recall bias is likely. In large retrospective surveys of this kind, there is a real possibility of unearthing spurious relationships.

Combined approach

The Isle of Wight allergy prevention study was the first to show that a combination of strict avoidance of food

and reduction in house dust mite allergens during infancy could have a profound effect on the development of atopy in genetically at risk children. There was a reduction in the incidence of asthma, atopic dermatitis and food allergy in early childhood [34], although this effect lost statistical significance in later follow-up at 4 years [35]. However, atopy, as defined by positive skin prick test responses, was consistently reduced. Recently, Arshad *et al.* [36**] published the 8-year follow-up of their cohort, showing a reduction in asthma and bronchial hyperresponsiveness as well as atopy in the intervention group. This study supports the hypothesis that allergen avoidance in infancy in high-risk children may reduce the development of allergic sensitization leading to less atopic dermatitis in infancy and asthma in later childhood.

Secondary prevention

Environmental allergen control is recommended as an essential part of most asthma management guidelines. Patients with asthma and aeroallergen sensitivities are given appropriate advice on allergen avoidance and such measures can indeed reduce asthma symptoms, the need for medication, and airway hyperresponsiveness [37]. A number of studies have confirmed the effectiveness of house dust mite avoidance measures and specifically the use of mattress impermeable covers in reducing the levels of house dust mite allergens [38,39**]. The compliance to allergen avoidance methods can be enhanced by the provision of mattress covers [40] and advice on allergen avoidance being reinforced by a medical indoor environment counsellor [38].

Two double-blind RCTs published during 2003 produced conflicting results regarding the effectiveness of mite impermeable bed coverings on asthma. In a small study of 60 children with house dust mite sensitive asthma [41], mattress and pillow encasings resulted in a significant reduction in mite allergen levels and consequently a reduction in the need for inhaled steroids to control asthma after 9 and 12 months. Another double-blind RCT, however, has challenged the established view that reduction in house dust mite allergen levels is associated with improvement in asthma. Woodcock *et al.* [39**] failed to show any effect of allergen-impermeable bed covers and a reduction in house dust mite allergen levels in the secondary prevention of asthma.

In perennial allergic rhinitis due to dust mite allergy, a double-blind RCT of mattress impermeable covers showed a reduction in mite allergen levels but no effect on symptoms [42]. In allergic rhinitis, a systematic review of published RCTs concluded that although it was possible to reduce house dust mite allergen levels with current avoidance methods, there is little evidence at present that these reductions translate into

improvements in clinical outcomes such as symptoms and medication requirement [43].

A small RCT from Iceland [44] shows that it is possible to reduce the level of major cat allergen (Fel d 1) with environmental measures (without removing the cat). This had a beneficial effect on patients with cat-induced nasal allergy in terms of improvement in symptoms and nasal inspiratory flow rate.

With intensive intervention measures it is possible to achieve a significant (80–90%) reduction in the level of cockroach allergen in inner city homes [45] where exposure to cockroach allergen is said to be the major cause of asthma morbidity. However, it has not been shown conclusively if this reduction leads to improvement in relevant asthma outcomes.

Conclusion

Prevention of atopy remains in its infancy. Food allergen avoidance during early childhood with exclusive breast feeding and perhaps, in addition, a maternal exclusion diet during lactation and delayed introduction of solid foods may prevent the development of atopic dermatitis and infantile wheeze. A combined approach of food and dust mite allergen avoidance seems promising in preventing childhood asthma. Further RCTs are needed with long-term follow-up before definitive advice can be given.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

- 1 Kurukulaaratchy R, Fenn M, Twiselton R, *et al.* The prevalence of asthma and wheezing illnesses amongst 10-year old schoolchildren. *Respir Med* 2002; 96:163–169.
- 2 Arshad SH, Kurukulaaratchy R, Fenn M, *et al.* Rhinitis in 10 year old children and early life risk factors for its development. *Acta Paediatr* 2002; 91:1–5.
- 3 Kurukulaaratchy RJ, Fenn MH, Waterhouse LM, *et al.* Characterization of wheezing phenotypes in the first 10 years of life. *Clin Exp Allergy* 2003; 33:573–578.
- 4 Kuehr J, Frischer T, Meinert R, *et al.* Mite allergen exposure is a risk for the incidence of specific sensitization. *J Allergy Clin Immunol* 1994; 94:44–52.
- 5 Wahn U, lau S, Bergman R, *et al.* Indoor allergen exposure is a risk factor for sensitisation during the first three years of life. *J Allergy Clinical Immunol* 1997; 99:763–769.
- 6 Arshad SH, Tariq SM, Matthews SM, Hakim EA. Sensitisation to common allergens and its association with allergic disorders at age 4 years: a whole population birth cohort study. *Pediatrics* 2001; 108:e33.
- 7 Oddy WH, Peat JK, de Klerk NH. Maternal asthma, infant feeding and the risk of childhood asthma. *J Allergy Clinical Immunol* 2002; 110:65–67.
- 8 Custovic A, Taggart SC, Francis HC, *et al.* Exposure to house dust mite allergen and the clinical activity of asthma. *J Allergy Clinical Immunol* 1996; 98:64–72.
- 9 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. Multicentre Allergy Study Group. *Lancet* 2000; 356:1392–1397.
- 10 Custovic A, Hallam CL, Simpson BM, *et al.* Decreased prevalence of sensitization to cats with high exposure to cat allergen. *J Allergy Clin Immunol* 2001; 108:537–539.
- 11 Holloway JA, Warner JO, Vance GH, *et al.* Detection of house dust mite allergen in amniotic fluid and umbilical cord blood. *Lancet* 2000; 356:1900–1902.
- 12 Platts-Mills TA, Woodfolk JA. Cord blood proliferative responses to inhaled allergens: is there a phenomenon? *J Allergy Clinical Immunol* 2000; 106:441–443.
- 13 Smillie FL, Elderfield JA, Patel F, *et al.* Lymphoproliferative responses in cord blood and at one year: no evidence for the effect of in utero exposure to dust mite allergen. *Clinical Exp Allergy* 2001; 31:1194–1204.
- 14 Sporik R, Holgate ST, Platts-Mills TAE, Cogswell JJ. Exposure to house dust mite allergen (Der p 1) and the development of asthma in childhood. *New Engl J Med* 1990; 323:502–507.
- 15 Schiessl B, Zemann B, Hodgkin-Pickart LA, *et al.* Importance of early allergen contact for the development of a sustained immunoglobulin E response in a dog model. *Int Arch Allergy Immunol* 2003; 130:125–134.
- An excellent animal model highlighting the importance of early contact with allergen.
- 16 Kramer MS. Maternal antigen avoidance during pregnancy for preventing atopic disease in infants of women at high risk [Cochrane review]. The Cochrane Library 2001; (1):CD000133. Oxford: Update Software.
- 17 WHO document. Prevention of allergy and allergic asthma. 2003. WHO/ NMH/MNC/CRA/03.2.
- Current recommendations of the World Health Organization for the prevention of allergy and asthma.
- 18 Schoetzau A, Filipiac-Pittroff B, Franke K, *et al.* Effect of exclusive breast feeding and early solid food avoidance on the incidence of atopic dermatitis in high risk infant at one year of age. *Pediatr Allergy Immunol* 2002; 13:234–242.
- 19 Tariq S, Matthews S, Stevens M, *et al.* The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. *J Allergy Clin Immunol* 1998; 101:587–593.
- 20 Sears MTR, Greene JM, Willan AT, *et al.* Long term relation between breast feeding and development of atopy and asthma in children and young adults: a longitudinal study. *Lancet* 2002; 360:901–907.
- 21 Kull I, Wickman M, Lilja G, *et al.* Breast feeding and allergic diseases in infants: a prospective birth cohort study. *Arch Dis Child* 2002; 87:478–481.
- 22 Chulada PC, Arbes SJ Jr, Dunson D, Zeldin DC. Breast-feeding and the prevalence of asthma and wheeze in children: analyses from the Third National Health and Nutrition Examination Survey, 1988–1994. *J Allergy Clin Immunol* 2003; 111:328–336.
- 23 Kramer MS. Maternal antigen avoidance during lactation for preventing atopic disease in infants of women at high risk [Cochrane review]. The Cochrane Library 2001; (1):CD000132. Oxford: Update Software.
- 24 Siltanen M, Kajosaari M, Poussa T, *et al.* A dual long-term effect of breastfeeding on atopy in relation to heredity in children at 4 years of age. *Allergy* 2003; 58:524–530.
- 25 Seidman EG, Singer S. Therapeutic modalities for cow's milk allergy. *Ann Allergy Asthma Immunol* 2003; 90 (6 Suppl 3):104–111.
- 26 von Berg A, Koletzko S, Grubl A, *et al.* German Infant Nutritional Intervention Study Group. The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomised double-blind trial. *J Allergy Clin Immunol* 2003; 111:467–470.
- A large RCT evaluating the role of hydrolyzed formulas in primary prevention of atopy.
- 27 Arshad SH, Bojarskas J, Tsitoura S, *et al.* and the SPACE study group. Prevention of sensitisation to house dust-mite by allergen avoidance in school age children: a randomised controlled study. *Clin Exp Allergy* 2002; 32:843–849.
- 28 Halmerbauer G, Gartner C, Schierl M, *et al.* SPACE Collaborative Study Team. Study on the Prevention of Allergy in Children in Europe (SPACE): allergic sensitization at 1 year of age in a controlled trial of allergen avoidance from birth. *Pediatr Allergy Immunol* 2003; 14:10–17.
- A large multinational European study assessing the prevention effect of simple dust mite avoidance measures on primary prevention of atopy in infants at high risk.
- 29 Tsitoura S, Nestoridou K, Botis P, *et al.* for the SPACE group. A randomized trial to prevent sensitization to mite allergens in toddlers and preschoolers by allergen reduction and education: one-year results. *Arch Pediatr Adolesc Med* 2002; 156:1021–1027.

- 30 Mahrshahi S, Peat JK, Marks GB, *et al.* Eighteen-month outcomes of house dust mite avoidance and dietary fatty acid modification in the Childhood Asthma Prevention Study (CAPS). *J Allergy Clin Immunol* 2003; 111:162–168.

A RCT of house dust mite avoidance measures and dietary intervention with supplements of ω 3 fatty acids on the development of atopy in high-risk infants.

- 31 van Strien RT, Koopman LP, Kerkhof M, *et al.* Mattress encasings and mite allergen levels in the Prevention and Incidence of Asthma and Mite Allergy study. *Clin Exp Allergy* 2003; 33:490–495.
 - 32 Brunekreef B, Smit J, de Jongste J, *et al.* The prevention and incidence of asthma and mite allergy (PIAMA) birth cohort study: design and first results. *Pediatr Allergy Immunol* 2002; 13 (Suppl 15):55–60.
 - 33 Svanes C, Heinrich J, Jarvis D, *et al.* Pet-keeping in childhood and adult asthma and hay fever: European community respiratory health survey. *J Allergy Clin Immunol* 2003; 112:289–300.
 - 34 Arshad SH, Matthews S, Gant C, Hide DW. Effect of food and house-dust mite allergen avoidance on development of allergic disorders in infancy. *The Lancet* 1992; 339:1493–1497.
 - 35 Hide DW, Matthews S, Tariq S, Arshad SH. Allergen avoidance in infancy and allergy at 4 years of age. *Allergy* 1996; 51:89–93.
 - 36 Arshad SH, Bateman B, Matthews SM. Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomised controlled study. *Thorax* 2003; 58:489–493.
- This report of an 8-year follow-up of a RCT in infants at high risk of atopy is significant in showing that avoidance of food and house dust mite allergen in infancy may have a long-term preventive effect on the development of atopy and asthma.
- 37 Bush RK. Environmental controls in the management of allergic asthma. *Med Clin North Am* 2002; 86:973–989.

- 38 de Blay F, Fourgaut G, Hedelin G, *et al.* Scientific Committee of the MIEC study. Medical Indoor Environment Counselor (MIEC): role in compliance with advice on mite allergen avoidance and on mite allergen exposure. *Allergy* 2003; 58:27–33.

- 39 Woodcock A, Forster L, Matthews E, *et al.* Medical Research Council General Practice Research Framework. Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. *N Engl J Med* 2003; 349:225–236.

This large RCT with a year of follow-up indicates that mattress impermeable covers, a standard recommendation for dust mite avoidance in patients with dust mite allergic asthma, may not be effective in secondary prevention of asthma.

- 40 Joseph KE, Adams CD, Cottrell L, *et al.* Providing dust mite-proof covers improves adherence to dust mite control measures in children with mite allergy and asthma. *Ann Allergy Asthma Immunol* 2003; 90:550–553.
- 41 Halcken S, Host A, Niklassen U, *et al.* Effect of mattress and pillow encasings on children with asthma and house dust mite allergy. *J Allergy Clin Immunol* 2003; 111:169–176.
- 42 Terreehorst I, Hak E, Oosting AJ, *et al.* Evaluation of impermeable covers for bedding in patients with allergic rhinitis. *N Engl J Med* 2003; 349:237–246.
- 43 Sheikh A, Hurwitz B. House dust mite avoidance measures for perennial allergic rhinitis: a systematic review of efficacy. *Br J Gen Pract* 2003; 53:318–322.
- 44 Björnsdóttir US, Jakóbinudóttir S, Runarsdóttir V, Juliusson S. The effect of reducing levels of cat allergen (Fel d 1) on clinical symptoms in patients with cat allergy. *Ann Allergy Asthma Immunol* 2003; 91:189–194.
- 45 Arbes SJ Jr, Sever M, Archer J, *et al.* Abatement of cockroach allergen (Bla g 1) in low-income, urban housing: a randomised controlled trial. *J Allergy Clin Immunol* 2003; 112:339–345.