

## Review article

# Can we apply clinical studies to real life? Evidence-based recommendations from studies on development of allergic diseases and allergy prevention

**A. Høst<sup>1</sup>, S. Halken<sup>2</sup>**

<sup>1</sup>Department of Pediatrics, Odense University Hospital  
and <sup>2</sup>Department of Pediatrics, Sønderborg Hospital,  
Denmark

Arne Høst, Department of Pediatrics, Odense University  
Hospital, DK-5000 Odense C, Denmark

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Allergic diseases represent a major and increasing health problem in industrialized countries.

The prevalence of allergic diseases in childhood (asthma, atopic dermatitis, and allergic rhinoconjunctivitis) has increased considerably in developed countries (1,2), in the last 30 years.

In population-based studies a cumulative prevalence of allergic diseases in childhood around 25–30% has been reported, asthma in 7–10%, atopic dermatitis in 15–20% and allergic rhinoconjunctivitis in 15–20% (1–7).

The allergic diseases impose a heavy burden and cause major morbidity in childhood, asthma representing the most frequent chronic disease causing absence from school (8–12). Thus, effective allergy preventive measures are highly warranted.

It is very important to take into consideration the natural course of the disease when evaluating possible preventive measures. In infancy the main allergic symptoms are atopic dermatitis, gastrointestinal symptoms, and recurrent wheezing, whereas bronchial asthma and allergic rhinoconjunctivitis are the main problems later in childhood (13,14). Adverse reactions to foods, mainly cow's milk protein, are most common in the first years of life, whereas allergy to inhalant allergens mostly occurs later (13,15). Correspondingly, specific immunoglobulin (Ig)E antibodies against milk and egg are most frequent during the first 2–3 years of life, whereas specific IgE against inhalant allergens is

predominant later in childhood (14,16). Although the presence of IgE antibodies does not necessarily mean clinical active disease such antibodies to allergens (hen's egg white, cow's milk) in infants predict sensitization and allergy before 7–10 years of life (17–20).

Allergic diseases are complex and multifactorial. The development and phenotypic expression of allergic diseases depend upon an interaction between genetic and environmental factors. At present, it is estimated that genetic factors account for around 50% of asthma and allergy (21). Although it is well documented that atopic heredity is associated with an increased risk for development of allergic diseases (22–24), it has also been demonstrated that many children who develop 'atopic' diseases during the first years of life come from families without an atopic heredity (14,22,25).

Therefore, some preventive measures may be beneficial in the general population and supplementary measures may be beneficial and recommendable only for high-risk individuals. Varying definitions of high-risk infants have been used, but according to a recent joint statement (26) high-risk infants are defined as infants with a well defined increased risk of developing allergic disease; that is, infants with at least one first degree relative (parent or sibling) with a documented allergic disease. In some studies 'high-risk' has been defined as double parental heredity or single heredity (parent or sibling) combined with elevated cord blood IgE.

Considering that environment and genetics differ in different parts of the world, preventive measures may differ between affluent and nonaffluent groups.

The aim of this review is to evaluate clinical studies on development and prevention of allergic diseases with regard to the validity of results for possible implementation of evidence-based recommendations for allergy prevention.

## **Terminology**

### Allergic diseases

The field of allergy has developed rapidly during the last decades and our knowledge about immunologic mechanisms has improved our understanding. However, there has been some controversies on the definition of allergic diseases and the use of different terms such as atopy/allergy and atopic/allergic (27). Thus, the term 'atopic' has been used synonymously with 'IgE-mediated', whereas others also consider 'atopy' as a constitutional trait, a clinically useful term describing typical 'atopic' diseases such as atopic dermatitis, asthma and rhinoconjunctivitis (27). Regarding the terms 'atopic symptoms' and 'allergic symptoms' the confusion has been even more pronounced, considering that many studies on allergy development/prevention have used the term 'atopic symptoms' and 'allergic symptoms' interchangeably without any clear definition or distinction. Thus, e.g., 'recurrent wheezing', gastrointestinal symptoms (diarrhoea, vomiting, colic) have often been described as 'atopic' symptoms or 'allergic' symptoms without any confirmation of an IgE mediated or another immunological reaction (13,15,27).

Recently, a revised nomenclature for allergic and related reactions that can be used independently of target organ or patient age group has been published (27). In this position paper the term hypersensitivity has been defined as 'objective, reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects'. Allergy is a hypersensitivity reaction initiated by immunological mechanisms (defined or strongly suspected), whereas the term nonallergic hypersensitivity has been proposed when immunological mechanisms cannot be proven. Allergy can be antibody- or cell-mediated. In most patients, the antibody typically responsible for an allergic reaction belongs to the IgE isotype and these patients may be said to suffer from IgE-mediated allergy. In non-IgE-mediated allergy, different mechanisms may be responsible (IgG, immune complexes, cell-mediated).

Hopefully, the use of this revised nomenclature for allergy will improve the value and comparability of results from future studies. Retrospectively, previous

studies might also be reviewed with advantageous results and improved understanding in the light of this nomenclature.

### Clinical studies

*Development of allergic disease.* When evaluating possible risk factors for the development of allergic diseases and the possible effect of preventive measures, it is important to stress some factors. The study design of both noninterventional and interventional studies should be true prospective studies including well-defined inclusion criteria (unselected versus selected high-risk infants), well-defined diagnostic criteria, a sufficient duration of follow-up, and a proper sample size for adequate statistical evaluation (Table 1). Besides, interventional studies should include, double blinding, and a control for confounders as well as proper registration of compliance and follow-up of drop-outs. Most importantly, adequately concealed random allocation in clinical trials should be ensured (28,29).

Owing to recall bias and selection bias, retrospective studies should not be used for the evaluation of predictive/risk factors for the development of allergic diseases. Likewise, cross-sectional studies are not suitable for the assessment of cause-effect relationships between the exposure to allergens/adjuvant factors and the development of allergic diseases. Generally, it should also be remembered that prospective noninterventional studies can be used to generate hypotheses on the relationship between the cause and effect in development of allergic diseases (Table 2). Proper confirmation of a possible cause-effect relationship requires demonstration of the causative mechanism and effect of elimination/prevention of the suspected causative factor, and furthermore temporality and dose-response effect should be documented (Table 3, 30).

*Prevention of allergic disease.* Different forms of prevention of allergy in childhood have been defined:

*Primary prevention* addresses healthy children with the aim to prevent development of allergic disease.

*Secondary prevention* addresses already diseased children with the aim to prevent symptoms and further progression.

*Tertiary prevention* addresses patients with chronic disease in order to prevent progression and deterioration.

Sensitization may precede development of allergy or may be a normal and harmless phenomenon, which may even be present already prenatally (31–33). The detection of sensitization depends of many factors, e.g., the sensitivity of the test. Therefore, the aim of primary prevention must be to prevent development of disease and not only sensitization.

It can also be argued whether measures to reduce the

Table 1. Important factors influencing outcome of studies on allergy development/prevention

|                                                    |
|----------------------------------------------------|
| Prospective, retrospective, cross-sectional design |
| Randomization                                      |
| Unselected versus selected high risk sample        |
| Age of the population                              |
| Duration of treatment/intervention                 |
| Blind ascertainment                                |
| Strict well defined diagnostic criteria            |
| Control for known confounding factors              |
| Compliance and drop-out                            |
| Sufficient follow-up period                        |
| Sample size/adequate statistical power             |

risk for development of new allergic symptoms in diseased children, e.g., prevention of development of asthma in children with atopic dermatitis or allergic rhinoconjunctivitis, are primary or secondary prevention.

Preventive measures may include both exposure to allergens and adjuvant risk/protective factors and pharmacological treatment. These measures may address the general population, children at risk for development of atopic disease (high-risk infants), children with early symptoms of allergic disease or children with chronic disease. Some preventive measures may be beneficial for the general population and supplementary measures may be beneficial and recommendable only for high-risk individuals, and different preventive approaches may be helpful in different forms of atopic diseases.

In this review we focus mainly on prospective studies on allergy development and primary prevention of allergy evaluating possible evidence-based recommendations.

#### Best evidence for recommendations

The randomized controlled trial is traditionally the gold standard for judging the benefits of treatment/intervention mainly because it is conceptually easier to attribute any observed effect to the treatment/intervention being compared. In contrast to this, in nonrandomized studies the outcomes may be caused by differences among people being given the two treatments/interventions. Such unrecognized confounding factors can always interfere with attempts to correct for identified differences between groups. Therefore, a hierarchy of evidence, with randomized controlled studies at the top, controlled observational studies in the middle, and uncontrolled studies and opinions at the bottom have been proposed (28,34). The World Health Organization (WHO) has followed these considerations in the recommendations regarding statements of evidence (Table 4) and grades of recommendations (Table 5). Thus, for practical purposes recommendations on allergy prevention should primarily be based on the results of randomized controlled studies on condition that the demands of high quality as described above are

Table 2. Assessment of cause-effect relationships between exposure to allergens/adjuvant factors and the development of allergic disease. Evaluation of different kind of studies

| Study                        | Utility             |
|------------------------------|---------------------|
| Retrospective                | Not useful          |
| Cross-sectional              | Not useful          |
| Prospective noninterventioal | Generate hypotheses |
| Prospective interventional   | Proper confirmation |

fulfilled. However, high quality observational studies may extend evidence over a wider population and are likely to be dominant in the identification of risk factors/predictive factors and when randomized controlled studies be unethical or impractical (28). One example is studies on the possible allergy preventive effect of breast-feeding, where correct randomization to breast-feeding or formula feeding is unethical and impossible. Another example is studies on the influence of exposure to tobacco smoking, where you cannot randomize exposure to tobacco smoke. In spite of attempts to adjust for the influence of such factors in studies on allergy development/prevention, there will always be (great) uncertainty on the validity. Furthermore, some possible confounding factors, e.g., tobacco smoking, breast-feeding and socio-economic status seem to be interrelated, making proper statistical adjustment difficult (impossible?).

#### Present evidence-based recommendations

Unselected infants (nonhigh-risk)

**Dietary measures.** From prospective noninterventioal studies, breast-feeding has been associated with a lower risk of atopic dermatitis, food allergy (especially cow's milk allergy) and recurrent wheezing/asthma (18,35–42). Whether breast-feeding helps to prevent allergy can not be properly investigated because of lack of proper allocation of breast-feeding or formula feeding (15,26,43–46). Common factors in studies reporting a benefit of breast-feeding are breast-feeding for at least 4–6 months and solid food introduction after 4 months of age (47,48). There is no evidence of preventive effect of special maternal diet neither during pregnancy nor lactation (49–52).

**Environmental measures.** Many longitudinal studies have shown a significant association between parental

Table 3. The criteria for proving causality between an environmental exposure and a noninfectious illness (30)

|                                         |
|-----------------------------------------|
| Biological plausible                    |
| Analogous associations                  |
| Temporality                             |
| Dose-response effect                    |
| Consistency                             |
| Decrease in effect when exposure ceases |

Table 4. Statements of evidence

|     |                                                                                                                                             |
|-----|---------------------------------------------------------------------------------------------------------------------------------------------|
| Ia  | Evidence obtained from meta-analyses of randomized controlled trials                                                                        |
| Ib  | Evidence obtained from at least one randomized controlled trial                                                                             |
| IIa | Evidence obtained from at least one well-designed controlled trial without randomization                                                    |
| IIb | Evidence obtained from at least one other type of well-designed quasi-experimental study                                                    |
| III | Evidence obtained from well-designed nonexperimental descriptive studies, such as comparative studies, correlation studies and case studies |
| IV  | Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities                            |

(particularly maternal) tobacco smoking and increased wheezing and asthma in children (53–61). This association is strongest up to 6 years of age (59,62). The severity and frequency of symptoms are found to be related to the extent of exposure in the home. Passive smoking has been associated with sensitization to indoor allergens in some studies (63,64), but not in others (62). Importantly, maternal smoking during pregnancy is significantly associated with reduced respiratory function in early infancy and recurrent wheezing during infancy and early childhood (53,55,57,58).

There is evidence of a cause–effect relationship between exposure to indoor pollutants (other than tobacco smoke) (65) and outdoor pollution inducing respiratory symptoms in individuals with established disease (66–68). The possible role of pollutants in the development of asthma and allergic airway disease needs further elucidation (69).

#### Selected high-risk infants

**Dietary measures** Prospective randomized controlled studies have shown a preventive effect of extensively hydrolyzed (hypoallergenic) formulas in combination with avoidance of cow's milk proteins and solid foods during  $\geq 4$  months in high-risk infants on the cumulative incidence of atopic dermatitis and food allergy (especially cow's milk allergy) until the age of 4–7 years (70–76). Thus, a real prevention, and not only a postponement of the onset of the disease, has been documented. An effect of dietary allergy prevention has been demonstrated only in high-risk infants and not in nonhigh-risk infants (46). At present clinical trials are ongoing comparing the relative preventive effects of products with highly reduced allergenicity (extensively hydrolyzed) with those formulas with moderately reduced allergenicity (partially hydrolyzed). Previously, some preventive effect of partially hydrolyzed formulas has been

reported (77–83). Recent data indicate a greater effect with extensively hydrolyzed formula (72,73). There is no evidence that soy formulas or other formulas based on whole proteins other than cow's milk proteins are less allergenic than cow's milk based formulas (70,78,84,85). Thus, if exclusive breastfeeding (26) for 4–6 months is not possible in high-risk infants, a documented hypoallergenic formula and avoidance of solid foods are recommended for the first 4 months of life. There is no conclusive evidence for a protective effect of a maternal exclusion diet neither during pregnancy nor during lactation (26) as well as there is no evidence of an allergy preventive diet after the age of 6 months (15).

**Environmental measures** The significant association between parental tobacco smoking and increased wheezing and asthma is even more pronounced in high-risk children (53–64). The effect of exposure to indoor allergens seems to be most pronounced in children with atopic predisposition and with exposure during the first months/year of life. There seems to be a synergistic effect of several coexisting environmental factors (64). The indoor environment of homes has changed over the last decades and there is evidence of an increase in concentration of indoor allergens (house dust mites and pets) (86) and air pollutants (65). There is a clear association between airway hyper-responsiveness and airway inflammation owing to allergic sensitization (87–89). Chronic asthma is associated with sensitization to indoor allergens, which are more important than the outdoor allergens, probably because of time spent indoors (13,90,91). There seems to be a dose-dependent relationship between exposure and sensitization (13,92–95), as well as an association between sensitization and the development of asthma (36,88,92,93,96–100). Although no direct association has been found between early exposure to indoor allergens and the development of allergic/nonallergic asthma (98), an

Table 5. Grades of recommendations

|    |                                                                                                                                                                                                                    |
|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A. | Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation evidence levels Ia, Ib)                           |
| B. | Requires the availability of well-conducted clinical studies but no clinical trials on the topic of recommendation (evidence levels IIa, IIb)                                                                      |
| C. | Requires evidence obtained from well-designed descriptive studies, comparative studies, correlation studies and case studies (evidence level III)                                                                  |
| D. | Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (level IV) |

Table 6. Primary prevention. Evidence-based recommendations\*

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For all infants

- I No special diet during pregnancy or for the lactating mother
- II Exclusively breast feeding for at least 4 months
- III Avoidance of solid foods until 4 months of age
- IV Avoidance of exposure to tobacco smoke, also during pregnancy

Further recommendations for high risk infants\*\*

- I If supplement is needed during the first 4 months a documented hypoallergenic formula is recommended
  - II Reduced allergen exposure early in life (house-dust mites, furred pets, cockroaches)
- 

\*Recommendations based on the results of prospective controlled randomized (when possible) studies meeting the criteria described in Table 1. Furthermore, prospective controlled nonrandomized studies of high quality as regards the effect of breast-feeding and exposure to tobacco smoking have been included.

\*\*High-risk infants: infants with a well defined increased risk of developing allergic disease, that is, infants with at least one first degree relative (parent or sibling) with documented allergic disease.

association between exposure to indoor allergens and the development of allergic asthma cannot be ruled out (20,88,92,96,99). The association between exposure to pets and the risk of asthma has been difficult to evaluate because of a different study design and selection bias, e.g., parents of atopic predisposed or asthmatic children are more likely to remove pets from the home (92,93). A systematic review (92) concludes that exposure to pets appears to increase the risk of asthma and wheezing in children. Epidemiological studies suggest that in areas with low levels of allergens in homes, the prevalence of sensitization is low (93). So far, a few prospective, randomized studies have investigated the efficacy of the avoidance of indoor allergens (house-dust mites) (27,101–104). These studies have produced the first indication that a reduction in house-dust mite allergen levels in homes of such infants may reduce the prevalence of sensitization to mites and recurrent wheezing during the first years of life. Recently, a prospective study has documented that mite avoidance measures can 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 (105), and preliminary data from the same randomized controlled study indicate a 50% reduction of airway atopic symptoms during the first year of life (106).

Thus, in homes of high-risk infants, current evidence supports measures to reduce the level of indoor allergens, such as house-dust mites and pets. Furthermore, as for nonhigh-risk infants, exposure to tobacco smoke should be avoided.

Children with allergic symptoms (secondary prevention)

Concerning secondary prevention, avoiding exposure to relevant allergens is an effective way to treat allergic diseases such as food allergy, allergic asthma, and allergic rhinoconjunctivitis when the offending allergen can be identified and effective avoidance is feasible. Several controlled randomized studies have shown that allergen (especially house-dust mite and animal dander)

avoidance measures are effective both in reducing the levels of allergens and improvement of disease control (104,107–129).

Furthermore, specific subcutaneous immunotherapy has been demonstrated to be an effective treatment for patients with allergic rhinoconjunctivitis or allergic asthma in randomized controlled studies with extracts of house-dust mites, pollen, and animal dander (especially cat) (130–136).

A few studies of pharmacological (e.g., ketotifen, cetirizine) intervention in young children with atopic dermatitis have reported a significant reduction in the development of asthma (137,138).

### Future perspectives

The results from ongoing randomized, controlled prospective studies on primary prevention on asthma and allergies are awaited. Probably these studies will increase our knowledge on the effect and value of especially environmental allergy preventive measures, possibly also elucidating compliance and cost effectiveness. Preliminary studies have hypothesized a role of many different factors in the development of asthma and allergy, such as obesity, dietary factors (salt intake, antioxidants, n3/n6 fatty acids), intestinal microbial flora and probiotics, viral and bacterial infections and vaccinations. Prospective, long-term follow-up studies of high quality are warranted to elucidate these hypotheses. At present no evidence-based recommendations can be given regarding these factors.

### Implementation of preventive measures

According to the present knowledge some allergy-preventive measures may be beneficial in the general population, and supplementary measures may be beneficial and recommendable only for high-risk individuals. Considering that environment and genetics differ in different parts of the world, preventive measures may also differ between affluent and non-affluent groups.

Fortunately, the evidence-based recommendations

on primary allergy prevention are simple and without major economic burden in most societies. Importantly, the extent of the recommended measures do not impose any harmful restrictions neither regarding infant feeding, indoor environment nor social activities of the family. It can be argued whether stigmatization of infants at risk for development of allergic disease occurs. This risk is probably low considering the simple and nonrestrictive preventive measures, e.g., breast-feeding for at least 4 months can be recommended for

every infant irrespective of atopic predisposition, and no one would oppose against tobacco smoke free air for all infants!

The following evidence-based recommendations depicted in Table 6 are based on the results of prospective controlled randomized (when possible) studies meeting the criteria described in Table 1. Furthermore, prospective controlled nonrandomized studies of high quality as regards the effect of breast-feeding and exposure to tobacco smoking have been included.

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