

Prevention of allergic disease in childhood: clinical and epidemiological aspects of primary and secondary allergy prevention

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Introduction and background

Atopic diseases represent a major and increasing health problem in industrialized countries. The prevalence of atopic diseases in childhood (asthma, atopic dermatitis, and allergic rhinoconjunctivitis) has increased considerably in developed countries (1) in the last 30 yr. Although several studies have shown this increase, it has been argued that increased awareness and improved ability to diagnose atopic diseases might account, at least in part, for this increase. However, population-based studies using identical methods of ascertainment at intervals of 10–15 yr have also shown a significant increase in the prevalence of atopic diseases in children (2–7).

Therefore, possible effective allergy preventive measures are exceedingly warranted. Preventive strategies may address the normal population or a defined 'high-risk' population, and different approaches may be needed for different forms of atopic diseases. Preventive strategies should include effective measures aiming at primary, secondary and tertiary prevention.

Natural course

The expression of allergic diseases may vary with age, and symptoms may disappear and be replaced by other symptoms. In infancy the main atopic symptoms are atopic dermatitis, gastrointestinal symptoms, and recurrent wheezing, whereas bronchial asthma and allergic rhinoconjunctivitis are the main problems later in childhood. Adverse reactions to foods, mainly cow's milk protein (CMP), are most common in the

first year of life, whereas allergy to inhalant allergens mostly occurs later.

Characteristically, sensitization evolves in the order of exposure: food, indoor allergens, outdoor allergens. Sensitization to milk and egg most frequently occurs during the first 2–3 yr of life, while sensitization to inhalant allergens occurs later in childhood with increasing prevalence with age (8–10). Sensitization to indoor airborne allergens (house dust mites (HDM) and pets) often occurs at a lower age than sensitization to pollen (birch and grass) (9, 11, 12). The cumulative prevalence of different allergic diseases and of proven IgE-mediated allergy related to the different allergic symptoms is shown in Table 1.

It has been shown that children with atopic dermatitis have an increased risk for development of asthma (13), children with allergic rhinoconjunctivitis often develop asthma and that children with asthma often have allergic rhinoconjunctivitis (12, 14). The prognosis of food allergy (FA) is good and children with FA often outgrow their FA; but they are prone to the development of allergy against inhalant allergens and both asthma and allergic rhinoconjunctivitis, especially in case of IgE-mediated FA (15–17).

Recent prospective studies have reported early sensitization against cow's milk, hen's egg and HDM highly predictive for sensitization and also for clinical allergic disease, persistent atopic dermatitis and asthma later in childhood (18–20) especially in high-risk (HR) infants (10, 21–23) or infants with early atopic manifestations such as atopic dermatitis or wheezing (24, 25). Thus, IgE-mediated allergic disease early in childhood is associated with a high risk of severe allergic disease later on. This natural course of the allergic diseases – the so called 'allergic march' – is very important to take into consideration, when evaluating factors that may influence the development of allergic diseases.

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Table 1. Atopic diseases in childhood. Prevalence of disease and prevalence of allergy in children with atopic disease

	Prevalence (%)	Proven IgE mediated (%)
Food allergy	7–8	40–60
Atopic dermatitis	15–20	20–70
Asthma/recurrent wheezing <5 yr	31–34	30–50
Asthma >5 yr	7–10	60–90

Frequencies of IgE-mediated reactions vary with age and selection. Different phenotypes, e.g. infectious asthma vs. atopic asthma.

The objective for this review was to evaluate possible preventive measures as regards prevention of development of allergic disease in childhood – primary prevention – and also some aspects of the effect of specific allergy treatment as regards secondary prevention in children with allergic asthma and allergic rhinoconjunctivitis.

Development of allergic diseases

The development and phenotypic expression of atopic disease depends on a complex interaction between genetic and several environmental factors such as environmental exposure to food and inhalant allergens, and non-specific adjuvant factors (e.g. tobacco smoke, air pollution, and infections) (Fig. 1). At present, it is estimated that genetic factors account for around 50% of asthma and allergy (26). It is unlikely that a change in genetic factors can explain the increased prevalence of asthma and allergy seen during the last decades. It is evident that environmental factors play a major role in the development of sensitization and allergic disease, and that many different environmental factors may contribute to the increase in the prevalence of the allergic diseases.

When evaluating possible risk factors for the development of allergic diseases and the possible effect of preventive measures, several factors have

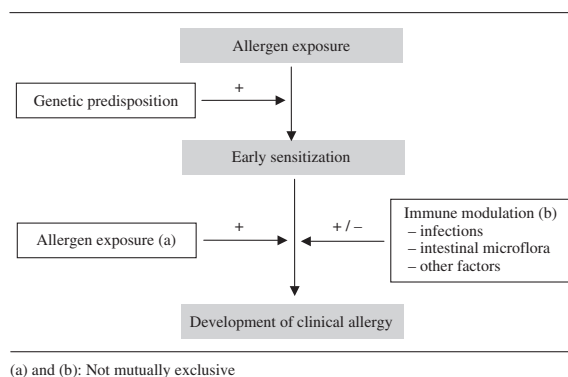


Fig. 1. Development of allergic disease. (a) and (b): not mutually exclusive.

to be taken into account. The study design should be prospective and include accepted well-defined diagnostic criteria/outcome measures, a sufficient duration of follow-up, and a proper sample size for adequate statistical evaluation. Furthermore, interventional studies should include proper randomization, double blinding and a control for confounders, as well as proper registration of compliance and follow-up of dropouts.

Due to recall bias and selection bias, neither retrospective nor cross-sectional studies are suitable for assessment of cause–effect relationships between exposure to allergens/adjuvant factors and development of allergic diseases. In general, prospective non-interventional studies can be used to generate hypotheses on the relationship between cause and effect in development of allergic diseases; however, proper confirmation of a possible cause–effect relationship requires demonstration of the causative mechanism and effect of elimination/prevention of the suspected causative factors (27, 28).

Atopic heredity

It has been shown that around 30% of newborns have at least one parent/or older sibling with previous or current atopic disease, around 5% of newborns have double parental atopic heredity and around 10% have one sibling and one parent with atopic heredity. Around 60–65% are without atopic heredity (29–33). In children without atopic heredity around 10% develop allergic disease, whereas 20–30% of children with single atopic heredity (parent or sibling) and around 40–50% of infants with double parental heredity have been shown to develop atopic disease (29, 33). However, it should be emphasized that the extent of exposure to environmental factors, such as allergens and tobacco smoke as well as the extent of possible preventive measures such as breastfeeding, pharmacological measures, etc. will always influence such estimates heavily.

Dietary factors

Breastfeeding. More than 60 yr ago Sanford and Grulee reported that undiluted cow's milk gave a sevenfold increase in the risk of 'eczema' at 9 months of age in a huge cohort of children compared with babies that were breastfed and fed mixed food (34). One cohort study has demonstrated an association between early cow's milk formula feeding and development of cow's milk protein allergy (CMA) (35). In a Finnish study of non-selected, non-high risk newborns followed until 17 yr of age, 6 months exclusively

breastfeeding was associated with less 'eczema' and FA at 1 and 3 yr as well as a lower 'score of respiratory allergy' (not well defined) up to 17 yr of age compared with exclusively breastfeeding for less than 3 months (36). Another prospective study (37) found that non-atopic children (negative skin prick test) at age 6 yr, who had not been breastfed had increased risk of wheezing recurrently when compared with breastfed children (odds ratio 3.03, 95% CI 1.06–8.69), but the same association was not found for atopic children. In a recent Australian study (38–42) introduction of milk other than breastmilk before 4 months of age was a significant risk factor for all asthma and 'atopy' outcomes in children up to 6 yr (odds ratio 1.25, 95% CI 1.02–1.52), and for current asthma (odds ratio 1.31, 95% CI 1.05–1.64). Breastfeeding has also been shown to reduce the risk of wheezy bronchitis during infancy (43, 44). Meanwhile, contradictory results exist, e.g. in a recent large prospective study from 3 to 21 yr of age, the authors concluded that breastfeeding for at least 4 wk does not protect children from atopy and asthma and may even increase the risk (45). However, the methods and data presented in that study do not seem to confirm the conclusion. Thus, e.g. data on breastfeeding were documen-

ted retrospectively at the age of 3 yr and the information on 'atopic' heredity is uncertain without clear definitions and without inclusion of atopic dermatitis and atopic siblings. No significant effect of exclusively breastfeeding for at least 4 wk was found and no data or conclusion on exclusively breastfeeding for a longer duration are presented.

Prospective birth cohort studies including data on preventive effects of breastfeeding on FA, atopic dermatitis, sensitization and respiratory symptoms are shown in Table 2 (35–39, 41, 42, 44, 46–54).

Common factors apparent in studies reporting benefit of breastfeeding were: (a) prolonged breastfeeding (>4–6 months) and (b) late solid food introduction (after 4–6 months).

A possible protective effect of breastfeeding on the development of allergic diseases may be due to either: (a) a protective effect of human milk (the constituents) or (b) avoidance of 'high-dose' of cow's milk proteins.

In a few studies (45, 53, 54) an association between breastfeeding and asthma or atopic dermatitis may be explained as 'reverse caution', meaning that those with the highest degree of atopic heredity will tend to be breastfed for the longest period.

Table 2. Dietary allergy prevention – breastfeeding. Non-interventional prospective studies in unselected infants

Study	n	Follow-up (years)	Diet	Diet period (months)	Health effect
Saarinen et al. (46)	236 43% +FH	3	Excl BF	6	↓ FA and AD at 1 and 3 yr in –FH ↓ FA and AD at 1 and 3 yr in +FH
Gruskay (47)	328 +FH 580 –FH	15	BF vs. Soy/CMP	≥4	↓ AD and Asthma
Pratt (48)*	122 +FH 76 –FH	5	Excl BF	≥3	↓ Eczema in children +FH → Eczema in children –FH
Moore et al. (49)*	475 +FH	1	Excl BF	≥1	↓ Eczema at 3 and 6 months
Høst et al. (35)	1749	1	Excl BF vs. CMF	0–3	Incidence of CMA: 0.5%† ↑ CMA at 1 yr
Saarinen and Kajosaari (36)*	150	17	Excl BF	6	↓ Respiratory allergy score* at 17 yr
Wright et al. (50)	1006	4 months	BF	4	↓ Wheezing
Wright et al. (37)	988	6	BF	Any	↓ Wheezing at 6 yr in non-atopics
Elder et al. (51)	560 pre-term	1	BF	Any	↓ Wheezing
Wilson et al. (44)	674	1	Excl. BF	≤15 wk	↑ Respiratory illness
Tariq et al. (52)	1218	4	Excl. BF	≤3	↑ Asthma
Oddy et al.‡ (38)	2187	6	BF	≤4	↑ Asthma
Wright et al. (53)	1246	11	BF	4	↓ Wheeze up to 6 yr
Oddy et al. (41, 42)	2602	6	Excl BF	≤4	↑ Asthma
Bergmann et al. (54)*	1314	7	Excl BF	≥1	↑ Atopic eczema§

AD, atopic dermatitis; CMA, cow's milk allergy; FA, food allergy; FH, family history of atopy; BF, breastfeeding compared with formula feeding.

Effect of infants diet indicated by arrows: ↑, increase; ↓, decrease; →, no change in the incidence of disease/symptoms in infants having the diet as mentioned.

*Diagnostic criteria loose (diagnostic uncertainties).

†Of 1749 subjects, 39 developed CMA, in which nine with CMA were exclusively BF, but had received supplement of CM formula during 0–3 days in newborn nursery. None of 210 exclusively breastfed without supplement of CM formula developed CMA.

‡Logistic regression analyses adjusted for important confounders: sex, GA, ETS, early childcare.

§Reverse causation cannot be excluded.

Solid foods. As for introduction of CMP before 4 months of age, the introduction of complementary foods (solid foods) before 4 months of age has been associated with a higher risk of atopic dermatitis (44, 55) up the age of 10 yr (56) (Table 3).

Other dietary factors. Based on the results of cross-sectional studies (57–59) there is some evidence that dietary factors such as low intake of fresh fish, omega-3 fatty acids, high sodium intake or inadequate intake of antioxidants may influence respiratory symptoms and asthma. However, prospective studies are needed to elucidate and confirm these possible causal relationships.

Environmental factors

Exposure to inhalant allergens. Airway hyperresponsiveness in children is often associated with allergic sensitization (60–62). Chronic asthma is associated with sensitization to indoor allergens, which are more important than the outdoor allergens, probably because of time spent indoors (63–65). In a longitudinal follow-up of 881 children to 18 yr in New Zealand children born in winter exhibited a greater prevalence of sensitization with cats and mites (62).

There seems to be a dose-dependent relationship between exposure to aeroallergens and sensitization (63, 66–70), as well as an association between sensitization and development of asthma (61, 66, 67, 69–73). A dose-response relationship between exposure to HDM and development and severity of asthma has been demonstrated (70–72, 74). Other longitudinal studies have shown that sensitization to HDM and animal dander antedate, and are risk factors for development of asthma in children (10, 21, 24, 25, 60, 61). However, in a recent prospective observational study (69) no direct significant association between early exposure to indoor

allergens (HDM and cat allergens) and asthma up to the age of 7 yr was found. Although no direct association has been found between early exposure to indoor allergens and development of allergic/non-allergic asthma (69), an association between exposure to indoor allergens and development of allergic asthma cannot be ruled out (61, 66, 71, 72, 74). An association with allergen exposure should only be expected as regards allergic asthma.

Data from recent cross-sectional and retrospective studies have suggested that early exposure to pets might provide an asthma-protective effect for children (67, 75). The association between exposure to pets and the risk of asthma has been difficult to evaluate because of different study design, and selection bias may explain this controversy (66, 67), e.g. parents of atopic predisposed or asthmatic children are more likely to remove pets from the home and active to avoid pets outside home (70, 76–78). Active avoidance of allergen, both as a consequence of disease and as a primary preventive effort, complicates interpretation of sensitization during childhood and may very well explain different results in different studies. In addition, exposure outside home (e.g. schools, day-care centres, homes of friends and relatives) and contamination of 'pet-free' homes and even clothing have shown to result in hidden exposure sufficient to induce sensitization and symptoms (79–85). Thus, the community prevalence of keeping pets (community exposure), especially cats, might influence the results of studies of pet exposure.

Recent prospective observational studies suggest that early pet exposure is associated with a reduced risk of developing asthma until 4 yr of age (86), dog exposure in early life might prevent the development of asthma-like symptoms, but not allergic sensitization until 4 yr of age (87) and exposure to two or more cats in the first year of life may reduce subsequent risk of allergic sensitization against a panel of allergens, although not to cats, until 7 yr of age (88). Meanwhile, in none of these studies selection bias can be excluded, most of the information is collected by means of questionnaires and the analyses did not include sibling asthma/allergy, which might heavily influence the families' choice of having pets. In one study the follow-up rate was very low (57%), a very high percentage of parents had asthma (21%) and allergy (49%) and atopic heredity was not clearly defined (88). Although two of these studies (86, 88) included allergen measurements in the methods, these values were not included in the analyses. A systematic review (66) concludes that exposure to

Table 3. Non-interventional studies – role of solid food introduction

Study	n	Follow-up (years)	Diet	Diet period (months)	Health effect
Kajosaari and Saarinen (55)	135 +FH	1	Solid foods	≤6	↑ FA and atopic eczema at 1 yr
Fergusson et al. (56)*	1210	10	Solid foods	≤4	↑ Childhood eczema
Wilson et al. (44)	674	1	Solid foods	≤15 wk	↑ Wheeze

FA, food allergy; FH, family history.

↑ indicates the increase in the effect of infant diet.

*Diagnostic criteria loose (diagnostic uncertainties).

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 (67).

Several studies indicate a positive correlation between exposure to pets, especially during the first year(s) of life, and sensitization and subsequent development of atopic disease [for review see (89)]. In a recent published Swedish prospective study (70) of infants referred with asthma it was found that exposure to cats during the first 2 yr of life was associated with increased sensitization to cat allergens and more severe asthma at 4 yr of age. Moreover synergistic associations between early exposure to cat, parental smoking, signs of poor ventilation, and sensitization to cat and dog was found as well as exposure to high levels of cat allergen in the home in combination with parental smoking at the age of 2 yr was found to be associated both with the development of severe asthma and continued sensitization to cat. One recently published prospective study (90) with follow-up from birth to 5 yr of age showed that exposure to cat/cat allergen at age 2 months was significantly associated with an increased risk of wheezing at or after the age of 3 yr among children whose mothers had a history of asthma, whereas the risk was reduced in children whose mothers had no such history.

The allergens associated with asthma depend on climatic, seasonal and social factors and housing conditions. In temperate and humid regions allergy to HDM shows the strongest association with asthma followed by allergy to furred pets (especially cats). In the USA in arid climates allergy to the fungus *Alternaria* spp. is important, and in urban communities allergy to cockroach may be important, especially in inner cities. These relationships have been reviewed by Platts-Mills et al. (65).

Allergic rhinitis is mostly associated with allergy against outdoor allergens, e.g. birch and grass, but in case of perennial symptoms also indoor allergens is relevant (12). Recent studies demonstrated that being born in spring or early summer was a risk factor for development of seasonal allergic rhinitis until the age of 7 yr, a positive dose response was indicated as at least two pollen seasons were needed before manifest symptoms (91). Another recent study showed that exposure to high levels of birch pollen in infancy increased the risk of sensitization to the same allergen as well as the risk of pollen- and animal dander-induced allergic asthma (92).

A clear association between exposure and sensitization as well as a clear association

between sensitization and development of asthma has been documented. It has been hypothesized that the airway inflammation in asthmatics might precede the development of sensitization to environmental allergens. This does not seem to be the normal course in development of atopy and asthma considering the above-mentioned course of the allergy march in high-risk infants and the documented predictive capacity of early sensitization to food and airborne allergens as regards development of allergic asthma (10, 13, 16, 18, 19, 21, 23–25, 52, 60, 91–93). Nor is there any convincing evidence of such a hypothesis in the group of so-called non-atopic asthmatics with asthma symptoms caused by viral infections as elucidated in recent studies (94, 95).

Exposure to tobacco smoke. Several studies have shown a significant association between parental (particularly maternal) smoking and increased wheezing and asthma in children (96–98). This association is strongest up to 6 yr of age (96, 97). A Danish prospective non-interventional cohort study of 276 unselected infants (99) revealed that at least two episodes of wheezing before the age of 18 months were diagnosed in 25% of infants, who were daily exposed to tobacco smoke at home, and/or in day care, and in 30% of children whose mothers smoked daily. The corresponding figure for infants who were not exposed to tobacco smoke was 15% ($p < 0.05\%$). In the same study 66% of unselected children were daily exposed to tobacco smoke at home and/or in day care, 58% were exposed at home by at least one parent and 42% by the mother. In this and later studies (99–102) it was also shown that HR infants were significantly less exposed especially from the mothers, as only 25% of these mothers were cigarette smokers. In infants and young children with recurrent wheezing exposure to passive smoking is associated with a significantly increased risk for persistent wheezing later on. The severity and frequency of symptoms is related to the extent of exposure in the home (96, 98). Furthermore, passive smoking has been associated with sensitization to indoor allergens in some studies (70, 97, 98, 103, 104), but not in others (96). Importantly, maternal smoking during pregnancy is significantly associated with reduced respiratory function in early infancy and recurrent wheezing during infancy and early childhood (105–114).

Domestic air quality. In countries with a so-called 'western life style', most people spend more than 95% of their time in well-insulated modern buildings with reduced ventilation. Consequently,

an increased load of HDM and mould has become a normal phenomenon (115). Furthermore, an increased burden of particulate materials associated with bio-fuel combustion and smoking is possible as well as an increased load of chemical vapours and gasses including nitrogen dioxide, formaldehyde, and volatile organic compounds. There seems to be an increasing significance of such indoor pollutants, although further prospective studies on the possible cause-effect relationship as regards development of particularly atopic respiratory diseases are warranted (116, 117).

Outdoor pollution. There is convincing evidence of a cause-effect relationship between exposure to outdoor pollution and induction of allergic respiratory symptoms (118). As regards the possible relationship between outdoor air pollution and development of asthma/allergic airway disease, the findings of many studies are weak or contradictory (118–121).

Immune modulation. Although viral respiratory infections frequently trigger acute exacerbations of asthma, the relationship between such infections and asthma is not clear, in part because of the difficulty in defining asthma in young children (122).

Recent studies indicate that early viral infections are primarily associated with the so-called infectious type of asthma with a more favorable prognosis as regards recovery before 10–11 yr of age (94, 95, 123). However, early viral infections do not seem to increase the risk of later allergic asthma (123, 124).

Family size (number of siblings) has been hypothesized to be inversely related to the risk of atopy (125), but prospective studies have not been able to confirm this finding (62, 93, 126). Recently, it has been suggested that tuberculosis and even BCG (Bacille Calmette-Guerin) vaccination might have a preventive effect on the development of asthma and atopy due to a change in the TH1/TH2 balance in favor of the TH1 response (127). However, recent investigations have shown that BCG vaccination does not prevent atopy in children (126, 128, 129). The possible influence of other vaccinations, i.e. pertussis vaccination on the development of atopic responses in children (126, 130, 131) has been investigated; but at present there is no evidence of a causal relationship.

Intestinal microbial flora. It has been hypothesized that the intestinal microbial flora may influence the development of sensitization

(132–135). Two of these studies (132, 133) are cross-sectional including a small number of children at the ages of 2 yr and 13 months with and without atopic symptoms. In one prospective study (134) of 76 atopic predisposed infants a significant difference in the bacterial cellular fatty acid profile of stool samples was found at 3 wk, but not at 3 months of age in atopic infants as compared with non-atopic infants. Atopic infants (n = 18) were defined as having at least one positive skin prick test to any of 16 allergens at the age of 12 months. The authors conclude that differences in the neonatal gut microflora precede the development of atopy, suggesting a crucial role of the balance of indigenous intestinal bacteria for the maturation of human immunity to a non-atopic mode. Meanwhile, the study does not provide firm evidence for such a conclusion. Convincing evidence for this theory, as well as the hypothesis (speculation) that an unclean lifestyle with lots of infections during early childhood may prevent development of atopic disease, needs confirmation by prospective studies.

Other factors. Many other factors have been implicated in hypotheses and speculations on the possible cause-effect relationship or increased susceptibility to development of asthma and other allergic diseases. Some of these factors seem to be important such as low birth weight, day care outside home, and low socio-economic status (62, 136, 137); but confirming results from prospective studies are needed. Present data from cross-sectional studies are contradictory (137, 138).

Based on results from a cross-sectional study a so-called anthroposophic lifestyle (139) and 'living on a farm' (140) has been proposed to be associated with a lower prevalence of atopy in children. However, prospective studies on the possible influence of such possible protective lifestyle factors are needed.

Prevention of allergic diseases

Prevention may consist of a variety of prophylactic measures and can be directed to the avoidance of sensitization, the avoidance of development of disease manifestations in an asymptomatic individual and the avoidance of disease manifestations and progression of disease in a symptomatic individual. Thus, allergy prevention could aim at:

- Reducing the incidence of allergic diseases.
- Reducing the risk for development of new atopic manifestations in diseased individuals.

- Reducing the severity of the disease and the proportion of patients with severe disease.
- Increasing the possibility of remission.
- Increasing the quality of life in the patients.

Different levels of prevention of allergic diseases in childhood have been proposed:

- 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 often transitory harmless phenomenon especially in early childhood (141), which may even be present already prenatally (17, 142, 143). The detection of sensitization depends on 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 risk for development of new allergic symptoms in diseased children are primary or secondary prevention, e.g. prevention of development of asthma in children with atopic dermatitis or allergic rhino conjunctivitis.

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 (HR 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 HR individuals, and different preventive approaches may be helpful in different forms of atopic diseases.

Target groups for intervention

Primary prevention. From prospective studies many possible predictive factors of development of allergic diseases have been identified. Although it is well documented that atopic heredity is associated with an increased risk for development of allergic diseases (29–31), it has also been demonstrated that most children who develop atopic symptoms during the first years

of life come from families without an atopic heredity. Thus, the majority of children with recurrent wheezing/asthma do not belong to HR groups for development of atopic disease (29), whereas a higher proportion of children with allergic disease, including also other manifestations than asthma, will have atopic heredity (33).

Infants with a pronounced atopic predisposition may have a primary immunoregulatory defect, which can be identified by various methods, e.g. elevated cord blood (CB) IgE, low numbers of T cells, disturbed ratio of T-helper/T-suppressor cells, and decreased function of T-suppressor cells (144). Unfortunately, none of the tests are suitable for general allergy risk screening. However, elevated CB IgE has been shown to be a better predictor of specific sensitization especially to inhalant allergens later in childhood than parental history (30, 145).

In a prospective study (30) of a 1-yr birth cohort we were able to identify a HR group with rather high positive and negative predictable values (PPV and NPV) as regards development of severe allergic disease (atopic symptoms combined with a high IgE response) – especially allergic asthma until the age of 5 yr (Tables 4 and 5). In this study the optimal HR group was defined by either double parental atopic predisposition or single atopic predisposition [one parent and/or one or more older sibling(s)], the latter combined with a CB IgE ≥ 0.3 kU/l.

At present the combination of atopic heredity and elevated CB IgE seems to result in the best predictive discrimination as regards development of allergic disease (29, 30, 144, 145). CB IgE may therefore help to define HR groups appropriate for allergy-preventive measures (30, 31, 144, 145).

Defining an HR group as either double parental atopic predisposition or severe single (perennial or ≥ 2 different symptoms in one parent and/or one or more siblings) the latter combined with CB IgE ≥ 0.3 kU/l resulted in a HR group at 8–10 % of a birth cohort, compared with 16–20% if CB IgE is not used and 30–40% if all with at least single atopic predisposition is included (30).

Secondary prevention. Obvious target groups for secondary allergy preventive measures could be children with early/mild atopic symptoms before severe chronic disease has developed, especially in case of co-existing early sensitization to foods (milk, egg) or inhalant allergens (HDM, cat).

Table 4. Prediction of allergy (i.e. allergic disease + high IgE) at 5 yr of age (30)

	PPV	NPV	Sensitivity	Specificity
FH	9.7	91.7	51.7	52.5
CB-IgE $\geq$ 0.3 kU/l	18.6	95.6	66.7	71.3
CB-IgE $\geq$ 0.5 kU/l	15.8	92.2	25.0	86.9
FH + CB-IgE $\geq$ 0.5 kU/l	13.0	91.3	10.0	93.4
FH + CB-IgE $\geq$ 0.3 kU/l	24.5	94.0	43.3	86.9
High-risk group 1	11.9	91.2	8.3	93.1
High-risk group 2	26.0	93.3	33.3	90.7

FH, family history; CB-IgE, cord blood IgE; PPV, positive predictable value; NPV, negative predictable values.

PPV = true positives/(true positives + false positives); NPV = true negatives/(true negatives + false negatives); sensitivity = true positives/(true positives + false negatives); specificity = true negatives/(true negatives + false positives).

High-risk groups 1 and 2: biparental atopic predisposition or severe single predisposition + CB-IgE $\geq$ 0.5/0.3 kU/l.

Table 5. Prediction of asthma and allergic asthma (i.e. asthma + high IgE) at 5 yr of age (30)

	PPV	NPV	Sensitivity	Specificity
Bronchial asthma				
High-risk group 1	26.2	95.9	26.2	95.9
High-risk group 2	27.3	97.1	50.0	92.2
Allergic bronchial asthma				
High-risk group 1	6.4	98.1	20.0	93.3
High-risk group 2	20.3	99.7	86.7	90.2

CB-IgE, cord blood IgE; PPV, positive predictive value; NPV, negative predictive value.

PPV = true positives/(true positives + false positives); NPV = true negatives/(true negatives + false negatives); sensitivity = true positives/(true positives + false negatives); specificity = true negatives/(true negatives + false positives).

High-risk groups 1 and 2: biparental atopic predisposition or severe single predisposition + CB-IgE $\geq$ 0.5/0.3 kU/l.

Dietary intervention

Unselected/non-high-risk infants. Only a few prospective intervention studies (Table 6) have been performed in infants without a hereditary atopic predisposition. In premature unselected infants Lucas (146) found no difference in the development of atopic symptoms or CMA whether the infants were fed human bank milk or cow's milk-based formula (CMF). In other studies (147–149) it was concluded that CMF given during the first few days of life did not increase the risk of atopic disease when determined at the age of 2 (147), 5 (150) and 4–6 yr (149). These studies implemented an intervention diet only during the first few days of life, included low birth weight infants in one (149), and the outcome was based on data from medical files and questionnaires obtained at

7, 11 and 14 yr. In one study (147, 150) the diagnostic criteria were unspecific and outcome measures were mainly based on questionnaires. A recent randomized study including a large number ($n = 6209$) of full term, unselected newborns (151) indicated that feeding of CMF at maternity hospital increases the risk of CMA when compared with feeding an extensively hydrolyzed whey formula, but exclusively breastfeeding for 8 wk did not eliminate the risk of CMA. Meanwhile, the dietary intervention only included the first 4 days of life and no data on the diet after that period are given.

Another large prospective study investigated the overall health benefits of an allergen-reduced dietary regimen in a large unselected study population ($n = 1130$ healthy newborns) (152, 153) allocated (not randomized) to an intervention and a non-intervention cohort according to place of birth. The authors concluded that an allergen-reduced dietary recommendation that includes a partially hydrolysed whey hydrolysate infant formula led to improved general health status, mainly due to improvements in skin findings when compared with a control cohort (152). However, the two study cohorts were significantly different as regards duration of breastfeeding, introduction of solid foods, education of parents, household pets, number of older siblings, exposure to tobacco smoke, and urban residence. This study did not include specific allergic symptoms as an outcome measure and does not allow any conclusions as regards allergy prevention.

Table 6. Dietary allergy prevention: interventional studies in unselected infants

Study	n	Follow-up (years)	Diet	Health effect
Lucas et al. (146)*	777	1 1/2	Human bank milk vs. CMF	→ Atopic disease → CMA
Lindfors et al. (149)†	183	4–6	BM $\pm$ CMF‡	→ Atopic symptoms
Schmitz et al. (148)	189	1	pHF vs. CMF‡	→ Total and asp-CM-IgE
de Jong et al. (147, 150)	1533	2	CMF‡ vs. no CMF	→ Atopic symptoms → RAST
Saarinen et al. (151)	5385	18–34 months	CMF‡ vs. eHF/BM	↑ CMA

CMA, cow's milk allergy; CMF, cow's milk formula; BM, breastmilk; pHF, partially hydrolyzed formula; eHF, extensively hydrolyzed formula.

Effect of infants diet indicated by arrows: ↑, increase; →, no change in the incidence of disease/symptoms in infants having the diet as mentioned.

*Premature infants.

†Low birth weight.

‡Included diet only for the first few days.

High-risk infants. As reviewed in a position paper of ESPACI (154) and a recent joint statement of ESPACI and ESPGHAN (155) prospective studies on HR infants have shown a preventive effect of different dietary allergy prevention programs on the cumulative incidence of FA especially CMA and atopic dermatitis. An effect of dietary allergy prevention has only been demonstrated in HR infants, i.e. infants with at least one first-degree relative (parent or sibling) with documented atopic disease (doctor diagnosed), possibly combined with elevated CB IgE in case of single atopic predisposition. Due to great variations in study design and diagnostic criteria it is difficult to compare the effect of these programs.

1. Breastfeeding: From previous studies (Table 7) (100, 146, 156–161) it is presumed that breastfeeding has an allergy preventive effect compared with CMF feeding, but the extent of the preventive effect remains to be determined. Meta-analyses (162–164) (Table 8) showed that exclusive breastfeeding for at least 3 months, in infants with atopic heredity resulted in a reduced odds ratio of 0.58 (95% CI: 0.4–0.92) for atopic dermatitis and an odds ratio of 0.52 (95% CI: 0.35–0.79) for recurrent wheezing in the first 5 yr of life. The only prospective, randomized study used banked human milk vs. CMF in a preterm infant cohort, and it was found that CMF feeding increased the risk of developing eczema and CMA by 18 months in the subgroup of neonates with an atopic heredity (146).

In HR infants, exclusively breastfeeding during ≥4 months in combination with avoidance of solid foods have resulted in a significant reduction of the cumulative incidence of CMA and atopic dermatitis during the first 4 yr of life. In our studies (100, 102) breastfed children were less exposed to tobacco smoke, especially from their mothers, they were less exposed to pets, they had complementary food introduced at a later age, they were admitted to day care outside home at a later age and they belonged to higher social classes (Table 9). Confounding factors may therefore highly influence the results of comparisons.

There is no conclusive evidence for a protective effect of a maternal exclusion diet during pregnancy (Table 10) (165–167). A few studies indicate that the preventive effect of breastfeeding on development of atopic dermatitis may be enhanced by maternal avoidance of potential food allergens (milk, egg, and fish) while breastfeeding (157, 168, 169), whereas other studies do not confirm this finding (167, 170–172) (Table 10). In

Table 7. Dietary intervention in 'high-risk' infants. Prospective studies including control group. Infant diet – breastfeeding ≥4 months

Study	n	Follow-up (months)	Diet	Health effect
Chandra et al. (156)*	121	24	BF	↓ AD and wheeze
Miskelly et al. (158)*	487	12	BF	↓ Atopy
Burr et al. (160)*	440	7 yrs	CMF = Soy	→ Atopy
			BF	↓ Wheeze in non-atopics
			CMF = Soy	→ Wheeze
Vandenplas et al. (159)*	45	4	BF	↓ Atopy
Chandra et al. (157)*	221	18	BF	↓ CMA
			CMF = Soy	↓ AD
Lucas et al. (146)	160	18	BF	→ AD
	777			↓ Atopy
				↓ CMA
pre-terms				
Chandra et al. (192)*	263	18	BF	↓ AD and atopy
			CMF = Soy	→ AD and atopy
Halken et al. (100)*	141	18	BF	↓ CMA
Schoetbau et al. (161)*	1121	12	Excl BF (16 wk)	↓ AD
				AD in family: ↑ risk AD
				AD: ×4 ↑ risk of asp-CM-IgE
				AD: ×8 ↑ risk asp-egg-IgE

AD, atopic dermatitis; CMA, cow's milk allergy; CMF, cow's milk formula; BF, breastfeeding.

Effect of infants diet indicated by arrows: ↑, indicate increase; ↓, decrease; →, no change in the incidence of disease/symptoms in infants having the diet as mentioned.

*Not randomized to breastfeeding.

our intervention studies (100–102, 173) the mothers had unrestricted diets during pregnancy and lactation, and the effect as regards prevention of FA seemed not to be less than other comparable studies. Thus, our results do not support a recommendation of maternal diet during pregnancy or during lactation.

The issue whether breastfeeding has an allergy preventive effect remains controversial due to the lack of evidence in some studies and due to the fact that infants cannot ethically be randomly assigned to breastfeeding or formula feeding to enable a definitive study (155, 174).

Low concentrations of food allergens especially CMP are shown to be present in human milk when consecutive testing is carried out (175). According to the low incidence of CMA in exclusively breastfed infants at 0.5% in unselected infants (35), and 1.3% in HR infants (102) in prospective birth cohort studies, this low-degree exposure seems to induce tolerance rather than disease.

Recent studies indicate that variations in the composition of human milk – e.g. low levels of alpha-linolenic acid and relationship between the

Table 8. Results from three meta-analyses on the relationship between exclusive breastfeeding during the first 3 months of life and development of atopic disease

	Effect measure	Studies (n) included/ period (years)	Summary* OR (95% CI)	Population	
				Atopic heredity† OR (95% CI)	Combined‡ OR (95% CI)
Gdalevich et al. (163)	Atopic dermatitis	18/1966–2000	0.68 (0.52–0.88)	0.58 (0.41–0.92)	–1.43 (0.72–2.86)
Gdalevich et al. (164)	Asthma by 2–5 yr	12/1966–1999	0.70 (0.60–0.81)	0.52 (0.35–0.79)	0.99 (0.48–2.03)
Bloch et al. (162)	Allergic rhinitis	6/1966–2000	0.74 (0.54–1.01)	0.87 (0.48–1.58)	0.68 (0.47–0.99)

*Analysis of pooled data.

†Analysis of high-risk populations.

‡Analysis of combined high-risk and non-high-risk populations.

Table 9. Exposure to environmental factors in a birth cohort of atopic pre-disposed infants fed human milk or a hydrolyzed cow's milk-based formula. Breastfed high-risk infants differed from formula fed high-risk infants regarding the following characteristics (102)

	Breastfed	Formula fed
Age at introduction of solid foods (months)	5	4
Exposure to tobacco smoke at home (%)	46	46
Exposure to tobacco smoking by mother (%)	13	29
Exposure to pets (%)	33	42
Socio-economic class	Higher	–

Table 10. Dietary intervention in 'high-risk' infants. Prospective studies including control group. Effect of maternal exclusion diet during pregnancy and/or lactation

Study	n	Follow-up (years)	Maternal diet	Health effect
Fälth-Magnusson et al. (165)	180	0	Pregnancy	→ Total IgE → Spec. IgE
Fälth-Magnusson and Kjellman (166)	180	5	Pregnancy	→ Atopy
Lilja et al. (167)	63	1 1/2	Pregnancy	→ Atopy
Chandra et al. (169)	109	1	Pregnancy and lactation	↓ AD in BF children → AD in CMF children
Zeiger et al. (185, 186)	225	4	Pregnancy and lactation	↓ FA (CMA)
Lilja et al. (167)	107	1 1/2	Pregnancy and lactation	→ Atopy
Businco et al. (168)	101	2	Lactation	↓ Atopy
Chandra et al. (157)	225	1 1/2	Lactation	↓ AD
Lilja et al. (167)	107	1 1/2	Lactation	→ Atopy
Sigurs et al. (170)*†	115	4	Lactation	→ Atopy ↓ AD at 3 months, 6 months and 4 yr
Hattevig et al. (171)*†	105	10	Lactation	→ Atopy, AD at 10 yr → SPT, RAST at 10 yr

AD, atopic dermatitis; CMA, cow's milk allergy; FA, food allergy; CMF, cow's milk formula; BF, breastfeeding. Effect of maternal diet indicated by arrows: ↓, decrease; →, no change in the incidence of disease/symptoms in infants having the diet as mentioned. *Groups assigned by hospital rather than true randomization. †Follow-up at different time points of the same study population.

n-3 and the n-6 fatty acids (176) or varying concentrations of cytokines (177) may in part explain some of the controversies regarding the

protective effect of breastfeeding against allergic disease. No association between nucleotide and polyamine levels in human milk and atopic development during the first year of life has been found (178). However, prospective long-term follow-up studies with a proper sample size are desirable for confirmation of these possible relationships.

2. Formulas: Some prospective studies have shown that *soy* formulas are as allergenic as conventional CMF, and on this basis they should not be recommended for the prevention of FA (154, 157), but controversy still exists (93, 179–182). One study (93) found no preventive effect of soy formula, whereas another (180) indicated a possible preventive effect of soy formula but only to allergen-non-specific atopic symptoms. Further studies may be useful to clarify the allergenicity of soy formula in infants who are prone to the development of allergy. Prospective intervention studies (93, 157, 180) have compared the preventive effect of soy formula with CMF in HR infants, but none included controlled elimination/challenge procedures in order to diagnose FA.

Extensively hydrolysed formulas (eHF) have been investigated in studies on prevention of FA in HR infants. Several prospective studies (Table 11) (100, 101, 157, 173, 183–188) show a preventive effect of eHF in combination with avoidance of CMP and solid foods during ≥4 months in HR infants on the cumulative incidence of atopic dermatitis and FA, especially CMA until the age of 4 yr. Definition of HR infants varies and diagnostic criteria differ considerably in the published studies. Some studies describe the development of possible atopic symptoms rather than specific allergic disease. The development of FA especially CMA has been evaluated in some studies based on well described controlled elimination/challenge procedures (100–102, 159, 185–187, 189, 190). In a Danish controlled intervention study (101) we found a significant reduction in the cumulative

Table 11. Dietary intervention in 'high-risk' infants. Prospective studies including control group. Infant diet – hypoallergenic formula ≥4 months

Study	n	Follow-up (years)	Diet	Health effect
Vandenplas et al. (159)*	45	4 months	pHF	↓ CMA, atopy
Vandenplas et al. (189)*	67	1 1/2	pHF vs. CMF	CMA 15.6%, atopy 21.8% vs. CMA 42.8%, atopy 48.6%
Vandenplas et al. (190)*	58	5	pHF vs. CMF	CMA 29% vs. 60% (cumulated)
Chandra and Hamed (192)*	263	1 1/2	pHF	↓ Eczema, atopy
Chandra (193)*	216	5	pHF BF	↓ Eczema, atopy, FA, asthma
Chan et al. (194)†	110	30 months	pHF	↓ Atopic dermatitis
Chandra et al. (157)†	221	1 1/2	eHF	↓ Eczema
Mallet and Henocq (188)	177	4	eHF	↓ Eczema
Zeiger et al. (185–187)	225 165	1 1/2, 4, 7	eHF	↓ FA/CMA (cumulated) at 1 1/2 and 4 yr
Halken et al. (100)	141	1 1/2 (5)	eHF	↓ CMA (3.6%)
Oldæus et al. (195)	50	1 1/2	eHF	↓ Atopic symptoms 51%
	45		pHF	↓ Atopic symptoms 64%
	46		CMF	↓ Atopic symptoms 84%
Halken et al. (102)	478	1 1/2	pHF vs. eHF	CMA 4.7% vs. 0.6% (p = 0.05)

CMA, cow's milk allergy; FA, food allergy; CMF, cow's milk formula; BF, breastfeeding; eHF, extensively hydrolyzed formula; pHF, partially hydrolyzed formula.

*Diagnostic criteria inclusive food challenge procedure and time for investigation unclear.

†Controlled challenges not performed.

incidence of atopic symptoms from 74% to 32% due to reduced cumulative prevalence of atopic dermatitis (31% vs. 14%, $p < 0.01$), recurrent wheezing (37% vs. 13%, $p < 0.01$), vomiting/diarrhea (20% vs. 5%, $p < 0.01$), infantile colic (24% vs. 9%, $p < 0.01$) and FA from 17% to 6% until the age of 18 months in the prevention group when compared with a control group. The infants in the prevention group were recommended and fed breast milk and/or an eHF exclusively, combined with avoidance of solid foods for the first 4–6 months of life, and they were compared with a historical, but identically defined control group from the same area having no dietary restrictions. Due to ethical reasons we were not able to randomize HR infants to a control group having ordinary cow's milk-based formula at that time. The same experienced pediatricians using the same well-defined diagnostic criteria, as described in 'definitions', investigated the intervention and the control

groups. In all children with symptoms suggestive of CMA controlled elimination/challenge procedures were performed. In this study (100) moreover a significant reduction in the cumulative incidence of documented CMA from 20% in the control group to 3.6% in the prevention group until the age of 18 months was found. No difference between two eHFs: an extensively hydrolyzed casein product (Nutramigen) and an extensively hydrolyzed and ultrafiltrated whey formula (Profylac), was found. Although differences in study design these results were comparable with another intervention study (185–187) in which the dietary restrictions were much more extensive and for a longer duration – up to 3 yr for some foods. In our studies (100, 173) the cumulative incidence of FA and CMA was significantly reduced at follow-up at the age of 5 yr, and in the study by Zeiger (185–187) the cumulative incidence of FA and CMA was significantly reduced until the age of 4 yr. Thus, a real prevention, and not only a postponement of the onset of the disease, was documented. In none of these studies an effect as regards respiratory allergy was found at follow-up at 5 and 7 yr.

Partially hydrolysed formulas (pHF) (with moderately reduced allergenicity) have been investigated in randomized prospective studies (Table 11) (159, 189–194) in HR infants, and an allergy preventive effect has been reported. Because of great variations in study design and diagnostic criteria, the relative efficacy of the different interventions tested in the various studies cannot be compared directly (159, 189, 190, 192, 193). One of these studies (189, 190) reported a very high prevalence of CMA; the reason for this is unclear, but it may be due to less strict diagnostic criteria or selection bias. Recent data from studies comparing the allergy preventive effect of pHF and eHF indicate a greater effect with eHF in two (102, 195) of three studies (102, 195, 196) with well-defined diagnostic criteria. A Swedish study (195) reported a lower cumulative incidence of atopic symptoms up to the age of 18 months with both an eHF and a pHF diet, compared with a CMP-based formula; a greater effect was reported with eHF. We performed a prospective randomized, double-blind study from birth to 18 months of age comparing the allergy preventive effects of two eHFs (Nutramigen® and Profylac®) and one pHF (NanHA®) (102). This study included a 1-yr birth cohort of HR infants ($n = 478$) randomized at birth to one of the three hydrolyzed formulas if breastfeeding was not possible or sufficient. Only a few infants were never breastfed, most of the infants were breastfed exclusively ($n = 232$)

or had varying amounts of supplement with formula (n = 246) until the age of 4 months. Introduction of complementary foods was not recommended until the age of 4 months. After the age of 4 months no dietary restrictions were recommended, and all mothers had an unrestricted diet during pregnancy and lactation. In this study the overall incidence of confirmed CMA was low (1.3%) and significantly lower in infants fed eHF (0.6%) when compared with pHF (4.7%). Thus, the study shows a better allergen-specific preventive effect of eHF, but does not exclude an effect of a pHF also.

3. Combined dietary and environmental intervention: In two properly conducted studies (Table 12) combined dietary and environmental preventive measures have been applied not allowing evaluation of the causative measure of effect (183, 184, 197, 198) (Table 12).

4. Solid foods: The introduction of complementary foods during the first 4–6 months of life has been associated with a higher risk of atopic dermatitis (55). A preventive effect of breastfeeding or hydrolyzed formulas has only been shown in studies including avoidance of complementary foods during at least the first 4 months of life. In our studies (100–102, 173) the infants were recommended to avoid introduction of supplementary foods until 4–6 months of age. After this period no dietary restrictions were recommended and the parents introduced solid foods gradually and initially in small amounts. Thus, at the age of 12 months most fruits, vegetables, meat, cow's milk, egg and fish were introduced successfully into the children's diet. Only few and mild reactions, primarily to egg, were registered.

5. Duration of the diet: The duration and the dietary restrictions vary in different studies. All studies showing a preventive effect have included solely breastfeeding or eHF and avoidance of cow's milk and solid foods for at least 4–6 months. Studies including restrictive diets for a long period >12–24 months and studies with dietary restrictions for only 4–6 months have shown comparable results. In our intervention studies the infants were recommended dietary restrictions for the first 6 months in the first study (100, 101, 173) and 4 months in the last one (102). After that period the children were fed normal infant diets without any restrictions including a conventional CMP formula when formula was needed. Both these regimens resulted in a very low incidence of CMA and other food allergies until the age of 18 months (100–102, 173). In another recent study (199) no significant effect of supplement with hydrolysate formula (eHF) compared with CMF after the age of 6 months in breastfed HR infants was found. Controlled studies concerning the possible preventive effect of avoidance of other potential food allergens, e.g. egg, fish etc. after the age of 4–6 months of life have not been published. Thus, there is no evidence of allergy preventing effect of restrictive diets after 6 months of age.

6. Probiotics: One recent prospective study (135) has investigated probiotics in primary prevention of atopic disease. This study showed a preventive effect of supplementing the diet of HR infants by probiotics 2–4 wk prenatal and in the first 6 months of life. Meanwhile, the effect was only shown as regards point prevalence of mild atopic dermatitis at the age of 2 yr and no effect was shown as regards sensitization/proven allergic disease. This theory needs confirmatory evidence.

Table 12. Combined dietary and environmental intervention in 'high-risk' infants. Prospective studies including control group

Study	n I/C	Follow-up (years)	Intervention		Effect of intervention (I vs C)
			Dietary	Environmental	
Arshad et al. (183), and Hide et al. (184, 197)	120 58/62	2 and 4	9 months exclusive BF/eHF	Mattress encasing + acaracide	↓ HDM SPT 5.2 vs. 24%* ↓ Allergy†
Chan-Yeung et al. (198)	493 251/242	1	12 months BF/pHF SF after 6 months	Mattress encasing + benzoate	↓ A/AR RR 0.66 (0.44–0.98)

I, intervention group; C, control group; A, asthma; AR, allergic rhinoconjunctivitis; HDM, house dust mite allergen; BF, breastfeeding; eHF, extensively hydrolyzed formula; pHF, partially hydrolyzed formula; RR, relative risk (95% confidence interval).

*p < 0.02.

†Allergy = asthma, allergic rhinitis, atopic dermatitis, food allergy + pos SPT.

Environmental intervention

Unselected/non high-risk infants. Whilst there is no direct evidence for the increase in allergen exposure, the indirect evidence is overwhelming. Most people with so-called 'Western life-style' spend more than 95% of their time indoors and children spend more time indoors than ever before. The indoor environment of homes (introduction of central heating, wall-to-wall carpeting, etc.) has changed over the last 3 decades, making it more suitable for dust mite population growth. The number of indoor pets has increased, resulting in increased community exposure. Houses have become better insulated, with lower air-exchange rates, and a consequent

substantial increase in concentration of potentially harmful substances in indoor air (e.g. allergens, air pollutants).

Based on the concept that pillows with synthetic filling are non-allergenic compared with feather pillows, the use of pillows with synthetic filling has increased over the past few decades (200). Meanwhile, recent studies have shown that synthetic pillows accumulate HDM allergens faster (201), and contain more HDM allergen (201) and cat and dog allergen (202) than feather pillows. The prevalence of asthma is negatively associated with use of feather pillows when compared with synthetic pillows (200).

The relationship between allergen exposure and development of allergic disease is confounded by a number of important factors and individuals are exposed to a mixture of several allergens, irritants and pollutants, which may act and interact in different ways by several mechanisms. Moreover, the measures of reservoir allergen measured in most studies are at the best surrogate measures of personal inhaled exposure.

Several cross-sectional and prospective studies documents that there is a close dose-response relationship between HDM allergen exposure in the home and development of IgE-mediated sensitization and subsequent asthma. Concerning pets, especially cat allergen, the results are much more contradictory, but prospective studies indicate that early life exposure to cat is associated with an increased risk of sensitization to cat and increased risk of developing asthma symptoms in HR children.

High-risk infants. The effect of exposure to tobacco smoke and to indoor allergens seems to be most pronounced in children with atopic predisposition and in children with exposure during the first months/year of life. There seems to be a synergistic effect of several co-existing environmental factors (70, 103).

So far, a few prospective, randomized studies have investigated the efficacy of the avoidance of indoor allergens (HDM) (197, 198, 203). These studies have produced the first indication that a reduction in HDM allergen levels in homes of HR infants may reduce the prevalence of sensitization to HDM and recurrent wheezing during the first years of life. One prospective, randomized study (183, 184, 197) has investigated the efficacy of avoidance of indoor allergens (HDM) in HR infants followed from birth until the age of 4 yr. The intervention included dietary avoidance measures and HDM avoidance measures with encasing of mattresses and acaracides. A significant reduction in sensitization and allergic

symptoms at the ages 1, 2, 3 and 4 yr were found, as well as significant reduction in number of children who were sensitized against HDM. A reduction (not statistically significant) was found as regards the incidence of asthma at 4 yr. However, the small number of children and the difficulty of diagnosing asthma in this age group may explain this finding. In another prospective randomized study (198) in HR infants avoidance of pets, HDM avoidance measures (mattress encasing and benzyl benzoate powder for carpets and furniture's) and dietary measures (breast-feeding supplemented with pHF when necessary up to 1 yr) resulted in a modest, but significant reduction in the risk of possible or probable asthma or rhinitis at the age of 12 months. As most children in the intervention group and the control group were breastfed for a long period and had only little supplement, the effect was ascribed to the environmental measures. Recently, a large prospective, prenatally randomized, cohort study indicated 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 resulting in a 50% reduction of airway atopic symptoms during the first year of life, most pronounced for attacks of severe wheeze with shortness of breath, prescription of medication for wheezy attacks, and wheeze after exertion (204, 205). Moreover, cat ownership was significantly associated with sensitization to cats (205). As the diagnosis of asthma is difficult in this age group, and sensitization to inhalant allergens most often occurs at a later age further follow-up of these studies is necessary.

A recent prospective, randomized but open study (203) included infants less than 1 yr of age with atopic dermatitis and sensitization to egg/milk/soy but not HDM. In this study it was found that reduction of exposure to HDM allergens with encasing of mattresses significantly reduced the risk of sensitization to HDM allergens after 1 yr.

Thus, in homes of HR infants, current evidence supports measures to reduce the level of indoor allergens, such as HDM and pets. Furthermore, as for non-HR infants, exposure to tobacco smoke, damp housing conditions and indoor pollutants should be avoided.

Children with allergic symptoms (secondary prevention).

1. Allergen avoidance: Avoiding exposure to relevant allergens is a logical way to treat allergic diseases (e.g. allergic asthma) when the offending allergen can be identified and effective avoidance

is feasible. Allergen avoidance in a mountain environment improves lung function and normalizes markers of allergic inflammation in children with allergic asthma (206–210). Several controlled randomized studies have shown that allergen (especially HDM allergens and animal dander) avoidance measures are effective both in reducing the level of allergens and in improvement of disease control (203, 210–230). Some efficacy in allergen reduction has been reported by washing, steaming and vacuum cleaning procedures (231–233). Meanwhile, most of the previous studies included small number of patients, a short follow-up period and only a small degree of evaluation of changes in the severity of the asthma symptoms and asthma medication. In a large prospective, double-blind placebo-controlled study (234) we were able to show that encasing of mattresses and pillows, with semi permeable polyurethane encasings (Allergy Control®) when compared with placebo encasings, resulted in a significant perennial reduction in HDM allergen concentrations in mattresses and a significant reduction of the needed dose of inhaled steroids by approximately 50% (mean dose: 408 μg $\rightarrow$ 227 $\mu\text{g}/\text{day}$) in children with physician-diagnosed asthma and documented HDM allergy after 1-yr follow-up. Despite the reduction in pharmacologic treatment the children were well treated with few symptoms and a normal lung function during the follow-up period. The HDM allergy was documented by a positive bronchial challenge with HDM allergen at inclusion. This is the first study documenting a clinical relevant steroid sparing effect of allergen avoidance by means of mattress encasings in children with asthma and HDM allergy. Moreover, the study confirms the clinical importance of allergen exposure in children with allergic asthma.

2. Other environmental measures (avoidance of irritants, especially tobacco smoke): The association between parental smoking and recurrent wheezing and asthma in children is well documented, with severity and frequency of symptoms related to the extent of exposure. Avoidance of passive smoking reduces morbidity and use of medication and improves lung function in asthmatics. Tobacco smoke appears to be one of the most important preventable asthma inducers and triggers.

Specific immunotherapy

Specific immunotherapy (SIT) has been demonstrated in many studies to be an effective treatment for patients with allergic rhinoconjunctivitis. Recently, SIT with subcutaneous injections has

been shown to be effective in allergic asthma in randomized controlled trials with extracts of HDM, pollen, and animal dander (especially cat). A significant reduction in asthma symptoms and medication, and a reduction in both non-specific as well as allergen-specific airway hyperresponsiveness has been documented (235–240).

Rhinitis frequently precedes the onset of asthma, and patients who also have bronchial hyper responsiveness are more likely to develop asthma (241–244). Up to 50% of patients with hay fever show bronchial hyper responsiveness during the season (245, 246). Previous studies indicate a potential preventive effect of SIT as regards bronchial hyperresponsiveness in children with asthma and allergy to cat (247, 248) and HDM (240, 249) and the development of asthma in patients with allergic rhinoconjunctivitis (250, 251). In the European multi-center Preventive Allergy Treatment Study (PAT study) (252) we aimed at investigating the possible preventive effect of SIT in children aged 7–13 yr with allergic rhinoconjunctivitis and grass and/or birch pollen-allergy as regards development of asthma and new sensitivities. The children were randomized to SIT for 3 yr or a control group. Children in both groups received optimal symptomatic treatment and followed prospectively for 5 yr. A 10-yr follow-up is planned. Treatment with local steroids was avoided. Before start of SIT 20% had mild asthma during the pollen season(s). Among those without asthma significantly fewer in the immunotherapy group developed asthma when compared with the control group (19/79 = 24% vs. 32/72 = 44%) after the first 3 yr; and methacholine bronchial provocation test results improved significant in the active group. The results after 5 and 10 yr are awaited. This is the first study showing that SIT has the potential for preventing the development of asthma in children with hay fever and pollen allergy, and that it may be possible to interfere with the natural course of allergic diseases.

Other studies indicate that SIT may have a preventive effect as regards development of new sensitivities (253–255), but long-term follow-up of good prospective studies inclusive of the PAT study are awaited.

Conclusion and perspectives

The development and phenotypic expression of atopic diseases depends on a complex interaction between genetic factors, environmental exposure to allergens, and non-specific adjuvant factors, such as tobacco smoke, air pollution and infections.

According to present knowledge from prospective non-interventional studies, atopic predisposition is associated with a significantly increased risk for development of atopic disease in childhood. However, the majority of children who develop atopic disease, particularly recurrent wheezing and asthma, during early childhood do not belong to HR groups for development of atopic disease.

In the evaluation of the clinical significance of different environmental factors it is important to be aware of the existence of different phenotypes of the allergic diseases, e.g. there is compelling evidence of at least two different phenotypes of asthma – a so-called infectious type triggered by viral infections, and allergic asthma associated with atopic predisposition and sensitization to particularly indoor allergens.

Breastfeeding and late introduction of solid foods (>4 months) are associated with a reduced risk of FA (especially CMA), atopic dermatitis, recurrent wheezing and asthma. A clear association between exposure to indoor allergens and sensitization as well as a clear association between sensitization and development of asthma has been documented, especially in HR infants. Several studies have documented a relationship between prenatal as well as postnatal exposure to tobacco smoke, and development of asthma as well as increased morbidity in asthmatics. The first year(s) of life seems to be an especially vulnerable period, where exposures to several risk factors such as tobacco smoke and indoor allergens [HDM and molds (often associated with high indoor humidity) and animal dander (especially cat)] seem to act in a synergistic manner.

Many other factors have been incriminated, mostly from cross-sectional and/or case-control studies. These factors include early infections, vaccinations, intestinal flora, family size (number of siblings and sibling order) and dietary factors such as low intake of n-3 fatty acids, antioxidants or high sodium intake. At present there is no convincing evidence for the possible influence of these factors on the development of atopic disease. As regards the influence of 'indoor pollution' (chemical vapors, gasses, formaldehyde and volatile organic compounds) and outdoor pollution, there is evidence of a cause-effect relationship between exposure to pollutants and induction of respiratory symptoms, whereas the role of pollutants for the development of asthma and atopic airway disease seems less important and needs further elucidation.

Generally, the increased prevalence of atopic diseases in childhood has particularly been

registered in countries with a so-called 'western lifestyle', and there has been an eager search for 'the responsible factor'. However, atopic diseases are multifactorial, and it appears unlikely that one or a few factors are responsible for the changing prevalence and pattern of atopic diseases. At present data show evidence of the effect of dietary allergy preventive measures as regards FA, especially CMA and atopic dermatitis. There is no evidence for prenatal dietary intervention during pregnancy.

In planning intervention to prevent the development of allergic diseases we need to target the factors for which there is valid evidence of their effect and for which the preventive measures can be controlled. It is obvious that an attempt to make an allergy prevention strategy should include environmental as well as dietary measures. Moreover, it seems reasonable to act on the present evidence and give advice to the parents, while we continue to test intervention strategies both to evaluate their efficacy and to resolve the components which are necessary and which confer the greatest benefits.

In all infants breastfeeding should be encouraged for at least 4–6 months, and likewise exposure to tobacco smoke should be avoided during pregnancy as well as during early childhood. In HR infants a documented eHF is recommended if exclusive breastfeeding is not possible for the first 4 months of life. In homes of HR infants, current evidence supports measures to reduce the levels of indoor allergens, e.g. pets and HDM.

Some studies indicate that early allergen-specific treatment reduces the need for pharmacologic treatment and may influence the natural course of the disease in preventing development of new symptoms and sensitivities. In children with allergic asthma and HDM allergy, HDM allergen avoidance measures, including encasing of mattresses and possibly pillows and blankets/duvets should be an integrated part of the treatment. SIT may be effective in preventing development of asthma in children with allergic rhinoconjunctivitis, and may therefore be a part of the treatment at an early stage of the disease.

Implementation of preventive measures

Simple dietary recommendations for HR infants have proven beneficial as regards reduction of the risk for development FA, especially CMA. Thus, if exclusive breastfeeding for 4–6 months is not possible in HR infants, a documented hypoallergenic formula and avoidance of solid foods are recommended for the first 4 months of life.

As direct evidence of the primary risk factors leading to the increase in asthma prevalence does not exist, it is necessary to test the hypothesis of changing the exposure to the risk factors for which there is a good evidence of an association with asthma. Evidence for risk factors with a direct causal role is most complete for indoor allergens, especially HDM. General health promotion may address the needs of the general population whereas more focused and specialized intervention strategies may be appropriate for those at high risk. As genetics and environment differ in different parts of the world, prevention measures may also differ.

Preventive effect of dietary measures

Intervention	Effect
Exclusively breastfeeding, at least 4 months For nutritional reasons WHO recommends breastfeeding for the first 6 months for all children	↓ Cumulative incidence of CMA until 18 months ↓ Cumulative incidence of AD until 3 yr ↓ Recurrent wheeze/asthma until 6 (-17) yr
eHF* combined with avoidance of solid foods ≥4–6 months	↓ Cumulative incidence of CMA until 5 yr and AD until 4 yr
pHF* combined with avoidance of solid foods ≥4–6 months	Some effect, although less than eHF
• No convincing evidence for a preventive effect of maternal diet during pregnancy or lactation • No convincing evidence for a preventive effect of a diet after the age of 4–6 months • An allergy preventive effect has been documented only in high-risk-infants	

*Exclusively or as a supplement to breastfeeding.

Primary prevention: evidence-based recommendations

- For all infants
- No special diet during pregnancy or to the lactating mother.
 - Exclusively breastfeeding preferably for 6 months but at least 4 months. If supplement is needed conventional cow's milk-based formula is recommended.
 - Avoidance of solid food until preferably the age of 6 months but at least 4 months.
 - Avoidance of exposure to tobacco smoke – also during pregnancy.
- Further recommendations for infants with a high risk for allergic disease*:
- If supplement is needed during the first 4 months, a documented hypoallergenic formula is recommended. After the age of 4 months high-risk children can be nourished like non-high-risk children.
 - Reduced allergen exposure early in life (house dust mites, pets, cockroaches).
-
- Based on allergy prevention studies exclusively breastfeeding and avoidance of solid foods for at least 4 months seems to be sufficient for allergy prevention; but according to dietary recommendations from WHO, exclusively breastfeeding for 6 months is recommended.
 - Regarding non-dietary recommendations avoidance of exposure to tobacco smoke – also during pregnancy – is most important for all children.

*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.

Secondary prevention: evidence-based recommendations

Avoidance of tobacco smoke.
Patients who have perennial asthma, rhinitis or atopic dermatitis and who are allergic to house dust mites or animal dander should try to reduce their exposure to the relevant allergens. Recommended measures include:
Reduction of indoor relative humidity below 50% if possible.
Encasing of mattresses with documented protective coverings.
Washing of pillows in hot water (>55°C) regularly or encasing of pillows with documented protective coverings.
Washing of bedding in hot water (>55°C) regularly.
Removal of carpets in bedroom.
Vacuum cleaning regularly.

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This thesis is based on the following previously published papers, which will be referred to in the text by their numbers in the reference list:

30. HANSEN LG, HALKEN S, HØST A, MØLLER K, ØSTERBALLE O. Prediction of allergy from family history and cord blood IgE levels. A follow-up at the age of 5 years. Cord blood IgE IV. *Pediatr Allergy Immunol* 1993; 4: 34–40.
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None of these papers has been a part of an academic thesis.

Denne afhandling er den 10. marts 2004 af Syddansk Universitets Sundhedsvidenskabelige Fakultetsråd antaget til forsvar for den medicinske doktorgrad.

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Forsvaret finder sted den 18. juni 2004 kl.14.00 i Store Auditorium, Winsløwparken 15,1, Odense Universitetshospital, 5000 Odense C

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ISSN 0906-5784

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Pediatric Allergy and Immunology, Blackwell Munksgaard, Copenhagen

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Abstract

Halken S. Prevention of allergic disease in childhood: clinical and epidemiological aspects of primary and secondary allergy prevention.

Pediatr Allergy Immunol 2004; 15 (Suppl. 16): 1–32.

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The development and phenotypic expression of atopic diseases depends on a complex interaction between genetic factors, environmental exposure to allergens, and non-specific adjuvant factors, such as tobacco smoke, air pollution and infections.

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.

The objective for this review was to evaluate possible preventive measures as regards prevention of development of allergic disease in childhood – primary prevention – and also some aspects of the effect of specific allergy treatment as regards secondary prevention in children with allergic asthma and allergic rhinoconjunctivitis.

In one prospective observational study of a birth cohort of unselected infants we evaluated possible predictive/risk factors. In two prospective intervention studies including 1 yr birth cohorts of high-risk (HR) infants we investigated the effect of feeding HR infants exclusively breast milk (BM) and/or hydrolyzed cow's milk-based formula the first 4–6 months as regards: (i) the allergy preventive effect of BM/ extensively hydrolysed formula (eHF) compared with ordinary cow's milk-based formula, (ii) the effect of two different eHFs, a whey (Profylac®) and a casein-based (Nutramigen®) formula, as regards development of cow's milk protein allergy (CMA), and (iii) a comparison of the preventive effect of eHF (Profylac®/Nutramigen®) with a partially hydrolyzed cow's milk-based formula (pHF) (NanHA®) as regards development of CMA. None of the mothers had a restricted diet during pregnancy or lactation period.

In two prospective randomized intervention studies we evaluated the preventive effect of specific allergen avoidance and specific immunotherapy (SIT) in children with allergic asthma and allergic rhinoconjunctivitis, respectively.

The combination of atopic heredity and elevated cord blood IgE resulted in the best predictive discrimination as regards development of allergic disease. The optimal high-risk group was defined by

either double parental atopic predisposition or single atopic predisposition, the latter combined with a cord blood IgE ≥ 0.3 kU/l. 66% of unselected infants were daily exposed to tobacco smoke, which was a significant risk factor for recurrent wheezing until the age of 1.5 yr. HR infants were breastfed for a longer period and less exposed to tobacco smoke than unselected infants. Exclusively BM/eHF for at least 4 months was associated with a significantly reduced cumulative prevalence of CMA [3.6% (5/141) vs. 20% (15/75) in the control group] up to 5 yr. The effect of the two different eHFs was similar. Exclusively breastfed infants were significantly less exposed to tobacco smoke and pets, had solid foods introduced later and belonged to higher social classes. pHF was significantly ($p = 0.05$) less effective than eHF as regards prevention of development of CMA. A diet period of 4 months seems to be as efficient as 6 months or more as regards development of CMA.

A few ongoing prospective, randomized intervention studies have produced the first indication that avoidance of indoor allergens such as house dust mite (HDM) in HR infants may reduce the incidence of severe wheeze and sensitization during the first 1–4 yr of age. Long-term follow-up is awaited.

In a prospective, double-blind placebo-controlled study in children with doctors diagnosed asthma and documented HDM allergy, we found that semipermeable polyurethane mattress and pillow encasings (Allergy Control®) when compared with placebo encasings resulted in a significant perennial reduction of HDM exposure and a significant reduction in the needed dose of inhaled steroids by approximately 50% (mean dose: $408 \mu\text{g} \rightarrow 227 \mu\text{g/day}$) after 1-yr follow-up. In another randomized prospective study we investigated the possible preventive effect of SIT in children with allergic rhinoconjunctivitis and grass/birch pollen allergy as regards development of asthma. Among those without asthma significantly fewer in the SIT group developed asthma when compared with the control group ($19/79 = 24\%$ vs. $32/72 = 44\%$) after the first 3 yr; and methacholine bronchial provocation test results improved significantly in the SIT group.

The results of our studies support the evidence that the risk for development of early allergic manifestations e.g. CMA and atopic dermatitis can be reduced significantly by simple dietary measures for the first 4 months of life. In all infants breastfeeding should be encouraged for at least 4–6 months, and exposure to tobacco smoke should be avoided during pregnancy and early childhood. In HR infants a documented

hypoallergenic formula (at present eHF) is recommended if exclusive breastfeeding is not possible for the first 4 months. In homes of HR-infants, current evidence supports measures to reduce the levels of indoor allergens, e.g. HDM and pets.

In symptomatic children allergen-specific treatment may influence both the symptoms and the prognosis. Allergen avoidance can reduce the need for pharmacological treatment, SIT may have the potential for

preventing the development of asthma in children with allergic rhinoconjunctivitis, and it may be possible to interfere with the natural course of allergic diseases.

Key words: allergy prevention; allergy prediction; cow's milk allergy; hypoallergenic formula; children

Definitions

Adverse reaction

Reproducible clinically abnormal response to a substance, which usually does not give any reactions.

Allergic Rhinitis/conjunctivitis

Rhinitis or conjunctivitis lasting at least 1 month or appearing at least twice caused by exposure to a particular allergen and diagnosed by a physician.

Allergic urticaria

Urticaria appearing at least twice caused by exposure to a particular allergen and diagnosed by a physician.

Allergy

Hypersensitivity reaction initiated by immunological mechanism(s). A variety of immunological mechanisms may be involved in allergic reactions and allergy may be IgE-mediated or non-IgE mediated. Thus, the definition depends on methods of analysis.

Asthma (bronchial asthma)

At least three episodes of wheezing requiring bronchodilator treatment and diagnosed by a physician. In schoolchildren the diagnosis of asthma should be verified by the objective registration of variation in lung function spontaneously or due to therapy, e.g. an increase in $FEV_1 \geq 12\%$ after inhalation of a β -2-agonist.

Atopy

A personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as asthma, rhinoconjunctivitis or eczema/dermatitis.

Atopic dermatitis (AD = AEDS)

Areas of scaly, erythematous and itchy eczematous rash primarily of the face, the scalp and at/in the flexural folds revealed by physical examination. Only eczema with at least two locations in typical areas and chronically/relapsing with duration of at least 3 months was registered.

Atopic predisposition

At least one first-degree relative with documented atopic disease (bronchial asthma, allergic rhinoconjunctivitis, atopic dermatitis, food allergy).

Atopic symptoms

Bronchial asthma, atopic dermatitis, allergic rhinoconjunctivitis, allergic urticaria and/or food allergy.

Cow's milk protein allergy (CMA)

Proven or likely immunologically mediated (any of types I–IV) reaction to cow's milk protein associated with reproducible adverse reactions, giving symptoms from the gastrointestinal tract, the skin or the respiratory tract. Diagnosed by controlled elimination/challenge procedures.

The diagnosis of CMA should be confirmed by controlled elimination/challenge procedures. Reproducible atopic symptoms (skin, gastrointestinal, and respiratory) temporally associated with CM ingestion. The following criteria should be fulfilled: (a) definite disappearance of symptoms after each of two dietary elimination's of cow milk and cow milk products, (b) recurrence of identical symptoms after one challenge, and (c) exclusion of lactose intolerance and coincidental infection. All challenges were performed open, but with equivocal results the challenge was repeated and blinded.

Food allergy (FA)

Proven or likely immunologically mediated reaction to food(s) associated with reproducible adverse reactions, giving symptoms from the gastrointestinal tract, the skin or the respiratory tract. Diagnosed by controlled elimination/challenge procedures.

High-risk infants

The definition of high-risk infants varies considerably in different studies, from single atopic heredity to double atopic heredity and in some studies combined with elevated cord blood IgE with different cut-off values.

In our studies high-risk infants were defined as having double parental doctors diagnosed and treated atopic disease (asthma, hay fever, atopic dermatitis, allergic urticaria, and food allergy), or

severe single atopic predisposition combined with CB IgE ≥ 0.3 kU/l. Severe atopic predisposition was present, when one parent and/or one or more older sibling had, or had had atopic disease with perennial symptoms or symptoms from more than one organ system.

Hypoallergenic infant formulas

- Nutramigen (MeadJohnson, USA), an extensively hydrolyzed casein formula. MW < 1.500 kDa.
- Profylac (ALK, Denmark), an extensively hydrolyzed, ultrafiltrated whey formula. MW < 8 kDa.
- Nan HA (Nestle, Switzerland), a partially hydrolyzed whey formula. MW in the range of 5–40 kDa (15, 21, 22).

Prevention

- 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.

Recurrent wheezing

At least two episodes of wheezing, most often associated with respiratory infections, requiring bronchodilator treatment and diagnosed by a physician.

Sensitization

Any immune response to a foreign antigen, most often measured as an *IgE*-mediated sensitization, which is an *IgE* response to a foreign antigen (allergen) as measured by *in vitro* *IgE* determination or SPT.

Positive predictive value (PPV) = true positives / (true positives + false positives).

Negative predictive value (NPV) = true negatives / (true negatives + false negatives).

Sensitivity = true positives / (true positives + false negatives).

Specificity = true negatives / (true negatives + false positives).

Abbreviations

A	asthma (bronchial asthma)
AD = AEDS =	atopic dermatitis
AR	allergic rhinitis
BF	breast fed /feeding
BM	breast milk
CB	cord blood
CI	confidence interval
CM	cow's milk
CMA	cow's milk protein allergy
CMF	cow's milk based formula
CMP	cow's milk protein
DBPCFC	double-blind placebo-controlled food challenges
ESPACI	European Society for Pediatric Allergy and Clinical Immunology
ESPGHAN	European Society for Pediatric Hepatology, Gastroenterology and Nutrition
FA	food allergy
FH	family history
HDM	house dust mite
eHF	extensively hydrolyzed formula
pHF	partially hydrolyzed formula
IgE	immunoglobulin class E
asp IgE	IgE directed against a specific allergen
OR	odds ratio
PPV	positive predictive value (predictive value of a positive test)
NPV	negative predictive value (predictive value of a negative test)
RW	recurrent wheezing
SIT	specific immunotherapy
SPT	skin prick test
WHO	World Health Organization