

Prediction and prevention of atopic allergy

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During the last three decades, a two- to threefold increase in the prevalence of major allergic diseases, i.e., bronchial asthma, allergic rhinitis, and atopic dermatitis, has been reported (1). Positive skin prick tests ("atopy") and allergic diseases seem to be significantly more common in affluent than developing countries (2). The results have been confirmed by validated questionnaires in the International Study of Asthma and Allergies in Childhood (ISAAC), in which information about allergic manifestations in several hundred thousand children from all over the world (3) has been collected.

The importance of a family history of allergy for the development of allergic disease has been recognized for centuries. Subjects with a family history of allergy have a two- to threefold higher risk of developing allergic disease than subjects with no such history (4), and they are particularly prone to develop IgE antibodies and allergic manifestations if exposed to allergens at an early age (5). Many other risk factors for atopic allergy have been identified, such as exposure to tobacco smoking during pregnancy, infancy, and childhood (6); urban living (7); and indoor humidity or mold growth (8) (Fig. 1). These factors are important for the development and progression of atopic diseases, not only in affluent but also in developing societies (2). Therefore, prevention of atopic diseases should be possible by reducing exposure to known risk factors, particularly among those who are genetically predisposed to atopic allergy. Taken together, however, the cited risk factors can explain only a small part of the increase in atopic diseases during the last decades. Research efforts should focus on the cause(s) of the recent increase

in allergic disease – associated with a Western lifestyle and a high socioeconomic status. Preventive measures should reduce exposure to allergens and adjuvants known to cause allergic disease, particularly – but not exclusively – among those at high risk of developing allergy (primary prevention) and those who already suffer from allergy (secondary prevention).

This paper will summarize attempts to predict and prevent the onset of atopic allergy; in particular, publications since 1982 (9).

Prediction

An evidence-based prevention program for subjects identified as at high risk of allergy is a prerequisite for attempts to predict allergy in healthy subjects (10). Subjects at high risk of allergy (>40%) may be identified as neonates or infants. Allergic diseases preferentially develop in genetically predisposed subjects in response to repeated contact with exogenous factors, and research has focused on various aspects of the family history of allergy and tests in the neonate indicating that the baby has or has not inherited a trait associated with atopic disease; e.g., a high serum IgE level.

The usefulness of a particular test for the prediction of later developing atopic disease may be assessed by calculating the following:

- 1) the *sensitivity*: the percentage of sick subjects identified by a positive test
- 2) the *specificity*: the percentage of healthy subjects having a negative screening test

- 3) the *positive predictive value*: the percentage of subjects with a positive test developing disease during the observation period
- 4) the *negative predictive value*: the percentage of subjects with a negative test not developing disease during the observation period.

For a screening test to be useful, it is not enough to offer a high positive predictive value – the sensitivity of the test must be high or moderately high and the specificity must be high. A simple summary of all attempts to predict allergy accurately by tests is that no test meets all these criteria, nor is the family history of allergy particularly useful, but combinations of tests and a carefully taken family history may at least help to find candidates for clinical trials of prevention programs.

In the early 1970s, IgE determination with PRIST® was compared with other methods (11). The PRIST method allowed the determination of low IgE concentrations. During the collection of a reference material of healthy, nonatopic children from nonatopic families, we found a considerable variation in IgE values in children of the same age (12). Among the healthy infants with the highest IgE values, the development of atopic disease during the subsequent 18 months was 10 times higher than if the serum IgE concentration was lower. A “predictive value” of a raised IgE level in cord blood was shown in a few cases (13). On the hypothesis that babies at high risk of allergy might be identified by adding neonatal IgE determination to a carefully taken family history of allergy, we started collecting cord serum samples from consecutive live births in Linköping, Sweden, in 1974. A few years later, cord-blood IgE values (with the PRIST method) and questionnaire data from the first 18 months of life were available from 1701 children born in 1974–5, and 1654 of them were

Table 1. Examples of investigations used for prediction of allergic/atopic disease in healthy neonates, infants, and young children (reference citations in parentheses)

Parents/siblings	Family history of allergy (14, 15, 24)
Mothers	IgG/IgA to cow's milk, egg, and wheat in colostrum (26, 53)
Neonates	Serum IgE in cord blood (14, 18, 21–23, 54) Specific IgE (55, 56) IgG to milk, egg, and wheat (57) IgG anti-IgE (27) Eosinophils (24, 58) Platelets (24) Lymphocytes, cytokine profile, stimulation index of mononuclear cells (28, 59–61) Phosphodiesterase/mononuclear leukocytes (62) Skin quality (24) Histamine skin prick test (24)
Infants	Blood tests or skin tests as in neonates (59, 63, 64) Eosinophils (65) Metachromatic cells (66)

followed-up with questionnaires to 11 years of age (14–16). Questionnaire data had a high validity in a sample of the children seen by a pediatrician who was not aware of the cord-blood IgE value before either a cumulative diagnosis of allergic disease had been established or no allergy had been found. The positive predictive value of a high cord-blood IgE level (≥ 0.9 kU/l) was about 80%, confirming the initial results. However, the sensitivity of the test was only 26% for any atopic disease manifestation from birth to 11 years of age. The sensitivity was higher for more serious and multiple manifestations or allergic disease with current symptoms reported in every questionnaire during the study. The specificity of cord-blood IgE determination was high (94%). In the same cohort of children, the sensitivity of an immediate family history of allergy was 45% with a specificity of 74%. Thus, neither of the evaluated predictors was found to be suitable for allergy-risk screening in the general population. When we combined the information of the cord-blood IgE and the family history, the sensitivity increased to 56% – still not ideal for use in a screening program. Several other groups have also assessed cord-blood IgE determination for allergy-risk screening with somewhat varying results, which were initially encouraging and then showed the low sensitivity of the test (17–21). Nowadays, there is agreement that cord-blood IgE determination, used as a single test, is not suitable for allergy-risk screening (22, 23).

With a simple scoring system for obvious (2 points) or probable (1 point) atopic disease in the mother, father, and group of siblings, prediction was slightly improved, particularly if a high score (5–6) coincided with elevated cord-blood IgE or blood eosinophilia in the neonatal period (24). Many tests have been applied, including tests in

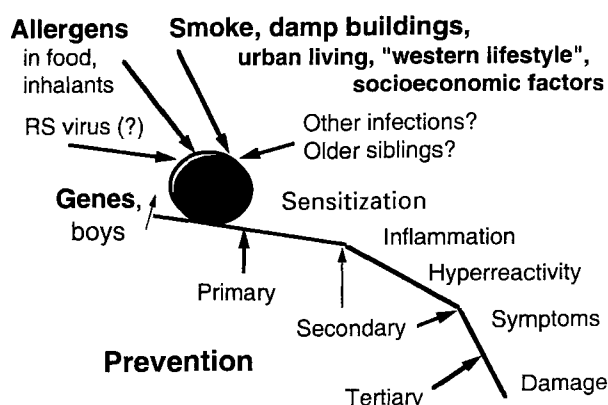


Fig. 1. Risk factors for development of atopic allergy, protective factors, and potential means for prevention.

Table 2. Summary of recommendations by board of pediatric allergists in Sweden to families of babies at high risk of developing atopic allergy (revised 1997)

Pregnancy	Refrain from smoking Do not keep furred pets Breast-feeding to be promoted
Early feeding	Breast-feeding to be promoted, preferably to 6 months of age, and if there is need for substitute, use <i>extensively</i> hydrolyzed cow's milk-based formula Do not give hen's egg, fish, or nuts/peanuts before 12 months
Environment	No solids before 4 months of age No smoking at home Do not keep furred pets indoors Take action against indoor damp and high indoor humidity, as evidenced by water condensation on inner of two windowpanes during winter; if indoor air is perceived as dry, try to reduce temperature and avoid pollutants or too high humidity

parents, neonates, and infants, all, however, showing a low level of sensitivity, often about 20%, or a low specificity (a high number of false-positive tests) (Table 1).

Furthermore, many of the tests are complicated and not available at ordinary laboratories. For instance, some tests may help us to understand some of the mechanisms of interaction between the mother and her fetus/baby (25–27), and/or mechanisms of sensitization (28), but they are not suitable for general screening purposes. Thus, a family history of allergy, if carefully taken from the mother *and* the father, is still the best method we have to predict a high risk of subsequent allergy. Children with two atopic parents (or parents with multiple allergic manifestations) constitute a particular risk group for allergic disease before 11 years of age (15), but children with a biparental history of allergy were only a minority (10%) of all children with atopic disease at any time from birth to 11 years (15). Therefore, if we want to achieve a considerable reduction in the development of atopic allergy, preventive measures should be recommended to everyone, as lifestyle already during pregnancy (particularly smoking) may affect, among other things, the level of airway reactivity in the baby (29) and the development of allergic manifestations later (6, 30).

Prevention

Controlled trials of allergy prevention have been performed only in infants at high risk of developing atopic allergy. Preventive measures recommended to the general population are based on results of epidemiologic studies, calculating the "attributable proportion" of various exposures (31–33). Exposure during infancy (and smoking during pregnancy) seems crucial for later development of

allergic disease. The importance of allergen exposure *in utero* remains to be elucidated (34). Maternal immunity may modify the outcome of allergen exposure via placenta and breast milk.

Breast-feeding seems to be essential for many aspects of health, including the transfer of maternal immunity to the child, thereby protecting against certain respiratory tract infections (35) and gastrointestinal disorders, and stimulating the maturation of the immune system (36). Breast-feeding is now so common that it is difficult to perform studies of its importance, as practically all children are breast-fed from the beginning. It was recently shown, however, that adolescents, breast-fed for 1 month or more, had significantly less respiratory allergy than those not breast-fed at all or for less than 1 month (37). Breast-feeding for 9 months or more (and feeding with an extensively hydrolyzed cow's milk-based formula) significantly reduced wheezing before 18 months of age (38).

There are no studies supporting recommendations to eliminate highly allergenic foods from the pregnant mother's diet (39). Elimination of such foods during lactation has shown controversial results (40–42) and is now recommended only if the baby has symptoms or signs of allergic disease. Retrospective studies support the introduction of "Beikost" (solid food) after, but not before, 4–6 months of age (43, 44).

The effect of comprehensive prevention programs in babies at high risk of allergy was moderate and usually transient (45). Poor compliance may partly explain the results. Elimination diet has been shown to reduce food allergy and atopic dermatitis, but not asthma, while environmental measures reduced respiratory symptoms and sensitization to indoor allergens (46, 47).

Recommendations given to families of *newborn babies regardless of family history of allergy* should include a nonsmoking policy during pregnancy and when living/working with infants and (young) children. Indoor humidity (e.g., that favoring survival of various mites and growth of molds) should be kept low, if feasible. Breast-feeding should be encouraged due to its many favorable effects. There are no data supporting exclusive breast-feeding after 6 months of age. It may be wise not to keep furred pets indoors during infancy, particularly if a baby has a family history of allergy.

Additional efforts may be necessary for *babies at high risk of allergy*, including the use of an extensively hydrolyzed cow's milk formula (38, 45, 48), should breast milk not suffice for the nutrition of the baby to at least 4 months and preferably to 6 months of age (48). There is no consensus regarding attendance or not at day-care centers (49, 50). There is no need to avoid certain

vaccinations, such as that with pertussis vaccine (51). The current prevention program available for high-risk families in Sweden is shown in Table 2.

Prospectives

Research must address the issue of early identification of babies at high risk of atopic allergy. The cause(s) of the increase in allergy during the past 20–30 years and the causes underlying the differences in sensitization and symptoms between, for example, urban and rural living should be identified. Studies on the effect of changes in hygiene and infections are of particular interest (52). It is to be hoped that it will be possible to manipulate the immune balance toward a Th1-like response to environmental allergens without causing autoimmune diseases.

References

1. Working Group Sardinia. Evidence for an increase in atopic disease and possible causes. *Clin Exp Allergy* 1993;23:484-92.
2. Bråbäck L, Breborowicz A, Julge K, et al. Risk factors for respiratory symptoms and atopic sensitization in the Baltic area. *Arch Dis Child* 1995;72:487-93.
3. Strachan D, Sibbald B, Weiland S, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). *Pediatr Allergy Immunol* 1997;8:161-76.
4. Kjellman N-IM. Atopic disease in seven-year-old children. *Acta Paediatr Scand* 1977;66:465-71.
5. Holt P, McMennamin C, Nelson D. Primary sensitisation to inhalant allergens during infancy. *Pediatr Allergy Immunol* 1990;1:3-13.
6. Halken S, Høst A, Nilsson L, Taudorf E. Passive smoking as a risk factor for development of obstructive respiratory disease and allergic sensitization. *Allergy* 1995;50:97-105.
7. Bråbäck L, Kälvesten L. Urban living as a risk factor for atopic sensitization in Swedish schoolchildren. *Pediatr Allergy Immunol* 1991;2:14-19.
8. Verhoeff A, Burge H. Health risk assessment of fungi in home environments. *Ann Allergy Asthma* 1997;78:544-56.
9. Kjellman N-IM. Prediction and prevention of atopic allergy. *Allergy* 1982;37:463-73.
10. Aas K, Åberg N, Bachert C, et al. European Allergy White Paper. Allergic diseases as a public health problem. Brussels: UCB Institute of Allergy, 1997.
11. Johansson SGO, Berglund A, Kjellman N-IM. Comparison of IgE values as determined by different solid phase radioimmunoassay methods. *Clin Allergy* 1976;6:91-8.
12. Kjellman N-IM. Predictive value of high IgE levels in children. *Acta Paediatr Scand* 1976;65:465-71.
13. Kjellman N-IM, Johansson SGO. IgE and atopic allergy in new-borns and infants with a family history of atopic disease. *Acta Paediatr Scand* 1976;65:601-7.
14. Croner S, Kjellman N-IM, Eriksson B, Roth A. IgE screening in 1701 new-born infants and the development of atopic disease during infancy. *Arch Dis Child* 1982;57:364-8.
15. Croner S, Kjellman N-IM. Development of atopic disease in relation to family history and cord blood IgE levels. Eleven-year follow-up in 1654 children. *Pediatr Allergy Immunol* 1990;1:14-20.
16. Croner S, Kjellman N-IM. Atopic disease in preadolescence – an evaluation of questionnaires, association with cord blood IgE and month of birth. *Pediatr Allergy Immunol* 1991;2:135-40.
17. Michel FB, Bousquet J, Greiller P, Robinet-Levy M, Coulomb Y. Comparison of cord blood immunoglobulin E concentrations and maternal allergy for the prediction of atopic disease in infancy. *J Allergy Clin Immunol* 1980;65:422-30.
18. Businco L, Marchetti F, Pellegrini G, Perlini R. Predictive value of cord blood IgE levels in "at risk" new-born babies and influence of type of feeding. *Clin Allergy* 1983;13:503-8.
19. Hansen L, Høst A, Halken S, et al. Cord blood IgE. II. Prediction of atopic disease. *Allergy* 1992;47:397-403.
20. Merrett T, Burr M. Is the determination of cord blood total IgE levels any value in the prediction of atopic disease? *Clin Exp Allergy* 1992;22(4):552.
21. Ruiz RGG, Richards D, Kemeny DM, Price JF. Neonatal IgE: a poor screen for atopic disease. *Clin Exp Allergy* 1991;21:467-72.
22. Hide DW, Arshad SH, Twiselton R, Stevens M. Cord serum IgE: an insensitive method for prediction of atopy. *Clin Exp Allergy* 1991;21:739-43.
23. Kjellman N-IM. IgE in neonates is not suitable for general allergy risk screening. *Pediatric Allergy Immunol* 1994;5:1-4.
24. Odelram H, Kjellman N-IM, Björkstén B. Predictors of atopy in new-born babies. *Allergy* 1995;50:585-92.
25. Lilja G, Dannaeus A, Fälth-Magnusson K, et al. Immune response of the atopic woman and foetus; effects of high- and low-dose food allergen intake during late pregnancy. *Clin Allergy* 1988;18:131-42.
26. Fälth-Magnusson K. Breast milk antibodies to foods in relation to maternal diet, maternal atopy and the development of atopic disease in the baby. *Int Arch Allergy Appl Immunol* 1989;90:297-300.
27. Vassella C, Odelram H, Kjellman N-IM, Borres M, Vanto T, Björkstén B. High anti-IgE levels at birth are associated with a reduced allergy incidence in early childhood. *Clin Exp Allergy* 1994;24:771-7.
28. Kondo N, Kobayashi Y, Shinoda S, et al. Cord blood lymphocyte responses to food antigens for the prediction of allergic disorders. *Arch Dis Child* 1992;67:1003-7.
29. Young S, Le Souëf PN, Geelhoed GC, et al. The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. *N Engl J Med* 1991;324:1168-73.
30. Nilsson L. Risk factors for atopic disease in childhood [Linköping University Medical Dissertations No. 556]. Linköping: Linköping University, 1998.
31. Wickman M, Nordvall SL, Pershagen G. Risk factors in early childhood for sensitization to airborne allergens. *Pediatr Allergy Immunol* 1992;3:128-33.
32. Lindfors A, Wickman M, Hedlin G, Pershagen G, Rietz H, Nordvall S. Indoor environmental risk factors in young asthmatics: a case-control study. *Arch Dis Child* 1995;73:408-12.
33. Pershagen G. Challenges in epidemiologic allergy research. *Allergy* 1997;52:1045-9.
34. Warner J, Jones A, Miles E, Colwell B, Warner J. Maternofetal interaction and allergy. *Allergy* 1996;51:447-51.
35. Rylander E, Pershagen G, Eriksson M, Nordvall L. Parental smoking and other risk factors for wheezing bronchitis in children. *Eur J Epidemiol* 1993;9:517-26.

36. Hanson L. Human milk and host defence: immediate and long term effects. *Acta Paediatr* 1998 (in press).
37. Saarinen U, Kajosaari M. Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. *Lancet* 1995;346:1065-9.
38. Oldaeus G, Anjou K, Björkstén B, Moran J, Kjellman N-IM. Extensively and partially hydrolysed infant formulae for allergy prophylaxis. *Arch Dis Child* 1997;77:4-10.
39. Fälth-Magnusson K, Kjellman N-IM. Allergy prevention by maternal elimination diet during late pregnancy – a 5-year follow-up of a randomized study. *J Allergy Clin Immunol* 1992;89:709-13.
40. Hattevig G, Kjellman B, Sigurs N, Björkstén B, Kjellman N-IM. Effect of maternal avoidance of eggs, cow's milk and fish during lactation upon allergic manifestations in infants. *Clin Exp Allergy* 1989;19:27-32.
41. Sigurs N, Hattevig G, Kjellman B. Maternal avoidance of eggs, cow's milk and fish during lactation: effect on allergic manifestations, skin-prick tests and specific IgE antibodies in children at age 4 years. *Pediatrics* 1992;89:735-9.
42. Herrmann M-E, Dannemann A, Grüters A, et al. Prospective study on the atopy preventive effect of maternal avoidance of milk and eggs during pregnancy and lactation. *Eur J Pediatr* 1996;155:770-4.
43. Kajosaari M, Saarinen UM. Prophylaxis of atopic disease by six months total solid food elimination. *Acta Paediatr Scand* 1983;72:411-14.
44. Fergusson D, Horwood L, Shannon F. Early solid feeding and recurrent childhood eczema, a 10-year longitudinal study. *Pediatrics* 1990;86:541-6.
45. Zeiger R. Dietary manipulations in infants and their mothers and the natural course of atopic disease. *Pediatr Allergy Immunol* 1994;5(Suppl 1):33-43.
46. Halken S, Høst A, Hansen L, Østerballe O. Effect of an allergy prevention programme on incidence of atopic symptoms in infancy. *Allergy* 1992;47:545-53.
47. Hide DW, Matthews S, Tariq S, Arshad SH. Allergen avoidance in infancy and allergy at 4 years of age. *Allergy* 1996;51:89-93.
48. ESPACI Working Group, Businco L, Dreborg S, et al. Hydrolysed cow's milk formulae. Allergenicity and use for treatment and prevention. *Pediatr Allergy Immunol* 1993;4:101-11.
49. Gustafsson D, Andersson K, Fagerlund I, Kjellman N-IM. Significance of indoor environment for the development of symptoms prospectively to eighteen months of age. *Allergy* 1996;51:789-95.
50. Strachan D, Harkins L, Johnston I, Andersson H. Childhood antecedents of allergic sensitization in young British adults. *J Allergy Clin Immunol* 1997;99:6-12.
51. Nilsson L, Kjellman N-IM, Björkstén B. Investigation of effect of pertussis vaccines on atopic disease during a randomized controlled trial. *Arch Pediatr Adolesc Med* 1998 (in press).
52. Rook G, Stanford J. Give us this day our daily germs. *Immunol Today* 1998;19:113-16.
53. Machtinger S, Moss R. Cow's milk allergy in breast-fed infants: the role of allergen and maternal secretory IgA antibody. *J Allergy Clin Immunol* 1986;77:341-7.
54. Hansen L, Høst A, Halken S, et al. Cord blood IgE. III. Prediction of IgE high response and allergy. *Allergy* 1992;47:404-10.
55. Høst A, Husby S, Gjesing B, Larsen J, Løwenstein H. Prospective estimation of IgG, IgG subclass and IgE antibodies to dietary proteins in infants with cow milk allergy. *Allergy* 1992;47:218-29.
56. Oldæus G. Cows' milk hydrolysates. Prevention and treatment of cows' milk allergy [Linköping University Medical Dissertations No. 552]. Linköping: Linköping University 1998.
57. Fälth-Magnusson K, Kjellman N-IM, Magnusson K. Antibodies IgG, IgA and IgM to food antigens during the first 18 months of life in relation to feeding and atopic disease. *J Allergy Clin Immunol* 1988;81:868-75.
58. Calbi M, Scarpellino B, Giacchetti L. Usefulness of neonatal eosinophil counts as a marker of atopy? *Pediatr Allergy Immunol* 1993;4:86-8.
59. Lilja G, Öman H. Prediction of atopic disease in infancy by determination of immunological parameters: IgE, IgE- and IgG-antibodies to food allergens, skin prick tests and T-lymphocyte subsets. *Pediatr Allergy Immunol* 1991;2:6-13.
60. Miles E, Warner J, Lane A, Jones A, Colwell B, Warner J. Altered T lymphocyte phenotype at birth in babies born to atopic parents. *Pediatr Allergy Immunol* 1994;5:202-8.
61. Borres M, Einarsson R, Björkstén B. Serum levels of interleukin-4, soluble CD23 and IFN- γ in relation to the development of allergic disease during the first 18 months of life. *Clin Exp Allergy* 1995;25:543-8.
62. Odelram H, Björkstén B, Chan S, Hanifin J, Kjellman N-IM. Neonatal leukocyte cAMP-phosphodiesterase determination is not suitable for allergy prediction. *Allergy* 1994;49:677-9.
63. Hattevig G, Kjellman B, Björkstén B. Appearance of IgE antibodies to ingested and inhaled allergens during first 12 years of life in atopic and non-atopic children. *Pediatr Allergy Immunol* 1993;4:182-6.
64. Sigurs N, Hattevig G, Kjellman B, Kjellman N-IM, Nilsson L, Björkstén B. Appearance of atopic disease in relation to serum IgE antibodies in children followed up from birth for 4 to 15 years. *J Allergy Clin Immunol* 1994;94:757-63.
65. Borres M, Odelram H, Irander K, Kjellman N-IM, Björkstén B. Peripheral blood eosinophilia in infants at three months of age is associated with subsequent development of atopic disease in early childhood. *J Allergy Clin Immunol* 1995;95:694-8.
66. Borres M, Irander K, Björkstén B. Nasal metachromatic cells in infants in relation to allergic disease and family history of atopy. *Pediatr Allergy Immunol* 1991;2:184-9.