

Allergy prevention by maternal elimination diet during late pregnancy—A 5-year follow-up of a randomized study

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The 209 mothers to be, enrolled in a randomized, prospective, allergy-prevention study from allergy-prone families, totally abstained from cow's milk and egg from gestational week 28 to delivery. This article presents the development of allergic disease at 5 years of age in their children, compared with the development of allergic disease in the children of the control mothers who took normal food throughout pregnancy. The prevalence of allergic disease could be evaluated in 198 children (95%). Allergic disease was monitored with questionnaires, skin prick testing, serum-IgE determinations, and physical examination. Eczema, allergic rhinoconjunctivitis, and asthma was equally common in the groups. Persistent food intolerance to egg was significantly more common in children of the mothers receiving the diet. This long-term follow-up confirms our previous findings that maternal elimination diet during late pregnancy does not prevent the development of allergic disease in the genetically predisposed child. (J ALLERGY CLIN IMMUNOL 1992;89:709-13.)

Key words: Allergy prevention, maternal diet

Manipulation of the maternal diet has been suggested as one method to prevent the development of allergic disease in the child and has been used, among other preventive measures, in several studies.¹⁻⁷ Some studies indicate a protective role of maternal elimination of highly allergenic foods during pregnancy and lactation^{1,2} or during lactation only.³ Other studies fail to prove any preventive effect of elimination diet^{4,5} or increased intake of allergenic foods during pregnancy.^{6,7}

Beginning in 1983, we have performed a randomized, prospective study enrolling 209 mothers to be from families with at least one allergic family member.^{4,5} Women in the D group totally avoided cow's milk and egg, the most common food allergens for Swedish infants, from gestational week 28 to delivery,

Abbreviations used

D:	Receiving elimination diet during pregnancy
ND:	Not receiving elimination diet during pregnancy
SPT:	Skin prick test
AD:	Atopic dermatitis
ARC:	Allergic rhinoconjunctivitis
BO:	Bronchial obstruction

whereas mothers in the ND (control) group took normal food, including these items throughout pregnancy. The development of allergic disease in the children was monitored at 6 weeks, 3 months, 6 months, and 12 months. At 18 months, the prevalence of allergic disease was evaluated blindly by one pediatric allergist and was equal in the groups up to that age. A questionnaire, when the children were 3½ years, revealed that the parents estimated the occurrence of allergic disease in the groups equal at that age also.⁸

At 18 months, the most common manifestations of atopy were AD and food allergy.⁵ Because allergic symptoms, like rhinoconjunctivitis and asthma, often develop at older ages, a new evaluation of allergic disease was performed when the children were 5 years of age. This study reveals the results of SPTs, antibody analysis, physical examination, and questionnaires

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completed by the parents when the children were 5 years of age.

MATERIAL AND METHODS

Subjects

The study group consisted of 209 mothers and their 210 children, born from February 1983 to June 1984.^{4,5} One child had died because of a malignancy, which left 209 children to be evaluated at 5 years of age, and 186 of these children still lived in the Linköping area.

At the start of the study, 101 mothers randomized to an exclusion D group and 108 mothers to an ND group. Because of maternal noncompliance to the diet, however, 22 mothers left the D group during pregnancy. Conversely, seven mothers insisted they receive the diet without allocation for it. Consequently, 86 mothers were receiving an exclusion diet during pregnancy (D group) and 123 mothers were not (ND group). The genetic load for allergic disease, estimated from the parental history combined with results of SPTs and IgE determination of the parents, did not differ between the D and ND groups. Neither was there any significant difference between early exposure of the infants to tobacco smoke and pets. The babies in the D group were breast-fed for a longer period than the babies in the ND group (7.3 months compared to 5.9 months; $p < 0.005$).

The aim of the study was to evaluate the effect of maternal elimination diet during pregnancy only. By the mothers' own choice, however, some mothers continued to restrict their intake of cow's milk and egg during the first 6 weeks of lactation also; 10 mothers receiving the diet continued a strictly egg- and milk-free diet, whereas 57 D and 24 ND mothers took reduced amounts of cow's milk and egg (at most 2 dl of milk per day and two eggs per week).⁵

Follow-up procedures

During the week of the child's 5-year anniversary, the parents were addressed by letter and asked to complete a questionnaire regarding allergic symptoms in the child. Parents were also offered a visit to a registered nurse, specialized in pediatric allergy, to obtain an SPT and blood sampling; 66 children in the D group and 89 children in the ND group were observed by the nurse. At the visit to the nurse, the answers in the questionnaires were discussed for further clarification. The nurse referred children considered to have allergic disease, severe enough to require medication ($N = 47$, 20 D- and 27 ND-group children), to a physical examination by a pediatrician.

Forty-three families who declined the visit to the nurse were interviewed by the nurse by phone to clarify the questionnaire.

Based on all available information about each child, a "summarized" classification regarding allergic disease could be made by the authors. Children classified as "allergic" had a history that suggested allergy, verified by a positive SPT for the suspected allergen, and/or a diagnosis of allergic disease by a pediatrician. "Probably allergic" means a history that indicated allergic disease, but the history was not confirmed by a positive SPT or doctor's evaluation, for

example, when the child was living outside the catchment area and could not be evaluated further. "No allergy" means no history of allergic disease, negative SPTs, or one single positive SPT without any symptoms ($N = 5$). The parental opinion about the severity of the child's allergic disease was not available when this classification was performed.

Questionnaires

The parents were asked about signs and symptoms of food intolerance, eczema, rhinoconjunctivitis, or asthma, and whether the child had received any medication for allergic disease. The parents were also asked to classify the allergic symptoms of the child in one of four groups: no allergy at all, mild allergy of no practical importance for the daily living of child and family, moderate allergy causing some inconvenience for the child, and severe allergy disabling the child in daily life.

The questions also covered environmental factors, such as exposure to pets and tobacco smoke.

Questionnaire replies were obtained from 84 D-group and 114 ND-group families.

SPT

SPT was performed according to the puncture method with a lancet with 1 mm tip. The allergens used were pasteurized cow's milk with protein content, 3.4 gm/L, and egg and milk extracts (Dome/Hollister-Stier Laboratories, Slough, England, 1:20 wt/vol extracts). The SPTs to milk and egg were performed in duplicates. Single pricks were performed to wheat (Dome/Hollister-Stier Laboratories) and to birch, timothy, cat, mites (*Dermatophagoides farinae* and *D. pteronyssinus*), and mold (*Cladosporium*) with Phazet (Pharmacia Diagnostics AB, Uppsala, Sweden). Histamine chloride, 10 mg/ml, served as reference. The wheal was marked on the skin with a filter-tipped pen, and the mark was then covered with a transparent tape. The tape was later attached to a paper for measuring the reprint of the wheal. The SPT was regarded as positive when the mean wheal diameter was at least 3 mm. SPTs were performed in 64 D- and 91 ND-group children.

Antibody analysis

A venous sample was obtained and centrifuged, and serum was kept frozen until analysis, which was performed in one run for all samples. The IgE level was measured with Phadebas IgE PRIST according to the instructions of the manufacturer (Pharmacia Diagnostics AB). Determination of IgE was performed in 66 D- and 89 ND-group children.

Physical examination

A pediatric physical examination was performed in selected children ($N = 47$) referred by the specialized nurse. Most examinations ($N = 36$) were performed by one author (K. F. M.). For diagnosing AD, the classification system proposed by Hanifin and Rajka was used.⁹ To evaluate BO, a simple running exercise test was performed for 6 minutes according to the clinical praxis of the department. A fall in the peak expiratory flow rate of $>15\%$ was considered

enough to verify a suspicion of asthma. Children who reported airway obstructive symptoms at every respiratory infection but failed to demonstrate this fall of flow rate were classified as having probable asthma.

Ethics and statistics

Informed consent was given by all parents, and the study was approved by the Human Research Ethics Committee of the Medical Faculty at the University of Linköping. Before the start of the study, an experienced statistician was consulted about the study design. Based on information from previous studies performed in the area regarding the risk for allergy development with a certain family history,¹⁰ a reduction of this risk of at least 25% was set as a goal to make the effort of the diet period worthwhile. Accepting, at most, a 5% risk to overlook a true difference between the groups, the population to be studied was calculated altogether as 180 mother/baby pairs in the two groups.

In this follow-up study, information from the parents was obtained of about 198 children, that is, 95% of the original study population. Since the visit to the nurse was accepted by only 155 children, a type II error in the results by inadequate sample size could, however, not be definitely ruled out.

The results of the SPT and the questionnaires were compared with chi-square test, and the IgE levels were compared with Mann-Whitney U test. The number of children with egg intolerance was compared with Fisher's exact test.

RESULTS

Study compliance

The proportion of observations obtained in the D/ND groups was similar regarding questionnaire replies, performed SPTs, IgE analysis, and physical examinations.

Possible confounding factors

Smoke exposure. Children, 30/198, were exposed to smoke in their homes. Another five were exposed to smoke at day care (in the homes of day-care mothers). The difference was statistically significant between D- and ND-group children (9/84 versus 26/114; $p < 0.05$).

Exposure to pets. There was no significant difference between the groups regarding exposure to pets. In total, 47.2% of the children were in contact with indoor pets at least once a week, most commonly with cats (18.3%) or dogs (12.7%).

Symptoms according to the questionnaires

Food intolerance. All children were reported to take cow's milk without discomfort. Four children were still intolerant to egg and were receiving an egg-free diet. When these children were challenged with egg, they developed urticaria and/or colic or diarrhea. Two of these children were also SPT positive to egg. An-

TABLE I. Allergic diseases in the children, in percent, adapted from the reports of the parents

Group	D	ND	<i>p</i>
AD	29	24	NS
ARC	13	14	NS
BO	29	25	NS

NS, Not significant.

other two children had a positive SPT to egg but could tolerate minor amounts of prepared egg. They had previously received a totally egg-free diet.

The mothers of these six children had all received an exclusion diet during pregnancy. Because of their own choice, they had also received a restriction diet during early lactation. Three of these mothers had been taking a strictly cow's milk and egg-free diet for the first 3 months, whereas the other three mothers had been taking reduced amounts. In total, 6/84 D-group children had a total or partial egg intolerance at 5 years, compared to 0/114 in the ND group ($p < 0.05$).

One child from the ND group had a history of fish intolerance, including urticaria when he touched raw fish, and he had a positive SPT to fish.

Twenty-four children were reported to be food intolerant to other foods like tomato ($N = 11$), citrus fruits ($N = 9$), shellfish ($N = 2$), banana ($N = 1$), and strawberry ($N = 1$). Six children reported intolerance to birch-associated allergens like nuts ($N = 4$), celery ($N = 1$), and apple ($N = 1$). Five of these children had a positive SPT to birch.

The total number of children with intolerance to any food item was 16/84 D-group and 20/114 ND-group children (not significant).

Eczema. In 59 children, there was a report of periodical skin problems that involved flexure regions and caused itching. Eight children had chronic skin problems, which were verified at a pediatric physical examination. Of 51 children with a report of eczema who were submitted to SPTs, there were 24 SPT-positive and 27 SPT-negative subjects. Of the SPT-positive subjects, nine had a history of ARC also. The proportion of children with eczema in each group is presented in Table I. There was no significant difference between the groups.

ARC. A history of rhinitis, suspected to be of allergic origin, was found in 27 children. In 20 of these children, the parental suspicion of sensitivity to a specific allergen could be confirmed in the SPT. Most common was birch positivity ($N = 10$), timothy ($N = 7$), and cat ($N = 3$). Seven children had neg-

TABLE II. Summarized assessment by the authors of allergic disease (in percent)

Allergy	D	ND	p
No	65	63	NS
Probable	6	11	NS
Definite	29	26	NS

NS, Not significant.

The assessment was based on the information from questionnaires, SPT, and physical examination. For additional explanations about probable and definite allergy, please see under METHODS.

ative SPTs in spite of a convincing history. Children in the D group, 11/84, reported ARC symptoms compared to 16/114 children in the ND group (not significant).

BO. Parents reported prolonged cough (more than 2 weeks after a respiratory tract infection), or wheezing at infections, or at physical exercise at least on one occasion, up to 5 years, in 52 children (Table I). Four of these children lived outside the Linköping region and could not be investigated. Of the 48 children living in the area, 31 had experienced symptoms during the last year and were evaluated by a pediatrician. A diagnosis of suspected or obvious bronchial asthma was found (14 D-group and 12 ND-group children) in 26 children. Two children were considered healthy, and two received a diagnosis of ARC. Of 46 children with a report of BO who underwent SPT, 16 had positive and 30 had negative SPTs.

Parental opinion about allergy in the child. The parents were assessing the occurrence and severity of allergic disease in their children similarly in the D and ND groups. The number of children reported to have no allergy, mild allergy, and moderate or severe allergy were 45/28/10/1 in the D group and 67/30/17/0 in the ND group, respectively (not significant). Seven children had had allergic symptoms from both skin, eye/nose, and bronchi during the last year, three in the D group and four in the ND group, respectively.

Signs at examination

SPT positivity. Of 155 children who underwent SPT, there were 36 SPT-positive subjects, 12 D-group and 24 ND-group children (not significant). There were 63 positive SPTs altogether, namely, birch (N = 21), timothy (N = 19), cat (N = 10), *D. farinae* (N = 3), *D. pteronyssinus* (N = 3), *Cladosporium* (N = 3), and egg (N = 4). There were no positive SPTs to milk or wheat.

Serum-IgE levels. The median values were similar, 32 kU/L in the D and 29.4 kU/L in the ND group.

The proportion of subjects revealing an elevated value for the age (IgE, >30 kU/L) was also similar.

Summarized assessment of allergy in the children. The combined evaluation of all available information about each child demonstrated similar results in the groups (Table II) and corresponded well to the parental opinion.

Correlation between evaluation at 18 months and 5 years. Of children judged as nonallergic at 5 years, 66% had been judged as healthy at 18 months also. Of children considered to have suspected or definite allergy at 5 years, 75%, had been judged as being allergic also at 18 months.

DISCUSSION

In this study, we have investigated signs and symptoms of allergic disease in children at 5 years of age to evaluate the possible long-term effect of maternal elimination diet during pregnancy. The follow-up compliance at 5 years for blood sampling and SPT was not quite as good as at 18 months.⁵ Several families had moved out of our catchment area. Another important factor was blank denial from the child to participate in blood sampling and SPTs. The parents were unwilling to force the child to participate, in particular if the child had demonstrated no signs of allergic disease. However, the proportions of observations obtained from the two groups were similar, and the questionnaire reply rate was 95%, which should elicit a reasonable opportunity to compare the groups. Possible confounding factors, like differences in the severity of the family history for allergic disease and early exposure to smoke or pets, were similar in the groups.

In concordance with our previous, blinded examinations when the children were 18 months of age,⁵ we found no major difference between the D and ND groups. As expected, the panorama of allergic symptoms had shifted from AD toward allergic rhinitis and asthma, but this development had occurred similarly in both groups.

All children with partially or totally egg intolerance had mothers who had received the elimination diet during pregnancy and, partly also, during early lactation. Although the number of observations is small and should be judged with caution, it should be noted that intervention in the maternal diet might possibly be harmful if it interacts with the normal induction of tolerance.

The absence of allergy prevention claimed in this study may appear to diverge from the results reported by other groups^{1, 2} that found a protective effect of maternal elimination diet. It should be remembered that there are important differences in the study de-

sign. The aim of this study was to monitor the effect of maternal elimination diet during pregnancy exclusively, whereas the other studies combined elimination diet during pregnancy and lactation and also included preventive measures regarding the infant diet.^{1,2} The preventive effect demonstrated in the combined elimination-diet studies cited^{1,2} is presumably achieved during the lactation period, which has also been suggested previously.²

For the mother to be, the length of the diet-intervention period is of considerable practical importance, and elimination diet should not be recommended unless proven effective and safe. Regardless of the scientific aims of the authors, some of the mothers participating in this study continued an elimination or restriction diet during the first weeks of lactation also. This should theoretically have favored the D group, since maternal elimination diet during lactation in families with high-risk allergy has been suggested as a method for allergy prevention.³ Also, the babies of the D group had been breast-fed for a longer period, and were also exposed to smoke at a lesser extent at 5 years. In spite of this, the outcome for the children of the D and ND groups regarding allergic disease was similar.

Apart from the relative maternal noncompliance regarding the diet during the early lactation, our area has been excellent for the accomplishment of a prospective intervention study. The population is well educated, genetically homogenous, and has a long tradition of acceptance of follow-up procedures, both prenatally and at the well-baby clinic. The accomplishment of the study was considered an important mission also for the families involved.

In summary, the 5-year follow-up of the children reveals no support to the theory that maternal elimination diet during late pregnancy can protect the genetically predisposed child from allergy.

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REFERENCES

1. Chandra RK, Puri S, Surayia C, Cheema PS. Influence of maternal food antigen avoidance during pregnancy and lactation on incidence of atopic eczema in infants. *Clin Allergy* 1986;16:563-9.
2. Zeiger RS, Heller S, Mellon M, et al. Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study. *J ALLERGY CLIN IMMUNOL* 1989;84:72-89.
3. Hattevig G, Kjellman B, Sigurs N, Björkstén B, Kjellman NIM. 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.
4. Fälth-Magnusson K, Öman H, Kjellman NIM. Maternal abstinence from cow milk and egg in allergy risk pregnancies: effect on antibody production in the mother and the newborn. *Allergy* 1987;42:64-73.
5. Fälth-Magnusson K, Kjellman NIM. Development of atopic disease in babies whose mothers were receiving exclusion diet during pregnancy—a randomized study. *J ALLERGY CLIN IMMUNOL* 1987;80:868-75.
6. Lilja G, Dannaeus A, Fälth-Magnusson K, Graff-Lonnevig V, Johansson SGO, Kjellman NIM. Immune response of the atopic woman and fetus: effects of high- and low-dose food allergen intake during late pregnancy. *Clin Allergy* 1988;18:131-42.
7. Lilja G, Dannaeus A, Foucard T, Graff-Lonnevig V, Johansson SGO, Öman H. Effects of maternal diet during late pregnancy and lactation on the development of atopic diseases in infants up to 18 months of age—in vivo results. *Clin Exp Allergy* 1989;19:473-9.
8. Fälth-Magnusson K, Kjellman NIM, Magnusson KEM. Effects of various types of diets on food allergy in the infant. *Acta Paediatr Scand* 1989;351(suppl):53-6.
9. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Dermatol Venerol* 1980;92(suppl):44-7.
10. Kjellman NIM. Atopic disease in seven-year-old children: incidence in relation to family history. *Acta Paediatr Scand* 1977;66:465-71.