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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

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ABSTRACT. Two matched groups of children with a family history of atopy/allergy were observed from birth. In one group (n = 65) the mothers had a diet free from eggs, cow's milk, and fish during the first 3 months of lactation, whereas the mothers in the other group (n = 50) had a normal diet. Atopic/allergic manifestations, skin-prick tests, and specific IgE antibodies to egg white and cow's milk during the first 18 months of life have been reported previously. At 4 years of age the children underwent a clinical examination, skin-prick tests, and determination of specific IgE antibodies in serum against certain food and inhalant allergens. Both the cumulative incidence and the current prevalence of atopic dermatitis were significantly lower in the group of children whose mothers had adhered to a hypoallergenic diet during lactation, whereas all other atopic manifestations were similar. The number of children with positive skin-prick tests and specific IgE antibodies did not differ significantly, but the number of positive skin-prick tests and specific IgE antibody reactions in serum was significantly lower in the children of mothers adhering to the diet, indicating a milder degree of sensitization in these children. *Pediatrics* 1992;89:735-739; *atopy/allergy, lactation, hypoallergenic diet, skin-prick test, IgE antibodies.*

ABBREVIATIONS. AD, atopic dermatitis; D, maternal antigen avoidance diet; ND, no maternal antigen avoidance diet; SPT, skin-prick test.

Previous studies have demonstrated that sensitization to egg white and cow's milk occurs early during infancy, even in exclusively breast-fed infants.^{1,2} As the most likely source of sensitization is the passage of small doses of antigen into the breast milk,³⁻⁵ we evaluated the effect of maternal avoidance of eggs, cow's milk, and fish during the first 3 months postpartum on the development of atopic symptoms and specific IgE antibodies in infants during the first 18 months of life.^{6,7} The incidence of atopic dermatitis (AD) was significantly lower during the first 6 months, but not later, in infants of mothers adhering to a hypoallergenic diet (D group) compared with a group of infants of mothers with no dietary restrictions (ND group). Furthermore, the maternal dietary

restrictions resulted in a significantly lower rate of sensitization in the infants in the D group during the time of restrictions.^{6,7}

In the present study we report the results of a follow-up of the children in the D and ND groups at 4 years of age.

SUBJECTS AND METHODS

Patient Selection

From August 1984 to March 1986 all pregnant women visiting the antenatal clinics of the central hospitals of Skövde and Borås in southwestern Sweden were asked by the midwives about atopy/allergy in their families. Mothers in Skövde were recruited to the D group and mothers in Borås to the ND group. The D group comprised 65 and the ND group 50 children. Children were included in the study if they had a double heredity for atopic disease (D = 59, ND = 44) or if they had single heredity and a cord blood IgE level of ≥ 0.9 kU/L (D = 6, ND = 6). Double heredity was defined as atopic disease in both parents (D = 27, ND = 23), in 1 parent and 1 sibling (D = 27, ND = 19), or in 2 siblings (D = 5, ND = 2). Only nonsmoking families without indoor pets were admitted. When the children were 18 months of age, all parents were still nonsmokers and no family had indoor pets. Later, 10 parents in the D group and 7 parents in the ND group started smoking, and 5 families in the D group and 4 in the ND group acquired indoor pets.

The diet of the mothers in the D group started immediately after birth and continued for 3 months, was free from eggs, cow's milk, and fish products. They all subsequently returned to their normal diet. Cow's milk was introduced in the diet of the two groups of infants after 6 months and eggs and fish after 9 months. At age 4 years all children had a normal diet except those with allergic symptoms to a certain food, which had to be avoided.

The selection criteria for the study groups have been reported in detail previously. We consider the two groups comparable because the same antenatal and postnatal criteria were used and the groups were similar with regard to heredity for atopic disease, the percent of mothers excluded for not fulfilling antenatal criteria and infants not fulfilling the postnatal criteria or not completing the study (two and four, respectively), the pattern of breast-feeding, the number of dietary errors, and the distribution of cord blood IgE values.^{6,7}

Clinical Criteria

The clinical criteria for atopic manifestations and adverse reactions have been described previously.^{6,7} Briefly, AD was defined as a pruritic, chronic or chronically relapsing, noninfectious dermatitis of typical morphology and distribution based on the suggestions by Hanifin and Rajka.⁸ The eczema was regarded as severe if it was generalized and/or if there was need for hospitalization, as moderate if localized and requiring frequent application of steroid ointments, and as mild if no or only mild steroid ointments were needed for 1 to 3 days.

An episode of bronchial obstruction was accepted only if the diagnosis was made by a physician and after examination of the case record by one of the authors. Three or more episodes of bronchial obstruction were regarded as asthma. Rhinitis was con-

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sidered to be allergic if it appeared at least twice after exposure to a particular allergen. Positive exposure to an allergen was defined as an obvious reaction within 1 hour after exposure on at least two occasions. To ensure uniform diagnostic classification, the records of all the children were evaluated repeatedly and jointly but not blinded during the study period by the three investigators involved in the clinical assessment.

Examination

The children had been examined at birth and at 3, 6, 9, 12, and 18 months.^{6,7} For this study we evaluated all 115 children at 4 years of age (median 3¹¹/₁₂ years, range 3³/₁₂ to 4¹²/₁₂ years) using a standard history questionnaire, skin-prick tests (SPTs), and determination of specific serum IgE antibodies. All children in the D group were examined by one investigator (G.H.), and all children in the ND group were examined by another (N.S.). The sera were frozen and stored at -20°C for analysis after all the children had completed the follow-up procedure.

Laboratory Methods

Skin-prick tests were performed on the volar aspects of the forearms in all children. Food allergens were as follows: egg white and cow's milk extracts from Dome/Hollister-Stier in a concentration of 1:20 (weight/volume) and hazel nut and peanut extracts from ALK (Soluprick) in a concentration of 1:100 for hazel nut and 1:20 for peanut (weight/volume). Reactions against the inhalant allergens—cat, birch, and *Dermatophagoides pteronyssinus*—were tested using an allergen-coated steel needle (Phazet Pharmacia Diagnostics AB, Uppsala, Sweden) with an allergen amount corresponding to the allergen concentration of 100 000 Biological units/mL according to the Nordic Committee on allergen standardization. A Phazet with histamine-dihydrochloride in a concentration of 10 mg/mL and an uncoated Phazet served as positive and negative controls. Four hundred forty-one pricks were done in the children in the D group and 326 in the children in the ND group. The SPT was regarded as positive when the mean diameter of the wheal, ie, half the sum of the largest diameter and its perpendicular, was 3 mm or greater and the mean diameter of the negative control was less than one third of the allergen reaction.

Sixty-four sera from children in the D group and 46 from those in the ND group were available for analysis. The parents of four children in the ND group declined serum sampling. Two of these children never had atopic symptoms and two had mild atopic dermatitis. Serum was obtained from all children in the D group, but one sample was not analyzed because of a technical error.

Total IgE concentrations were determined in all sera by Phadebas IgE PRIST (Paper RadioImmunoSorbent Test)(Pharmacia Diagnostics AB) in accordance with the manufacturer's recommendations.

Specific IgE antibodies were determined by a modified Phadebas RAST (RadioImmunoSorbent Test) (Pharmacia Diagnostics AB) procedure. Sera that were RAST-negative, ie, <0.35 Phadebas RAST Units (PRU)/mL, were tested a second time with an extra-sensitive assay allowing identification of antibodies in levels of ≥0.1 PRU/mL as described in detail elsewhere.¹ For fish and wheat the lowest identification level was 0.2 PRU/mL.

IgE antibodies to fish, wheat, *Dermatophagoides pteronyssinus*, timothy, birch, and mixed animal danders were determined. Three hundred eighty-four analyses were performed for determination of these antibodies in sera from children in the D group and 276 from those in the ND group. Antibodies to egg white and cow's milk were determined only in children with previous levels of IgE antibodies at 18 months ≥0.35 PRU/mL, corresponding to RAST class 1. Furthermore, 64 sera from children in the D group and 45 from those in the ND group were tested with Phadiatop Pediatric (Pharmacia Diagnostics AB), a screening assay for sensitization consisting of a mixed disk with food and inhalant allergens. The results are expressed as "positive" or "negative."

Statistics

The χ^2 test was used to test the significance of the differences between the two groups. "Not significant" signifies $P > .05$. The odds ratio and 95% confidence intervals were also calculated. The Mann-Whitney nonparametric test was used for the estimation of differences in total IgE concentrations in children in the D group vs those in the ND group.

Ethics

All parents of the children gave their informed consent. The study was approved of by the Human Research Committees of the Medical Faculties of the Universities of Linköping and Göteborg.

RESULTS

Atopic Symptoms

As shown in Table 1 and the Figure, both the cumulative incidence and the current prevalence of AD were significantly lower in children in the D group than in children in the ND group at 4 years of age ($P = .007$ and $P = .03$, respectively), whereas the frequencies of atopic respiratory symptoms were similar. Six of the 19 eczematous children in the ND group had a moderate to severe eczema compared with 1 of the 8 eczematous children in the D group.

At age 4 years, allergic symptoms to egg white were reported in one of the children in the ND group and in five of the children in the D group. Obvious gastrointestinal symptoms after ingestion of cow's milk was found in one child in the ND group and in two children in the D group. Allergic symptoms to pollen and/or danders were reported by four children from the ND group and seven from the D group (not significant).

SPT and Serum IgE Antibodies

The number of children with a positive SPT did not differ significantly between the D and ND groups (Table 2). The rate of positive tests, ie, the proportion of positive pricks in the total number of pricks done in the children from the D group (12 of 441) was significantly lower ($P = .01$) than that in the children from the ND group (22 of 326). The odds ratio was 0.39 and the 95% confidence limit was 0.18 to 0.83. Seven of the 8 SPT-positive children in the D group and 10 of the 11 SPT-positive children in the ND group had current atopic manifestations. Four (50%) of 8 of the D-group children with current AD and 9 (47%) of 19 of the ND-group children with AD had at least one positive SPT.

The number of children with specific serum IgE antibodies did not differ significantly in two groups (Table 3). The rate of positive specimens, ie, the proportion of positive tests out of all the analyses made, was significantly lower ($P = .03$) in the children from the D group (39 of 384) than in the children from the ND group (44 of 276). The odds ratio was 0.60 and the 95% confidence interval was 0.37 to 0.97.

Eight of the 10 D-group children and 9 of the 11 ND-group children with IgE antibodies ≥ 0.35 PRU/mL against at least one tested allergen had current atopic manifestations. The rates of sensitization of children with AD were similar in the D and ND groups. Specific IgE antibodies were thus found in 5 (63%) of 8 children in the D group and 10 (59%) of 17 children in the ND group with current AD.

A positive Phadiatop Pediatric at age 4 was found in 11 (17%) of 64 tested children from the D group and in 12 (27%) of 45 tested children from the ND group (not significant). Nineteen of all the 23 children with a positive Phadiatop Pediatric also had specific

TABLE 1. Cumulative Incidences (Cum Inc) and Current Prevalences (Prev) of Atopic Manifestations at Age 4 in 65 Children of Mothers Practicing Food Allergen Avoidance During Lactation (D) and 50 Children of Mothers Not on Food Restrictions (ND)*

Atopy	Group	Cum Inc		OR	CI	Prev		OR	CI
		No.	%			No.	%		
Eczema	D	19	29	0.325	0.139–0.753	8	12	0.229	0.081–0.635
	ND	28	56			19	38		
Asthma	D	7	11			6	9		
	ND	6	12			4	8		
Bronchial obstruction	D	8	12			6	9		
	ND	6	12			4	8		
Rhinoconjunctivitis	D	8	12			8	12		
	ND	5	10			4	8		

* Odds ratio (OR) and 95% confidence interval (CI) for statistically significant differences. Statistically significant differences ($<.05$) between values for the D and ND groups are in *italics*.

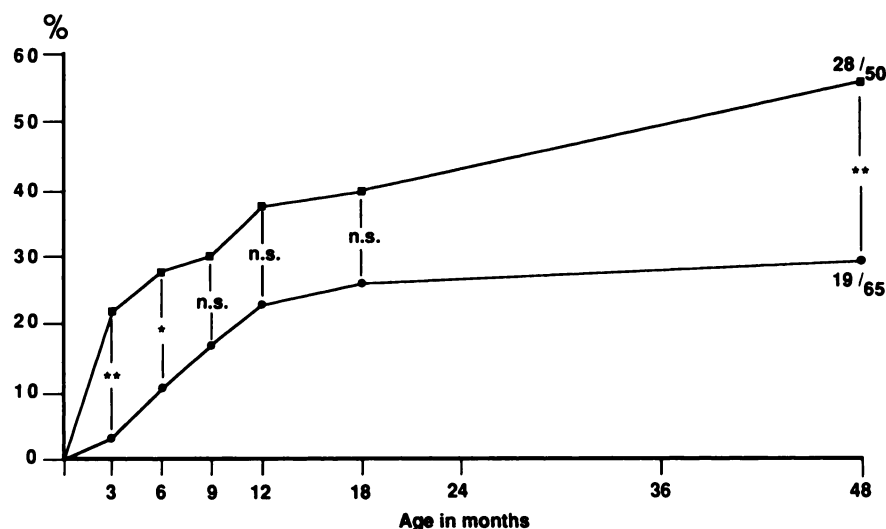


Figure. Cumulative incidence of atopic dermatitis in 4-year-old children of mothers practicing food antigen avoidance during lactation (●) and 4-year-old children of mothers not on food restriction (■). Not significant (n.s.), $P > .05$; significant (*), $.05 \geq P \geq .01$; significant (**), $.01 > P \geq .001$.

TABLE 2. Number of Children With a Positive Skin-Prick Test to One or More of Seven Allergens

Allergen	D*	ND†
Egg white	2	4
Cow's milk	2	2
Hazel nut	1	2
Peanut	0	3
Birch	5	5
Cat	2	4
<i>Dermatophagoides pteronyssinus</i>	0	2
Total no. of children tested	65	50
Total no. (%) of children with ≥ 1 positive test	8 (12)	11 (22)

* Children of mothers adhering to a hypoallergenic diet during lactation.

† Children of mothers with no dietary restrictions during lactation.

TABLE 3. Number of Children With IgE Antibodies to Any of Six Allergens*

Allergen	IgE Antibodies ≥ 0.35 PRU/mL		IgE Antibodies 0.10–0.34 PRU/mL	
	D	ND	D	ND
Fish	0	2	1	0
Wheat	1	3	1	4
<i>Dermatophagoides pteronyssinus</i>	0	1	3	1
Birch	7	4	4	6
Timothy	6	5	3	4
Animal danders	7	8	6	6
Total no. tested	64	46	64	46
Total no. (%) with ≥ 1 positive test	10 (16)	11 (24)	8 (13)	7 (15)

* For wheat and fish the detection limit was 0.20 PRU/mL.

IgE antibodies ≥ 0.35 PRU/mL to one or several of the six antigens. The remaining four children had specific IgE antibody levels between 0.10 and 0.35 PRU/mL. Seven (64%) of 11 children in the D group and 8 (67%) of 12 children in the ND group with a positive test had current atopic symptoms.

Two of the five D-group children and four of the six ND-group children with RAST class levels of IgE

antibodies to egg white and/or cow's milk at 18 months still had IgE antibody levels ≥ 0.35 PRU/mL at 4 years of age.

Total IgE levels were similar in both groups. Median and upper 90th percentile values in the D group were 22 and 384 kU/L, and the corresponding values for the ND group were 23 and 203 kU/L.

DISCUSSION

The only statistically significant clinical difference between the children in the D and ND groups at 4 years of age was a lower incidence of AD in the D group, which was also found previously at 3 and 6 months but not at 9, 12, and 18 months. At 9, 12, and 18 months there was a tendency toward a lower rate of AD in the D group (Figure), and a larger study population might have demonstrated a significant difference for these ages.

Similar to our previous results, the rates of atopic respiratory symptoms did not differ between the two groups. As such symptoms often appear later, continuing follow-up might disclose a difference.

More children with allergic symptoms to egg white and cow's milk were found in the D than in the ND group at age 4, but the difference was not significant and the number of children too small to allow any far-reaching speculations. It is not out of place, however, to raise the question whether an early introduction of antigens may be beneficial for induction of tolerance.⁹

In analogy with previous results, the number of children with a positive SPT or specific IgE antibodies did not differ significantly at age 4. However, similar to the results at age 3 months, ie, the time of termination of the maternal dietary restrictions, there was at 4 years of age a lower rate of specimens with IgE antibodies in the D group. Furthermore, at age 4 a lower rate of positive SPTs in the D group was found. The findings indicate a tendency toward a milder degree of sensitization in the children in the D group. These results fit in well with the finding of a lower rate of AD in the D group, as sensitization is one important factor in the pathophysiology of AD.^{10,11} The analyses for IgE antibodies were performed in the same laboratory, whereas the SPTs were done at two different hospitals. Although the technique was identical, the fact that different nurses were engaged might have contributed to the differences in the SPT results.

The reason for not analyzing egg white and cow's milk antibodies in all sera at age 4 was that in a series of "normal-risk" infants followed from birth to 7 years of age, none developed either allergic symptoms or RAST class levels of IgE antibodies to egg or cow's milk after the first year of life.²

The fact that the two groups of infants were recruited in two different hospitals can be criticized. However, a true randomization might have involved the risk of mothers in the ND group adapting to the diet of the mothers in the D group. We think that our repeated discussions during the whole study period ensured a uniform classification of diagnoses in the two groups of children. A thorough examination of the comparability of the two matched groups disclosed no differences.^{6,7} The groups were similar with regard to heredity, but after the start of our study it has become obvious to us that a high cord blood IgE level is a poor predictor of atopy due to a low sensitivity.^{12,13} In planning a new study we would not have chosen cord blood IgE as an inclusion criterion.

The groups were matched through recruitment from two towns of equal size located 60 miles apart in geographically and socioeconomically similar areas, with equal sizes of the general hospitals of the towns and similar number of deliveries per year. Both towns are situated in the same climatic zone and have similar proportions of rural surroundings and town settlements. Neither of the towns is heavily industrialized and a difference in air pollution is not likely. A similar number of parents started smoking and acquired indoor pets in both groups after 18 months. There were no differences in the dietary habits among the children in the two groups. It is possible, however, that other factors not known to us may have emerged during the last 2½ years.

The effects of diet manipulation during infancy on later atopic manifestations have been studied and debated for more than 50 years.¹⁴⁻¹⁶ There are five other studies that evaluated the effects of maternal hypoallergenic diet during lactation.¹⁷⁻²¹ All but one of these studies include other manipulations, such as maternal dietary restrictions during pregnancy and/or different diets for the infants in the study group and the control infants. In the one study that allows an evaluation of the maternal dietary restriction during lactation per se, both a lower rate of AD and milder degrees of dermatitis were found during the first 18 months in the infants of mothers with restricted diet.¹⁹

Our results are encouraging but we still believe that it is too early to advocate antigen avoidance during lactation to families with atopy. Further studies, preferably with randomized and larger groups with a longer period of maternal dietary restriction, are desirable.

In conclusion, a maternal diet devoid of cow's milk, egg, and fish during the first 3 months of lactation decreased both the current prevalence and the cumulative incidence of AD at age 4 in children with atopic disease heredity. Furthermore, the rate of sensitization may be lower in the children of mothers adhering to the diet during lactation.

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TEEN-AGE BOYS: LOST MARKET IN MAGAZINE LAND

Say you're a typical 14-year-old boy. You like sports, video games, cars and junk food. But occasionally you wonder: Did that girl really want me to kiss her or was she totally grossed out? Am I the groovemeister I think I am or just a garden-variety geek?

When girls are confronted by such adolescent travails, they turn to *Seventeen*, *Sassy*, *YM* or *Teen*, four magazines dedicated to the teen-age girl. But teen-age boys have only one magazine to call their own - *Boy's Life* - and that is known for its coverage of hobbies like stamp-collecting rather than the emotional peaks and valleys of the teen years.

At a time when publishers are deluging the market with magazines for men, and when niches from bow-hunters to back-pain sufferers have their own journals, teen-age boys remain the forgotten people. They may read *Sports Illustrated* for sports, *Playboy* for thrills, *Rolling Stone* for music or comics for fun, but their own lives remain unexamined in the pages of magazines. Advertisers and publishers say that's because teen-age boys read less than girls, buy less and wouldn't be caught dead contemplating such touchy-feely things as how they look or feel.

Crossen C. Teen-age boys are the lost market in magazine land. *The Wall Street Journal*. September 7, 1990.

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