

Effect of exclusive breast-feeding and early solid food avoidance on the incidence of atopic dermatitis in high-risk infants at 1 year of age

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The aim of this study was to assess the preventive effect of exclusive breast-feeding and early solid food avoidance on atopic dermatitis (AD) in infancy in an epidemiological setting. The data are from a dietary clinical trial in a prospective cohort of healthy term newborns at risk of atopy. It was recommended to breast-feed for at least 4 months and to avoid solid food in the same time-period. Eight hundred and sixty-five infants exclusively breast-fed, and 256 infants partially or exclusively formula-fed, were followed-up until the end of the first year following birth. AD and sensitization to milk and egg were considered as study end-points. The 1-year incidence of AD was compared between the two study groups. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were calculated by multiple logistic regression. In the breast-fed group, the adjusted OR for AD was 0.47 (95% CI 0.30–0.74). The strongest risk factor was the occurrence of AD in the subject's core family. The risk of infants with AD to be sensitized to milk was four times higher, and to egg eight times higher, than in infants without AD. Age at first introduction and diversity of solid food did not seem to modify the protective effect of breast-feeding on AD. However, the GINI study was not designed for evaluating the effect of solid food feeding. A preventive effect of delayed solid diet and avoidance of potentially allergenic foods can only be estimated in prospective, well-designed, randomized studies. We conclude that in infants at atopic risk, exclusive breast-feeding for at least 4 months is effective in reducing AD in the first year of life.

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Atopic dermatitis (AD) is the most common atopic disease in infancy. Sixty per cent of affected individuals manifest characteristic lesions during the first year of life (1). Sampson (2) assumes that there are two forms of AD – one in which the disease is triggered by allergens with potential immunoglobulin E (IgE) dependency and one in which the disease appears to be IgE independent. In infancy and childhood, 30–40% of children with moderate-to-severe AD have IgE-mediated clin-

ical reactivity to food proteins (3–7). In these patients, strict dietary elimination of the offending food results in an improvement of the skin lesions (8,9).

In 1936, Grulee & Sanford (10) reported a highly preventive effect of exclusive breast-feeding on infantile eczema compared to cow's milk in a large cohort of infants. Since then, a great number of studies on this topic have been published, the results of which are contradictory. In a systematic review, Kramer

(11) has shown that the inconsistency of reports can partly be explained by methodological weaknesses. In particular, retrospective data collection of infant-feeding history is prone to recall bias, because mothers may forget details about duration and exclusivity of breast-feeding. Most studies failed to control for essential confounders. Furthermore, Duchén et al. (12) suggested that differences in the biological composition of human milk could explain the controversy in the allergy-prophylactic effect of breast-feeding.

A possible preventive effect of breast-feeding may be a result either of protective immune factors in the human milk (13) or delayed introduction of formula and solid foods by lactating mothers, thus avoiding early exposure to cow's milk and other food proteins. The evidence of a positive association between eczema and sensitization to foods leads to the assumption that early feeding of solid food may play a major role in the development of AD in infants. Fergusson et al. (14) reported that children exposed to a diverse solid food diet during their first 4 months of life had risks of eczema during the first 2 years of life that were ≈ 1.6 times higher than those of children who were not introduced to solid food. In a Finnish study on 135 infants who were exclusively breast-fed, eczema and food allergy were less frequent at the age of 1 year in the group of those children who had avoided solid food completely during the first 6 months of life compared with the group who started solid food feeding at ≈ 3 months of age (15).

This study is part of the German Infant Nutritional Intervention (GINI) program, a prospective, randomized cohort study that was conducted to assess the preventive effect of three different hydrolyzed infant formulae in comparison with conventional cow's milk formula in high-risk infants (von Berg A., Koletzko S., Grübl A. et al., manuscript in preparation).

For this paper the GINI cohort was used to investigate whether breast-feeding has a protective effect on AD in the first year of life. AD incidence was compared between a study group who were exclusively breast-fed and a study group who were exclusively or supplementarily formula-fed during the first 16 weeks of life. Furthermore, we examined whether the co-intervention advice of early solid food avoidance had an additional effect on the incidence of AD. Finally, sensitization to milk and egg, the two major allergens in infancy, was evaluated. The study protocol was approved

by the local ethical committees of the study centers.

Subjects and methods

Subjects

Between September 1995 and July 1998, a total of 2,252 healthy term newborns with a family history of atopy were recruited in 16 maternity wards in the regions of Munich, Bavaria ($n=1,165$) and Wesel, North-Rhine-Westfalia ($n=1,087$). Informed consent to participate in the study was obtained from the parents of the newborns. Infants were randomly assigned to one of four study formulas, one of which was a cow's milk-based formula (CMF). Between 197 and 236 subjects of each of the four study groups, i.e. a total of 865 infants, were exclusively breast-fed (HM) during the first 16 weeks of life. Two hundred and fifty-six infants received the CMF during the intervention period, but only 45 of them (17.6%) were exclusively bottle-fed. On average, CMF was introduced in the second week of life (median), and duration of bottle-feeding was 12 weeks (median). Altogether, 1,121 subjects with compliance to milk-feeding recommendations and complete 1-year follow-up were included in this study. Parents and study observers were blinded with regard to the randomized CMF. The breast-fed group was only single blinded.

Dietary recommendations

Parents received detailed recommendations on the infant's nutrition, both verbally and in writing. Mothers were encouraged to breast-feed for at least 4 months. If breast-feeding was not possible, insufficient or refused, feeding the randomized formula was advised for the intervention period of 16 weeks. Furthermore, it was recommended not to introduce solid foods during this time-period and thereafter to introduce only one new food per week. Potentially allergenic foods such as cow's milk and dairy products, eggs, fish, tomatoes, nuts, soy products, and citrus fruits were to be avoided during the whole first year.

Study instruments and follow-up

The infant's nutrition during the first 24 weeks of life was recorded in a diary, on a weekly basis, by mothers. Mothers noted the kind of milk and the time of introduction, as well as the type of new solid foods that were introduced. Maternal compliance was assessed by the diary data (16).

Solid diet was classified according to type of food, such as dairy products, egg, cereals, legumes, vegetables, fruits, nuts, meat products, fish, and other foods. A measure of the diversity of the infant's early diet was constructed by summing the number of different types of solid food that the child was fed during the first 24 weeks.

Additional questionnaire information included atopic status of family members, birth data, socio-demographic factors, information on living conditions, smoking habits, and health problems of the infant. During the first year of life, the infants were seen by a physician in the study center when 1, 4, 8, and 12 months of age. At these visits, a structured interview and a physical examination of the subjects were performed. Infants with skin lesions and suspicion of AD were seen by the study staff between these regular follow-up visits.

Definition and diagnosis of atopic dermatitis

Criteria used in the diagnosis of AD were:

- typical morphology and distribution of skin lesions (face, neck and scalp, flexural folds, hands and extensor sides of extremities);
- pruritus (signs of scratching); and
- a tendency towards chronicity (duration of least 14 days and/or relapsing).

The morphologic diagnosis was based on the skin examination by an observer specially trained in pediatric allergology, who was not aware of the infant's feeding history. A final diagnosis of definite AD cases was made by an algorithm, which combined the above defined diagnostic criteria.

Determination of total and specific IgE

Subjects were screened as follows: for total IgE at birth, and at 4 and 12 months of age; for serum IgE antibodies to α -lactalbumin, β -lactoglobulin, and casein at 4 and 12 months of age; and for serum IgE antibodies to ovalbumin at 12 months of age. Total IgE was determined using the Pharmacia CAP System IgE FEIA (Pharmacia, Freiburg, Germany) with a detection limit of 0.35 kU/l. Specific antibodies were determined using the Pharmacia CAP System RAST FEIA (Pharmacia). Values of > 0.35 kU/l were considered positive.

Risk factors and confounders

The following factors were controlled:

- atopic risk level (single: one parent or sibling atopic; double: both parents atopic);

- number of members in the core family with AD;
- level of cord-blood IgE (≤ 0.35 kU/l, > 0.35 kU/l);
- nationality of parents (both parents German, at least one parent foreign);
- parental school education (low = elementary school/no degree; medium = secondary school; high = German high school graduation);
- gender of the subject;
- pet keeping; and
- maternal smoking.

Statistical methods

The 1-year incidence of AD and the odds ratio (OR) for the HM group with the CMF group as reference were calculated. For control of potential confounders, multiple logistic regression models were used. Factors without influence on the exposure or outcome variables were excluded from the multiple logistic regression model in a backward stepping procedure. For the final model, adjusted ORs with 95% confidence intervals (CI) are given. The statistical analysis was performed using the Statistical Analysis System (SAS, version 6.12). All statistical tests were performed two-sided.

Results

The HM group differed significantly from the CMF group with regard to the following variables: higher atopic risk level ($p=0.036$); higher level of parental school education ($p=0.001$); less maternal smoking after pregnancy ($p=0.001$); and lower prevalence of pets at home ($p=0.001$) in the HM group. The rate of breast-feeding mothers was higher in the more urban region of Munich ($p=0.001$). The distribution of the following variables was similar in both study groups: number of family members affected with AD; cord blood IgE level; parental nationality; infant's gender; and number of own siblings.

The 1-year-incidence of AD was 9.5% (82/865) in the HM group and 14.8% (38/256) in the CMF group ($p=0.015$) (Table 1). Of the exclusively bottle-fed subjects, 13.3% (six of 45) developed AD as did 15.2% (32/211) of the partially bottle-fed infants. Double atopic risk level, occurrence of AD in the core family, and cord blood IgE above the detection limit of 0.35 kU/l, were all strong risk factors for AD in infancy. Furthermore, significantly higher AD rates were found in families where both parents

Table 1. One-year incidence of atopic dermatitis (AD) and prevalence of sensitization at 4 and 12 months of age in relation to exposure, genetic risk factors, and potential confounders

	AD incidence (%)	p-value*	Sensitization to milk allergens 4 months	p-value*	Sensitization to milk allergens and/or ovalbumin 12 months	p-value*
Diet		0.015		0.106		0.457
CMF	38/256 (14.8%)		2/215 (0.9%)		19/197 (9.6%)	
HM	82/865 (9.5%)		20/698 (2.9%)		73/632 (11.6%)	
Atopic risk level		0.009		0.978		0.009
Single	69/763 (9.0%)		15/625 (2.4%)		52/568 (9.2%)	
Double	51/358 (14.3%)		7/288 (2.4%)		40/261 (15.3%)	
AD in core family		0.001		0.997		0.962
No family member	49/651 (7.5%)		11/527 (2.1%)		55/500 (11.0%)	
1 member	58/388 (15.0%)		11/315 (3.5%)		30/264 (11.4%)	
> 1 member	13/82 (15.9%)		0/71 (0.0%)		7/65 (10.8%)	
Cord blood IgE		0.033		0.295		0.001
≤0.35 kU/L	52/544 (9.6%)		9/452 (2.0%)		28/399 (7.0%)	
>0.35 kU/L	29/191 (15.2%)		5/142 (3.5%)		30/144 (20.8%)	
Nationality		0.032		0.342		0.287
Both parents German	113/987 (11.5%)		18/805 (2.2%)		79/738 (10.7%)	
At least one parent non-German	7/132 (5.3%)		4/107 (3.7%)		13/90 (14.4%)	
Parental school education		0.960		0.462		0.711
Low	7/52 (13.5%)		2/40 (5.0%)		5/41 (12.2%)	
Medium	23/244 (9.4%)		1/205 (0.5%)		18/187 (9.6%)	
High	90/824 (10.9%)		19/667 (2.9%)		69/600 (11.5%)	
Gender		0.270		0.988		0.015
Male	67/572 (11.7%)		11/458 (2.4%)		59/433 (13.6%)	
Female	53/549 (9.7%)		11/455 (2.4%)		33/396 (8.3%)	
Maternal smoking		0.863		0.309		0.864
Yes	13/127 (10.2%)		1/103 (1.0%)		10/95 (10.5%)	
No	106/987 (10.7%)		21/805 (2.6%)		81/729 (11.1%)	
Pets in the home		0.042		0.022		0.046
Yes	15/214 (7.0%)		0/169 (0.0%)		11/163 (6.8%)	
No	105/886 (11.9%)		22/726 (3.0%)		80/653 (12.3%)	

CMF, cow's milk formula; IgE, immunoglobulin E; HM, human milk.

*Cochran–Mantel–Haenszel statistics.

were German, and in families with no pets at the infants' age of 4 months.

At the age of 4 months, the rate of sensitization to at least one of the three tested milk allergens was low in both study groups (HM 2.9%, CMF 0.9%, $p = 0.11$). Besides pet keeping, no significant association between sensitization and the tested factors were found. At the age of 12 months, the prevalence of sensitization to milk allergens had increased in both groups (HM 5.4%, CMF 4.1%, $p = 0.46$). The sensitization rate to ovalbumin was 8.6% in the HM group and 7.5% in the CMF group ($p = 0.62$). Double atopic risk level, cord blood IgE > 0.35 kU/l, male gender, and the absence of pets, were significantly associated with higher rates of sensitization to milk allergens and/or ovalbumin.

The crude OR for exclusive breast-feeding was 0.60 (95% CI 0.40; 0.91). After adjustment for atopic risk factors and confounders (Table 2), the OR further decreased to 0.47 (95% CI 0.30; 0.74). This means that the risk of AD was reduced by $\approx 50\%$ in the HM group compared to the CMF group. A family history

of AD proved to be the strongest discriminating factor ($p = 0.0002$) in the model, where children with a family history of this condition had risks of AD that were more than twice those of children without a family history of this condition. Other strong factors were atopic risk level, which might be associated with AD in the family, as well as pet keeping and foreign parental nationality, both inversely associated with AD risk.

Between the two study groups, there was no significant difference in sensitization to milk protein and/or ovalbumin in the first year of life. The adjusted OR was 1.30 in the HM group (95% CI: 0.74; 2.28) (Table 3). In the logistic regression model, a double atopic risk level, cord-blood IgE values > 0.35 kU/l, and male gender proved to be positively associated with sensitization. There was an inverse association between pet keeping and sensitization to milk and egg allergens. At 4 and 12 months of age, the risk of being sensitized to milk allergens was four times higher in infants with AD than in infants without AD (Table 4). The risk of being sensitized to ovalbumin was even

Table 2. Results of multiple logistic regression model for the 1-year incidence of atopic dermatitis (AD)

	Adjusted odds ratio	95% CI
Diet		
CMF	1	
HM	0.47	(0.30; 0.74)
Atopic risk level		
Single	1	
Double	1.53	(1.02; 2.28)
AD in core family		
No family member	1	
≥ 1 member	2.14	(1.44; 3.17)
Gender		
Female	1	
Male	1.26	(0.86; 1.87)
Parental school education		
Low	1	
Medium	0.69	(0.27; 1.80)
High	0.88	(0.36; 2.17)
Pets at home		
No	1	
Yes	0.53	(0.30; 0.96)
Nationality		
Both parents German	1	
At least one parent non-German	0.42	(0.19; 0.93)
Maternal smoking		
No	1	
Yes	0.83	(0.43; 1.62)

Results are expressed as adjusted odds ratios (OR) and 95% confidence intervals (CI).
CMF, cow's milk formula; HM, human milk.

higher in the group of infants with AD (adjusted OR 8.1, 95% CI: 4.5; 14.5).

The study groups differed considerably in regard to the age of the infant when solid food was first introduced to the diet and to the number of diverse food types fed in the first

6 months of life (Table 5). During the first 16 weeks after birth, only 5.4% of the breast-feeding mothers, but 30.9% of the bottle-feeding mothers, had introduced solid food to the infant's diet. Until 24 weeks of age, 49% of the breast-fed infants, but only 19% of the

Table 3. Results of multiple logistic regression model for the 1-year incidence of sensitization to milk and/or egg

	Adjusted odds ratio	95% CI
Diet		
CMF	1	
HM	1.30	(0.74; 2.28)
Atopic risk level		
Single	1	
Double	1.57	(1.01; 2.45)
Cord-blood IgE		
≤ 0.35 kU/L	1	
> 0.35 kU/L	3.34	(1.93; 5.79)
No data	1.52	(0.92; 2.53)
Gender		
Female	1	
Male	1.72	(1.10; 2.67)
Pets at home		
No	1	
Yes	0.44	(0.22; 0.86)
Parental school education		
Low	1	
Medium	0.56	(0.20; 1.62)
High	0.65	(0.24; 1.75)

Results are expressed as adjusted odds ratios (OR) and 95% confidence intervals (CI).
CMF, cow's milk formula; IgE, immunoglobulin E; HM, human milk.

Table 4. Atopic dermatitis (AD) incidence in relation to sensitization to milk and egg

	AD incidence	Crude OR (95% CI)	Adj. OR* (95% CI)
Sensitization to milk at 4 months of age			
No	94/891 (10.6%)	1	1
Yes	7/22 (31.8%)	4.0 (1.6; 10.0)	4.0 (1.5; 10.5)
Sensitization to milk at 12 months of age			
No	76/786 (9.7%)	1	1
Yes	13/42 (31.0%)	4.2 (2.1; 8.4)	3.9 (1.9; 8.0)
Sensitization to egg at 12 months of age			
No	63/769 (8.2%)	1	1
Yes	27/70 (38.6%)	7.0 (4.1; 12.1)	8.1 (4.5; 14.5)

Results are expressed as crude and adjusted odds ratios (Adj. OR) and 95% confidence intervals (CI).

*Adjusted for: diet [human milk (HM), cow's milk formula (CMF)], atopic risk level, AD in family, gender, nationality, pets, and parental school education.

bottle-fed infants, had received no solid food. Mothers of subjects with a familial risk of AD had delayed solid food feeding beyond the first 6 months more frequently than mothers of subjects without a familial AD risk ($p=0.02$, data not shown). Table 6 shows a trend of AD incidence depending on age at first introduction of solid food and number of different food groups introduced to the subjects' diets in weeks 1–24. The protective effect of HM versus CMF varies in the strata, but a significant effect modification by solid food could not be found (Wald- χ^2 test, $p=0.58$ for age at first introduction, and $p=0.89$ for number of food groups).

Discussion

The results of this study indicate that exclusive breast-feeding during the first 16 weeks of life reduces the risk of AD in the first year by nearly 50%, compared with CMF feeding. As already shown by Halken et al. (17), mothers who decided to breast-feed for at least 16 weeks differed in certain aspects from mothers who weaned their infants earlier. The higher the atopic risk level in the family, the greater the mothers' willingness to breast-feed exclusively.

Breast-feeding was associated with a high degree of parental school education. Other allergy-preventive behaviors, such as avoidance of smoking and pet keeping, and delayed introduction of solid foods, were more frequent in the HM group. It is suggested that breast-feeding for a long duration is one of several behaviors followed by parents with a well-defined awareness of health prevention for the benefit of their infants at risk of atopy.

A family history of AD proved to be the strongest discriminating factor for infantile AD in the model. Infants with one or more than one family member affected with AD have a risk of developing AD themselves in the first year of life that is approximately twice that of infants without a family history of this disease. The inverse association between pet keeping and AD was unexpected. It is unknown as to whether these families did not keep pets as a result of AD, or whether the allergenic load of pet keeping might be a protective factor. This latter assumption would be supported by recent studies which have shown that immune responses to the major cat allergen are initiated prenatally by the fetus (18,19), and that high levels of cord blood immunoglobulin G (IgG) antibodies to cat allergen are associated with

Table 5. Age at first introduction of solid foods and number of different food groups fed in weeks 1–24 in the two study groups

	HM (n=865)	CMF (n=256)	p-value*
Age at first introduction of solid food			0.001
1–16 weeks	47 (5.4%)	79 (30.9%)	
17–24 weeks	386 (44.6%)	124 (48.4%)	
>24 weeks	422 (48.8%)	49 (19.7%)	
Missing	10 (1.2%)	4 (1.6%)	
Number of food groups introduced in weeks 1–24			0.001
0	422 (48.8%)	49 (19.1%)	
1–2	268 (31.0%)	99 (38.7%)	
>2	165 (19.1%)	104 (40.6%)	
Missing	10 (1.2%)	4 (1.6%)	

HM, human milk; CMF, cow's milk formula.

*Pearson χ^2 test.

Table 6. One-year incidence of atopic dermatitis and adjusted odds ratios with 95% CI for breast feeding (HM) versus cow's milk formula (CMF), stratified by groups of solid food diet

	HM (n=865)* n/N (%)	CMF (n=252)* n/N (%)	HM vs. CMF Adj. OR† (95% CI)
All	80/855 (9.4%)	37/252 (14.7%)	0.47 (0.30; 0.75)
Age at first introduction of solid food			
1–16 weeks	3/47 (6.4%)	10/79 (12.7%)	0.33 (0.08; 1.4)
17–24 weeks	32/386 (8.3%)	18/124 (14.5%)	0.48 (0.26; 0.91)
>24 weeks	45/422 (10.7%)	9/49 (18.4%)	0.55 (0.25; 1.2)
Number of food groups introduced in weeks 1–24			
0	45/422 (10.7%)	9/49 (18.4%)	0.55 (0.25; 1.2)
1–2	22/268 (8.2%)	17/99 (17.2%)	0.38 (0.19; 0.76)
>2	13/165 (7.9%)	11/104 (10.6%)	0.65 (0.27; 1.5)

* Sized reduced due to a total of 14 missing values in solid food diet.

† Adjusted for: atopic dermatitis in core family, atopic risk level, gender in the homogenous strata and additionally for nationality, maternal smoking, pets and parental education in the overall analysis.

fewer atopic symptoms during the first 8 years of life (20).

While the incidence of AD in the HM group was significantly lower than in the CMF group, sensitization at 4 and 12 months of age tended to be higher in the HM group ($p=NS$). Double atopic risk level, cord-blood IgE > 0.35 kU/l, and male gender were associated with an increased risk of sensitization to milk and/or egg allergen in the first year of life, whereas pet keeping decreased the risk. This latter result is consistent with observations from the ETAC study (21), which have shown that pet keeping significantly lowered the risk of sensitization to milk and egg.

Sensitization to foods does not necessarily mean that the underlying cause of AD is IgE-mediated food allergy. The clinical importance of early and transient sensitization in the immunological process of tolerance is not yet clear. A weak prenatal or postnatal sensitization may be a normal phenomenon without later allergic disease (19,22). On the other hand, patients with AD caused by food allergens do not always have food-specific antibodies (23). Nevertheless, the frequency of sensitization to milk allergens and/or ovalbumin was three to five times higher in the group of patients with AD than in those without AD. A clear association between elevated food-specific IgE antibodies and AD has been documented in other studies (24–26). It is suggested that sensitization to milk, egg, and other foods in infancy is a risk factor for AD.

A methodological problem in studies evaluating the preventive effect of human milk is that mothers cannot be randomly assigned to exclusive breast-feeding for a defined period of time. Self-selection of mothers led to an unequal distribution of risk and confounding

factors in the HM and CMF study groups. A potentially resulting bias was reduced by control for these variables by statistical methods. While CMF-feeding mothers did not know what kind of milk they were feeding, nursing mothers cannot be blinded. Thus, ascertainment of study outcome was only single-blinded in the HM group.

Adherence to solid food recommendations was higher in the HM group than in the CMF group. However, breast feeding, age at introduction, and diversity of solid food are not independent variables. Extended breast-feeding is associated with delayed solid food introduction and thus simultaneously with avoidance of an early diverse solid food diet. Factors responsible for extended breast-feeding, such as atopic risk status and parental education levels, might also be responsible for delaying solid food nutrition.

This study could not confirm the results of the New Zealand study (14), which showed that exclusive breast-feeding itself has no beneficial effect on AD rates, but that instead the observed preventive effect in breast-fed infants is the result of a reduced diversity of solid foods fed during the nursing period. There are several reasons that may explain the different results of both studies. The most important difference is that in the GINI study parents received detailed solid food recommendations as a kind of co-intervention, as well as advice to breast feed for at least 4 months. In contrast, the New Zealand study was part of a prospective observational development study without any nutritional intervention. The co-intervention advice in the GINI study resulted in a lower percentage of subjects fed solid food within the first 16 weeks of life (HM 5.4%, CMF 30.9%) compared with the New Zealand study (HM 38.3%, CMF 80.1%), and probably in the avoidance of potent food allergens. Furthermore,

other differences of the study designs, such as inclusion criteria, atopic risk level of subjects, data collection methods, and definition as well as confirmation of the end-points may have contributed to the different study results.

The present study cannot confirm the findings of the Finnish study (15), that total solid food avoidance for the first 6 months of life has an additional prophylactic effect on AD in infants exclusively breast-fed. Here again, substantial methodological differences between the two studies impede the comparability of results. In the GINI study, mothers of subjects with a particularly high risk of AD delayed solid food feeding beyond the first 6 months. This explains the unexpected result that AD incidence was highest in the group of subjects who were not fed solid foods within the first 24 weeks. It should be mentioned that the authors of the Finnish study stated that the influence of early or late solid food introduction seemed to be non-specific, as the food items given were in general not responsible for the atopic symptoms.

In all three studies, subjects were classified retrospectively according to the parental solid food feeding behaviour, that is, grouping of subjects was not randomized. Thus, it cannot be ruled out that yet unknown confounding factors are responsible for the different study results. Furthermore, in the GINI study a complete ascertainment of all foods fed during the intervention period was not feasible. Although mothers were instructed to note the main nutrients of the infant's diet, they were not asked to note all ingredients of commercial foods. As common food allergens are ubiquitous in commercial food products for infants, it is highly probable that major food allergens were fed to the infants without the parents' knowledge.

Conclusions

Exclusive breast-feeding for at least 4 months is recommended as a preventive measure for the development of AD in infants with an atopic family history. The long-term effect of exclusive breast-feeding cannot be judged by this study, but besides all other advantages of human milk, even a mere postponement of AD onset beyond the first year of life would be worthwhile to encourage mothers to provide this natural form of early infant nutrition. Based on this non-randomized, observational study we suggest that well-designed, prospective, randomized intervention studies are needed to estimate a preventive effect of early solid food avoidance.

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References

1. JONES SM. The role of food allergy and other allergic disease in atopic dermatitis. *Clin Rev Allergy Immunol* 1999; 17: 293–321.
2. SAMPSON HA. Food sensitivity and the pathogenesis of atopic dermatitis. *J R Soc Med* 1997; 90 (Suppl. 30): 2–8.
3. GUILLET G, GUILLET MH. Natural history of sensitizations in atopic dermatitis. *Arch Dermatol* 1992; 128: 187–92.
4. HOST A. Adverse reactions to foods: epidemiology and risk factors. *Pediatr Allergy Immunol* 1995; 6 (Suppl. 8): 20–8.
5. EIGENMANN PA, SICHERER SH, BORKOWSKI TA, COHEN BA, SAMPSON HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998; 101: E8.
6. BURKS AW, JAMES JM, HIEGEL A, et al. Atopic dermatitis and food hypersensitivity reactions. *J Pediatr* 1998; 132: 132–6.
7. SICHERER SH, SAMPSON HA. Food hypersensitivity and atopic dermatitis. Pathophysiology, epidemiology, diagnosis, and management. *J Allergy Clin Immunol* 1999; 104: S114–22.
8. JONES SM, SAMPSON HA. The role of allergens in atopic dermatitis. *Clin Rev Allergy* 1993; 11: 471–90.
9. NIGGEMANN B, BINDER C, DUPONT C, et al. Prospective, controlled, multi-center study on the effect of an amino-acid-based formula in infants with cow's milk allergy/intolerance and atopic dermatitis. *Pediatr Allergy Immunol* 2001; 12: 78–82.
10. GRULEE CG, SANFORD HN. The influence of breast and artificial feeding on infantile eczema. *J Pediatr* 1936; 9: 223–5.
11. KRAMER MS. Does breast feeding help protect against atopic disease? Biology, methodology, and a golden jubilee of controversy. *J Pediatr* 1988; 112: 181–90.
12. DUCHÉN K, CASAS R, FAGERAS-BÖTTCHER M, et al. Human milk polyunsaturated long-chain fatty acids and secretory immunoglobulin A antibodies and early childhood allergy. *Pediatr Allergy Immunol* 2000; 11: 29–39.
13. BURKS AW, SAMPSON H. Food allergies in children. *Curr Probl Pediatr* 1993; 23: 230–52.
14. FERGUSSON DM, HORWOOD LJ, SHANNON FT. Risk factors in childhood eczema. *J Epidemiol Community Health* 1982; 36: 118–22.
15. KAJOSAARI M, SAARINEN UM. Prophylaxis of atopic disease by six months' total solid food elimination. Evaluation of 135 exclusively breast-fed infants of atopic families. *Acta Paediatr Scand* 1983; 72: 411–4.
16. SCHOETZAU A, GEHRING U, FRANKE K, et al. Maternal compliance with nutritional recommendations in an allergy preventive programme. *Arch Dis Child* 2002; 86: 180–4.
17. HALKEN S, SKAMSTRUP HANSEN K, JACOBSEN HP, et al. Comparison of a partially hydrolyzed infant formula with two extensively hydrolyzed formulas for allergy prevention: a prospective, randomized study. *Pediatr Allergy Immunol* 2000; 11: 149–61.

18. WARNER JO, JONES CA, KILBURN SA, et al. Pre-natal sensitization in humans. *Pediatr Allergy Immunol Suppl.* 2000; 13: 6–8.
19. CASAS R, BJÖRKSTÉN B. Detection of Fel d 1-immunoglobulin G immune complexes in cord blood and sera from allergic and non-allergic mothers. *Pediatr Allergy Immunol* 2001; 12: 59–64.
20. JENMALM MC, BJÖRKSTÉN B. Cord blood levels of immunoglobulin G subclass antibodies to food and inhalant allergens in relation to maternal atopy and the development of atopic disease during the first 8 years of life. *Clin Exp Allergy* 2000; 30: 1–3.
21. ETAC STUDY GROUP. Determinants of total and specific IgE in infants with atopic dermatitis. *Pediatr Allergy Immunol* 1997; 8: 177–84.
22. HOST A. Development of atopy in childhood [Editorial]. *Allergy* 1997; 52: 695–7.
23. AGATA H, KONDO N, FUKUTOMI O, SHINODA S, ORII T. Effect of elimination diets on food-specific IgE antibodies and lymphocyte proliferative responses to food antigens in atopic dermatitis patients exhibiting sensitivity to food allergens. *J Allergy Clin Immunol* 1993; 91: 668–79.
24. HILL DJ, SPORIK R, THORBURN J, HOSKING CS. The association of atopic dermatitis in infancy with immunoglobulin E food sensitization. *J Pediatr* 2000; 137: 475–9.
25. LAAN MP, BAERT MR, BIJL AM, et al. Markers for early sensitization and inflammation in relation to clinical manifestations of atopic disease up to 2 years of age in 133 high-risk children. *Clin Exp Allergy* 2000; 30: 944–53.
26. GUSTAFSSON D, SJOBERG O, FOUCARD T. Development of allergies and asthma in infants and young children with atopic dermatitis – a prospective follow-up to 7 years of age. *Allergy* 2000; 55: 240–5.