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Breastfeeding and Risk of Atopic Dermatitis, by Parental History of Allergy, during the First 18 Months of Life

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The role of breastfeeding in allergic diseases remains controversial. The authors studied the association between breastfeeding and development of atopic dermatitis during the first 18 months of life among children with and without a parental history of allergy. A cohort study of 15,430 mother-child pairs enrolled in The Danish National Birth Cohort was carried out between 1998 and 2000. Data on breastfeeding, atopic dermatitis, and potential confounders was obtained from telephone interviews conducted during pregnancy and when the children were 6 and 18 months of age. The cumulative incidence of atopic dermatitis was 11.5% at 18 months of age. Overall, current breastfeeding was not associated with atopic dermatitis (incidence rate ratio (IRR) = 0.91, 95% confidence interval (CI): 0.80, 1.04). Exclusive breastfeeding for at least 4 months was associated with an increased risk of atopic dermatitis in children with no parents with allergies (IRR = 1.29, 95% CI: 1.06, 1.55) but not for children with one (IRR = 1.11, 95% CI: 0.94, 1.31) or two (IRR = 0.88, 95% CI: 0.69, 1.13) parents with allergies (test for homogeneity, $p = 0.03$). The authors found no overall effects of exclusive or partial breastfeeding on the risk of atopic dermatitis. However, the effect of exclusive breastfeeding for 4 months or more depended on parental history of allergic diseases.

breast feeding; child; cohort studies; dermatitis, atopic; hypersensitivity; parents

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

The role of breastfeeding in allergic diseases remains controversial. Previously, many studies reported a modest protective effect of breastfeeding on allergic diseases, especially for children with a genetic predisposition to such diseases (1). However, during the last few years, several studies have reported breastfeeding to be associated with an increased risk of asthma (2–4), atopy (3, 5), and atopic dermatitis (6–8). Several studies reported that the effect of breastfeeding depended on family history of allergic diseases; in two cohorts, the increased risk of asthma and atopy associated with breastfeeding seemed to be particularly strong for children of mothers with asthma or atopy (2, 4, 5), whereas two studies suggested a protective effect of breastfeeding on atopic dermatitis in children with a parental history of allergy (7, 8).

The aim of the present study was to examine the association of current breastfeeding and exclusive breastfeeding for 4 months with development of atopic dermatitis in offspring during the period up to 18 months of age for children with and without a parental history of allergy.

MATERIALS AND METHODS

Subjects

The study was based on mother-child pairs enrolled in The Danish National Birth Cohort (9), which consecutively recruited pregnant women from 1997 to 2002. All women who spoke Danish and intended to carry their pregnancy to term were invited to participate when they visited their

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general practitioner for the first pregnancy consultation. Participation involved four computer-assisted telephone interviews conducted by trained interviewers at gestational weeks 12 and 30 (interviews 1 and 2) and when the child was 6 and 18 months of age (interviews 3 and 4). A woman was called as many as four times for each interview. If she was not at home and was not available for interview, the interview was cancelled. Almost no women actively denied participation. Detailed questions about breastfeeding habits, itchy rash, and atopic dermatitis were integrated into interviews 3 and 4 in April 2000. Inclusion criteria for the present study involved maternal participation in these modified interviews. The women were also required to have completed the first and second interviews. Of the 28,481 women who fulfilled the criteria of completing interview 3 after April 2000 and interview 4 before our study was initiated in November 2002, 4,240 (15 percent) had not completed interview 1 and/or 2, 4,710 (17 percent) did not complete interview 3, and 4,101 (14 percent) did not complete interview 4. Thus, 15,430 participants were included in the study.

The Danish National Birth Cohort was approved by The Ethics Committees in Denmark and by the Data Protection Board. The steering committee for The Danish National Birth Cohort approved the use of data for the present study.

Breastfeeding

In interview 3, mothers were asked for how long they breastfed exclusively. Besides breast milk, only vitamins and water were allowed; thus, our definition differed slightly from the World Health Organization definition, which allows vitamins only. In addition, the mothers were asked 1) whether they were still breastfeeding and, if not, at what age they stopped; and 2) whether the child had received hydrolyzed formula. In interview 4, they were asked whether they breastfed after the child was 6 months of age and, if so, when they stopped.

Atopic dermatitis

In interview 4, the mothers were asked whether the child had ever had an itchy rash and, if so, about localization and age when affected. They were also asked whether the child had atopic dermatitis and, if so, whether a physician had verified the condition. Eighty-one women who answered that their child suffered from either an itchy rash or atopic dermatitis were invited to participate in a clinical examination by a dermatologist. Of these women, 60 took part in the study. The dermatologist determined whether the child had present atopic dermatitis, previous atopic dermatitis, another skin disease, or no skin disease. The combination of affirmative answers to 1) itchy rash or physician-verified atopic dermatitis *and* 2) recurrent rash or rash for at least 4 consecutive half-month periods *and* 3) localization in elbow creases, behind the knees, on the wrists/hands, or on the face or the presence of a generalized rash resulted in the highest sensitivity and specificity for atopic dermatitis as diagnosed by the dermatologist. The combination correctly identified 30 of the 37 children with atopic dermatitis and 21 of the 23 without atopic dermatitis according to the dermatologist, resulting in a positive predictive value of 94 percent (10). This combination of criteria was used in the present paper to define cases of atopic dermatitis. Age at onset was calculated as the middle day of the first half-month period in which the mother reported symptoms.

Background factors

Data on date of birth of the mother and the child, sex of the child, parental allergic diseases (asthma/hay fever/atopic dermatitis), atopic dermatitis in siblings, occupational class, educational level, smoking and consumption of alcohol, cohabitation, household income, pet keeping, living on a farm, number of siblings, use of day care, and clinically apparent infections in the first 6 months of life were obtained from the telephone interviews. The variable "infections" was designed as the sum of colds lasting more than 3 days, diarrhea lasting more than 3 days, and ear infections and pneumonia and was included as a time-varying variable, with age at onset of each infection as the middle day of the half-month period with symptoms. Data on birth characteristics were obtained from The Danish Medical Birth Registry.

Statistical analysis

The effect of breastfeeding, exclusive and nonexclusive, on atopic dermatitis was evaluated by calculating incidence rate ratios. These ratios were estimated by using Cox proportional hazards models with age as the underlying time. The effect of current breastfeeding was evaluated by including breastfeeding as a time-varying variable describing whether or not the child was breastfed. The effect of exclusive breastfeeding on atopic dermatitis was evaluated differently before and after 4 months of age. Until 4 months of age, the effect of exclusive breastfeeding on atopic dermatitis was evaluated as a time-varying covariate describing whether the child currently was being exclusively or not exclusively breastfed (i.e., receiving mixed feeding or not being breastfed at all). After 4 months of age, the effect of being exclusively or not exclusively breastfed at age 4 months on atopic dermatitis occurring between 4 and 18 months of age was evaluated as a time-fixed covariate. To evaluate potential confounders over all age groups, the two variables defining the effect of exclusive breastfeeding before 4 months of age (time-varying variable) and the effect of exclusive breastfeeding after 4 months of age (time-fixed covariate) were included in the same Cox model. In other words, in the model, the effect of exclusive breastfeeding was in relation to the first 4 months represented by the time-varying variable and after 4 months represented by the time-fixed variable. A similar approach was used in an additional analysis, with 6 months of age as the cutpoint instead of 4 months and with the time-fixed exclusive breastfeeding variable further divided according to duration.

For current breastfeeding and exclusive breastfeeding at age 4 months or older, the assumption of proportional hazards was evaluated by including an interaction term with age. No interactions were determined between either measure of breastfeeding and age. For other variables, the

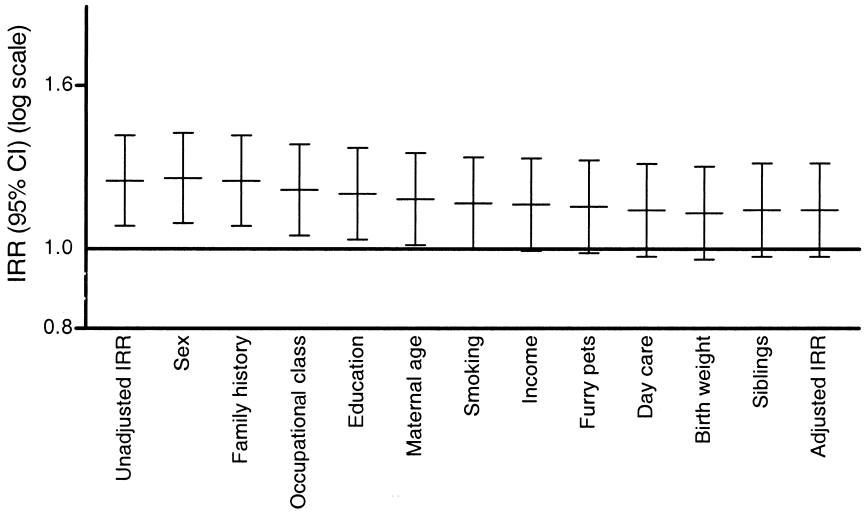

FIGURE 1. Effects of including confounders in the model on the estimate of the association between exclusive breastfeeding for at least 4 months and atopic dermatitis, The Danish National Birth Cohort, 1998–2000. Family history of allergy and sex were mandatory variables. IRR, incidence rate ratio; CI, confidence interval.

assumption was evaluated by using scaled Schoenfeld residuals. If divergence was indicated, the variable was included as a stratifying variable in the Cox regression. There was no indication that the results were biased because of divergence from the assumption of proportional hazards.

We assessed the confounding effect of all background variables on the incidence rate ratio for atopic dermatitis associated with exclusive breastfeeding for at least 4 months. The variables were ranked on the basis of the numerical change in the estimate, and a figure was created showing the impact on the estimate by adding the variables in decreasing order of numerical impact (figure 1). Variables that changed the estimate by more than 5 percent were retained and controlled for in all analyses. Potential effect modification by parental allergy on the effect of a breastfeeding variable on atopic dermatitis was investigated by testing the homogeneity of the effect of the breastfeeding variable for children with no, one, or two parents with allergies.

RESULTS

Of the 15,430 children participating in the study, 13,568 (88 percent) were exclusively breastfed at 1 month of age, 10,704 (69 percent) at age 4 months, and 930 (6 percent) at age 6 months. The figures for any breastfeeding were 10,641 (69 percent) at 6 months of age and 6,223 (40 percent) at 9 months of age. Table 1 presents the associations of various child and family characteristics with exclusive breastfeeding at 4 months of age.

According to our criteria for atopic dermatitis, 1,770 (11.5 percent) of the children had a history of previous or current atopic dermatitis at age 18 months. Of the 1,770 atopic dermatitis cases, age at onset was known for 1,765 of them. Currently breastfed children had the same risk of atopic dermatitis as children not currently breastfed (incidence rate ratio (IRR) = 0.91, 95 percent confidence interval (CI): 0.80, 1.04). There was no differential effect for children with no, one, or two parents with allergies (p for homogeneity = 0.28). During the first 4 months of life, currently exclusively breastfed children had the same risk of atopic dermatitis as children not currently exclusively breastfed (IRR = 0.86, 95 percent CI: 0.69, 1.08). The effect was not modified by parental history of allergy (p for homogeneity = 0.73). There was no overall effect of exclusive breastfeeding for at least 4 months on the risk of atopic dermatitis occurring between 4 and 18 months of age (IRR = 1.12, 95 percent CI: 0.98, 1.28), but the effect depended on parental history of allergy (p for homogeneity = 0.03; table 2).

Exclusive breastfeeding for at least 4 months compared with exclusive breastfeeding for less than 4 months was associated with an increased risk of atopic dermatitis in children without a parental history of allergic diseases (IRR = 1.29, 95 percent CI: 1.06, 1.55). This finding was not true for children with one (IRR = 1.11, 95 percent CI: 0.94, 1.31) or two (IRR = 0.88, 95 percent CI: 0.67, 1.13) parents with allergies. In families where both parents reported allergic disease and a sibling had atopic dermatitis, the estimate for exclusive breastfeeding for at least 4 months compared with less than 4 months was 0.69 (95 percent CI: 0.47, 1.00). Addressing the effect of exclusive breastfeeding for at least 4 months compared with less than 4 months according to type of allergic disease in the parents revealed that the effect of exclusive versus nonexclusive breastfeeding for at least 4 months for children with no parents with asthma was 1.14 (95 percent CI: 0.99, 1.30), whereas the effect for children with one or more parents with asthma was 0.89 (95 percent CI: 0.65, 1.22). The corresponding figures were 1.21 (95 percent CI: 1.04, 1.42) and 0.96 (95 percent CI: 0.78, 1.8) for hay fever and 1.14 (95 percent CI: 0.99, 1.30) and 0.78 (95 percent CI: 0.57, 1.08) for atopic dermatitis.

TABLE 1. Prevalence ratios for exclusive breastfeeding for at least 4 months according to characteristics of the child and the family, The Danish National Birth Cohort, 1998–2000

Characteristic	Percentage of the cohort*	Exclusively breastfed		Prevalence ratio for exclusive breastfeeding	95% CI†
		No.	%		
Sex of the child					
Boy	49	5,373	68	0.88	0.82, 0.95
Girl	51	5,331	71	1 (reference)	
No. of parents with allergic disease					
0	46	4,932	69	1 (reference)	
1	43	4,561	70	1.02	0.94, 1.11
2	11	1,211	70	1.04	0.96, 1.13
Occupational class of the mother					
High	13	1,667	81	1.30	1.26, 1.34
Medium	25	2,957	75	1.21	1.18, 1.24
Low	39	3,717	62	1 (reference)	
No job	9	846	62	0.99	0.92, 1.06
Student	10	1,080	72	1.36	1.25, 1.49
Other	4	437	71	1.14	1.08, 1.21
Maternal education (years)					
6–10	34	3,100	59	0.79	0.77, 0.81
≥11	66	7,602	75	1 (reference)	
Smoking in the presence of the child					
Yes	9	703	49	0.55	0.52, 0.59
No	91	10,001	72	1 (reference)	
Household income (DKr) per year					
<500,000	39	3,929	65	1 (reference)	
≥500,000	48	5,486	74	1.31	1.25, 1.38
Unknown	13	1,289	66	1.03	0.96, 1.10
Maternal age (years)					
<25	8	683	53	0.71	0.67, 0.76
25–29	39	3,950	66	0.79	0.73, 0.85
30–34	37	4,313	75	1.01	0.99, 1.04
≥35	16	1,758	73	1 (reference)	
No. of older siblings					
0	43	4,318	64	1 (reference)	
1	39	4,343	73	1.32	1.25, 1.39
2	14	1,680	76	1.49	1.37, 1.61
3	3	301	75	1.47	1.23, 1.75
≥4	1	62	71	1.26	0.90, 1.75
Pet keeping					
Yes	43	4,369	65	0.80	0.76, 0.84
No	57	6,335	72	1 (reference)	
Day care at age 6 months					
Yes	12	1,080	57	0.67	0.63, 0.71
No	88	9,624	71	1 (reference)	
Birth weight (g) of the child					
<2,500	3	210	56	0.80	0.73, 0.95
2,500–2,999	8	790	63	0.89	0.85, 0.94
3,000–3,499	28	2,947	68	0.97	0.94, 1.00
3,500–3,999	37	3,969	72	1.02	0.99, 1.04
≥4,000	24	2,585	70	1 (reference)	

* Some percentages do not total 100 because of rounding.
† CI, confidence interval.

TABLE 2. Adjusted* incidence rate ratios for atopic dermatitis between 4 and 18 months of age according to exclusive breastfeeding at 4 months of age and parental history of allergy, The Danish National Birth Cohort, 1998–2000

Parental history of allergy	Exclusively breastfed at 4 months of age	No. of cases/ person-years at risk	Adjusted IRR†	95% CI†
No parents with allergies	Yes	293/5,305	1.29	1.06, 1.55
	No	95/2,433	1 (reference)	
One parent with allergies	Yes	416/4,688	1.11	0.94, 1.31
	No	152/2,086	1 (reference)	
Two parents with allergies	Yes	129/1,210	0.88	0.67, 1.13
	No	61/504	1 (reference)	
p for homogeneity			0.03	

* Adjusted for sex, occupational class of the mother, maternal education, smoking in the presence of the child, household income, pet keeping, number of siblings, maternal age, day care at 6 months of age, and birth weight.

† IRR, incidence rate ratio; CI, confidence interval.

The association between exclusive breastfeeding and atopic dermatitis in children of nonallergic parents was explored in several ways. When the children were grouped according to duration of exclusive breastfeeding, we found an increasing risk of atopic dermatitis with each month of exclusive breastfeeding (p for trend = 0.003). Dividing the children into those who were exclusively, partially, or not breastfed at 4 months of age revealed that the effects of exclusive breastfeeding (IRR = 1.43, 95 percent CI: 1.15, 1.78) and partial breastfeeding (IRR = 1.31, 95 percent CI: 0.92, 1.86) on atopic dermatitis were of the same magnitude compared with not being breastfed at that age. The estimate for any breastfeeding versus no breastfeeding at 4 months of age was 1.43 (95 percent CI: 1.15, 1.77). Excluding from the analysis all 292 users of hydrolyzed formula who had neither a parental history of allergy nor a sibling with atopic dermatitis did not reduce the associations between exclusive breastfeeding and atopic dermatitis after 4 months of age (IRR = 1.32, 95 percent CI: 1.09, 1.60). Finally, controlling for the number of early infections occurring before 6 months of age did not change the estimate (IRR = 1.33, 95 percent CI: 1.10, 1.62).

DISCUSSION

During the study period, the Danish National Board of Health recommended exclusive breastfeeding for at least 4 months and partial breastfeeding for at least 9 months. It was emphasized that infants who had a family history of allergy should be exclusively breastfed for 4–6 months. In our study, more than two thirds of the women breastfed exclusively for at least the first 4 months after delivery, and more than one third continued to breastfeed for 9 months, irrespective of whether their child had a parental history of allergy. Overall, partial or exclusive breastfeeding did not have a strong impact on the development of atopic dermatitis during the first 18 months of life. However, the effects of exclusive breastfeeding appeared to be influenced by parental history of allergy, although the magnitude of the interaction was small.

The strengths of our study include the large sample size and the population-based cohort design. Thorough information on breastfeeding and symptoms of atopic dermatitis was obtained in early infancy by interviewers unaware of the associations to be studied. With no natural cutoff between children with and without atopic dermatitis, the choice of diagnostic criteria will always be a trade-off between sensitivity and specificity. We based the diagnosis of atopic dermatitis on a strict set of criteria to ensure a high positive predictive value, which was found to be 94 percent (10). The criteria are very similar to those used and thoroughly validated by others in clinical situations and, from a clinical perspective, are reasonable.

The observed cumulative prevalence of 11.5 percent tends to be lower than reported in other cohort studies of children in the same age group. However, some cohort studies were allergy-risk-enriched or created with the specific purpose of studying allergic diseases, thus potentially introducing selection bias among participants. Our result is in line with a recent community-based British study applying the United Kingdom working criteria plus a detailed clinical history of children aged 2 years (14 percent, 95 percent CI: 11 percent, 17 percent) (11). In the latter study, the cumulative prevalence of maternally reported physician-diagnosed eczema was much higher (31 percent), and almost half of the mothers (45 percent) reported that their child had ever had eczema. It was concluded that those children with maternally reported eczema or physician-diagnosed eczema are likely to include some with other eczema types or other rashes. When risk factors for disease are studied, a specific diagnosis is particularly important. Because of the large sample size, we were able to control for numerous potential confounders, which reduced the increased risk of atopic dermatitis associated with exclusive breastfeeding observed in the crude analysis. Importantly, we conducted the statistical analyses as survival analyses. Thus, breastfeeding only before the

TABLE 3. Adjusted† incidence rate ratios of atopic dermatitis according to duration of exclusive breastfeeding for children of nonallergic parents, The Danish National Birth Cohort, 1998–2000

Stopped exclusive breastfeeding between	Atopic dermatitis cases (%)	No. of children in the group	Risk of atopic dermatitis between 6 and 18 months of age			
			Adjusted IRR‡	95% CI‡	*p* for homogeneity	Increase in IRR (95% CI) per additional month of breastfeeding
Never breastfed	11.8	280	1.93	0.83, 4.47		
0 and 1 month§	9.6	1,582	1 (reference)			
1 and 2 months	9.8	742	1.05	0.54, 2.06		
2 and 3 months	9.6	761	1.03	0.54, 1.96	0.05	1.08 (1.03, 1.14)*
3 and 4 months	11.2	1,361	1.37	0.85, 2.21		
4 and 5 months	11.6	6,543	1.62	1.19, 2.21		
5 and 6 months	11.8	3,231	1.67	1.17, 2.37		
Still exclusively breastfed at 6 months of age	11.5	930	1.60	0.94, 2.72		

* *p* for trend = 0.003.

† Adjusted for sex, occupational class of the mother, maternal education, smoking in the presence of the child, household income, pet keeping, number of siblings, maternal age, day care at 6 months of age, and birth weight.

‡ IRR, incidence rate ratio; CI, confidence interval.

§ This group was considered the reference because the group that never breastfed was small and possibly different in other aspects than in breastfeeding habits.

appearance of atopic dermatitis was considered in the analyses.

Weaknesses of the study design include the fact that the genetic predisposition of the children was assessed by self-reported parental allergy obtained from the mother. Mothers of children who develop allergic diseases may be more likely to report allergic diseases in the parents. However, the impact of this bias on the association between breastfeeding and atopic dermatitis is likely to be minor.

A protective effect of exclusive breastfeeding for at least 4 months was observed for children with a very strong family history of allergic diseases, supporting the conclusions of a recent meta-analysis (12) in which a preventive effect of breastfeeding was reported for children with a positive family history of allergic diseases (odds ratio = 0.58, 95 percent CI: 0.41, 0.92). However, the meta-analysis also reported a negative, nonsignificant effect of breastfeeding of 1.43 (95 percent CI: 0.72, 2.86) for children with no family history of allergy. Our findings could support such an increased risk of atopic dermatitis associated with breastfeeding in children of nonallergic parents. The increased risk seemed to be present no matter which type of allergic disease the parents suffered from.

If there was indeed a negative relation between breastfeeding and development of allergic diseases in children of nonallergic parents, one might expect to find a dose-response relation between duration of exclusive breastfeeding and disease. We found an increasing risk of atopic dermatitis with each month of exclusive breastfeeding. However, more than a trend, data indicated that the increased risk was limited to those who were breastfed, exclusively or nonexclusively, for 4–6 months (table 3). There was no dose-response effect in terms of exclusive breastfeeding for 6 months being worse than exclusive breastfeeding for 4 months or of exclusive breastfeeding being worse than partial breastfeeding compared with not being breastfed at all.

By performing survival analyses, we were able to exclude false associations caused by mothers extending breastfeeding because the child developed atopic dermatitis. However, we speculate that women who breastfeed for at least 4 months do so because they are aware that their child has an increased risk of developing allergy. In our study, duration of breastfeeding was independent of parental history of allergy, and excluding infants who received hydrolyzed formula without having a parental history of allergy did not diminish the association. However, other factors could lead to more intensive breastfeeding of children with an inherently higher risk of atopic dermatitis. The women who breastfed for at least 4 months differed from those who did not with regard to, for instance, educational level, smoking, pet keeping, and use of day care (table 1). Although we controlled for these factors in the analyses, it is possible that mothers who follow the recommendation behave differently in other ways that enhance the risk of allergy in their offspring. In addition, we cannot exclude the possibility that women who breastfeed, exclusively or nonexclusively, are more aware of their children's skin problems and/or report more atopic dermatitis.

It has been suggested that as hygienic conditions continue to improve, early infections may be increasingly important for the maturation of the immune system. Thus, breastfeeding may be a risk factor for allergic diseases because it prevents early infections (3). However, on the basis of our

study, this possibility is unlikely to explain the increased risk of atopic dermatitis associated with exclusive breastfeeding in children of nonallergic parents, since the findings were similar after we controlled for the number of clinically apparent infections occurring before 6 months of age. Therefore, the effect of exclusive breastfeeding on atopic dermatitis seems unrelated to its well-known protective effects on clinically apparent infections.

While we could think of several reasons why the effect of breastfeeding might be biased in a negative direction, it is difficult to imagine any kind of bias that would lead to an overestimation of the beneficial effect of breastfeeding. Thus, we believe our data are incompatible with a large increased risk of atopic dermatitis associated with breastfeeding, and the beneficial effect of breastfeeding might be underestimated.

Four population-based studies of breastfeeding and atopic dermatitis have been published after the meta-analysis was published (12). Bergmann et al. (6) reported an overall increasing risk of atopic dermatitis with each month of any breastfeeding. In contrast, Kull et al. (13) found a small protective effect of exclusive breastfeeding. To our knowledge, only two studies have investigated the effect according to parental history of allergy. Miyake et al. (7) found an increased risk of atopic dermatitis associated with exclusive breastfeeding for at least 3 months on current atopic dermatitis in Japanese adolescents. In line with our observations, the negative effect was most pronounced in children of nonallergic parents. Because of a retrospective design, their results should be interpreted with caution. Likewise, Siltanen et al. (8) reported a significant increased risk of atopic dermatitis associated with exclusive breastfeeding for 3 months on atopic dermatitis at age 4 years in Finnish children with no parental history, whereas a protective effect was observed for children with a history of parental allergy. Thus, the meta-analysis and the subsequent studies support our findings of an increasingly beneficial effect of breastfeeding on atopic dermatitis associated with an increasingly strong parental history of allergic diseases.

In conclusion, we found no strong overall effect of either exclusive or partial breastfeeding on atopic dermatitis, although family history of allergy appeared to affect the risk. We recommend that future studies take into account the interaction between parental history of allergy and breastfeeding. The available data suggest that breastfeeding—clearly worth recommending for many reasons—should not be recommended as a possible means to protect against atopic dermatitis in the general population. However, a protective effect in children with a strong family history may be possible.

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