

EFFECT OF BREAST-FEEDING ON THE DEVELOPMENT OF ATOPIC DERMATITIS DURING THE FIRST 3 YEARS OF LIFE—RESULTS FROM THE GINI-BIRTH COHORT STUDY

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Objective To investigate if exclusive breast-feeding for 4 months is associated with atopic dermatitis during the first 3 years of life.

Study design Data on 3903 children were taken from yearly parental-administered questionnaires from a birth cohort study in Germany (recruited 1995-1998) comprised of a noninterventional (NI) and an interventional (I) subgroup. Outcomes were physician-diagnosed atopic dermatitis (AD) and itchy rash. Multiple logistic regression was performed for the entire cohort and stratified by family history of allergy and by study group adjusting for a fixed set of risk factors for allergies.

Results Exclusive breast-feeding (52 % of children) was not associated with higher risk for AD either in the entire cohort (OR_{adj}, 0.95; 95% CI, 0.79-1.14) or if stratified by family history of AD. In the I subgroup, but not in the NI subgroup, exclusive breast-feeding showed a significant protective effect on AD if compared with conventional cow's milk formula (OR_{adj}, 0.64; 95% CI, 0.45-0.90).

Conclusion These findings do not support the hypothesis that exclusive breast-feeding is a risk factor for development of atopic dermatitis but is protective if compared with conventional cow's milk. Observational studies might not be able to effectively control for selection bias and reverse causation. (*J Pediatr* 2004;144:602-7)

See editorial, p 564.

In the 1930s, a large nine-month follow-up study in the United Kingdom found that breast-feeding had an impressive protective effect on the development of eczema.¹ Since then, the environment, living conditions and prevalence of allergic diseases have changed considerably. The impact of breast-feeding on the development of allergies has been investigated continuously ever since. However, the large body of evidence has not succeeded in convincingly proving the protective effect of breast-feeding; the issue remains controversial today.²⁻¹¹ Nevertheless, the overall beneficial effect of breast-feeding on a child's health was never questioned, but the lingering discussion on the topic recently had a fresh revival by a reported increased risk of asthma and atopy in breast-fed New Zealanders born in the 1970s.² This prospective study not only failed to prove a protective effect, but even more controversial, posed the question whether breast-feeding might yet be a risk factor for the development of allergic diseases. Although the authors and the editorial did not dispute the many valid reasons to encourage breast-feeding, the findings caused a considerable stir in both the lay media and the scientific community.⁴⁻⁶ Most previous reports on this issue have focused on finding protective effects of breast-feeding,¹¹ but Sears et al were not the first to report a possible increased risk^{8,12-18} of asthma^{19,20} and allergies.^{10,21} Just recently, two studies also found breast-feeding to be a risk factor for atopic eczema.^{22,23} The general public in developed countries is well aware of the problem

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AD	Atopic dermatitis	ISAAC	International Study of Asthma and Allergies in Childhood
GINI	German Infant Nutritional Intervention program	NI	Noninterventional subgroup
I	Interventional subgroup	OR _{adj}	Adjusted odds ratio

of increasing prevalence of allergies, so these recent adverse reports could have negative public health implications on infant feeding practices. This debate prompted us to further investigate the issue using data from our large birth cohort designed to investigate risk factors and the natural course of allergic disease in Germany. This cohort is comprised of a population-based noninterventional (NI) subgroup and a high-allergy risk group participating in a randomized intervention trial (I-subgroup). Our aim was to investigate whether breast-feeding is associated with the development of atopic dermatitis during the first three years of life.

SUBJECTS AND METHODS

Study Design and Subjects

We used questionnaire data from a birth cohort of healthy term neonates enrolled between 1995 and 1998 in two regions in Germany (urban Munich, rural Wesel).^{24,25} This cohort is comprised of two groups.

Group I (interventional) are infants with a family history of allergy participating in an intervention study that is described in detail elsewhere (German Infant Nutritional Intervention Program [GINI]).^{26,15} Briefly, this study was a prospective randomized double-blind trial to investigate the effect of hydrolyzed formulas compared with a conventional cow's-milk formula in preventing allergies. The study formulas were given only if the recommended exclusive breast-feeding for the first 4 months was not feasible, so some of the randomized infants did not receive the intervention. At birth, dietary recommendations to avoid allergenic food were given. In addition to filling in yearly self-administered questionnaires on health, nutrition and living conditions, parents participated in structured interviews at the study centers and kept weekly diaries on the child's nutrition and health for 24 weeks.

Group NI (non-interventional) are infants whose parents did not wish to participate in the intervention trial, or who did not have a family history of allergy. This group was sent the yearly self-administered questionnaires only and did not receive any dietary recommendations.

Written informed consent was obtained from all participating families and the study protocol was approved by the local ethics committees.

Questionnaires

DEFINITION OF FEEDING REGIMEN. The child's parents were asked at age 1 year: "What kind of milk did your child drink during (each of) the first 6 months of life?" The child was defined as "exclusively breast-fed" if parents selected "exclusively human milk" for all of months 1 to 4. Otherwise the child was labeled "partly/not breast-fed." A child was further defined to be "conventional cow's-milk formula fed" if it had been fed conventional cow's-milk formula during the first 4 months with/without hypoallergenic formula and with/without breast milk (for the blinded intervention study, this information was collected from the weekly diaries).

DEFINITION OF ATOPIC DERMATITIS (AD). Parents were asked: "Did a physician diagnose any of the following diseases during the 1st/2nd/3rd year of life: [...] allergic or atopic eczema/dermatitis? [...]" If the parents selected yes, the child was defined to have "physician-diagnosed atopic dermatitis," which was the primary outcome. The symptom "itchy rash" was defined by ISAAC (International Study of Asthma and Allergies in Childhood) core questions²⁷ as intermittent itchy rash affecting the skin creases for at least 6 months.

RISK FACTORS FOR ALLERGIC DISEASES. Additional questionnaire information included solid food feeding, sociodemographic factors, living conditions, smoking habits, family history of allergy (AD, asthma, hay fever, urticaria, food allergy).

Statistical Analysis

Multiple logistic regression was performed to analyze the effect of exclusive breast-feeding and outcomes controlling for a fixed set of known risk factors of allergies (sex, geographic area, parental education, maternal smoking, pet keeping, family history of allergy and introduction of solid food during the first four months). A subgroup analysis, excluding partly breast-fed children, was performed to compare exclusively breast-fed children with exclusively bottle-fed children only. Another subgroup analysis excluded children with AD during the first year of life. Stratified analyses were performed to account for possible effect modification by family history or study group.

Sensitivity analyses were conducted using the additional detailed information available for the I-subgroup. The exposure "exclusive breast-feeding" was alternatively defined using information from the weekly diaries for weeks 1 through 16. AD was alternatively defined using information from the physical examination by the study physician and information about medication use as described in detail elsewhere.^{15,26}

Results are presented as adjusted odds ratios (OR_{adj}) with 95% CIs. SAS for Windows (version 8.02, SAS Institute 1999-2001, Cary, NC) was used for statistical analyses.

Statistical Power

Statistical significance was defined at the two-sided $P = .05$ level. Assuming a 20% three-year prevalence for AD in the unexposed group, the overall final data set generated >80% power to detect an odds ratio of 1.25. In the subgroups, power was between 45% and 77% to detect an odds ratio of 1.25, and >90% to detect an odds ratio of 1.5. For power calculations PS Version 2.1.30 (February 2003) was used.²⁸

RESULTS

Study Population

Of the 5538 infants recruited at birth, 4194 (75.7 %) had completed 3-year questionnaires. Complete data on feeding regimen and physician-diagnosed AD for the first 3 years of

Table I. Characteristics of study population (percent)

N (100%)	Entire cohort (3903)	I subgroup [†]		NI subgroup [‡]	
		Breast-fed for 4 months		Breast-fed for 4 months	
		Exclusively [§]	Partly/Not	Exclusively [§]	Partly/Not
		(900)	(684)	(1131)	(1188)
Intervention study [†]	40.6	100.0	100.0	0	0
Boys	50.7	49.0	54.7*	49.2	51.3
Urban study area (Munich)	47.6	57.7	46.9*	52.7	35.6*
Parental school education:					
>10 y (Abitur)	60.3	76.5	53.2*	67.5	45.3*
10 y	30.1	20.4	36.8	26.8	36.6
<10 y	9.6	3.1	9.9	5.7	18.1
Pet-keeping	23.9	18.9	30.8*	20.5	26.8*
Maternal smoking	21.0	15.6	31.9*	11.8	27.7*
Solid food [¶]					
Any	25.0	5.4	25.3*	10.1	53.8*
Potentially allergenic [#]	3.4	0.2	1.0*	0.7	9.9*
Family members with allergy					
None	39.6	0	0	65.2	67.9
1 Parent and/or ≥1 sibling	44.2	68.7	68.7	28.7	26.3
Both parents	16.2	31.3	31.3	6.1	5.8
AD in family	22.5	42.9	36.0*	12.2	8.8*

* $P < .05$, χ^2 test.

[†]Infants with family history of allergy, double-blind trial with randomization to hydrolyzed formulae or cow's milk formula at birth, dietary recommendations, use of study formulae if recommended breast-feeding was not feasible.

[‡]Infants with and without parental history of allergy whose parents answered yearly self-administered questionnaires only.

[§]Human milk only during the first 4 months of life (questionnaire at age 1 year).

^{||}Asthma and/or allergic rhinitis and/or AD and/or food allergy and/or urticaria (questionnaire at birth).

[¶]Months 1 to 4.

[#]Egg, cow's milk, fish, nuts, soy, cacao.

life were available for 3903 of these (93.1%). Approximately half (52.0%) of these infants were exclusively breast-fed, whereas 522 (13.4%) were exclusively bottle-fed during the first 4 months. The overall prevalence of physician-diagnosed AD and intermittent itchy rash for at least 6 months were 20.0% and 9.1% respectively. These prevalences did not differ between the exclusively breast-fed and the partly/not breast-fed group. However, Table I shows that the exclusively breast-fed group differs significantly in many aspects from the partly/not breast-fed group in both study subgroups.

Association of Exclusive Breast-feeding and Outcomes

In the entire cohort there was no effect of exclusive breast-feeding on physician-diagnosed AD or itchy rash during the first 3 years of life compared with partly/not breast-feeding (Table II). Reducing the reference group to exclusively bottle fed infants did not alter the results, nor did exclusion of cases during the first year of life (data not shown).

There was no effect of exclusive breast-feeding on physician-diagnosed AD in infants with a family history of AD (OR_{adj}, 0.92; 95% CI, 0.67-1.25) and in infants without family history of AD (OR_{adj}, 0.97; 95% CI, 0.77-1.21). This

holds also true for itchy rash (OR_{adj}, 1.18; 95% CI, 0.78-1.78; and 0.92, 0.65-1.29, respectively).

Sensitivity Analyses in the I Subgroup

Classification of "exclusively breast-fed" using the weekly diaries resulted in a proportion of exclusively breast-fed infants of 45.5% (675/1484) compared with 58.0% (860/1484) if the one-year questionnaire was used. There was no significant alteration of the overall results shown above either by using this alternative definition of exposure or by using an alternative definition of AD based on physical examination (data not shown).

I-Subgroup and NI Subgroup

Five-hundred fifty-five infants in the I subgroup received hypoallergenic formula with/without breast milk (37.4%), 254 were fed conventional cow's milk formulae during the first 4 months (17%). Of these, 51 infants were additionally fed hypoallergenic formula. In the NI subgroup the respective numbers were 1106/ 2162 exclusively breast-fed (51.2 %), 201 infants with hypoallergenic formulae (9.3%) and 855 with conventional cow's milk (40.1%). Of these, 147 were also fed hypoallergenic formulae.

Table II. Association of being exclusively breast-fed for the first 4 months of life and AD and itchy rash up to age 3 years, overall and stratified by study group

	Exclusively breast-fed for 4 months vs partly/not breast-fed [¶]				
	N	OR _{crude}	N	OR _{adj} [*]	95% CI
Entire cohort					
Physician-diagnosed AD [†]	3903	1.08	3751	0.95	(0.79-1.14)
Itchy rash [‡]	3692	1.18	3550	1.02	(0.78-1.32)
I subgroup [§]					
Physician-diagnosed AD [†]	1584	1.04	1500	0.89	(0.68-1.15)
Itchy rash [‡]	1503	0.96	1422	0.87	(0.60-1.25)
NI subgroup					
Physician-diagnosed AD [†]	2319	1.06	2251	1.03	(0.79-1.33)
Itchy rash [‡]	2189	1.20	2128	1.20	(0.83-1.75)

*Adjusted for: study area, sex, maternal smoking first year, parental education, pets, number of family members with allergy, AD/asthma in core family, introduction of any solid food during the first 4 months.

†Physician's diagnosis of allergic or atopic eczema/dermatitis (questionnaires).

‡Intermittent itchy rash affecting the skin creases for at least 6 months (questionnaires).

§Infants with family history of allergy, participating in a double-blind trial with randomization to hydrolyzed formulae or cow's milk formula at birth. Blinded study formula were used in recommended breast-feeding was not feasible.

||Infants with and without parental history of allergy whose parents answered yearly self-administered questionnaires only. No dietary recommendations or study formula were given.

¶(Conventional cow's milk formula during the first 4 months and/or hypoallergenic formula) with/without breast milk.

Table III shows the effects of exclusive breast-feeding and receipt of hypoallergenic formulae compared with the conventional cow's milk group. There is a considerable difference between the two study subgroups. The protective effect of breast-feeding in the I subgroup was seen for cases in the first year as well as in the third year, though it was not statistically significant (physician-diagnosed AD first year: OR_{adj}, 0.73; 95% CI, 0.47-1.13; third year: OR_{adj}, 0.67; 95% CI, 0.44-1.02; and itchy rash first year: OR_{adj}, 0.62; 95% CI, 0.37-1.06; third year: OR_{adj}, 0.85; 95% CI, 0.40-1.80). There was no difference of the effect of breast-feeding on physician-diagnosed dermatitis and itchy rash if stratified by family history of AD (I subgroup: family history of AD: OR_{adj}, 0.76; 95% CI, 0.46-1.25 and 0.74, 0.38-1.44, respectively. No family history: OR_{adj}, 0.56; 95% CI, 0.35-0.91 and 0.75, 0.33-1.70, respectively. The model was not computable in the NI subgroup because of small numbers).

DISCUSSION

In this large birth cohort designed to investigate determinants and the natural course of allergic disease, we did not find evidence that exclusive breast-feeding increases the risk of developing AD during the first 3 years of life. Our study was powerful enough to detect even moderately-sized risk ratios that would be expected according to the literature.^{2,22} Moreover, we found a protective effect of exclusive breast-feeding compared with conventional cow's-milk formula in the high-risk I subgroup independent from a family history of AD. This protective effect is seen in the first year, which has already been reported in a previous analysis of this study group,¹⁵ but it is still found for prevalent cases in the third year (though statistically not significant). Interestingly,

this protective effect could not be shown in the NI subgroup. We think this difference might rather be the result of study design and reverse causation than the result characteristics of the two subgroups. We believe that the concept of reverse causation is crucial in the interpretation of results from observational studies. It is important because most studies that aim to analyze the effect of breast-feeding on allergic diseases are observational studies.

The idea of reverse causation came from the finding that use of hypoallergenic formula, which was clearly protective in the I subgroup (Table III), appeared as a risk factor in the NI subgroup. After consideration it seemed reasonable that in an observational study where parents freely chose which formula to use, mothers would rather feed hypoallergenic formula than conventional cow's-milk formula if a child has suspected allergic symptoms. Thus receipt of hypoallergenic formula would be positively associated with symptoms and allergic outcomes and the "real effect" of the hypoallergenic formulae cannot be assessed. This is not the case in a blinded randomized trial, as in the I subgroup, where the choice of formula was not influenced by symptoms of the child. Hence, we consider the protective effect found in the I subgroup valid, but not the results from the NI subgroup (Table III).

Although breast-feeding ethically and naturally could not be randomized and blinded in our study, we think it is possible that similar mechanisms as described for the hypoallergenic formulae might apply. In Table III, the protective effects of breast-feeding and hypoallergenic formula are consistent in the I-subgroup. Conversely, both feeding regimens appear as risks, though not statistically significant, in the NI subgroup. Because breast-feeding is still the acknowledged and recommended first choice to feed infants and to prevent allergies, some mothers might try harder to continue

Table III. Association of feeding regimen[†] during the first 4 months and AD up to age 3 years by study group

	Exclusively breast-fed vs conventional cow's milk formula ^{**}			Hypoallergenic formula [#]	
	N	OR _{adj} [*]	95% CI	OR _{adj} [*]	95% CI
I subgroup ^{§#}					
Physician-diagnosed AD [†]	1484	0.64	(0.45-0.90)	0.58	(0.41-0.81)
Itchy rash [‡]	1406	0.74	(0.44-1.23)	0.92	(0.56-1.53)
NI subgroup					
Physician-diagnosed AD [†]	2162	1.19	(0.88-1.60)	1.30	(0.85-1.99)
Itchy rash [‡]	2045	1.44	(0.92-2.26)	1.28	(0.69-2.38)

*Adjusted for: geographic area, sex, maternal smoking first year, parental education, pets, number of family members with allergy, AD/asthma in core family, introduction of any solid food during the first 4 months.

†Physician's diagnosis of allergic or atopic eczema/dermatitis (questionnaires).

‡Intermittent itchy rash affecting the skin creases for at least 6 months (questionnaires).

§Infants with family history of allergy, participating in a double-blind trial with randomization to hydrolyzed formulae or cow's milk formula at birth.

||Blinded study formula were used if recommended breast-feeding was not feasible.

||Infants with and without parental history of allergy whose parents answered yearly self-administered questionnaires only. No dietary recommendations or study formula were given.

¶Defined by weekly diaries for I subgroup.

#Hypoallergenic formula with/without breast milk.

**Conventional cow's milk formula during the first 4 months with/without breast milk and with/without hypoallergenic formula.

breast-feeding once a child starts showing symptoms compared with mothers of nonsymptomatic children. In an observational study such as the NI subgroup, a possible protective effect of breast-feeding might be masked or even appear as a risk because of a very healthy reference group. Therefore, we do not believe that valid conclusions can be drawn from the results in the NI subgroup. However, we think the comparison of the two subgroups is important because it shows possible limitations of observational studies. Reverse causation might also explain recently published findings that breast-feeding is associated with an increased risk of atopic eczema in a German observational cohort study²² and in a Japanese cross-sectional study on adolescents. Miyake et al²³ found that breast-feeding was associated with AD in 12- to 15-year-olds, but not with wheezing or rhino-conjunctivitis. It is possible that AD in these adolescents developed in early infancy during the period of breast-feeding, whereas wheezing and rhino-conjunctivitis had a later onset and thus could not influence the choice of feeding regimen.

Limitations of the Study

We are aware that data from self-administered questionnaires may be inaccurate to some extent. However, using more detailed information available for the I subgroup did not change the overall results. "Itchy rash," defined by ISAAC core questions for 6-year-olds as "intermittent itchy rash affecting the skin creases for at least 6 months," is a very strict definition and we believe it does not represent AD very well in our study population. The cumulative incidence is only half of "physician-diagnosed AD," which was 20%. This 20% incidence is in agreement with another birth cohort in Germany that reported a 20% to 50% cumulative

incidence of atopic eczema up to 36 months of age depending on family history of atopic eczema.²⁹ Because of the relatively small number of cases with "itchy rash," the effects in subgroup analyses are partly unstable. Thus, interpretation of subgroup results refers mainly to "physician-diagnosed AD."

CONCLUSION

In this large birth cohort designed to investigate risk factors of allergic diseases, we did not find any evidence that exclusive breast-feeding increases the risk of development of AD. However when a subgroup with blinded randomization of formulae was compared with a conventional cow's-milk formula reference group, exclusive breast-feeding showed a significant protective effect. This effect could not be shown in the observational subgroup. These results suggest that observational studies might not be able to effectively control for bias by health behavior of affected families choosing the feeding regimen of the child.

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APPENDIX

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