

Breastfeeding duration is a risk factor for atopic eczema

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Summary

Background The results of numerous studies on the influence of breastfeeding in the prevention of atopic disorders are often contradictory. One of the most important problems is confounding by other lifestyle factors.

Objective The aim of the present study was to analyse the effect of any breastfeeding duration on the prevalence of atopic eczema in the first seven years of life taking into account other risk factors.

Methods In an observational birth cohort study 1314 infants born in 1990 were followed-up for seven years. At 3, 6, 12, 18, 24 months and every year thereafter, parents were interviewed and filled in questionnaires, children were examined and blood was taken for *in vitro* allergy tests. Generalized Estimation Equations (GEE)-models were used to model risk factors for the prevalence of atopic eczema and for confounder adjustment

Results Breastfeeding was carried out for longer if at least one parent had eczema, the mother was older, did not smoke in pregnancy, and the family had a high social status. The prevalence of atopic eczema in the first seven years increased with each year of age (OR 1.05; 95% CI 1.01–1.09 for each year), with each additional month of breastfeeding (1.03; 1.00–1.06 for each additional month), with a history of parental atopic eczema (2.06; 1.38–3.08), and if other atopic signs and symptoms appeared, especially specific sensitization (1.53; 1.25–1.88), and asthma (1.41; 1.07–1.85). Although breastfeeding should be recommended for all infants, it does not prevent eczema in children with a genetic risk.

Conclusion Parental eczema is the major risk factor for eczema. But in this study, each month of breastfeeding also increased the risk

Keywords atopic eczema, children, breastfeeding

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Introduction

Breastfeeding is considered the first and most important measure in the primary prevention of atopic disorders. Since Grulée and Sanford in 1936 reported a 7-fold prevalence of eczema in cow's milk-fed compared to breastfed infants, breastfeeding remained the cornerstone of recommendations, although the following decades of research produced contradictory results [1,2]. Until now, no study design was based on a randomized, double-blind allocation of subjects to either feeding type, except for a recent cluster-randomized study in Belarus [3]. The breastfeeding decision, success and duration, are associated with confounding lifestyle factors.

The claimed property of breastmilk to protect from atopic disorders could be the result of a reduced exposure to alimentary allergens in early life. Breastfeeding could also be protective by the immunological properties of breastmilk which

neutralize foreign proteins, to prevent catching infections, to produce a favourable intestinal flora, and to induce tolerance, e.g. by transforming growth factor (TGF)- β [4–7].

But, since breastmilk contains proteins secreted by the mother which are not identical to the infant's own protein repertoire, the alimentary exposure to foreign proteins is more than nil. Specific immunoglobulin (Ig)E to human milk proteins has been detected in sera of atopic infants [8]. Additionally, alimentary proteins not totally digested but absorbed by the mother may be secreted into her milk [9,10]. Although this allergen load is small compared to the load caused by breastmilk substitutes based on cow's milk, elimination diets of the mothers or even the cessation of breastfeeding were reported to prevent or to improve symptoms of food allergy and eczema in breastfed infants [11–13]. Other breastmilk constituents could also play a role in the development of atopic symptoms. Breastmilk from atopic mothers or breastmilk given to atopic infants differed in the concentration of several ingredients, e.g. fatty acids, TGF- β , cytokines or cow's milk-specific IgA antibodies [7,14–17].

Beside other strong influential factors, e.g. the genetic disposition [17], breastfeeding duration, exclusivity of breastfeeding,

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the composition of the mother's milk, as well as the amount and sort of nutritional supplements, may affect the development of atopic disorders.

The aim of the present study was to analyse in an observational birth cohort study the effect of the duration of any breastfeeding, even if not exclusive, on the prevalence of atopic eczema in the first seven years of life, taking into account other influential factors.

Methods

Methods have been described in detail elsewhere [18]. In brief, 1314 of 7609 infants born through 1990 at six German delivery wards were recruited as a birth cohort for follow-up. Of these, 499 were considered at high risk because of two atopic family members or an elevated cord blood IgE value. The controls had been drawn from the remaining newborns by a dynamic randomization procedure, and presented a mixed atopy risk. Finally, an atopy risk-enriched birth cohort was observed. From a parental questionnaire comprising diagnoses, relevant symptoms of atopic diseases and allergy tests 11 validated screening parameters were used to define the atopic status of parents [19]. In this study children were allocated to either of three parental history groups: Neither parent had ever had an atopic disorder, at least one parent had ever had an atopic disorder other than eczema, or at least one parent had ever suffered from atopic eczema.

Social status was constructed by utilizing the educational and occupational level of the parent contributing the highest share to the family income (in 90% of families this was the father) and the income level itself. Education, occupation and income were each assigned to one of four classes and then summarized, resulting in scores ranging from 4 to 12. The sum was divided by 4 resulting in three SES classes: low, middle or high [20]. Parents participating in the study gave their written informed consent. The study was approved by the Ethics Committee of the Charité Virchow Hospital, Humboldt University, Berlin.

Children and their families were invited to follow-up visits at 1, 3, 6, 12, 18 and 24 months of age and once every year thereafter. By the age of 7 years, participation rate had decreased to 939 (71.5%) of the original sample of 1314 children. A small though significant difference ($P < 0.05$) was found between participation rate in children from atopic families (73.8%), and those from non-atopic families (69.4%). Participating families were of slightly, though not significantly, higher social class. At follow-up visits, parents filled in a questionnaire, including questions on feeding habits of their infants, and gave a structured interview. Mothers continuously protocolled food offered to their infants, which guaranteed a good recall precision to the questionnaire items on feeding habits during the preceding interval. Any breastfeeding duration in months, even if not exclusive, was calculated from this source.

Physical examinations were conducted by trained physicians in a standardized manner at 3, 6, 12, 18, 24, 36, 60, 72 and 84 months of age. An elemental description of morphological skin phenomena and their localization was used to construct a computer algorithm for the definition of atopic eczema according to the morphological criteria given by Hanifin and Rajka [21]. A similar but simpler scheme was used by the

mother for case history in the preceding period. Additional sources, like the diagnosis by the family physician, were also taken into account for the definition of atopic eczema, asthma or rhinoconjunctivitis. Period prevalence was defined as the occurrence of an atopic manifestation in the preceding observational period. Lifetime prevalence was defined as ever occurred manifestation, up to the target age. Further details of diagnostic criteria were described in an earlier publication [22].

Blood samples were taken from the cord, and at 12, 24, 36, 60, 72 and 84 months of age. Not all parents agreed to blood sampling at follow-up, less so for those of non-atopic children ($P < 0.05$). On average, blood samples could be collected from 64.6 to 72.3% of children participating at each visit. Total IgE and specific IgE were determined by CAP-RAST-Feia of Pharmacia (Freiburg, Germany). A value of more than 0.35 kU/L against one of nine food and inhalant allergens was used as a threshold for specific sensitization, an elevated cord blood IgE was defined as a value above 0.9 kU/L.

The Chi-square and the Kruskal-Wallis test were applied to compare prevalence rates between groups. The determinants for duration of breastfeeding were assessed by linear regression. Generalized Estimation Equations (GEE)-models were used to model risk factors for the prevalence of atopic eczema and for confounder adjustment [23]. The GEE-model is an extension of the logistic regression model for correlated responses and takes into account that eczema conditions of the children are repeatedly examined in the time-course of the study. Therefore, it is not necessary to model a dichotomized response (actually, a lifetime prevalence), but rather information on eczema condition for every single follow-up can be utilized. All statistical analyses were performed by SAS[®] (SAS Institute Inc. Cary, NC, USA), the GEE-models have been fitted by the GENMOD procedure.

Results

In 1990, 92% of mothers had started breastfeeding in the delivery ward. Two percent of newborns had additionally received glucose solution. But 49% were fed some kind of formula as a supplement, most of them cow's milk-based, 13% based on hydrolysed protein. The distribution of breastfeeding duration is shown in Fig. 1. Obviously, the distribution was skewed to the right. Four hundred and eighty mothers were still breastfeeding at 6 months. The prevalence of prolonged breastfeeding, i.e. over 6 months, was slightly but not significantly higher for children with atopic parents. The mean breastfeeding duration accounted for 18.5 weeks in infants with non-atopic parents, 20.3 weeks if at least one parent had an atopic disorder except for eczema, and 22.9 months if at least one parent had eczema ($P = 0.0596$).

The period prevalence of atopic eczema is depicted in Fig. 2. The period prevalence was rising continuously, with a slight acceleration at 3 years of age. In a multivariate regression model, the duration of breastfeeding (in months) could be explained by eczema of at least one parent, age of the mother, high social status of the family and a mother not smoking during pregnancy, i.e. atopic, older, non-smoking women with high social status were breastfeeding for a longer period, Table 1.

In a GEE-model, variables were included which were considered to be potentially influential to the development of atopic

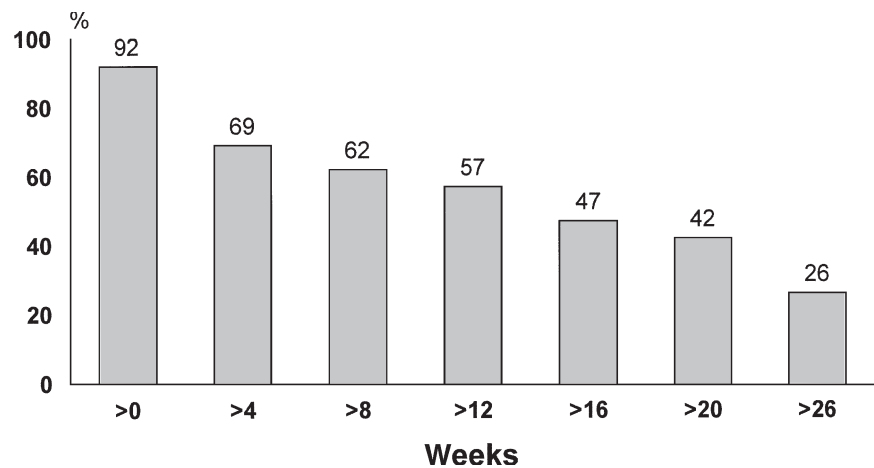


Fig. 1. Percentage of mothers breastfeeding for at least a specific time-period. At the beginning, mothers breastfeeding for less than one week and not breastfeeding at all were combined. $n = 1214$.

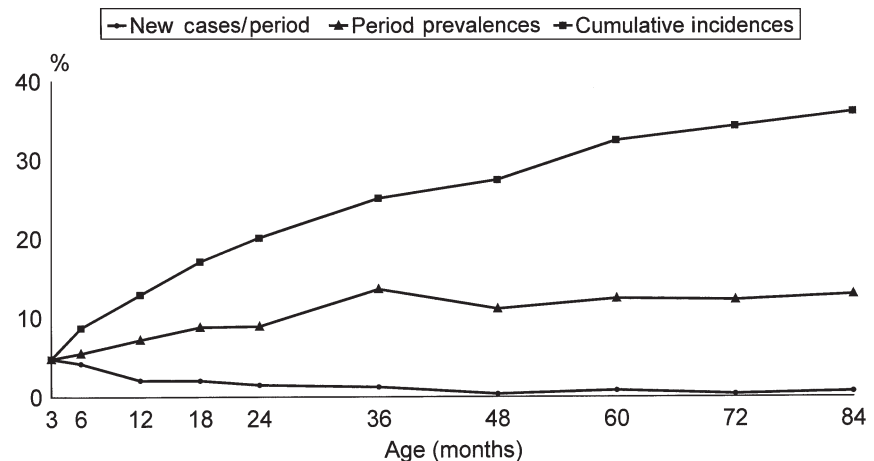


Fig. 2. Period prevalence, lifetime prevalence and new cases per observational period for atopic eczema in the first seven years of life.

Table 1. Determinants of breastfeeding duration (months)

	Parameter	95% CI	P-value
Constant	0.5674	-1.1880; 2.3228	0.5261
Parents other atopic disorder	0.1644	-0.3319; 0.6607	0.5159
Parents eczema	0.9581	0.1437; 1.7726	0.0210
Age of mother (years)	0.1153	0.0600; 0.1705	0.0001
Social status high	1.0236	0.2252; 1.8220	0.0119
Social status middle	0.0208	-0.7916; 0.8332	0.9600
Gender	-0.0761	-0.5423; 0.3900	0.7487
Parity	0.2239	-0.0587; 0.5064	0.1202
Smoking in pregnancy	-1.6134	-2.1680; -1.0589	0.0001

Multivariate linear regression model. 95% CI = 95% confidence intervals.

eczema or important confounding variables to duration of breastfeeding (see Table 1). No automatic variable selection method was done, instead we did extensive sensitivity analysis and fitted the model repeatedly with different sets of variables. It could be shown that the period prevalence of atopic eczema in the first seven years, i.e. the chance of the child to have eczema in the target observational period, could be explained by the age of the child, by breastfeeding duration (in months), by atopic eczema of a parent, by the child ever having had specific sensitization or asthma. But it could not be explained by other parental atopic disorders, by social status, by the number of upper respiratory tract infections in

the first year of life, by gender of the child, by smoking in pregnancy, by age, parity of the mother, or by elevated cord blood IgE, Table 2.

To demonstrate the stability of the findings, the results of an ordinary logistic regression analysis for the lifetime prevalence of atopic eczema are added to Table 2, which confirm the results of the GEE-model. There are only minor differences in the parameters between both models.

The risk of breastfeeding was not confined to a long breastfeeding duration: from the first month on, every additional month of breastfeeding exhibited a similarly increased risk for the development of eczema, Table 3.

Table 2. Risk factors for the period prevalence of atopic eczema at any observational period through the first seven years of life

	OR _{pp}	95% CI _{pp}	P	OR _{lt}
Age of child (years)	1.050	1.011; 1.090	0.011	
Breastfeeding duration (months)	1.029	1.002; 1.057	0.034	1.042
Atopy parents, except eczema	1.109	0.833; 1.477	0.480	0.873
Eczema parents	2.062	1.382; 3.077	0.000	2.032
Social status high	1.349	0.859; 2.117	0.194	1.479
Social status middle	0.944	0.587; 1.520	0.814	1.055
Specific sensitization ever	1.529	1.245; 1.878	0.000	2.024
Allergic rhinoconjunctivitis ever	1.723	1.316; 2.254	0.000	2.147
Asthma ever	1.410	1.073; 1.854	0.014	1.299
Number of URTI, first year	0.992	0.934; 1.053	0.786	1.094
Gender (male)	0.913	0.698; 1.195	0.507	0.873
Smoking in pregnancy	0.985	0.721; 1.346	0.923	0.905
Age of mother	0.983	0.948; 1.018	0.337	0.993
Parity	1.042	0.917; 1.185	0.524	1.074
Cord blood IgE > 0.9 kU/L	0.995	0.963; 1.027	0.752	1.005

Multivariate logistic regression for correlated data was by Generalized Estimating Equation (GEE) for repeated measurements. Odds ratios (OR_{pp}) and 95% confidence intervals (95%CI_{pp}). For comparison, the OR_{lt} from an ordinary univariate logistic regression model is added, calculating the lifetime prevalence of atopic eczema as an outcome variable. URTI = Upper respiratory tract infections.

Table 3. The influence of differences in duration (dichotomized) of breastfeeding on the development atopic eczema in the first seven years of life. GEE model, adjusting for the confounding variables of Table 2

	OR _{pp}	95% CI _{pp}
Ever breastfed/never breastfed	1.615	0.933; 2.795
Breastfed ≥ 1 months/ < 1 month	1.187	0.854; 1.648
Breastfed ≥ 2 months/ < 2 months	1.384	1.025; 1.869
Breastfed ≥ 3 months/ < 3 months	1.192	0.899; 1.580
Breastfed ≥ 4 months/ < 4 months	1.292	0.991; 1.685
Breastfed ≥ 5 months/ < 5 months	1.273	0.977; 1.658
Breastfed ≥ 6 months/ < 6 months	1.183	0.907; 1.543
Breastfed ≥ 7 months/ < 7 months	1.318	0.988; 1.759
Breastfed ≥ 8 months/ < 8 months	1.294	0.943; 1.776
Breastfed ≥ 9 months/ < 9 months	1.318	0.943; 1.842

Odds ratios (OR) and 95% confidence intervals (95%CI).

Discussion

A mother who breastfeeds her infant is convinced that she does her best to prevent atopy. She will be disappointed if her infant, although being breastfed, develops atopic eczema. The risk is increased the longer the mother is breastfeeding, as the results of this study demonstrate. Under the conditions of the present study, each month of breastfeeding elevated the risk of developing atopic eczema in the first seven years by about 3%.

Is this due to confounding? In the present study as in others, a long breastfeeding duration was more prevalent with higher education or higher social class [24–26]. Children were breastfed more often and longer, if at least one parent had atopic eczema in this study. Atopic eczema has a genetic trait. This could be confirmed by a higher chance of the child having atopic eczema with a parental history of atopic eczema or when he suffered himself from other atopic disorders like specific sensitization or asthma [25,26]. When all risk factors were taken into consideration simultaneously, as in the logistic regression equations, some of them were absorbed by others, but breastfeeding duration remained a risk factor for atopic eczema.

Multiple regression analysis cannot exclude reverse causation, i.e. that mothers extended breastfeeding once infants had eczema. Although Isolauri et al. observed that atopic eczema in exclusively breastfed infants improved when breastfeeding was stopped, she did not have controls to confirm that this was due to the cessation of breastfeeding [13]. But still, their conclusions would be in line with our interpretation that prolonged breastfeeding could maintain eczema, at least in some infants.

Half of the children in this study received formula, cow's milk-based in nearly all cases, additionally to breastmilk in the first days of life. As described earlier, supplements in our delivery hospitals were either avoided or hydrolysates were preferred when there was a history of parental atopy [27]. Anyhow, it cannot be excluded that some high risk infants may have received cow's milk protein in the first days of life in our study. Cow's milk allergy and the development of eczema could be the consequence of this early cow's milk exposure, although findings from other studies are contradictory in regard to this hypothesis [28–31]. The timing of the exposure and the amount of ingested cow's milk were considered to be crucial in the development of cow's milk allergy in breastfed infants in

the study by Saarinen and Savilahti [32]. In their study as in ours, prolonged exclusive breastfeeding was associated with the development of cow's milk allergy and sensitization.

The definition of eczema in the present study required a special expression of the disease, represented in a specified area to be involved. We did not include severity scores in the first three years of life. Therefore, we cannot exclude that breastfeeding may have ameliorated the severity of eczema.

Kramer et al. in a recent study in Belarus, for the first time succeeded in an experimental approach to breastfeeding intervention by randomizing interventional sites to breastfeeding promotion [3]. Infants at these sites compared to control sites were significantly more likely to be breastfed, and had a significant reduction in the risk of atopic eczema in the first year, i.e. 3.3% vs. 6.3%. We used a precise definition of eczema, but the lifetime prevalence of eczema in the first 12 months in our study was 12.5%, i.e. two to four times as high in our study compared to theirs. Kramer and coworkers interpreted the protective effect of breastfeeding in their study with caution. But nevertheless, we cannot claim that the results of our observational study prove that breastfeeding is generally not protective. Rather, our results mirror the real situation in our country. They can help a mother to understand that her infant may develop eczema although she breastfeeds, even for a long period, because other factors may be stronger, e.g. genetics, own diet, supplements and trigger factors. Since even parental eczema is only a risk factor for eczema of the child and not a strong predictor, we will observe that children without a positive family history who are breastfed for a long time will develop eczema. Further studies should help to precisely identify those infants, in whom the risk of (still) being breastfed outweighs the outstanding advances of breastfeeding.

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