

# Breastfeeding and infant eczema in the first year of life in the KOALA birth cohort study: a risk period-specific analysis

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# Breastfeeding and Infant Eczema in the First Year of Life in the KOALA Birth Cohort Study: A Risk Period–Specific Analysis

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## ABSTRACT

**OBJECTIVE.** We studied the association between breastfeeding and eczema, taking into account the possible influence of reverse causation, with risk period–specific analyses.

**METHODS.** Information on breastfeeding, determinants, and outcomes at 1 year of age was collected with repeated questionnaires for 2405 mother–infant pairs participating in the KOALA (Child, Parent and Health: Lifestyle and Genetic Constitution [in Dutch]) birth cohort study. By using multivariate logistic regression analysis, we compared an overall analysis with risk period–specific analyses.

**RESULTS.** By the age of 1 year, 535 infants (22.2%) had developed eczema. In an overall analysis, we found a weak nonsignificant trend toward a reduced risk of eczema in the first year of life with increasing duration of breastfeeding (lowest risk for those breastfed for  $\geq 7$  months versus never breastfed). In the risk period–specific analysis (confined to infants “at risk” for eczema onset after 3 months of age), no indication for reverse causation was found (results were not very different, compared with the overall analysis). Infants who were breastfed from birth on had a slightly (although not statistically significantly) increased risk for eczema in the first 3 months of life, compared with infants who were formula fed from birth on.

**CONCLUSIONS.** Our results indicated that no strong effect of breastfeeding on eczema in the first year of life was present. This conclusion was strengthened by risk period–specific analysis, which made the influence of reverse causation unlikely.

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### Key Words

eczema, breastfeeding, infant, cohort, epidemiology, bias, reverse causation

### Abbreviations

KOALA—Child, Parent and Health: Lifestyle and Genetic Constitution (in Dutch)

OR—odds ratio

CI—confidence interval

PPGP—pregnancy-related pelvic girdle pain

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**T**O DATE, THE results of studies addressing the effect of breastfeeding on the development of allergic diseases have been controversial.<sup>1,2</sup> Discussion of this topic revived after several studies reported that breastfeeding seemed to be a risk factor, instead of a protective factor, in the development of allergic diseases.<sup>3-6</sup> Criteria for improved study design were proposed by Kramer<sup>1</sup> in 1988, in an attempt to resolve the inconsistencies. Several studies focused on other methodologic explanations for the inconsistent results.<sup>7-10</sup>

Bias may occur as a result of disease-related modification of exposure, a concept introduced by Kull et al<sup>7</sup> and also known as reverse causation<sup>8</sup> or protopathic bias<sup>11</sup> in the literature. It is widely known that prolonged breastfeeding has many health benefits for the child. It is possible that mothers extend their breastfeeding if their child has suspected symptoms of eczema.<sup>4</sup> However, mothers may cease breastfeeding because the child has persistence of allergic symptoms as a result of sensitization to dietary antigens of the mother's diet that are present in breast milk.<sup>12,13</sup> In this study, we assess the association between breastfeeding and the development of allergic disease in infants 1 year of age, avoiding reverse causation with a risk period-specific analysis.

## METHODS

### Study Subjects

The KOALA (Child, Parent and Health: Lifestyle and Genetic Constitution [in Dutch]) Birth Cohort Study is a prospective birth cohort study in the Netherlands. The design, inclusion criteria, and exclusion criteria have been described in detail elsewhere.<sup>14</sup> Briefly, from October 2000 to December 2002, we recruited participants with diverse lifestyles (conventional and alternative). Pregnant women with a conventional lifestyle ( $n = 2343$ ) were recruited from an ongoing prospective cohort study on pregnancy-related pelvic girdle pain (PPGP) in the Netherlands.<sup>15</sup> Enrollment of pregnant women aimed at 14 to 16 weeks of gestation. At 34 weeks of gestation, PPGP subjects were asked to participate in the KOALA study. In addition, pregnant women with an alternative lifestyle ( $n = 491$ ) were recruited through several "alternative" channels, including organic food shops, anthroposophic doctors and midwives, Steiner Schools, and magazines. The KOALA study was approved by the ethics committee of the University Hospital Maastricht, and all parents provided informed consent for the study.

### Data Collection

During pregnancy and during the first 2 years after delivery, information on breastfeeding, other determinants, and allergic outcomes were collected for all members of the cohort, with repeated questionnaires at 34 weeks of gestation and at 3, 7, 12, and 24 months. On

the date of analysis, the 12-month follow-up assessment was completed. In the present study, the presence of all questionnaires at 3 months, 7 months, and 1 year after delivery was used as a criterion for selecting participants for analysis of the relationships of interest.

### Definitions of Exposures

Breastfeeding was categorized (according to the timing of our questionnaires) as follows. The category "never" served as the reference category and consisted of all infants who never received breastfeeding. All breastfed infants were categorized into the following categories, according to the age at which any breastfeeding ceased: before 4 months of age, 4 to 6 months, or  $\geq 7$  months.

### Outcome Measurements

Information on the development of eczema (based on International Study of Asthma and Allergies in Childhood questions) was obtained in the 3-month, 7-month, and 12-month questionnaires. For the overall analysis, we defined eczema in the first year on the basis of the 7-month and 12-month questionnaires. Parents were asked, "Has your child ever had an itchy rash that was coming and going in the past months?" If this question was answered affirmatively, then infants were defined as having developed eczema in the first year of life. Cases of only diaper rash, rash around the eyes, and/or scalp scaling were excluded. For the risk period-specific analyses, we distinguished 2 risk periods, namely, 0 to 3 months (cases of eczema that started in the first 3 months, including cases that did not persist after 3 months) and  $\geq 4$  months (cases of eczema that started after 3 months of age).

### Definitions of Confounders

Adjustments were made for the following potential confounders: age at first introduction of solids, defined in periods (after age of 4 months, after age of 5 months, after age of 6 months, or after age of 7 months) in which the infant received any solid food (eg, dairy products, porridge, or fruit mash) for the first time; gender of infant; recruitment group (conventional cohort or alternative cohort); maternal smoking during pregnancy (yes or no); infant's exposure to environmental tobacco smoke (yes or no); maternal age at delivery (in years); maternal education (primary school, preparatory vocational, or lower general secondary education [low], vocational, higher general secondary, or preuniversity education [middle], or higher vocational or academic education [high]); presence of parental allergic disease (ie, self-reported eczema, hay fever, house dust mite allergy, food allergy, and/or asthma) (both parents non-allergic, only father allergic, only mother allergic, or both parents allergic); number of siblings (no siblings, 1 sibling, or  $\geq 2$  siblings); and presence of older allergic

siblings (no siblings, older allergic sibling, or older non-allergic sibling).

### Statistical Methods

Relationships were analyzed by using logistic regression analysis. Results are presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs) and were adjusted for potential confounders, which were placed in the logistic regression model simultaneously. Effect modification by recruitment group (conventional or alternative), presence of an allergic parent, or presence of an allergic sibling was assessed by using the likelihood ratio test, comparing models with and without interaction terms. To avoid an influence of disease onset on exposure (reverse causation), we performed risk period-specific analyses, considering exposure only before the risk period.

### RESULTS

Of the 2834 infants enrolled at birth, 2405 parents had completed the 3 questionnaires at infant's age of 1 year (3 months, 7 months, and 12 months after delivery); that is, 1941 (83%) of 2343 participants in the conventional cohort and 464 (95%) of 491 participants in the alternative cohort were eventually included in our analyses. The participation rate of KO-ALA participants recruited from the PPGP study was 39%. The response rates for the 3-month, 7-month, and 12-month questionnaires were 94%, 92%, and 90%, respectively.

Table 1 shows the baseline characteristics of the 2 recruitment groups combined. We noted several differences between the cohorts; mothers in the alternative cohort had a higher rate and longer duration of breastfeeding, compared with the conventional cohort ( $\geq 7$  months: 71% and 28%, respectively). Also, they showed greater delay in the age of first introduction of solid foods ( $>7$  months: 39% and 21%, respectively). Other characteristics that differed between the alternative cohort and the conventional cohort were maternal smoking during pregnancy (yes:  $<1\%$  and 8%, respectively), exposure to environmental tobacco smoke (yes:  $<1\%$  and 4%, respectively), maternal age (mean: 34 years and 32 years, respectively), maternal education (high education: 73% and 43%, respectively), and number of siblings ( $\geq 2$  siblings: 21% and 13%, respectively). In all analyses, we considered recruitment group as a potential effect modifier for the relationship between breastfeeding and eczema. However, we found no significant interaction between recruitment group and breastfeeding in the logistic regression models (always  $P > .5$  for interaction). Therefore, we present all results for the groups combined. Also, no interaction between breastfeeding and the presence of an allergic parent or an older allergic sibling was found ( $P > .28$ ).

The results of the overall analysis are presented in Table 2. The results showed a tendency toward a lower

**TABLE 1** Baseline Characteristics ( $N = 2405$ )

Breastfeeding, $n$ (%)	
Never	358 (15)
0–3 mo	745 (31)
4–6 mo	430 (18)
$\geq 7$ mo	872 (36)
Age at introduction of solid foods, mean $\pm$ SD, mo	3 $\pm$ 1
Male gender of infant, $n$ (%)	1231 (51)
Maternal smoking during pregnancy (34 wk), $n$ (%)	150 (6)
Infant exposed to ETS at age 1 y, $n$ (%)	88 (4)
Maternal age at time of delivery, mean $\pm$ SD, y	32 $\pm$ 4
Maternal education, $n$ (%)	
Low	222 (9)
Middle	1009 (42)
High	1174 (49)
Parental allergic disease, $n$ (%)	
Both parents nonallergic	1165 (48)
Only father allergic	460 (19)
Only mother allergic	510 (21)
Both parents allergic	270 (11)
No. of siblings, $n$ (%)	
0	1058 (44)
1	966 (40)
$\geq 2$	358 (15)
Presence of older allergic siblings, $n$ (%)	
No siblings	1058 (44)
Older nonallergic sibling(s)	947 (39)
Older allergic sibling(s)	377 (16)

Values may not add up to the total number because of missing values. ETS indicates environmental tobacco smoke.

**TABLE 2** Overall Analysis of Breastfeeding and Incidence of Eczema in the First 1 Year of Life

Breastfeeding	Total No.	No. (%)	Eczema in First 1 y of Life	
			OR <sup>a</sup> (95% CI)	Adjusted OR <sup>b</sup> (95% CI)
Never	358	79 (22)	1.0 (reference)	1.0 (reference)
0–3 mo	745	168 (23)	1.02 (0.76–1.39)	0.98 (0.71–1.34)
4–6 mo	430	100 (23)	1.07 (0.77–1.50)	0.94 (0.66–1.34)
$\geq 7$ mo	872	188 (22)	0.97 (0.72–1.31)	0.80 (0.57–1.12)
Total	2405	535 (22)		

All infants were included in the analysis.

<sup>a</sup>  $P = .76$  for trend.

<sup>b</sup> Adjusted for age at introduction of solid foods, gender, recruitment group, maternal smoking during pregnancy, infant's exposure to environmental tobacco smoke, maternal age, maternal education, parental allergic disease, number of siblings, and presence of older allergic siblings ( $P = .13$  for trend).

risk of eczema in the first year of life associated with breastfeeding, but this was not statistically significant. For the risk period of  $\geq 4$  months, we considered only eczema cases with onset after 3 months, and we combined the exposure categories of 4 to 6 months and  $\geq 7$  months into 1 category of  $\geq 4$  months to avoid reverse causation. The results again showed a tendency toward a lower risk of eczema developing between 4 and 12 months of life associated with breastfeeding, which was not statistically significant (Table 3).

The effect of starting breastfeeding on early development of eczema (0–3 months;  $n = 514$ ) was analyzed



**TABLE 3** Period-Specific ( $\geq 4$  Months) Analysis of Breastfeeding and Incidence of Eczema Between 4 and 12 Months

Breastfeeding	Total No.	No. (%)	Eczema Between 4 and 12 mo	
			OR <sup>a</sup> (95% CI)	Adjusted OR <sup>b</sup> (95% CI)
Never	578	79 (14)	1.0 (reference)	1.0 (reference)
0–3 mo	1019	126 (12)	1.00 (0.68–1.46)	0.98 (0.66–1.46)
$\geq 4$ mo	578	79 (14)	0.84 (0.59–1.20)	0.77 (0.52–1.15)
Total	1891	246 (13)		

The incidence of eczema in the risk period of 4 to 12 months was analyzed (ie, excluding infants with onset of eczema before 3 months of age).

<sup>a</sup>  $P = .22$  for trend.

<sup>b</sup> Adjusted for age at introduction of solid foods, gender, recruitment group, maternal smoking during pregnancy, infant's exposure to environmental tobacco smoke, maternal age, maternal education, parental allergic disease, number of siblings, and presence of older allergic siblings ( $P = .14$  for trend).

subsequently, among infants who were excluded in the risk period ( $\geq 4$  months)-specific analysis mentioned above. A slightly higher risk of early eczema was found for infants who were breastfed from birth on (ever breastfed), compared with infants who were formula fed from birth on (never breastfed), but this was not statistically significant (early eczema in ever-breastfed group: 450 of 2047 infants, 22.0%; never-breastfed group: 64 of 358 infants, 17.9%; adjusted OR: 1.30; 95% CI: 0.96–1.77). Notably, the risk of infants whose mothers attempted breastfeeding but could not establish it (breastfeeding of  $< 4$  weeks; 22% with eczema) was not essentially different from that of infants who managed breastfeeding for  $> 4$  weeks but ceased before 4 months of age (23% with eczema).

## DISCUSSION

In the present study, we found no association between breastfeeding and the development of eczema in the first year of life. We found a tendency toward a lower risk of eczema that started at  $\geq 4$  months of age and a tendency for a higher risk of early eczema, but both were not statistically significant. When we compared the overall analysis and the risk period ( $\geq 4$  months)-specific analysis, the results were not very different. Therefore, we conclude that there was no substantial reverse causation. An advantage of our study is the relatively short time intervals between subsequent follow-up questionnaires, which makes the influence of recall bias less likely. Follow-up rates were high, which limits the possibility of differential bias regarding baseline characteristics or outcomes. However, families with allergic complaints tend to be over-represented in studies on causes of atopy. The difference between participants and non-participants may be explained by self-selection, because people with a positive family history of allergic disease tend to be more interested in participating in studies on health-related topics. Also, participants in the KOALA study had more intention to breastfeed than did non-participants.<sup>14</sup> However, relative risk associations are not

biased, in our opinion, because relative risks are based on proportions and not absolute numbers.

Two other studies also found no relationship between breastfeeding and eczema.<sup>16,17</sup> Other observational studies and a meta-analysis found a protective association between duration of breastfeeding and eczema.<sup>8,18–23</sup> Some studies even found breastfeeding to be a risk factor for the development of eczema.<sup>3,4,6</sup> For example, Bergmann et al<sup>4</sup> showed that the prevalence of atopic eczema in the first 7 years increased by 3% with each additional 1 month of breastfeeding. However, those authors suggested that the possibility that their results were influenced by reverse causation could not be ruled out. The idea that early atopic symptoms influence the duration of breastfeeding was demonstrated recently by Lowe et al.<sup>24</sup> Reverse causation could be an explanation for the inconsistent results between different studies.<sup>4,7–9</sup> Also, reverse causation may be more likely to be evident in the relationship between exclusive breastfeeding and risk of developing eczema. Recently, Zutavern et al<sup>9</sup> suggested that reverse causation is a relatively new problem because, in older studies, public awareness of the health-promoting effects of breastfeeding was smaller.

Two solutions have been proposed in the literature to avoid reverse causation. First, survival analysis (Cox regression analysis) is a suitable method to consider only breastfeeding before the appearance of eczema.<sup>17</sup> However, survival analysis requires data on the exact onset of eczema in small time intervals, which many studies lack. Second, reverse causation can be avoided by excluding infants with onset of disease during lactation.<sup>7,9,25</sup> This is equivalent to a risk period-specific analysis confined to infants at risk (avoiding overlap between exposure and disease outcome). Such an analysis has the additional advantage that it keeps track of infants with early symptoms (such as the infants with early eczema in our study).

In the present study, the results of such a risk period-specific analysis were not substantially different, compared with the results of the overall analysis. In our opinion, we have demonstrated that our main finding (breastfeeding does not influence the risk of eczema in the first year of life) is unlikely to be biased by reverse causation. In addition, we examined more specifically all infants with reported eczema in the first 3 months (ie, infants with early symptoms who were excluded in the risk period-specific analysis). Infants who were ever breastfed had a slightly (although not statistically significantly) increased risk of eczema at the age of 3 months, compared with completely (from birth) formula-fed infants. With regard to this finding, our analysis did not address both the duration of breastfeeding and the onset of eczema. To avoid reverse causation, the discrimination between starting breastfeeding versus formula feeding from birth is the only useful comparison. That is, no overlap occurs between exposure immediately after

birth and onset of disease; because the disease is not yet present immediately after birth, the choice of the feeding regimen immediately after birth cannot be biased by disease.

## CONCLUSIONS

We found no strong evidence for a protective effect of breastfeeding on eczema in the first year of life. We think that our results were strengthened by avoiding reverse causation as a potential bias. Controlling for reverse causation can be accomplished by risk period-specific analyses in which only exposure before the risk period is taken into account. Our findings do not necessarily mean that reverse causation will be absent in other study populations in which the presumed protective effect of breastfeeding is more widely advocated. Therefore, in studies addressing the controversial relationship between breastfeeding duration and the development of allergic diseases, exploring reverse causation is a prerequisite for retrieving results with a minimal chance of bias.

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