

# Breast-feeding duration and infant atopic manifestations, by maternal allergic status, in the first 2 years of life (KOALA study).

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# Breast-Feeding Duration and Infant Atopic Manifestations, by Maternal Allergic Status, in the First 2 Years of Life (KOALA Study)

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**Objective** To investigate the potential effect of modification by maternal allergic status on the relationship between breast-feeding duration and infant atopic manifestations in the first 2 years of life.

**Study design** Data from 2705 infants of the KOALA Birth Cohort Study (The Netherlands) were analyzed. The data were collected by repeated questionnaires at 34 weeks of gestation and 3, 7, 12, and 24 months postpartum. Total and specific immunoglobulin E measurements were performed on venous blood samples collected during home visits at age 2 years. Relationships were analyzed using logistic regression analyses.

**Results** Longer duration of breast-feeding was associated with a lower risk for eczema in infants of mothers without allergy or asthma ( $P_{trend} = .01$ ) and slightly lower risk in those of mothers with allergy but no asthma ( $P_{trend} = .14$ ). There was no such association for asthmatic mothers ( $P_{trend} = .87$ ). Longer breast-feeding duration decreased the risk of recurrent wheeze independent of maternal allergy ( $P_{trend} = .02$ ) or asthma status ( $P_{trend} = .06$ ).

**Conclusions** Our findings show that the relationship between breast-feeding and infant eczema in the first 2 years of life is modified by maternal allergic status. The protective effect of breast-feeding on recurrent wheeze may be associated with protection against respiratory infections. (*J Pediatr* 2007;151:347-51)

The role of breast-feeding in allergic disease remains a matter of debate. The postulated protective effect of breast-feeding may act through several mechanisms. One possible mechanism is through the exclusion of potentially allergic components, like cow's milk or food products introduced in the infant's diet. Alternatively, breast-feeding provides the infant with immunomodulatory, anti-inflammatory, nutritional, and other components present in human breast milk.

Wright et al<sup>1</sup> reported higher immunoglobulin E (IgE) levels in breast-fed children compared with never breast-fed children of mothers with high IgE levels. A study of Bavarian farmers study found an increased risk for doctor-diagnosed asthma related to breast-feeding in children whose mothers had asthma themselves.<sup>2</sup> In children of asthmatic mothers, longer exclusive breast-feeding was found to be associated with a greater risk of asthma, but asthma was unrelated to feeding status in children without maternal asthma.<sup>3</sup> In contrast, an Australian study found an association between exclusive breast-feeding and a statistically significant lower risk of asthma that was independent of maternal asthma and the child's atopic status.<sup>4</sup>

In the present study, we examined whether maternal allergy or asthma status is an effect modifier in the relationship between breast-feeding duration and the development of infant atopic manifestations (eczema, recurrent wheeze) in the first 2 years of life. We also studied the relationships between breast-feeding duration and increased total IgE

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and p 359

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CI Confidence interval  
IgE Immunoglobulin E

OR Odds ratio  
UK-WP UK Working Party

levels and allergic sensitization at age 2 in children of mothers with and without increased total IgE levels or sensitization.

## METHODS

### Study Population

The study subjects were mother–infant pairs previously enrolled in the KOALA Birth Cohort Study between 2000 and 2002.<sup>5</sup> We recruited participants with diverse lifestyles (“conventional” and “alternative”) who were at 34 weeks of gestation. The women with a conventional lifestyle ( $n = 2343$ ) were recruited from an ongoing prospective cohort study on pregnancy-related pelvic girdle pain in The Netherlands. The women with an alternative lifestyle ( $n = 491$ ) were recruited through various channels, including organic food shops, anthroposophic doctors and midwives, Steiner schools, and magazines. The study design was approved by the Ethics Committee of Maastricht University, and all parents signed written informed consent.

### Data Collection

During pregnancy and throughout the first 2 years of the child’s life, information on breast-feeding, other determinants, and atopic manifestations was collected for all members of the cohort by repeated questionnaires at 34 weeks of gestation and at 3, 7, 12, and 24 months after birth. Home visits to children age 2 years by trained nurses to collect blood samples and perform clinical examination by trained nurses, using UK Working Party (UK-WP) criteria were started in September 2004.

All infants of participants ( $n = 2834$ ) with a completed informed consent and the presence of the first questionnaire (34 weeks of gestation) were included in the study. We excluded infants with congenital diseases known to affect immunity, such as Down syndrome, and those with missing information on the main determinant, breast-feeding.

### Breast-Feeding Exposure

Breast-feeding was categorized as follows, according to the age at which breast-feeding was stopped: never breast-fed (reference category), 0 to 3 months, 4 to 6 months, 7 to 9 months, and >9 months.

### Maternal Allergic History

To study effect modification by maternal allergy or asthma on the relationship between breast-feeding duration and infant eczema and recurrent wheeze, we defined 3 strata: (1) no maternal allergy or asthma; (2) maternal allergy, no asthma, defined as self reported doctor’s diagnosed eczema, allergy for house dust mite/pets, or allergic rhinoconjunctivitis (eg, hay fever); and (3) maternal asthma, defined as self-reported or physician-diagnosed asthma, irrespective of other allergic diseases. Maternal increased total IgE levels and sensitization were both defined as present (yes/no).

### Infant Atopic Manifestations

Eczema (by Questionnaire, Adapted from International Study of Asthma and Allergies in Childhood).

In the 7-, 12-, and 24-month postpartum questionnaires, parents were asked: “Has your child ever had an itchy rash that came and went in the past months?” If the parent answered “yes” at least once, the infant was defined as having developed eczema in the first 2 years of life. Cases of diaper rash, rash around the eyes, or scalp scaling were excluded.

### Atopic Dermatitis (According to UK-WP Criteria)

To specify eczema reported by parents as described earlier, we defined atopic dermatitis according to UK-WP criteria<sup>6</sup> for all infants who were visited at home at age 2 years. In this study, infants with a UK-WP atopic dermatitis probability score >0.9 were considered as having probable presence of atopic dermatitis.

Recurrent wheezing in the first 2 years of life was defined as reported presence of wheezing with at least 4 attacks between age 0 and 7 months and mentioned in the 7-month postpartum questionnaire, between age 7 and 12 months and mentioned in the 12-month postpartum questionnaire, or between age 13 and 24 months and mentioned in the 24-month postpartum questionnaire.

### Measurements and Definitions of Allergic Sensitization (Mother and Infant)

Maternal venous blood samples were obtained during home visits at 34 to 36 weeks of gestation. Infants’ venous blood samples were obtained during home visits at 2 years postpartum. Total IgE levels were analyzed as described earlier.<sup>7,8</sup> For values <150 IU/mL, a sandwich radioimmunoassay (RIA) was used;<sup>7</sup> for values >150 IU/mL, a competitive RIA was used.<sup>8</sup> All blood samples were analyzed for specific IgE against hen’s eggs, cow’s milk, peanuts, birch, grass pollen, cat, dog, and house dust mite using a radioallergosorbent test as described previously.<sup>8</sup> Calculation was performed by means of a standard curve obtained by radioallergosorbent testing with a dilution series of a chimeric monoclonal IgE antibody against the major allergen Der p 2 and Sepharose-coupled recombinant Der p 2.<sup>9</sup> The detection limits for total and specific IgE were 0.50 IU/mL and 0.10 IU/mL, respectively. High maternal total IgE was arbitrarily defined as total IgE level >100 IU/mL; high total IgE for infants was arbitrarily defined as total IgE level >10 IU/mL. Mother and infant were considered sensitized if specific serum IgE levels were >0.3 IU/mL against at least 1 of the food or inhalant allergens tested.

### Statistical Analysis

Relationships were analyzed using logistic regression. Results are presented as unadjusted odds ratios (OR) and adjusted ORs with corresponding 95% confidence intervals (CIs). All potential confounders were simultaneously included in the logistic regression model to adjust the analyses.

Potential confounders were (1) age at introduction of cow's milk products, defined as artificial formulas (including hypoallergenic formulas), (raw) milk, porridge, yogurt, and other dairy products, categorized according to age at first introduction as 0 to 3 months, 4 to 6 months, 7 to 9 months, and after 9 months, and (2) age at introduction of other food products (eg, fruit mash), categorized according to the age at first introduction as 0 to 3 months, 4 to 6 months, and after 7 months. Other potential confounders were infant's sex, recruitment group (conventional/alternative lifestyle), antibiotic medication (yes/no), maternal smoking during pregnancy (yes/no), infant's exposure to environmental tobacco smoke (yes/no), maternal age at delivery, maternal education (primary school, preparatory vocational or lower general secondary education [low], vocational education, higher general secondary or pre-university education [middle], or higher vocational or academic education [high]), presence of paternal allergic disease (yes/no), number of siblings (no siblings, 1 sibling, or 2 or more siblings), and presence of older allergic siblings (no siblings, older allergic sibling[s], or older nonallergic sibling[s]).

To assess whether our results were prone to reverse causation (by introducing hypoallergenic formulas after the development of eczema), we explored the use of hypoallergenic formulas associated with atopic manifestations. For the test for trend, we repeated the logistic regression analyses with the categories of breast-feeding duration (coded as 1 to 5) as a continuous variable in the logistic regression analyses, again adjusting for all potential confounders. Effect modification by recruitment group was assessed using the likelihood ratio test, comparing models with and without interaction terms.

## RESULTS

Of the 2834 infants enrolled at birth, 3 were excluded because of Down syndrome and 126 because of missing information on breast-feeding, leaving 2705 infants for the study. The response rate for the questionnaire at age 2 years was 93% ( $n = 2516$ ). Home visits at age 2 years were made in 818 infants. Most infants were breast-fed (85%;  $n = 2287$ ). Mothers in the alternative recruitment group had a higher rate and a longer duration of breast-feeding compared with those in the conventional recruitment group (Table I; available at [www.jpeds.com](http://www.jpeds.com)). Also, they showed greater delay in the age of introduction of cow's milk products (Table I). Other characteristics that differed between both groups were maternal age, maternal smoking during pregnancy, environmental tobacco smoking, maternal education, number of siblings, and antibiotic medication use (Table I).

Infants receiving hypoallergenic formulas at any time between birth and age 3 months ( $n = 185$ ) showed a higher risk of eczema in the first 2 years of life compared with infants given nonhypoallergenic formula feeding (unadjusted OR = 1.81; 95% CI = 1.31 to 2.49) even when adjusting for all potential confounders (adjusted OR = 1.97; 95% CI = 1.30 to 3.00). Because these results may be explained by reverse causation (ie, hypoallergenic formulas were introduced after

the development of eczema), we excluded the participants who introduced hypoallergenic formulas (0 to 3 months) from all subsequent analyses.

Overall, longer breast-feeding duration showed a statistically significant trend toward a lower risk of eczema ( $P_{trend} = .03$ , adjusted for confounders). Longer duration of breast-feeding was associated with a statistically significant lower risk for eczema in infants of mothers without allergy or asthma ( $P_{trend} = .01$ ; Table II). In mothers with allergy but no asthma, the results trended in the same direction but were not statistically significant ( $P_{trend} = .14$ ; Table II). For asthmatic mothers, there was no (inverse) association between breast-feeding duration and infant eczema ( $P_{trend} = .87$ ; Table II). There was no association between breast-feeding duration and atopic dermatitis according to UK-WP criteria ( $n = 866$ ; number of cases = 117) in either the overall analysis or the 3 different maternal strata (results not shown;  $P_{trend} > .05$ ).

Longer breast-feeding duration was associated with a lower risk of recurrent wheeze in infants of mothers with no allergy or asthma ( $P_{trend} = .02$ ), with allergy but no asthma ( $P_{trend} = .02$ ), and with asthma ( $P_{trend} = .06$ ). The breast-feeding category 7 to 9 months showed the lowest risk of infant recurrent wheeze in all groups (OR = 0.11; 95% CI = 0.02 to 0.70) (Table II).

Duration of breast-feeding did not influence the risk of high total IgE levels in infants of mothers who themselves had increased total IgE levels or in mothers with normal IgE levels (Table III; available at [www.jpeds.com](http://www.jpeds.com)). Also, we found no association between breast-feeding duration and infant sensitization in infants of mothers with or without sensitization (Table III).

The differences in the ORs of unadjusted and adjusted analyses (Table II) were the result of strong confounding effects of a positive paternal history of allergic disease, age at introduction of cow's milk and other food products, and infant's use of antibiotics.

## DISCUSSION

We found that longer duration of breast-feeding was associated with a decreased risk for recurrent wheeze in the first 2 years of life, regardless of the mother's allergy history. Moreover, longer duration of breast-feeding was associated with a decreased risk of eczema (by questionnaire) in infants of mothers without allergy or asthma. When atopic dermatitis (according to UK-WP criteria), increased total IgE levels, or sensitization were taken as the outcome, no associations with breast-feeding duration were found.

Overall, our results for eczema provide evidence of a protective effect of breast-feeding. We found a protective effect of breast-feeding duration on eczema in the first 2 years of life in mothers without allergy or asthma; this effect was less clear in mothers with allergy but no asthma and absent in mothers with maternal asthma. These findings imply effect modification by maternal allergic status for the relationship between breast-feeding and infant eczema. Nevertheless,

**Table II. Associations between breast-feeding duration and the development of infant eczema and recurrent wheeze during the first 2 years of life according to presence of allergy and/or asthma in the mother**

Maternal status	Infant eczema				Infant recurrent wheeze				
	N	n (%)	OR (95% CI)	OR <sub>adj</sub> (95% CI)*	N	n (%)	OR (95% CI)	OR <sub>adj</sub> (95% CI)*	
No allergy, no asthma									
BF									
Never	231	61 (26%)	1.00	1.00	167	25 (15%)	1.00	1.00	
0 to 3 months	494	132 (27%)	1.02 (0.71 to 1.45)	0.90 (0.61 to 1.31)	353	55 (16%)	1.05 (0.63 to 1.75)	1.11 (0.62 to 2.00)	
4 to 6 months	259	70 (27%)	1.03 (0.69 to 1.54)	0.71 (0.42 to 1.20)	198	24 (12%)	0.78 (0.43 to 1.43)	0.84 (0.36 to 1.95)	
7 to 9 months	245	74 (30%)	1.21 (0.81 to 1.80)	0.69 (0.40 to 1.19)	194	11 (6%)	0.34 (0.16 to 0.72)	0.37 (0.14 to 1.00)	
>9 months	309	75 (24%)	0.89 (0.60 to 1.32)	0.51 (0.29 to 0.89)	247	17 (7%)	0.42 (0.22 to 0.80)	0.43 (0.16 to 1.11)	
<i>P<sub>trend</sub></i>			.83	.01	<i>P<sub>trend</sub></i>			.00	.02
Maternal allergy, no asthma									
BF									
Never	87	27 (31%)	1.00	1.00	67	15 (22%)	1.00	1.00	
0 to 3 months	215	71 (33%)	1.10 (0.64 to 1.87)	0.90 (0.52 to 1.57)	139	22 (16%)	0.65 (0.31 to 1.36)	0.56 (0.25 to 1.23)	
4 to 6 months	111	43 (39%)	1.41 (0.78 to 2.54)	0.86 (0.43 to 1.71)	84	13 (16%)	0.63 (0.28 to 1.45)	0.44 (0.16 to 1.26)	
7 to 9 months	114	42 (37%)	1.30 (0.72 to 2.34)	0.68 (0.34 to 1.38)	89	6 (7%)	0.25 (0.09 to 0.69)	0.18 (0.05 to 0.61)	
>9 months	125	46 (37%)	1.29 (0.72 to 2.32)	0.63 (0.31 to 1.29)	101	10 (10%)	0.38 (0.16 to 0.91)	0.32 (0.10 to 1.00)	
<i>P<sub>trend</sub></i>			.28	.14	<i>P<sub>trend</sub></i>			.01	.02
Maternal asthma									
BF									
Never	27	7 (26%)	1.00	1.00	16	5 (31%)	1.00	1.00	
0 to 3 months	75	28 (37%)	1.70 (0.64 to 4.53)	1.39 (0.51 to 3.78)	47	13 (28%)	0.84 (0.24 to 2.89)	0.40 (0.10 to 1.51)	
4 to 6 months	36	15 (42%)	2.04 (0.69 to 6.05)	1.40 (0.44 to 4.42)	24	7 (29%)	0.91 (0.23 to 3.58)	0.48 (0.10 to 2.32)	
7 to 9 months	37	12 (32%)	1.37 (0.46 to 4.13)	0.70 (0.22 to 2.27)	24	3 (13%)	0.31 (0.06 to 1.57)	0.11 (0.02 to 0.70)	
>9 months	42	22 (52%)	3.14 (1.10 to 9.00)	1.67 (0.53 to 5.21)	35	6 (17%)	0.46 (0.12 to 1.80)	0.22 (0.04 to 1.09)	
<i>P<sub>trend</sub></i>			.08	.87	<i>P<sub>trend</sub></i>			.01	.06

May not add up to total numbers because of missing values.

BF, breast-feeding; OR<sub>adj</sub>, adjusted odds ratio.

\*Based on logistic regression analysis adjusted for: the age at introduction of cow's milk products, the age at introduction other food products, infant sex, recruitment group, infant's use of antibiotics, maternal smoking during pregnancy, infant's exposure to environmental tobacco smoke, maternal age at delivery, maternal education, presence of paternal allergic disease, number of siblings and presence of older allergic siblings.

these results need to be interpreted with caution because only mothers without allergy or asthma who breast-fed for >9 months showed a statistically significantly lower risk for eczema in the first 2 years of life. In addition, the different results in the 3 maternal strata may be explained by differing reporting behaviors on symptoms of infant eczema between mothers with or without allergy and/or asthma.

Infants' eczema and sensitization were considered as separate outcomes instead of combining them as atopic eczema, because sensitized infants do not necessarily exhibit symptoms of eczema and vice versa.<sup>10</sup> Consequently, we use the term "eczema" instead of "atopic eczema." On the other hand, we use the term "atopic dermatitis" for infants fulfilling the UK-WP criteria according to Williams et al.<sup>6</sup> The associations between breast-feeding and eczema could not be confirmed by our results on atopic dermatitis according to the UK-WP criteria. We speculate that breast-feeding is associated only with a milder eczematous condition that has already disappeared at the time of the home visit. Another explanation for these discrepant findings is that the UK-WP criteria

included specific predilection sites of atopic dermatitis (flexural involvement),<sup>6</sup> whereas the questionnaire data were based on the presence of an itchy rash anywhere (except diaper rash, rash around the eyes, and scalp scaling), and thus may include nonatopic eczema.

Wright et al<sup>3</sup> found an increased risk for asthma and wheeze in breast-fed children compared with never-breast-fed children whose mothers had asthma themselves. Interestingly, the same authors also reported higher IgE levels in breast-fed versus never-breast-fed children of mothers with high IgE levels.<sup>1</sup> In the present study, we found no effect of breast-feeding on total IgE levels in infants of mothers with or without high total IgE levels. We also found no effect of breast-feeding on sensitization in the infants of mothers with and without sensitization, suggesting no effect modification by maternal sensitization. We conclude that maternal atopic status is not a major effect modifier of the effect of breast-feeding on infants' atopic manifestations. However, it should be noted that total and specific IgE levels are only weakly associated with atopic eczema and wheeze.<sup>10</sup> Allergic sensi-

tization may not be a prerequisite for childhood eczema.<sup>11</sup> An Australian study also showed no statistical interaction between breast-feeding and maternal asthma status for the risk of asthma in childhood.<sup>4</sup>

Our results indicate that longer breast-feeding duration protects against recurrent wheeze irrespective of maternal allergic status. Wright et al<sup>12</sup> followed infants during regular visits to a health maintenance organization and found that in the first 4 months of life, any breast-feeding was associated with a decreased incidence of wheezing illnesses. Another study showed that breast-feeding for  $\geq 6$  months was slightly protective against transient wheezing, whereas it was a moderate risk factor for late-onset wheezing.<sup>13</sup> Wheezing in young children may represent a heterogeneous group of conditions.<sup>14</sup> It is a relatively common symptom in infancy, and not all wheezing will necessarily become asthma in later life. We propose that our findings on recurrent wheeze actually reflect that breast-feeding protects against respiratory infections in early childhood. Indeed, infections have been found to be related to wheezing symptoms. For instance, Lemanske et al<sup>15</sup> reported that in the first year of life, a virus could be found during a wheezing episode in 78% of severe wheezers and in 63% of mild wheezers. Earlier, Chantry et al<sup>16</sup> found that full breast-feeding for  $\geq 6$  months provided more protection against respiratory tract infection than full breast-feeding for  $>4$  but  $<6$  months.

There are several reasons why effect modification by maternal allergic status is important. First, it has been stated that a lack of stratification by maternal asthma and allergic predisposition in the child may have obscured how the relationship between breast-feeding and atopic manifestations changes with the child's age and atopic status.<sup>17</sup> Second, the milk composition may differ in allergic and nonallergic mothers in such a way so as to affect atopic manifestations in the child.<sup>3</sup> Not only cytokines, but also long-chain polyunsaturated fatty acid levels, may differ between atopic and nonatopic mothers.<sup>18-20</sup>

Taken together, we demonstrated that only the relationship between breast-feeding and infant eczema in the first 2 years of life may be modified by maternal allergic status, because a protective effect of breast-feeding duration on eczema seemed to be present mainly for mothers without allergy or asthma, after adjustment for confounders including age at introduction of cow's milk or other food products. The protective effect of breast-feeding against recurrent wheeze was

observed irrespective of maternal allergic status, and we speculate that these results may reflect protection against respiratory illness.

## REFERENCES

1. Wright AL, Sherrill D, Holberg CJ, Halonen M, Martinez FD. Breast-feeding, maternal IgE, and total serum IgE in childhood. *J Allergy Clin Immunol* 1999;104:589-94.
2. Oberle D, Von Kries R, Von Mutius E. Asthma and breast-feeding. *Thorax* 2001;56:896.
3. Wright AL, Holberg CJ, Taussig LM, Martinez F. Maternal asthma status alters relation of infant feeding to asthma childhood. *Adv Exp Med Biol* 2000;478:131-7.
4. Oddy WH, Peat JK, de Klerk NH. Maternal asthma, infant feeding, and the risk of asthma in childhood. *J Allergy Clin Immunol* 2002;110:65-7.
5. Kummeling I, Thijs C, Penders J, Snijders BE, Stelma F, Reimerink J, et al. Etiology of atopy in infancy: the KOALA Birth Cohort Study. *Pediatr Allergy Immunol* 2005;16:679-84.
6. Williams HC, Burney PG, Hay RJ, Archer CB, Shipley MJ, Hunter JJ, et al. The UK Working Party's diagnostic criteria for atopic dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. *Br J Dermatol* 1994;131:383-96.
7. Stallman PJ, Aalberse RC. Estimation of basophil-bound IgE by quantitative immunofluorescence microscopy. *Int Arch Allergy Appl Immunol* 1977;54:9-18.
8. Aalberse RC, Koshte V, Clemens JG. Immunoglobulin E antibodies that cross-react with vegetable foods, pollen, and *Hymenoptera* venom. *J Allergy Clin Immunol* 1981;68:356-64.
9. Schuurman J, Perdok GJ, Lourens TE, Parren PW, Chapman MD, Aalberse RC. Production of a mouse/human chimeric IgE monoclonal antibody to the house dust mite allergen Der p 2 and its use for the absolute quantification of allergen-specific IgE. *J Allergy Clin Immunol* 1997;99:545-50.
10. Kusel MM, Holt PG, de Klerk N, Sly PD. Support for 2 variants of eczema. *J Allergy Clin Immunol* 2005;116:1067-72.
11. Williams H, Flohr C. How epidemiology has challenged 3 prevailing concepts about atopic dermatitis. *J Allergy Clin Immunol* 2006;118:209-13.
12. Wright AL, Holberg CJ, Martinez FD, Morgan WJ, Taussig LM. Breast-feeding and lower respiratory tract illness in the first year of life. *Group Health Medical Associates. BMJ* 1989;299:946-9.
13. Rusconi F, Galassi C, Corbo GM, Forastiere F, Biggeri A, Ciccone G, et al. Risk factors for early, persistent, and late-onset wheezing in young children. SIDRIA Collaborative Group. *Am J Respir Crit Care Med* 1999;160:1617-22.
14. Henderson J, North K, Griffiths M, Harvey I, Golding J. Pertussis vaccination and wheezing illnesses in young children: prospective cohort study. *The Longitudinal Study of Pregnancy and Childhood Team. BMJ* 1999;318:1173-6.
15. Lemanske RF, Jackson DJ, Gangnon RE, Evans MD, Li Z, Shult PA, et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *J Allergy Clin Immunol* 2005;116:571-7.
16. Chantry CJ, Howard CR, Auinger P. Full breast-feeding duration and associated decrease in respiratory tract infection in US children. *Pediatrics* 2006;117:425-32.
17. Wright AL, Holberg CJ, Taussig LM, Martinez FD. Factors influencing the relation of infant feeding to asthma and recurrent wheeze in childhood. *Thorax* 2001;56:192-7.
18. Bottcher MF, Jenmalm MC, Garofalo RP, Bjorksten B. Cytokines in breast milk from allergic and nonallergic mothers. *Pediatric Res* 2000;47:157-62.
19. Thijs C, Houwelingen A, Poorterman I, Mordant A, van den Brandt PA. Essential fatty acids in breast milk of atopic mothers: comparison with non-atopic mothers, and effect of borage oil supplementation. *Eur J Clin Nutr* 2000;54:234-8.
20. Duchon K, Yu G, Bjorksten B. Atopic sensitization during the first year of life in relation to long-chain polyunsaturated fatty acid levels in human milk. *Pediatr Res* 1998;44:478-84.

**Table I. Baseline characteristics in both recruitment groups**

	Conventional (n = 2229)		Alternative (n = 476)		Total (n = 2705)	
Breast-feeding, n (%)						
Never	407	(18%)	11	(2%)	418	(16%)
0 to 3 months	913	(41%)	64	(13%)	977	(36%)
4 to 6 months	357	(16%)	71	(15%)	428	(16%)
7 to 9 months	285	(13%)	115	(24%)	400	(15%)
>9 months	267	(12%)	215	(45%)	482	(18%)
Age at introduction of cow's milk products, n (%)						
0 to 3 months	1016	(46%)	51	(11%)	1067	(39%)
4 to 6 months	615	(29%)	137	(29%)	788	(29%)
7 to 9 months	459	(21%)	242	(51%)	701	(26%)
>9 months	46	(2%)	28	(6%)	74	(3%)
Unknown	57	(3%)	18	(4%)	75	(3%)
Use of hypoallergenic formulas, n (%)						
Yes	163	(7%)	22	(5%)	185	(7%)
Age at introduction of other foods products, n (%)						
3 months	178	(8%)	20	(4%)	198	(7%)
4 to 6 months	1846	(83%)	411	(86%)	2257	(83%)
≥7 months	48	(2%)	27	(6%)	75	(3%)
Unknown	157	(7%)	18	(4%)	175	(7%)
Sex of infants, no of boys (%)	1133	(51%)	240	(50%)	1373	(51%)
Maternal age in years, mean (SD)	31	(4)	34	(4)	32	(4)
Maternal smoking during pregnancy, n (%)	189	(9%)	3	(1%)	192	(7%)
Environmental tobacco smoking, n (%)	110	(5%)	2	(<1%)	112	(4%)
Maternal education, n (%)						
Low	256	(12%)	18	(4%)	274	(10%)
Middle	857	(39%)	83	(17%)	940	(35%)
High	993	(45%)	362	(76%)	1355	(50%)
Unknown	123	(6%)	13	(3%)	136	(5%)
Parental allergic disease, n (%)						
Both parents nonallergic	878	(40%)	186	(40%)	1064	(39%)
Only father allergic	460	(21%)	110	(23%)	570	(21%)
Only mother allergic	496	(22%)	105	(22%)	601	(22%)
Both parents allergic	288	(13%)	69	(15%)	357	(13%)
Unknown	107	(5%)	6	(1%)	113	(4%)
Number of siblings, n (%)						
0 siblings	1804	(81%)	369	(78%)	2173	(80%)
1 sibling	286	(13%)	81	(17%)	367	(14%)
2 or more siblings	42	(2%)	22	(5%)	64	(2%)
Unknown	97	(4%)	4	(1%)	101	(4%)
Presence of older allergic siblings, n (%)						
No siblings	1804	(81%)	369	(78%)	2173	(80%)
Older nonallergic sibling(s)	249	(13%)	71	(15%)	320	(12%)
Older allergic sibling(s)	85	(2%)	35	(7%)	120	(4%)
Unknown	91	(4%)	1	(<1%)	92	(3%)
Infant's use of antibiotics, n (%)						
Yes	430	(19%)	56	(12%)	486	(18%)
Unknown	187	(8%)	15	(3%)	202	(8%)

SD, standard deviation.

\*Numbers may not add up to the total because of missing values.

**Table III. Associations between breast-feeding duration and infant increased total IgE and sensitization at age 2 years, according to presence of increased total IgE/sensitization in the mother**

Maternal status	Infant increased total IgE				Infant sensitization				
	N	n (%)	OR (95% CI)	OR <sub>adj</sub> (95% CI)	N	n (%)	OR (95% CI)	OR <sub>adj</sub> (95% CI)	
Maternal total IgE ≤100 IU/mL					No maternal sensitization				
BF									
Never	68	24 (35%)	1.00	1.00	Never	52	11 (21%)	1.00	1.00
0 to 3 months	150	70 (47%)	1.60 (0.89 to 2.90)	1.81 (0.95 to 3.46)	0 to 3 months	97	23 (24%)	1.35 (0.56 to 3.25)	1.35 (0.53 to 3.43)
4 to 6 months	124	75 (61%)	2.81 (1.52 to 5.19)	2.34 (0.93 to 5.93)	4 to 6 months	81	26 (32%)	1.52 (0.60 to 3.82)	2.03 (0.60 to 6.88)
7 to 9 months	117	63 (54%)	2.14 (1.16 to 3.96)	1.71 (0.65 to 4.45)	7 to 9 months	74	17 (23%)	1.80 (0.74 to 4.39)	2.72 (0.80 to 9.25)
>9 months	142	85 (60%)	2.73 (1.50 to 4.98)	1.80 (0.67 to 4.82)	>9 months	91	22 (24%)	0.98 (0.39 to 2.48)	1.59 (0.45 to 5.66)
<i>P</i> <sub>trend</sub>					<i>P</i> <sub>trend</sub>				
Maternal total IgE >100 IU/mL					Maternal sensitization				
BF									
Never	21	10 (48%)	1.00	1.00	Never	35	9 (26%)	1.00	1.00
0 to 3 months	37	20 (54%)	1.29 (0.44 to 3.78)	1.34 (0.43 to 4.19)	0 to 3 months	88	28 (32%)	1.16 (0.51 to 2.61)	1.35 (0.57 to 3.18)
4 to 6 months	18	11 (61%)	1.75 (0.49 to 6.30)	1.49 (0.34 to 6.64)	4 to 6 months	61	21 (34%)	1.76 (0.78 to 3.97)	2.86 (0.91 to 8.92)
7 to 9 months	29	15 (52%)	1.19 (0.39 to 3.68)	0.88 (0.22 to 3.45)	7 to 9 months	73	28 (38%)	1.11 (0.47 to 2.62)	1.91 (0.58 to 6.25)
>9 months	23	19 (83%)	5.21 (1.32 to 20.67)	4.66 (0.94 to 23.18)	>9 months	71	18 (25%)	1.19 (0.52 to 2.70)	2.39 (0.72 to 7.96)
<i>P</i> <sub>trend</sub>					<i>P</i> <sub>trend</sub>				

May not add up to total numbers because of missing values.

BF, breastfeeding.

\*Based on logistic regression analysis adjusted for age at introduction of cow's milk products, age at introduction other food products, sex of infant, recruitment group, infant's use of antibiotics, maternal smoking during pregnancy, infant's exposure to environmental tobacco smoke, maternal age at delivery, maternal education, presence of paternal allergic disease, number of siblings, and presence of older allergic siblings.