

Breast-feeding reduces the risk for childhood eczema

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Background: The evidence for a preventive effect of breast-feeding on the development of eczema in childhood remains controversial.

Objective: To investigate the effect of breast-feeding in various phenotypes of eczema to 4 years.

Methods: A birth cohort of 4089 children made up the study base.

Data on breast-feeding, allergic symptoms, and potential confounders were obtained from questionnaires when the children were 2 months and 1, 2, and 4 years old. At 4 years, blood specific IgE was analyzed. Children with symptoms of eczema and asthma during the period of breast-feeding were excluded in most analyses on risk assessment of eczema and asthma, respectively, to avoid disease-related modification of exposure. **Results:** Exclusive breast-feeding for ≥ 4 months reduced the risk for eczema at the age of 4 years (odds ratio [OR], 0.78; 95% CI, 0.63-0.96) irrespective of combination with asthma, sensitization to common allergens, or parental allergic disease. This decreased risk was most evident for children with onset of eczema during the first 2 years persisting to 4 years (OR, 0.59; 95% CI, 0.45-0.77). Among children with early-onset eczema, irrespective of persistency, followed by late onset of asthma or early-onset asthma irrespective of persistency, followed by late-onset eczema to 4 years, a protective effect of breast-feeding was also seen (OR, 0.48; 95% CI, 0.30-0.76).

Conclusion: Breast-feeding 4 months or more reduces the risk for eczema and onset of the allergy march to age 4. (J Allergy Clin Immunol 2005;116:657-61.)

Key words: Allergy, asthma, allergy march, BAMSE, breast-feeding, children, eczema, sensitization

Compared with childhood asthma, less scientific evidence is available on the effect of breast-feeding on eczema, and it remains unclear whether prolonged dura-

Abbreviation used

BAMSE: Children, Allergy, Milieu, Stockholm, Epidemiological survey

OR: Odds ratio

tion of breast-feeding (≥ 4 months) reduces the risk for childhood eczema.¹ Diverging results have been reported. Some studies suggest that breast-feeding decreases the risk of eczema, whereas others point to an increased risk of eczema associated with breast-feeding.²⁻⁷ However, in a meta-analysis of prospective studies, an inverse association between exclusive breast-feeding during the first 3 months and eczema was found among children with a family history of atopy.⁸

Many recent studies assessing the effect of human breast milk on the prevention of eczema have had significant limitations. Some have been cross-sectional with retrospective collection of exposure.⁹ Others have had limited power, duration of follow-up, or description of phenotypes, and in no other previous studies has the possibility of disease-related modification of breast-feeding behavior been addressed.²⁻⁶ All this might explain to some extent the diverging results.

Our understanding of the mechanisms involved in early development of allergic diseases is incomplete, but human milk given to the baby promotes an intestinal environment rich in bacteria thought to induce a shift toward a T_H1-predominant cytokine response, which possibly promotes development of oral tolerance.¹⁰⁻¹³

In a recent article, we demonstrated a risk reduction by breast-feeding on asthma in a prospective birth cohort followed for 4 years (Children, Allergy, Milieu, Stockholm, Epidemiological survey [BAMSE]).¹⁴ The aim of the current study was to examine the association between breast-feeding and eczema at 4 years of age in relation to asthma, sensitization, and parental allergic disease.

METHODS

Study design

A prospective birth cohort (BAMSE) of 4089 newborn infants was established in Stockholm from 1994 to 1996, made up of 75% of all eligible children in a predefined area of Stockholm. The study has been described in detail elsewhere.¹⁵ When the infants were newborn (median age, 2 months), data on parental allergic disease and various exposures were obtained by questionnaire. At 1, 2, and 4 years of age, the parents answered questionnaires with main focus on symptoms

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related to eczema and asthma, as well as feeding and other key exposures. The response rate on the 4-year questionnaire was 90%, and from 3608 children (88%), complete data sets on key variables from all questionnaire sampling occasions were available. All children with questionnaire response at age 4 years ($n = 3670$) were invited to a clinical investigation including blood sampling, and of these, 2965 children (73%) participated. Permission for the study was obtained from the Ethics Committee of Karolinska Institutet, Stockholm.

Classification of exposure, heredity, and disease

Breast-feeding. Exclusive breast-feeding denotes the period when the infants were given only breast milk, and no formula, cow's milk, or solid foods had been introduced. Partial breast-feeding means that the child received infant formula or solid food in addition to breast milk.

Heredity. Parental allergic disease was defined as a history of physician-diagnosed eczema or asthma/hay fever in combination with allergy to furred pets, pollen, or both in at least 1 (any) or both parents (double).

Eczema. Eczema was defined as dry skin in combination with itchy rash for at least 2 weeks with typical localization during the last 12 months and/or a doctor's diagnosis of eczema.¹⁶

Asthma. At 4 years of age, asthma was defined as at least 4 episodes of wheezing during the last 12 months or at least 1 episode of wheezing during the same period if the child was on inhaled steroids.

Onset of eczema, asthma, and persistency. To assess the development of eczema or asthma, age at onset and duration was considered. Early-onset transient eczema or asthma denotes that the child was fulfilling the criteria for eczema or asthma during the first 2 years of life but not later. For asthma at this age, at least 3 episodes of wheezing were required in addition to respiratory symptoms treated with inhaled steroids or signs of hyperreactivity without ongoing upper respiratory infection. Early-onset persistent eczema implies that the child fulfilled the eczema criteria not only at 4 years but also during the first 2 years of life.

In this article, we applied the World Allergy Organization's revised nomenclature.¹⁷

Allergy march. Allergy march indicates children with early onset of eczema, irrespective of persistency, concomitant with asthma at age 4 years or early-onset asthma, irrespective of persistency, concomitant with eczema at age 4 years.

Sensitization. Blood samples were collected from 2614 children (88% of children who came for examination). Analysis of specific serum IgE antibodies against individual inhalants (cat, dog, horse, birch, timothy, mugwort, *Dermatophagoides pteronyssinus*, and *Cladosporium*) and food (milk, egg, fish, soy, peanut, and wheat) allergens were performed with ImmunoCAP (Pharmacia CAP System, Uppsala, Sweden). An IgE antibody level ≥ 0.35 kU/L was considered positive.

Statistical methods

The relationship between breast-feeding and health outcomes was analyzed with logistic regression, and results are presented as adjusted odds ratios (ORs) with 95% CIs. Several models were tested to identify potential confounders. At analyses of the effect of breast-feeding on eczema, adjustments were made for parental allergic diseases only, because this variable affected the OR by 10% or more. Analyses including the outcome variable asthma also included adjustment for maternal age and smoking during pregnancy or at enrollment. Breast-feeding was analyzed as a dichotomized variable with the 25th percentile as the cutoff point (4 months).¹⁴ To avoid disease-related modification of exposure, the duration of

breast-feeding was analyzed in 3 different modes. Initially, the association between eczema and duration of breast-feeding as reported in the questionnaire was analyzed in the whole cohort. Second, the association was assessed after exclusion of children with eczema during the period of breast-feeding ($n = 265$). Third, when the outcome of eczema and asthma was combined, children with onset of wheeze during this period were excluded ($n = 185$).

The Wald test was used to test for interaction by heredity and sensitization on the effect of breast-feeding on eczema. All statistical analyses were performed with STATA Statistical Software release 8.0 (College Station, Tex).

RESULTS

The median duration of exclusive breast-feeding was 5 months (25th and 75th percentile, 4 and 6 months, respectively). At the age of 4 years, 20.5% of the children fulfilled the criteria of eczema ($n = 741$), and 22.5% ($n = 807$) had eczema or asthma. After exclusion of children with early symptoms of eczema and wheezing, to avoid disease-related modification of exposure, there were 19.4% ($n = 667$) with eczema or asthma at 4 years of age, 15.7% ($n = 494$) with eczema but not asthma, and 1.6% ($n = 50$) with both eczema and asthma.

Of the 2614 children with blood samples, 24% had detectable IgE antibodies (ie, ≥ 0.35 kU/L) to common food and airborne allergens.

The distribution of selected exposure characteristics in relation to breast-feeding and eczema at 4 years of age is shown in Table I. Length of breast-feeding was associated with maternal age and maternal smoking during pregnancy or at enrollment (median age, 2 months), whereas only parental allergic disease was associated with eczema.

Exclusive breast-feeding for 4 months or more reduced the risk for eczema at the age of 4 years (OR, 0.88; 95% CI, 0.72-1.08), although this result was not statistically significant. After excluding children with onset of eczema during the breast-feeding period, the risk reduction was slightly strengthened (OR, 0.78; 95% CI, 0.63-0.96; Table II). Partial breast-feeding after exclusive breast-feeding ended did not add any additional effect to the risk reduction (data not shown). The association between breast-feeding and eczema tended to be similar in children with parental heredity of allergy (OR, 0.74; 95% CI, 0.55-0.99) compared with children without (OR, 0.83; 95% CI, 0.62-1.13). Although the point estimate was not statistically significant in the nonheredity group, no evidence of statistical interaction was seen (P interaction = .57). This also held true for children with and without sensitization.

The protective effect of breast-feeding seemed to differ in children with early-onset transient, late-onset, and early persistent eczema (Table III). Exclusive breast-feeding for 4 months or more did not reduce the risk for late-onset eczema. For early transient, and in particular for early-onset persistent eczema and exclusive breast-feeding, an inverse association was seen (OR, 0.76; 95% CI, 0.58-0.99; and OR, 0.59; 95% CI, 0.45-0.77, respectively). When stratifying the children into parental allergic

TABLE I. Distribution of selected exposure characteristics in relation to eczema at 4 years of life

	N	Exclusive breast-feeding ≥ 4 mo			Eczema at 4 y		
		n	%	95% CI	n	%	95% CI
Mother's age (y)							
≥ 25	3347	2696	80	(79.1-81.9)	679	20	(18.9-21.7)
< 25	267	188	70	(64.5-75.8)	62	23	(18.4-28.9)
Sex							
Female	1787	1413	79	(77.1-80.9)	372	21	(18.9-22.7)
Male	1828	1472	80	(78.6-82.3)	369	20	(18.3-22.1)
Heredity*							
None	2025	1605	79	(77.5-81.1)	332	16	(14.8-18.0)
Any	1268	1023	81	(78.5-82.9)	309	24	(22.0-26.8)
Double	285	229	80	(75.2-84.8)	92	32	(27.0-38.1)
Maternal smoking during pregnancy or at enrolment							
No	3136	2559	82	(80.2-82.9)	632	20	(18.7-21.6)
Yes	478	325	68	(63.6-72.1)	109	23	(19.2-26.9)

*Physician-diagnosed eczema or asthma/hay fever in combination with allergy to furred pet or pollen in 1 (any) or both (double) parents.

disease or not, the risk reduction was generally unchanged. However, one exception was children with heredity and early-onset transient eczema, in whom no risk reduction was seen. The preventive effect of breast-feeding appeared similar among children categorized in the 3 different phenotypes of eczema (early transient, early-onset persistent, and late-onset eczema) irrespective of sensitization to inhalant or food allergens.

Fifty of the children with eczema at age 4 years also fulfilled the criteria for asthma (Table IV). Among those with severe allergic disease, breast-feeding for 4 months or more was associated with a reduced risk (OR, 0.52; 95% CI, 0.28-0.95). The risk reduction for children with eczema alone was OR, 0.78 (95% CI, 0.62-0.99) after breast-feeding for 4 months. Children with onset of both eczema and/or wheeze during lactation were excluded in this analysis.

In the BAMSE cohort in total, 4.5% of the children ($n = 166$) had started with early-onset eczema or asthma irrespective of persistency, followed by asthma or eczema at age 4, respectively. After exclusion of children with early symptoms of eczema and wheeze during the breast-feeding period, the proportion of corresponding number of children was 2.9% ($n = 92$). In this group of children, breast-feeding for 4 months or more reduced the risk for this complex manifestation by an OR of 0.48 (95% CI, 0.30-0.76; Table IV).

DISCUSSION

In a recent article based on the BAMSE birth cohort, we showed that exclusive breast-feeding for 3 months or more followed by a period of partial breast-feeding for another 3 months reduced the risk for asthma at 4 years with more than 50%.¹⁴ In the current study, with children from the same cohort and followed for the same period, we found that irrespective of sensitization to common food or inhalant allergens or parental allergic diseases, exclusive

TABLE II. Association between exclusive breast-feeding and eczema at 4 years* in relation to parental allergic heredity and sensitization

	Duration of breast-feeding	Eczema at 4 y			
		N	n	OR†	(95% CI)
Eczema	< 4 mo	702	142	1.0‡	
	≥ 4 mo	2646	446	0.78	(0.63-0.96)
Eczema and heredity (P interaction = .57)					
No heredity	< 4 mo	403	64	1.0	
	≥ 4 mo	1504	205	0.83	(0.62-1.13)
Heredity	< 4 mo	288	77	1.0	
	≥ 4 mo	1131	240	0.74	(0.55-0.99)
Eczema and sensitization (P interaction = .94)					
No sensitization	< 4 mo	355	66	1.0	
	≥ 4 mo	1481	223	0.77	(0.56-1.05)
Sensitization	< 4 mo	123	37	1.0	
	≥ 4 mo	386	100	0.79	(0.39-1.21)

*Children with first episode of itchy rash during exclusive breast-feeding have been excluded.

†Adjusted for parental heredity.

‡Reference group.

breast-feeding for 4 months or more reduced the risk for eczema at 4 years with about 20%. In particular, this was evident for children with early persistent eczema.

Children with early-onset of sensitization or signs of allergic disease may persist in their disease, but in other forms. In the literature, this is referred to as the allergy march.¹⁸ We observed a preventive effect by exclusive breast-feeding on the allergy march phenotype: early onset of eczema irrespective of persistency followed by asthma irrespective of persistency or vice versa. In most investigations, even longitudinal investigations, outcomes are studied separately, but children and also adults seldom have eczema, asthma, or rhinoconjunctivitis alone. In particular, among infants and children before school age, one manifestation may switch to another, often with a period of overlap.^{18,19}

TABLE III. Exclusive breast-feeding in relation to onset of eczema during the first 4 years of life* among children with or without heredity of allergic disease and sensitization

	Duration of breast-feeding	N	Early-onset transient			Late-onset eczema			Early-onset persistent		
			n	OR†	(95% CI)	n	OR†	(95% CI)	n	OR†	(95% CI)
Eczema	<4 mo	699	84	1.0‡		48	1.0‡		93	1.0‡	
	≥4 mo	2644	271	0.76	(0.58-0.99)	216	1.1	(0.77-1.49)	230	0.59	(0.45-0.77)
Eczema and heredity											
No heredity	<4 mo	402	49	1.0		23	1.0		40	1.0	
	≥4 mo	1504	127	0.64	(0.45-0.91)	101	1.1	(0.67-1.74)	104	0.64	(0.434-0.94)
Heredity	<4 mo	286	35	1.0		25	1.0		52	1.0	
	≥4 mo	1129	141	0.94	(0.62-1.40)	115	1.1	(0.67-1.69)	125	0.56	(0.38-0.80)
Interaction				<i>P</i> interaction = .17			<i>P</i> interaction = .96			<i>P</i> interaction = .60	
Eczema and sensitization											
No sensitization	<4 mo	347	41	1.0		27	1.0		38	1.0	
	≥4 mo	1474	134	0.68	(0.47-0.99)	115	0.91	(0.58-1.41)	108	0.62	(0.41-0.93)
Sensitization	<4 mo	122	20	1.0		6	1.0		31	1.0	
	≥4 mo	384	56	0.78	(0.43-1.39)	40	1.86	(0.75-4.59)	60	0.53	(0.31-0.89)
Interaction				<i>P</i> interaction = .70			<i>P</i> interaction = .16			<i>P</i> interaction = .63	

*Children with first episode of itchy rash during exclusive breast-feeding have been excluded.

†Adjusted for heredity.

‡Reference category.

TABLE IV. Association between exclusive breast-feeding and different phenotypes of eczema up to 4 years of age*

Duration of breast-feeding	Eczema at 4 y			
	N	n	OR†	(95% CI)
Eczema with no asthma at age 4 y				
<4 mo	669	119	1.0‡	
≥4 mo	2456	373	0.78	(0.62-0.99)
Eczema and asthma at age 4 y				
<4 mo	669	16	1.0	
≥4 mo	2456	34	0.52	(0.28-0.95)
Allergy march§				
<4 mo	434	30	1.0	
≥4 mo	1751	62	0.48	(0.30-0.76)

*Children with first episode of itchy rash and/or wheeze during exclusive breast-feeding have been excluded.

†Adjusted for parental allergy, maternal age, and maternal smoking during pregnancy or at enrollment.

‡Reference category.

§Early-onset eczema, irrespective of persistency, concomitant with asthma at age 4 years, or early-onset asthma, irrespective persistency, concomitant with eczema at age 4 years.

One strength of our study is the comparatively large group with long duration of breast-feeding. The appreciable number of children with eczema makes allocation possible into different phenotypes depending on onset and duration of disease, which has not been done before. The definition of eczema used in the study has been shown to have high sensitivity (92%) and specificity (100%).¹⁶ Furthermore, we controlled for disease-related modification of exposure by excluding children with onset of eczema or wheeze during breast-feeding. However, excluding children with early symptoms of eczema may be a limitation with regard to generalization of the findings. The excluded children with very early symptoms might

differ in various aspects, etiology, severity, and further development of disease.

The observed prevalence of eczema at 4 years was 20.5%. In addition, another 13% had had eczema between 1 and 2 years, but not at 4 years, which emphasizes the need for allocation into different phenotypes when risk factors of eczema, asthma, and sensitization are studied. The prevalence of eczema at 4 years of age in our study is somewhat higher compared with the Multicentre Allergy Study with children at the same age, and compared with the recent study from the Danish National Birth Cohort, which followed children to 18 months only.^{6,7}

The association between breast-feeding and eczema is not unanimous in different studies. In the GINI birth cohort study, exclusive breast-feeding did not have any effect on the risk for eczema. However, in the Multicentre Allergy Study with children followed to 7 years, breast-feeding seemed to increase the risk of eczema to 7 years of age. In neither of these 2 studies was disease-related modification of exposure controlled for. In a Danish study, exclusive breast-feeding for at least 4 months was associated with an increased risk of eczema among children without parental allergy, but a decreased risk if parental heredity was present. The difference in results compared with our study may be explained by several factors: first, there was a difference in duration of follow-up. The Danish children were followed for 18 months and with retrospective collection of outcome data from this time point. The children in our cohort were followed for 4 years and with collection of outcome data at 1, 2, and 4 years of age. Second, children with parental allergy tend to have onset of allergic disease earlier than children without parental allergy.²⁰ Thus, because the children in the Danish study had been followed for 18 months only, fewer children without parental allergic disease would have had their

onset of eczema. Third, parental allergic disease was defined differently in the 2 studies. In our study, it was required that, in addition to physician-diagnosed asthma, allergic rhinitis, and eczema, 1 parent should report allergic symptoms after contact with pets or during pollen season. In the Danish study, reported parental specific allergy was not required.

With a birth cohort design and with data on exposures obtained before the children have symptoms of allergic disease, the results are less subject to bias compared with studies with a cross-sectional design and retrospective collection of exposure data. However, even with a birth cohort design, and in particular in countries where breast-feeding usually is extended over a period of 3 to 4 months, the likelihood increases that the baby might have onset of allergic disease during breast-feeding. This is even more likely if parental allergy is present. In such cases, some mothers would be expected to continue to breast-feed their babies for an even longer period.^{7,21,22} In this situation, breast-feeding might easily overlap the start of eczema or asthma. If not controlled for in the analysis, the risks will increase spuriously. In our previous study of the effect of breast-feeding on asthma, as well as in this study, we controlled for this bias by excluding children in whom overlap of breast-feeding and symptoms was present.¹⁴ An alternative approach is to choose a model where duration of breast-feeding is set to time for onset of itchy rashes, which was used in the Danish study. When a similar model was used in the current study, the OR was unchanged.

In conclusion, the results of our study indicate that exclusive breast-feeding for 4 months or more reduces the risk for eczema during the first 4 years of life, irrespective of parental allergy. Breast-feeding also appears to reduce the risk of the allergy march in terms of early-onset eczema or asthma, concomitant with asthma or eczema, respectively, during the first 4 years. Therefore, breast-feeding should be recommended as one possible way to reduce the risk of onset of eczema and asthma to the age of 4 years.

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REFERENCES

1. Van Odijk J, Kull I, Borres MP, Brantzaeg P, Edberg U, Hansson LA, et al. Breast feeding and allergic disease: a multidisciplinary review of the literature (1966-2001) on the mode of early feeding in infancy and its impact on later atopic manifestations. *Allergy* 2003;58:833-43.
2. Kramer MS, Chalmers B, Hodnet ED, Sevkovskaya Z, Dzikovitch I, Shapiro S, et al. Promotion of breastfeeding intervention trial (PROBIT). *JAMA* 2001;285:413-20.
3. Kerkhof M, Koopman LP, van Strien RT, Wijga A, Smit J, Aalberse RC, et al, and the PIAMA study group. Risk factors for atopic dermatitis in infants at high risk of allergy: the PIAMA study. *Clin Exp Allergy* 2003;33:1336-41.
4. Kull I, Wickman M, Lilja G, Nordvall SL, Pershagen G. Breastfeeding and allergic disease in infants: a prospective birth cohort study. *Arch Dis Child* 2002;87:478-81.
5. Lauberau B, Brockow I, Zirngibl A, Koletzko S, Gruebl A, von Berg A. Effect of breast-feeding on the development of atopic dermatitis. *J Pediatr* 2004;144:602-7.
6. Stabell Benn C, Wohlfart J, Aaby P, Benfeldt E, Fleisher Michaelsen K, Björkstén B, et al. Breastfeeding and risk for atopic dermatitis by parental history of allergy during the first 18 months. *Am J Epidemiol* 2004;160:217-23.
7. Bergmann RL, Diepgen TL, Kuss O, Bergmann KE, Kujat J, Dudenhausen JW, et al, and the MAS study-group. Breastfeeding duration is a risk factor for atopic eczema. *Clin Exp Allergy* 2002;32:205-9.
8. Gdalevich M, Mimouni D, David M, Mimouni M. Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. *J Am Acad Dermatol* 2001;45:520-7.
9. Miyake Y, Yura A, Iki M. Breastfeeding and the prevalence of symptoms of allergic disorders in Japanese adolescents. *Clin Exp Allergy* 2003;33:312-6.
10. Prescott SL. Early origins of allergic disease: a review of processes and influences during early immune development. *Curr Opin Allergy Clin Immunol* 2003;3:125-32.
11. Björkstén B, Sepp E, Julge K, Voor T, Mikelsaar M. Allergy development and the intestinal microflora during the first year of life. *J Allergy Clin Immunol* 2001;108:516-20.
12. Manickasingham SP, Edwards AD, Schultz O, Reis e Sousa C. The ability of murine dendritic cells subsets to direct T helper cell differentiation is dependent on microbial signals. *Eur J Immunol* 2003;33:101-7.
13. Karlsson H, Hessel C, Rudin A. Innate immune response of human neonatal cells to bacteria from the normal gastrointestinal flora. *Infect Immun* 2002;70:6688-96.
14. Kull I, Almqvist C, Lilja G, Pershagen G, Wickman M. Breastfeeding reduces the risk of asthma during the first four years of life. *J Allergy Clin Immunol* 2004;114:755-60.
15. Wickman M, Melen E, Berglund N, Lennart Nordvall S, Almqvist C, Kull I, et al. Strategies for preventing wheezing and asthma in small children. *Allergy* 2003;58:742-7.
16. Bohme M, Lannerö E, Wickman M, Nordvall SL, Wahlgren CF. Atopic dermatitis and concomitant diseases patterns in children up to two years of age. *Acta Derm Venereol* 2002;82:98-103.
17. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;113:832-6.
18. Illi S, von Mutius E, Lau S, Nickel R, Gruber C, Niggemann B, et al, Multicenter Allergy Study Group. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004;113:925-31.
19. Wickman M, Lilja G, Söderström L, van Hage Hamsten M, Ahlstedt S. Quantitative analysis of IgE antibodies to food and inhalant allergens in 4-year old children reflects their likelihood of allergic disease. *Allergy* 2005;60:650-7.
20. Kurukulaaratchy RJ, Matthews S, Arshad SH. Does environment mediate earlier onset of the persistent childhood asthma phenotype? *Pediatrics* 2004;113:345-50.
21. Oddy WH, Holt PG, Sly PD, Read AW, Landau LI, Stanley FJ, et al. Association between breast-feeding and asthma in 6 year old children: findings from a prospective study. *BMJ* 1999;319:815-9.
22. Böttcher MF, Jennmalm MC. Breastfeeding and the development of atopic disease during childhood. *Clin Exp Allergy* 2002;32:159-61.