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Prolonged exclusive breastfeeding is associated with increased atopic dermatitis: a prospective follow-up study of unselected healthy newborns from birth to age 20 years

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Clinical and Experimental Allergy

Summary

Background Exclusive breastfeeding for the first 6 months is recommended by the World Health Organization and considered allergy preventive. However, it is not known whether prolonging exclusive breastfeeding for over 6 months provides further benefit in allergy prevention.

Objective The aim of this prospective 20-year follow-up study was to find out whether the allergy protective effect can be enhanced by prolonging strictly exclusive breastfeeding for ≥ 9 months of age.

Methods A total of 200 unselected healthy newborns were enrolled in the study. Their mothers were encouraged to maintain exclusive breastfeeding for as long as possible. The number of infants on strictly exclusive breastfeeding was 167 at 2, 116 at 6, 36 at 9 and 7 at 12 months of age. Of the 200 infants, 42% had a family history of allergy. The children were re-assessed at ages 5 ($n = 163$), 11 ($n = 150$) and 20 years ($n = 164$) with clinical examination, skin prick testing, and parental and personal structured interviews.

Results Exclusive breastfeeding prolonged for ≥ 9 months was associated with atopic dermatitis ($P = 0.002$) and symptoms of food hypersensitivity ($P = 0.02$) at age 5 years, and with symptoms of food hypersensitivity at age 11 years ($P = 0.01$), in children with a family history of allergy.

Conclusion Prolonging strictly exclusive breastfeeding for ≥ 9 months was not helpful in allergy prevention, instead, it was associated with increased atopic dermatitis and food hypersensitivity symptoms in childhood.

Keywords allergy, atopic dermatitis, exclusive breast feeding, food hypersensitivity, infant feeding

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Introduction

Breastfeeding, the optimal source of infant nutrition, has been shown to protect the infant against infectious diseases [1–3], obesity [4] and several chronic illnesses [5, 6] including allergic symptoms, especially childhood asthma [7, 8]. However, studies on the effects of breastfeeding on the development of allergy have yielded controversial results, some studies indicating an allergy-preventive effect [9–11], while other studies have been unable to confirm such an effect [12–14], or the protective effect has been limited to early childhood, long-term follow-up indicating increased atopic symptoms among

the breastfed subjects [15–17]. In a large cluster-randomized trial, an intervention promoting breastfeeding decreased the risk of atopic eczema during the first year of life [18]. Exclusive breastfeeding for the first few months of life is widely promoted [19, 20], and the World Health Organization recommends it to be maintained up to the age of 6 months [21]. It is not known whether the allergy-protective effect of breastfeeding can be enhanced by continuing strictly exclusive breastfeeding even longer, for over the first 6 or even 9 months. The design of the present prospective 20-year follow-up study on unselected healthy newborns allowed us to examine the effect

of the duration of exclusive breastfeeding on the subsequent development of allergy, and whether prolonging exclusive breastfeeding for up to 9 months is useful in allergy prevention.

Materials and methods

Study population

This prospective follow-up study was begun in 1981 in order to study the nutritional effects of exclusive breastfeeding [22, 23]. The 200 participating families and their infants were recruited during their stay at the maternity hospital. All the participants were enrolled between June and September in 1981. The inclusion criteria were a healthy full-term infant with appropriate weight for gestational age, a 1-min Apgar score of at least 8, and a healthy, non-smoking mother with uncomplicated pregnancy and delivery. Altogether 90% of the families invited agreed to participate the study. As only two families dropped out during the first year, 198 infants, 114 girls and 84 boys, completed the first-year follow-up [22, 23].

Exclusive breastfeeding was defined as the infant being fed exclusively maternal human milk without any supplementary formula or solid foods, only water and routine vitamins were allowed. All mothers begun and were encouraged to maintain strictly exclusive breastfeeding for as long as possible. The infants did not receive any cow's milk-based formula at the maternity hospital. If supplementary milk was needed, the infants were given donated human milk at the maternity hospital and at home. Thus, all the infants received some length of exclusive breastfeeding. Exclusive breastfeeding was continued until it became insufficient for the child. This was verified by offering the child a dose of donated human milk after breastfeeding. When supplemental human milk had been needed twice, exclusive breastfeeding was considered terminated, and the child was gradually weaned to a cow's milk-based formula (Tutteli®; Valio, Helsinki, Finland). For the infants no longer on exclusive breastfeeding, solid foods were introduced from age 3 months, while for those still on exclusive breastfeeding, the introduction of solid foods was postponed until the exclusive breastfeeding was terminated. The mothers and their infants were seen at the outpatient clinic of the Hospital for Children and Adolescents routinely at ages 2, 4, 6, 9 and 12 months and those still on exclusive breastfeeding were also seen at ages 10 and 11 months [23]. In addition, all medical care and counseling needed during the infant's first year were provided by the paediatrician responsible for the first-year follow-up, and the families were free to contact the paediatrician and to visit the outpatient clinic between the scheduled visits, when necessary. Owing to the careful follow-up and frequent contacts between the visits, the exact duration of exclusive breastfeeding was reliably recorded.

Family history of allergy

Family history of allergy was considered positive if the child had a first-degree relative, i.e. mother, father or sibling, with allergic symptoms during the infant's first year of life. Of the 198 children, 84 (42%) had a family history of allergy. Fifty-two (26%) children had a maternal, 33 (17%) a paternal and seven (4%) a biparental family history of allergy.

Duration of exclusive breastfeeding

The subjects were divided into four groups according to the duration of exclusive breastfeeding, i.e. exclusive breastfeeding for < 2, 2–< 6, 6–< 9 and ≥ 9 months. Children with a family history of allergy and those without a family history of allergy were distributed similarly among the four study groups (Table 1).

Follow-up examinations

Of the 198 children, 163 (82%) were re-assessed at age 5 years, 150 (76%) at age 11 years and 164 (83%) at age 20 years with clinical examination, skin prick testing (SPT), and parental (ages 5 and 11 years) and personal (age 20 years) structured interviews by a single physician (M. J. T. K. at the 5- and 11-year re-examinations, M. P. at the 20-year re-examination) unaware of the early feeding history. Before the 5- and 11-year visits, the parents filled in a questionnaire concerning the possible allergic symptoms in the child, and the information in the questionnaires was confirmed by personal interviews.

Skin prick testing (SPT)

SPTs were performed on 160 at age 5 years, on 149 at age 11 years, and on 164 subjects at age 20 years with standardized allergen extracts (ALK, Copenhagen, Denmark) of birch, alder, timothy, Kentucky blue, mugwort, cat, dog, *Dermatophagoides pteronyssinus*, cow's milk, egg and codfish; histamine hydrochloride solution (10 mg/mL) and a diluent control were included.

Table 1. Infants with a family history of allergy (FHA) and those without a family history of allergy were distributed similarly among the four study groups

	Total	Negative FHA	Positive FHA
Duration of exclusive breastfeeding			
< 2 months	35 (18%)	19 (17%)	16 (19%)
2–< 6 months	48 (24%)	27 (24%)	21 (25%)
6–< 9 months	80 (40%)	49 (43%)	31 (37%)
≥ 9 months	35 (18%)	19 (17%)	16 (19%)
N	198	114	84

A positive SPT was defined as a test reaction with a mean diameter equal to or greater than half of the diameter of the histamine weal [24].

Definitions of allergic symptoms

Atopic dermatitis was defined as a chronic or relapsing itchy dermatitis with a characteristic morphology and distribution [25]. Atopic dermatitis was recorded if it was present at a follow-up examination, or atopic dermatitis had been diagnosed by a physician and there was a history of relapsing eczema with typical localization during the preceding year. Allergic rhinitis (AR) was defined as recurrent non-infectious rhinitis at pollen seasons or on aeroallergen exposure. Allergic conjunctivitis was defined as itching and watery discharge of the eyes at pollen seasons or on aeroallergen exposure. Recurrent wheezing was recorded if the subject had a diagnosis of bronchial asthma, or two or more separate episodes of respiratory distress and wheezing. Food hypersensitivity symptoms were defined as a history of repeated itching or swelling of the lips, the oral mucosa or the throat, urticarial eruption, or severe vomiting after ingestion of a specific food. As performing double-blind placebo-controlled food challenges [26] was not feasible, we chose to rely on the history of food hypersensitivity, which was recorded in a personal interview by a physician and based on reports of typical symptoms appearing after ingestion of a specific food. At age 20 years, food hypersensitivity symptoms were no longer taken into account.

Verified atopy was recorded if the subject had one or several allergic symptoms and a positive SPT to at least one of the common allergens tested.

Statistical methods

Statistical analyses were performed with StatView 5.0 (SAS Institute, Cary, NC). χ^2 and Fisher's exact tests and logistic regression were used to measure statistical significance, and $P < 0.05$ was taken as indicating statistical significance. Multivariate logistic regression was used for examining the effect of confounding factors. The potential confounding factors taken into account were maternal age (<26 or ≥ 26 years), maternal educational level (high or intermediate/low), infant's gender, smoking in the household during the infant's first year, sibship size (<3 or ≥ 3), and day care attendance at age 1 year. Multivariate logistic regression analyses were calculated separately for subjects with and without a family history of allergy.

Ethical considerations

This study was approved by the Ethical Review Board of the Hospital for Children and Adolescents and the Ethical

Review Board for Internal Medicine, Helsinki University Hospital. Written informed consent was obtained from the parents at the beginning of the study, and from the participants of the 20-year re-examination.

Results

Frequency of atopic manifestations in infancy, childhood and adolescence

As previously published, 14 (7%) children showed signs of atopy during their first year of life [27]. One or several allergic symptoms were recorded in 40 (25%) of the 160 children seen at age 5 years. The prevalence of allergic symptoms had increased to 46% at age 11 years and to 52% at age 20 years.

At age 5 years, the most frequent symptoms were atopic dermatitis (18%) and food hypersensitivity (12%). Of the 28 children with atopic dermatitis, 11 (39%) had symptoms of food hypersensitivity as well. Low prevalences of AR (3%) and allergic conjunctivitis (4%) were recorded at age 5 years, but they had increased to 23% and 20% at age 11 years, and to 41% and 31% at age 20 years, respectively. The prevalence of food hypersensitivity symptoms was at the same level at ages 5 and 11 years, 12% and 11%, respectively.

Of the 28 children with atopic dermatitis at age 5 years, 21 (75%) and, of the 19 children with food hypersensitivity symptoms, 12 (63%) were SPT negative, whereas SPT positivity was observed in 10% of the 120 symptom-free children. Of the 16 children with food hypersensitivity symptoms at 11 years of age, eight (50%) were SPT negative, whereas 20% of the 81 symptom-free children were SPT positive. At age 20 years, 67 (79%) of the 85 subjects with allergic symptoms had a positive SPT, and 24% of the 79 symptom-free subjects were SPT positive.

Demographic characteristics of the study population

Smoking in the household during the infant's first year occurred in 34 families, and it was recorded more often in the group with exclusive breastfeeding for <2 months (28%, $P = 0.05$) than in the infants with exclusive breastfeeding for 2– <6 , 6– <9 or ≥ 9 months. Day care attendance at age 1 year was least frequent, 57%, in the group with exclusive breastfeeding for <2 months and most frequent, 85% ($P = 0.04$), in the group with exclusive breastfeeding for 2– <6 months.

The duration of exclusive breastfeeding and the development of allergic symptoms in childhood and adolescence

The possible association of the duration of exclusive breastfeeding and the development of atopic manifestations

Table 2. The effect of exclusive breastfeeding prolonged for over 9 months as compared with a shorter duration of exclusive breastfeeding in children with a family history of allergy (positive FHA) and in children without a family history of allergy (negative FHA) calculated with multivariate logistic regression*

	Positive FHA		Negative FHA		Total population	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
5 years of age (<i>n</i> = 132)						
Allergic symptoms	6.1 (1.5–24.8)	0.01	1.4 (0.3–6.1)	0.66	2.4 (0.9–5.9)	0.07
Atopic dermatitis	6.5 (1.5–28.7)	0.01	1.5 (0.3–7.3)	0.63	3.0 (1.1–8.3)	0.03
Food hypersensitivity	5.3 (1.2–24.1)	0.03	1.0 (0.1–7.5)	0.97	2.5 (0.8–7.6)	0.11
Verified atopy [†]	0.1 (0.2–6.4)	0.99	–	0.99	2.1 (0.5–9.0)	0.30
11 years of age (<i>n</i> = 126)						
Allergic symptoms	0.7 (0.2–2.6)	0.61	0.5 (0.1–1.7)	0.25	0.6 (0.3–1.5)	0.30
Atopic dermatitis	0.2 (0.0–2.1)	0.19	1.1 (0.2–6.0)	0.91	0.5 (0.1–1.7)	0.24
Food hypersensitivity	7.9 (1.4–50.0)	0.02	4.3 (0.1–284)	0.49	1.9 (0.5–7.0)	0.33
Verified atopy [†]	0.4 (0.1–1.5)	0.16	0.5 (0.1–2.4)	0.36	0.5 (0.2–1.5)	0.23
20 years of age (<i>n</i> = 132)						
Allergic symptoms	1.9 (0.4–8.7)	0.43	0.4 (0.1–1.3)	0.10	0.7 (0.3–1.7)	0.42
Atopic dermatitis	2.7 (0.3–21.6)	0.36	0.7 (0.1–3.7)	0.70	1.2 (0.4–3.5)	0.80
Verified atopy [†]	1.5 (0.3–6.6)	0.63	0.4 (0.1–1.6)	0.18	0.7 (0.3–1.7)	0.42

*Independent variables used in the model: duration of exclusive breastfeeding (<9 months/≥9 months), sex, maternal age, maternal educational level, smoking in the household during the first year, day care attendance at the age of 1 year, sibship size 3 or more.

[†]Allergic symptoms and SPT positivity.

OR, odds ratio; CI, confidence interval.

was analysed with logistic regression. In order to control for the effects of the potential confounding factors, multivariate logistic regression analyses were performed (Table 2).

At age 5 years, the prevalence of allergic symptoms was highest, 41%, in the children who had received exclusive breastfeeding for 9 months or more (odds ratio [OR] 2.8, 95% confidence interval [CI] 1.2–6.2, *P* = 0.01) as compared with the children who had exclusive breastfeeding for less than 9 months. Significantly higher prevalences of atopic dermatitis (35%; OR 3.9, CI 1.6–9.3, *P* = 0.002, Fig. 1) and symptoms of food hypersensitivity (26%; OR

3.3, 95% CI 1.2–9.0, *P* = 0.02) were recorded in the children who had exclusive breastfeeding for 9 months or more as compared with those with exclusive breastfeeding for less than 9 months (Table 3). While the length of exclusive breastfeeding did not have a significant effect on the prevalence of atopic dermatitis at ages 11 and 20 years, the prevalence of food hypersensitivity symptoms at age 11 years was significantly higher in the children who had exclusive breastfeeding for 9 months or more (OR 3.6, 95% CI 1.2–10.5, *P* = 0.01, Table 3). The duration of exclusive breastfeeding did not have a significant effect on the prevalences of AR or allergic conjunctivitis.

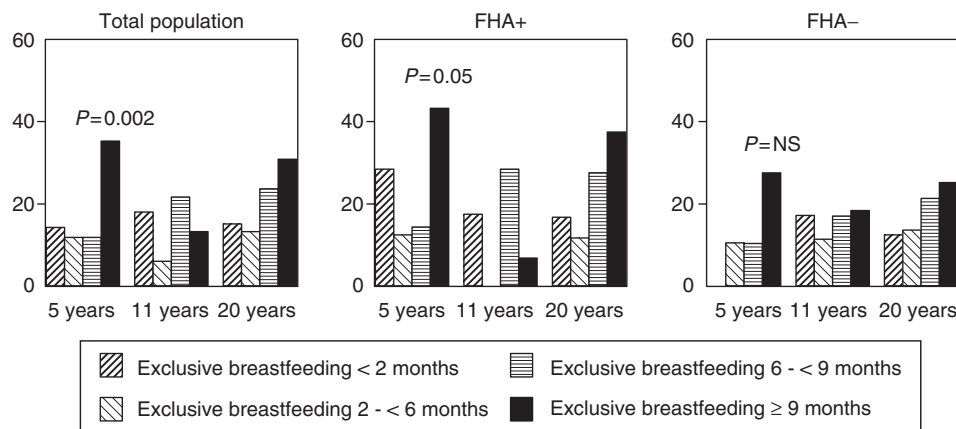


Fig. 1. Influence of the duration of exclusive breastfeeding on the prevalence (%) of atopic dermatitis at the ages of 5, 11 and 20 years. FHA+, subjects with a family history of allergy; FHA–, subjects without a family history of allergy.

Table 3. Allergic symptoms and verified atopy at ages 5, 11 and 20 years according to the duration of exclusive breastfeeding

		Duration of exclusive breastfeeding (months)					
	<i>N</i> *	< 2	2– < 6	6– < 9	≥9	<i>P</i> †	OR (95% CI) ‡
5 years (<i>n</i> = 160)							
<i>N</i> (total)		28 (18)	33 (21)	65 (41)	34 (21)		
Atopic dermatitis	28 (18)	4 (14)	4 (12)	8 (12)	12 (35)	0.002	3.8 (1.6–9.3)
Food hypersensitivity	19 (12)	2 (7)	2 (6)	7 (11)	8 (26)	0.02	3.3 (1.2–9.0)
Recurrent wheezing	5 (3)	1 (4)	0	1 (2)	3 (9)	0.03	6.1 (0.9–38.4)
Verified atopy‡	12 (8)	2 (7)	2 (6)	4 (6)	4 (12)	0.29	1.9 (0.6–7.0)
11 years (<i>n</i> = 149)							
<i>N</i> (total)		22 (15)	33 (22)	63 (42)	31 (21)		
Atopic dermatitis	25 (17)	4 (18)	2 (6)	14 (22)	5 (16)	0.62	0.9 (0.3–2.8)
Food hypersensitivity	16 (11)	0	3 (9)	6 (10)	7(23)	0.01	3.6 (1.2–10.5)
Recurrent wheezing	9 (6)	0	2 (6)	5 (8)	2 (7)	0.89	1.1 (0.2–5.6)
Verified atopy‡	41 (28)	7 (32)	10 (30)	17 (27)	7 (23)	0.66	0.7 (0.3–1.8)
20 years (<i>n</i> = 164)							
<i>N</i> (total)		27 (16)	39 (24)	66 (40)	32 (20)		
Atopic dermatitis	35 (21)	4 (15)	5 (13)	16 (24)	10 (31)	0.13	1.9 (0.8–4.6)
Recurrent wheezing	20 (12)	4 (15)	4 (10)	7 (11)	5 (16)	0.51	1.4 (0.5–4.3)
Verified atopy‡	66 (40)	12 (44)	18 (46)	25 (38)	11 (34)	0.45	0.7 (0.3–1.6)

Numbers and percentages of symptomatic subjects are shown.

*Number of subjects with a given symptom or verified atopy.

†Unadjusted P values, odds ratios (OR) and 95% confidence intervals (CI) calculated by logistic regression for the difference between exclusive breastfeeding for ≥ 9 months and for < 9 months.

‡Allergic symptoms and SPT positivity.

Recurrent wheezing at age 5 years was most frequent among the children who had exclusive breastfeeding for 9 months or more, the difference reaching statistical significance ($P=0.03$) despite the small number of children with recurrent wheezing (Table 3). At age 20 years, the prevalences of allergic symptoms or SPT positivity were not associated with the duration of exclusive breastfeeding (Tables 2 and 3).

The association of exclusive breastfeeding and allergic symptoms in children with atopic heredity

At ages 5 and 20 years, higher prevalences of allergic symptoms ($P=0.01$ and 0.04), SPT positivity ($P=0.04$ and 0.03) and verified atopy ($P=0.03$ and <0.01) were observed in the children with a family history of allergy than in those without a family history of allergy. At age 11 years, the prevalence of allergic symptoms was similar, whereas the prevalence of SPT positivity was higher in the children with a family history of allergy than in those without a family history of allergy ($P=0.02$). The effect of maternal heredity on the prevalence of allergic symptoms appeared stronger than that of paternal heredity, the prevalences being 41%, 50% and 72% at ages 5, 11 and 20 years among the subjects with a maternal heredity, 22%, 35% and 55% among the subjects with a paternal heredity, and 71%, 80% and

100% among the seven subjects with a biparental history of allergy, respectively.

Among the 72 children with a family history of allergy seen at age 5 years, the prevalence of allergic symptoms was highest, 56%, in the children who had exclusive breastfeeding for 9 months or more (OR 3.3, CI 1.0–10.3, $P=0.01$), the prevalences being 36%, 20% and 30% in children who had exclusive breastfeeding for less than 2 months, for 2 to less than 6 months, and for 6 to less than 9 months. Atopic dermatitis was recorded in 17 (24%) and symptoms of food hypersensitivity in 12 (17%) of the 72 children with a family history of allergy. The highest prevalences of atopic dermatitis, 44% (OR 3.7, 95% CI 1.1–12.1, $P=0.03$, Fig. 1), and food hypersensitivity symptoms, 38% (OR 5.1, 95% CI 1.3–19.1, $P=0.01$), were recorded in the children who had received exclusive breastfeeding for 9 months or more. These differences remained significant after adjusting for potential confounding factors (Table 2).

At 11 years of age, allergic symptoms were recorded in 30 (46%) of the 65 children with a family history of allergy. Among these, food hypersensitivity symptoms were recorded most often in the children who had received exclusive breastfeeding for 9 months or more (43%; OR 6.9, 95% CI 1.7–28.1, $P=0.004$), the difference remaining significant after adjusting for potential confounding factors (Table 2). None of the children with a family history of

allergy and exclusive breastfeeding for 2 to less than 6 months had atopic dermatitis at age 11 years (Fig. 1).

The association of exclusive breastfeeding and allergic symptoms in children without atopic heredity

Among the 88 children without a family history of allergy seen at age 5 years, the prevalence of atopic dermatitis was highest, 28% (OR 4.2, 95% CI 1.1–15.9, $P=0.02$), in those who had received exclusive breastfeeding for 9 months or more, the prevalence being 0%, 11%, and 11% in children with exclusive breastfeeding for less than 2 months, for 2 to less than 6 months, and for 6 to less than 9 months (Fig. 1). However, when the potential confounders were taken into account, the difference was not significant (Table 2). Thus, exclusive breastfeeding for 9 months or more was not significantly associated with allergic symptoms or SPT positivity among the subjects without a family history of allergy.

Discussion

We examined whether prolonging strictly exclusive breastfeeding for over 6 or even 9 months is beneficial in allergy prevention. However, exclusive breastfeeding for 9 months or more was associated with a higher risk of atopic dermatitis and symptoms of food hypersensitivity at 5 years, and of food hypersensitivity at 11 years of age. At age 20 years, the prevalences of allergic symptoms were similar in subjects with differing lengths of exclusive breastfeeding. The prevalence of SPT positivity was not affected by the duration of exclusive breastfeeding. Allergic symptoms and SPT positivity were strongly predicted by a family history of allergy, especially maternal heredity, which conforms with previous studies [28].

This prospective 20-year follow-up study is unique in design, as it involves an unselected cohort of healthy infants and mothers, and all the participants irrespective of atopic heredity were encouraged to maintain strictly exclusive human milk feeding as long as it was nutritionally sufficient for the infant. Since the study was originally set up to examine the nutritional value of strictly exclusive breastfeeding [23], the possible allergy-preventive effect was not emphasized as a motivation of maintaining exclusive breastfeeding. Therefore, the potential bias of infants of allergic families being self-selected to receive a prolonged exclusive breastfeeding was avoided, and the children with and those without a family history of allergy were equally likely to receive a prolonged exclusive breastfeeding (Table 1). Care was taken to avoid any inadvertent exposure to infant formulae, and the duration of exclusive breastfeeding was recorded in a prospective manner with careful monitoring during the first year. The participation rates at the re-examinations were very high; as much as 83% of the original cohort

participated the 20-year re-examination. In order to control for the effect of exposure to tobacco smoke, only non-smoking mothers were included in the study, and smoking in the household during the infant's first year was taken into account as a potential confounder along with several other important background factors. Therefore, this prospective follow-up study avoids many of the methodological drawbacks the earlier studies on breastfeeding and allergy have been criticized of [29, 30]. In a study on human subjects, random assignment of infants to exclusive breastfeeding or formula feeding or a double-blind study design is not ethically or practically feasible. Hence, it is difficult to completely rule out the possibility of confounding. This should be kept in mind when interpreting the results of the present and the previous studies on breastfeeding.

Exclusive breastfeeding is considered useful for the prevention of allergy [8], as many of the previous studies indicate that exclusive breastfeeding for 3–4 months protects against atopy [9–11, 31–35] as compared with early introduction of cow's or soy milk formula. In a large cluster-randomized trial in Belarus, an intervention promoting breastfeeding was shown to increase the duration and exclusivity of breastfeeding, and to decrease the incidence of atopic eczema during the first year of life [18]. However, the study by Bergmann *et al.* [36] indicates that prolonging non-exclusive breastfeeding may increase the risk of atopic eczema. Miyake *et al.* [37] reported based on a cross-sectional study that breastfeeding may be associated with increased atopic eczema among children aged 12–15 years. Wright *et al.* [15, 16] found exclusive breastfeeding for 4 months to protect against early recurrent wheezing, whereas it was associated with an increased risk of asthma at age 6 years in the offspring of asthmatic mothers. A similar result, i.e. increased asthma at age 5–6 years in the breastfed children of asthmatic mothers, was reported by Oberle *et al.* [38]. Bergmann *et al.* state that they are not able to exclude the possibility of reverse causation, i.e. the mother continuing breastfeeding for a prolonged time once her infant has developed eczema.

In our study, excluding the children with signs of atopy during the first year [26] in whom the reverse causation might have been possible, did not change the results; the prevalences of atopic dermatitis and food hypersensitivity symptoms remained significantly higher in the children who had received exclusive breastfeeding for 9 months or more. Therefore, reverse causation does not explain the results of the present study.

In our study, 75% of the children with atopic dermatitis and 63% of those with food hypersensitivity symptoms at age 5 years were SPT negative, suggesting atopic dermatitis of the intrinsic type [39], and possibly non-IgE-mediated mechanisms of food hypersensitivity. The prevalences of food hypersensitivity symptoms must be

interpreted with caution as they are based on personal reports and may, therefore, represent an overexpression.

The allergy-preventing effect of exclusive breastfeeding may be due to reduced exposure to dietary antigens as well as to the effects of the immunologically active factors in human milk. As well as antimicrobial substances, breast milk contains a wide variety of immunomodulating agents, including both anti-inflammatory and proinflammatory mediators [40, 41], and small amounts of allergens, such as dietary protein antigens [42]. Differences in the leucocyte, cytokine and chemokine composition of milk from atopic and non-atopic mothers have been observed [43–45]. It remains to be clarified whether the effect of some of these breastfeeding-related factors turns unfavourable when exclusive breastfeeding is maintained for up to 9 months.

The effect of prolonged exclusive breastfeeding on the development of allergic symptoms appears to be strongest during the first years of life, whereas it seems to be weaker in later childhood and in early adulthood. This is possibly due to the effects of environmental factors, which may gain in importance after infancy and early childhood.

To our knowledge, this prospective follow-up study represents a unique experiment on the effects of exclusive breastfeeding prolonged for over 9 months. Studies on the growth and iron balance in this cohort have indicated that maintaining exclusive breastfeeding for over 6–9 months may result in a slower growth rate and iron deficiency [22, 46]. Moreover, we now demonstrate that prolonging exclusive breastfeeding and postponing the introduction of solid foods for over 9 months is not helpful in prevention of atopy; instead, it may be associated to an increased risk of subsequent atopic dermatitis and symptoms of food hypersensitivity in children with a family history of allergy. These results are in agreement with the World Health Organization's Expert Consultation recommending exclusive breastfeeding for the first 6 months, with introduction of complementary foods and continued breastfeeding thereafter [20].

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