

Breast-feeding and atopic disease: A cohort study from childhood to middle age

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Background: The literature regarding the association between breast-feeding and atopic diseases has been contradictory.

Objective: We have assessed the relationship between breast-feeding and atopic disorders in a cohort followed into middle age.

Methods: The Tasmanian Asthma Study is a population-based prospective cohort study that has followed participants from the age of 7 to 44 years. Exclusive breast-feeding in the first 3 months of life was examined as a risk factor for atopic diseases by using multiple logistic regression and generalized estimating equation analyses.

Results: At age 7 years, exclusively breast-fed children with a maternal history of atopy had a marginally lesser risk of current asthma than those not exclusively breast-fed (odds ratio [OR], 0.8; 95% CI, 0.6-1.0). However, after age 7 years, the risk reversed, and exclusively breast-fed children had an increased risk of current asthma at 14 (OR, 1.46; 95% CI, 1.02-2.07), 32 (OR, 1.84; 95% CI, 1.06-3.3), and 44 (OR, 1.57; 95% CI, 1.15-2.14) years. Exclusively breast-fed children also had a reduced risk of food allergy at age 7 years but an increased risk of food

allergy (OR, 1.26; 95% CI, 1.1-1.5) and allergic rhinitis (OR, 1.2; 95% CI, 1.0-1.3) at 44 years.

Conclusion: Exclusively breast-fed babies with a maternal history of atopy were less likely to develop asthma before the age of 7 years, but more likely to develop asthma after the age of 7 years.

Clinical implications: The current recommendation to breast-feed high-risk infants for protection against early wheezing illness can be confirmed. However, the recommendation should be reconsidered for protection against allergic asthma and atopy in the longer term. (*J Allergy Clin Immunol* 2007;120:1051-7.)

Key words: Breast-feeding, asthma, allergic rhinitis, food allergy, maternal atopy

The effect of breast-feeding on risk of allergic diseases such as asthma, allergic rhinitis, and eczema has been controversial over recent years. Numerous studies have examined the relationship between breast-feeding and risk of allergic disease. A systematic review of 12 prospective studies found that exclusive breast-feeding in the first months of life was associated with reduced rates of asthma and that the protective effect was greatest in high-risk children.¹ Another recent multidisciplinary review examined more than 4000 articles relating to breast-feeding and allergic disease and concluded that breast-feeding in the first 4 months of life reduced the risk of asthma.² Clinical practice guidelines internationally³⁻⁵ for the prevention of allergic disease recommend exclusive breast-feeding for the first 4 to 6 months of life, particularly for babies of atopic mothers.⁶ However, several prospective birth cohort studies have found breast-feeding to be a risk factor for asthma rather than a protective factor.⁷⁻¹²

Although several studies have examined risk of asthma and atopy into early adolescence,^{10,13,14} fewer have followed subjects into adulthood¹² and none into middle age. The differing duration of follow-up may explain the discrepancies between studies. This is particularly important for the development of allergies that are known to have a peak incidence in late adolescence.¹⁵ The aim of this study was to examine the effect of exclusive breast-feeding in the first 3 months of life on risk of current asthma and atopy throughout childhood and into middle age.

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Abbreviations used

GEE: Generalized Estimating Equation
OR: Odds ratio

METHODS**Tasmanian Asthma Study**

In 1968, a cohort of 8583 Tasmanian children (probands) born in 1961 and their parents ($n = 16,267$) and siblings ($n = 21,044$) were surveyed for respiratory problems. Probands had medical examinations including lung function measurements. Subsequently, 4 follow-up surveys were performed at the ages of 13 years (in 1974), 20 years (in 1981), 31 years (in 1992), and 44 years (in 2004) on either the total or the subgroups of the probands (Fig 1). The methodology and some results of previous surveys have been reported elsewhere.¹⁶⁻¹⁹ The 36-year follow-up of the Tasmanian Asthma Study involved a postal survey of all traced 1968 probands ($n = 7312$; 85.2%). The methodology of tracing participants has been reported previously.²⁰ A response rate of 78.4% ($n = 5729$) was achieved to the postal survey. The 1992 and 2004 follow-up studies were approved by the Human Research Ethics Committee at the University of Melbourne.

Definitions

Breast-feeding was defined by the question, "How was he/she fed in the first three months of life?" in the 1968 survey. The parent could answer (1) breast-fed only, (2) bottle-fed only, or (3) breast-fed and bottle-fed. *Exclusively breast-fed* was defined as the breast-fed only group. *Ever asthma* was defined as a positive response to the question, "Has he/she at any time in his/her life suffered from attacks of asthma or wheezy breathing?" The same question was asked in all surveys. In 1968 and 1974, the parents answered on behalf of their children, but in 1992 and 2004, the probands answered for themselves. *Current asthma* was defined by a positive response to ever asthma followed by answering "in the last 12 months" to the question, "How long since the last attack?" *Maternal history of atopy* was defined as children with a mother who reported a history of either asthma or allergic rhinitis in the 1968 survey. *Paternal history of atopy* was defined as children with a father who reported a history of either asthma or allergic rhinitis in the 1968 survey. *Sibling history of atopy* was defined as children with any siblings with a reported history of either asthma or allergic rhinitis in the 1968 survey.

Persistence of asthma was defined as subjects who had asthma at age 7 years and at 1 of the other time points (age 14, 32, 44 years). *Developed asthma* was defined as subjects who did not have asthma at age 7 years and had current asthma at 1 of the other time points (age 14, 32, 44 years). *Infantile eczema* was defined as a positive response to the question, "Did he/she have infantile (baby) eczema?" in the 1968 survey. *Food allergies* were defined as a positive response to the question, "Have you been told by a doctor that he/she is allergic to any foods or medicines?" in the 1968 survey. *Specific allergies* to food, medicines, dust, animals, or pollens at age 44 years were defined as a positive response to the question, "Have you ever been allergic to: a) foods; b) medicine; c) dust; d) animals; e) pollen, grass, trees or flowers?" in the 2004 survey. *Ever eczema* was defined by the question, "Have you ever had eczema or any kind of skin allergy?" as reported in the 2004 survey. *Ever allergic rhinitis* was defined as a positive response to the question, "Have you ever had hay fever (that is sneezing, running or blocked nose when you do not have a cold or flu)?" in the 2004 survey.

Statistical methods

Crude associations between exclusive breast-feeding and current asthma and other atopic diseases ever were evaluated using χ^2 tests and by computing crude odds ratios (ORs) and corresponding 95% CIs. We used multiple logistic regression models to estimate the effect of exclusive breast-feeding on current asthma and other outcome variables, adjusting for possible confounders such as sex, maternal smoking, ever pneumonia in 1968, paternal atopy, siblings atopy, and adult smoking. Socioeconomic status was also included and estimated by father's occupation in 1968 and education level achieved by age 44 years. The interaction between maternal history of atopy and exclusive breast-feeding was examined in all the associations of interest. To account for the stratified sampling used in the 1991 study, the associations between exclusive breast-feeding and current asthma and other atopic diseases ever were examined while stratifying by the sampling variable (asthma status in 1968). If the relevant associations were similar across strata, the sampling variable was then included in multivariate analysis of the association between exclusive breast-feeding and these outcomes.

To account for the repeated measures design (asthma status was recorded in 1968, 1974, 1992, and 2004), we used Generalized Estimating Equations (GEEs). The Huber-White sandwich estimator was used to estimate the variance-covariance matrix of the model parameters with an exchangeable correlation structure.²¹ All tests were 2-tailed, and a P value below .05 was considered to be statistically significant. All analyses were performed by using Stata Release 7 (Stata Statistical Software, Release 7; Stata Corp, College Station, Tex).

RESULTS**Population characteristics**

Of the 8280 children with information on feeding in the first 3 months of life, 39.2% (3248) had been exclusively breast-fed. Table I shows the baseline demographic and clinical characteristics of the cohort by exclusive breast-feeding status. There was no difference in sex between the 2 groups. Exclusively breast-fed children were more likely to have more than 2 siblings, less likely to be a twin, and no more likely to have infantile eczema. Mothers of exclusively breast-fed children were younger and less likely to be working or to be a smoker. These mothers also reported less asthma but slightly more allergic rhinitis.

Breast-feeding and risk of current asthma

There was no overall association between exclusive breast-feeding and risk of current asthma at different ages in the total cohort. However, the association between breast-feeding and asthma risk differed according to the presence or absence of maternal atopic disease. In children of a mother with atopic disease, breast-feeding was marginally protective against current asthma at age 7 years. Interestingly, this risk was reversed by the age of 14 years, and breast-feeding became a risk factor for current asthma at ages 14, 32, and 44 years in those with a maternal history of atopic disease (Table II). The interactions between a maternal history of atopic disease and exclusive breast-feeding were statistically significant at all ages except age 32 years.

The results from the GEE analysis confirmed the lack of association between exclusive breast-feeding and risk

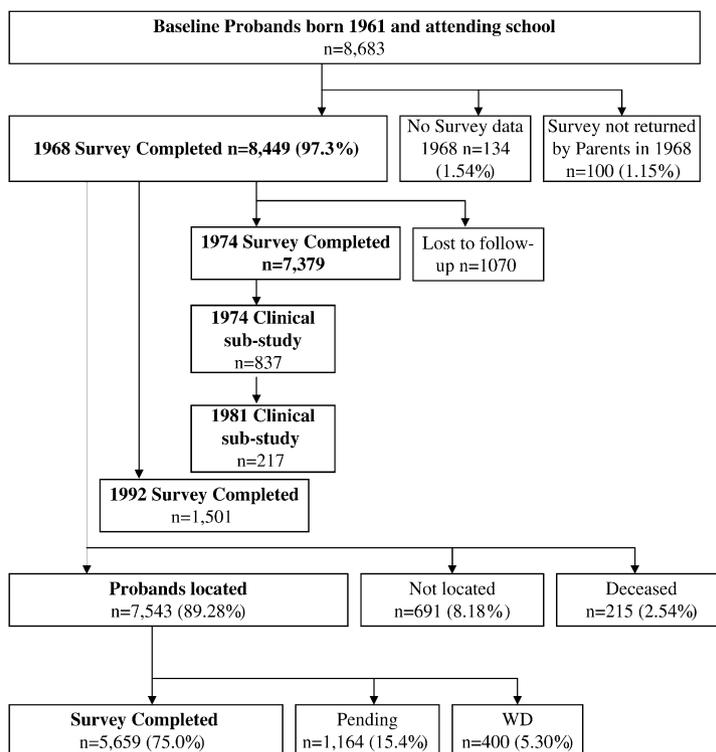


FIG 1. Overview of the Tasmanian Asthma Study. WD, Withdrawn.

TABLE I. Baseline demographic and clinical characteristics of the cohort

Characteristic	Exclusively breast-fed	Not exclusively breast-fed	P value
Maternal age (y, mean ± SD)	N = 3186 33.1 ± 5.80	N = 4666 33.6 ± 6.21	<.001
Paternal age (y, mean ± SD)	N = 3091 36.7 ± 6.7	N = 4533 37.1 ± 7.10	<.001
Sex (male)	51.0% (1655/3248)	51.4% (2587/5032)	.69
>2 siblings	72.9% (2367/3248)	70.0% (3521/5032)	.004
Australian born	96.6% (3124/3234)	96.1% (4814/5011)	.03
Twins	0.9% (29/3184)	3.0% (147/4882)	<.0001
Mother working	20.7% (663/3202)	23.1% (1086/4704)	.01
Maternal asthma	9.8% (316/3211)	11.8% (557/4709)	.006
Maternal allergic rhinitis	23.7% (760/3209)	22.0% (1038/4711)	.09
Maternal smoking	31.0% (993/3203)	40.2% (1893/4705)	<.0001
Paternal asthma ever	11.0% (345/3132)	10.6% (488/4622)	.50
Paternal allergic rhinitis ever	18.7% (585/3126)	16.2% (743/4602)	.003
Paternal smoking	57.5% (1792/3115)	62.5% (2830/4530)	<.0001
Family history of asthma	19.0% (592/3120)	20.4% (927/4545)	.13
Family history of allergic rhinitis	36.5% (1137/3112)	33.4% (1514/4528)	.005
Maternal history of asthma or allergic rhinitis	26.3% (844/3204)	26.5% (1244/4696)	.90
Infantile eczema	9.3% (300/3239)	10.2% (513/5021)	.20

of current asthma in the total cohort ($P = .12$). Similar to analysis described, after stratification by presence of maternal atopic disease, GEE analysis observed an association between exclusive breast-feeding and current asthma in children with a mother with atopic disease (OR, 1.37; 95% CI, 1.01-1.87; $P = .04$). Moreover, a significant interaction term between breast-feeding and maternal history of atopic disease on current asthma confirmed

this association (OR, 1.46; 95% CI, 1.02-2.09; $P = .04$). Exclusion of 1992 data from the GEE model because of a large number of missing observations in current asthma did not alter the estimated associations (without data from 1992, OR, 1.38; 95% CI, 1.02-1.90).

We also examined whether the protective effect of breast-feeding was related to the age of onset of asthma in those with current asthma under the age of 7 years

TABLE II. Prevalence of current asthma by breast-feeding history stratified by maternal atopy

Outcomes	With maternal atopy			Without maternal atopy			P value
	Exclusively breast-fed [% (n)]	Not exclusively breast-fed [% (n)]	OR (95% CI), P value	Exclusively breast-fed [% (n)]	Not exclusively breast-fed [% (n)]	OR (95% CI), P value	
Current asthma							
7 y†	15.3% (129/843)	19.9% (247/1242)	0.75 (0.58-0.97), .03	8.9% (210/2359)	8.4% (290/3449)	1.12 (0.91-1.37), .28	.02
14 y†	10.4% (77/740)	7.7% (83/1072)	1.46 (1.02-2.07), .04	4.7% (100/2112)	4.8% (145/2997)	1.10 (0.83-1.45), .52	.15
32 y‡	26.7% (50/187)	21.5% (58/270)	1.84 (1.03-3.29), .04	16.5% (69/418)	15.2% (85/559)	1.06 (0.69-1.62), .80	.34
44 y§	16.3% (92/564)	12.8% (98/764)	1.57 (1.15-2.14), .005	9.8% (152/1548)	10.8% (224/2074)	0.89 (0.72-1.10), .29	.009
14-44 y*	—	—	1.37 (1.01-1.87)	—	—	0.93 (0.75-1.14)	.04

*Repeated-measures analysis.

†Adjusted for pleurisy/pneumonia in 1968, sex, maternal smoking, sibling atopy, and paternal atopy.

‡Adjusted for pleurisy/pneumonia in 1968, sex, maternal smoking, sibling atopy, paternal atopy, education level, ever smoking, and asthma in 1968.

§Adjusted for pleurisy/pneumonia in 1968, sex, maternal smoking, sibling atopy, paternal atopy, education level, and ever smoking.

||P for interaction between breast-feeding and maternal atopy.

TABLE III. Risk of childhood asthma stratified by age at asthma onset in exclusively breast-fed children with maternal history of atopic disease

Asthma status	Exclusively breast-fed (N = 833)	Not exclusively breast-fed (N = 1230)	OR (95% CI)*, P value
No asthma	77.6% (646)	72.7% (894)	1.0
Under 3 y	16.1% (134)	21.1% (259)	0.73 (0.57-0.95), 0.02
Over 3 y	6.4% (53)	6.3% (77)	0.95 (0.64-1.40), 0.80

*Adjusted for pleurisy/pneumonia by 1968, sex, maternal smoking, sibling atopy, and paternal atopy.

(Table III). The protective effect of breast-feeding was associated with asthma that started before the age of 3 years. Of these children, more than 70% no longer had current asthma by the age of 14 years, indicating that the protective effect of breast-feeding was primarily for early-onset (<3 years) childhood asthma that resolved by 14 years. Exclusive breast-feeding was also protective against ever having had pneumonia or pleurisy by age 7 years (OR, 0.86; 95% CI, 0.76-0.98) and having current bronchitis or cough at age 7 years (OR, 0.87; 95% CI, 0.79-0.96; $P = .007$).

Breast-feeding and risk of eczema

We found a protective effect of exclusive breast-feeding on infantile eczema in those with a history of maternal atopic disease (OR, 0.67; 95% CI, 0.49-0.92; $P = .02$), but not in those without a maternal history of atopic disease (OR, 1.05; 95% CI, 0.83-1.32; $P = .69$). Breast-feeding had no effect on flexural eczema at age 7 years (OR, 1.10; 95% CI, 0.92-1.33; $P = .29$) or ever eczema at age 44 years (OR, 1.06; 95% CI, 0.95-1.19; $P = .31$).

Breast-feeding and risk of allergies

The association between risk of allergies or allergic rhinitis and exclusive breast-feeding is shown in Table IV. Exclusive breast-feeding was associated with a reduced risk of food allergies at age 7 years but an increased risk at age 44 years for the entire cohort. The risk of allergic rhinitis was also increased in those who were exclusively breast-fed again for the entire cohort; however, this risk

was only evident at age 44 years. Exclusive breast-feeding was a risk factor for allergies to aeroallergens such as animal dander and pollen. The interaction between maternal atopy and exclusive breast-feeding was not significant in any of these associations.

DISCUSSION

Our study for the first time provides an explanation why some studies of breast-feeding have observed a protective effect against asthma and atopy,^{13,22-28} whereas other studies showed an increased risk.^{7,12} We are the first to analyze data from early childhood well into middle age. Spanning this extensive period covers the current gap in understanding of the effect of breast-feeding on asthma risk. We have shown that exclusive breast-feeding is protective against asthma and infantile eczema in children with a maternal history of asthma or allergic rhinitis. However, this risk is reversed after the age of 7 years, and breast-feeding then becomes a risk factor for current asthma in those children with a familial predisposition. Exclusive breast-feeding was also found to be protective against food allergies in early life but to increase the risk of food allergies and allergic rhinitis in later life in all subjects.

Our study sought to clarify the controversy surrounding the association between allergic diseases and breast-feeding. Several studies^{13,22-28} and 2 recent meta-analyses^{1,2} have reported a protective effect of breast-feeding

TABLE IV. Risk of allergic rhinitis and allergies in exclusively breast-fed children

Allergic outcomes	Exclusively breast-fed	Not exclusively breast-fed	OR* (95% CI)
Foods or medicines at age 7 y	5.7% (185/3231)	8% (212/2643)	0.75 (0.62-0.92)
Foods at age 44 y	12.3% (263/2146)	10.1% (305/3012)	1.25 (1.05-1.51)
Medicine at age 44 y	14.8% (317/2146)	16.6% (500/3012)	0.89 (0.76-1.04)
Dust at age 44 y	16.4% (351/2146)	15.4% (464/3012)	1.16 (0.99-1.36)
Animals at age 44 y	12.0% (258/2146)	10.2% (308/3012)	1.26 (1.05-1.51)
Pollen at age 44 y	32.5% (698/2146)	29.0% (873/3012)	1.24 (1.09-1.40)
Ever allergic rhinitis at age 44 y	52.4% (1119/2134)	49.8% (1491/2993)	1.14 (1.01-1.28)

*Adjusted for maternal atopy, current asthma at 44 years, sex, sibling atopy, paternal atopy, and current smoking status in 2004.

in the first few years of life. We found exclusive breast-feeding did have a protective effect against risk of current asthma, infantile eczema, and food allergies at 7 years of age. However, the protective effect toward asthma and eczema was only present in the subgroup of children with a high familial risk because they had a mother with allergic disease. This contrasts somewhat with the results of the 2 meta-analyses that found a larger effect size in children with a positive family history, but still observed an effect in children without this familial predisposition.^{1,2} Although there was no evidence of heterogeneity in the meta-analysis,¹ the studies included were significantly smaller than our study and had a substantially shorter duration of follow-up. One large cohort study is preferable to pooling multiple smaller studies. Furthermore, the duration of follow-up and age at which outcomes are assessed have a very significant effect on whether a protective effect of breast-feeding is observed.

After the age of 7 years, however, breast-feeding was no longer protective against current asthma. The increased risk of current asthma associated with breast-feeding was consistent at the ages of 14, 32, and 44 years for subjects with a maternal history of allergic disease, and this was confirmed by the repeated measures analysis. The risk was highest in subjects who developed asthma after the age of 7 years rather than subjects with persistent asthma from childhood. We also observed a significantly increased risk of allergic rhinitis and animal, pollen, and food allergies by the age of 44 years.

The longitudinal Dunedin Multidisciplinary Health and Development Research Study found a similar consistent positive association between exclusive breast-feeding and risk of current asthma at the ages of 9 and 26 years, and also an increased risk of allergies at 13 and 21 years.¹² In the United Kingdom 1970 birth cohort of more than 13,000 children, eczema and allergic rhinitis at 5 years were reported more often in children who had been breast-fed than those who had not.⁹ Furthermore, the Tucson Children's Respiratory Study found breast-feeding was associated with lower rates of recurrent wheeze before the age of 6 years, but was a risk factor for asthma and recurrent wheeze between 6 and 13 years.¹⁰ Similar to our study, the Tucson study found this association only in a high-risk subgroup, atopic children of mothers with asthma.

A recent meta-analysis of the effect of breast-feeding on the development of allergic rhinitis found that overall, breast-feeding did not have an effect on allergic rhinitis risk.²⁹ However, in studies that looked at subjects without a family history of allergic disease, there was a borderline protective effect of breast-feeding. The studies in this meta-analysis had a maximum follow-up of participants to 4 years of age. The development of allergic sensitization to inhaled allergens begins to rise around 3 years of age and peaks during adolescence.¹⁵ Therefore, studies without follow-up into adolescence may miss a substantial number of allergic rhinitis cases, which may explain the lack of associations with breast-feeding.

Is there a biologically plausible explanation for the reversal of risk after the age of 7 years? One possibility is that asthma in childhood is a different condition from asthma developed later in life. It has been postulated by several researchers that asthma in childhood can be divided into several distinct phenotypes: early transient wheeze, late-onset wheeze, and persistent wheeze.³⁰ These different childhood wheezing phenotypes have different prognoses and are likely therefore to have different etiologies. It has been suggested that the early transient wheezing phenotype represents wheezing associated with recurrent viral infections, whereas the late-onset and persistent wheezing phenotypes reflect atopic asthma.³⁰ We found the protective effect of breast-feeding was mainly in those children who developed asthma before the age of 3 years and that more than 70% of these children no longer had current asthma by age 14 years. These children would best fit within the early transient wheezing group. The protective effect of breast-feeding against this early transient wheezing phenotype may be explained by a reduced number of early life respiratory infections. This hypothesis is supported by our observation that breast-feeding was protective against pneumonia or pleurisy and current bronchitis or cough by age 7 years. Further support comes from other studies finding that risk of early transient wheeze caused by respiratory tract infections is reduced by breast-feeding.^{10,11,31} In particular, an Italian study that found breast-feeding for more than 3 months was protective against the development of transient early wheezing but was a risk factor for late-onset wheeze.¹¹

Why does breast-feeding appear to increase the risk of asthma and allergies after the age of 7 years? Possible

explanations include maternal transmission of IgE responses and other factors related to the hygiene hypothesis such as a lack of exposure to infections in early life.³² It has been shown that atopic mothers have higher levels of T_H2 cytokines (IL-4, IL-5, and IL-13) compared with nonatopic mothers.^{33,34} These differences may result in different IgE levels in the child, which may contribute to risk of allergies.⁸ Work in mice has shown that breast milk is sufficient but not necessary to mediate allergen-independent maternal transmission of asthma to the offspring.³⁴ Another possible mechanism for the increased risk could be explained in the context of the hygiene hypothesis, that a reduced exposure to infections in childhood increases the risk of allergic disease.³² We found breast-fed children had fewer infections (both bacterial and viral) and were more likely to be first born and in a higher social class, all factors related to the hygiene hypothesis. This reduced exposure to infections in the breast-feeding group provides a possible explanation for a higher risk of allergies, allergic rhinitis, and asthma.

The questions used in all surveys to define asthma were identical; the only difference was that parents answered on behalf of their children in the 1968 and 1974 surveys. It is therefore unlikely that differences in the definitions of asthma between surveys resulted in a detection bias that contributed to altered associations between breast-feeding and asthma. However, it is possible the rising prevalence of asthma in the last 30 years may have introduced ascertainment bias.³⁵

Other limitations of our study include the retrospective collection of information on breast-feeding, gathered when the child was 7 years of age, which may have introduced recall bias. Although it is unlikely that a mother would forget whether she breast-fed, she might not recall whether breast-feeding was totally exclusive. This could have resulted in some nondifferential misclassification, but this would have biased risk estimates toward the null. The question regarding breast-feeding was categorical; therefore, we were unable to examine whether there was any dose-response relationship with duration of breast-feeding.

The use of parental/participants' reporting of atopic conditions is a limitation because it is likely to be less reliable than physician reporting and the use of objective measures of atopic status such as skin prick tests. However, it should be noted that the question used to define asthma has been validated against physician diagnosis.³⁶ Reverse causation may explain some of the negative associations between asthma and breast-feeding (ie, children with early signs of atopic disease may be breast-fed for longer).³⁷ However, we did not observe an increased prevalence of infantile eczema in children who were exclusively breast-fed and instead, infantile eczema was negatively associated with breast-feeding. One of the unique aspects of our study is the large sample size. Because the magnitude of effect of breast-feeding on long-term outcomes is small, we were able to detect such effects, which may explain why other studies have produced variable outcomes.

In conclusion, our study advances the understanding of the effect of breast-feeding on risk of allergy. We have shown that in babies of atopic mothers (ie, high-risk babies), breast-feeding, although important for the protection of the infant against early wheezing illness (asthma), eczema, and food allergies, does not appear to protect against the development of asthma, allergic rhinitis, or food and inhalant allergies in the long term. These results have important implications for the recommendation to breast-feed to protect against allergies and asthma. This is particularly relevant because current recommendations regarding the beneficial effects of breast-feeding for the prevention of allergic diseases in the long term are directed to atopic mothers, who make up the subgroup in which the increased risk of asthma in later life was identified. Therefore, on the basis of the results of this study and the other available evidence, the recommendation to breast-feed high-risk infants for protection against early wheezing illness can be confirmed. However, for protection against allergic asthma and atopy in the long term, the recommendation should be reconsidered.

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