

Original article

Atopic disease and breast-feeding— cause or consequence?

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Background: A number of studies have observed an association between breast-feeding and increased risk of development of asthma and eczema. It has been proposed that these results might be due to early signs of atopic disease in the infant causing mothers to prolong breast-feeding.

Objective: We sought to determine whether early symptoms of atopic disease (eczema, food reaction, or asthma) or positive skin prick test responses reduce the likelihood of ceasing breast-feeding.

Methods: A prospective birth cohort of 620 infants from Melbourne, Australia, was used. Telephone interviews every 4 weeks were conducted until 64 weeks and then again at 78 and 104 weeks to determine duration of breast-feeding (both exclusive and total) and evidence of atopic disease. Because of the varying time of onset of atopic symptoms, they were modeled as time-varying covariates in Cox models.

Results: Only 52 (8.4%) infants did not establish breast-feeding, whereas an additional 103 (25.0%) did not establish exclusive breast-feeding. Early signs of atopic disease or sensitization were independently associated with an approximately 28% reduction in risk of ceasing exclusive breast-feeding (adjusted hazard ratio, 0.72; 95% CI, 0.53-0.97); $P = .029$), but there was no evidence for a relationship with risk of ceasing breast-feeding completely (adjusted hazard ratio, 1.12; 95% CI, 0.92-1.37; $P = .262$).

Conclusion: Early signs of atopic disease might prolong the duration of exclusive breast-feeding. This could mask a protective effect of breast-feeding or even result in breast-

feeding appearing to be a risk factor for the development of atopic diseases. Future investigation of the relationship between breast-feeding and atopic diseases should consider this possibility. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Breast-feeding, atopic disease, atopic dermatitis, asthma, allergy prevention

Historically, there has been widespread support for the concept that breast-feeding is protective against asthma and atopic disease.¹⁻⁴ However, a number of prospective birth cohort studies⁵⁻¹⁰ have recently suggested that breast-feeding might in fact be a risk factor for the development of atopic disease and asthma. These findings have led Friedman and Zeiger¹¹ to conclude in a recent review that "...one can still not make a definitive statement that breast-feeding will help prevent sensitization to allergens in infants or later respiratory illness such as asthma."

A primary criticism of these articles has been that their findings might be attributable to *reverse causation*.¹²⁻¹⁴ Infants at the highest risk of atopic disease (because of a strong family history of atopic disease or presence of early signs, such as infantile eczema) might be breast-fed for longer in the hope that breast-feeding might reduce the risk of long-term atopic disorders or at least delay the onset of symptoms. If infants at the highest risk of development of atopic disease are preferentially breast-fed for prolonged periods, this could result in a reduction in the observable protective effect of breast-feeding or even a spurious association with increased risk of atopic disease. None of the studies that have concluded that breast-feeding is a risk for atopic conditions have adjusted for atopic disease in infancy.⁵⁻¹⁰ Therefore these studies are unable to refute the possibility that such factors influenced decisions concerning breast-feeding.

Using data from the Melbourne Atopy Cohort Study (MACS), a prospective birth cohort study of 620 infants with a family history of atopic disease, we examined the possibility that preferential breast-feeding of infants with early signs of atopic disease might explain an association between breast-feeding and increased risk of atopic disease. A major strength of the MACS data was that the children were followed at 4-week intervals until after their first birthday. Frequent follow-up allowed us to determine whether early signs of atopic disease in the infant were associated with duration of breast-feeding after adjusting

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Abbreviations used

HR: Hazard ratio

MACS: Melbourne Atopy Cohort Study

for other factors that have been shown to influence duration of breast-feeding.^{15,16} Our hypothesis was that early signs of atopic disease reduced the likelihood of ceasing breast-feeding.

METHODS

The MACS recruited 620 infants born between February 1990 and November 1994 before birth. Previous publications have described the recruitment process in more detail.^{17,18} The study was approved by the Mercy Maternity Hospital, and informed consent was obtained from the mothers. Expectant mothers were invited to enroll their unborn infants into MACS if 1 or more of that infant's first-degree family members had atopic eczema, asthma, hay fever, or severe food allergy. During pregnancy, details were recorded on family demographics, medical history, and environmental exposures (including maternal, paternal, and "household" smoking). Mothers were asked whether either they or the biologic father and any siblings of the fetus enrolled in the MACS had symptoms of asthma, hay fever, eczema, or severe food allergies.

Mothers were encouraged to breast-feed and to delay introduction of solid foods until the infant was 6 months of age. At 6 months, low-allergen solids (eg, rice, apple, and pear) were recommended, and at 12 months, an appropriate diet for age was encouraged.

After the birth of the infant, an allergy-trained nurse administered (by telephone) a survey every 4 weeks until the age of 64 weeks and then at 78 weeks and 2 years of age. The survey documented exposure to foods and any illnesses in the previous 4 weeks. Survey responses were used to determine the total duration of breast-feeding and the duration of exclusive breast-feeding. Duration of exclusive breast-feeding was defined as the duration from birth to the first exposure to any food other than breast milk. A reaction to a food was deemed to have occurred if within 2 hours of ingesting that food the child had an acute skin rash (usually perioral but occasionally widespread), a flare up of preexisting eczema, periorbital edema, signs of anaphylaxis, or vomiting. We have previously demonstrated good agreement between parent-reported food reactions occurring within 2 hours of ingestion and immediate food challenges.¹⁹ Infants were deemed to have asthma if a physician diagnosed the condition. Any rash (excluding rash that only affected the nappy region or scalp) that was treated with topical steroid-based preparations was deemed to be eczema. Skin prick tests were conducted at 6 and 12 months according to a standard technique (allergen extracts used were milk, egg, peanut, dust mite, cat, and rye grass).²⁰ A positive skin prick test response was defined as a mean wheal diameter of 2 mm or greater than that produced by the saline control.

The risks of ceasing exclusive breast-feeding and any breast-feeding were analyzed separately by using methods of survival analysis. Infants were excluded from the analysis if they did not establish breast-feeding (defined as not breast-feeding at 2 weeks after birth) because these infants could not be at risk of ceasing breast-feeding. Similarly, infants were excluded from the analysis of exclusive breast-feeding if they did not establish exclusive breast-feeding (defined as not exclusively breast-feeding at 2 weeks after birth).

The distribution of time to cessation of breast-feeding was estimated by using the Kaplan-Meier method. Cox proportional-

hazards regression was used to assess associations between early signs of atopic disease (eczema, food reaction, asthma, use of asthma medications, or positive skin prick test response to 1 or more allergens) and risk of ceasing breast-feeding. Hazard ratios (HRs) of less than 1 indicate lower rates of cessation of breast-feeding. Indicators of early expression of atopic disease in the infant were modeled as time-varying covariates²¹ because an early sign of atopic disease could only influence duration of breast-feeding from the time that it was first noted and if breast-feeding was occurring at that time. Stata software (release 8; Stata Corp, College Station, Tex) was used to construct survival curves and to estimate HRs (with 95% CIs). Variables considered as potential confounders in the Cox models were atopic diseases in either parent and any older siblings (asthma, eczema, hay fever, and food allergy treated separately), the infant's sex, the presence of older siblings, maternal and paternal age and years of education, pet ownership, smoking status (smoker within past 6 months vs not), and use of gas heating and cooking facilities. Variables were retained in the multivariable model if they had previously been associated with risk of ceasing breast-feeding^{15,16} or had a *P* value of less than .05. The proportional hazards assumption was tested for all associations, and no evidence of nonproportional hazards was observed for any covariate.

RESULTS

Parents of the MACS infants were predominantly Australian born, married, and home owner-occupiers (Table I). The most common form of self-reported allergic disorders in parents was hay fever (maternal, 60.6%; paternal, 46.2%; Table I). Almost 60% (371/620) of the MACS infants had 1 or more older siblings, and of these, more than 90% had at least 1 sibling affected by an atopic disorder (Table I). Less than a quarter (150/620) of the cohort had only 1 family member with an atopic disease. There was approximately an equal sex balance in MACS infants (302/620 were female). The most common clinical sign of atopic disease in infants during the first year of life was eczema (34.2% [207/605]), which is reflected in the higher proportion of children with eczema during breast-feeding (23.4%) and exclusive breast-feeding (7.5%) than the other atopic diseases (Table II).

Only 52 (8.4%) infants did not commence breast-feeding (*n* = 37) or did not continue breast-feeding for 2 or more weeks (*n* = 15). An additional 103 infants established breast-feeding but did not establish exclusive breast-feeding, resulting in a total of 75.0% (464/619) of the cohort establishing exclusive breast-feeding for 2 or more weeks. In infants who established breast-feeding (or exclusive breast-feeding), the median total duration of breast-feeding was 48 weeks (interquartile range, 26-64 weeks), and the median duration of exclusive breast-feeding was 18 weeks (interquartile range, 10-22 weeks; Fig 1).

An early sign of atopic disease was associated with approximately a 28% (95% CI, 3%-47%) reduction in the risk of ceasing exclusive breast-feeding after adjusting for potential confounding factors (Table III). Comparison with univariate estimates of HRs shows that adjustment for confounders did not alter the relationship, and the effect of atopic diseases on duration of exclusive breast-

TABLE I. Baseline demographic and clinical characteristics of study cohort (n = 620)

	Maternal (n = 620)	Paternal (n = 617)	
Mean age, y (SD)	31.2 (4.4)	33.4 (5.3)	
Mean years of education (SD)	13.4 (1.9)	13.5 (2.0)	
Born in Australia/New Zealand (n)	86.8% (538/620)	82.5% (510/618)	
Married (n)	91.0% (564/620)	91.3% (563/617)	
Owner-occupied residence (n)	79.7% (494/620)	80.4% (493/613)	
Smoking history			
Current (n)	6.3% (39/620)	18.2% (112/615)	
Never (n)	74.4% (461/620)	66.5% (409/615)	
Receiving social security (n)	3.6% (22/620)	3.1% (19/613)	
Baseline family history of atopic disease			
	Maternal (n = 620)	Paternal (n = 615)	Any older sibling (n = 371)
Food allergies			
Milk	19.9%*	9.9%	44.05%†
Egg	8.6%*	4.9%	28.11%†
Other	30.7%	15.3%	50.27%†
Any	38.6%	21.3%	62.53%†
Eczema	38.9%*	20.5%	64.15%
Asthma	43.3%*	25.7%	59.03%
Hay fever	60.6%*	46.2%	36.59%‡
Any atopic disease	82.7%	61.0%	90.8%

*n = 619.

†n = 370.

‡n = 369.

TABLE II. Prevalence (as percentage with 95% CI) of early signs of atopic disease and sensitization in the infant within the first year of life, during total breast-feeding, and during exclusive breast-feeding

	First year of life (n = 601)*	During breast-feeding (n = 607)†	During exclusive breast-feeding (n = 617)‡
Early asthma	20.3% (17.2-23.7)	14.2% (11.5-17.2)	1.6% (0.8-3.0)
Early eczema	33.88% (30.1-37.8)	23.4% (20.1-27.0)	7.5% (5.5-9.8)
Early asthma medication	17.8% (14.9-21.1)	11.2% (8.8-14.0)	0.5% (0.1-1.4)
Early food reaction	8.5% (6.4-11.0)	7.1% (5.2-9.4)	§
Early positive SPT response	39.4% (35.5-43.5)	23.7% (20.4-27.3)	0.5% (0.1-1.4)
Any early signs of atopic disease	65.6% (61.6-69.3)	45.1% (41.1-49.2)	8.8% (6.6-11.3)

SPT, Skin prick test.

*Excludes 19 infants who were lost to follow-up during the first year of life.

†Excludes 13 infants who were lost to follow-up while still breast-feeding without signs of atopic disease but includes 12 infants who were still breast-fed at 2 years of age but had not shown a sign of atopic disease.

‡Excludes 3 infants who were lost to follow-up while still exclusively breast-fed and who had not shown a sign of atopic disease.

§Exclusively breast-fed infants, by definition, cannot experience a food reaction.

feeding was driven predominantly by early signs of eczema (Table IV). The other markers of atopic disease showed effects in the same direction, but only 12 infants had signs of asthma compared with 46 infants who showed signs of eczema during exclusive breast-feeding (Table II). Only 1 infant had evidence of eczema in the first 4 weeks of life while still being exclusively breast-fed. There was strong evidence that the presence of a maternal food allergy was associated with a reduction in the risk of ceasing exclusive breast-feeding (HR, 0.76; 95% CI, 0.62-0.92; Table III).

In contrast, there was no evidence that early expression of atopic disease was associated with risk of completely ceasing breast-feeding (HR, 1.12; 95% CI, 0.92-1.37;

Table III). However, there was strong evidence that the presence of self-reported maternal food allergy was associated with a reduction in the risk of ceasing breast-feeding (HR, 0.75; 95% CI, 0.63-0.90).

DISCUSSION

In this study early signs of atopic disease were independently associated with an approximately 30% reduction in the risk of ceasing exclusive breast-feeding after adjusting for potentially confounding factors.^{15,16} In other words, children who had signs of atopy were likely to be exclusively breast-fed for a longer period of time than

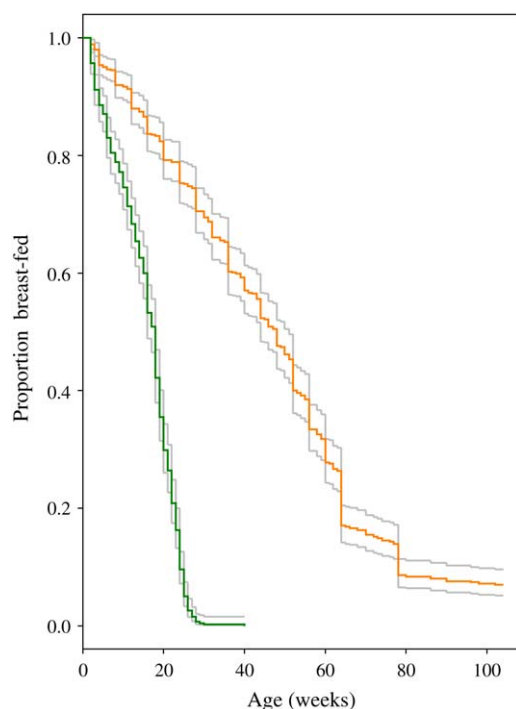


FIG 1. Duration of breast-feeding according to 2 definitions: any ($n = 567$) and exclusive ($n = 464$) breast-feeding. Definition of breast-feeding: *orange line*, any breastfeeding; *green line*, exclusive breastfeeding; *gray line*, 95% CI.

infants who did not have signs of atopic disease while being breast-fed. We found no evidence of an association with total duration of breast-feeding. This might be due to community beliefs that exclusive breast-feeding is important in protecting against atopic disease, rather than simply any breast-feeding. This study is unique in its exploration of this issue. Frequent collection of both exposure (early atopic disease) and outcome (breast-feeding) data are required to accurately determine the temporal sequence of these events. Moreover, these exposures need to be modeled as time-varying covariates because of the variable time of onset of symptoms of atopic disease.

We have used survival analysis to determine whether early signs of atopic disease increase the duration of breast-feeding. Possibly a more intuitive analysis of these data would be to create an “early atopic disease” group and a “no early atopic disease” group and compare the median duration of breast-feeding for each. However, because atopic disease can be noted at any age, such an analysis would not be valid. To enter the early atopic disease group, infants must have both a sign of atopic disease and be breast-feeding at that time. If breast-feeding has ceased, then signs of atopic disease could not influence its duration. Infants breast-fed for only a short period would predominantly be placed in the no early atopic disease group, lowering this group’s median duration because breast-feeding did not continue long enough for atopic disease to become apparent. In addition, infants who entered the early atopic disease group would

effectively have their full duration of breast-feeding ascribed to the effect of atopic disease and not just the proportion that occurred after the sign was noted. Simply examining the median duration of breast-feeding between the groups would produce results that were systematically biased and overestimated the increase in breast-feeding associated with signs of atopic disease. Modeling early atopic disease as a time-varying covariate allowed us to estimate its effect from the time it was first noted. A further advantage of survival analysis is that it enabled infants with censored breast-feeding data (either because of loss to follow-up or discontinuation of collection of breast-feeding data at 2 years of age) to be validly included in the analysis.

A number of recent studies have identified breast-feeding as a potential risk factor for the development of allergic diseases.⁵⁻¹⁰ In an atopic disease-enriched sample, Bergman et al⁷ found that each additional month of breast-feeding was associated with approximately a 3% increased risk of atopic eczema during the first 7 years of life. Wright et al⁶ observed an 8-fold increase in the odds of having asthma by the age of 13 years associated with total breast-feeding of greater than 4 months’ duration but only if the child’s mother had asthma. This relationship was particularly strong if the child himself or herself was atopic. In a population-based New Zealand cohort, Sears et al⁵ showed that any duration of breast-feeding longer than 4 weeks was associated with an increased risk of having a positive skin prick test response and asthma at 13 years and older.

Lack of adjustment for family history of atopic disease and early signs of atopic disease in the infant in these studies⁵⁻⁷ allows for the possibility that the findings have been influenced by reverse causation (preferential breast-feeding of infants with early signs of atopic disease). None of the studies has adjusted for early signs of atopic disease in the infant.⁵⁻⁷ To date, only 2 reports from 1 study have adjusted for possible modification of breast-feeding by early atopic disease.^{22,23} In both cases the protective effect of breast-feeding against atopic disease was strengthened when infants with signs of atopic disease while breast-feeding were excluded from the analysis.

The risk of reverse causation due to early signs of atopic disease in the infant depends on how breast-feeding has been classified. For early atopic disease in the child to extend the duration of breast-feeding, the first signs of atopic disease must occur while the infant is still being breast-fed (because it is unlikely for a mother to resume breast-feeding). Bergman et al⁷ used a continuous measure of breast-feeding, and Wright et al⁶ used 4 months’ duration of breast-feeding. Having a long duration of breast-feeding as a cut-off point or treating breast-feeding as a continuous variable increases the opportunity for early atopic disease in the child to result in an alteration of breast-feeding behavior, making reverse causation more likely. Bergman et al⁷ acknowledge this possibility in their discussion. In contrast, for early signs of atopic disease in the child to produce a change in the breast-feeding categorization used in the study by Sears et al,⁵ an infant

TABLE III. Associations between early atopic disease and risk of ceasing breast-feeding (exclusive and total) from multivariable Cox regression model, including potential confounding factors

Variables	Exclusive breast-feeding*		Any breast-feeding†	
	HR (95% CI)	P value	HR (95% CI)	P value
Any early atopic disease	0.72 (0.53-0.97)	.029	1.12 (0.92-1.37)	.262
Maternal food allergy	0.76 (0.62-0.92)	.006	0.75 (0.63-0.90)	.003
Any sibling(s) with asthma or eczema‡	1.07 (0.77-1.47)	.691	0.82 (0.60-1.11)	.199
No siblings‡	0.92 (0.67-1.27)	.627	0.72 (0.53-0.97)	.031
Maternal smoking§	1.90 (1.28-2.83)	.002	1.65 (1.14-2.39)	.008
Maternal years of education	0.92 (0.87-0.97)	.002	0.88 (0.84-0.93)	.000
Maternal age (y)	0.98 (0.96-1.01)	.184	0.96 (0.93-0.98)	.000
Gas cooking facility	1.26 (1.05-1.52)	.015	1.17 (0.98-1.40)	.079

*Excludes 155 infants who did not establish exclusive breast-feeding.

†Excludes 52 infants who did not establish exclusive breast-feeding.

‡Compared with infants with siblings, all of whom do not have asthma or eczema.

§Smoking within previous 6 months versus no smoking during previous 6 months.

would need to have had a sign of atopic disease within 4 weeks and then be breast-fed for more than 4 weeks as a result. In MACS, an atopic disease-prone cohort, only 4 (0.65%) infants showed a sign of atopic disease within 4 weeks of birth. This proportion would be even smaller in a population-based cohort, as used by Sears et al.⁵ Therefore it is unlikely that this phenomenon occurred frequently enough in their cohort of 1037 infants to have significantly affected their results. However, this does not preclude the possibility that the observed results could be due to reverse causation because Sears et al⁵ also did not adjust for atopic disease in siblings or atopic diseases other than asthma and hay fever in parents. Similarly, Bergman et al⁷ and Wright et al⁶ made no adjustments for atopic disease in siblings, and Wright et al did not adjust for parental atopic diseases other than asthma.

The current study examined the effect of early symptoms and signs of atopy on the risk of ceasing breast-feeding. Full exploration of the reverse causation issue requires an assessment of the associations between family history of atopic disease (both sibling and parental) and the decision to commence breast-feeding, as well as the decision to continue breast-feeding. This could not be done with this data set because the sampling frame for this study was limited to children with a family history of atopic disease. This cohort did not contain children free of a family history of atopic disease to act as an appropriate reference group to determine the effect of sibling and parental atopy on breast-feeding behavior. Despite the limited sampling frame, we did observe that maternal food allergy was associated with a reduced risk of ceasing breast-feeding, both total and exclusive. It should be noted that family history of food and other allergic diseases was self-reported and not verified. Previous studies have found that self-reported food intolerances can be verified by using strict criteria in approximately only one fifth of cases in adults.²⁴ As such, many of these mothers probably do not have a verifiable food allergy. However, they do have perceived food intolerance, and this perception might be just as important in altering breast-feeding behavior.

TABLE IV. Univariate associations between early atopic disease factors and duration of exclusive breast-feeding expressed as HR (instantaneous relative risk) for ceasing breast-feeding (n = 465)

Early atopic disease factors*	HR (95% CI)	P value
Any early atopic disease	0.69 (0.52-0.93)	.015
Early asthma	0.90 (0.48-1.70)	.748
Early eczema	0.66 (0.48-0.90)	.010
Early asthma medications	0.78 (0.25-2.44)	.672
Early positive SPT response	0.91 (0.28-2.96)	.869

SPT, Skin prick test.

*Excludes 155 infants who did not establish exclusive breast-feeding.

It is possible that reverse causation effects might be different in this cohort when compared to general birth cohorts. The rate of breast-feeding of MACS infants was high, possibly due to the study's design. In the MACS, all infants had a family history of atopic disease, the focus was on the development of atopic disease, and there was frequent contact with an allergy-trained nurse. High rates of breast-feeding might make it more difficult to detect any influence of early atopic disease on breast-feeding behavior, when compared to a general population. However, it could help identify such an effect because more infants would be breast-feeding when atopic disease was first noted, and the MACS has greater variability in duration of breast-feeding when compared to a general population. In the MACS, any effect of family history on increasing breast-feeding rates might be difficult to observe because all infants had a family history, unlike in a general cohort. However, the parents of infants of enrolled in the MACS might have been more likely to recognize the early signs of eczema (and modify their behavior) than parents from unselected populations, creating greater potential for reverse causation. For these reasons, it remains unclear what effect early manifestations of atopic disease might have on duration of breast-feeding in general birth cohort studies, and this should be addressed in future research.

This study has a few limitations. The MACS was not designed to fully explore the reverse causation issue. No data were recorded about the role atopic diseases played in the decisions concerning initiation and continuation of breast-feeding. While our analysis was able to assess whether adjustments for most of the factors that have been identified as risk factors for cessation of breast-feeding in Australian women^{15,16} altered the relationship between early atopic disease and duration of breast-feeding, we were unable to assess the impact of maternal body mass index because this was not recorded at the time of recruitment.

CONCLUSIONS

We have observed that signs of atopic disease in infants are associated with a reduced risk of ceasing exclusive breast-feeding and therefore have the potential to lead to reverse causation in the relationship between duration of breast-feeding and risk of development of atopic conditions. It is possible that reverse causation has already created spurious associations between breast-feeding and increased risk of atopic disorders or reduced the protective effect observed in other articles. The effect of perceived risk of atopic disease on decisions concerning breast-feeding might differ between cohorts. Because of the range of benefits associated with breast-feeding and the uncertainty concerning any association between breast-feeding and the risk of atopic disease, the findings of such studies should not be overemphasized when formulating public health policy or advising individual mothers. A randomized controlled trial is required to definitively determine the effect of breast-feeding on the development of atopic diseases but is not feasible for both ethical and logistical reasons.²⁵ Therefore future observational research that addresses the association between breast-feeding and the risk of development of atopic conditions needs to address the possibility of reverse causation and make appropriate adjustments.

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