

The role of breast-feeding in the development of allergies and asthma

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Breast-feeding is the preferred method of infant nutrition for numerous reasons. However, its role in the prevention of allergic disease remains controversial. Reasons for this controversy include methodological differences and flaws in the studies performed to date, the immunologic complexity of breast milk itself and, possibly, genetic differences among patients that would affect whether breast-feeding is protective against the development of allergies or is in fact sensitizing. The preponderance of evidence does suggest, however, that there would be much to lose by not recommending breast-feeding. In general, studies reveal that infants fed formulas of intact cow's milk or soy protein compared with breast milk have a higher incidence of atopic dermatitis and wheezing illnesses in early childhood. Consistent with these findings, exclusive breast-feeding should be encouraged for at least 4 to 6 months in infants at both high and low risk of atopy and irrespective of a history of maternal asthma. (*J Allergy Clin Immunol* 2005;115:1238-48.)

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

Since 1939, when Grulee and Sanford¹ reported a significantly lower incidence of eczema in infants who were breast-fed compared with bottle-fed babies, further research has been unable to provide the definitive answer whether the development of allergic disease can be prevented by breast-feeding. One clear possible explanation for this is that methodological differences among studies and design flaws in many make data difficult to compare. However, there may be other reasons for the heterogeneity of these results as well. Breast milk itself is inherently complex immunologically. Allergens present in breast milk may in some cases be sensitizing and in other cases protective, depending on a variety of factors. There also may be genetic differences in infant/mother

Abbreviations used

AAP: American Academy of Pediatrics
ESPACI: European Society of Allergology and Clinical Immunology
ESPGHAN: European Society of Paediatric Gastroenterology, Hepatology and Nutrition
OR: Odds ratio
s-IgA: Secretory IgA

pairs that have an effect on whether breast-feeding would be sensitizing or protective.

It is not controversial that breast-feeding is the preferred method of infant nutrition in most cases because of its nutritional, immunological, and psychological benefits. It has also been included as a hallmark in the prevention of allergy in guidelines by both the American Academy of Pediatrics (AAP)² and the European Societies for Paediatric Allergology and Clinical Immunology and Paediatric Gastroenterology, Hepatology and Nutrition (ESPACI/ESPGHAN).³ Because the data regarding allergy prevention are conflicting, the question of what is to be lost by not breast-feeding is raised when it comes to the prevention of atopy. In this Rostrum, the current data at the core of the controversy are summarized, and an attempt is made to answer this complex question.

IMMUNOLOGIC COMPLEXITY OF BREAST MILK

One of the major reasons that studies into the effect of breast-feeding with regard to the development of allergies remain so inconclusive may be the complexity of the interaction between breast milk and an infant's intestinal milieu and immune system. Some elements in breast milk are thought to act to protect the infant from developing allergies, whereas others might act in the opposite fashion (Table I).

It has long been known that secretory IgA (s-IgA) is passed from mother to infant via breast milk or colostrum. Low levels of s-IgA in breast milk have been associated with increased risk of cow's milk allergy in infants, although not in all studies.⁴ Moreover, lower levels of s-IgA to ovalbumin have been noted in colostrum and mature milk of mothers with allergy compared with

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mothers without allergy, although presence of these antibodies was not predictive of allergies in their infants.⁵ It has been thought, however, that s-IgA might confer passive protection to the infant's immune system.

The concentrations of cytokines and chemokines may also play a role in the immunogenicity of breast milk. IL-4, IL-5, and IL-13, the cytokines most intimately involved with IgE production and the induction of eosinophils, are present in higher concentrations in the breast milk of atopic mothers compared with their counterparts without allergy. TGF- β , one of the predominant cytokines in human breast milk,⁶ increases the ability of the infant to produce IgA against β -lactoglobulin, casein, gliadin, and ovalbumin.⁷ Soluble CD-14 may also be protective against the development of allergies in that it is present in high concentrations in breast milk and is thought to be important in the induction of a T_H1 response to bacteria.^{8,9}

The compositions of polyunsaturated fatty acids and polyamines have also been proposed to affect the allergenicity versus the immunoprotectiveness of breast milk. A high arachidonic acid to eicosapentaenoic acid ratio in breast milk has been thought to be associated with a higher risk of atopy in the infant,⁵ although a recent article¹⁰ has suggested that the opposite may be the case. High levels of spermine and spermidine may be immunoprotective by decreasing the permeability of the intestinal mucosa.¹¹ Higher levels of eosinophil cationic protein in breast milk have been associated with a higher incidence of cow's milk allergy and atopic dermatitis in infant recipients.¹² It is unclear how these disparate mechanisms of immunomodulation express themselves in infant mother pairs or whether one will be able to predict, on a case by case basis, how breast milk will effect the development of allergies in a given child. Perhaps an understanding of genetic factors may allow for better predictability in the future. It will require future study to determine the real effect of the complex interaction of these immunomodulatory factors in breast milk between mother and infant in the development of allergic disease.

ALLERGY GENES

Although a full review of the current state of knowledge of allergy genes is beyond the scope of this article, the future of the predictability of any measures instituted in an allergy prevention program, including breast-feeding, might depend on such information. Many polymorphic genetic markers have been linked to an atopic phenotype.¹³ Although some loci appear to be associated with allergy in the population at large, others seem to be predictors of susceptibility only within certain ethnic groups. Some genes whose polymorphisms have been implicated as possible markers of allergic disease include 5q31, encoding the IL-4 gene¹⁴ and other cytokine genes¹⁵; 11q13, which encodes the β -chain of the high-affinity IgE receptor^{16,17}; numerous Toll-like receptor genes¹⁸; and 6p21 and 12q13, which encode for the HLA-D region and IFN- γ , respectively.

TABLE I. Factors in breast milk that are currently being evaluated as either inducing or protecting against food allergies

	Inducing	Protective
Antigens	Sensitizing allergens	Tolerizing allergens
Cytokines	IL-4 IL-5 IL-13	TGF- β Soluble CD14
Immunoglobulins		s-IgA to ovalbumin
Polyunsaturated fatty acids	Arachidonic acid C22:4n-6 C22:5n-6	Eicosapentaenoic acid Docosapentaenoic acid Docosatetraenoic acid α -Linoleic acid n-3 Polyunsaturated fatty acids
Chemokines	RANTES IL-8	
Eosinophil-derived granular proteins	Eosinophil cationic protein	
Polyamines		Spermine Spermidine

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EXPOSURE TO INFECTION

Infection in early childhood may have a dual effect. Early infection with respiratory syncytial virus and other viruses predispose susceptible infants to wheezing episodes. Breast milk may provide antiviral antibodies and other factors that reduce the incidence of these infections and subsequent wheezing. On the other hand, certain infections may be protective for allergy development by stimulating the T_H1 immune pathway. An important variable in assessing the role of breast-feeding in the development of allergies is the fact that children who are being breast-fed are likely to be spending more time with their mothers and less time in daycare settings than would their bottle-fed counterparts. Much has been written lately about the hygiene hypothesis, the theory that an infant at high risk for developing atopy who has been exposed to frequent infections may preferentially develop a T_H1-predominant immune system rather than a T_H2-predominant one thereby decreasing the risk of allergy. On the other hand, it has long been noted that certain early infections such as respiratory syncytial virus may predispose to higher rates of asthma or wheezing illness in toddlers and grade school children.

The reader is referred to several excellent reviews on this topic.¹⁹⁻²¹ Briefly, there is growing evidence that frequent infections in early childhood may be a protective factor against the development of allergy. Recent studies have noted that attendance at daycare or the presence of older siblings in the house is associated with lower rates of

asthma by age 6 years, although, not surprisingly, higher rates of wheezing in infancy.²² Intracellular microorganisms may particularly have a strong immunomodulatory effect, causing long-lived memory immunity and a strongly polarized T_H1 response.²⁰ By promoting intestinal colonization of lactobacilli and bifidobacteria, breast-feeding may be protecting against allergy by stimulating T_H1 responses in breast-fed infants.²³ An association has been reported between frequent use of antibiotics during infancy²⁴ and an increased risk of developing asthma in later childhood. This association is not clear however, because a recent study has suggested that antibiotic use during pregnancy may be more strongly associated with early asthma,²⁵ and a prospective study by Celedon et al²⁶ has shown no relationship between early antibiotic use and asthma.

Therefore, although breast-feeding is clearly advantageous to the general health of the infant by decreasing some respiratory and gastrointestinal infection rates, studies regarding its effect on the development of subsequent atopy may need to be interpreted taking into account the complex immunomodulatory role of early infections.

ALLERGENS IN BREAST MILK

Food antigens have long been known to be detectable in breast milk. β -Lactoglobulin, casein, and bovine γ -globulin have been detected in nanogram concentrations in the breast milk of women not specifically avoiding cow's milk products during lactation.²⁷ Egg²⁸ and wheat²⁹ allergens have been detected in breast milk as little as 2 to 6 hours after maternal ingestion and can be detected as long as 4 days later. Peanut proteins have been measured in breast milk by both ELISA and immunoblot analysis.³⁰ Atopic infants already sensitized to these foods may have disease exacerbation after ingesting breast milk containing these allergens and have disease amelioration after maternal avoidance of these foods.³¹ Although it is clear that these antigens can be detected, it is uncertain whether they might lead to sensitization or tolerance of these foods in the recipient of the breast milk, or what variables affect these two possible outcomes.

STUDIES EVALUATING THE ROLE OF BREAST-FEEDING IN THE DEVELOPMENT OF ATOPY

Spawned by the work of Grulee and Sanford¹ in 1939, whose nonrandomized study of 20,000 infants suggested that breast-feeding reduces the incidence of eczema, numerous studies have attempted to examine further the role of breast-feeding in the development of allergy. Differences in methodology and inevitable flaws in design make these studies difficult to compare, and no single definitive study has yet been published. Methodological differences include whether a study is prospective or

retrospective, interventional versus observational or self-selective versus randomized. Design flaws in many studies include small sample size, lack of randomization, brief duration of breast-feeding, lack of immunologic confirmation, and lack of blinding during evaluation. Moreover, the extent of breast-feeding exposure (never versus ever or exclusive versus partial) and duration of breast-feeding between different studies need to be known. A detailed description of the atopic outcome must be defined precisely, including disorder (specific disorders such as atopic dermatitis [eczema], food allergy, recurrent wheezing versus asthma, allergic rhinitis, or any of the above atopic manifestations) or sensitization (skin test or *in vitro* testing for specific IgE). Finally, the period (infancy, early childhood, adolescence/adulthood) at which outcomes are determined must be considered, because differential effects by age have been reported. However, despite these difficulties, many trends can be observed and conclusions drawn from a review of the literature.

Results of these studies can be divided into 3 contradictory categories: breast-feeding (1) decreases the risk of developing atopy to some degree, (2) increases the risk, or (3) has no effect. Many studies also differentiate between the effects of breast-feeding in high-risk versus low-risk infants. High risk for atopy is generally defined as either high cord blood IgE or a positive family history.

STUDIES SHOWING THAT BREAST-FEEDING PROTECTS AGAINST THE DEVELOPMENT OF ATOPY

In the late 1970s and 1980s, several studies comparing breast-fed to cow's milk formula-fed infants demonstrated a decreased incidence of atopic dermatitis,³² fewer episodes of wheezing,³² and lower serum IgE³³ in infants who were nursed. These studies varied in their conclusions whether this protective effect was relevant for all infants³⁴ or for high-risk infants only.³² One of these cohorts was the subject of a 17-year follow-up suggesting that the protective effect of breast-feeding could be demonstrated in a decreased risk of respiratory allergies in later childhood as well.³⁴ Lucas et al³⁵ performed the first randomized prospective study evaluating the role of breast-feeding in the prevention of allergy. A total of 446 premature infants were randomized to receive either cow's milk formula or banked human breast milk. Of infants with a positive family history of allergy, 41% had a chance of developing an allergic reaction by age 18 months if fed cow's milk formula, compared with 16% of those fed on breast milk. This difference was not demonstrated in the cohort taken as a whole. Although this was a particularly interesting group to study, because the delayed gut maturity in premature infants would itself be considered a risk factor for allergy, the conclusions were limited because of a lack of supporting immunologic data.

Several well designed studies have been published more recently and are summarized in Table II.³⁶⁻⁴² In evaluating data collected in a randomized study of 3903

TABLE II. Recent prospective birth cohort studies on effect of breast-feeding on atopy

Study	Birth cohorts	Comparison	Outcome, OR (95% CI)
Kramer et al ³⁶ (Belarus)	Unselected RC (n = 16,491)	BF support/promotion group vs controls (43% of intervention group was exclusively BF at 3 mo)	1-y AD: 0.54 (0.31-0.95)
Kull et al ^{37,38} (Sweden)	Observational (n = 773 vs 3013)	Sole BF ≥ 4 mo vs < 4 mo	(a) 2-y AD: 0.85 (0.7-1) (b) 2-y Asthma cumulative prevalence, 0.7 (0.5-0.8) (c) 4-y Asthma period prevalence, 0.72 (0.53-0.97)
Oddy et al ⁴² (Australia)	Observational (n = 2602)	Predominant BF ≥ 4 mo vs < 4 mo	1-y Wheeze and ≥ 2 acute visits: 0.6 (0.4-0.8)
Kerkhof et al ⁴⁰ (Netherlands)	High-risk RC (n = 708)	Sole BF ≥ 3 mo vs < 3 mo	1-y AD: 0.4 (0.2-1.0)
Laubereau et al ⁴¹ (Germany)	High-risk RC (n = 2030 vs 522)	Sole BF ≥ 4 mo vs cow's milk formula	AD in first 3 y: 0.64 (0.45-0.90)

AD, Atopic dermatitis; BF, breast-feeding; RC, randomized controlled study.

children as part of the German Infant Nutritional Intervention Program, Laubereau et al⁴¹ report that in those high-risk infants participating in an interventional study comparing hydrolyzed formulas to cow's milk formula, exclusive breast-feeding had a significant protective effect on the development of atopic dermatitis in the first 3 years of life compared with cow's milk. Two other recent large, prospective birth cohort studies, one Swedish³⁸ and one Australian,³⁹ demonstrated a lower risk of asthma at 4 and 6 years of age respectively in infants who were breast-fed exclusively for 4 months. A very large (17,046 infant-mother pairs) prospective, interventional study from Belarus was published in 2001³⁶ demonstrating a 46% reduction in the incidence of atopic dermatitis in infants whose mothers participated in a program designed to facilitate breast-feeding compared with infants whose mothers did not have such support. These infants were not necessarily exclusively breast-fed.

STUDIES SHOWING A NEUTRAL EFFECT OR THAT BREAST-FEEDING MAY INDUCE THE DEVELOPMENT OF ATOPY

Other studies in the 1970s and 1980s showed no protective effect could be demonstrated vis-à-vis the development of food allergy in breast-fed infants compared with their cow's milk formula-fed counterparts.⁴³⁻⁴⁶ One of these studies was limited by the lack of supporting immunologic data.⁴⁵

Some studies performed over the last decade have suggested that breast-fed infants have an increased risk of developing allergies compared with those fed cow's milk formula, particularly high-risk infants. For example, a recent prospective but nonrandomized German study⁴⁷ concluded that infants with high cord blood IgE were at higher risk of becoming sensitized to egg if they were breast-fed for greater than 5 months. In addition, in infants with both high cord blood IgE and a family history of

allergy, a higher incidence of atopic dermatitis was noted at 1 year of age in subjects who were exclusively breast-fed for this prolonged period. Other studies that have suggested that breast-feeding increases atopy are summarized in Table III⁴⁸⁻⁵³ along with comments related to potential methodological limitations.

The Multicenter Atopy Study, a long-term observational birth cohort of more than 1300 German children, addressed this issue.⁵² It reported an association between breast-feeding and an increased risk of atopic dermatitis occurring any time from birth to age 7 years (OR, 1.03; 95% CI, 1.00-1.06 for each additional month of breast-feeding, $P = .034$) after adjusting for confounders. The adverse association was noted for any (not just exclusive) breast-feeding of at least 1 month's duration, suggesting that an important maternal infant interaction may have occurred early postnatally through breast milk that promoted atopic dermatitis. The absence of a dose-response effect of breast-feeding duration in increasing atopic dermatitis risk raises concerns that a confounding factor not addressed adequately in the multivariate analysis might account for these divergent findings. One such factor noted by the authors and for which statistical adjustment attempts were made was the longer duration of breast-feeding by mothers in families with a parent with atopic dermatitis.

In support of the Multicenter Asthma Study was an observational study from New Zealand that enrolled at 3 years 62.5% (n = 1037) of a cohort previously taking part in a separate earlier neonatal study.⁵⁴ This study reported that breast-feeding for 4 weeks or longer was associated with a significantly increased risk of asthma at ages 9 to 26 years (OR, 1.8; 95% CI, 1.4-2.5;), $P < .0001$ and sensitization to aeroallergens at age 13 years (OR, 1.9; 95% CI, 1.4-2.6). Unfortunately, evaluations of this cohort were not performed before 9 years, depended on retrospective recall of breast-feeding histories at age 3 years, and lost nearly 40% of the original cohort to follow-up because of relocation to areas outside of the study's recruitment region by the time the study started. Peat

TABLE III. Studies reporting an increase in atopy with breast-feeding

Study	Cohort	Finding	Comment
Taylor et al ⁴⁸	13,135 British 5-y-olds	Any BF: increased AD	Recall bias
Kaplan and Mascie-Taylor ⁴⁹	14,000 British 7-y-olds	Any BF: increased asthma at 7 y	Recall bias
Rusconi et al ⁵⁰	16,333 Italian 6-7-y-olds	BF ≥ 6 mo: increased transient asthma; decreased late-onset asthma; no change in persistent asthma	FH not controlled Recall bias No control FH atopy
Wright et al ⁵¹	1246 Tucson birth cohort: birth-13-y-olds	BF ≥ 4 mo: increased recurrent wheeze at age ≥ 6 y	BF recall at 2 y Questionnaires
Bergmann et al ⁵²	1314 German children: birth-7-y-olds	> BF > AD to age 7 y: OR, 1.03 (1.02-1.06)	Parent AD > factor Nursery cow's milk common
Miyake et al ⁵³	5614 Japanese middle school children	BF first 3 mo: increased AD	Recall bias Only in high-risk
Sears et al ⁵⁴	1037 New Zealand birth cohort: 3-26-y-olds	BF 4 wk or longer: increased current asthma 9-26 y; + skin tests at 13 y	Recall bias (?) Lack of dose-response

AD, Atopic dermatitis; BF, breast-feeding; FH, family history.

et al⁵⁵ evaluated the study and noted design limitations that could have confounded the findings. These included (1) infrequent exclusive breast-feeding practices and frequent intact cow's milk ingestion in the nursery, (2) no interaction by atopic family history, (3) absence of a dose-response, and (4) biased early recall of feeding patterns in infancy because the cohort was enrolled at age 3 years. Sears et al⁵⁶ rebutted many of the criticisms but agreed with items 1 to 3. He presented evidence that maternal recall was corroborated more than 98% of the time with nurse home visit records obtained in the earlier neonatal study. The potential confounding effect of evaluating only 60% of the original cohort may also be a factor, as noted. Notwithstanding the above criticisms, Sears et al⁵⁶ raise potentially important issues that can be addressed if many of the observational and interventional studies reporting a reduced risk of atopy associated with breast-feeding (Table III) continue following their cohort to later childhood.

BREAST-FEEDING BY MOTHERS WITH ASTHMA

In recent years, a new concern has been raised regarding breast-feeding by atopic mothers. Breast milk from atopic women has been noted to contain higher levels of IL-4, IL-8, RANTES, IgE, and n6/n3 polyunsaturated fatty acids, all thought to induce sensitization to allergens in the infant recipient. On the other hand, TGF- β 1 and TGF- β 2 levels, which are thought to protect against the development of allergies, are no higher in these mothers.⁵

Clinical concerns were raised by Wright et al⁵¹ as part of the Tucson Children's Respiratory Study, a prospective longitudinal study of 1246 newborns. Although in the first 2 years of life, exclusive breast-feeding was associated with a significantly lower rate of wheezing irrespective of maternal asthma, beginning at 6 years of age, exclusive breast-feeding was related to a higher rate of asthma in atopic children of mothers with asthma.

On the other hand, an Australian study³⁹ found no statistically significant correlation between maternal asthma and the development of subsequent asthma on the breast-fed child (Fig 1). Because both of these studies demonstrated an overall protective effect of breast-feeding on the development of atopy and asthma in early childhood, at this time, breast-feeding should still be encouraged, even by the mother with asthma.

CRITICAL EVALUATIONS AND META-ANALYSES OF PUBLISHED DATA

A large, critical review of the literature from 1966 to 2001 by van Odjik et al⁵⁷ was published in 2003. A total of 4323 articles were reviewed, and more than 90% were excluded as noninformative. Fifty-six were considered conclusive and were analyzed. Retrospective and prospective studies were included in the analysis, but exposures and health effects had to be recorded and relevant, cohort selection had to be satisfactory, and the statistics had to be adequate. The studies were reviewed by committee, not by meta-analysis. In this analysis, the committee found that exclusive breast-feeding reduced asthma risk, and that any breast-feeding reduced recurrent wheeze for at least the first decade in all children, regardless of atopic risk. This protection increased with duration of breast-feeding as long as 4 months. Breast-feeding was also determined to protect against atopic dermatitis in infancy but not atopy in later life. Furthermore, this protection was found to be even greater in children at high risk for atopy and lowered the risk of cow's milk allergy in this population.

Because of the contradictory nature of so much of the published data, all of the prospective studies in developed countries that examined the effect of breast-feeding on the development of atopic dermatitis⁵⁸ and asthma⁵⁹ from 1966 to 2000 in which certain criteria of validity were met were the subject of a recent meta-analysis. Accepted studies noted (1) blinded maternal feeding history recall of

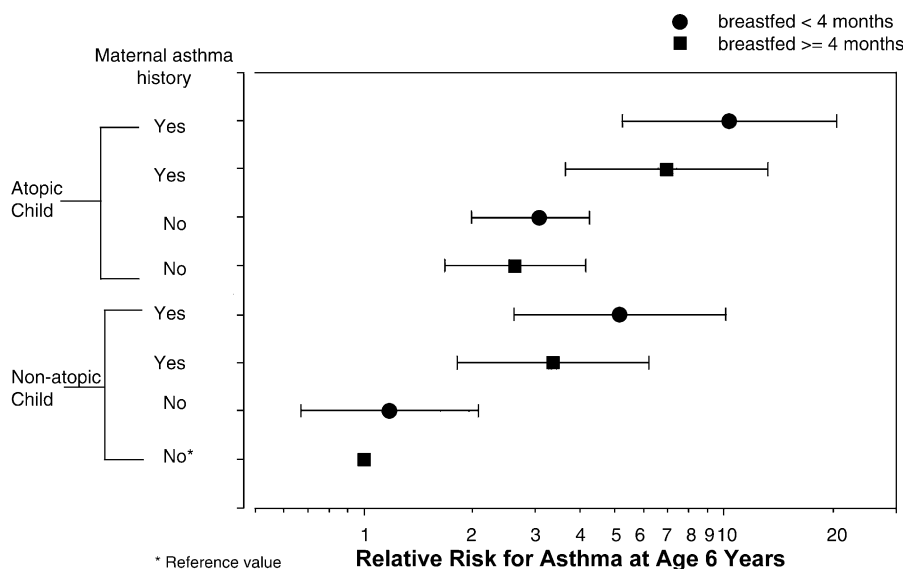


FIG 1. Data suggesting that maternal asthma does not affect the protective effect of breast-feeding on doctor diagnosis of asthma at 6 years in an Australian birth cohort of 2602 infants. Reprinted with permission.³⁹

less than 12 months, (2) duration of any breast-feeding and of exclusive breast-feeding for at least 3 months, (3) strict diagnostic outcomes, (4) blind assessments, (5) time of onset of disease, and (6) control for confounding factors and effects in high-risk children. The meta-analyses evaluated only prospective studies in developed countries. They included 18 studies of more than 4000 subjects with a mean follow-up of 4.5 years (1-5 years) for the analysis of atopic dermatitis⁵⁸ and 12 studies of more than 8000 subjects with a mean follow-up of 4.1 years (1-8.4 years) for the analysis of asthma.⁵⁹ This statistical analysis revealed a significant protective effect of breast-feeding on the development of atopic dermatitis in the cohort as a whole (OR, 0.77; 95% CI, 0.60-0.98) and especially in children at higher risk for atopy (OR, 0.58; 95% CI, 0.41-0.92).⁵⁸ No protective effect was demonstrated in the children at low risk for atopy when evaluated separately (Fig 2, A). Similarly, in a related meta-analysis published by the same group, exclusive breast-feeding for the first 3 months of life offered protection against the development of childhood asthma in those children at high risk for atopy, but not in those at low risk (Fig 2, B).⁵⁹ In contrast, a meta-analysis that evaluated exclusive breast-feeding for at least 3 months on the development of allergic rhinitis failed to show a significant protective effect in the entire cohort of children or those with a family history of atopy. This last analysis was rather futile because of the few studies ($n = 6$), the young age of the children (mean age, 2.4 years), the high frequency of upper respiratory illnesses at this age, the diagnostic limitations, and the usual onset of allergic rhinitis after age 3 years.⁶⁰

In evaluating these publications, it seems clear that the better designed studies as determined by the meta-analysis demonstrate that breast-feeding does protect against the development of atopic dermatitis in infants and may

protect against the development of wheezing illnesses to at least 4 years of age. It is not clear whether it protects against sensitization to allergens or whether it leads to any long-term benefits in preventing respiratory allergies later in life.

DURATION OF BREAST-FEEDING

If not breast-feeding is associated with an increase in the development of atopic disease, then how long should exclusive breast-feeding be continued to mitigate this consequence? In 1983, Kajosaari and Saarinen⁶¹ demonstrated a clear benefit of withholding solid foods in solely breast-fed infants for 6 months as opposed to only 3 months as measured by 1 year cumulative prevalence of eczema. This benefit appeared to be lost by 5 years of age.

More recently, the results of a Swedish prospective birth cohort study demonstrated by 2 years of age a significant decrease in wheezing (OR, 0.78; 95% CI, 0.65-0.93), asthma diagnosis (OR, 0.66; 95% CI, 0.51-0.87), atopic dermatitis (OR, 0.8; 95% CI, 0.7-1.0), and multiple allergic manifestations (OR, 0.66; 95% CI, 0.48-0.90) in infants breast-fed for ≥ 4 months as opposed to infants who breast-fed for a shorter period (Fig 3).³⁷ Furthermore, an additional protective effect was seen in children with a family history of atopy who breast-fed for 6 months. Oddy et al⁶² reported in an Australian birth cohort study that the cumulative incidence of wheeze was higher and the age of asthma diagnosis lower if exclusive breast-feeding were continued for less than 4 months compared with 4 or more months (Fig 4).

Studies such as these have led the AAP² and ESPACI/ESPGHAN³ to recommend exclusive breast-feeding for 6 months or 4 to 6 months, respectively.

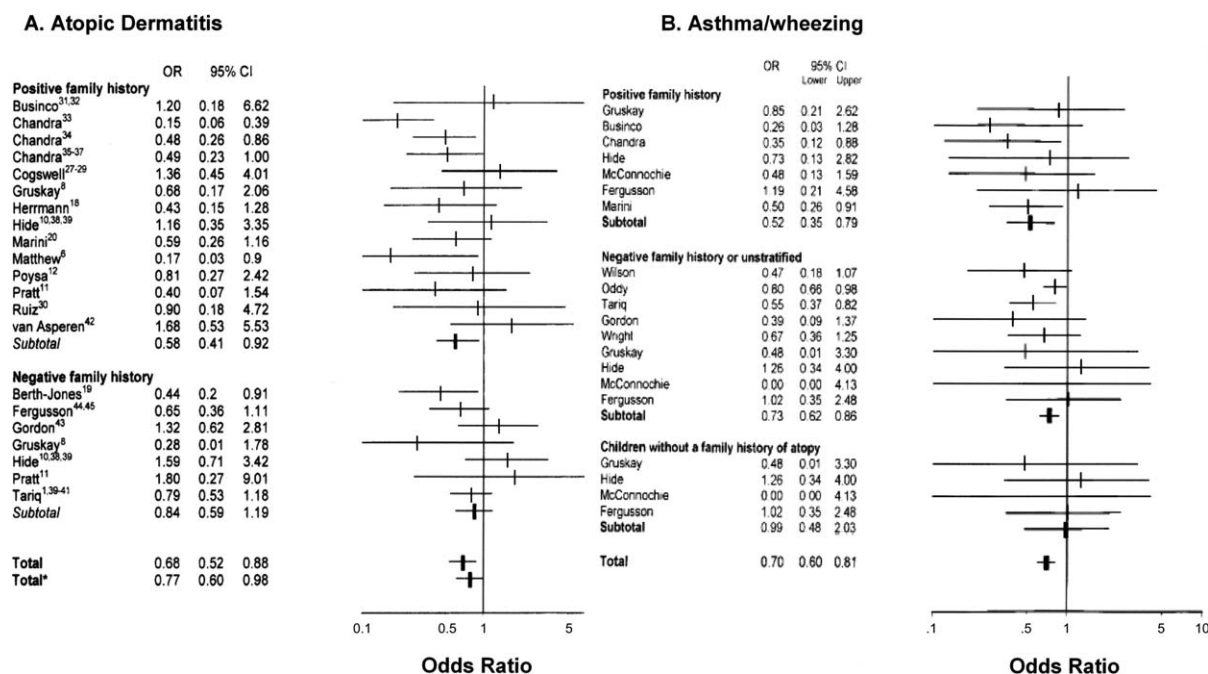


FIG 2. Meta-analyses of studies demonstrating a protective effect of exclusive breast-feeding compared with cow's milk feeding on the development of atopic dermatitis/eczema (**A**) (*analyses after exclusion of studies with unblinded outcomes; numbers next to authors refer to references in original article; reprinted with permission from the American Academy of Dermatology, Inc⁵⁸) and asthma/wheezing (**B**) (reprinted with permission from Mosby, Inc⁵⁹) in infants with allergic parents.

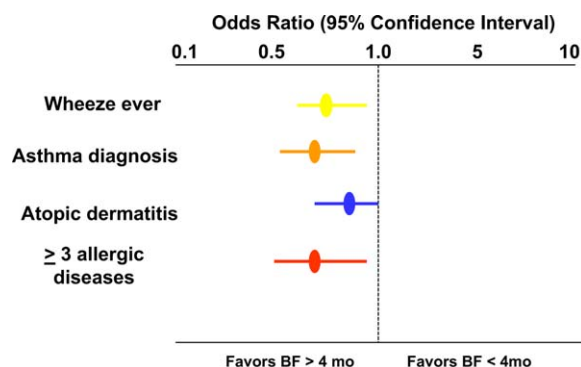


FIG 3. Demonstration of favorable OR ratio suggesting positive effect of allergy prevention at age 2 years with prolonged duration of exclusive breast-feeding (BF) in a Swedish birth cohort of 4089 infants followed for 2 years.³⁷

MATERNAL AVOIDANCE DIETS DURING LACTATION

In searching for an explanation for the wide variety of results demonstrated in decades of studies evaluating the role of breast-feeding in the development of atopy, a logical suggestion has been that the presence of food antigens in breast milk might sensitize the infant if the mother does not avoid these foodstuffs in her diet during lactation. It is also invoked as a potential exposure route

responsible for the development of atopic disease and sensitization in approximately 6% of exclusively breast-fed infants.⁴⁴ However, results of studies in the 1980s and 1990s examining this hypothesis have been just as contradictory, making definitive recommendations elusive.

In 1989, 2 studies were published^{63,64} suggesting that hypoallergenic lactation diets might lead to protection against atopic disease in infants. One, by Hattevig et al,^{63,65} studied 2 groups of high-risk infants. Both groups were breast-fed and their diets supplemented with protein hydrolysate formula. The study group consisted of infants of mothers who avoided egg, cow's milk, and fish in the first 3 months of lactation, whereas the mothers of infants in the control group had no restrictions in their diets. The infants in the study group were noted to have significantly less atopic dermatitis than the control group infants. IgE levels to milk and egg did not differ in the 2 groups at 6 months of age, thought to be a result of the fact that these foods were introduced into the maternal diets before then. A 10-year follow-up study⁶⁵ showed no long-lasting effect on the development of allergic disease in those children whose mothers followed the restrictive diet. Chandra et al⁶⁴ reported similar findings in a prospective, randomized controlled study. The incidence of atopic dermatitis was less than half by 18 months in infants whose mothers avoided egg, milk, soy, peanut, and fish during lactation compared with infants whose mothers did

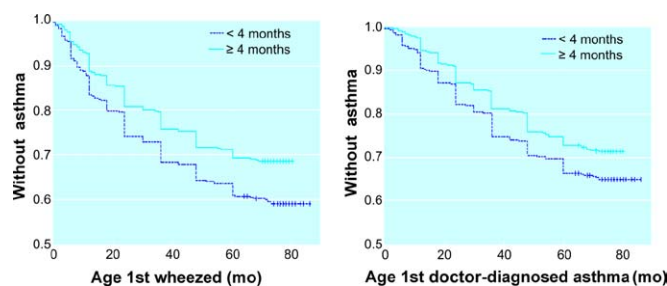


FIG 4. Kaplan-Meier analyses for (left) age of first symptomatic wheeze and (right) age of diagnosis of asthma, stratified by duration of exclusive breast-feeding in an Australian birth cohort of 2187 infants followed for 6 years. Reprinted with permission.⁶²

not follow this lactation diet. No confirmatory immunologic data were presented.

To the contrary, in a nonrandomized but controlled study, Herrmann et al⁶⁶ demonstrated no protective effect on the development of atopy in infants whose mothers avoided egg and milk during 3 months of lactation. Furthermore, Pollard et al⁶⁷ actually demonstrated an increased incidence of atopic dermatitis and food sensitization in infants of mothers on avoidance diets.

Unfortunately, the number of studies has been too small for a recent Cochrane meta-analysis⁶⁸ to yield definitive results, although overall, data suggest a positive effect of maternal elimination diets on the development of atopic dermatitis during the first 12 to 18 months of life. It should be kept in mind that although such a diet can be safely used in a nursing mother if care is taken to ensure her proper nutrition, adherence to such a diet is extremely difficult and impractical in most cases. Furthermore, one still cannot say for certain whether food antigens in breast milk will induce allergy or be immunoprotective in any given recipient.

Potentially confounding the reported added benefit of lactation avoidance diets to breast-feeding is the possibility of food sensitization through dermal food exposure. If dermal food sensitization were a real phenomenon, then a maternal lactation diet could be beneficial not only because of a lower concentration of food allergens in breast milk but also because of reduced direct contact of food allergens on mother and secondarily on infant. Proof of principle of primary IgE food sensitization through dermal food exposure was shown recently in a murine food allergy model.⁶⁹ A similar phenomenon may be functional in human beings. The Avon longitudinal study of nearly 16,000 children reported that peanut allergy in children was independently associated with oozing skin rash and the use of skin care products containing peanut oil and not at all associated with maternal ingestion of peanut products during lactation.⁷⁰

PROBIOTICS IN BREAST-FEEDING

In recent years, immunomodulation is being explored as a means of preventing atopy. The administration of

probiotics or lactobacilli, nonpathogenic organisms which have been known to protect the gut against colonization with pathogens, is being evaluated as a means to encourage a T_H1-predominant immune system. Kalliomaki et al⁷¹ have reported a decrease in atopic dermatitis in infants whose mothers were given probiotics 4 weeks prepartum and during lactation. A concomitant decrease in total serum or food specific IgE was not demonstrated. However, an increase in TGF- β 2 levels in breast milk was reported.⁷² Much more research would be required before the use of probiotics could be recommended as an adjunct to breast-feeding in an effort to affect the development of allergies in infants.

SUPPLEMENTAL HYPOALLERGENIC FORMULAS

In evaluating the role of breast-feeding in the prevention of atopy, it is necessary also to examine the role of formulas that are so frequently used in supplemental infant feeding. Extensively hydrolyzed formulas were first developed 60 years ago and have been an extremely important way of feeding infants with malabsorption, milk intolerance, and milk allergy. An ideal hydrolyzed formula should contain no peptides larger than 1.5 kd and no intact proteins, and should show protein determinate equivalents less than 10⁵ to 10⁶ of the original protein. Moreover, it should demonstrate no anaphylaxis in animals and should be shown to be safe in infants with cow's milk allergy in both double-blind, placebo-controlled food challenge and open challenge.⁷³

Three extensively hydrolyzed casein hydrolysate formulas are currently widely available in the United States: Alimentum (Ross Products, Abbott Laboratories, Columbus, Ohio), Nutramigen (Mead Johnson Nutritionals, Evansville, Ind), and Pregestimil (Mead Johnson Nutritionals, Evansville, Ind). These formulas have small enough peptides and have been shown to be sufficiently safe in children with cow's milk formula to be considered hypoallergenic.⁷⁴

There is enough rationale that these formulas might be a natural adjunct to breast-feeding in a regimen designed for allergy prevention. The concentration of β -lactoglobulin

in these extensively hydrolyzed formulas is similar to that of breast milk,⁷⁵ and they are nutritious and well tolerated. Numerous studies have demonstrated their effectiveness in this regard.^{76,77} A Cochrane meta-analysis found significant evidence that feeding with hydrolyzed formula reduces infant allergies compared with feeding with cow's milk formula (OR, 0.63; 95% CI, 0.47-0.85).⁷⁸

However, although infants tend to accept these formulas fairly readily when they are introduced to their diet before they develop a taste for more allergenic formulas, palatability and cost remain limiting factors in widespread use of extensive hydrolysates in allergy prevention. For this reason, partially hydrolyzed formulas such as Good Start (NanHA outside the United States; Nestle, Vevey, Switzerland) have been developed. This formula has numerous peptides >4 kd and can cause allergic reactions in 40% to 60% of children with cow's milk allergy and are contraindicated for use in individuals with cow's milk allergy.⁷⁹ However, partial hydrolysates have been shown to be somewhat effective in allergy prevention, although generally less so compared with extensively hydrolyzed formulas.^{76,77} An in-depth discussion of the results of the numerous studies examining the role of both extensively and partially hydrolyzed formulas in the development of atopy is beyond the scope of this article, but several deserve mention.

In 1993, in a well-controlled study, Halcken et al⁷⁶ reported a similar incidence of cow's milk allergy in children fed an extensively hydrolyzed formula and children who were breast-fed. Several recent European studies have examined the effects of extensively and partially hydrolyzed formulas on allergy prevention.^{77,80} All have shown superiority of extensively hydrolyzed formula over partial hydrolysates. However, in a randomized, double-blind interventional study,⁸⁰ an extensive casein hydrolysate and a partial whey hydrolysate formula were found to be superior to an extensive whey hydrolysate in the prevention of allergic manifestations in infants with a family history of atopic dermatitis but still inferior to an extensively hydrolyzed casein formula. The authors speculated that this unexpected finding may have been caused more by the method of hydrolysis used to produce the extensive whey hydrolysate than by the actual degree of hydrolyzation. The AAP recommends a hypoallergenic formula or possibly a partial hydrolysate formula, and ESPACI/ESPGHAN recommend a formula with confirmed reduced allergenicity for allergy prevention if exclusive breast-feeding is not practiced. There may be greater support for extensively hydrolyzed products at this time for allergy prevention, but their greater expense and lower palatability have limited their use, leading in practice to the use of partially hydrolyzed products as an alternative. Furthermore, large, independent, multicenter, head-to-head comparative studies of extensive and partial protein hydrolysates would help to determine which one should be the first choice for allergy prevention in high-risk infants.

Hypoallergenic, extensively hydrolyzed formulas (and certainly partial hydrolysates) cannot be considered non-

allergenic. Allergic reactions have been reported with extensively hydrolyzed formulas in children with cow's milk allergy,^{81,82} and residual allergenicity has been demonstrated by ELISA inhibition assays using mAbs to milk proteins.⁸² Elemental, amino acid-based formulas such as Neocate (SHS International, Rockville, Md) and EleCare (Ross Products, Abbott Laboratories) may be safe in most patients who cannot tolerate protein hydrolysate formulas and are an excellent source of nutrition for highly allergic youngsters.⁸³ However, high cost and low palatability limit their potential use in an allergy prevention regimen.

CONCLUSION

It is widely accepted that breast-feeding is the ideal form of infant nutrition. Breast milk is highly nutritious, and the psychological benefits of mother-infant bonding that occur through nursing are myriad. However, despite decades of research and the fact that the AAP² and ESPACI/ESPGHAN³ recommend breast-feeding as part of an allergy prevention program, 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. The preponderance of evidence does suggest that, overall, exclusive breast-feeding for at least 4 months seems to protect against the development of atopic dermatitis in infants and early childhood wheezing.

This brings us back to our original question. What do we have to lose by not recommending breast-feeding? Even if, as some studies suggest, breast-feeding might sensitize some children to more allergenic foods at an early age, other studies suggest it is protective. Though we are not yet at a point where we can accurately predict which of these outcomes is more likely on a case by case basis, the clinical benefits cannot be overlooked. To suggest that this chance of sensitization would be a reason to forego the nutritional, psychological, and other immunological benefits of breast-feeding would be unwise. Breast-feeding should be encouraged for infants both at high risk and low risk for atopy. It should also be recommended irrespective of maternal history of asthma.

Draconian maternal lactation diets in which mothers are asked to forego all dairy and egg products should be reconsidered, because there is probably little place for recommending such a diet to lactating mothers at this time. Perhaps mothers should be encouraged to avoid peanuts, because they might be sensitizing to an infant via direct absorption through the skin rather than through the breast milk itself.

Extensively hydrolyzed formulas should be encouraged as supplements to breast milk in high-risk infants, if necessary. Partially hydrolyzed formulas may be a reasonable substitute because of their palatability and lower cost, but more studies must be conducted to confirm this.

As such, consistent with the tenets of not interfering with Mother Nature and at the same time attempting to do no harm with interventions, exclusive breast-feeding for 4 to 6 months should remain the keystone for promoting

allergy health, as recommended by the AAP² and ESPACI/ESPGHAN.³

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