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No definitive blood, pulmonary function, or other tests can definitively establish a diagnosis of these allergic atopic diseases

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Breastfeeding and Allergy: The Evidence

by Michael S. Kramer

Key insights

Although exclusive breastfeeding (EBF) confers a risk reduction for atopic dermatitis during infancy, no clear risk reduction is observed for asthma, allergic rhinitis, positive allergen skin tests, or food allergy. Interactions between specific allergy-promoting genes and infant feeding, as well as the effects of other nutritional and environmental exposures, need to be carefully explored.

Current knowledge

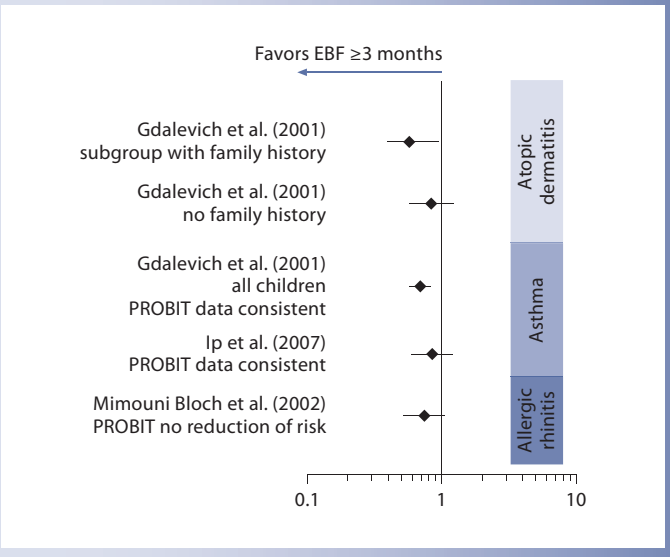
Early and limited studies on the links between breastfeeding and allergic disease have fuelled debate. Furthermore, bias, misclassification and other methodological issues complicate the analysis and interpretation of such infant feeding studies. The robust PROBIT trial demonstrated a protective effect of a breastfeeding promotion intervention on reducing the risk of atopic dermatitis during infancy. More evidence is required for other atopic diseases.

Practical implications

The evidence supports that EBF ≥3 months confers a protective effect against atopic dermatitis during infancy. Future studies need refinement in the classification and methodological issues in order to improve our understanding of the mechanisms involved in each of the different allergic diseases.

Recommended reading

Kramer MS, Matush L, Vanilovich I, Platt RW, Bogdanovich N, Sevkovskaya Z, et al: Effect of prolonged and exclusive breast feeding on risk of allergy and asthma: cluster randomised trial. BMJ 2007;335:815–820.



Summary OR are shown, except for the randomized trial by Kramer et al. (cluster-adjusted OR) in Belarusian children (see text for details).

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Breastfeeding and Allergy: The Evidence

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Key Messages

- **Exclusive breastfeeding for at least 3 months reduces the risk of atopic dermatitis, at least during infancy.**
- **No clear risk reduction is evident, however, for asthma, allergic rhinitis, positive allergen skin tests, or food allergy.**
- **Future epidemiologic and basic laboratory research should explore interactions between specific allergy-promoting genes and infant feeding, as well as effects of other nutritional (e.g. specific micronutrients) and environmental exposures on the risk of allergic disease.**

Key Words

Allergic rhinitis · Allergy · Asthma · Atopic dermatitis · Atopy · Breastfeeding · Eczema · Food allergy · Hay fever · Infant formula

Abstract

Whether breastfeeding protects against the development of allergic disease has been a frequent subject of study and debate for 75 years. This paper summarizes the published evidence concerning the risks of atopic dermatitis, asthma, allergic rhinitis, positive allergen skin tests, and food allergy associated with infant feeding. The summary is based largely on systematic reviews and meta-analyses carried out by other authors. In addition, I also incorporate the evidence from our long-term follow-up of Belarusian children participating in a cluster-randomized trial of a breastfeeding promotion intervention.

Introduction

Whether breastfeeding protects against the development of allergic disease has been a frequent subject of study and debate for 75 years [1–3]. With the renaissance of breastfeeding beginning in the 1970s, a number of studies reported lower risks of atopic eczema (atopic dermatitis), asthma, hay fever, and positive allergy skin tests in breastfed children, or equivalently, higher risks in infants fed conventional cow milk- or soy-based formulas [4–10]. Many of those studies reported a greater degree of protection with more exclusive and/or more prolonged breastfeeding [8–14], and several found larger effects in atopy-prone children, usually defined by a first-degree family member (mother, father, or sibling) with one or more atopic diseases [4, 5]. Some studies, however, have shown either no risk reduction or even a risk increase with breastfeeding [4–6, 15, 16].

In this paper, I summarize the published evidence concerning the risks of allergic diseases associated with infant feeding, largely based on systematic reviews and meta-analyses carried out by other authors [4–6, 17]. In addition, I also incorporate the evidence from our long-

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term follow-up of Belarusian children participating in a cluster-randomized trial of a breastfeeding promotion intervention.

Methodological Issues

Methodological challenges are inevitable when designing, analyzing, and interpreting observational studies of health outcomes in relation to infant feeding. Although some of these challenges are generic, several particular methodological issues arise when studying atopic disease (table 1). For example, misclassification of infant feeding based on different degrees or durations of breastfeeding is common to all studies relating health outcomes to infant feeding, but it is even more of a problem for atopic disease, because it is difficult to hypothesize what degree of exclusivity or duration may be necessary to provide a protective effect. On the one hand, even a small amount of a foreign protein antigen such as cow milk or soy protein could theoretically sensitize an infant to those antigens. On the other hand, the relationship between the development of allergic disease and sensitization to cow milk, soy, or other foreign antigens contained in infant formulas remains unclear [18]. The role of immunologic tolerance, whereby early introduction of antigens in sufficient doses actually reduces hypersensitivity to the same antigens later in infancy or childhood, further complicates the interpretation of a graded (dose-response) effect [19, 20].

Another methodological issue concerns the diagnosis of the atopic conditions themselves. As most pediatricians and family physicians are well aware, not every child who itches has atopic dermatitis, not every child who wheezes has asthma, and not every child who sneezes has hay fever. No blood, pulmonary function, or other tests can definitively establish a diagnosis of these allergic atopic diseases. This problem results in heterogeneity in the phenotypes represented by infants classified as having atopic diseases among the various studies carried out at different times in the past. Moreover, the potential for biased diagnosis is considerable in prospective (cohort) studies in which the physician making the diagnosis is aware of the infant feeding history. Retrospective (case-control) studies are not immune to this problem either, because knowledge of the presence or absence of allergic disease can influence (even if unconsciously) ascertainment of the infant feeding history.

As mentioned earlier, several early studies have reported effect modification, i.e. greater or lesser protective effects of breastfeeding in infants at high versus low risk of atopic disease (based on family history) [4–6, 21]. If true, the effects of infant feeding in studies restricted to children at high risk of allergic disease may yield different results from those of studies in which low-risk children, or a mixture of children at high and low risk, are included.

A final and important methodological issue is publication bias: preferential submission and acceptance of papers with 'positive' findings, i.e. reports of increased risks in children who were fed formula. There is simply no way to know how many negative studies were never submitted for publication or were rejected despite their authors' repeated submissions. This potential for publishing positive findings will inevitably lead to an inherent bias in the published evidence base.

Many of the above-noted methodological issues could theoretically be overcome through the use of a randomized controlled trial design. However, it is not feasible, and is probably unethical, to randomize mothers and their infants to breast- versus artificial feeding, or even to different durations or degrees of breastfeeding. On the other hand, randomization to a breastfeeding promotion intervention is both feasible and ethical. Trials attempting to influence the initiation of breastfeeding versus formula feeding are somewhat less feasible, because the mother's initial feeding choice is usually made well before the birth, and sometimes even before the pregnancy. Moreover, that choice is influenced by many persons, including the future mother's parents, other relatives, parents-in-law, partner, friends, and health care professionals.

Trials attempting to influence the initiation of breastfeeding versus formula feeding are somewhat less feasible, because the mother's initial feeding choice is usually made well before the birth, and sometimes even before the pregnancy.

Implementing a randomized controlled trial of an intervention to promote breastfeeding exclusivity and duration, rather than initiation, is far more practical. If the intervention is successful in increasing the exclusivity and duration of breastfeeding and yields two groups (experimental vs. control) with substantially different durations and degrees of breastfeeding, analysis by intention-to-treat (i.e. according to randomized group, rather than

Table 1. Methodological challenges in studies involving infants/children

Challenge	Particularities of atopic disease
Misclassification of infant feeding (degree/duration of breastfeeding)	Difficult to hypothesize what is required to provide a protective effect
Exclusivity vs. use of formulas	The relationship between the development of allergic disease and foreign protein antigen is unclear (e.g. dose/tolerance)
Diagnosis of atopic disease	Heterogeneity in the phenotypes of infants classified as having atopic diseases; potential for biased diagnosis in prospective (cohort) studies
Effect modification	High vs. low risk of disease, definition
Publication bias	Applicable to all studies
Ethical issues and choice	Applicable to all studies

Table 2. ISAAC results: number (%) positive and OR (95% CI) for experimental versus control groups

Question	Experimental (n = 7,101)	Control (n = 6,763)	Cluster-adjusted OR (95% CI)
Ever wheezing	778 (11.0)	651 (9.6)	1.1 (0.6–1.8)
Wheezing: last 12 months	238 (3.4)	188 (2.8)	1.0 (0.7–1.6)
Ever had asthma	97 (1.4)	68 (1.0)	1.2 (0.7–1.9)
Ever had hay fever symptoms	384 (5.4)	257 (3.8)	1.1 (0.6–1.9)
Hay fever symptoms: last 12 months	262 (3.7)	192 (2.8)	1.0 (0.6–1.8)
Recurrent itchy rash	350 (4.9)	241 (3.6)	1.3 (0.7–2.2)
Ever had eczema	69 (1.0)	72 (1.1)	1.0 (0.5–1.8)

feeding actually received), combined with a large sample size, should enable a rigorous assessment of the effect of differences in breastfeeding exclusivity and duration on atopic disease outcomes. This is the strategy we used in PROBIT (Promotion of Breastfeeding Intervention Trial) [22, 23], the methods and results of which are summarized in more detail below.

Atopic Dermatitis

A systematic review and meta-analysis of cohort (prospective) studies carried out by Gdalevich et al. [4] in 2001 and further reviewed by Ip et al. [17] showed a large and statistically significant risk reduction in atopic dermatitis with exclusive breastfeeding (EBF) for ≥3 months. The risk reduction was more pronounced in children with a first-degree positive family history of atopic disease [pooled odds ratio (OR) 0.58, 95% confidence interval (CI) 0.41–0.92] than in those not restricted to those with a positive family history [OR 0.84 (0.59–1.19)]. The impressive results in high-risk children are likely to be biased, however, by the inclusion of the three studies by Chandra et al. [3, 24–28] – all of which reported large and statistically significantly increased risks in artificially fed infants – since their work has been clouded by suspicion of data fabrication.

The detailed methods of PROBIT have been previously reported [22]. It is a cluster-randomized trial of a breastfeeding promotion intervention modeled on the World Health Organization/United Nations International Children's Emergency Fund Baby-Friendly Hospital Initiative, which was developed to promote and support breastfeeding, particularly among mothers who choose to initiate breastfeeding [29]. The units (clusters) of randomization were maternity hospitals and one affiliated polyclinic (outpatient clinic where children are followed for well child and illness care) for each hospital, with double randomization based on both a random number table

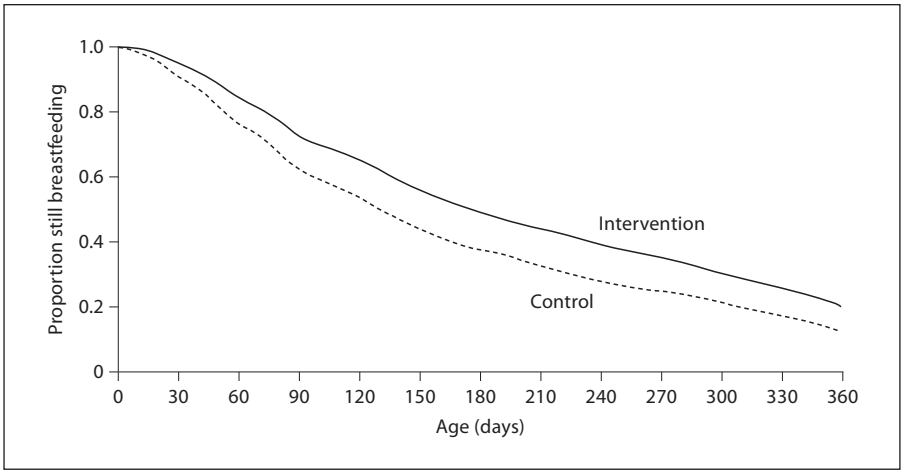

Fig. 1. Proportion of intervention and control infants in PROBIT who continued to breastfeed (to any degree) during the 1st year of follow-up (reproduced with permission [22]).

and a coin flip. The control maternity hospitals and polyclinics continued the practices and policies in effect at the time of randomization.

We recruited 17,046 mothers and healthy breastfed infants from 31 maternity hospitals/polyclinics during their postpartum stay; all infants were born in 1996 or 1997, weighed at least at 2,500 g at birth, and had completed at least 37 weeks of gestation. The children were followed up at 1, 2, 3, 6, 9, and 12 months of age, when polyclinic pediatricians completed a data form containing detailed information about infant feeding; measurements of weight, length, and head circumference, and the occurrence of symptoms of gastrointestinal or respiratory tract infection, rash, and other illnesses since their previous visit. As shown in figure 1, the experimental intervention led to a substantial difference in the duration of any breastfeeding that was maintained throughout the 1st year of life. In addition, the prevalence of EBF was 7-fold higher in the experimental group at 3 months (43.3 vs. 6.4%, $p < 0.001$), although was low in both groups at 6 months (7.9 vs. 0.6%, $p = 0.01$) [22]. The cluster-adjusted hazard ratio for weaning was 0.70 (95% CI 0.59–0.83), and for discontinuation of EBF was 0.29 (0.19–0.46).

Rashes were classified as atopic dermatitis if they lasted at least 2 weeks or recurred after clearing for at least 1 week, were itchy, and occurred on the face and/or extensor surfaces of the arms and/or legs [22]. A rash meeting the criteria for atopic dermatitis occurred in 3.3% of the infants in the experimental group versus 6.3% of those in the control group, for a cluster-adjusted OR of 0.54 (0.31–0.95). Somewhat surprisingly, we also found a protective effect against rashes that did not meet the criteria for atopic dermatitis [9.9 vs. 13.5%; cluster-adjusted OR 0.59 (0.38–0.92)], suggesting that many of those rashes may also have been atopic [22].

When children in PROBIT were followed up at age 6.5 years, questions related to the presence or absence of atopic dermatitis (recurrent itchy rash and ever having had eczema) were taken from the International Study of Asthma and Allergy in Childhood (ISAAC) questionnaire [30]. Positive responses on these two questions were reported in 4.9 versus 3.6 and 1.0 versus 1.1% of the experimental versus control children, respectively; neither difference was statistically significant (table 2) [23]. Because these questions were based on parental recall, however, and the percentages were quite low, the absence of a significant difference between the 2 groups based on the questionnaire may well reflect a less valid assessment compared with the symptom-based checklist completed by the pediatrician during study visits in the 1st year of life, as reported above.

Asthma

The systematic review by Gdalevich et al. [5] of prospective (cohort) studies relating infant feeding to asthma in childhood reported a summary OR of 0.70 (95% CI 0.60–0.81) for the protective effect of EBF for ≥3 months. Once again, the effect appeared somewhat greater in children with a positive family history [summary OR 0.52 (0.35–0.79)] than in those without such a history [0.73 (0.62–0.86)].

As with the meta-analysis of studies of atopic dermatitis, however, the results for asthma in children with a positive family history are likely to be biased by inclusion of the study by Chandra and Hamed [26], which is sus-

Table 3. PROBIT SPT results: number (%) positive and OR (95% CI) for experimental versus control groups

Antigen	Experimental (n = 5,551)	Control (n = 5,595)	OR (95% CI)
House dust mite	805 (14.5)	603 (10.8)	1.1 (0.5–2.4)
Cat	648 (11.7)	491 (8.8)	1.2 (0.5–2.8)
Birch pollen	526 (9.5)	393 (7.0)	1.2 (0.5–2.9)
Mixed northern grasses	712 (12.8)	491 (8.8)	1.0 (0.5–2.3)
Alternaria	480 (8.6)	340 (6.1)	1.5 (0.5–4.4)
≥1 positive test	1,496 (27.0)	1,013 (18.1)	1.2 (0.5–2.6)

pected to be based on fabricated data. The updated meta-analysis by Ip et al. [17], which excluded the Chandra and Hamed [26] study but included several more recent studies published since the meta-analysis of Gdalevich et al. [5], yielded a nonsignificant summary OR associated with EBF ≥3 months of 0.86 (95% CI 0.62–1.18).

In PROBIT, our diagnosis of asthma was based on the ISAAC questionnaire administered at the 6.5-year follow-up. The ISAAC questions relating to asthma included questions on whether the child had ever wheezed, whether the child had wheezed in the previous 12 months, and had ever had asthma [30]. The cluster-adjusted OR (experimental vs. control groups) for positive responses to these 3 questions were 1.1 (0.6–1.8), 1.0 (0.7–1.6), and 1.2 (0.7–1.9), respectively (table 2) [23]. These results are thus consistent with those of the updated meta-analysis by Ip et al. [17] and do not suggest a protective effect of breastfeeding against asthma.

Allergic Rhinitis

Mimouni Bloch et al. [6] carried out a meta-analysis of studies relating the effect of EBF ≥3 months and the subsequent risk of allergic rhinitis (hay fever). Only a small number of studies was found reporting on this outcome. A nonsignificant protective effect was found [summary OR 0.74 (95% CI 0.54–1.01)]. In fact, the effect actually appeared to be stronger in unselected children [summary OR 0.68 (0.47–0.99)] than in those with a positive family history [OR 0.87 (0.48–1.58)]. Of note, Chandra's studies [24–28] did not report on this atopic outcome.

In PROBIT, the relevant questions from the ISAAC questionnaire related to ever having had hay fever symptoms and hay fever symptoms in the 12 months prior to the interview (table 2). No risk reduction was seen in the intervention group [cluster-adjusted OR 1.1 (0.6–1.9) and 1.0 (0.6–1.8), respectively] [23].

Positive Allergen Skin Tests

To my knowledge, no systematic review or meta-analysis has been published with respect to studies of atopic sensitization, based on observed hypersensitivity to cutaneous administration of common allergens. In our PROBIT follow-up at 6.5 years, we carried out skin prick tests (SPTs) to 5 inhalant antigens: house dust mite, cat, birch pollen, mixed northern grasses, and *Alternaria* [23]. Saline was included as a negative control and histamine (1 mg/ml) as a positive control. The criteria for a positive result were a mean wheal reaction ≥3 mm or a flare reaction ≥10 mm, calculated as the mean of the longest and orthogonal diameters after subtracting the mean diameters for the saline control. A negative test result required a positive histamine test, i.e. a mean diameter (minus the mean diameter with saline) ≥3 mm for wheal or ≥5 mm for flare reactions [23].

The SPT results in the experimental and control groups are shown in table 3. Positive SPTs were observed slightly more frequently in the experimental group than in the control group, although none of the cluster-adjusted ORs were close to achieving statistical significance [23].

Food Allergy

Relatively few studies have examined the effect of breastfeeding on food allergy, and I am aware of no systematic review or meta-analysis on the subject. Studies have used variable definitions of food allergy, often based on parental reports and rarely on cutaneous antigen hypersensitivity testing or double-blind challenges and dechallenges with the specific food to which the subject reports being allergic. Despite reports of cow's milk allergy developing after discharge in otherwise exclusively breastfed infants who received cow's milk formula during the first few days of life [31], controlled studies have not

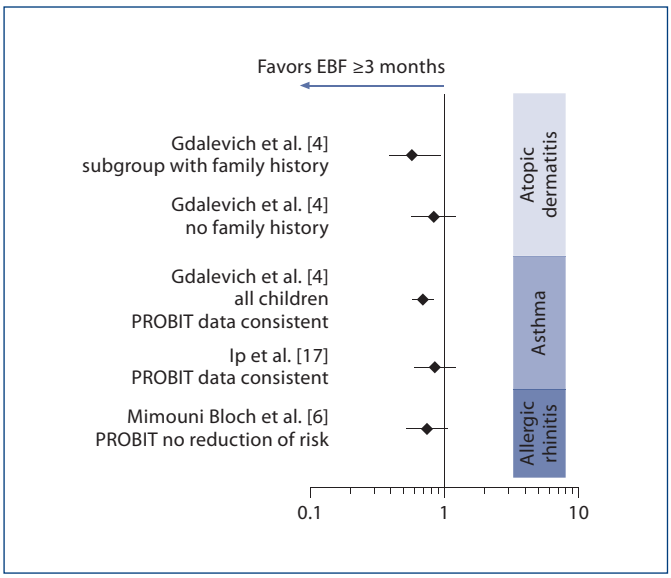

Fig. 2. Summary forest plot showing the protective effect of EBF ≥3 months in atopic dermatitis, including the summary ORs from a systematic review [4] and meta-analysis [17], as well as the PROBIT cluster-adjusted data [22] (see text for details).

demonstrated increased risks of cow-milk or other food allergies in infants fed formula or those breastfed for shorter durations or lesser degrees [11, 32, 33]. One recent Australian study with long-term follow-up reported a significantly lower risk of food allergy at age 7 years in infants exclusively breastfed for the first 3 months of life, but a significantly higher risk at 14 years [34].

Conclusion

Both the meta-analyses by Gdalevich et al. [4] and Ip et al. [17] and the results of PROBIT [22] suggest a strong protective effect of prolonged and exclusive breastfeeding (≥3 months) on reducing the risk of atopic dermatitis, at least in infancy (fig. 2). The evidence is far weaker, however, for other atopic diseases, including asthma, allergic rhinitis, positive allergen skin tests, and food allergy.

Future studies should examine other environmental effects, including exposure to molds and other in- and outdoor environmental contaminants. Given some suggestion of effect modification (stronger protective effects of breastfeeding in children at high risk of atopic disease, based on a positive first-degree family history), studies on gene-environment interactions should assess the extent to which nutritional (including specific micronutrients) and environmental influences interact with specific high-risk genetic polymorphisms to affect risk of allergic outcomes. Future studies should attempt to refine and subclassify the atopic phenotypes to explore the effects of infant feeding and other nutritional and environmental influences as they may relate to more homogeneous phenotypes based on modern, in-depth analysis of genetic, epigenetic, and proteomic markers in an attempt to better understand biological pathways and mechanisms underlying the development of allergic diseases.

Disclosure Statement

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