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Why is there still confusion about the impact of breast-feeding on the risk of allergy development?

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Abstract

The incidence of allergies has tripled in Sweden and other highly developed countries in the past 20 years. Allergies are now the most common chronic disease in childhood, affecting approximately one-third of Swedish schoolchildren. In response to this development, Swedish authorities formulated advice to parents on how to reduce the risk of their children becoming allergic. One such recommendation was to breast-feed exclusively for 4 (or 6) months and postpone the introduction of solid foods. Since the early 1970s, breast-feeding has tripled in Sweden, but simultaneously, allergies have also tripled in Sweden and other wealthy Western countries. There is reason to examine the foundations for the advice to breast-feed to hinder allergy development.

What is allergy?

Allergy is defined as immune-mediated hypersensitivity. The allergic individual mounts an immune response to harmless substances, termed allergens, present in the environment. Renewed exposure produces symptoms that are caused by an activation of immunological and inflammatory reactions. Development of an immune response to an allergen is termed sensitization and is a prerequisite for the development of allergy. However, sensitization is not equivalent to allergy, because an individual can be sensitized without developing typical symptoms when exposed to the allergen. The reasons for this are not known, but probably relate to complex networks of factors that down-regulate various inflammatory reactions.

Different immunological mechanisms may produce allergies. Hence, allergies may be divided into three groups based on the pathological mechanisms: immunoglobulin E (IgE)-mediated allergy, also termed atopic allergy; T-cell-mediated allergy, or contact allergy; and other types of allergy.

IgE-mediated allergy (atopic allergy)

In this case, sensitization signifies production of IgE antibodies to allergens present in food or the environment. These IgE antibodies bind to mast cells that are loaded with histamine and other potent inflammatory mediators, and are situated around blood vessels and in the airways and gastrointestinal mucosa. Upon renewed exposure to the sensitizing allergen, small amounts of intact allergen are taken up via the mucosal surfaces and reach tissue mast cells armed with IgE antibodies to the allergen. Binding of the allergen to IgE leads to activation of the mast cell becomes activated and release of first histamine and later leukotrienes and cytokines, which together induce vascular leakage, tissue swelling and infiltration by eosinophilic granulocytes that characterize IgE-mediated reactions. In the lung, bronchial constriction and mucus production take place, which contribute to the typical asthma symptoms. Other characteristic IgE-mediated allergic symptoms are rhinitis (hay fever), conjunctivitis (itchy, running eyes), urticaria (skin blebs) and atopic eczema (chronic itchy lesions in typical locations). In the worst case, a generalized allergic reaction termed anaphylaxis may occur, when a sensitized individual is exposed to the allergen with systemic vasodilatation and a drop in blood pressure.

The allergens involved in IgE-mediated reactions may vary between geographical regions. However, they are always proteins of small to moderate size, typically present in foods, pollens or secretions from animals present in the surroundings of humans.

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Thus, in Sweden, proteins present in cow's milk, egg, fish, cat secretions, and birch and grass pollens are the most common allergens. An atopic individual has an increased tendency to produce IgE antibodies to all antigens and often develops allergy to several allergens. Usually, IgE antibodies to milk and egg proteins are the first to appear in combination with atopic eczema. Later, IgE antibodies to inhalant allergens such as proteins in cat dander, grass and birch pollens occur, giving rise to symptoms such as hay fever and asthma.

T-cell-mediated allergy (contact allergy)

Here, the allergens are typically small organic or inorganic molecules that pass across the skin barrier. Examples include nickel and chromium, latex, and components in cosmetics, hair dyes, and so on. Sensitization in this case equals development of T-cells specific for the contact allergen in question. Renewed exposure in a sensitized individual to the culprit allergen leads to recruitment of specific T-cells, which in turn activate macrophages. A typical red, hard and itching lesion develops. The skin is the preferred site for contact allergy.

Whereas IgE-mediated allergies run in families, there is no association at the family or individual level between IgE-mediated and contact allergy. Thus, contact allergy is equally prevalent among atopic and non-atopic individuals.

Other types of allergy

In theory, it is possible that any type of immune reaction to a harmless environmental substance can produce allergy. In some cases it is not known which mechanism is most important in causing the inflammatory reaction. One example is coeliac disease, an immune-mediated hypersensitivity reaction to gluten. In this disease, there is destruction of small intestinal villi with intense infiltration by lymphocytes in the mucosa. T-cell-mediated destruction is thought to play a role, but there is also massive production of IgG antibodies and these could also mediate injury, for example by activating complement. A similar picture is seen in cow's milk allergy with delayed symptomatology. As opposed to cow's milk allergy with immediate symptoms (vomiting, urticaria and sometimes airway symptoms), which is IgE mediated, the delayed type is characterized by failure to gain weight similar to the clinical presentation of coeliac disease. Cow's milk allergy of the delayed type is often transient in nature and is not associated with any increased risk of developing IgE-mediated allergy, such as hay fever, later in life.

The allergy epidemic

It is the IgE-mediated allergies that have increased dramatically in the whole industrialized world during the past few decades. As they are directed to common antigens that have been present in our surroundings for thousands of years, there is no simple explanation for the phenomenon. IgE-mediated allergies were first observed among affluent and well-educated European citizens and are still much more common in areas with high standards of living than in poor and underdeveloped regions (1). The hypothesis that fits best with available epidemiological data is the hygiene hypothesis, originally put forward by the British epidemiologist David Strachan in 1989. He examined large British cohorts born in 1958 and 1970 and observed that those who had many older siblings less often had hay fever and eczema than those who were first-born or had no siblings (2). Combining this observation with the known association between affluence and allergy, Strachan proposed that exposure to certain microbes in early childhood might be necessary for the proper maturation of the developing immune system, and that lack of such exposure would lead to immune dysregulation and allergy development. This is supported by the observation that animals reared without microbes are less able to become tolerant to dietary antigens (3, 4). The hygiene hypothesis has gained increased support over the past 20 years owing to the observations that early exposure to farm animals and pets is a major protective factor against allergy development. The lifestyle factors that are strongly and significantly associated with protection from allergy, as evidenced by a large number of carefully conducted studies and studies from different geographical areas, are summarized in Table 1.

Does breast-feeding protect against allergy development?

Further examination of the British cohorts born in 1958 and 1970 by epidemiologists revealed that breast-feeding for at least a month was associated with a higher risk of developing hay fever and asthma by 16 years of age compared to complete

Table 1. Factors[a] that are known to exert a significant protective effect on allergy development and an estimate of their protective effect

Factors known to be protective against allergy development	Typical OR	References
Having many siblings (especially older siblings)	0.5 for large family vs single child	Reviewed in ref. 5
Growing up in poverty	0.5–0.8	Reviewed in ref. 6
Growing up on a farm with animal production	0.1–0.7	7–11
Growing up with a cat or dog	0.4–0.8	12–15

[a] The four factors listed in the table have consistently shown a negative association with allergy development in studies examining different geographical regions and populations. An estimate of typical odds ratio (OR) of developing allergy for a child exposed to the factor versus not exposed to the factor is given.

bottle-feeding (16). This was long before authorities began to promote breast-feeding to prevent allergy development. Hence, the effect could not be explained by increased breast-feeding by mothers who themselves were allergic, in order to protect their children from developing allergy. However, it is important to note that the negative effect of breast-feeding was small compared with the negative effects of small family size and economic affluence for allergy development. This was pointed out as a major conclusion of the study.

Most studies of the role of lifestyle factors and allergy development include baby feeding as one parameter and there is a massive number of reports on the effect of breast-feeding on allergy development. The first review of the subject was published in 1988 and given the title "Does breast feeding help protect against atopic disease? Biology, methodology, and a golden jubilee of controversy" (17). The golden jubilee referred to the fact that 50 years had passed since the first claim that breast-feeding protected against infantile eczema was published in 1936 (18). This study was conducted long before IgE was discovered and we cannot know the true nature of this eczema. The alternative to breast-feeding at that time was diluted cow's milk, far from today's humanized infant feeding formulae.

The author of the review pointed out that all studies conducted so far suffered from various flaws, but that the "positive" studies (pointing to a protective effect of breast-feeding) and "negative" studies (showing an adverse effect or no effect exerted by breast-feeding on allergy development) were faulty in different ways. Positive studies often measured breast-feeding accurately, but their statistical analysis was often inadequate, for example by not using blinded observers of the clinical symptoms. Negative studies often had a better study design, but suffered from inadequate measures of breast-feeding. This was often due to a retrospective design investigating allergy at school age and asking the mothers retrospectively for how long they had breast-fed. Kramer concluded that it could not be determined from the studies conducted until that date whether breast-feeding was protective, had no effect or increased the risk of developing allergies. However, he noted that the larger and better designed studies failed to show any protection. Hence, any protective effect of breast-feeding would probably be small (17).

Despite the absence of any hard data pointing to breast-feeding as a significant modulator of the risk of developing allergy, Swedish authorities started to promote breast-feeding to protect against allergy development in the early 1980s. Before this, breast-feeding had been advocated since the mid-1970s because of its excellent nutritious value and protective effect against infections, effects which have been extensively documented and corroborated (19).

Later studies

The early studies suffered from either short follow-up times (when using a prospective design) or adequate follow-up time but retrospective assessment of breast-feeding. Only in the past 5 years have carefully designed longitudinal studies using a prospective design become available. One such study, the German MAS study, demonstrated a significantly increased risk of developing eczema in exclusively breast-fed children. For each month of exclusive breast-feeding, the risk of developing eczema was increased by 3% (20). The risk remained after control for confounding factors such as maternal age, parental smoking, atopy and social class. Recently, a significantly increased risk of developing atopic eczema in the first 18 months of life was observed in breast-fed children of non-allergic parents in a Danish study, while a small and non-significant protective effect was seen in children born to atopic parents (21). The reverse has also been claimed: a protective effect of breast-feeding against atopic eczema in the Swedish BAMSE study (22). However, the effect was statistically non-

significant and any effects on sensitization and IgE levels were not revealed.

The most recent review summarized the role of breast-feeding in allergy as follows: "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 immunological 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" (23).

Thus, despite thousands of papers written on the subject, it has still not been convincingly shown whether breast-feeding protects, increases the risk, or has no effect on allergy development in the child. What is clear, however, from all available studies and from meta-analysis (23), is that any effect (positive or negative) is small compared with the four important protective factors: poverty, large family size, farming environment and early exposure to pets (Table 1). For example, if breast-feeding gave an odds ratio of 0.90 for an allergic manifestation which was found in a recent study (22), 27% of breast-fed infants would develop this manifestation, compared with 30% of bottle-fed infants. In comparison, growing up on a small family farm with daily exposure to animals reduces the risk of developing asthma from 11% to less than 1% (7) and growing up with a pet halves the risk of developing asthma (12). From this, it should be clear that a woman's choice to breast-feed or not, or the length of the period of breast-feeding, will have negligible effects on the risk of allergy development in her child.

Some reasons for the confusion

It may come as a great surprise to many people that it still cannot be determined whether breast-feeding is protective or increases the risk of allergy development. A major reason for the confusion is the multitude of inconsistencies and flaws in study design in many studies, some of the most common of which are:

- appearance of IgE antibodies is taken as evidence of allergy
- wheezing in infancy is labelled as allergic asthma
- all eczematous skin lesions are judged as evidence of allergy without demonstration of raised IgE antibody levels
- symptoms (and sometimes IgE antibodies) are evaluated during breast-feeding. A true protective effect should also persist when breast-feeding has terminated.

As explained earlier, the definition of allergy is immune-mediated hypersensitivity. This means that the allergic individual must have demonstrably increased immunity to the allergen and experience symptoms when exposed to this allergen. A person who has IgE antibodies against an allergen, e.g. the major cat allergen Fel d 1, but does not produce any symptoms when exposed to cats, is not allergic. In many studies, presence of IgE antibodies has been equated with allergy. However, it is common that infants develop a transient IgE response to different food antigens upon their introduction into the diet, antibodies which later disappear as tolerance develops (24). In truly allergic people, these IgE antibodies continue to increase and also give rise to allergic symptoms.

Nor is a person allergic who has asthma or asthma-like symptoms if the symptoms are not caused by hypersensitivity to an allergen. This person may have other conditions producing identical or similar symptoms. For example, small children often wheeze during respiratory infections. Such wheeze has no relation to the risk of developing allergic asthma at school age (21).

Breast-feeding protects strongly and significantly against infections (19), including respiratory tract infections. Thus, wheezing in the first years of life is less frequent in breast-fed than in bottle-fed infants (21, 25). However, an Italian study revealed that although breast-feeding was protective against early wheezing, it increased the risk of late wheezing in the same cohort (25), the latter probably representing allergic asthma. Along the same lines, early day-care exposure leads to increased wheezing in the first years of life (respiratory infections), but reduced wheezing (asthma) at school age (25, 26).

Similarly, not all eczematous lesions are necessarily evidence of allergy. Quite confusingly, the definition of atopic eczema does not require proof of any immunological hypersensitivity, but only that itching skin spots are present in typical locations (27).

Another concern is the problem of defining protection. Most people would agree that this would mean a reduced risk of developing allergy that is demonstrable after cessation of breast-feeding. Postponement of symptoms is, thus, not protection from allergy. However, many studies have compared, for example, the prevalence of eczema in breast-fed and bottle-fed infants at the stage when the former still received breast milk. Breast milk may reduce uptake of foreign substances across the gut wall and, consequently, lower the exposure of breast-fed infants to food allergens. Furthermore, breast milk has potent non-specific anti-inflammatory effects (19). Symptoms of allergy could thereby be partially masked during breast-feeding. If the breast-fed infants develops allergy to the same extent as bottle-fed infants once they are both on solid foods, there has been no true protective effect of breast-feeding on allergy development.

Why would breast-feeding reduce the risk of allergy development?

The original theory behind the hypothesis that breast-feeding would protect against allergy development was that the infant's exposure to foreign dietary antigens would be lower, thereby reducing the risk of sensitization. This belief also underlies recommendations of postponing introduction of certain allergens into the diet of the infant.

However, extremely low doses of antigen suffice to induce sensitization. Infants with an allergic disposition may develop IgE responses to cow's milk and egg proteins while still being exclusively breast-fed (28, 29). It is not known whether the small amounts of food antigens present in maternal milk contribute to this sensitization, or whether exposure occurs via some other route.

Further, allergy is not caused by excessive exposure to allergens; allergy is failure to develop tolerance to common antigens found in the environment. Development of tolerance also requires exposure to antigen. It has not been demonstrated that postponing exposure to an antigen facilitates development of tolerance to this antigen. On the contrary, it is generally easier to develop tolerance to an antigen the earlier in life one encounters an antigen.

How could breast-feeding increase the risk of allergy development?

As we have seen, several studies demonstrate an increased risk of developing allergies in children who have been breast-fed. One plausible mechanism would be the potent anti-infectious effects of breast-feeding. It has been amply demonstrated that breast-feeding protects the baby against infections, particularly invasive bacterial infections such as pneumonia and septicaemia (30). This is largely due to the fact that secretory IgA in the breast milk coats bacteria present on the infant's mucosal surfaces and prevents their close interaction with the mucosal surface and translocation across the epithelial barrier (30).

Most data point to the importance of exposing the mucosal immune system of the infant to microbes in order for tolerance to develop properly. There is a consistent inverse relationship between lifestyles that predispose to infections and to allergy, respectively: populations that have many infections have little allergy and the reverse holds true (31, 32). If allergies are caused by too few microbes, there is reason to believe that exclusive breast-feeding could increase the risk of allergy development by reducing microbial exposure. In fact, the immune system of bottle-fed infants is more activated than that of breast-fed ones (33).

Breast milk has evolved to meet the nutritious needs of the infant and also to provide passive protection from infection, which has been the major cause of infant death until recently in industrialized societies and remains the number one killer in many parts of the world. Allergies did not exist during most of the period when humans evolved. It is unreasonable to ask for protection from this modern disease by breast milk, the composition of which has evolved during millions of years.

On the formulation of advice

As most studies suggest a very moderate effect of breast-feeding on allergy development, be it positive or negative, it is evident that allergy is not an argument either for or against breast-feeding. Despite this, many paediatric associations have recommended breast-feeding by arguing that it protects against allergy (23). The argument is probably that since breast-feeding is good (for nutrition and against infections), there is no harm in recommend-

ing it, even with false arguments. But all advice has side-effects. These include interference with the individual's right to choose, interference with the family's autonomy, increased time expenditure, and the creation of anguish and guilt. No advice should be given without a firm scientific basis and a prior thorough analysis of expected positive and negative effects. The advice to breast-feed to protect the child from allergy development does not fulfil these basic requirements.

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