Nutrition Intervention in Allergy Prevention

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# Breastfeeding, Childhood Asthma, and Allergic Disease

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## Key Messages

- Breastfeeding may protect against the development of asthma and allergic disease in children, although this topic has been controversial for more than 8 decades.
- Breastfeeding is recommended for at least the first 6 months of life and up to 2 years for immunological development of the infant.
- Breastfeeding may influence immune responses through the bioactive, immune-modulating properties of breast milk, or through the impact of milk type on intestinal microbiota.
- The composition of breast milk cytokines deserves further investigation, because cytokines may provide protection against wheeze and subsequent asthma in childhood.

**Keywords**
Breastfeeding · Allergic disease · Childhood asthma

**Abstract**
The worldwide prevalence of childhood asthma has been increasing considerably, and the protection afforded by breastfeeding in its development has been the subject of controversy for more than 80 years. Previous systematic reviews have generally found a protective effect of breastfeeding on allergic outcomes, although many studies have methodological limitations. Although breastfeeding is protective against lower respiratory tract infection during infancy, such protection has not been demonstrated for asthma in all studies. Breastfeeding has health benefits for the mother and child. Exclusive breastfeeding for the first 6 months of an infant's life, with continued breastfeeding for up to 2 years or longer, is recognized as the "gold" standard for infant feeding because human milk is uniquely suited to the human infant, and its nutritional content and bioactivity promote a healthy development. There is increasing concern that the practice of delaying complementary foods until 6 months may exacerbate the risk of allergic disease. Breast milk contains immunological components that protect against infections and allergic disease in infancy. The composition of human breast milk is complex, containing factors that interact with the infant immune system and intestinal milieu including allergens, cytokines, immunoglobulins, polyunsaturated fatty acids, and chemokines. Transforming growth factor β is a cytokine in human milk involved in maintaining intestinal homeostasis, inflammation regulation, and oral tolerance development. Modern day society, with increased standards of hygiene, has changed the gut flora of Western infants, potentially impacting the risk of developing immune-mediated diseases including allergic disease and

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asthma. Microbial diversity is intrinsic to healthy immune maturation and function. Compared to breastfed infants, formula-fed infants had lower bacterial diversity and an altered intestinal microbiota in the first few weeks of life associated with an increased risk of eczema and asthma. Favorable gut colonization through continued breastfeeding may promote tolerance as well as protection when complementary feeding is initiated.



## Introduction

*Breastfeeding and Childhood Illness*

Breastfeeding has numerous health benefits for the mother and child [1]. Exclusive breastfeeding for the first 6 months of an infant's life, with continued breastfeeding for up to 2 years or longer, is recognized as normal and the "gold" standard for infant feeding [2, 3]. This is because human maternal milk is uniquely suited to the human infant, and its nutritional composition and non-nutritive bioactive factors promote healthy development and ultimately survival. Breast milk contains immune factors such as IgA antibodies protecting against many health problems in infancy, such as necrotizing enterocolitis, overweight and obesity, diabetes, infections, and allergic disease [2, 4], as well as reducing the risk of diseases later in life [5].

In the past 30 years, the evidence for global breastfeeding recommendations has evolved remarkably. Epidemiological studies combined with growing insights from epigenetics, stem cell research, and the "developmental origins of health and disease" hypotheses offer strong and solid support to the concept that breast milk is best for human infants. Never before in science history has so much been known about the complex significance of breastfeeding for mothers and their children.

However, the protection afforded by breastfeeding against the development of childhood asthma and allergic disease has been the subject of controversy in the literature. Although breastfeeding is protective against lower respiratory tract infection during infancy, such protection has not been demonstrated for asthma in all studies. Issues related to study design, analytical methods, and confounding have greatly complicated the interpretation and comparison of studies. Furthermore, asthma has a complex phenotype in which numerous genetic and environmental determinants interact. Consequently, the effect of any single determinant is likely to be small and the independent effects difficult to quantify. Asthma is common at a population level, and breastfeeding is amenable to intervention, so a small effect may have implications for public health. For this reason, it is important to establish whether breastfeeding modifies the risk of childhood asthma, even if the effect is small.

Against this background of breast milk significance, there is evidence that breastfeeding may protect against the development of asthma and allergic disease in children although this has been controversial since it was first observed more than eight decades ago [6, 7].

*Definition of Infant Feeding*

The World Health Organization [8] defines "exclusive breastfeeding" as feeding with breast milk "only" with no other liquid, solids, or vitamin drops. An infant who receives water or juice but not formula is considered "predominantly breastfed," whereas an infant who receives formula milk, if only for one feed, is considered "partially breastfed," and "never breastfed" refers to a situation where breastfeeding was never initiated. Thereafter, to meet their evolving nutritional requirements, infants should receive nutritionally adequate and safe complementary foods while breastfeeding continues for up to 2 years of age or beyond [9].

*Definition of Allergic Disease*

The definitions of allergic disease are varied and inconsistent across studies. For example, different studies have used allergen sensitization, self-report, or doctor diagnosis to define presence of food allergy, with the first two definitions correlating poorly with food challenge for diagnosis of food allergy (the gold standard). Similarly, diverse outcome definitions have been applied in studies evaluating the impact of breastfeeding on eczema, asthma, and allergic rhinitis [4].

To limit the scope of this review, the focus is largely on asthma. Asthma represents a chronic, complex, polygenic interaction in individuals with varying environmental exposures [10]. Asthma is the most chronic disease of childhood and the leading cause of morbidity in children globally as measured by emergency department visits, hospitalizations, and days of missed school [11, 12]. Childhood asthma prevalence worldwide has been increasing over decades, and a number of theories are proposed to explain this startling trend. An overview of current thinking in relation to the breastfeeding, asthma, and allergic disease debate is given – from epidemiological, nutritional, immunological, and gut microbial colonization perspectives.



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## Determinants of Childhood Asthma and Allergic Disease

The disease has a broad spectrum of possible determinants extending from genetics to lifestyle to environmental factors. Environmental allergens such as smoking in the household, house dust mite, grasses, or pollens may be implicated. Lifestyle and environmental factors including obesity, living in an urban environment, dietary patterns including fast food and poor diet quality, formula milk feeding, gut flora imbalance, smoking, pollution, and infection (viral) have been associated with asthma exacerbations in childhood [12]. Susceptibility to asthma may be increased by early life factors including low birthweight, preterm birth, young maternal age, and male gender. On the other hand, early exposure to respiratory infections may protect, although certain infections may increase the risk [13]. Breastfeeding is implicated because it has been shown to protect against early respiratory and other infections [14].

***Breastfeeding has been shown to protect against early respiratory and other infections***

### *Epidemiological Studies on Breastfeeding, Asthma, and Allergic Disease*

Epidemiological studies in the debate as to whether breastfeeding can have a role in protecting against allergic disease and asthma in early childhood provide conflicting results. While breastfeeding is recommended for all infants irrespective of allergic heredity [15], with protective effects of breastfeeding on asthma reported in young children [16–18], other studies of children at high [19, 20] or low risk [21] or adults [22, 23] show no protective effects.

### *Systematic Reviews*

Previous systematic reviews have found a protective effect of breastfeeding on allergic outcomes, although most studies have methodological limitations, such as heterogeneity or noncompliant standards. A recent review and meta-analysis aimed to identify and summarize publications on breastfeeding and childhood asthma risk in the general population as well as stratify analyses and meta-regression to explore sources of heterogeneity [24]. Compared with other reviews, this review includes a large number of studies, restricts search and study selection minimally, and includes studies of different methodologies, operational definitions for breastfeeding and asthma, and sets of confounders [24]. These criteria may have increased the variability of effect estimates. Limitations were overcome by performing meta-analyses in standardized subgroups and meta-regressions with a broad array of predictors. An assessment of the methodological quality of the studies using criteria based on Kramer's standards [25] was made and a score based on these criteria was included in the analyses, which addressed heterogeneity between studies. The authors of this review found evidence that children breastfed longer have a lower risk for developing asthma (Fig. 1). Risk reduction was pronounced in children 0–2 years of age, decreasing with age, but still evident at school age with greater effects in early life supporting the theory of protection from early infection. Studies were highly heterogeneous, and results were similar when only longitudinal cohort studies or studies of high methodological quality were included.

Few studies have attempted to assess the association of breastfeeding over the spectrum of allergic conditions: asthma, eczema, allergic rhinitis, and food allergy, which is important because of the substantial overlap in allergic diseases with shared phenotypes. The systematic review of Lodge et al. [26] aimed to analyze current evidence through proven search methods, investigate the heterogeneity and quality of included studies, and contextualize results with respect to the findings related to breastfeeding and allergic outcomes. In this review of various study types, weak evidence that breastfeeding is protective for allergic disease is evident. In spite of heterogeneity in the studies of this review, there is strong evidence that breastfeeding is associated with a reduced risk of asthma (Fig. 2).

Studies were further grouped into those reporting eczema up to or beyond 2 years [26] (Fig. 3). A reduced risk of eczema below 2 years was observed after pooling 6 cohort study estimates comparing exclusive breastfeeding for more than 3–4 months with other feeding types (re OR 0.74, 95% CI 0.57–0.97, $I^2$ 62%). Weak evidence that breastfeeding reduced the risk of eczema up to 2 years was observed.

A review that included all study types published in 2011 considering breastfeeding and wheezing illness beyond 5 years of age only showed no association, highlighting an enormous controversy in this area [27]. The authors of this review recommend that further studies should aim to be of the highest quality and specific diagnostic criteria for asthma to be included.


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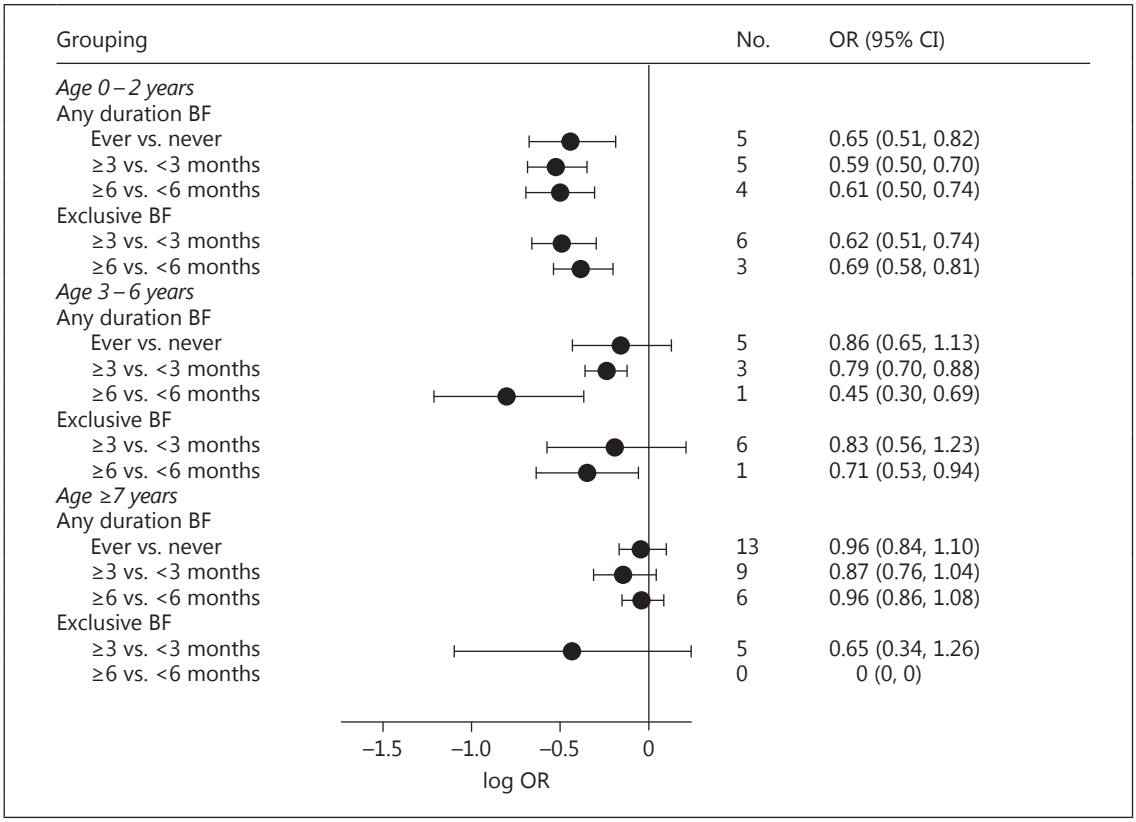


**Fig. 1.** Pooled odds ratios (ORs) and 95% confidence intervals (CIs) of meta-analyses performed for "recent asthma" in groups determined by age, outcome, breastfeeding (BF) type, and breastfeeding cutoff (stringent categorization). Reproduced from Figure 3 of Dogaru et al. [24] with permission from the authors, December 2016. See [24] for a full list of publications.

*A Birth Cohort "Case" Study*

One cohort study assessed the association between breastfeeding and asthma from 1 to 8 years and found that breastfeeding for more than 4 months was associated with significantly reduced asthma prevalence regardless of family history and without evidence of attenuation [28]. The study population, 3,963 Dutch children born in 1996/1997 participating in the PIAMA birth cohort study, was followed for 8 years. Asthma was defined as at least one attack of wheeze and/or dyspnoea and/or prescription of inhalation steroids in the previous 12 months. Chronic asthma was defined as asthma diagnosis at 8 years with asthma diagnosis in at least 2 other years. Specific IgE to common airborne allergens and bronchial hyperresponsiveness were measured according to a standard protocol [29]. Breastfeeding was defined as the duration of any breastfeeding (no breastfeeding, breastfeeding for 1–16 weeks, breastfeeding for more than 16 weeks). "Generalized estimating equation" modelling was applied to test for associations between breastfeeding and repeated respiratory outcomes until 8 years adjusting for gender, maternal education, smoking during pregnancy, and current smoking and stratified by parental allergy. Because 10% of baseline data were missing, missing data were imputed. Final imputation, however, made no difference to the study findings.

In this study, asthma risk was shown to be lower in children breastfed for more than 16 weeks compared to those not breastfed [28]. Children breastfed for the longer duration had significantly fewer chronic asthma symptoms. Having an allergic or nonallergic mother did not change these associations. Breastfeeding for more than 16 weeks was inversely associated with sensitization to airborne allergens at 8 years with no association observed for bronchial hyperresponsiveness. Breastfeeding was associated with a lower asthma risk at all



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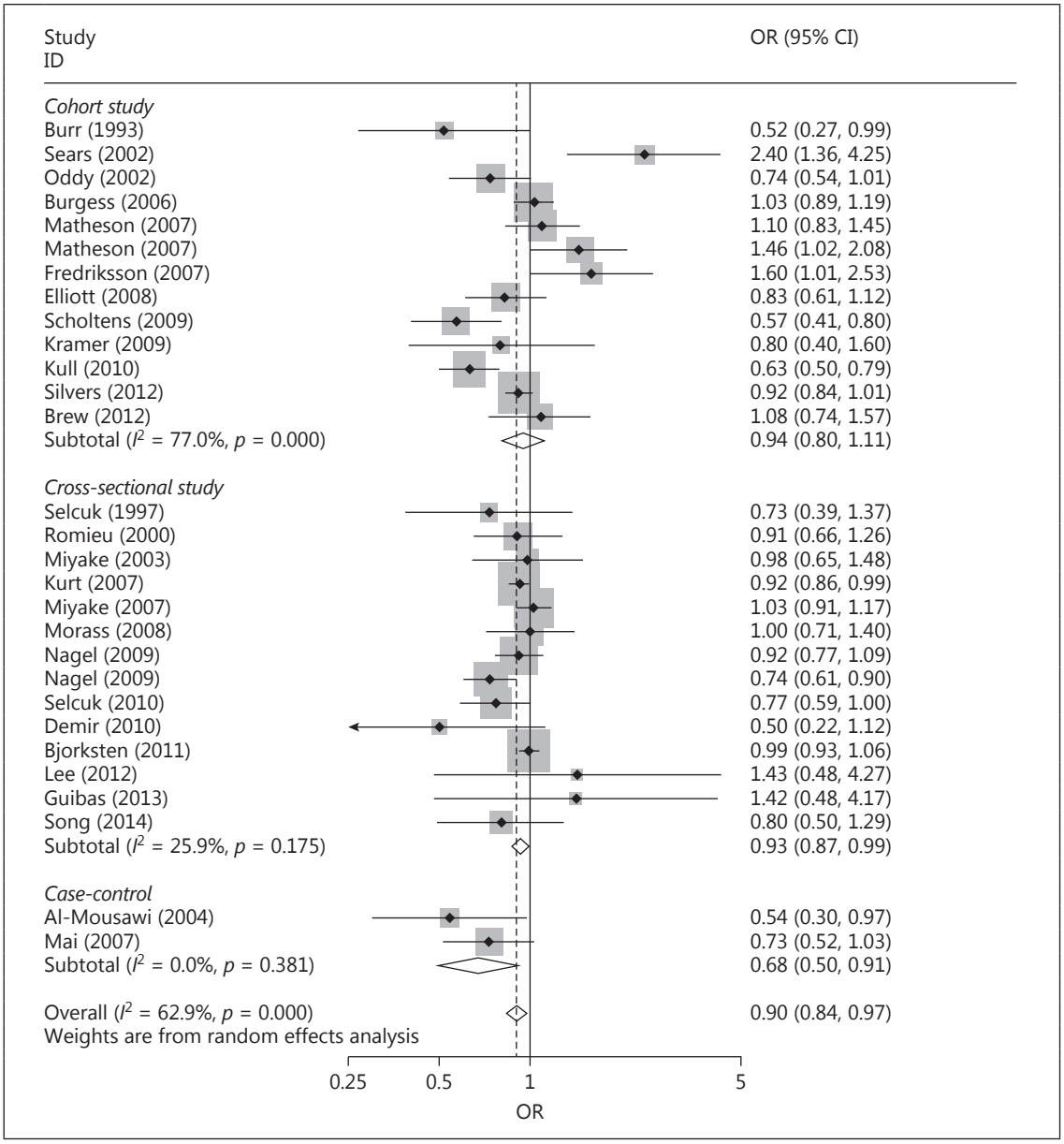


**Fig. 2.** Meta-analysis: more versus less breastfeeding and risk of asthma in children aged 5–18 years. OR, odds ratio; CI, confidence interval. Reproduced with permission from Lodge et al. [26]. See [26] for a full list of publications.

years regardless of parental history. Repeated measures analysis showed a lower risk of wheeze and asthma from 1 to 8 years in babies breastfed for a longer duration, suggesting that breastfeeding affects long-term outcomes. Strengths of the study include longitudinal design, follow-up until 8 years, repeated measures of data collection, a large study population, low attrition rate, and multiple imputation. The birth cohort design with longitudinal analysis allowed demonstration that breastfeeding protects against asthma throughout childhood both with and without a family history and contributing significantly to the breastfeeding and childhood asthma debate.



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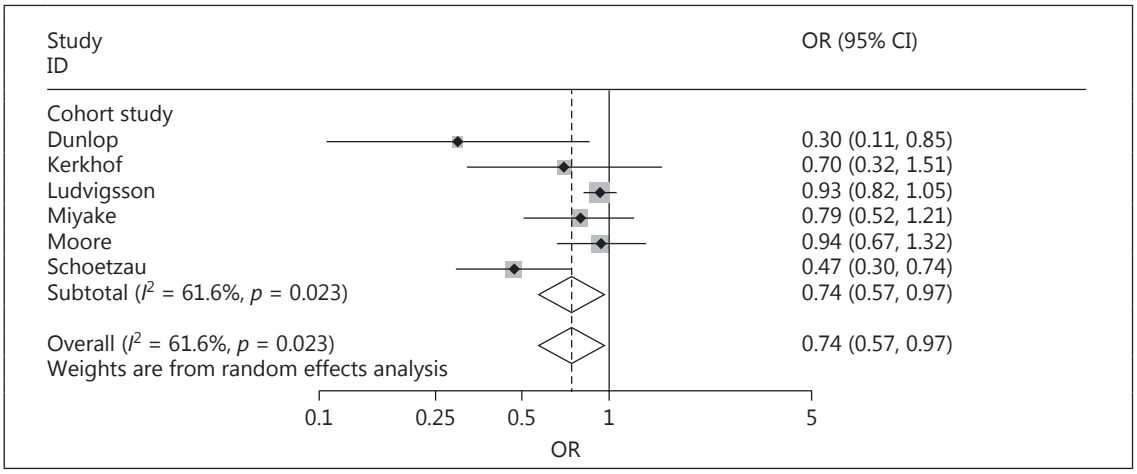


**Fig. 3.** Meta-analysis: exclusive breastfeeding >3– 4 months compared with less and risk of eczema up to 2 years of age. OR, odds ratio; CI, confidence interval. Reproduced with permission from Lodge et al. [26]. See [26] for a full list of publications.

## How May Breastfeeding Protect against Allergic Disease?

*Timing of Introduction of Solids*

There is increasing concern that the current practice of delaying complementary foods to 6 months of age may exacerbate the risk of immune disorders such as eczema and allergic disease. In addition, evidence suggests that favorable gut colonization through continued breastfeeding may promote tolerance as well as protection when complementary feeding is initiated. Conflict exists between some allergy prevention guidelines that currently recommend delaying the introduction of allergenic foods until at least >12 months, whereas the new recommendations are for the introduction of allergenic foods between 4 and 6 months [30] and not before 6 months [9]. Prescott et al. [31] suggested that early introduction of certain allergenic foods is safe and may build tolerance. Other researchers support the hypothesis that later introduction of foods increases allergenic responses [32]. Koplin et al. [32] showed, following adjustment for confounding, that a later introduction to egg increased rates of egg allergy (OR 3.4, 95% CI 1.8–6.5, at >12 months) compared to introducing egg between 4 and 6 months. These results have major implications for practice and future research as they suggest that the introduction of cooked egg at 4–6 months of age may protect against egg allergy and that delaying introduction to egg may exacerbate it. Confirmation of these findings may result in strong changes to infant feeding guidelines, which currently recommend delaying the introduction of allergenic foods until at least >12 months.

The prevalence of peanut allergy among children in Western countries has doubled in the past 10 years, and therefore a study to evaluate strategies in preventing the development of peanut allergy in infants at high risk for the allergy was conducted [33]. The early introduction of peanut significantly decreased peanut allergy development among high-risk children and modulated immune responses to peanuts. In response to these findings, guidelines have recently changed in relation to peanut allergy in the United States [34].

*Bioactive Components in Milk*

Breastfeeding protects against wheeze in infancy [14], and several components of human milk have been postulated as conferring this protective effect [35]. Protection may be through a myriad of factors in milk including bioactive enzymes, hormones, growth factors, cytokines, and immunological agents. These findings augment and stimulate host defense development [36, 37], suggesting that bioactive components of milk are important in neonatal development and biologically plausible mechanisms through breastfeeding may impact asthma etiology. Breastfeeding has been associated with protection against early respiratory infections [13], and the observed association between breastfeeding and asthma at early ages may be mediated by the protection of breastfeeding against infections. Breastfeeding may provide an imme-



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**Table 1.** Factors in breast milk that are being evaluated as inducing or protecting against food allergies

| | Inducing | Protective |
|---|---|---|
| Antigens | sensitizing allergens | tolerizing allergens |
| Cytokines | IL-4<br>IL-5<br>IL-13 | TGF-β<br>soluble CD14 |
| Immunoglobulins | | s-IgA to ovalbumin |
| Polyunsaturated fatty acids | arachidonic acid<br>C22:4n-6<br>C22:5n-6 | eicosapentaenoic acid<br>docosapentaenoic acid<br>docosatetraenoic acid<br>α-linoleic acid<br>n-3 polyunsaturated fatty acids |
| Chemokines | RANTES<br>IL-8 | |
| Eosinophil-derived granular proteins | eosinophil cationic protein | |
| Polyamines | | spermine<br>spermidine |

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diate line of defense against infectious agents, compensating directly for immaturity of the newborn immune system in its ability to resist infection [38]. However, it is not clear which components of this complex biological fluid account for any potential protective effect.

*The Composition of Breast Milk*

One of the reasons that studies of breastfeeding and allergic disease remain inconclusive could be the complexity of interaction between breast milk, the infant intestinal milieu, and the developing immune system. Some elements in breast milk may protect the infant from developing allergies, whereas others may act in an opposing way (Table 1).

The components of breast milk have immunomodulatory activity, including antigens (allergens), cytokines, immunoglobulins, polyunsaturated fatty acids, and chemokines [18]. It is known that secretory IgA (s-IgA) is passed from mother to infant through breast milk or colostrum. s-IgA may confer passive protection to the infant immune system. Low levels of s-IgA in breast milk are associated with an increased risk of cow's milk allergy in infants. Lower s-IgA levels to ovalbumin have been shown in colostrum and mature milk of allergic mothers compared to mothers without allergy, although the presence of these antibodies was not predictive of allergies in their infants [39].

*Cytokines*

Cytokines are small soluble glycoproteins acting in an autocrine-paracrine fashion by binding to specific cellular receptors, operating in networks, and orchestrating immune system development and function [40]. Human milk was revealed to contain cytokines more than 20 years ago [41], and early milk has an abundance of cytokines at a time when neonatal organ systems are immature.

Cytokine concentrations may play a role in breast milk immunogenicity. IL-4, IL-5, and IL-13 cytokines intimately involved with IgE production and eosinophil induction exist in higher concentrations in breast milk of atopic mothers compared with nonatopic mothers. Soluble CD-14 may protect against allergy development due to its high concentrations in breast milk and importance in the $T_H1$ induction response to bacteria [42].

*Transforming Growth Factor-β*

Transforming growth factor-β (TGF-β) is a cytokine identified in human milk [43], containing TGF-β1, TGF-β2, and other isoforms at mRNA and protein levels with TGF-β2 being the major isoform (95%) [44]. The immunoactive factors in breast milk may influence the development and maturation of the mucosal immune system of the infant [45–50], and mounting evidence suggests that TGF-β, a multifunctional polypeptide, may be a key immunoregulatory factor for the establishment of this response, by promoting IgA production as well as induction of oral tolerance [44, 49, 51–54]. TGF-β increases the infant's ability to produce IgA against β-lactoglobulin, casein, gliadin, and ovalbumin [44]. In an infant


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prone to cow's milk allergy, an increased TGF-β content of mother's milk may be beneficial by promoting IgG-IgA antibody production and inhibiting IgE- and cell-mediated reactions to cow's milk [39, 54].

Original work [55, 56] showed that TGF-β1 was a growth factor exhibiting pleiotropic regulatory effects on developmental and physiological pathways. Disruption of the TGF-β1 gene by homologous recombination in murine embryonic stem cells generated mice that carry the disrupted allele. Homozygotic animals for the mutated TGF-β1 allele showed no gross developmental abnormalities about 20 days after birth, but they then succumbed to a wasting syndrome with a multifocal, mixed inflammatory cell response and tissue necrosis leading to organ failure and death [55]. Letterio et al. [49] observed that TGF-β-deficient mice survived while breastfeeding (i.e., TGF-β1 gene knockout), indicating that maternal sources of TGF-β1 via both placental transfer and milk are essential for normal development and postnatal survival.

The role of milk-borne TGF-β in exposed lactating mice to an airborne allergen assessed the development of asthma in progeny. Breastfeeding-induced tolerance relied on the presence of TGF-β during lactation, was mediated by regulatory CD4+ T lymphocytes, and was dependent on TGF-β signaling in T cells [57]. Airborne allergens transferred from mother to newborn through breast milk induced antigen-specific tolerance in the offspring resulting in protection against allergic disease. Breast milk-mediated transfer of an antigen and TGF-β to the neonate resulted in oral tolerance induction and antigen-specific protection from allergic disease. Further, oral administration of TGF-β in vivo in animal studies results in biological activity sufficient to promote oral tolerance [58].

New insights into the mechanisms underlying tolerance induction in neonates pinpoint maternal influence through "breast milk-mediated antigen transfer" as crucial in the process. Because the amount of TGF-β in maternal milk is less in mothers with atopic disease [59–61], these and other findings [48] suggest that this milk cytokine may influence the development of allergic disease and asthma.

The publication of these reviews relating to TGF-β regulation to immune responses [62, 63] and other studies highlight the importance of milk TGF-β [64], although the mechanistic pathways by which TGF-β modulates development and maintenance of the immune system and its role in regulation of tolerance and immunity has not yet been fully described.

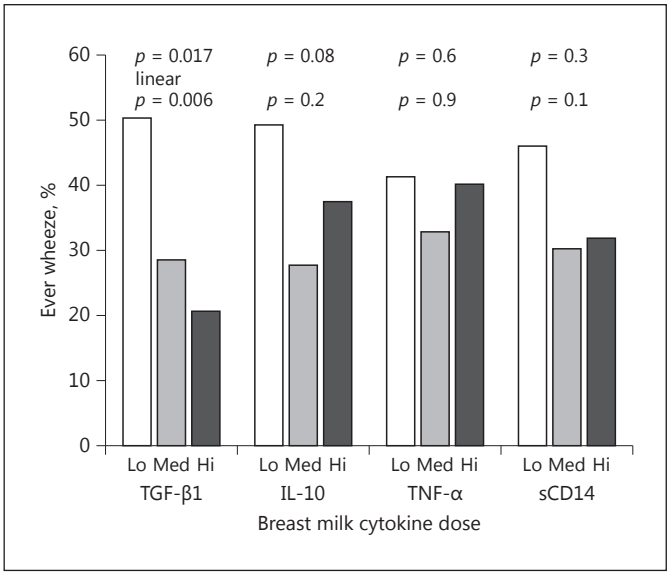


**Fig. 4.** Percent with ever wheeze at 1 year of age by tertiles of cytokine dose: $\chi^2$ analysis. Reproduced with permission from Oddy et al. [66].

*Probiotics*

The administration of probiotics may increase human milk TGF-β concentration depending on the probiotic strain. Inverse effects have been seen with *Lactobacillus reuteri* [65], and because concentrations of human milk TGF-β may be critical in determining immune function, more work is needed in this area.

*Case Study: Infant Immune Study*

Data on breastfeeding and infant wheeze were collected from birth to 1 year from 243 mothers as part of the Infant Immune Study in Tucson, AZ, USA [66]. Breast milk samples obtained at 11 days postpartum (mean age) and assayed by ELISA for concentrations of TGF-β1, IL-10, TNF-α, and soluble form of CD14 as well as cytokine dose and its relationship with wheeze were assessed. An increasing duration of breastfeeding was associated with decreased prevalence of wheeze ($p = 0.039$). A higher TGF-β1 dose was associated with less wheeze ($p = 0.017$) at 1 year, showing a linear trend with wheeze ($\chi^2$ $p = 0.006$) when considered as a dose (Fig. 4). The risk of wheeze decreased (OR 0.22, 95%CI 0.05–0.89, $p = 0.034$) with increasing dose of TGF-β1 (identified from longer duration of breastfeeding and TGF-β1 concentration level, as compared to short duration of breastfeeding and low TGF-β1 concentration level) when adjusted for sex, gestational age, maternal smoking, exposure to other



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children, maternal education, and maternal asthma. The dose of TGF-β1 from breast milk had a significant relationship with infant wheeze at 1 year. Because wheeze is a risk factor for asthma in childhood, this relationship is significant.

The authors concluded that TGF-β from human milk is a family of growth factors involved in maintaining intestinal homeostasis, inflammation regulation, allergy development, and promotion of oral tolerance development. The dose of human milk TGF-β1 and TGF-β2 may modulate or regulate immunological responses of infants in early postnatal life. The composition of breast milk cytokines deserves further investigation, because cytokines may provide protection against wheeze and subsequent asthma in childhood.

*Polyunsaturated Fatty Acids and Polyamines*

Polyunsaturated fatty acids and polyamines may impact on the allergenicity and/ or immune protectiveness of breast milk. A high arachidonic acid to eicosapentaenoic acid ratio in breast milk may be associated with a higher risk of allergic disease and atopy, although this is controversial [67]. How these various mechanisms of immunomodulation are expressed in mother-infant pairs is not known. Genetic factors may allow better predictability but require future investigation to determine the complex interaction effects of immunomodulatory factors in milk and development of allergic disease [68].

*Intestinal Microbiota*

Modern day society, with increased standards of hygiene, has changed the gut flora of Western infants, potentially impacting the risk of developing immune-mediated diseases including allergic disease and asthma [69]. In adults, intestinal microbiota consists of several hundred, mostly anaerobic, bacterial species. Formed through successive establishment of different bacteria in infancy and early childhood, this system is complex. Facultative and aerotolerant bacteria establish first, followed by more and more strict anaerobes, and commensal microbes provide major incentive for immune system maturation.

The microbial colonization of the newborn intestine is influenced by delivery and feeding mode, family structure, and other lifestyle behaviors. Gut microbiota are required for normal immune development, regulation of gut inflammatory responses, and oral tolerance induction to new foods [70]. The specific microbial changes associated with protection against allergic disease remain uncertain, and more recent data suggest that microbial diversity may be of relevance [69, 71, 72]. Altered intestinal microbiota in the first few weeks of life is associated with increased risk of eczema and asthma in infancy [7, 73–75]. Mice raised in a germ-free environment failed to develop oral tolerance and had persistent Th2-dependent responses [76]. This immune deviation may be experimentally corrected by *Bacteroides fragilis* seeding, but only during the neonatal period.

Breastfeeding for 4–6 months may assist in the development of a healthy gut microbiota by providing bifidobacteria and lactic acid bacteria that reinforce colonization [77] and by supplying galacto-oligosaccharides that promote a healthy microbiota composition. A wide variety of galacto-oligosaccharides are found in breast milk, exhibiting bifidogenic effects in the infant gut. Breast milk also contains nucleotides, IgA, and antimicrobial factors such as lactoferrin, which can modulate the infant gut microbiota composition.

Breastfeeding facilitates the exchange of microbes between mother and infant, and bacterial diversity could be intrinsic to healthy immune maturation and function. Minor differences are seen in microbial content between breast- and formula-fed infants, reflecting improved infant formulas in the past 30 years [69]. Bifidobacteria and lactobacillus are found in both breast- and formula-fed babies, although formula-fed babies have more prevalent and higher counts of *Clostridium difficile*, *Bacteroides*, enterococci, and Enterobacteriaceae, while staphylococci are more numerous in breastfed infants. Generally, formula-fed infants had lower bacterial diversity. Further research is required to define the microbial stimulus for normal development, investigate the mechanisms involved, and confirm the role of microbiota in protection for allergic disease.

*The Debate Continues*

The debate whether breastfeeding protects against allergic disease and asthma in children continues, and it is still not possible to make a definitive conclusion regarding this relationship. Much of the difficulty is in the various study designs applied to ask the question. In addition, other factors impact breast milk and its link to allergic disease, such as the mother's diet, the infant's diet, maternal microbiota and exposure to allergens in the environment, timing of introduction to other foods, and composition of the mother's milk (nutritional, immunomodulatory, bioactive). Many of these factors have not been assessed in studies considering the research question "does breastfeeding impact allergic disease?" Research needs to consider confounding, effect modification, and interactions. More research into the bioactive factors


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within breast milk (such as TGF-β) is required to identify possible effect modifiers. Finally, exclusive breastfeeding for 6 months continues to be the keystone for the promotion of allergy health and continues to be recommended by international pediatric societies and academies [78, 79].

## Disclosure Statement

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