

INVITED REVIEW

Understanding the evidence for and against the role of breastfeeding in allergy prevention

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Summary

The relationship between breastfeeding and allergic disease risk has been controversial. This article reviews the current evidence for the role of breastfeeding in the prevention of allergic disease. We found considerable methodological limitations inherent in most studies evaluating the effect of breastfeeding in allergic disease. Nevertheless, since randomized control trials in breast feeding research would be considered unethical, the evidence remains limited to poorer quality observational studies where participation and recall bias can severely affect the objectivity of the data collected. Furthermore, reporting of type of breastfeeding (exclusive, full or partial) may be biased by a participant's inherent belief system of what they think they should be doing. Current evidence is inconclusive regarding the effect of breastfeeding on the development of eczema, with the most recent systemic review reporting no protective effect. There is insufficient data regarding the effects of breastfeeding on objective measures of food allergy at any age. Studies show a paradoxical effect of breastfeeding on the prevention of asthma, with an apparent protective effect against early wheezing illness in the first years of life yet an increased risk of asthma in later life; however, these findings must be interpreted with caution. Existing studies fail to adequately adjust for confounders, including the critical issues of protection against early life respiratory illnesses and reverse causation. Therefore, it is possible that the effect of breastfeeding on early wheezing illness reflects protection against respiratory infection, the predominant trigger of wheezing in early childhood, rather than a true reduction in risk of asthma. In summary, future research that takes into account the potential contribution of confounding factors and effect modifiers is needed to clarify the role of breastfeeding in development of allergic disease and to inform current clinical guidelines on the prevention of allergic disease.

Abbreviations AD, atopic dermatitis; AR, allergic rhinitis; ASCIA, Australasian Society of Clinical Immunology and Allergy; BM, breast milk; CMF, cows milk formula; DDAD, doctor diagnosed atopic dermatitis or eczema; Dr Diag, doctor diagnosis; ESPACI, European Society for Paediatric Allergology and Clinical Immunology; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology, and Nutrition; Excl BF, exclusive breast feeding; FHx, family history; IgA, secretory immunoglobulin A; IgE, immunoglobulin E; IRR, incidence rate ratio; ISAAC, International study of asthma and allergies in children; LF, lactoferrin; LRT, lower respiratory tract; NHMRC, National Health and Medical Research Council; OR 95% CI, odds ratio and 95% confidence interval; SF, solid food; SIDS, sudden infant death syndrome; TAHS, Tasmanian Longitudinal Health Study; WHO, World Health Organisation; Whz, wheeze.

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Introduction

Breastfeeding has many reported health benefits for both mother and child, and as the most natural way to

feed babies, also has many positive psychological benefits including optimizing early mother-infant bonding. Breast milk contains numerous immune factors including IgA antibodies. There is evidence suggesting that

breastfeeding protects against a variety of health problems in infancy and childhood including SIDS, necrotizing enterocolitis, childhood obesity, diabetes, severe infections and allergic diseases, as well as reducing the risk of cardiovascular disease and cancer in later life. This review will discuss both the biological plausibility and potential role of breastfeeding in the prevention of allergic disease including food allergy, eczema, asthma and allergic rhinitis. Importantly, we will also discuss the significant methodological issues that limit interpretation of the current evidence base.

Breastfeeding was first suggested to prevent the development of allergic disease in 1936 when Grulee and Sanford reported it was associated with a lower incidence of eczema [1]. Since that time, the debate has raged over whether or not breastfeeding does in fact protect against the development of allergies and allergic diseases. Although proponents of prolonged and exclusive breastfeeding often argue the many benefits of breastfeeding, it has been surprisingly difficult to gather evidence for beneficial effects in the prevention of allergic disease. The reasons for this are many and varied and will be discussed below. As a result of these limitations in evidence base, peak expert bodies have generated an array of guidelines that are at times in conflict with each other and these will also be discussed.

Definitions of infant feeding – a source of confusion when comparing studies

There are a myriad of ways by which infants receive nutrition in the first few months of life, leading to a broad range of infant feeding practices. Infants can be fed by breastfeeding alone, supplemented partially with expressed breast milk, infant formula (including cow's milk based formulae either unmodified or partially hydrolysed, goat's milk formula, soy-based formula or medicated formulae including extensively hydrolysed and amino-acid based formulae or polymeric formulas), fully formula fed, or any of the above supplemented with solids.

The World Health Organisation has published criteria for infant feeding practices [2]. The WHO criteria for 'exclusive breastfeeding' requires feeding with breast milk (including milk expressed or from a wet nurse) and does not allow intake of any other liquids or solids with the exception of oral rehydration solution, drops and syrups (vitamins, minerals, medicines) [2]. An infant who receives water, water-based drinks or juices but not non-human milk formula is considered to be 'predominantly breastfed' and no longer 'exclusively breastfed'. An infant who receives any non-human milk formula, even for one feed, is considered to be 'partially breastfed'. Partially breastfed refers to the combined use

of breast milk and formula either as a routine or on a variable basis due to work or social commitments and/or the inability to effectively express breast milk. 'Never breastfed' refers to situations where mothers never initiate breastfeeding or are unable to establish breastfeeding. Research studies have used a variety of definitions for breastfeeding that are not always consistent with the above WHO definitions, and in many cases have failed to report a specific definition for breastfeeding. These variations in definitions used and the inconsistency of reporting of definitions can contribute significantly to study heterogeneity when trying to establish the impact of breastfeeding on a disease outcome.

Methodological considerations when evaluating an evidence base for guidelines

Study design

There have been several reviews of the methodological challenges inherent in the study of breastfeeding [3]. The single most problematic methodological limitation in the investigation of the benefits of breastfeeding in allergic disease is the inability to randomize infants to a non-breastfeeding 'control' arm and to undertake a randomized control trial for the generation of level one evidence [4]. Furthermore blinding of breastfeeding is impossible. Even if expressed breast milk was used in a blinded fashion to improve the quality of study design, the possibility that breast milk supply would be compromised by the absence of infant stimulation of the breast poses a significant ethical dilemma. Consequently, observational studies offer the only population-based approach to investigate the potential beneficial effects of breastfeeding, acknowledging the obvious inherent limitations associated with this approach.

Another important limitation is the potential bias due to parent-selection of feeding preferences. One form of such a bias, 'reverse causation', is already well recognized to influence feeding preferences in families with infants at high risk of allergic disease, and is presumed to result from recommendations for prolonged and exclusive breastfeeding in current guidelines for prevention of allergic disease. Indeed, Lowe *et al.* [5] reported that families at high risk of allergic disease are more likely to select this form of feeding. Therefore the association between breastfeeding for more than 6 months and an increased risk of allergic disease observed in their cohort of 620 high-risk infants can potentially be explained by the fact that high-risk families choose to breast feed longer rather than by the fact that breast feeding increases the risk of allergic disease. In addition to adjusting for family history risk which may drive behaviour that is not causally associated with the outcome of allergic disease, other factors could

potentially act as confounders including socio-economic status (with lower rates of breastfeeding amongst those with lower education levels and SES), smoking, country of origin and region specific feeding guidelines (discussed further below), and must be adequately adjusted for as part of the data analysis.

Inconsistency of definitions for breastfeeding and disease outcomes across studies

Another methodological caveat in studies examining the effects of breastfeeding on allergic disease development is that the majority have not provided clear definitions for breastfeeding and/or are unable to accurately report the nature of breastfeeding in the subjects (exclusive, predominantly, partially or never breastfed). This inconsistency in the reporting and classification of extent of breastfeeding significantly complicates our ability to compare results from different studies. This is particularly true when considering food allergy as an outcome since complementary formula most frequently is based on cow's milk protein and early exposure to unmodified cow's milk protein may significantly impact on the risk of developing cow's milk allergy. Indeed, there have been conflicting reports that exposure to cow's milk protein in early infancy can both increase and decrease the risk of developing cow's milk allergy as well as eczema [6], which are likely to have been confounded by this issue. Furthermore the secretion of intact cow's milk protein (beta-lactoglobulin) in breast milk has been well described [7], and the level of allergenic protein content in breast milk can vary not only from mother to mother but from feed to feed within the same woman. A further factor to consider is that timing of introduction of solids can significantly effect intestinal microbial colonization and may potentially also confound the effect of breastfeeding on allergic disease outcomes. Therefore studies investigating benefits of breastfeeding need to adjust for the timing of introduction of solids, the duration of breastfeeding, and infant exposure to cow's milk protein, as well as capturing information on maternal diet.

The definitions of allergic disease are similarly 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 the gold standard food challenge for diagnosis of food allergy. Similarly diverse outcome definitions have been applied in studies evaluating the impact of breastfeeding on eczema, asthma, and allergic rhinitis.

Differences in study populations

It is likely that breast milk composition will vary between individuals and these variations may influence

the effects of breast milk on prevention of allergic disease. For example, the levels of TGF β within breast milk were shown to vary widely between individuals, possibly related to atopic history of the mothers or probiotic intake, and higher levels were associated with protection against allergic disease outcomes [8]. The myriad of breast milk factors that may mediate the beneficial effects of breast milk on prevention of allergic disease are discussed in the following section. Previous studies have not taken the potential impact of effect modifiers into account and these differences may contribute to the divergent findings of studies.

How might breastfeeding protect against allergic disease?

In evaluating the evidence for or against a protective effect of breastfeeding on the development of allergic disease, it is relevant to consider plausible biological mechanisms by which breastfeeding might confer beneficial effects.

Immune modulatory components of human milk

The composition of human breast milk is complex and contains many factors that interact with the infant's intestinal milieu and immune system. Components of breast milk that have immune modulatory activity include antigens (allergens), cytokines, immunoglobulins, polyunsaturated fatty acids, and chemokines [9]. Secretory Immunoglobulin A (IgA) is the predominant antibody isotype in human breast milk and exhibits specificity for an array of common intestinal and respiratory pathogens [10]. Lactoferrin (LF) is the major protein in mature milk and has several effects including microbicidal, immunostimulatory, and anti-inflammatory actions, mediated through inhibition of the production of several proinflammatory cytokines [11]. Hence, both IgA and lactoferrin may modulate the intestinal microbiota composition, which plays an important role in the development of allergic disease (discussed in the next section). A variety of leucocytes with immune protective functions, are present in colostrum and mature milk, including macrophages, neutrophilic granulocytes, and lymphocytes [10]. The exact role of these cells in the development and maturation of the infant's immune system is not clear but it has been hypothesized that they may both compensate for the immature function of the neonatal immune system and promote its maturation. Other components of human breast milk include hormones, growth factors, and partially digested milk peptides [12].

The cytokines, TGF β and IL10, are particularly relevant when considering the tolerogenic potential of breast milk [8, 13]. A systematic review has shown that

TGF β levels in human breast milk were positively associated with protection against allergic disease outcomes in infancy and early childhood [8]. Food and airborne allergens present within breast milk are also an important aspect of the tolerogenic potential of breast milk. Maternal exposure to common airborne and dietary allergens as well as the efficiency of antigen transfer across mammary epithelium may therefore be important factors influencing the protective effects of breastfeeding on development of allergic disease. Recent animal studies suggest that the co-presentation of food or inhaled allergen together with immunomodulatory compounds within breast milk is sufficient to induce tolerance to that allergen [14–16]. Furthermore, the presence of allergen-IgG immune complexes within breast milk induced tolerance in offspring without a requirement for TGF β [17]. Allergen-immune complexes were observed in mother mice that were already sensitized to the allergen and then re-exposed to that allergen while breastfeeding [17]. Consistent with these findings from animal models, epidemiological evidence suggests that introduction of foods while the infant is breastfeeding may promote tolerance [18], although a more recent study failed to observe a protective effect of breastfeeding during egg introduction on the development of egg allergy [19].

In summary, numerous breast milk components can have important effects on the immune system of the developing infant, to either promote or impair the development of tolerance and conversely the development of allergic disease.

Establishment of a healthy intestinal microbiota

Microbial colonization of the newborn intestine is required for normal immune development, which in turn is important for regulation of gut inflammatory responses and oral tolerance induction to new foods introduced into an infant's diet [20, 21]. Mice raised in a germ free environment fail to develop oral tolerance and have persistent Th2 dependent responses [22]. This immune deviation can be experimentally corrected by seeding with *Bacteroides fragilis*, but only if this occurs during the neonatal period [22]. Moreover, an altered intestinal microbiota in the first few weeks of life is associated with increased risk of eczema and asthma in infancy [1, 23–25]. However, the specific microbial changes associated with protection against allergic disease remain uncertain and more recent data suggest that microbial diversity may be of greater relevance [26, 27].

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 [28], and by supplying galacto-oligosaccharides

that promote a healthy microbiota composition. A wide variety of galacto-oligosaccharides are found in breast milk, and have documented bifidogenic effects in the infant gut. In addition to galacto-oligosaccharides, breast milk contains nucleotides, IgA, and antimicrobial factors such as lactoferrin, which can modulate the infant gut microbiota composition. Breastfeeding also facilitates exchange of microbes between mother and infant. Weaning breaks the constant supply of oligosaccharides and microbes from the mother, and microbiota differences between breastfed and formula fed infants largely disappear beyond 6 months of age [29].

Timing of introduction of foods

The timing of introduction of foods is directly related to the duration of exclusive breastfeeding and should therefore be considered when reviewing the evidence for or against the role of breastfeeding in the prevention of allergic disease. Emerging data suggest that early introduction of certain allergenic foods is safe and may confer protection against development of allergic disease [30]. We recently assessed the impact of timing of introduction of allergenic foods using data from the Health-Nuts study [19]. Later introduction of egg into the diet was associated with higher rates of egg allergy, with the adjusted odds ratio for introduction of egg after 12 months being 3.4 [95% CI 1.8–6.5] compared with introduction at 4–6 months of age [19]. Interestingly, introduction of cooked egg, such as scrambled, baked or fried, was more protective than introducing egg in baked goods, with the risk of egg allergy in infants who had cooked egg introduced into their diet at 4–6 months being five times lower than those infants who had cooked egg introduced into their diet at the normally recommended time of 10–12 months of age after adjusting for confounding factors. In contrast, there was no protective effect amongst infants who were first introduced baked egg into their diet between 4 and 6 months presumably because a lower dose exposure did not confer a beneficial effect against egg allergy. Similarly, a higher rate of peanut allergy was reported in school aged children living in the UK as compared to those living in Israel [31]. The authors hypothesized that the lower prevalence of peanut allergy in Israel is related to earlier introduction of peanut-based snacks during infancy as compared to avoidance of peanut in the diet for the first 2 years of life in the UK. It should be noted, however, that this would not explain the reduced prevalence of other allergic diseases such as egg and tree nut allergy, as well as eczema that was reported in the Israeli children.

Based on these observations, it is plausible that breastfeeding might influence infant immune responses and the development of allergic disease either directly

via its diverse immune modulating properties or indirectly through its effects on intestinal microbiota.

The effect of breastfeeding on the development of allergic disease

We will now turn to discussing the evidence surrounding breastfeeding and prevention of allergic disease by considering each allergic condition separately.

Food allergy

Studies examining the association between breastfeeding and food allergy are limited and are listed in Table 1. A major obstacle faced by studies evaluating food allergy as an outcome is that the gold standard for confirming the presence of food allergy is a formal food challenge which is labour intensive, expensive, and impractical to conduct in large epidemiological studies. Consequently, only one of the studies in Table 1 applied the definition of food allergy as an allergic reaction following food ingestion [32], whereas other studies relied upon surrogate markers for identification of food allergy such as IgE sensitization to food allergens (demonstrated by positive skin prick test or presence of food-specific IgE in serum) [33–35] or self reported food allergy [36]. A large longitudinal Swedish birth cohort study reported a reduced risk of clinical reaction to food at 2 years of age [32] and a reduced risk of sensitization to cow's milk and wheat at age 8 years in children exclusively breast fed for ≥ 4 months [33]. A large Australian longitudinal study found that exclusive breastfeeding for the first 3 months of life was associated with a reduced risk of parent reported food or medicine allergy at age 7 years but an increased risk of self reported food allergy at age 44 years [36]. Conversely, in a German study of allergy in childhood, subgroup analyses in newborns with or without elevated cord blood IgE and a family history of allergy revealed that exclusive breastfeeding for ≥ 5 months was associated with an increased risk of sensitization to egg white at 1 year (but not at 2 years) in children who had elevated cord blood IgE, but not in children who had a family history of allergy or both a family history and high cord blood IgE [35]. Finally the Isle of White birth cohort reported no association between breastfeeding for ≥ 3 months and peanut sensitization at 4 years of age although detailed data on the type of breastfeeding were not provided [34].

Currently there is insufficient evidence to suggest whether breastfeeding does or does not protect against food allergy. Further studies using more rigorous food allergy definitions would be valuable.

Atopic dermatitis

Atopic dermatitis has a widely variable presentation and definitions of atopic dermatitis/eczema adopted in epidemiological studies have been inconsistent, making comparisons between studies difficult. Several diagnostic criteria are commonly used, including the UK working party diagnostic criteria [37] that is partially based on original criteria proposed by Hannifin and Rajka [38], and the ISAAC study questionnaire definition [39]. Along with the variation in the definition of eczema/atopic dermatitis there is also considerable variation in the definition of breastfeeding that is used between studies. Most of the studies reported herein in relation to eczema have used exclusive breastfeeding for a set period of months, ranging from ≥ 3 to 5 months.

There have been two systematic reviews and meta-analyses of prospective cohort studies on the association between breastfeeding and atopic dermatitis and they have revealed different findings [40, 41]. The first review published in 2001 [40] found that breastfeeding in the first 3 months was associated with a reduced incidence of AD, with a stronger effect in those with a family history of allergic disease. Conversely, a more recent review published in 2009 [41] found no association between AD and exclusive breast feeding for the first 3 months even when stratified by parental atopy.

We have performed a comprehensive assessment of all the studies examining the association between breastfeeding and eczema/AD (Table 2). Not only is there considerable variation in the definition of eczema used between studies but the age at which eczema is assessed varies widely. There are no studies examining long-term eczema risk into adulthood, with the longest follow-up completed only to the age of 7 years [42]. The majority of studies have found neither an increase nor a decrease in risk of eczema associated with breastfeeding [43–53]. A positive association between exclusive breastfeeding for up to 4 months and eczema in early childhood (up to age 7 years) has been shown in five studies [35, 42, 53–55]. However the issue of reverse causation, that is self-selection to prolonged breastfeeding in infants with atopic manifestations, was not uniformly taken into account. One of these studies did attempt to account for reverse causation by excluding children who developed eczema during the period of breastfeeding, and confirmed a persistent significant positive association between exclusive breastfeeding and eczema in children with a family history of allergic disease [56].

A negative/inverse association between exclusive breastfeeding for ≥ 3 months and eczema in early childhood (up to age 4 years) was found in five studies [32, 50, 57–59]. Two of these studies that reported a negative association between exclusive breastfeeding (for 16

Table 1. Studies examining the association between breastfeeding and food allergy

Study author	Country	No.	Study type	Follow-up	BF definition	Food allergy definition	Association with food allergy	Limitations/strengths
Businco [44]	Italy	101	High risk birth cohort	Birth – 24 months	Excl BF 6 months vs. partial BF with supp with soy or CMF	Dr diag gastrointestinal allergy	No difference in risk of Dr diag gastrointestinal allergy in children excl BF $\geq$ 6 months (Unadj OR = 0.65, 95% CI 0.01–8.4)	Prospective recall of BF; no adjustment for confounders; Dr diagnosis of outcome; possibility of possibility of reverse causation not addressed
Saariinen [94]	Finland	150	Birth cohort	Birth – 17 years	Excl BF > 6 months; BF 1–6 months; BF < 1 month	Food allergy = history of skin rash, urticaria, lip swelling, pain/aching/throat or severe vomiting after ingesting certain foods	Food allergy at 3 years highest in the group BF for < 1 month. No OR presented only%	Prospective recall of BF; no adjustment for confounders; Dr diagnosed outcomes; possibility of possibility of reverse causation not addressed
Marini [54]	Italy	80*	High risk (both parents atopy) birth cohort	Birth – 36 months	(Unclear what definition used)	Gastrointestinal disorders + urticaria (0–6 months) = urticaria defined if it appeared twice within 1 hour of exposure to antigen; moderate or severe gastrointestinal symptoms defined as vomiting &/or diarrhoea	BF not associated with gastrointestinal disorders + urticaria (0–6 months) (OR = 1.3 95% CI 0.5–3.1)	BF not clearly defined; adjustment for confounders; Dr diagnosed outcomes; possibility of possibility of reverse causation not addressed
Tariq [34]	Isle of Wight	1218	Birth cohort	Birth – 4 years	BF $\geq$ 3 months if excl not defined	Peanut sensitization = SPT	No association between BF and peanut sensitization (no OR reported)	BF recall when child was greater than 1 year; adjustment for confounders; SPT objective outcome; possibility of possibility of reverse causation not addressed
Wetzig [35]	Germany	325	High risk	Birth – 2 years	BF $\geq$ 5 months	Specific IgE for hens egg	Increased risk of sensitization to hens' egg at 1 year in BF children (unadj OR = 4.9, 95% CI 1.2–20.4). [in group with increased IgE levels at birth]; No association between BF and hens egg sensitization at 2 years nor with lactoprotein at 1 or 2 years	Unclear when BF information collected; No adjustment for confounders; Dr diagnosed outcomes and objective outcome of SPT; possibility of possibility of reverse causation not addressed
Kull [32]	Sweden	3791	Birth cohort	Birth – 2 years	Excl BF $\geq$ 4 months; Partial BF for $\geq$ 6 months also assessed	Reaction to food = any of the following symptoms directly after consumption of food: AD, urticaria, oedema of lips/eyes, pruritus around eyes, running nose, asthma or Dr diag food allergy	No difference in risk of reaction to food in children BF $\geq$ 4 months (OR = 0.91, 95% CI 0.75–1.1). No association with partial BF	BF recall when child was greater than 1 year old; adjustment for confounders; parent reported outcomes; possibility of possibility of reverse causation not addressed

(continued)

Table 1 (continued)

Study author	Country	No.	Study type	Follow-up	BF definition	Food allergy definition	Association with food allergy	Limitations/strengths
Matheson [36]	Australia	8280	Population-based cohort	7–44 years	Excl BF 3 months	Self reported allergy to foods or medicines at age 7 years & self reported allergy to foods at age 44 years	Reduced risk of allergy to foods at 7 years in those excl BF (OR = 0.75, 95% CI 0.62–0.92) & increased risk of allergy to foods at 44 years in those excl BF (OR = 1.25, 95% CI 1.05–1.51)	BF recall when child was 7 years old; adjustment for confounders; parent and self reported outcomes; possibility of possibility of reverse causation not addressed
Kull [33]	Sweden	2370	Birth cohort	Birth – 8 years	Excl BF ≥ 4 months	Determination of serum IgE antibodies to common inhalant and food allergens at 4 and 8 years. ImmunoCAP phadiatop	At 8 years, reduced risks of sensitization to phadiatop or fx5 (OR = 0.79, 95% CI 0.64–0.99). Individually BF associated with reduced risk cow's milk sensitization (OR = 0.66, 95% CI 0.47–0.94) and Wheat sensitization (OR = 0.62, 95% CI 0.39–0.98). [in children without any allergy symptoms during BF period]	BF recall when child was 1 year; adjustment for confounders; objective outcome; possible reverse causation addressed

AD, atopic dermatitis; Dr Diag, doctors diagnosis; Excl BF, exclusive breast feeding; IgE, Immunoglobulin E.

*High-risk group recruited for allergy prevention study which included an intervention group ($n = 279$) randomly allocated to one of two infant formula groups if breast feeding supplementation was required or stopped for any reason and the parents not participating in the formula intervention were also followed up and formed the $n = 80$ non-intervention group.

Table 2. Studies examining the association between breastfeeding and atopic dermatitis/eczema

Study author	Country	No.	Study type	Follow-up	BF definition duration	Atopic dermatitis definition	Association with AD	Limitations/strengths
Hide [43]	UK	843	Birth cohort	Birth – 52 weeks	Excl BF ≥ 6 months	DDAD	No difference in risk of AD in children excl BF ≥ 6 months (unadj OR = 1.03, 95% CI 0.50, 1.98)	Prospective recall of BF; no adjustment for confounders; Dr diagnosed outcomes
Gruskay [95]	US	908	Birth cohort	Birth – 15 years	Any BF in the first 3 months	AD = erythematous, intensely pruritic papulovesicular eruptions occurring in cheeks, antecubital, popliteal spaces with weeping, oozing & crusting	No adjusted OR presented and not calculable from data presented	BF not exclusive but recalled prospectively; no adjustment for confounders; Dr diagnosis of outcomes; Possibility of reverse causation not addressed
Businco [44]	Italy	101	High-risk birth cohort	Birth – 24 months	Excl 6 months	DDAD	No difference in risk of AD in children excl BF ≥ 6 months (unadj OR = 1.3 95% CI 0.1, 12.2)	Prospective recall of BF; No adjustment for confounders; Dr diagnosis of outcomes;
van Asperen [46]	Australia	79	Birth cohort	Birth – 20 months	Excl BF for 2 months or 4 months vs. CMF &/or solids	AD = defined as examination evidence of areas of scaly, erythematous, pruritic dermatitis primarily involving flexural folds, face, cheeks or areas behind the ears but excluding xeroderma alone	No difference in risk of AD in those excl BF for 2 months (unadj OR = 1.62 95% CI 0.56–4.78); no difference risk of AD in those excl BF for 4 months (unadj OR = 1.68 95% CI 0.53, 5.53)	Possibility of reverse causation not addressed
Pratt [45]	UK	198	Birth cohort. divided by FHx of atopy	Birth – 4½/ 5 years	Excl BF ≥ 12 weeks	Eczema = (i) dry skin, cradle cap & mild erythema round mouth, (ii) some or all of these features with an area of skin usually on the face or behind ears red scaly cracked or weeping, (iii) extensive eruptions involving face, trunk, & limbs; (ii and iii) regarded as eczema	Children with atopic FHx no difference risk of AD at 4½/ 5 years in those excl BF ≥ 12 weeks (unadj OR = 0.6 95% CI 0.1, 2.6). Children without atopic FHx no difference risk of AD at 4½/5 years in those excl BF ≥ 12 weeks (unadj OR = 1.1, 95% CI 0.2, 6.5)	Prospective recall of BF; No adjustment for confounders; Dr diagnosis of outcomes; Possibility of reverse causation not addressed
Poyasa [47]	Finland	91	High risk-birth cohort	Birth – 5 years	BF 3–6 months or ≥ 6 months vs. BF ≤ 3 months	Atopic eczema = pruritic dermatitis accompanied by dry skin on the face in infancy (1 year) & on flexural surfaces of the extremities at 5 years	No difference in risk of AD if BF 3–6 months (unadj OR = 0.81, 95% CI 0.06, 7.4); no difference in risk of AD if BF > 6 months (unadj OR = 1.1 95% CI 0.26, 5.7)	BF recall when child was 1 year old; no adjustment for confounders; Dr diagnosis of outcomes; possibility of reverse causation not addressed
Saarinén [94]	Finland	150	Birth cohort	Birth – 17 years	Excl BF > 6 months; BF 1–6 months; BF < 1 month	DDAD at 3, 5, 10 & 17 years	DDAD at 1 and 3 years lowest in > 6 months BF group. No OR presented only%	Prospective recall of BF; no adjustment for confounders; Dr diagnosis of outcomes; possibility of reverse causation not addressed

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Table 2 (continued)

Study author	Country	No.	Study type	Follow-up	BF definition duration	Atopic dermatitis definition	Association with AD	Limitations/strengths
Herrmann [96]	Germany	138	High-risk maternal dietary intervention study	Birth – 12 months	Excl BF $\geq$ 3–4 months	AD = history of dry skin and three of pruritic dermatitis at typical sites, facial or extensor eczematous or lichenified dermatitis, peri auricular fissures	No data on BF and AD risk presented	Prospective recall of BF; no adjustment for confounders; Dr diagnosis of outcomes; possibility of reverse causation not addressed
Marini [54]	Italy	80*	High risk (both parents atopy) birth cohort	Birth – 36 months	(Unclear what definition used)	DDAD = itchy eczematous rash increases/face/scalp between 0 and 1 year	Increased risk of AD at 1 year in BF children (OR = 1.8 95% CI 1.0, 3.2)	BF not clearly defined; adjustment for confounders; Dr diagnosis of outcomes; Possibility of reverse causation not addressed
Wetzig [35]	Germany	325	High risk	Birth – 2 years	BF $\geq$ 5 months	SCORAD scale	Increased risk of eczema in children excl BF $\geq$ 5 (unadj OR = 2.68, 95% CI 1.1, 6.6) [children with increased IgE levels at birth and FHx]	Unclear when BF information collected; no adjustment for confounders; Dr diagnosis of outcomes; possibility of reverse causation not addressed
Bergmann [42]	Germany	1314	Birth cohort	Birth – 7 years	Excl BF for each month (continuous)	DDAD at 7 years	Increased risk of AD with each increasing month of BF (OR = 1.03, 95% CI 1.002–1.06)	BF recall prospectively; adjustment for confounders; Dr diagnosis of outcomes; possibility of reverse causation not addressed
Kull [32]	Sweden	3791	Birth cohort	Birth – 2 years	Excl BF $\geq$ 4 months partial BF for $\geq$ 6 months also assessed	AD = itchy rash for 2 weeks with typical distribution (face/outer limbs/fold of elbows, behind knees/wrists or fronts of ankles and dry skin) or Dr Diag eczema	Decreased risk of AD if BF $\geq$ 4 months (OR = 0.85, 95% CI 0.71, 1.0). No association with partial BF	BF recall when child was greater than 1 year old; adjustment for confounders; parent reported outcomes; possibility of reverse causation not addressed
Schoetzaue [57]	Germany	1121	High-risk birth cohort	Birth – 1 year	Excl BF 16 weeks vs. CMF	AD = typical distribution on Dr examination, pruritus (scratching), duration 14 days, relapsing	Decreased risk of AD in children excl BF 16 weeks (OR = 0.47, 95% CI 0.30, 0.74)	Prospective recall of BF; adjustment for confounders; clinically assessed outcomes; possibility of reverse causation not addressed
Kerhof [58]	Netherlands	708	High-risk Birth cohort (PIAMA)	Birth – 1 year	Excl BF $\geq$ 13 weeks	AD at 1 year = itchy skin condition, involvement of arms & legs, general dry skin, visible dermatitis flexures, cheeks, limbs	Decreased risk of AD in children excl BF $\geq$ 13 weeks (OR = 0.4 95% CI 0.2–1.0) [OR for children with visible eczema at 1 year visit]	Prospective recall of BF; adjustment for confounders; Dr diagnosis of outcomes; possibility of reverse causation not addressed

(continued)

Table 2 (continued)

Study author	Country	No.	Study type	Follow-up	BF definition duration	Atopic dermatitis definition	Association with AD	Limitations/strengths
Kramer [48]	Belarus	3483	Population-based study nested in clinical trial	Birth – 12 months	Excl BF 3 months vs. excl BF $\geq$ 6 months	Eczema = rash lasting $\geq$ 2 weeks or recurred after clearing for 1 week, itchy, localized to face or extensor surfaces of arms & legs	No difference in risk of eczema in children excl BF 3 months compared to those excl BF $\geq$ 6 months (OR = 1.14, 95% CI 0.65–2.02)	Prospective recall of BF; adjustment for confounders; Dr diagnosis of outcomes; possibility of reverse causation not addressed
Benn [55]	Denmark	15430	Birth cohort	Birth – 18 months	Excl BF < 4 months vs. excl BF $\geq$ 4 months	AD between 4 and 18 months = Itchy rash, Dr diag atopic dermatitis, recurrent rash, localized increases	Increased risk of AD between 4 and 18 months in children BF for $\geq$ 4 months (IRR = 1.29, 95% CI 1.06, 1.55) only in those with no FHx of allergy	BF recall when child was 6 month & 18 month; adjustment for confounders; validation of outcome definition; possible reverse causation addressed
Laubereau [49]	Germany	3903	High-risk birth cohort intervention trial	Birth – 3 years	Excl BF for 4 month vs. partly/not BF	DDAD at 3 years and itchy rash (ISAAC)	Reduced risk of AD in children excl BF for 4 months (OR = 0.64, 95% CI 0.45, 0.90)	Prospective recall of BF; adjustment for confounders; parent reported outcomes
Kull [50]	Sweden	3670	Prospective birth cohort (BAMSE)	Birth – 4 years	Excl BF $\geq$ 4 months	AD = dry skin combined with itchy rash for at least 2 weeks with typical localization during last 12 months &/or Dr Diag eczema	No difference in risk of AD if BF $\geq$ 4 months (OR = 0.88, 95% CI 0.72, 1.08). When children with AD during BF period removed a reduced risk of AD if BF $\geq$ 4 months (OR = 0.78, 95% CI 0.63, 0.96)	BF recall when child was >1 year old; adjustment for confounders; parent reported outcomes; possible reverse causation addressed
Lugvigsson [51]	Sweden	8346	Birth cohort	Birth – 1 year	Excl BF < 4 months vs. BF $\geq$ 4 months	Any AD = $\geq$ 1 episode of itchy eczema	No difference in risk of AD in children BF < 4 months compared to longer BF (OR = 1.07, 95% CI 0.94, 1.21). No effect of FHx.	BF recall when child was 1 year old; adjustment for confounders; parent reported outcomes; possibility of reverse causation not addressed
Rothenbacher [59]	Germany	803	Birth cohort	Birth – 2 years	Never excl BF; excl BF < 3 months; excl BF 3–6 months; excl BF 6–9 months; excl BF $\geq$ 9 months	DDAD at 2 years	Decreased risk of AD in those excl BF 6–<9 months compared to those excl BF < 3 months (OR = 0.42, 95% CI 0.19, 0.91)	Prospective recall of BF; adjustment for confounders; Dr diagnosed outcomes; Possibility of reverse causation not addressed

(continued)

Table 2 (continued)

Study author	Country	No.	Study type	Follow-up	BF definition	Atopic dermatitis definition	Association with AD	Limitations/strengths
Linneberg [70]	Denmark	34793	Birth Cohort	18 months	Excl BF < 2 months; Btw 2 & 4 months; > 4 months	Itch rash and Dr diag localized increases	Increased risk of AD if BF Btw 2 & 4 months (OR = 1.14 95% CI 1.02–1.27); and if BF > 4months (OR = 1.12, 95% CI 1.00–1.25)	Prospective recall of BF at 6 & 18 months; adjustment for confounders; parent reported outcomes; validation of diag of eczema; Possibility of reverse causation not addressed
Mirshahi [52]	Australia	616	High risk (CAPS)	Birth 5 years	Fully BF 3 or 6 months (may not have been excl)	Eczema = flexural eczema or history of itchy rash coming and going for ≥ 3 months	No difference in risk of eczema in children BF excl 3 months (OR = 1.52, 95% CI 0.96, 2.40) or 6months (OR = 1.42, 95% CI 0.94, 2.16)	Prospective recall of BF but may not have been excl; adjustment for confounders; parent reported outcomes; possible reverse causation addressed
Larsson [73]	Sweden	4779	Longitudinal rural-based cohort	1–3 years – 5 years follow-up (aged btw 6–9 years)	> 6 months BF; 3–6 months; < 3 months; none (ref)	Parent reported eczema	No association between BF duration and eczema	BF recall when child was older than 1 year old and exclusivity not defined; adjustment for confounders; parent reported outcomes; possibility of reverse causation not addressed
Miyake [53]	Japan	763	Birth cohort	Birth – 24 months	Excl BF < 4 month vs. excl BF ≥ 4 months	ISAAC questions, itchy rash for 6 months, in the last 12 months and affecting creases	No difference in risk of AD in children excl BF ≥ 4 months (OR = 1.23, 95% CI 0.84, 1.81); In children without FHx increased risk of AD in those excl BF ≥ 4 months (OR = 2.41, 95% CI 1.10, 5.55) [excluding 64 children with suspected AD at btw 2–9 months]	Prospective recall of BF; adjustment for confounders; parent reported outcomes; possible reverse causation addressed

AD, atopic dermatitis; BM, breast milk; CMF, cows milk formula; DDAD, doctor diagnosed atopic dermatitis or eczema; Dr Diag, doctor diagnosis; FHx, family history; IRR, incidence rate ratio; ISAAC, International study of asthma and allergies in children; SCORAD, SCORing atopic dermatitis.

*High-risk group recruited for allergy prevention study which included an intervention group ($n = 279$) randomly allocated to one of two infant formula groups if breast feeding supplementation was required or stopped for any reason and the parents not participating in the formula intervention were also followed up and formed the $n = 80$ non-intervention group.

and 13 weeks, respectively) and eczema were undertaken in high-risk birth cohorts and assessed eczema risk in the first year of life [57, 58]. Another large German birth cohort study assessing eczema to 3 years of age found a reduced risk of AD in children breast fed for ≥ 4 months only in those with a family history of allergic disease [49]. Other studies have also reported inverse associations between breastfeeding and eczema, but found no interaction with a family history of allergic disease [32, 50, 59]. Only one study compared different durations of breast feeding, with the protective effect of exclusive breast feeding only observed in the group breast fed for between 6 and <9 months [59].

Our assessment of the studies examining the association between breastfeeding and eczema/AD is in line with the review by Yang *et al.* [41]. Current evidence does not support a beneficial effect of breastfeeding on development of eczema. There are an equal number of studies reporting a beneficial or negative effect, although the majority of studies reported no effect on eczema in early childhood.

Asthma

The relationship between breastfeeding and asthma has been controversial with numerous studies being published since the late 1970s. Several extensive reviews/meta-analyses have been conducted in an attempt to summarize and consolidate the evidence on the relationship between breastfeeding and asthma. In 2001 Gdalevich and colleagues [60], conducted a meta-analysis reviewing all studies published between 1966 and 1999 and identified 12 prospective studies that met their inclusion criteria. Overall they found a protective effect of exclusive breastfeeding on bronchial asthma [60]. Although authors of this review took great care to include studies with detailed and prospective collection of exposure data (breastfeeding), the use of 'bronchial asthma' as a surrogate definition for asthma was less rigorous. Bronchial asthma was defined as all of the following: asthma diagnosed by a physician, consecutive reporting of wheezing beyond 1 year, and treatment for lower respiratory tract allergy. Another multidisciplinary review by van Odiijk *et al.*, [61] also concluded that there was an overall protective effect of breastfeeding on allergic disease which included asthma and wheeze but the definitions of asthma and wheeze were not reported. We have summarized the studies reported in these two extensive reviews and additional studies reported since 2003 in Table 3. Over 30 studies have now been conducted evaluating the relationship between asthma and breastfeeding with conflicting results.

The definitions of 'asthma' in the studies of breastfeeding presented herein are varied, as were the age

ranges at which subjects were assessed. This is particularly relevant since recent prospective studies have clarified that wheezing in young children represents a heterogeneous group of wheezing conditions rather than a single disorder [62, 63] and that not all children who wheeze in the first years of life go on to develop asthma. It is therefore important to understand that wheezing in early life may not necessarily represent true asthma persisting beyond early childhood when evaluating the impact of breastfeeding on asthma.

Based on our assessment of the studies presented in Table 3, there is consistent evidence that breastfeeding, of any type, is protective against the development of wheezing in early life, before approximately 7–8 years of age [32, 36, 64–75]. This protective effect of breastfeeding appears to be strongest for wheezing in the first 2–3 years of life [32, 36, 59, 67–72], which is consistent with breastfeeding protecting against upper and lower respiratory tract infections [76].

The effect of breastfeeding on asthma that persists beyond early childhood is less clear. A number of studies have suggested that breastfeeding may have opposite effects on wheezing in early life as compared to wheezing in later childhood and adulthood which is more likely to represent asthma. A large study by Rusconi *et al.*, [67] ($n = 16\,333$) reported that breastfeeding was associated with a reduced risk of 'Transient Wheeze' [defined as lower respiratory tract infection (LRTI) with wheeze before 2 years and no current wheeze in the last 12 months at 6–7 years of age] but an increased risk of 'Late-Onset Wheeze' (defined as no LRTI with wheeze before 2 years but wheeze in the last 12 months at 6–7 years of age). The Tucson Children's Respiratory Study found that breastfeeding was associated with lower rates of recurrent wheeze before the age of 6 years, but was a risk factor for asthma and recurrent wheeze between 6 and 13 years [68]. Similarly, the Tasmanian Longitudinal Health Study (TAHS) observed that exclusive breastfeeding for the first 3 months of life was associated with a reduced risk of asthma before the age of 7 years but an increased risk of asthma between 14 and 44 years [36]. Furthermore the Dunedin Multidisciplinary Health and Development Research Study found that breastfeeding was associated with an increased risk of current asthma between 9 and 26 years but did not examine the association between breastfeeding and asthma before 9 years of age [77]. Taken together, there is accumulating evidence from observational studies that breastfeeding may protect against wheezing in early childhood (up to age 6–7 years) but increase the risk of asthma in late childhood and adulthood. Given the limitations of evidence derived from observational studies, and in particular the issue of reverse causation, these findings highlight the need

Table 3. Studies examining the association between breastfeeding and wheezing/asthma

Study author	Country	No.	Study type	Follow-up	BF definition duration	Wheezing/asthma definitions	Association with wheeze/asthma	Limitations/strengths
Hide [43]	UK	843	Birth cohort	Birth – 52 weeks	Excl BF $\geq$ 6 months	Asthma = 1 or more LRT obstructive disease episode	Reduced risk of Asthma in children excl BF $\geq$ 6 months (Unadj OR = 0.37, 95% CI 0.13–0.88)	Prospective recall of BF; No adjustment for confounders; Dr diagnosed outcomes
Gruskay [95]	US	908	Birth cohort	Birth – 15 years	Any BF in the first 3 months	Asthma = recurrent attacks of cough/dyspnoea with wheezing and prolonged expiration reversible with sympathomimetic agents	No adjusted OR presented and not calculable from data presented.	BF not exclusive but recalled prospectively; no adjustment for confounders; Dr diagnosed outcomes; reverse causation not addressed
Businco [44]	Italy	101	High-Risk Birth Cohort	Birth – 24 months	Excl 6 months	Dr diag asthma	No difference in risk of Asthma in children excl BF $\geq$ 6 months (unadj OR = 0.15, 95% CI 0.003–1.17)	Prospective recall of BF; no adjustment for confounders; Dr diagnosed outcomes; reverse causation not addressed
Fergusson [97]	New Zealand	1110	Birth cohort	Birth – 4 years	Milk diet 0–4 months – BF only; bottle Solid diet 0–4 months – yes/no	Childhood asthma = at least 2 medical attendances for wheezing and diag by dr at asthma or wheezing bronchitis	No adjusted OR presented and not calculable from data presented	BF recall from 4 month visit and introduction of other foods recorded; Dr diagnosed outcomes; No adjustment for confounders; reverse causation not addressed
van Asperen [46]	Australia	79	Birth cohort	Birth – 20 months	Excl BF for 2 months or 4 months compared to those who had received milk formulae and/or solids	Whz: defined as any history of wheezing	No difference in risk of whz in those excl BF 2 months (unadj OR = 0.56, 95% CI 0.18, 1.82); or those excl BF 4 months (unadj OR = 0.62, 95% CI 0.13, 2.35)	Prospective recall of BF; no adjustment for confounders; Dr diagnosed outcomes; reverse causation not addressed
McConnochie [98]	USA	223	Clinic patients, cross sectional	Mean age 8.4 years	Excl for 6 months	Current whz; Dr Diag Asthma any age; Whz without cold; Whz with and without colds	Current whz UnAdj RR = 1.74 p = 0.07; Dr diag asthma UnAdj RR = 2.64 p = 0.05; whz without cold UnAdj RR = 2.27 p = 0.04; Whz with & without colds UnAdj RR = 2.31 p = 0.05	BF recall when child was >1 year old; adjustment for confounders RR presented but no CI; parent reported outcomes; reverse causation not addressed
Saariinen [94]	Finland	150	Birth Cohort	Birth – 17 years	Excl BF > 6 months; BF 1–6 months; BF < 1 month	Respiratory allergy = asthma diagnosed at hospital with reversal of whz by bronchodilator on three or more occasions	Respiratory Allergy at 5, 10, 17 years highest in the BF for < 1 month group. No OR presented only%	Prospective recall of BF; No adjustment for confounders; Dr diagnosed outcomes; reverse causation not addressed

(continued)

Table 3 (continued)

Study author	Country	No.	Study type	Follow-up	BF definition duration	Wheezing/asthma definitions	Association with wheeze/asthma	Limitations/strengths
Wright [64]	USA	1246	Birth cohort	Birth – 6 years	Any BF vs. not BF (not Excl)	Recurrent whz at 6 years = whz > 4 times in last years	Overall group no association between whz at 6 years and no BF (OR = 1.49, 95% CI 0.8–2.77). In non-atopics risk of whz at 6 years in was increased in those not BF (OR = 3.03, 95% CI 1.05–8.69)	Prospective recall of BF in first years of life; No adjustment for confounders; parent reported outcomes and Dr diagnosed outcomes; reverse causation not addressed
Marini [54]	Italy	80*	High risk (both parents atopy) birth cohort	Birth – 36 months	(unclear what definition used)	Whz at least 3 episodes or Dr Diag whz	Increased risk of whz 1–3 years (OR = 2.0, 95% CI 1.1–3.9)	BF not clearly defined; adjustment for confounders; Dr diagnosed outcomes; reverse causation not addressed
Tariq [65]	UK	1218	Birth cohort	Birth – 4 years	Formula before 3 months	Asthma at 4 years = 3 episodes whz lasting 3 days	Increased risk of asthma at 4 years in those fed formula before 3 months (OR = 1.8, 95% CI 1.2–2.6)	BF recall when child was >1 year; adjustment for confounders; parent reported outcomes; reverse causation not addressed
Wilson [99]	Scotland	545	Birth cohort	Birth – 7.3 (mean age) years	Excl BF > 15 weeks; Partial BF < 15 weeks; bottle fed	One or more respiratory symptoms [†]	Reduced risk respiratory symptoms if BF excl 15 weeks	Prospective recall of BF in first 2 years of life; No adjustment for confounders; parent reported outcome; reverse causation not addressed
Oddy [66]	Australia	2187	Birth cohort	Birth – 6 years	Exclusive BF vs. Introduction of other milk bf 4 months	Dr diag asthma at 6 years; >3 episodes of whz in last years; whz last 12 months	Reduced risk of Dr diag asthma at 6 years if excl BF (OR = 0.8, 95% CI 0.66–0.98); reduced risk of > 3 whz episodes in last years if excl BF (OR = 0.7 95% CI 0.57, 0.88); reduced risk of whz last 12 months if excl BF (OR = 0.76, 95% CI 0.61, 0.95)	BF recall when child was 1 year old; adjustment for confounders; parent reported outcomes; reverse causation not addressed
Rusconi [67]	Italy	16333	ISAAC Italy cross sectional	6–7 years	BF 1–6 months; BF > 6 month; never BF	Transient Whz = LRTI with whz bf 2 years/no current whz; Persistent Whz = LRTI with whz bf 2 years & current whz; Late onset Whz = Whz last 12 months	Never BF vs. > 6 months BF; transient whz OR = 0.78 (0.66–0.92); persistent whz OR = 0.87 (0.71–1.08); late onset whz OR = 1.21 (1.00–1.46)	BF recall when child was 6–7 years old; adjustment for confounders; parent reported outcomes; reverse causation not addressed
Takemura [100]	Japan	23828	Cross sectional	Range 6–15 years (mean age 10 years)	Excl BF, bottle or mixed for first 3months of life	Asthma – Dr diag/whz/freq whz *no asthma = no to all questions	Bottle fed vs. BF only asthma at follow-up OR = 1.20 (1.05–1.36)	BF recall when child was 6–15 years old; adjustment for confounders; parent reported outcomes; reverse causation not addressed

(continued)

Table 3 (continued)

Study author	Country	No.	Study type	Follow-up	BF definition duration	Wheezing/asthma definitions	Association with wheeze/asthma	Limitations/strengths
Wright [68]	USA	1246	Birth cohort	Birth – 13 years	Excl BF < 4 vs. Excl BF $\geq$ 4 months	Recurrent whz bf 2 years; any asthma between 6 and 13 years	Excl BF $\geq$ 4 months associated with a reduced risk of recurrent whz (OR = 0.45, 95% CI 0.2–0.9); excl BF $\geq$ 4 months associated with an increased risk of any asthma between 6 and 13 years (OR = 8.7, 95% CI 3.4–22.2)	Prospective recall of BF in first years of life; adjustment for confounders; parent reported outcomes and Dr diagnosed outcomes; reverse causation not addressed
Kull [32]	Sweden	3791	Birth cohort	Birth – 2 years	Excl BF $\geq$ 4 months Partial BF for $\geq$ 6 months also assessed	Asthma – 3 episodes of wheeze	Reduced risk of asthma before 2 years if BF $\geq$ 4 months (OR = 0.66, 95% CI 0.51–0.87)	BF recall when child was >1 year old; adjustment for confounders; parent reported outcomes; reverse causation not addressed
Sears [77]	New Zealand	1661	Birth cohort	9–21 years	BF > 4 weeks vs. not BF	Current asthma/ Wheeze with AHR	Longitudinal analysis 9–21 years; Current asthma OR = 2.33 (1.46–3.72) no effect of FH	BF recall when child 3 years of age but validated against nurse records but exposed to formula in hospital after birth; adjustment for confounders; parent & self reported outcomes; reverse causation not addressed
Rothenbacher [59]	Germany	803	Birth cohort	Birth – 2 years	Never excl BF; Excl BF < 3 months; Excl BF 3–6 months; Excl BF 6–9 months; Excl BF $\geq$ 9 months	Dr Diag bronchial asthma at 2 years	Risk of asthma at 2 years in those BF for: 6–9 months OR = 0.42 (0.21–0.82); $\geq$ 9 months OR = 0.35 (0.18–0.66) in those with no FHx	Prospective recall of BF; adjustment for confounders; Dr diagnosed outcomes; reverse causation not addressed
Silva [69]	Brazil	80	Case control	0.5–25 months	Excl BF > 1 month	Persistent whz – >3 Dr diag whz whz – <3 Dr diag whz	Reduced risk of persistent whz in children BF > 1 month (OR = 0.14, 95% CI 0.03–0.76)	BF recall when child was between 0.5 and 25 months; adjustment for confounders; Dr diagnosed outcomes; reverse causation not addressed
Burgess [101]	Australia	4964	Birth cohort	Birth – 14 years	Never BF; < 3 weeks 3–6 weeks; 7 weeks –3 months; $\geq$ 4 months (not excl)	Parental reported asthma at 14 years	No association between risk of asthma at 14 years and BF $\geq$ 4 months (OR = 1.03, 95% CI 0.9–1.2). Not affected by FHx	BF recall at 6 months but no data on exclusivity; no adjusted results presented; parent reported outcomes
Linneberg [70]	Denmark	34793	Birth cohort	18 months	Excl BF < 2 months; between 2 and 4 months; > 4 months	Whz ever = 1 episode of whz before 18 months of age	Reduced risk of whz ever if BF Btw 2 & 4 months (OR = 0.87 95% CI 0.81–0.93); and if BF > 4 months (OR = 0.76, 95% CI 0.71–0.81)	Prospective recall of BF at 6 & 18 months; adjustment for confounders; parent reported outcomes; reverse causation not addressed

(continued)

Table 3 (continued)

Study author	Country	No.	Study type	Follow-up	BF definition duration	Wheezing/asthma definitions	Association with wheeze/asthma	Limitations/strengths
Fredriksson [102]	Finland	1933	Population-based	Baseline 1–6 years old follow-up after 6 years	Excl BF 0–3 months (ref); Excl BF 4–6 months; Excl BF 7–9 months; Excl BF 10–12 months; 12 month+ >4 weeks (Not excl)	Parent reported Dr diag asthma at between 7 and 14 years	Risk of persistent phlegm U-shaped relationship (increased risk with low BF and high BF). No association with asthma or whz (indications of a trend)	BF recall when child was >1 year old; adjustment for confounders; parent reported outcomes; reverse causation not addressed
Mandhane [103]	New Zealand	1661	Birth cohort	9–21 years			Not included reanalysis of scars data with interactions between FHx and gender (very small numbers in subgroups)	
Matheson [36]	Australia	8280	Population-based cohort	7–44 years	Excl BF 3 months	Asthma or whz breathing at 7, 14, 32, 44	Reduced risk of asthma at 7 years in children excl BF 3 months (OR = 0.75; 0.58–0.97) and increased risk of asthma between 14–44 years in children excl BF 3 months (OR = 1.37 95% CI 1.01–1.87, repeated measure)	BF recall when child was 7 years old; adjustment for confounders; parent reported outcomes; reverse causation not addressed
Mirshahi [52]	Australia	616	High risk (CAPS)	Birth 5 years	Fully BF 3 months or 6 months may not have been excl	Probable current asthma = whz preceding 12 months at 5 years in children Dr diag with asthma ever or positive bronch test	No association between risk of asthma and ever BF (OR = 0.59, 95% CI 0.3–1.16). No association between asthma and BF excl 3 months (OR = 0.93, 95% CI 0.56–1.53)	Prospective recall of BF; adjustment for confounders; parent reported outcomes; possible reverse causation addressed
Elliot [71]	UK	9166	Birth cohort	Birth – 7 years	Never BF; Excl BF < 4 months; Excl BF > 4 months	Whz in first 3 years = parent reported whz 6, 18, 30 or 42 months	Reduced risk of whz in first 3 years if BF < 4 months (OR = 0.88, 95% CI 0.79–0.97) and if BF > 4 months (OR = 0.83, 95% CI 0.70–0.98). No relationship with whz, atopy 7 years or BHR at 8 years	BF recall prospectively; adjustment for confounders; parent reported outcomes; possible reverse causation addressed
Hetzner [104]	US	7900	National population cohort	9 months–kindergarten	(1) Excl BF, (2) excl formula, (3) formula with SF, (4) BF with SF, (5) BF & formula (6) BF & formula & SF	Asthma = parental report; respiratory infection	No association btw any form of BF/formula/SF and asthma. Consistent increased risk of resp Infect in all groups compared to BF only group	BF recall when child was 9 months; adjustment for confounders; parent reported outcomes

(continued)

Table 3 (continued)

Study author	Country	No.	Study type	Follow-up	BF definition duration	Wheezing/asthma definitions	Association with wheeze/asthma	Limitations/strengths
Larsson [73]	Sweden	4779	Longitudinal rural-based cohort	1, 3, 5 years follow-up (aged btw 6–9 years)	> 6 months BF; 3–6 months; < 3 months; none (ref)	Dr diag asthma in three groups: no DDA at baseline; no DDA or whz ever at baseline; no DDA but Whz at baseline	No BF associated with increased risk of: DDA in those with no DDA at baseline (HR 2.64, 1.28–5.46); DDA in those with whz at baseline (HR 4.1, 1.2–13.7) – [anything < 6 months of BF significant in this group]	BF recall when child was older than 1 year old and exclusivity not defined; adjustment for confounders; parent reported outcomes; reverse causation not addressed
Midodzi [105]	Canada	2711	NLSCY – longitudinal study	0–23 months	No details provided	Non-whz; Preschool whz; primary School whz; intermittent whz; persistent whz	BF associated with pre-school whz (OR = 1.54, 95% CI 1.13–2.09) and intermittent whz (OR = 1.94, 95% CI 1.22–3.09)	BF recall details unclear; adjustment for confounders; parent reported outcomes; reverse causation not addressed
Miyake [56]	Japan	763	OMCHS study prospective birth cohort study	Birth – 16–24 months	Excl BF < 4 month; Excl BF ≥ 4 months	Probable current asthma = whz preceding 12 months at 5 years in children	No association between whz and BF ≥ 4 months (OR = 1.05, 95% CI 0.73–1.5), nor asthma ever and BF ≥ 4 months (OR = 1.07, 95% CI 0.52–2.2). No effect of FFHx	Prospective recall of BF; adjustment for confounders; parent reported outcomes; reverse causation not addressed
Morass [72]	Austria	1761	Population-based cross sectional	Pre-school children mean age 5.5 years	Excl BF < 4 month; Excl BF ≥ 4 months	ISAAC questions on whz last 12 months & Dr diag asthma	Reduced risk of Dr diag A in those BF ≥ 4 months (OR = 0.5, 95% CI 0.2–1.0) No association with whz	BF recall when child was >1 year old; adjustment for confounders; parent reported outcomes; reverse causation not addressed
Guedes [74]	Brazil	268	Institutional-based cohort study	Birth – 5 years	Excl BF < 6 month; Excl BF ≥ 6 months	Asthma = 2 episodes of reversible airway narrowing, characterized by whz by 5 years	Decreased risk of asthma at 5 years in those BF ≥ 6 months (OR = 0.33, 95% CI 0.18–0.59)	Prospective recall of BF; adjustment for confounders; Dr diagnosed outcomes
Scholten [75]	Netherlands	3115	Birth cohort	Birth – 8 years	No BF; 1–16 weeks BF; >16 weeks BF (not excl)	Asthma at 8 years = whz, dyspnoea, steroid meds	Risk of asthma at 8 years if BF 1–16 weeks (OR = 0.82, 95% CI 0.61–1.09); or BF > 16 weeks (OR = 0.57, 95% CI 0.41–0.80)	BF recall when child 3 month & 1 year; adjustment for confounders; parent reported outcomes; reverse causation not addressed

DDAD, doctor diagnosed atopic dermatitis or eczema; Dr, doctor; Excl BF, exclusive breast feeding; ISAAC, International study of asthma and allergies in children; LRT, lower respiratory tract; SF, solid food; Whz, wheeze.

*High-risk group recruited for allergy prevention study which included an intervention group ($n = 279$) randomly allocated to one of two infant formula groups if breast feeding supplementation was required or stopped for any reason and the parents not participating in the formula intervention were also followed up and formed the $n = 80$ non-intervention group.

[†]One or more respiratory symptoms = cough, wheeze or breathlessness by questionnaire at anytime since birth or in last 12 months (current).

Table 4. Studies examining the association between breastfeeding and allergic rhinitis/atopy

Study author	Country	No.	Study type	Follow-up	BF definition duration	Allergic rhinitis/atopy definitions	Association with allergic rhinitis/atopy	Limitations/strengths
Hide [43]	UK	843	Birth cohort	Birth – 52 weeks	Excl BF ≥ 6 months	Chronic rhinitis = persistent upper airways obstruction or snuffles	No difference in risk of chronic rhinitis in children excl BF ≥ 6 months (unadj OR = 0.66, 95% CI 0.41–1.05)	Prospective recall of BF; no adjustment for confounders; Dr diagnosis of outcomes
Gruskay [95]	US	908	Birth cohort	Birth – 15 years	Any BF in the first 3 months	AR = history of rhinorrhea, sneezing and itching of nose with or without puffy eyes during the pollen season	No adjusted OR presented and not calculable from data presented	BF not exclusive but recalled prospectively; no adjustment for confounders; Dr diagnosis of outcomes; reverse causation not addressed
Businco [44]	Italy	101	High-risk birth cohort	Birth – 24 months	Excl 6 months	Dr diag rhinitis	Unable to calculate unadj ORs due to no BF with the outcome	Prospective recall of BF; no adjustment for confounders; Dr diagnosed outcomes; reverse causation not addressed
van Asperen [46]	Australia	79	Birth cohort	Birth – 20 months	Excl BF for 2 or 4 months compared to those who had received milk formulae and/or solids	Rhinitis: defined as any history of nasal discharge and/or blockage occurring continuously for at least 4 weeks and excluding obvious infective rhinitis	No difference in risk of rhinitis in those excl BF 2 months (unadj OR = 1.58, 95% CI 0.54–4.56); or excl BF 4 months (unadj OR = 1.5, 95% CI 0.46–5.14)	Prospective recall of BF; no adjustment for confounders; Dr diagnosed outcomes; reverse causation not addressed
Marini [54]	Italy	359	High risk (both parents atopy) Birth Cohort	Birth – 36 months	(unclear what definition used)	Rhinitis + conjunctivitis = 3 consecutive weeks of rhinorrhea associated with conjunctival symptoms without infectious features	BF not associated with Rhinitis + conjunctivitis 1–3 years (OR = 1.2, 95% CI 0.7–2.8)	BF not clearly defined; adjustment for confounders; Dr diagnosed outcomes; reverse causation not addressed
Strachan [106]	UK	11765	Population-based birth cohort	Birth & 11–16 years	Feeding in the first month = Breast only (ref) vs. breast & bottle vs. bottle only	Self reported doctor diagnosed hay fever	Compared to breast only, bottle only feeding in first month associated with reduced risk of hayfever (OR = 0.95, 95% CI 0.83–1.08)	BF recall at 1 month of age, unclear if exclusive; adjustment for confounders; parent reported outcomes; reverse causation not addressed
Tariq [65]	UK	1218	Birth cohort	Birth – 4 years	Formula bf 3 months	Rhinitis = two of 3 nasal symptoms of discharge, blockage, recurrent sneezing & eye symptoms	No association, no adjusted ORs presented for rhinitis	BF recall when child was greater than 1 year; adjustment for confounders; parent reported outcomes; reverse causation not addressed
Alm [107]	Sweden	295	Cross sectional	5–13 years	Exclusive BF for ≥ 4 months	Atopy = SPT positive or IgE positive to panel of common allergens	No association between excl BF ≥ 4 months and atopy (OR = 0.73, 95% CI 0.48–1.11)	BF recall when child was greater than 1 year old; adjusted for heredity & sex only; objective outcome

(continued)

Table 4 (continued)

Study author	Country	No.	Study type	Follow-up	BF definition duration	Allergic rhinitis/atopy definitions	Association with allergic rhinitis/atopy	Limitations/strengths
Oddy [66]	Australia	2187	Birth cohort	Birth – 6 years	Exclusive BF 4 months vs. Introduction of other milk bf 4 months	Atopy = SPT positive or IgE positive to panel of common allergens	Exclusive BF for 4 months associated with reduced risk of atopy (OR = 0.77, 95% CI 0.62–0.94)	BF recall when child was 1 year old; adjustment for confounders; objective outcome for atopy; reverse causation not addressed
Kull [32]	Sweden	3791	Birth cohort	Birth – 2 years	Excl BF ≥ 4 months Partial BF for ≥ 6 months also assessed	AR – reported sneezing, runny/nose, and red itchy eyes after contact with pets or pollen &/or dr diag AR	Reduced risk of AR if BF ≥ 4 months (OR = 0.73, 95% CI 0.54–0.99)	BF recall when child was >1 year old; adjustment for confounders; parent reported outcomes; reverse causation not addressed
Sears [77]	New Zealand	1661	Birth cohort	9–21 years	BF > 4 weeks vs. not BF	SPT (Cat, HDM, grass, alternaria) at 13 years	Increased risk of any allergen at 13 years (OR = 1.94, 95% CI 1.42–2.65). No effect of FHx	BF recall when child 3 years of age but validated against nurse records but exposed to formula in hospital after birth; adjustment for confounders; parent & self reported outcomes and objective measures of allergies; reverse causation not addressed
Matheson [36]	Australia	8280	Population-based cohort	7–44 years	Excl BF 3 months	Allergic rhinitis at 44 years	Increased risk of AR at 44 years in children excl BF 3 months (OR = 1.14, 95% CI 1.01–1.28)	BF recall when child was 7 years old; adjustment for confounders; parent reported outcomes; reverse causation not addressed
Elliot [71]	UK	9166	Birth cohort	Birth – 7 years	Never BF; Excl BF < 4 months; Excl BF > 4 months	Atopy 7 years = SPT to panel of common allergens	No association between BF and atopy at 7 years	BF recall prospectively; adjustment for confounders; parent reported outcomes; possible reverse causation addressed
Larsson [73]	Sweden	4779	Longitudinal rural-based cohort	1–3 years–5 years follow-up (aged between 6 and 9 years)	> 6 months BF; 3–6 months; < 3 months; none	Dr diag rhinitis	No association between BF duration and AR	BF recall when child was older than 1 year old and exclusivity not defined; adjustment for confounders; parent reported outcomes; reverse causation not addressed

AR, allergic rhinitis.

for further investigation of the long-term effects of breastfeeding on asthma.

Protective effect of breastfeeding against respiratory infections and the impact on asthma risk

When considering the relationship between breastfeeding and asthma, it is important to recognize that breastfeeding can also modulate the risk of respiratory tract infections in childhood, which can in turn influence asthma risk. Moreover, virus-associated wheezing in early life (that is related to abnormal lung development and resolves with lung maturation in childhood) and wheezing illness that persists into later childhood (that is strongly associated with atopy) are known to have different underlying pathogenic mechanisms. Breastfeeding is therefore expected to have differential effects on the various phenotypes of wheezing illness. This complex interrelationship between breastfeeding, infection, wheezing and asthma, may contribute to the paradoxical effects of breastfeeding on asthma observed in early vs. later life.

There is evidence from both developing and developed countries that breast feeding decreases the risk and severity of a wide range of infectious diseases including otitis media, upper and lower respiratory tract infections, diarrhoea, urinary tract infections, neonatal septicaemia, and necrotizing enterocolitis [78]. Respiratory infections are closely associated with the risk of asthma and the association appears to be dependent on the timing of infections during infancy, the number of infections, and the type or severity of the infection. Several studies have demonstrated that an increased number of lower respiratory tract infections (LRTI) are associated with the development asthma [79–81]. The association between upper respiratory tract infections (URTI) and asthma is less clear, with one study showing that having less than three URTI in the first year of life was associated with a reduced risk of asthma but having more than three URTI increased the risk of asthma [79]. There is also some evidence that non wheezing LRTI in the first year of life is associated with a reduced risk of atopy in childhood [79, 82]. So the effect of breastfeeding in reducing the occurrence, number, and severity of both URTI and LRTI has an important impact on the evaluation of breastfeeding effects on risk of asthma. Taking into account these diverse effects of breastfeeding on respiratory infections in early life, it is possible that the reduced risk for wheezing illness in the first few years of life associated with breastfeeding reflects a reduced risk for respiratory infection-associated wheezing (virus-associated wheezing illness). The reported positive association between breastfeeding and asthma in later years must also be interpreted with caution since it is not possible to exclude the likely confounding issue of reverse causation.

Allergic rhinitis

Once again, the definitions of allergic rhinitis (AR) used across the various studies were highly varied making direct comparisons between studies difficult. We have summarised the studies investigating the association between breast feeding and allergic rhinitis in Table 4. A meta-analysis of the effect of breastfeeding on the development of AR found that overall, breastfeeding had a non-significant protective effect on AR risk [83]. Contrary to what would be expected, in the subgroup analysis of subjects with a family history of allergic disease, no association between breastfeeding and AR risk was found, but a significant protective effect was instead observed in the subgroup without a family history. An important caveat of the studies included in the meta-analysis is that none included clinical assessment of subjects beyond 4 years of age. As the development of allergic sensitization to inhaled allergens begins to rise around 3 years of age and peaks during adolescence [84], studies without follow-up into adolescence may miss a substantial number of allergic rhinitis cases. Therefore the finding of a lack of association between breastfeeding and allergic rhinitis should be interpreted with caution. Indeed, two more recent studies that included more prolonged clinical follow-up of subjects beyond childhood found that breastfeeding was associated with an increased risk of AR in adulthood [36] and an increased risk of sensitization to inhaled allergens (Cat, HDM, Grass, Alternaria) at 13 years [77]. This increased risk of allergic rhinitis in later childhood and adulthood is similar to the findings reported for asthma, and could be confounded by the issue of reverse causation. These deficiencies emphasize the need to further clarify the effects of breastfeeding on long-term allergic disease outcomes.

What are the current clinical guidelines?

Effective strategies for prevention of allergic disease remain elusive and interventions to reduce the risk of allergic disease are limited. Current expert guidelines for prevention of allergic disease recommend exclusive breastfeeding for 4–6 months and the use of hydrolysed cow's milk formulas in place of standard formulas in high-risk infants when breastfeeding is not possible during the first 4–6 months of life. An extensive review of current infant feeding guidelines (including breastfeeding) in individual countries around the world has been undertaken by Grimshaw *et al.*, [85] and stratified by government and peak specialty bodies which at times are at variance with each other. The European Society for Paediatric Allergology and Clinical Immunology (ESPACI) and European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN)

jointly recommended exclusive breastfeeding for 4–6 months for prevention of food allergy [86]. Similarly, the American Academy of Pediatrics [87, 88] and Australasian Society of Clinical Immunology and Allergy [89] guidelines recommend exclusive breastfeeding for 4–6 months for the prevention of allergic disease.

One practical consideration is that the above advice for allergy prevention contradicts the WHO recommendations for infant feeding which advocate exclusive breastfeeding for at least 6 months for all infants. This WHO advice is based upon the clear benefits of breastfeeding on infant nutrition, hygiene, and infectious disease risk in developing countries. Nevertheless, the rate of exclusive breastfeeding in Africa, Asia, Latin America, and the Caribbean in infants younger than 2 months is only 47–57% [90]. This percentage falls further for infants aged between 2 and 5 months to 25–31%. In developed countries, the rate of breast feeding is considerably higher at approximately 60–70% of women commencing breast feeding [91, 92] but there is still considerable drop off by 6 months with only 21% of babies still being fed any breast milk [90, 93]. The conflicting recommendations for allergy prevention and infant feeding have caused confusion for those seeking advice on allergy prevention, and further clarification and resolution is required. Nevertheless, it is likely that expert guidelines may need to be tailored to individual regions as region specific factors such as prevalence of breastfeeding and general living conditions will impact upon recommendations for infant feeding. For example, feeding guidelines in developing countries with high rates of morbidity and mortality resulting from poor sanitation and contaminated water, which prohibit the safe use of formula feeding, may not be relevant to developed countries where sanitation is high but chronic immune-mediated diseases are prevalent.

Discussion

Breastfeeding in itself has a myriad of health benefits for both the mother and child, and can be recommended for these reasons. However, the current literature on breastfeeding and allergic disease, although extensive, fails to provide a conclusive answer as to whether or not breastfeeding confers a protective effect against the development of allergic disease. Importantly, it should be recognized that all existing studies suffer from significant methodological limitations such as reverse causation, recall bias, and lack of standardization in their definitions of breastfeeding and allergic disease outcomes. Interestingly, earlier studies were more likely to reveal beneficial effects than more recent studies. This may be due to the improved methodo-

logical quality of more recent studies, which have examined larger numbers of subjects and included adjustment for confounders in data analysis, or because conditions (for example in the environment) have changed to alter the impact of breast feeding on allergy. For example, one may speculate that recent changes in diet and intestinal microbiota associated with the Western lifestyle may have lessened the impact of breastfeeding on allergic disease in more recent studies, and future studies addressing these issues are warranted. The variability of results obtained from different studies may also relate to differences in study populations, since variations in breast milk composition and genetic factors may influence the effects of breast milk on development of allergic disease. Meta-analyses may miss an important effect of breastfeeding in specific sub-groups of individuals, however, the current literature does not allow this to be examined.

In summary, it is not possible to draw definitive conclusions regarding the role of breastfeeding in the prevention of allergic disease from the current literature due to the methodological limitations inherent in these studies. Moreover, there are many factors that may influence the potential tolerogenic effects of breast milk such as maternal and infant diet, the maternal microbiota, maternal exposure to food or airborne allergen at the time of breastfeeding, the timing of introduction of foods during infancy, as well as the composition of maternal breast milk (including levels of immunomodulatory factors and allergens) which have not been carefully assessed in previous studies. Furthermore, research that takes into account possible confounders and effect modifiers is needed to elucidate the interacting contributions of these factors and to clarify the conflicting findings of previous studies. In addition, more detailed investigation of the factors in breast milk that could exert immunomodulatory effects is required to identify potential effect modifiers when evaluating the role of breastfeeding in prevention of allergic disease.

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