



Modulation of allergy risk by breast feeding

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Purpose of review

Breastfeeding has been suggested as a candidate for primary prevention of allergies. However, recent comprehensive and thoughtfully written systematic reviews reported mixed results and that overall there is only little evidence for breastfeeding being protective against allergic disorders. As these reviews last searched for relevant studies on 2 October 2014, the aim of our review is to shed light on the association between breastfeeding and allergic disorders (asthma, eczema, allergic rhinitis) recently published.

Recent findings

These recent studies are varied and differ in size, settings, design, depth of data collecting, and quality of the study. Thus far, the results on the association between nonexclusive and exclusive breastfeeding with regards to asthma are mixed especially in young ages. Additionally, if eczema and allergic rhinitis are the outcomes of interest, this recent review does not provide a clearer picture.

Summary

The current guidelines by WHO and European Academy of Allergy and Clinical Immunology (EAACI) on breastfeeding till 6 months and exclusively breastfeeding for 4–6 months, respectively, for the prevention of allergies are not supported by the recent study results. Nevertheless, breastfeeding should be strongly recommended for other beneficial health effects than allergy prevention.

Keywords

allergies, breastfeeding, children, epidemiology

INTRODUCTION

The paradigm of developmental origins of chronic disease in adulthood in combination with more novel technologies in epigenetics, leads to increased attention on breastfeeding during the last decades. The recent WHO series on breastfeeding published in the *Lancet* [1[•],2] is a strong indicator for the emerging interest. The first part of the comprehensive review summarized findings from 28 systematic reviews and/or meta-analysis [2], of which 22 were commissioned for this review. The focus was on the impact of breastfeeding on a broad spectrum of health indicators for children and mothers. In fact for children, this review indicates a protection against infections in terms of diarrhoea, lower respiratory tract infections, and otitis media infections, as well as malocclusion, and on the other hand it can promote increased intelligence and a probable reduction in obesity and diabetes. Breastfeeding was not associated with allergic disorders, blood pressure, or cholesterol. The reported null finding between breastfeeding and allergic disorders is based on a systematic review by Lodge *et al.* [11^{••}], which will be presented in detail below. As Lodge *et al.* [11^{••}] searched for relevant studies on 2 October 2014 we thought to investigate whether

more recent studies published beyond the review by Lodge *et al.* [11^{••}] would lead to a different conclusion. Thus, the aim of our review is to shed light on the association between breastfeeding and allergic disorders (asthma, eczema, allergic rhinitis) published recently.

POTENTIAL MECHANISM TO PREVENT ALLERGIES BY BREASTFEEDING

There are a few known and suggested mechanisms as to why breastfeeding might prevent the development of allergies. First, breastfed infants are not exposed to potential allergenic components derived from cow's milk formula or other food and drinks.

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KEY POINTS

- Breastfeeding for primary prevention of allergies seems intuitive sensible, commonly recommended, but evidence from data is not clear.
- Although, one of the two most recent comprehensive systematic reviews concluded that there is '...no clear evidence of protection against allergic disorders,...' [2], the second stated that there is '...some evidence that breastfeeding is protective for asthma...' [11¹¹].
- The most recent original publications continued with conflicting findings on beneficial, adverse, and no effect studies on breastfeeding and allergic disorders.

Thus, exclusive breastfeeding might be of particular interest. Second, breast milk components such as immunoglobulin A, cytokines, and long chain fatty acids stimulate the immune response and shape the balance between the proinflammatory and anti-inflammatory status [3,4]. In light of this potential mechanism, a longer breastfeeding duration might be important regardless of its exclusivity. Therefore, the duration of any breastfeeding as well the duration of exclusive breastfeeding needs to be considered, especially when there are potential benefits against the development of allergies. Third, exclusively breastfed infants were suggested to have a higher microbial diversity in their intestinal microbiota, which influences the immune system and might serve as a protective factor for the onset of allergies later in life [5,6]. Finally, the beneficial effect of breastfeeding might be mediated by the known and consistently reported decreased risk of infectious diseases in breastfed infants [2].

SOME METHODOLOGICAL PROBLEMS TO ASSESS THE IMPACT OF BREASTFEEDING ON ALLERGIC DISORDERS

There are some severe methodological problems when assessing the impact of breastfeeding on general health indicators and also limitations when specific effects on the development of allergies are considered. Our current knowledge on health effects of breastfeeding is mainly based on observational surveys without any evidence from individual randomized trials because of ethical constraints. In fact, there was only one multicentre, cluster-randomized controlled trial that investigated the effect of an intervention to promote breastfeeding on health indicators [7]. Breastfeeding duration is highly dependent on maternal educational background and other social factors, but the direction of this association might be different across different

regions (developed and developing countries) and vary with time [2]. Therefore, a cautious and extensive adjustment for social factors is important, but even then residual confounding factors cannot be excluded. The potential beneficial effect of breastfeeding on the onset of allergies is based on the paradigm of allergen avoidance, for example, avoidance of cow's milk allergen. This is one reason to recommend exclusively breastfeeding for a certain period. The exclusive breastfeeding duration is of particular importance for the assessment of effects on allergies. Moreover, breastfeeding and breastfeeding duration play a role in health problems of the newborn, which leads the mother to extend breastfeeding. Thus, a longer duration of breastfeeding can be a consequence of health problems and not the other way around. This phenomenon is well described as reverse causation, which is in particular a problem when the impact on development of allergies is considered [8]. Finally, breastfeeding is also associated with coexposure to beneficial lifestyle factors such as no tobacco smoke exposure *in utero* and postnatally [9¹²].

BREASTFEEDING AND ALLERGIES

Summary of the only trial evaluating breastfeeding on allergy as outcome

The promotion of breastfeeding intervention trial is a multicentre, cluster-randomized controlled trial conducted in Belarus [7]. Mother–infant pairs were recruited ($n = 17\,046$) from 31 maternity hospitals randomized in a promotion of breastfeeding hospital group and a control hospital group. Mothers from the intervention group substantially increased total and exclusive duration of breastfeeding compared with control hospitals. Onset of childhood asthma did not differ between breastfeeding-promotion group and control group. However, the risk for eczema was substantially lower in the interventional arm of the trial assessed by typical symptoms during the first year of life [adjusted odds ratio (aOR) 0.54; 95% confidence interval (CI) 0.31, 0.95] [7], but not for extended follow-up for 6.5 years. No differences were reported by parents, when questions from the International Study on Asthma and Allergies in Children were used to assess eczema [10].

Summary of most recent systematic review and meta-analysis

Overall, the systematic review and meta-analysis of studies from 29 studies published until 2 October 2014 [11¹³] showed some beneficial effects against

asthma in children aged 5–18 years (aOR 0.90; 95% CI 0.84, 0.97) in favour of more versus less breastfeeding. Sensitivity analysis of high-quality studies did not show any more statistical significance. In addition, the overall beneficial effect was mainly driven by low or middle-income countries. The few studies ($n=8$) which reported effect estimates for exclusively breastfeeding for 3–4 months versus less, did not show a statistically significant decreased risk neither for the cohort studies ($n=5$; aOR 0.94; 95% CI 0.69, 1.29) nor for all other studies ($n=8$; aOR 0.89; 95% CI 0.71, 1.11). Results from a total of 42 studies could be used for the meta-analysis on eczema. Stratified analysis for study participants younger than 2 years of age, did not show any association between more versus less breastfeeding (OR 0.95; 95% CI 0.85, 1.07): for exclusive breastfeeding for 3–4 months the risk for eczema was decreased (OR 0.74; 95% CI 0.57, 0.97). No substantial decreased association was reported for longer follow-up beyond an age of 2 years (OR 1.07; 95% CI 0.98, 1.16). As many small studies reported a protective effect, publication bias is not unlikely. The few studies, which modelled reverse causation, did not find a strong signal. The meta-analysis for allergic rhinitis was stratified by age of 5 years. Pooling of five effect estimates for older than 5-year study participants showed non-significant increased risk comparing more to less breastfeeding (OR 1.05; 95% CI 0.99, 1.12), whereas the combined risk was decreased for younger children (OR 0.79; 95% CI 0.63, 0.98). The number of studies on allergic rhinitis was small, actually too small to study exclusive breastfeeding.

It is important to mention that the conclusion by Lodge *et al.* [11^{***}] is different from that of Victora *et al.* [2], although the latter is referring only to the systematic review by Lodge *et al.* (2016). Victora and colleagues' [2] statement that there is a no association between breastfeeding and allergic disorders is based on the high-quality studies referenced by Lodge *et al.* (2016), whereas poorer study findings were ignored.

Summary of observational studies published after last systematic review by Lodge *et al.* [11^{***}]

A subjective selection of the most important study results was briefly summarized.

Based on the current WHO guidelines of breastfeeding for 6 months and the EACCI guideline to breastfeed exclusively for 4–6 months, Bion *et al.* [9^{***}] investigated the impact of nonexclusive (0, >0–6, >6 months) and exclusive breastfeeding (0, >0–4, >4 months) on onset of asthma, eczema, rhinitis, and atopy. Data were collected from two

well described birth cohorts: The Isle of Wight (IoW) cohort of 1456 study participants and the Food Allergy and Intolerance Research (FAIR) of 988 study participants as replication cohort. Both the non-exclusive and exclusive breastfeeding groups were followed until age of 18 years (IoW) and 10 years (FAIR), respectively. Breastfeeding (any or exclusive) had no effect on asthma and allergic diseases in the IoW cohort. These findings were not replicated by the data of FAIR. Nonexclusive breastfeeding for more than 0–6 months and exclusive breastfeeding for more than 0–4 showed decreased risks for asthma (0.50; 95% CI 0.32–0.79 and 0.68; 95% CI 0.46–0.99). In addition, FAIR cohort showed a protective effect for long exclusive breastfeeding (>4 months) on rhinitis (0.36; 95% CI 0.18–0.71). The findings were cautiously adjusted for known and suggested confounders. The authors concluded that the results were inconsistent between the two cohorts. Using data from the IoW cohort, Ziyab *et al.* [12] found that Filaggrin gene loss-of-function variants modified the association between breastfeeding and eczema. As Filaggrin gene loss-of-function is associated with early onset of eczema symptoms, this gene variant might be associated with prolonged exclusive breastfeeding. Genetic markers are certainly under investigated so far, when the association between breastfeeding and allergic disorders is examined.

A large Dutch population-based birth cohort examined the association between duration of breastfeeding (any and exclusive) with asthma at age of 6 years and whether these associations might be modified by atopic status or medical history of infectious diseases [13^{***}]. A sample of 5675 children was analyzed. A shorter duration of breastfeeding (<2 months) showed increased risk for asthma at age of 6 years (2.19; 95% CI 1.29, 3.71). Exclusive breastfeeding for less than 4 months was not statistically significantly associated with asthma (1.48; 95% CI 0.89, 2.47). Additional adjustment for inhalant allergies did not substantially change the effect estimates. However, additional adjustment for early respiratory tract infection attenuated the risks for asthma. The authors concluded that breastfeeding seems to have a protective effect on asthma. The underlying mechanism is partly related to early respiratory tract infections, but not to atopy.

A further study investigated the impact of exclusive breastfeeding duration on asthma/whoop, eczema, allergic rhinitis, and allergic sensitization. Data from the high-risk Danish birth cohort study the Copenhagen prospective study on asthma in childhood were used, it contained a small sample of 335 children [14]. Duration of breastfeeding was not associated with allergic sensitization during the

first 6 years of life and with any of the other allergic conditions during the first 7 years of life. Although, the study is underpowered, it has several strengths: prospectively collected data, repeated clinical assessment of outcomes, comprehensive adjustment for potential confounding factors, and sensitivity analysis adjusting for reverse causation.

A case-control study analyzed exclusive breastfeeding and weaning in relation to onset of eczema during the first 2 years of life in a total of 902 children in Italy [15]. No breast milk or the introduction of weaning at age 1, 2, 3, 4, and 5 months showed decreased risk for eczema, although statistically significant for weaning only beyond the 3rd month. The authors concluded that the findings provide evidence against the protective role of prolonged exclusive (but not partial) breastfeeding.

A nationwide large survey in Japan examined the role of breastfeeding for hospitalization for asthma during the first 3.5 years of life [16]. A sample of 43 367 singleton and term newborns was followed up for 3.5 years. Data on hospitalization for asthma between 6 and 42 months was gathered from the parents. Partial breastfeeding durations for 1–2, 3–5, 6–7 months showed non-significant decreased risks for asthma compared with the small group of formula fed newborns as reference. Also, exclusive breast feeding for 6–7 months of age was not statistically significantly associated with a decreased risk for asthma.

Within another large nationwide web-based survey on environmental and lifestyle factors associated with eczema in Japan, the association between exclusive breastfeeding and eczema was reported. Data from 23 662 children aged 6–12 years showed in a multivariable model, that exclusive breastfeeding for at least 6 months increased the risk for current eczema (OR 1.14; 95% CI 1.06, 1.23) [17]. Owing to the cross-sectional study design over-reporting of longer breastfeeding for children with eczema is not unlikely and reverse causation was not considered as another source of bias in this study. The authors speculated that a delayed introduction of solid food as a consequence of long duration of exclusive breastfeeding duration could have led to the increased risk of eczema.

A further Asian study explored the association between breastfeeding and hospital admissions for asthma within an ongoing birth cohort in 8327 Hong Kong Chinese children [18[¶]]. Exclusive breastfeeding for at least 3 months was not associated with hospitalization for asthma from 3 months to 12 years (adjusted hazard ratio 0.89; 95% CI 0.63, 1.25). Also partial breastfeeding was not associated with asthma hospitalization for any length of time. Most of the study participants were never breastfed

(57%), whereas only 6% were exclusively breastfed for 3 months or longer. Thus, the never breastfed group was much bigger than in all the European settings [2] and also much bigger than the nationwide study in Japan [16]. Additionally, the association of breastfeeding and maternal educational level is different from most of the European settings. Although, exclusive breastfeeding in Hong Kong mothers is more common in less educated, it is more common in well educated mothers in Europe and North America (Rollins *et al.* [1[¶]]). Meanwhile, the association between breastfeeding and asthma/wheeze might be stronger in age below 3 years, the strength of this association is diminishing which may explain, the Japanese study of young study participants [16] that reported some indication for a beneficial effect, whereas the study on older children [18[¶]] did not.

Three more studies from Asia were published recently. A large cross-sectional study of 13 335 children aged 4–6 years reported a decreased risk for asthma (aOR 95% CI 0.81, 0.72–0.91) when exclusive breastfed children for 4–6 months were compared with never breastfed infants. Exclusive breastfeeding for more than 6 months was significantly associated with a reduced risk of hay fever (aOR, 95% CI 0.93, 0.89–0.97), rhinitis (0.97, 0.94–0.99), and eczema (0.96, 0.93–0.99). Longer duration of breastfeeding was only significantly protective in children without a family history of atopy [19]. A descriptive case-control study on 665 asthmatic children aged 14 years and younger with 665 age and sex matched controls reported less exclusive breastfeeding for cases compared with controls (51.2 versus 63.2%) [20].

A small cohort of 186 newborns from Taiwan was followed up for the first 4 years of life. Breastfeeding for more than 6 months was associated with lower risk for eczema at age 1 (aOR 0.33; 95% CI 0.07, 0.75) and 2 years (aOR 0.36; 95% CI 0.13, 0.94), but not at age 3 or 4. These beneficial effects in age 1 and 2 years were not driven by exclusive breast feeding, but partial breastfeeding. Breastfeeding duration was not associated with asthma and allergic rhinitis.

As settings of the recently published studies are mainly developed countries in the past and there is a lack of knowledge on associations between breastfeeding and allergies in developing countries, the following studies needs to be highlighted. The study by Bandoli *et al.* [21[¶]] examined whether nativity in a Latina population is a confounder or effect modifier of breastfeeding. Data from 704 Latina mothers living in Los Angeles were used to analyze the association between exclusive breastfeeding and asthmatic symptoms. The study participants participated in a 3.5 year follow-up of a nested case-control study,

where preterm or low birthweight newborns were included as cases. Thus, this study is not population based, but enriched with preterm and low birthweight children. Exclusive breastfeeding longer than 3 months was associated with a decrease risk of asthmatic symptoms (0.51; 95% CI 0.29, 0.90) compared with nonexclusive breastfeeding. Although foreign-born Latinas were more likely to initiate breastfeeding and continue breastfeeding compared with US-born Latinas, maternal nativity did not confound or modify the association between breastfeeding and asthma symptoms.

CONCLUSION

The most recent study findings showed mixed results on the association between nonexclusive and exclusive breastfeeding on asthma with respect to young ages. Evaluations of eczema and allergic rhinitis as outcomes of interest in recent study findings have not provided a clearer picture. These findings did not resolve the problem of heterogeneity across different studies, which was the key conclusion of the recent systematic review and meta-analysis by Lodge *et al.* [11[■]]. The current guidelines on breastfeeding to 6 months by WHO and 4–6 months exclusive breastfeeding by EACCI for the purpose of preventing allergies were not supported by recent study results. However, breastfeeding should be recommended because of other beneficial health effects

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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The most comprehensive and most recent review on breastfeeding and health.