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Symposium II: Infant and childhood nutrition and disease Infant nutrition and allergy

Zrinjka Mišak

Referral Centre for Paediatric Gastroenterology and Nutrition, Children’s Hospital Zagreb, Klaićeva 16, 10 000 Zagreb, Croatia

Over the past several decades, the incidence of atopic diseases such as asthma, atopic dermatitis and food allergies has increased dramatically. Although atopic diseases have a clear genetic basis, environmental factors, including early infant nutrition, may have an important influence on their development. Therefore, attempts have been made to reduce the risk of the development of allergy using dietary modifications, mainly focused on longer breast-feeding and delayed introduction or elimination of foods identified as potentially most allergenic. Recently, there is also an increasing interest in the active prevention of atopy using specific dietary components. Many studies have shown that breast-feeding may have the protective effect against future atopic dermatitis and early childhood wheezing. Concerning complementary feeding, there is evidence that the introduction of complementary foods before 4 months of age may increase the risk for atopic dermatitis. However, there is no current convincing evidence that delaying introduction of solids after 6 months of age has a significant protective effect on the development of atopic disease regardless of whether infants are fed cow’s milk protein formula or human subject’s milk, and this includes delaying the introduction of foods that are considered to be highly allergic, such as fish, eggs and foods containing peanut protein. In conclusion, as early nutrition may have profound implications for long-term health and atopy later in life, it presents an opportunity to prevent or delay the onset of atopic diseases.

Infant nutrition: allergy

The prevalence and severity of atopic manifestations in children has increased significantly over the last few decades^(1–4). As allergic diseases (including asthma, eczema, hay fever and food allergies) are complex multifactorial disorders involving a combination of genetic and environmental interactions, environmental factors must have been the key to explain the variations and changes in allergy prevalence^(2,5,6). It has been indicated that infant nutrition, among other environmental factors, has profound implications on the risk of atopy⁽⁷⁾. Specific nutritional intervention may prevent or delay the onset of atopic diseases in infants at high risk of developing allergy^(4,8).

This paper will review the literature on the effects of infant nutrition on the development of atopic disease, including the role of breast-feeding, timing of introduction of complementary foods and hydrolysed formulas.

Effect of breast-feeding

Although the advantages of breast milk as the optimal form of feeding for children in the first months of life cannot be overemphasised, the role of exclusive breast-feeding in the prevention of allergic diseases is not clear^(9,10). Since the 1930s, the effect of breast-feeding on the risk of

Abbreviation: ESPGHAN, European Society for Paediatric Gastroenterology and Nutrition.

Corresponding author: Dr Zrinjka Mišak, fax +38514600160, email zrinjka.misak@gmail.com

developing allergic diseases has been frequently studied and debated^(11–13). Conflicting findings have been reported from several studies investigating whether prolonged and exclusive breast-feeding increases, decreases or has no effect on the risks of asthma and allergy^(9,12,14). Some studies have reported greater degrees of protection with more exclusive and prolonged breast-feeding and several have noted a larger protective effect in children prone to atopy^(12,13). However, recent studies have raised concern that breast-feeding may not protect children and may even increase the risk^(12,15). In general, many of these studies have been non-randomised, retrospective or observational in design and, thus, inconclusive. Of course, it is not possible to truly randomise breast-feeding, which is always a confounding variable in these studies⁽¹³⁾.

It has been reported that among other environmental factors (early infections, early day-care attendance, presence of two or more siblings at birth and rural environment) breast-feeding for more than 3 months was protective for the development of asthma^(16–18). In 2001, two systematic reviews with meta-analysis on the risk of eczema and asthma reported lower incidence rates of these atopic diseases in children who were exclusively breastfed, with the stronger effect shown for infants with a family history of allergy^(19,20). A series of reports from the German Infant Nutritional Intervention Programme also found that breast-feeding reduces the incidence of atopic dermatitis, supporting the results of the meta-analysis^(13,19,21). The Prevention and Incidence of Asthma and Mite Allergy birth cohort study that included 3115 Dutch children showed that breast-feeding (>16 weeks *v.* no breast-feeding) was significantly associated with a lower asthma prevalence from 3 to 8 years of age, in children of both non-allergic and allergic mothers⁽²²⁾. Furthermore, a study from New Zealand that enrolled a total of 1105 children, showed a significant protective effect of breast-feeding on infant wheezing and other adverse respiratory outcomes that may be early indicators of asthma. Even after adjustment for confounders, each month of exclusive breast-feeding reduced the risk of doctor-diagnosed asthma by 20%, wheezing by 12% and inhaler use by 14%⁽²³⁾. Codispoti *et al.* showed that African-American infants receiving prolonged breast-feeding had significantly decreased risk of allergic rhinitis at the age of 3 years, although this breast-feeding effect was not seen in non-African-American children⁽²⁴⁾.

When compared with breast-feeding with supplemental cow's milk formula, exclusive breast-feeding for 4 months showed a protective effect on developing allergy in infants at high risk⁽¹³⁾. Breast-feeding with supplemental hydrolysed formula (both partially and extensively hydrolysed) also showed a positive effect compared with breast-feeding with supplemental cow's milk formula. However, breast-feeding with supplements of hydrolysed formulas showed no advantage compared with exclusive breast-feeding. Both groups showed a one-third decrease in the risk of atopic dermatitis compared with the risk of breast-feeding with supplements of cow's milk formula⁽²¹⁾.

Concerning asthma, in the study of Fonseca *et al.*, the authors concluded that prolonged breast-feeding (6 months or longer) could reduce the risk of asthma in boys who live in the city⁽²⁵⁾. Furthermore, breast-feeding seems to

decrease the wheezing episodes seen in younger children (<4 years of age) that are often associated with respiratory infections⁽¹³⁾.

In contrast to the above, a 2005 study published from Sweden found no effect of exclusive breast-feeding for less than 4 months on the incidence of atopic dermatitis in the first year of life with or without a family history of atopic disease⁽²⁶⁾. On the other hand, another 2005 study from Sweden found that exclusive breast-feeding for more than 4 months reduced the risk of atopic dermatitis at 4 years of age with or without a family history of allergy⁽²⁷⁾. In their review, Kramer and Kakuma also found no benefit of exclusive breast-feeding beyond 3 months of age on the incidence of atopic dermatitis in studies in which parents were not selected for risk of allergy⁽²⁸⁾.

Furthermore, Kramer *et al.* conducted a cluster-randomised trial on 13 889 infants and found that prolonged and exclusive breast-feeding had no protective effect on allergic symptoms and diagnoses or on positive skin-prick tests⁽¹²⁾. Other studies restricted to populations with increased risk have even reported the increased risk from breast-feeding of eczema, wheezy disorder, asthma and sensitisation. Some authors reported a small protective effect on eczema and a dual effect, protecting in high-risk infants but increasing risk in infants without such heredity⁽¹⁵⁾.

Pohlabein *et al.* observed a significantly increased risk of developing an atopic disease in children without a genetic allergic disposition who were exclusively breastfed for more than 4 months (OR 1.62, 95% CI 1.02, 2.56). In contrast, the appearance of allergic diseases in 2-year-old children with a family history of atopy was less common in breastfed children than in never-breastfed children. Nonetheless, when analysed in greater detail, children with a maternal-only predisposition had a considerably higher risk of allergic disease symptoms at the age of 2 years if they had been exclusively breastfed for more than 4 months than if they had never been breastfed. Children with a paternal-only predisposition had a significantly decreased risk if they had been breastfed for more than 4 months than if they had never been breastfed (OR 0.39, 95% CI 0.18, 0.83). Breast-feeding for ≤4 months seemed to have no influence on increased or decreased risk of allergic disease in children with either a paternal or maternal allergic predisposition⁽¹¹⁾.

An often-discussed explanation for the higher rates of allergies detected in children who have been breastfed for more than 4 months is the reversal of cause and effect. In other words, on detecting early signs of atopic disease in their infant, mothers who knew that their infants were at risk of developing allergy were more likely not only to breastfeed but also to breastfeed for a longer period of time (which would explain the higher number of children with allergic symptoms within the subgroup of children breastfed for more than 4 months)^(11,18,21). To control for such an effect, Pohlabein conducted an additional analysis excluding children with reported symptoms of allergic disease in the first 12 months of life and the results remained almost unchanged⁽¹¹⁾. Kusunoki *et al.*⁽¹⁸⁾ showed that children with mixed and complete breast-feeding showed a significantly lower prevalence of bronchial asthma

($P = 0.04$ and $P = 0.003$ respectively). On the other hand, the prevalence of atopic dermatitis and food allergy were significantly higher in those with complete breast-feeding ($P = 0.04$ and $P = 0.01$ respectively). However, there was a higher proportion of complete breast-feeding among those with greater risk of allergic diseases (presence of family history, either eczema or wheeze within 6 months after birth or food allergy in infancy) and when analysis included these risks as confounding factors, the promoting effects of breast-feeding on atopic dermatitis and food allergy disappeared suggesting that this effect was most likely because of reverse causation⁽¹⁸⁾. Giwerzman *et al.* has shown, in a birth cohort born of mothers with asthma, that duration of exclusive breast-feeding increased the infant's risk of eczema during the first 2 years of life. In contrast, the same study showed that breast-feeding protected infants from wheezy disorders and severe wheezy exacerbations⁽¹⁵⁾.

Overall, at the present time, firm conclusions about the role of breast-feeding in either preventing or delaying the onset of specific food allergies are not possible⁽¹³⁾. However, exclusive breast-feeding should always be encouraged.

Hydrolysed formula

When infants are not exclusively breastfed, partially hydrolysed formula (infant formula where cow's milk proteins were modified by hydrolysis processes) may be considered an effective measure to potentially reduce the risk of developing atopic dermatitis^(3,6,29–31). Specifically, it was observed that feeding with partially-hydrolysed whey-protein formula instead of intact protein cow's milk formula reduces the risk of atopic dermatitis in infants, particularly in infants with a family history of allergy^(3,6,13,14,29). Depending on the degree of modification, hydrolysed cow's milk formulas are differentiated into extensively and partially hydrolysed whey or casein hydrolysates⁽⁶⁾. However, comparative studies of the various hydrolysed formulas indicate that not all formulas have the same protective benefit^(6,13,21). Extensively and partially hydrolysed formulas can be used for primary prevention of allergy in infants at high atopic risk, while only extensively hydrolysed formulas are indicated for secondary prevention in patients with manifest cow's milk allergy. If atopic disease associated with cow's milk allergy has occurred, partially-hydrolysed formula is not recommended, because it contains potentially allergenic cow milk peptides⁽²¹⁾.

The role of partially hydrolysed and extensively hydrolysed formulas for the prevention of atopic disease has been the subject of many studies in both formula-fed and breastfed infants in the last 15 years⁽¹³⁾. The German Infant Nutritional Intervention Programme study showed that the incidence of atopic dermatitis was substantially reduced in those using the extensively hydrolysed casein-based formula and the partially-hydrolysed whey-based formula but not the extensively hydrolysed whey-based formula, compared with the incidence in those in the cow's milk formula group⁽²¹⁾. The prospective German birth cohort study GINIplus demonstrated that predisposed children

without nutritional intervention had a 2.1 times higher risk for eczema than children without a familial predisposition. In other words, the data demonstrate that early intervention with hydrolysed infant formulas can substantially compensate up until the age of 6 years for an enhanced risk of childhood eczema due to familial predisposition to allergy⁽³¹⁾.

Meta-analysis of clinical trial and intervention studies was conducted and included a total of eighteen articles on hydrolysed infant formula and the risk of atopic dermatitis. A statistically significant 44% reduced risk of atopic manifestations was found among infants receiving whey protein partially hydrolysed formula compared with infants receiving intact protein cow's milk formula (summary relative risk estimate 0.56, 95% CI 0.40, 0.77). In a sub-analysis of four studies that reported results specifically for atopic dermatitis, the incidence of atopic dermatitis was reduced by 55%⁽²⁹⁾.

The use of amino acid-based formulas for prevention of atopic disease has not been studied. Soya formulas, on the other hand, have a long history of use for atopic disease in infants. In a recent meta-analysis of five randomised or quasi-randomised studies, the authors concluded that feeding with soya formula should not be recommended for the prevention of atopy in infants at high risk of developing allergy⁽¹³⁾.

In conclusion, exclusive breast-feeding should be encouraged as the standard for infant nutrition in the first months of life^(29,30). However, when infants are not exclusively breastfed, partially hydrolysed formula may be considered an effective measure to potentially reduce the risk of developing atopic dermatitis^(3,6,30,31).

Effect of introducing solids

Despite the lack of evidence, there have been a lot of changes in the timing of first exposure to solid foods over the last 40 years. In the 1960s, most infants had been exposed to solids by 4 months of age, while in the 1970s guidelines recommended delayed introduction of solids until after 4 months. By the late 1990s, expert bodies began to recommend delaying solids until after 6 months of age⁽⁸⁾. Until very recently, for infants with a family history of allergy expert guidelines recommended delaying introduction of allergenic foods (including avoiding eggs until 2 years and nuts until 3 years of age), as well as delaying solid foods until after 6 months and continuation of breast-feeding for at least 12 months^(8,13,32). These recommendations have been challenged by recent population studies, creating the concern that the current practice of delaying complementary foods until 6 months of age may increase, rather than decrease, the risk of immune disorders^(1,9,13,33–35).

In a systematic review of thirteen studies, five studies found a positive association between early introduction of solid foods (before 4 months of age) and eczema, one study found an association with pollen allergy, and others reported no association between early introduction of solid foods and the development of allergic diseases⁽³⁶⁾. In contrast, Sariachvili *et al.* showed that early introduction (within the first 4 months) of solid foods was associated with a reduced risk for eczema among children with

allergic parents, whereas no significant effect was found among children with non-allergic parents⁽³⁷⁾. Furthermore, a review by Prescott *et al.* showed an increased risk of allergy if solids were introduced before 3–4 months⁽³⁴⁾. Some other prospective studies supported neither prolonged breast-feeding nor delayed introduction of solid foods for the prevention of allergic diseases in children^(9,35). The results from the population-based, prospective, cohort study by Nwaru *et al.* provided evidence for increased risk of allergic sensitisation to food and inhalant allergens with delayed introduction of solid foods^(9,38). However, the concept of reverse causality has to be considered in such studies because families with a history of allergic diseases or with infants with early signs of allergy may delay the introduction of solids. Therefore, separate analyses of data for the subgroup of children with parental history of asthma or allergic rhinitis were performed in the study by Nwaru *et al.* and results did not change, demonstrating no evidence of reverse causality⁽⁹⁾. These findings are consistent with those of Koplin *et al.* who showed that infants introduced to egg at 4–6 months had a lower risk of egg allergy than those introduced to egg after that time, particularly those introduced to egg at 10–12 months of age and after 12 months of age, even after adjusting for family history of allergy and infant-allergy symptoms⁽⁸⁾. Furthermore, a large, prospective, German population-based birth cohort study on asthma and allergic disease did not find evidence to support a delayed introduction of solids beyond 6 months of life for the prevention of atopic dermatitis and atopic sensitisation. However, in the analysis of data of that cohort at the age of 6 years, late introduction of solid foods was associated only with increased risk of sensitisation to food allergens and not with sensitisation to inhalant allergens, eczema, asthma or allergic rhinitis⁽³⁵⁾. Moreover, data from wheat allergic patients obtained from a longitudinal birth cohort study showed that delaying exposure to wheat until after 6 months was associated with an increased risk of wheat allergy, not a protective effect⁽³⁸⁾. It has also been shown that early introduction of fish into the child's diet was associated with less eczema development and a tendency to less asthma, while sensitisation was not associated with the timing of fish introduction⁽³⁹⁾. Moreover, countries where peanuts are commonly used as weaning foods, like Israel for example, have low incidence of peanut allergy⁽⁴⁰⁾. A UK birth cohort study investigated the effect of age at the introduction of solid foods on wheezing, eczema, and atopy among children 5–5 years of age and showed that late introduction of eggs and milk was associated with increased risk of eczema. However, the retrospective collection of data on the introduction of solid foods might have introduced recall bias in that study⁽⁹⁾.

Based on the current available data, it was proposed that early complementary food introduction may hasten and/or maintain oral mucosal tolerance rather than increase the risk of food allergy⁽³⁰⁾. Tolerance to food allergens appears to be driven by regular, early exposure to these proteins during a 'critical early window' of development⁽³⁴⁾. Although the timing of this window is not clear, current evidence suggests that this is most likely to be between 4 and 6 months of life and that delayed exposure beyond

this period may increase the risk of food allergy, coeliac disease and islet-cell autoimmunity^(8,33,34). There is also evidence that other factors such as favourable colonisation and continued breast-feeding promote tolerance and have protective effects during this period when complementary feeding is initiated⁽³⁴⁾.

In summary, the evidence supporting the benefit of delaying the introduction of allergenic foods (cow's milk, fish, eggs and peanuts) beyond 6 months of age is contradictory^(13,30). This issue must be explored further with carefully controlled interventional trials^(13,30,32). Also, at present, there are insufficient data to document a protective effect of any dietary intervention beyond 4–6 months of age for the development of atopic disease⁽¹³⁾. In 2008, based on the available data, the Nutritional Committee of the American Academy of Pediatrics updated the recommendations, and now it states that although solid foods should not be introduced before 4–6 months of age, there is currently no convincing evidence that delaying their introduction beyond this period has a significant protective effect on the development of atopic disease regardless of whether infants are fed cow's milk protein formula or human milk, and this includes delaying the introduction of foods that are considered to be highly allergenic, such as fish, eggs and foods containing peanut protein^(1,13). The Committee on Nutrition of the European Society for Paediatric Gastroenterology and Nutrition (ESPGHAN) recently concluded that complementary foods may be introduced safely between 4 and 6 months, and 6 months of exclusive breast-feeding may not always provide sufficient nutrition for optimal growth and development⁽⁴¹⁾.

The role of probiotics and prebiotics

There is accumulating evidence that early colonisation of the intestinal tract by an appropriate intestinal microbiota is important for the healthy maturation of the immune system, including appropriate programming of oral tolerance to dietary antigens⁽¹⁾. As it is generally agreed that the intestinal microbiota plays an important physiological role in the postnatal development of the immune system, many attempts have been made to influence the intestinal microbiota and thereby the occurrence of atopic manifestations⁽⁴²⁾. Therefore, as a potential means of preventing allergies, dietary interventions to modulate the intestinal microbiota of infants using probiotics and prebiotics have been explored⁽¹⁾.

Probiotics are defined as microbial cell preparations or components of microbial cells that have a beneficial effect on the health and well being of the host, while prebiotics are food ingredients that stimulate selectively the growth and activity of bifidobacteria and lactobacilli in the gut and thereby benefit health^(43,44). In human subjects, a number of randomised controlled trials have shown a preventative effect of probiotic or prebiotic feeding on the development and severity of atopic dermatitis in infants. However, other recent clinical studies of probiotic supplementation to infants at risk have failed to demonstrate clear benefits, with one study even reporting that probiotic intervention increased sensitisation to allergen. Explanations for varied results among studies include differences in types and

doses of the used bacterial strains, host factors (i.e. genetic predisposition to allergic disease, polymorphism in microbial recognition pathways etc.) and other environmental factors (diet, treatment with antibiotics and general microbial burden). Despite uncertainties regarding their efficacy, infant formulae are increasingly supplemented with probiotics, prebiotics or synbiotics⁽¹⁾.

Some trials show favourable results for probiotics with regard to atopic dermatitis and it was reported that prenatal and postnatal probiotic supplementation is an effective approach in preventing the development of eczema during 1 year of life in infants at high risk of allergy^(30,45). A pioneering placebo-controlled study in high-risk families with perinatal supplementation of the mothers' and infants' diet with *Lactobacillus* GG demonstrated a reduced prevalence of early atopic dermatitis in children⁽⁴⁶⁾. On the contrary, some controlled trials in infants at high risk of atopy failed to demonstrate a preventive effect of probiotics on the emergence of atopic dermatitis⁽⁴²⁾. Furthermore, probiotics have no proven preventive effect on the development of asthma⁽⁴⁷⁾.

Considering the above, the Committee of Nutrition of the ESPGHAN considers that there is still too much uncertainty to draw reliable conclusions from the available data and does not recommend the routine use of probiotic-supplemented formula in infants⁽⁴⁸⁾.

Concerning prebiotics, previous data in infants at higher risk of development of atopy demonstrate that a specific mixture of prebiotic oligosaccharides has a protective effect against allergic manifestations⁽⁴⁹⁾. Moreover, Gruber *et al.*⁽⁴²⁾ showed that formula supplementation with a specific mixture of acidic and neutral oligosaccharides is effective as primary prevention of atopic dermatitis also in low atopy risk infants. The authors speculated that the effect persists beyond the first birthday and may even result in a reduced incidence of respiratory allergy later in life⁽⁴²⁾. However, the ESPGHAN Committee of Nutrition considers that there is too much uncertainty to draw reliable conclusions from the available data. Considering that, the Committee does not recommend the routine use of formula supplemented with prebiotics in infants⁽⁴⁸⁾.

Although probiotics and prebiotics are theoretically promising candidates for prevention of atopic diseases, at this stage, the data that confirm their immunologic or therapeutic effects are still lacking and there is currently not enough evidence to support the use of probiotics and/or prebiotics for the prevention of allergic disease in clinical practice^(1,30,47,48). Further clinical results are required before definite recommendations on the use and effectiveness of prebiotics and probiotics in allergy prevention can be made⁽¹⁾.

Conclusion

It has been recognised that early childhood events, including diet, are likely to be important in the development of both childhood and adult diseases⁽¹³⁾. Attempts to reduce the risk of the development of allergy using dietary modification have evolved from passive allergen avoidance to active stimulation of the immature immune system using specific dietary components^(1,41).

Breast-feeding is widely regarded as the ideal food for infants, although its effect in the prevention of allergic diseases has not been conclusively demonstrated. However, there are certain ethical and methodological limitations of studies on breast-feeding, and therefore it is unlikely that current evidence will be improved significantly. ESPGHAN and the European Society for Paediatric Allergology and Clinical Immunology jointly recommend exclusive breast-feeding for 4–6 months for allergy prevention, while the WHO recommends exclusive breast-feeding for 6 months⁽³⁰⁾. Considering existing evidence, the most effective dietary measure for the prevention of allergic diseases even in high-risk patients is exclusive breast-feeding for 4–6 months^(13,41).

For infants at high risk of developing atopic disease who are not breastfed exclusively for 4–6 months or who are formula fed, there is modest evidence that atopic dermatitis may be delayed or prevented by the use of extensively or partially hydrolysed formulas, compared with cow's milk formula^(13,30). Concerning soy-based infant formula, there is no convincing evidence of its use for the purpose of allergy prevention⁽¹³⁾.

Until recently, for infants with a family history of allergy, it was recommended to delay introduction of allergenic foods (eggs until 2 years and nuts until 3 years of age), as well as to delay solid foods until after 6 months^(8,13,32). As the evidence that delaying or avoiding the introduction of allergenic foods prevents or delays the development of allergy is not persuasive regardless of whether infants are fed cow's milk protein formula or human milk, the recommendations have changed^(13,41). In 2008 ESPGHAN has issued a position paper on complementary feeding, which states that avoidance or delayed introduction of allergenic foods for allergy prevention is not recommended. It recommends that complementary foods should not be introduced before 17 weeks, and not after 26 weeks⁽⁴¹⁾.

In conclusion, as early nutrition may have profound implications for long-term health and atopy later in life, it presents an opportunity to prevent or delay the onset of atopic diseases. There have been attempts to reduce the risk of the development of allergy using dietary modifications, from promoting longer breast-feeding and delayed introduction of potentially allergenic foods to active prevention of atopy using specific dietary components. Still, there are many open questions and additional studies are needed to document the long-term effect of dietary interventions in infancy to prevent atopic disease.

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References

1. Cochrane S, Beyer K, Clausen M *et al.* (2009) Factors influencing the incidence and prevalence of food allergy. *Allergy* **64**, 1246–1255.
2. Asher MI (2009) Recent perspectives on global epidemiology of asthma in childhood. *Allergol Immunopathol (Madr)* **38**, 83–87.

3. Alexander DD, Schmitt DF, Tran NL *et al.* (2010) Partially hydrolyzed 100% whey protein infant formula and atopic dermatitis risk reduction: a systematic review of the literature. *Nutr Rev* **68**, 232–245.
4. Passariello A, Terrin G, Baldassarre ME *et al.* (2010) Adherence to recommendations for primary prevention of atopic disease in neonatology clinical practice. *Pediatr Allergy Immunol* **21**, 889–891.
5. Venter C (2009) Infant atopy and allergic diseases: an introduction to dietary aspects. *J Fam Health Care* **19**, 92–96.
6. von Berg A (2009) Modified proteins in allergy prevention. *Nestle Nutr Workshop Ser Pediatr Program* **64**, 239–247.
7. Fewtrell M, Wilson DC, Booth I *et al.* (2011) Six months of exclusive breast feeding: how good is the evidence? *BMJ* **342**, c5955.
8. Koplin JJ, Osborne NJ, Wake M *et al.* (2010) Can early introduction of egg prevent egg allergy in infants? A population-based study. *J Allergy Clin Immunol* **126**, 807–813.
9. Nwaru BI, Erkkola M, Ahonen S *et al.* (2010) Age at the introduction of solid foods during the first year and allergic sensitization at age 5 years. *Pediatrics* **125**, 50–59.
10. Dattner AM (2010) Breastfeeding and atopic dermatitis: protective or harmful? Facts and controversies. *Clin Dermatol* **28**, 34–37.
11. Pohlabein H, Mühlenbruch K, Jacobs S *et al.* (2010) Frequency of allergic diseases in 2-year-old children in relationship to parental history of allergy and breastfeeding. *J Investig Allergol Clin Immunol* **20**, 195–200.
12. Kramer MS, Matush L, Vanilovich I *et al.* (2007) Effect of prolonged and exclusive breast feeding on risk of allergy and asthma: cluster randomised trial. *BMJ* **335**, 815; Epublication 11 September 2007.
13. Greer FR, Sicherer SH, Burks AW *et al.* (2008) Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* **121**, 183–191.
14. van Odijk J, Kull I, Borres MP *et al.* (2003) Breastfeeding and allergic disease: a multidisciplinary review of the literature (1966–2001) on the mode of early feeding in infancy and its impact on later atopic manifestations. *Allergy* **58**, 833–843.
15. Giwercman C, Halkjaer LB, Jensen SM *et al.* (2010) Increased risk of eczema but reduced risk of early wheezy disorder from exclusive breast-feeding in high-risk infants. *J Allergy Clin Immunol* **125**, 866–871.
16. Midodzi WK, Rowe BH, Majaesic CM *et al.* (2010) Early life factors associated with incidence of physician-diagnosed asthma in preschool children: Results from the Canadian Early Childhood Development cohort study. *J Asthma* **47**, 7–13.
17. Arnedo-Pena A, Puig-Barberà J, Bellido-Blasco JB *et al.* (2009) Risk factors and prevalence of asthma in schoolchildren in Castellon (Spain): A cross-sectional study. *Allergol Immunopathol (Madr)* **37**, 135–142.
18. Kusunoki T, Morimoto T, Nishikomori R *et al.* (2010) Breastfeeding and the prevalence of allergic diseases in schoolchildren: Does reverse causation matter? *Pediatr Allergy Immunol* **21**(1 Pt 1), 60–66.
19. Gdalevich M, Mimouni D, David M *et al.* (2001) Breast-feeding and the onset of atopic dermatitis in childhood: A systematic review and meta-analysis of prospective studies. *J Am Acad Dermatol* **45**, 520–527.
20. Gdalevich M, Mimouni D & Mimouni M (2001) Breast-feeding and the risk of bronchial asthma in childhood: A systematic review with meta-analysis of prospective studies. *J Pediatr* **139**, 261–266.
21. von Berg A, Koletzko S, Grubl A, *et al.* (2003) The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: The German Infant Nutritional Intervention Study, a randomized double-blind trial. *J Allergy Clin Immunol* **111**, 533–540.
22. Scholtens S, Wijga AH, Brunekreef B *et al.* (2009) Breast feeding, parental allergy and asthma in children followed for 8 years. The PIAMA birth cohort study. *Thorax* **64**, 604–609.
23. Silvers KM, Frampton CM, Wickens K *et al.* (2009) Breast-feeding protects against adverse respiratory outcomes at 15 months of age. *Matern Child Nutr* **5**, 243–250.
24. Codispoti CD, Levin L, LeMasters GK *et al.* (2010) Breast-feeding, aeroallergen sensitization, and environmental exposures during infancy are determinants of childhood allergic rhinitis. *J Allergy Clin Immunol* **125**, 1054–1060.
25. Fonseca MJ, Moreira A, Moreira P *et al.* (2010) Duration of breastfeeding and the risk of childhood asthma in children living in Urban areas. *J Investig Allergol Clin Immunol* **20**, 357–358.
26. Ludvigsson JF, Mostrom M, Ludvigsson J *et al.* (2005) Exclusive breastfeeding and risk of atopic dermatitis in some 8300 infants. *Pediatr Allergy Immunol* **16**, 201–208.
27. Kull I, Bohme M, Wahlgren CF *et al.* (2005) Breast-feeding reduces the risk for childhood eczema. *J Allergy Clin Immunol* **116**, 657–661.
28. Kramer MS & Kakuma R (2002) Optimal duration of exclusive breastfeeding. *Cochrane Database Syst Rev*, Issue **1**, (In the Press).
29. Alexander DD & Cabana MD (2010) Partially hydrolyzed 100% whey protein infant formula and reduced risk of atopic dermatitis: a meta-analysis. *J Pediatr Gastroenterol Nutr* **50**, 422–430.
30. Grimshaw KEC, Allen K, Edwards CA *et al.* (2009) Infant feeding and allergy prevention: a review of current knowledge and recommendations. A EuroPrevall state of the art paper. *Allergy* **64**, 1407–1416.
31. von Berg A, Krämer U, Link E *et al.* (2010) Impact of early feeding on childhood eczema: development after nutritional intervention compared with the natural course – the GINI-plus study up to the age of 6 years. *Clin Exp Allergy* **40**, 627–636.
32. McLean S & Sheikh A (2010) Does avoidance of peanuts in early life reduce the risk of peanut allergy? *BMJ* **340**, c424.
33. Anderson J, Malley K & Snell R (2009) Is 6 months still the best for exclusive breastfeeding and introduction of solids? A literature review with consideration to the risk of the development of allergies. *Breastfeed Rev* **17**, 23–31.
34. Prescott SL, Smith P, Tang M *et al.* (2008) The importance of early complementary feeding in the development of oral tolerance: Concerns and controversies. *Pediatr Allergy Immunol* **19**, 375–380.
35. Zutavern A, Brockow I, Schaaf B *et al.* (2008) Timing of solid food introduction in relation to eczema, asthma, allergic rhinitis, and food and inhalant sensitization at the age of 6 years: Results from the prospective birth cohort study LISA. *Pediatrics* **121**, E44–E52.
36. Tarini BA, Carroll AE, Sox CM *et al.* (2006) Systematic review of the relationship between early introduction of solid foods to infants and the development of allergic disease. *Arch Pediatr Adolesc Med* **160**, 502–507.
37. Sariachvili M, Droste J, Dom S *et al.* (2010) Early exposure to solid foods and the development of eczema in children up to 4 years of age. *Pediatr Allergy Immunol* **21**(1 Pt 1), 74–81.

38. Poole JA, Barriga K, Leung DY *et al.* (2006) Timing of initial exposure to cereal grains and the risk of wheat allergy. *Pediatrics* **117**, 2175–2182.
39. Hesselmar B, Saalman R, Rudin A *et al.* (2010) Early fish introduction is associated with less eczema, but not sensitization, in infants. *Acta Paediatr* **99**, 1861–1867.
40. Du Toit G, Katz Y, Sasieni P *et al.* (2008) Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* **122**, 984–991.
41. Agostoni C, Decsi T, Fewtrell M *et al.* (2008) ESPGHAN Committee on Nutrition: Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* **46**, 99–110.
42. Gruber C, van Stuijvenberg M, Mosca F *et al.* (2010) Reduced occurrence of early atopic dermatitis because of immunoactive prebiotics among low-atopy-risk infants. *J Allergy Clin Immunol* **126**, 791–797.
43. Szajewska H & Mrukowicz JZ (2005) Use of probiotics in children with acute diarrhea. *Paediatr Drugs* **7**, 111–122.
44. Cummings JH & Macfarlane GT (2002) Gastrointestinal effects of prebiotics. *Br J Nutr* **87** Suppl. 2, S145–S151.
45. Kim JY, Kwon JH, Ahn SH *et al.* (2010) Effect of probiotic mix (*Bifidobacterium bifidum*, *Bifidobacterium lactis*, *Lactobacillus acidophilus*) in the primary prevention of eczema: a double-blind, randomized, placebo-controlled trial. *Pediatr Allergy Immunol* **21**, E386–E393.
46. Kalliomaki M, Salminen S, Arvilommi H *et al.* (2001) Probiotics in primary prevention of atopic disease: a randomized placebo-controlled trial. *Lancet* **357**, 1076–1079.
47. Vael C & Desager K (2009) The importance of the development of the intestinal microbiota in infancy. *Curr Opin Pediatr* **21**, 794–800.
48. Braegger C, Chmielewska A, Decsi T *et al.* (2011) Supplementation of infant formula with probiotics and/or prebiotics: A systematic review and comment by the ESPGHAN committee on nutrition. *J Pediatr Gastroenterol Nutr* **52**, 238–50.
49. Arslanoglu S, Moro GE, Schmitt J *et al.* (2008) Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. *J Nutr* **138**, 1091–1095.