Eur J Pediatr (2010) 169:911–917
DOI 10.1007/s00431-010-1141-7

REVIEW

Clinical practice

Breastfeeding and the prevention of allergy

C. M. Frank Kneepkens · Paul L. P. Brand

Received: 3 December 2009 / Accepted: 7 January 2010 / Published online: 5 February 2010

Abstract The increase in allergic disease prevalence has led to heightened interest in the factors determining allergy risk, fuelled by the hope that by influencing these factors one could reduce the prevalence of allergic conditions. The most important modifiable risk factors for allergy are maternal smoking behaviour and the type of feeding. A smoke-free environment for the child (to be), exclusive breastfeeding for 4–6 months and the postponement of supplementary feeding (solids) until 4 months of age are the main measures considered effective. There is no place for restricted diets during pregnancy or lactation. Although meta-analyses suggest that hypoallergenic formula after weaning from breastfeeding grants protection against the development of allergic disease, the evidence is limited and weak. Moreover, all current feeding measures aiming at allergy prevention fail to show effects on allergic manifestations later in life, such as asthma. In conclusion, the allergy preventive effect of dietary interventions in infancy is limited. Counselling of future parents on allergy prevention should pay attention to these limitations.

C. M. F. Kneepkens (✉)
Department of Paediatrics, VU University Medical Centre,
De Boelelaan 1117,
1081 HV Amsterdam, The Netherlands
e-mail: cmf.kneepkens@vumc.nl

P. L. P. Brand
Amalia Children's Clinic, Isala klinieken,
P.O. Box 10400, 8000 GK Zwolle, The Netherlands

P. L. P. Brand
UMCG Postgraduate School of Medicine,
University Medical Centre Groningen,
Groningen, the Netherlands

Keywords Allergy prevention · Breastfeeding · Atopy · Hypoallergenic formula

Introduction

In the second half of the twentieth century, the prevalence of immunoglobulin E (IgE)-mediated allergic conditions in the Western World has doubled [5]. The prevalence of allergic disease, in particular wheezing and asthma, varies considerably throughout the world, with the highest risk in Western countries [60]. It is assumed, therefore, that Western lifestyle increases the risk of development of allergic diseases [5, 60]. Although the identification of the factors responsible for this rise in allergy prevalence is important for allergy prevention, it is still largely unclear which environmental aspects are involved [22]. In this article, we briefly summarise the present knowledge on risk factors for allergic disease and provide an overview of the literature on allergy prevention, focussing on breastfeeding. This should serve as a foundation for the advice health care professionals provide to parents of children at increased risk of allergy.

Definitions

According to the 2003 nomenclature revision, allergy is defined as a hypersensitivity reaction initiated by specific immunologic mechanisms, with hypersensitivity being defined as causing objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons [30]. Atopy is defined as a personal and/or familial tendency, usually in childhood or adolescence, to become sensitised and produce

IgE antibodies in response to ordinary exposure to allergens, usually proteins [30]. In the context of this paper, 'allergy' refers to IgE-mediated or type I allergy, which is associated with atopy. For newborns, the risk of becoming atopic increases with the presence of atopy in first-degree family members [2]. Likewise, 'high-risk infants' are defined as those children who have one or more first-degree relatives with proven allergic disease, including food allergy, atopic eczema, allergic asthma and rhinoconjunctivitis and, therefore, are at increased risk of developing atopy and allergic disease.

Factors contributing to allergy risk

Genetic factors

IgE-mediated allergy has a strong hereditary component. It is more common in monozygotic than in dizygotic twins [2]. Our current knowledge of the role of genetic factors in allergy development is summarised in Table 1. Allergic diseases are considered complex genetic conditions, with involvement of many genes and environmental factors [7]. The genetic factors involved in different allergic conditions differ considerably. Notably, the genes involved in eczema are more closely linked to those in other skin conditions than to those in other allergic diseases [28, 50].

The practical usefulness of these observations is, however, limited. Presently, the only way to use genetics regarding allergy prevention is by identifying increased allergy risk based on positive family history, in particular for the same condition [2]. Generally, therefore, allergy prevention is aimed at these 'high-risk infants' [32].

Hygiene hypothesis

The hygiene hypothesis postulates that the increased prevalence of allergy is caused by reduced exposure to microbial stimuli in early life, resulting in insufficient stimulation of regulatory T cells [7, 53, 64]. The term was coined in 1989 by Strachan, who observed that the more older siblings a child had, the lower the risk of allergic rhinitis [57]. A detailed description of the large body of observational evidence supporting the hygiene hypothesis can be found elsewhere [6].

Although early exposure to microbial stimuli shapes the maturation of the neonatal immune system [25], this concept has not yet yielded effective measures for allergy prevention. BCG immunisation of newborns, for example, does not decrease allergy risk [38, 43]. Although a Finnish study showed up to 50% reduction of eczema risk in infants of mothers using probiotics in late pregnancy and during lactation [31], this has not been confirmed in comparable studies [1, 59], and a recent Cochrane review concluded probiotics to be ineffective in preventing allergic disease [49].

Table 1 Allergic conditions and heredity

All allergic conditions have a genetic background [7]
Every allergic condition is influenced by several genetic factors [7]
The genetic factors of different allergic conditions differ considerably—e.g., the genetic factors that are relevant to eczema are more similar to those of other skin conditions than to those of other allergic diseases [28, 50]
The increased prevalence of allergic disease in the Western world cannot be explained genetically [5]

Maternal food consumption

Although there is consensus that pregnant women should not follow elimination diets [34], maternal food consumption may still influence allergy risk in the offspring. For instance, there is some evidence that in children of mothers who were consuming fish at least once a week during pregnancy, the risk of eczema and allergic rhinitis in decreased [68], whereas daily (as opposed to incidental) maternal consumption of nuts or peanuts was associated with increased asthma risk [69]. These results would be consistent with the hypothesis that a disturbed equilibrium between $n-3$ and $n-6$ polyunsaturated fatty acid intake may cause an Th1–Th2 imbalance [61, 69].

Cigarette-smoke exposure

The risk of asthma and poor lung function is considerably higher when the mother smokes during pregnancy and when after birth the infant is exposed to cigarette smoke [10, 11, 36, 40, 71]. The association of smoking with other allergic conditions, such as eczema and allergic rhinitis, is less clear. Nevertheless, tobacco-smoke exposure is the most readily available modifiable risk factor for allergic disease in children, and every effort to help pregnant women to stop smoking is worthwhile.

Other environmental factors

Although allergy risk appears to be largely determined in the first few months of life, other environmental factors may play additional roles later in life. Several factors have been implicated, but the evidence is weak and limited. Exposure to antibiotics [39] and paracetamol [42, 70] in the first years of life may increase the risk of asthma. To what extent consumption of certain foods and nutrients by the child could influence the risk of allergic manifestations remains to be determined [61].

Role of breastfeeding

There is no discussion on the fact that breastfeeding is the optimal nutrition for infants [17], preferably exclusive breastfeeding and preferably up to the age of 6 months [17]. Despite the large body of evidence on the role of breastfeeding in the prevention of allergy, however, discussion on its allergy preventive effects continues, mainly because of methodological issues.

Why is it so difficult to obtain evidence?

A principal problem with all studies on the effect of breastfeeding on allergy prevention is that randomised controlled trials (RCTs) are impossible. By consequence, all studies in this field are observational [46, 65] and subject to several confounding factors and biases [46]. Firstly, the multi-factorial nature of allergic diseases implies that the modification of one single cause (breastfeeding) will only have limited effects. Secondly, recall bias plays a role in many studies that record feeding practices retrospectively. Furthermore, the statistical approach itself may unwantedly adjust for secondary factors considered confounders that actually are part of the causal pathway—or the other way around. In addition, genetic background may considerably influence the association between breastfeeding and allergy risk [46].

A major limitation of observational breastfeeding studies is 'confounding by behaviour'. Since the prevailing opinion is that breastfeeding decreases the allergy risk, the mothers of high-risk infants may be more inclined to breastfeeding than those of low-risk infants. Indeed, an increased incidence of allergic disease in intentionally breastfed children has been found in some studies [8, 29]. The fact, therefore, that systematic reviews nevertheless show an inverse relationship between breastfeeding and allergic disease suggests that the actual protective effect of breastfeeding could even be higher than reported.

Why would breastfeeding reduce allergy risk?

The biological plausibility of the allergy preventive effect of breastfeeding has been studied in a number of ways. Firstly, breast milk contains traces of food proteins consumed by the mother that could promote tolerance to these foods [56]. Other factors in human milk that may modulate mucosal immune processes include IgA, factors that promote gut maturation, oligosaccharides, nucleotides and leukocytes that control the growth of intestinal microbiota and long-chain polyunsaturated fatty acids [46]. For example, $n-3$ fatty acids have anti-inflammatory and immune modulating properties that could reduce allergy risk [14].

Studies in weaning piglets have provided additional evidence that breast milk may provide protection [51]. Several milk peptides were found to be able to down-regulate neonatal immune activity, suggesting that they may promote neonatal immune competence.

Does breastfeeding have a preventive effect?

Systematic reviews and meta-analyses of observational studies consistently show a protective effect of exclusive breastfeeding up to the age of at least 4 months [19, 45, 63, 65]. For example, one systematic review reported a decrease of asthma in children up to the age of 8 years of 27% in the general population, increasing to 48% in high-risk children [20]. Later, observational studies confirmed the protective effect of exclusive breastfeeding on early life manifestations of allergy, with little or no support, however, to the notion that asthma later in life might be prevented as well [16, 41]. It has been suggested that contrarily, asthma risk at later age might even be increased in breastfed high-risk children. This has recently been refuted, however, by a very large epidemiological survey from the UK [46].

As noted earlier, all observational studies on the allergy preventive effect of breastfeeding are subject to bias. Obviously, the same applies to systematic reviews and meta-analyses of such studies. To our knowledge the only study that approaches an RCT design is from Belarus [35]. In this cluster-randomised trial, maternity hospitals were randomised to implementation of the 'Baby Friendly Initiative' campaign of the WHO. Although breastfeeding in the first 3 months of life was seven times more common in the intervention group, there was no difference between intervention and control groups with regard to the prevalence of allergic disease and of positive skin prick tests up to the age of 6 years [35]. Although these results may not be considered representative of the Western situation, the study confirms that at the least, breastfeeding does not increase the prevalence of allergic disease in high-risk children.

Other preventive measures

Complementary bottle feeding in the neonatal period

A large Dutch randomised trial in an unselected population of breastfed infants showed that exposure to standard formula in the first days of life did not increase the prevalence of allergic disease [13]. There is no reason, therefore, to provide hypoallergenic formula to breastfed low-risk infants who need complementary formula. This also holds for high-risk infants, although it seems be counter-intuitive to give standard formula in this situation.

Table 2 Methodological problems in the studies with regard to the effects of hydrolysed formula on allergy in high-risk children [9]

Blinding—differences in taste and smell prevent adequate blinding of the parents, [21] which may compromise the appreciation of subjective symptoms and even lead to 'deblinding' of the researchers
Heterogenicity—studies differ strongly with respect to criteria for allergic disease and hypoallergenicity of formula [45]
Confounders—insufficient control for confounding variables
Compliance—bad smell and taste of hypoallergenic formula may result in low compliance
Severity of disease—prevention may be particularly effective for (very) mild cases
Postponement or cancellation—the effects of nutritional measures shrink with longer follow-up and may even reverse
Mechanism—pathophysiological mechanism is unclear

Hypoallergenic formula

Sooner or later, most breastfeeding mothers switch to formula feeding. In contrast to breastfeeding, it is perfectly possible to design RCTs for the comparison of the allergy prevention effects of standard formula with those of hypoallergenic (hydrolysed) formula. Systematic reviews of RCTs conclude that both partially and extensively hydrolysed formulas have a protective effect, in particular on atopic eczema in the first years of life [23, 45]. Based on this, several national and international organisations have issued the advice that high-risk children who are not breastfed should be given hypoallergenic formula in the first 3 to 6 months of life [26, 32, 45].

There seems to be a change of wind, however. Because the author of some of the most convincing studies has been accused of scientific fraud [54], the weight of the evidence has become a matter of discussion. As a result, the conclusions of the original 2003 Cochrane analysis were modified to conclude that: "In high risk infants who are unable to be completely breast fed, there is limited evidence that prolonged feeding with a hydrolysed formula compared to a cow's milk formula reduces infant and childhood allergy and infant CMA", the word 'limited' being added [47]. An international expert group, however, opposed to this weakened conclusion, reinforcing their original statement [45] that high-risk infants should use hypoallergenic formula once breastfeeding was not available [27].

How should we judge this discrepancy? It has been pointed out that the quality of the evidence is weak. Table 2 summarises the most important methodological drawbacks of the studies on hypoallergenic formula [9]. Clearly, the pathophysiological model that prompted the use of hypoallergenic formula is no longer valid. The notion that exposure to allergens results in sensitisation and that subsequent repeated exposure causes disease is outdated. Neither for airborne allergens nor for food allergens has a clear relationship been proven between allergen exposure and allergic disease development [13, 37]. Sensitisation to foods has been found in children who never consumed the actual food. Even the first documented contact with food allergens may result in allergic reactions [44]. The avoidance of exposure to airborne allergens such as house dust mite does not prevent house dust mite allergy and asthma [12]. Finally, it is unclear whether and how hypoallergenic formula could influence regulatory T-cell function [9].

There are more unsolved problems posed by intervention studies with hypoallergenic formula. Objective endpoints, such as serum concentrations of specific IgE against common allergens, have never been shown to differ between intervention and control groups [9]. It is likely that any protection from allergy primarily involves mild cases. With longer follow-up, the effect size of protection appears to decrease, suggesting that allergic manifestations are delayed rather than truly prevented [9]. The risks of prolonged use of hypoallergenic formula have been poorly studied [62]. A recent large observational 'real life' study from the Netherlands showed that the delayed introduction of cow's milk in the diet of high-risk infants was associated with increased atopy risk at the age of 2 years [55]. Long-term allergen avoidance in itself may induce the 'activation' of allergy in sensitised children [18]. As a result, the risk–benefit ratio of hypoallergenic formula use is unknown [9].

Considering all of the above, we tend to counsel parents of high-risk infants as follows: we encourage exclusive

Table 3 Summary of allergy prevention recommendations

All infants
Exclusive breastfeeding for at least the first 4 months of life
Continuation of breastfeeding up to 6 months of life
Complete avoidance of exposure to cigarette smoke, before as well as after birth
Introduction of supplementary feeding starting between 4 and 6 months of life
High-risk infants (positive family history)
Children who are not breastfed (anymore) should be given hydrolysed formula until 4 months of life
Partially hydrolysed formula is preferable above extensively hydrolysed formula
The parents should appreciate the limited effects of these measures

breastfeeding for at least 4 months; after weaning of breastfeeding, hypoallergenic formula may postpone manifestations of atopic eczema during the first 2 years of life and there is no reason to prefer extensively hydrolysed above partially hydrolysed formula [32, 47].

Introduction of complementary feeding

Until recently, it was common use to postpone the introduction of complementary feeding (solids) as part of allergy prevention measures until the age of 6 months [32]. This is in line with the WHO advice, aiming at exclusive breastfeeding for the first half year of life. There is no proof, however, that any further decrease of allergy risk is obtained by postponing the introduction of solids until after 4 months of life [55, 58, 72]. Likewise, there is no scientific basis for the avoidance of strongly allergenic foods, such as peanuts and chicken egg, beyond this age [27, 58]. On the contrary, there are reasons to believe that postponement of the introduction of, for instance, peanuts until the third year of life increases the prevalence of peanut allergy [67]. Current evidence suggests that the optimal window for the introduction of solids in non-high-risk as well as in high-risk children is between 4 and 6 months of age [52]—preferably while maintaining breastfeeding until 6 months of age [17, 52].

Breast milk mimicry

Given the apparent protective effects of breastfeeding, interventions have been tested that aimed at mimicking certain properties attributed to breast milk. These include the supplementation of formula with fish oil, probiotics and prebiotics. Recent meta-analyses, however, found insufficient evidence for a protective role of either fish oil supplements [4], probiotics [49] or prebiotics [48]. Probiotics might even have an adverse effect on wheezing [33].

Prevention of food allergy

Some words have to be said on the prevention of food allergy irrespective of other manifestations of allergy. Obviously, it can be anticipated that manipulation of the feeding of newborn infants specifically would influence the development of food allergy. Studies concentrating on food allergy prevention have, however, not produced more convincing results than other preventive studies [24, 66].

Apparently, exposure to (traces of) foods during the ‘window’ period of 4–6 months of age may serve as a means of inducing tolerance [29]. Early introduction of peanut into the infants’ diet in Israel is associated with a 10 times lower prevalence of peanut allergy [24] than in Great Britain, where peanut introduction is postponed [67]. The effect of postponement of solids may be even more outspoken in high-risk children [15]. The strict avoidance of allergens, therefore, might have a contrary effect [3, 67].

Recommendations

It should be concluded that there are only limited possibilities for allergy prevention. Table 3 gives an overview of the advice that present scientific evidence allows us to give to parents. Exclusive breastfeeding, avoidance of cigarette smoke and introduction of complementary foods between 4 and 6 months of life are measures that are applicable to all children, irrespective of their risk assessment. When exclusive breastfeeding is impossible, hydrolysed formula feeding might postpone mild manifestations of eczema in high-risk children. There is no reason to prefer extensively hydrolysed formula above partial hydrolysates.

Conflict of interest The authors declare that they do have do conflict of interest and no financial relationships that might have influenced the present work.

References

1. Abrahamsson TR, Jakobsson T, Bottcher MF et al (2007) Probiotics in prevention of IgE-associated eczema: a double-blind, randomized, placebo-controlled trial. J Allergy Clin Immunol 119:1174–1180
2. Alford SH, Zoratti E, Peterson EL et al (2004) Parental history of atopic disease: disease pattern and risk of pediatric atopy in offspring. J Allergy Clin Immunol 114:1046–1050
3. Allen CW, Campbell DE, Kemp AS (2009) Food allergy: is strict avoidance the only answer? Paediatr Allergy Immunol 20:415–422
4. Anandan C, Nurmatov U, Shiekh A (2009) Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis. Allergy 64:840–848
5. Asher MI, Montefort S, Bjorksten B et al (2006) Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 368:733–743
6. Bloomfield SF, Stanwell-Smith R, Crevel RWR, Pickup J (2006) Too clean, or not too clean: the hygiene hypothesis and home hygiene. Clin Exp Allergy 36:402–425

7. Bochner BS, Busse WW (2004) Advances in mechanisms of allergy. J Allergy Clin Immunol 113:868–875
8. Böttcher MF, Jenmalm MC (2002) Breastfeeding and the development of atopic disease during childhood. Clin Exp Allergy 32:159–161
9. Brand PLP, Vlieg-Boerstra BJ, Dubois AEJ (2007) Dietary prevention of allergic disease in children: are current recommendations really based on good evidence? Pediatr Allergy Immunol 18:475–479
10. Carlsen KH, Lødrup Carlsen KC (2005) Parental smoking and childhood asthma: clinical implications. Treat Respir Med 4:337–346
11. Cook DG, Strachan DP (1999) Summary of effects of parental smoking on the respiratory health of children and implications for research. Thorax 54:357–366
12. Custovic A, Gerth van Wijk R (2005) The effectiveness of measures to change the indoor environment in the treatment of allergic rhinitis and asthma: ARIA update (in collaboration with GA(2)LEN). Allergy 60:1112–1115
13. de Jong MH, Scharp-van der Linden VT, Aalberse R et al (2002) The effect of brief neonatal exposure to cows' milk on atopic symptoms up to age 5. Arch Dis Child 86:365–369
14. Dunstan JA, Mori TA, Barden A et al (2003) Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. J Allergy Clin Immunol 112:1178–1184
15. 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
16. Elliott L, Henderson J, Northstone K et al (2008) Prospective study of breast-feeding in relation to wheeze, atopy, and bronchial hyperresponsiveness in the Avon Longitudinal Study of Parents and Children (ALSPAC). J Allergy Clin Immunol 122:49–54, 54. e1-3
17. ESPGHAN Committee on Nutrition, Agostoni C, Braegger C, Decsi T et al (2009) Breast-feeding: A commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr 49:112–125
18. Flinterman AE, Knulst AC, Meijer Y et al (2006) Acute allergic reactions in children with AEDS after prolonged cow's milk elimination diets. Allergy 61:370–374
19. Galton Bachrach VR, Schwarz E, Bachrach LR (2003) Breast-feeding and the risk of hospitalization for respiratory disease in infancy. A meta-analysis. Arch Pediatr Adolesc Med 157:237–243
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. Gramsbergen IMC, Brand PLP (2003) Dubbelblinde vergelijking van de smaak van hypoallergene zuigelingenvoedingen [Double blind comparison of the taste of hypoallergenic infant feedings]. Ned Tijdschr Allergie 6:241–245
22. Gupta R, Sheikh A, Strachan DP, Anderson HR (2007) Time trends in allergic disorders in the UK. Thorax 62:91–96
23. Hays T, Wood RA (2005) A systematic review of the role of hydrolyzed infant formulas in allergy prevention. Arch Pediatr Adolesc Med 159:810–816
24. Heine RG, Tang ML (2008) Dietary approaches to the prevention of food allergy. Curr Opin Clin Nutr Metab Care 11:320–328
25. Holt PG, Upham JW, Sly PD (2005) Contemporaneous maturation of immunologic and respiratory functions during early childhood: implications for development of asthma prevention strategies. J Allergy Clin Immunol 116:16–24
26. Høst A, Koletzko B, Dreborg S et al (1999) Dietary products used in infants for treatment and prevention of food allergy. Joint statement of the European Society for Paediatric Allergology and Clinical Immunology (ESPACI) committee on hypoallergenic formulas and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) committee on nutrition. Arch Dis Child 81:80–84
27. Høst A, Halken S, Muraro A et al (2008) Dietary prevention of allergic diseases in infants and small children. Pediatr Allergy Immunol 19:1–4
28. Hudson TJ (2006) Skin barrier function and allergic risk. Nat Genet 38:399–400
29. Järvinen K-M, Suomalainen H (2001) Development of cow's milk allergy in breast-fed infants. Clin Exp Allergy 31:978–987
30. Johansson SGO, Bieber T, Dahl R et al (2004) Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol 113:832–836
31. Kalliomäki M, Salminen S, Arvilommi H et al (2001) Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. Lancet 351:1076–1079
32. Kneepkens CMF, van Drongelen KI, Aarsen C (2005) Landelijke standaard voedselallergie bij zuigelingen [National standard for food allergy in infants], 5th edn. Voedingscentrum, Den Haag
33. Kopp MV, Hennemuth I, Heinzmann A, Urbanek R (2008) Randomized, double-blind, placebo-controlled trial of probiotics for primary prevention: no clinical effects of Lactobacillus GG supplementation. Pediatrics 121:e850–e856
34. Kramer MS, Kakuma R (2006) Maternal dietary antigen avoidance during pregnancy or lactation or both, for preventing or treating atopic disease in the child. Cochrane Database Syst Rev 3:CD000133
35. 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 335:815–818
36. Kumar R (2008) Prenatal factors and the development of asthma. Curr Opin Pediatr 20:682–687
37. Lau S, Illi S, Sommerfeld C et al (2001) Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Lancet 356:1392–1397
38. Marks GB, Ng K, Zhou J et al (2003) The effect of neonatal BCG vaccination on atopy and asthma at age 7 to 14 years: an historical cohort study in a community with a very low prevalence of tuberculosis infection and a high prevalence of atopic disease. J Allergy Clin Immunol 111:541–549
39. Marra F, Lynd L, Coombes M et al (2006) Does antibiotic exposure during infancy lead to development of asthma?: a systematic review and metaanalysis. Chest 129:610–618
40. Martinez FD, Cline M, Burrows B (1992) Increased incidence of asthma in children of smoking mothers. Pediatrics 89:21–26
41. Matheson MC, Erbas B, Balasuriya A et al (2007) Breast-feeding and atopic disease: a cohort study from childhood to middle age. J Allergy Clin Immunol 120:1051–1057
42. Mitchell EA, Stewart AW, Clayton T et al (2009) Cross-sectional survey of risk factors for asthma in 6–7-year-old children in New Zealand: International Study of Asthma and Allergy in Childhood Phase Three. J Paediatr Child Health. doi:10.1111/j.1440-1754.2009.01504.x
43. Mommers M, Weishoff-Houben M, Swaen GM et al (2004) Infant immunization and the occurrence of atopic disease in Dutch and German children: a nested case-control study. Pediatr Pulmonol 38:329–334
44. Monti G, Muratore MC, Peltran A et al (2002) High incidence of adverse reactions to egg challenge on first known exposure in young atopic dermatitis children: predictive value of skin prick test and radioallergosorbent test to egg proteins. Clin Exp Allergy 32:1515–1519
45. Muraro A, Dreborg S, Halken S et al (2004) Dietary prevention of allergic diseases in infants and small children. Part III. Critical

review of published peer-reviewed observational and interventional studies and final recommendations. Pediatr Allergy Immunol 15:291–307
46. Oddy WH (2009) The long-term effects of breast-feeding on asthma ans atopic disease. Adv Exp Med Biol 639:237–251
47. Osborn DA, Sinn JK (2006) Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. Cochrane Database Syst Rev 4:CD003664
48. Osborn DA, Sinn JK (2007) Prebiotics in infants for prevention of allergic disease and food hypersensitivity. Cochrane Database Syst Rev 4:CD006474
49. Osborn DA, Sinn JK (2007) Probiotics in infants for prevention of allergic disease and food hypersensitivity. Cochrane Database Syst Rev 4:CD006475
50. Palmer CN, Irvine AD, Terron-Kwiatkowski A et al (2006) Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet 38:441–446
51. Politis I, Chronopoulou R (2008) Milk peptides and immune response in the neonate. Adv Exp Med Biol 606:253–269
52. 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
53. Romagnani S (2006) Regulatory T cells: which role in the pathogenesis and treatment of allergic disorders? Allergy 61:3–14
54. Smith R (2005) Investigating the previous studies of a fraudulent author. BMJ 331:288–291
55. Snijders BE, Thijs C, van Ree R, van den Brandt PA (2008) Age at first introduction of cow milk products and other food products in relation to infant atopic manifestations in the first 2 years of life: the KOALA Birth Cohort Study. Pediatrics 122:e115–e122
56. Spiekermann GM, Walker WA (2001) Oral tolerance and its role in clinical disease. J Pediatr Gastroenterol Nutr 32:237–255
57. Strachan DP (1989) Hay fever, hygiene, and household size. BMJ 299:1259–1260
58. Tarini BA, Carroll AE, Sox CM, Christakis DA (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
59. Taylor AL, Dunstan JA, Prescott SL (2007) Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: A randomized controlled trial. J Allergy Clin Immunol 119:184–191
60. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee (1998) Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). Eur Respir J 12:315–335
61. Tricon S, Willers SM, Smith HA et al (2006) Nutrition and allergic disease. Clin Exp Allergy Rev 6:117–188
62. Vandenplas Y, Alliët P, van Winckel M, Robberecht E (2001) Infant formulae: how well are they tested? Eur J Pediatr 160:405–406
63. 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
64. van Oosterhout AJ, Bloksma N (2005) Regulatory T-lymphocytes in asthma. Eur Respir J 26:918–932
65. van Rossum CTM, Büchner FL, Hoekstra J (2005) Quantification of health effects of breastfeeding. Review of the literature and model simulation: RIVM report 350040001/2005. RIVM, Bilthoven. Accessed at www.rivm.nl/bibliotheek/rapporten/350040001.pdf on 11 November 2009
66. Venter C, Pereira B, Voigt K et al (2009) Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. Pediatr Allergy Immunol 20:320–327
67. Wennergren G (2009) What if it is the other way around? Early introduction of peanut and fish seems to be better than avoidance. Acta Paediatr 98:1085–1087
68. Willers SM, Devereux G, Craig LC et al (2007) Maternal food consumption during pregnancy and asthma, respiratory and atopic symptoms in 5-year-old children. Thorax 62:773–779
69. Willers SM, Wijga AH, Brunekreef B et al (2008) Maternal food consumption during pregnancy and the longitudinal development of childhood asthma. Am J Respir Crit Care Med 178:124–131
70. Wong GW, Leung TF, Ma Y, Liu EK, Yung E, Lai CK (2007) Symptoms of asthma and atopic disorders in preschool children: prevalence and risk factors. Clin Exp Allergy 37:174–179
71. Xepapadaki P, Manios Y, Liarigkovinos T et al (2009) Association of passive exposure of pregnant women to environmental tobacco smoke with asthma symptoms in children. Pediatr Allergy Immunol 20:423–429
72. Zutavern A, von Mutius E, Harris J et al (2004) The introduction of solids in relation to asthma and eczema. Arch Dis Child 89:303–308