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Risk factors for food allergy

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J. Ezendam | H. van Loveren



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J. Ezendam
H. van Loveren

Contact:

J. Ezendam
Laboratory for Health Protection Research
Janine.Ezendam@rivm.nl

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Abstract

Risk factors for food allergy

The current state of knowledge on external factors that can increase the risk of food allergy is insufficient. It is therefore not possible to formulate recommendations aimed at reducing the prevalence of food allergy. These are the conclusions presented in a literature survey conducted by the National Institute for Public Health and the Environment (RIVM). There are indications that the prevalence of food allergy is increasing. This increase cannot be explained by genetic changes and may be explained by alterations in exposure to external factors, such as changes in diet or lifestyle. The importance of gaining insight into the external factors impacting on the development of food allergy is therefore important, since this information can be used to formulate specific recommendations to reduce the risk of food allergy

The prevalence of food allergy varies from 2% to 6% in children and from 2% to 3% in adults. Food allergy has a negative impact on the quality of life. The accidental consumption of products that contain the food allergen can even induce life-threatening symptoms.

In this literature study, the RIVM inventoried the impact of microbes, environmental toxicants, diet and lifestyle on the development of food allergy. The effects of the majority of these external factors on food allergy could not be determined because there were either too few studies or the results of different studies were conflicting. There is limited evidence that the consumption of fish oil supplements during pregnancy reduces the risk of egg allergy, but these findings need to be confirmed in larger clinical trials. There are also indications that the delayed introduction of food allergens in the diet of infants is a risk factor; a number of clinical studies are currently investigating this hypothesis.

Key words:

food allergy, risk factors, diet, lifestyle, environmental factors

Rapport in het kort

Risicofactoren voor voedselallergie

Het is niet duidelijk welke externe factoren het risico op voedselallergie kunnen verhogen. Het is daarom niet mogelijk om wetenschappelijk onderbouwde aanbevelingen op te stellen om het risico op voedselallergie te verlagen. Dit blijkt uit een literatuurstudie van het RIVM. Er zijn aanwijzingen dat voedselallergie steeds vaker voorkomt. Deze toename kan niet verklaard worden door genetische veranderingen en wordt waarschijnlijk veroorzaakt door veranderde blootstelling aan externe factoren, zoals wijzigingen in ons dieet of van onze levensstijl. Om aanbevelingen op te kunnen stellen om het risico op voedselallergie te verlagen is het belangrijk om inzicht te krijgen in externe factoren die van invloed zijn op voedselallergie.

Voedselallergie komt voor bij 2 tot 6% van de kinderen en 2 tot 3% van de volwassenen. Deze aandoening heeft een negatieve invloed op de kwaliteit van leven. Door per ongeluk producten te eten die het allergeen bevatten dat iemand niet verdraagt kunnen zelfs levensbedreigende symptomen ontstaan.

In deze literatuurstudie is gezocht naar de invloed van ziekteverwekkers, giftige stoffen, voeding en levensstijl op voedselallergie. Voor het merendeel van deze factoren blijken te weinig studies te zijn uitgevoerd of spreken de resultaten uit studies elkaar tegen. Er is beperkt bewijs dat inname van visoliesupplementen gedurende de zwangerschap het risico op ei-allergie verlaagt, maar deze bevindingen moeten in grotere klinische studies worden bevestigd. Daarnaast zijn er aanwijzingen dat het uitstellen van de introductie van voedselallergenen in het dieet van baby's tot na de leeftijd van zes maanden een mogelijke risicofactor is. Momenteel loopt er een aantal klinische studies om deze aanwijzingen verder wetenschappelijk te onderbouwen.

Trefwoorden:

voedselallergie, risicofactoren, voeding, levensstijl, omgevingsfactoren

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Summary

There is evidence that the prevalence of food allergy is increasing in Western countries, similar to other allergic diseases. This rapid rise cannot be explained by genetic changes and might be caused by alterations in environmental exposures. It is hypothesized that environmental factors that are able to impair the development of oral tolerance towards innocent dietary proteins could increase the risk on food allergy. The development of oral tolerance probably occurs during a critical period early in life and it is believed that during this period, environmental exposures will have the biggest impact either by increasing or decreasing the risk on food allergy. Identification of risk factors for food allergy is important in terms of primary prevention. To obtain more insight in factors involved, a systematic review was conducted to identify those risk factors.

A systematic literature review was carried out using electronic databases. The search strategies focused on the identification of microbial, dietary, environmental and lifestyle factors. For microbial exposure, search strategies focused on early life infections, family size, pet exposure and day care attendance. Dietary factors included breastfeeding, hypoallergenic infant formulas, age of introduction of solid foods, maternal and/or infant food allergen avoidance, food supplements (prebiotics, probiotics, fish oil supplements (N-3 polyunsaturated fatty acids), and vitamins) and organic foods. Lifestyle and environmental factors include anthroposophic lifestyle, tobacco smoke exposure, toxic chemicals, natural toxins, vaccinations and use of medicines, including antibiotics.

The literature search revealed that up to now, no studies were published that have investigated effects of exposure to environmental toxic substances, use of antibiotics or other medicines, vaccinations, and prebiotics on the development of food allergy.

Microbial exposures

The increased prevalence of atopic diseases has been associated with a reduced exposure to pathogenic microbes early in life, for example due to improvement of household hygiene and smaller family sizes. For food allergy, there is insufficient evidence for a protective role of microbial factors. The data for Epstein-Barr virus were conflicting and other early life infections were not protective for food allergy. Other microbial exposures, such as exposure to pets in infancy, were not associated with food allergy. Only one study found that day care attendance was a risk factor, instead of a protective factor, for food allergy, but more studies are needed to confirm this association. The mode of delivery has also been studied as a risk factor for food allergy. The microbial colonization of the gut is different in children born with a caesarian section compared to children born by vaginal delivery. There is limited data that children born by a caesarian section have a higher risk on sensitization to food allergens early in life. The data on clinical food allergy were conflicting, making it impossible to conclude that children born by caesarian section have a higher risk on developing food allergy.

Dietary factors

The results of studies investigating the effects of exclusive breastfeeding for 4 months were conflicting. Some studies find a decreased risk on food allergies, whereas others find no effect or an increase. The duration of exclusive breastfeeding is still under debate. The World Health Organization recommends a period of 6 months, while allergy experts advise 4-6 months. In case breastfeeding fails or is insufficient, many governments recommend the use of hypoallergenic (hydrolyzed) infant formulas for children at risk for allergies. Effects of these formulas on food allergy have been studied in one study. It was shown that extensive hydrolyzed infant formulas reduce the risk on cow's milk allergy. Effects on other food allergies have not been studied up to now. The effects of partially hydrolyzed infant formulas on food allergy were not investigated. Therefore, it can be concluded that more research is needed to substantiate the recommendations on hypoallergenic infant formulas in prevention of food allergy.

In the past it was recommended to delay the introduction of solid foods in the infants' diet beyond 6 months. However, no evidence was found for a protective effect on food allergy. In contrast, there is limited evidence that delayed introduction is a risk factor for food sensitization and allergy. Therefore, the current advice of many expert committees on infant nutrition is to start with solid feeds from 4 months of age and not to delay beyond the age of 6 months. Avoidance of food allergens during pregnancy and early in life has been advocated by many countries especially for families at risk of allergies. Food allergen avoidance by pregnant and breastfeeding women, however, did not confer any protection against food allergy. Delayed introduction of food allergens does not have any preventive effect on food allergies. The recommendations on maternal and infant food allergen avoidance have been abandoned some years ago. The new paradigm is that delayed introduction of food allergens is a risk factor. It is hypothesized that due to delayed introduction no exposure to food allergens takes place during the critical period of tolerance development, thereby increasing the risk on food allergies. There is some evidence that delayed introduction of peanut, egg, fish and wheat, increased the prevalence of allergies for these food allergens. The data on timing of cow's milk in the infants' diet are conflicting. The optimal timing of food allergen introduction is currently unknown. At the moment several randomized intervention trials are underway that investigate the effects of early introduction of egg, peanut and a combination of food allergens. These clinical trials might provide new insights into the optimal timing of food allergen introduction.

There is no evidence that combined pre- and postnatal or postnatal supplementation with microorganisms with intended probiotic activity prevents the development of food allergy. Fish oil supplementation during pregnancy seems protective for egg allergy early in life. These findings should be confirmed in larger epidemiological studies with a longer follow-up period in which other food allergies can be monitored as well. The effects of maternal vitamin D intake have been studied in one trial, demonstrating a protective effect on food sensitization. More studies are needed to confirm these data. The data on multivitamin use in children were conflicting and no conclusions can be drawn. The

effects of organic food consumption were studied in one study that found that this type of diet had no effect on food allergy.

Lifestyle and environmental factors

One study has investigated effects of anthroposophic lifestyle on food allergy. The results on food sensitization were conflicting and there was no difference in clinically diagnosed food allergy. There is insufficient data available on the impact of this lifestyle on food allergy. The effects of environmental tobacco smoke exposure during pregnancy and early in life on food allergy were conflicting and too limited. However, maternal cigarette smoking and smoking around children should be discouraged anyway, in view of all other adverse effects.

This systematic review provides an overview of the state-of-the-art knowledge on risk factors for food allergy. Unfortunately, the results of these studies were sometimes conflicting or inconclusive and for some environmental factors the available data were too limited. Therefore, it is too early to formulate a strategy for primary prevention of food allergy. Similarly, preventive strategies for other allergic diseases are still a matter of debate as well, due to inconsistent data. New findings from clinical studies that are currently ongoing might lead to modifications of the current recommendations.

1 Introduction

In the last decades the prevalence of atopic and other immune-mediated diseases has increased in developed countries (1). Time trends for allergic diseases have been demonstrated for asthma and hay fever (2-6) and atopic eczema (7, 8). In developed countries, the rise in these atopic diseases seems to have reached a plateau. However, in other parts of the world the prevalence of asthma and eczema is still increasing (7-9). There are indications that the prevalence of food allergy is increasing as well. The Centre for Disease Control and Prevention demonstrated an increase in reported food allergy in children of 18% between 1997 and 2007 (10, 11). In a cross-sectional immunosurveillance we have shown that in the Netherlands the prevalence of peanut sensitization has increased from 1996 to 2007. We found no evidence for an increase in cow's milk or egg sensitization (12, 13). An increase in peanut allergy was demonstrated in epidemiological studies from the UK (14, 15), Australia (16) and the USA (17-19), as well. In the USA study an increased prevalence of tree nut allergy was shown as well, whereas the prevalence of sesame allergy has not changed in this period (18).

Many epidemiological studies have been dedicated to finding explanations for this rise in allergic diseases. The rapid increase cannot be explained by genetic changes and therefore the focus has been on identification of environmental factors that either increase or reduce the risk on allergies. The current view is that exposure early in life to environmental factors has an impact on the developing immune system in a way that it either predisposes or protects from development of an allergic disease (20). The so-called 'atopic march' refers to a certain pattern that is observed in a proportion of the allergic population. The 'atopic march' starts early in life with atopic eczema and/or food allergy. These early manifestations, i.e. atopic eczema and cow's milk and egg allergy, resolve in the majority of children, but these children are often more prone to develop other allergies while growing up. The prevention of the first stages of the atopic march, i.e. food allergies and atopic eczema, might therefore be a good strategy to prevent other allergies as well. The most important determinants for allergy development are genetic susceptibility, but risk factors involved are largely unknown. The majority of epidemiological studies have focused predominantly on identifying risk factors for asthma, hay fever and eczema, but in the last years the focus has shifted towards factors influencing food allergy as well. In light of the 'atopic march' it can be envisaged that general risk factors exist, that increase the risk on multiple allergies. On the other hand, food allergy-specific risk factors might exist as well, for example maternal dietary intake of food allergens during pregnancy, age of introduction of food allergens in young children, and hypoallergenic infant formulas (21).

The search for risk factors for allergic diseases has focused predominantly on factors that are related to a modern/westernized lifestyle. These include: improvement of hygiene, changes in diet and use of vaccines and medicines. The 'hygiene hypothesis', first

postulated by Strachan (22), has received much attention in this field, and was launched by observations that hay fever was less prevalent in small families. Strachan proposed that improvement of hygiene conditions and smaller families would decrease the microbial burden early in life and this would have an impact on the developing immune system making it more susceptible to allergies (22, 23). This hypothesis always remained controversial and although many studies found evidence in favor of this hypothesis others failed to do so (24, 25). Furthermore, during the last two decades the hypothesis has evolved due to improvement of our understanding of the functioning of the immune system. The most recent formulation of the hypothesis is that a reduced microbial burden will impair the development of the mucosal immune system in the gut. This site is the most important place for the development of tolerance for allergens. This development takes place during pregnancy and early after birth. The so-called 'window of opportunity' is considered to be a period early in life, in which preventive strategies will have the most impact. Similarly, exposure to risk factors during this period can abrogate this immunoregulation and predispose subjects to allergies (26). New insights have complicated this area recently due to the discovery of the importance of individual susceptibility. For some environmental exposures it has been demonstrated that the impact depends on a certain genetic polymorphism. This is called gene-environment interactions and these associations will be missed in epidemiological studies that do not include assessment of genetic polymorphisms. The importance of the fillagrin mutation has been studied extensively, since this mutation causes a defect in the skin barrier and increases the susceptibility to develop eczema. The effects of early life exposure to cats have been identified as a risk factor for atopic eczema only in children with this fillagrin mutation and not in other children (27). It has been speculated that conflicting results in epidemiological studies might be partly explained by these gene-environment interactions. The role of gene-environment interactions in food allergy is currently unknown.

In order to understand why allergic diseases are increasing and to develop preventive strategies, it is important to identify determinants for food allergy. A systematic review was conducted to obtain insight into risk factors associated with the development of food allergy. The focus of this review will be on pre- and postnatal factors, including microbial, dietary, lifestyle and environmental factors.

2 Methods

2.1 Literature search

A systematic literature review was carried out by using PubMed and Scopus electronic databases. Review articles and meta-analyses were used to find important articles that were missed with the computerized literature search.

The search strategy focused on identification of risk factors that can be used in preventive strategies including:

- dietary factors:
 - breastfeeding;
 - hypoallergenic (hydrolyzed) infant formulas;
 - age of introduction of solid foods;
 - maternal and/or infant food allergen avoidance;
 - pre- and probiotics;
 - fish oil supplements (N-3 polyunsaturated fatty acid);
 - vitamins;
 - organic foods;
- microbial exposure:
 - early life infections;
 - pet exposure;
 - family size;
 - day care attendance;
 - caesarean section;
- lifestyle and environmental exposures:
 - anthroposophic lifestyle;
 - vaccinations;
 - medicine use including antibiotics;
 - tobacco smoke exposure;
 - environmental toxicants;
 - natural toxins.

Search strategies used above mentioned factors together with 'food allergy', 'food hypersensitivity' or 'food sensitization'.

2.2 Inclusion criteria

Studies were included when they provided information on the relationship between a specific external factor and food allergy. The following inclusion criteria were used:

- peer-reviewed articles in English or Dutch;
- published 1980 or later

Assessment of food allergy by questionnaires (self-reported), skin prick test or measurement of specific IgE (sensitization) or by food challenges (open or double blind placebo controlled).

2.3 Quality of the literature

The quality of the articles was assessed according to the following points:

- clear description of definition of study design and population;
- clear definition of food allergy assessment;
- adjustment for confounding factors.

The results of epidemiological studies can be biased by confounding factors. In the field of allergy two important confounders are a family history of atopy and early signs of atopy. These factors can bias the association between exposure to a certain factor and outcome, i.e. food allergy. For example, it has been shown that children that have one or more allergic family members are longer breastfed compared to children that are not at risk (28). The high-risk children will develop allergies more often. Hence, longer breastfeeding would then be associated with allergy and be considered a risk factor. This is called *confounding-by-indication*. Another possible confounder in these studies is called *reverse causation*. Parents of children who develop early atopic signs, such as eczema and wheeze, will be more likely to modify their lifestyle in order to prevent development of other allergies. They may delay introduction of allergenic foods or continue breastfeeding for a longer period. It has been demonstrated that children that developed eczema early in life were more likely to be breastfed for a longer period, than children without early atopic symptoms (29). Other possible confounders that should be considered are environmental tobacco smoke exposure and pets in the home (30). It is important that in epidemiological studies these possible confounders are taken into account, because these factors could have a large impact on the reliability of the observed associations. Results from epidemiological studies that have not adjusted for confounding factors should be considered as less reliable.

3 Microbial exposure

The increase in prevalence of atopic diseases has been associated with a reduced exposure of pathogens early in life. Epidemiological studies have shown that allergic diseases were less prevalent in children exposed to older siblings or other children at day-cares, to pets, and to farming environments. These observations were the basis for the 'hygiene hypothesis' (22, 23), which proposes that less exposure to infections in infancy can modify the development of the immune system in such a way that allergies are inhibited. The 'hygiene hypothesis' is still a matter of debate, since conflicting data were obtained in different studies (24, 25).

The role of microbial exposure in food allergy has been investigated in four studies that have assessed relation with early life infections; two studies have investigated the role of pet exposure and one study has investigated the role of day care attendance in relation to food allergy prevalence. Furthermore, effects of caesarean section on food allergy will be discussed in this chapter, since this seems to be related to differences in microbial colonization of the gut compared to vaginal delivery. A detailed overview of these studies can be found in Appendix 1, Tables 1-3. No studies were found about associations between family size or living on a farm and food allergy.

3.1 Infections early in life

In a small case-control study the association between *Helicobacter pylori* infections and food sensitization was assessed in children aged 5 to 15 years. There was no difference in food sensitization frequency between the groups (31). Hence, *Helicobacter pylori* infections did not reduce the prevalence of food sensitization.

In the Dutch KOALA birth cohort the relation between early life seropositivity for norovirus and rotavirus, as a measure for viral infections, and atopic diseases was investigated. At the age of 1 year, food sensitization was not different in children seropositive for these viruses, compared to those who were not infected. These data show no protection by early life intestinal viral infections and food sensitization in young children (32).

In a birth cohort skewed towards parental allergy (75% had at least one allergic parent), it was shown that seropositivity for cytomegalovirus was not associated with food sensitization at the age of 5 years. In contrast, infection with Epstein-Barr virus (EBV) was inversely associated with food sensitization. It was shown that infections before the age of 2 years were protective for food sensitization, whereas infections acquired between the ages of 2 and 5 years increased the risk of food sensitization (33).

In a cross-sectional study in school children aged 5 to 15 years, allergic sensitization was compared between Roma and non-Roma children. Roma children were significantly more seropositive for different infections (*Hepatitis A and B*, *T. gondii*, *H. pylori*, cytomegalovirus, *herpes simplex*) than non-Roma children. The latter were significantly seropositive for *M. pneumonia* and *respiratory syncytial virus*. Despite the higher microbial burden in non-Roma children, the frequency of

food sensitization was not different between the two groups. Hence, no protective effect of infections on food sensitization was found (34).

Most of the studies retrieved found no protective effect of childhood infections and food sensitization. Early life infection with Epstein-Barr virus was associated with reduced food sensitization, but in this study infections acquired after the age of 2 years increased the risk on food sensitization. There is insufficient evidence for a protective role of early life infections on food allergy.

3.2 Early life pet exposure

A prospective birth cohort in infants with at least one parent with asthma or rhinitis found no effects of pet (dog or cat) exposure in infancy and food allergy. The only association that was found was between dog exposure and reduced sensitization to inhalant and food allergens (35). In a population-based birth cohort, followed until the age of 18 years, no associations were found between peanut sensitization and dog or pet exposure early in life (36).

These studies show that exposure to pets early in life is not associated with food allergy.

3.3 Day care attendance

In a large cross-sectional study in children aged 1 to 6 years, the effects of day care attendance on different allergic diseases were studied. It was shown that children attending day care centers had a higher risk on parent-reported food allergy compared to children that were not attending day care centers (37).

Since only one study was found, which only assessed parent-reported food allergy, it is not possible to draw any conclusions.

3.4 Mode of delivery

It has been shown that the mode of delivery has an effect on the type and quantity of bacteria colonizing the gut directly after birth. Infants born by a caesarean section had lower numbers of bifidobacteria and bacteroides and were more often colonized with *Clostridium difficile* compared to vaginally born infants (38). It has been proposed that commensal bacteria in the gut play an important role in the development of immunological tolerance to dietary antigens (39). The differences in colonization of the gut due to caesarean section might impair the development of tolerance and thereby increase the risk on food allergies. The relationship between mode of delivery and food allergy has been investigated in seven studies, summarized in Appendix 1, Table 3.

In five studies, delivery by caesarean section was identified as a risk factor for food sensitization (40, 41), parent-reported food allergy (42) or cow's milk allergy (43, 44).

Laubereau et al. (2004) investigated the association in children with a family history of atopy. Delivery with a caesarean section was associated with a 2-fold higher risk of food sensitization at the age of 1 year compared to vaginal delivery. In a population-based birth cohort,

it was also shown that caesarean section was a risk factor for food sensitization; an increased risk of 1.6 was found (40).

In a population-based birth cohort, the prevalence of parent-reported food allergy at 12, 18 and 24 months was compared between children born by caesarean or vaginal delivery. Furthermore, the prevalence of egg allergy confirmed with oral egg provocations was compared between the groups. After adjustment for confounding factors, delivery by caesarean section was a risk factor for parent-reported food allergy, especially in children of allergic mothers. In those children a 7-fold higher risk was found, whereas in the total cohort the risk was 3.2-fold compared to children born by vaginal delivery. In children of allergic mothers, caesarean section was associated with an increased risk on egg allergy (OR 4.1), but this was not statistically significant (42).

Two studies focused specifically on the association between mode of delivery and cow's milk allergy. In these studies no adjustments were made for confounding factors. In a cross-sectional study the prevalence of IgE-mediated cow's milk allergy was higher in children born by a caesarean section compared to those who were born by vaginal delivery. The outcome might be confounded by another identified risk factor that was significantly different in the two groups. It was shown that early feeding with cow's milk based infant formulas was a risk factor for cow's milk allergy. In children born by caesarean section 93% received infant formula early in life, compared to 50% of the children born by vaginal delivery (44).

In a Finnish nested case-control study, information on mode of delivery, other possible risk factors and cow's milk allergy were obtained from national registers. The diagnosis of cow's milk allergy was based on a special reimbursement of the costs for extensive hydrolyzed infant formulas. In Finland, this special reimbursement is only provided after clinically diagnosed CMA. The prevalence of cow's milk allergy was 1.2 fold higher in children born by caesarean section (43). In this study, no adjustments for confounding factors were made and therefore it was decided that the results were inconclusive.

In two studies, no effect of mode of delivery was found on food allergy (45, 46). In a prospective birth cohort study, the relationship between mode of delivery and food allergy, confirmed with food challenges, was assessed. It was shown that the prevalence did not depend on the mode of delivery (45).

In a retrospective study, information from electronic medical records was used to find an association between mode of delivery and food allergy. In children aged 3 to 10 years old, mode of delivery was not a risk factor for food allergy (46).

The results on the relationship between delivery by caesarean section and food allergy are conflicting and in some studies inconclusive. There is limited evidence that children born by caesarean section have a higher risk on food sensitization at a young age. There are no studies that have followed these children for a longer period.

4 Dietary factors

4.1 Breastfeeding

It is generally accepted that breastfeeding is healthy and confers many benefits to mother and child (47). Breast milk contains several immunological active compounds, including cytokines, antibodies, lactoferrin, oligosaccharides, fatty acids and maternal immune cells. These factors are likely to have an effect on the development of the immune system including oral tolerance. Effects of breastfeeding have been studied in many studies focusing on different atopic diseases. The outcomes of these studies were sometimes conflicting: some studies showed beneficial effects, whereas others found no effect or even increased risk of allergies (29, 48). An important criticism is that the outcomes of some of these studies could be biased with confounding factors. The results of studies that have assessed effects of exclusive breastfeeding on food allergy are summarized in Appendix 2, Table 4. The results will be discussed for unselected populations, i.e. representative for the general population and for children with a higher risk of allergies, i.e. with high levels of cord blood IgE, a family history of atopy or atopic dermatitis.

In children not predisposed to allergies, five studies were found that assessed effects of breastfeeding on food allergy. Two studies found a protective effect of breastfeeding on food allergy (49-51), one study showed a protective effect at age 7, but in the same study breastfeeding was identified as a risk factor for food allergy at the age of 44 (52). Two studies showed no effect of breastfeeding (53, 54).

In a Finnish birth cohort study it was shown that breastfeeding for more than 1 month was protective of the development of food allergy at the ages of 1 and 3. There were no differences in the frequency of food allergy between children breastfed for 1 to 6 months and those breastfed for longer than 6 months, suggesting that longer duration does not provide more protection. In a subgroup analysis it was shown that the most pronounced protection was observed in children with a family history of allergy (50, 51).

In a large Swedish birth cohort it was shown that exclusive breastfeeding for 4 months or longer reduced sensitization against cow's milk and cod fish at the age of 8 years. These protective effects were still present after adjustment for confounding factors (49). Effects of breastfeeding on self-reported food allergy were studied in the Tasmanian Asthma Study, a prospective population-based cohort study that followed up 7-year-old children until the age of 44. It was shown that exclusive breastfeeding for 3 months or longer reduced the risk on self-reported food allergy. In contrast, at the age of 44, the prevalence of food allergy was higher in those that were breastfed exclusively (52). A drawback of this study is that self-reported food allergy is compared, which is often an overestimation due to individual perception.

In a population-based intervention study in preterm infants, the incidence of cow's milk allergy at 9 and 18 months was determined in infants exclusively breastfed for 5 weeks with those that received breastfeeding in combination with cow's milk formula. There was no difference in the frequency of cow's milk allergy in both groups (54).

No effects of breastfeeding were reported in a large survey in Japanese children aged 7-15 years. Exclusive breastfeeding for 6 months first appeared to be a risk factor for self-reported food allergy, but after adjusting for confounding factors, this effect was no longer present and breastfeeding did not affect the frequency of food allergy (53).

In children at risk for allergies, five studies were found. Protective effects of breastfeeding were found in one study (55, 56), in two studies breastfeeding was a risk factor (57, 58), and in two studies no effects were found (59, 60).

In a prospective birth cohort, it was shown that at the age of 18 months, cow's milk allergy was less prevalent in children exclusively breastfed for 6 months compared to those that were not. Furthermore, in children that were not exclusively breastfed during this period, the use of extensive hydrolyzed infant formulas was as effective as exclusive breastfeeding (55).

In other studies, however, breastfeeding appears to be a risk factor for egg sensitization. In infants younger than 6 months with atopic dermatitis, the rate of sensitization to three common childhood allergens (cow's milk, egg and soy bean) was assessed. These children had not yet eaten any solid foods. The rate of sensitization to egg was significantly higher in children that were breastfed compared to children that received only infant formula feeding. This increased risk was observed both in infants that were exclusively breastfed as in children that received mixed feeding (both breastfeeding and infant formulas) compared to children that received exclusively infant formulas. There were no differences in milk and soy sensitization between the three groups. Although not all egg sensitized children will develop clinical egg allergy, this study demonstrates that breastfeeding in this high-risk group might be a risk factor (57).

Similarly, in a prospective birth cohort consisting of children with elevated cord blood IgE levels and/or a family history of atopy, exclusive breastfeeding for 5 months or more, increased the risk on egg sensitization at the age of 1 in the subgroup of children with high cord blood IgE levels (58).

Finally, two studies found no beneficial or adverse effects on food allergy. In a birth cohort in children with a family history of atopy, exclusive breastfeeding for 6 months or more had no effect on food allergy prevalence up to the age of 5 (59). In a prospective birth cohort, the prevalence of sensitization to milk at 4 months and milk and egg at 12 months was not different between children exclusively breastfed for at least 4 months and those that were formula-fed (60).

The data on exclusive breastfeeding and protection of food allergy are conflicting, with studies showing either decreased or increased risk or no effect.

4.2 Hypoallergenic infant formulas

In case breastfeeding fails or is not sufficient, the standard feeding that is given to infants are formulas based on cow's milk. It has been hypothesized that food allergen avoidance in the first months of life could prevent the development of cow's milk allergy and possibly other allergies as well. Hydrolyzed formulas are divided based on the degree of hydrolysis, in partially and extensively hydrolyzed formulas, based on either whey or casein proteins. Hydrolysis is an enzymatic process that degrades proteins in smaller fragments, reducing their allergenicity. The partially hydrolyzed formulas are intended for primary prevention of allergic diseases, aiming at reducing the risk on allergies. In the Netherlands, parents of high-risk children are advised to use partially hydrolyzed infant formulas until 6 months of age if breastfeeding is not possible (61). The extensive hydrolyzed formulas are intended for secondary prevention for children with cow's milk allergy.

Only one study was found that investigated the effects of feeding extensive infant formulas on the development of cow's milk allergy in children with a family history of allergy. Mothers were encouraged to exclusively breastfeed their children for 6 months. When breastfeeding was not possible or insufficient children received either a whey-based or casein-based extensive hydrolyzed formula. It was recommended not to introduce cow's milk before the age of 6 months. After the age of 6 months, a normal unrestricted diet was recommended. The prevalence of cow's milk allergy at the age of 18 months was assessed and compared to a group that received exclusively breastfeeding for 6 months and a control group without any dietary advice. The highest prevalence of cow's milk allergy was found in the control group, 20% of the children developed cow's milk allergy. In the other groups, the prevalence of cow's milk allergy was lower: 5% in the children that were exclusively breastfed, 1.7% in children that received casein-based formulas and 4.7% in those that received whey-based formulas (55) (Appendix 2, Table 4).

There is limited evidence that using extensive hydrolyzed infant formulas can prevent the development of cow's milk allergy. Effects on other food allergies were not investigated. There were no studies that have assessed effects of partially hydrolyzed infant formulas in the prevention of food allergy.

4.3 Age of introduction of solid foods

The World Health Organization (WHO) recommends exclusive breastfeeding for 6 months, a period based mainly on reduced gastrointestinal infections in developing countries (62, 63). These recommendations have been adopted by many countries. Prevention guidelines differ per country, but in general most countries, including the Netherlands, advise parents to breastfeed for 4 to 6 months. In the Netherlands, solid food introduction is advised from 6 months of age, especially in high risk children. No specific advice is given on which solid foods should be introduced first. Avoidance of cow's milk in the first year is recommended, cow's milk based infant formulas should be provided instead (61).

There is, however, little evidence that delaying the introduction of solids including food allergens, has a preventive effect on allergies. A systematic literature study has shown that there was no evidence to support an association between early solid feeding and a higher risk on asthma, food allergy and rhinitis (64). More recent papers suggest that late introduction is not preventive but could be a risk factor for allergies. There appears to be a 'critical window' early in life where immune tolerance for proteins is developed. During this period, exposure to proteins is necessary in order to normally develop tolerance. The exact timing of this period in humans is not completely understood. For other immune-mediated diseases, it has been shown that 4 to 6 months of life seems to be a critical period for tolerance acquisition (65). Timing of introduction of cereals in the diet of infants played an important role in susceptibility for celiac disease. An increased risk was found in infants exposed to cereals between the ages of 0 to 3 months and in those who were exposed after 6 months compared to infants who started eating cereals between 4 and 6 months (66). Similarly, delaying the introduction of gluten after the age of 6 months increased the risk on celiac disease compared to those exposed between 4 and 6 months. Exposure prior to 4 months was also associated with an increased risk on celiac disease (67). Hence, for celiac disease, an autoimmune disease, a critical window appears to be present for the introduction of gluten-containing cereals.

A total of six studies were found that have studied the effects of timing of solid foods on food allergy development. One study was in high-risk children (68), three in population-based cohorts (69-71), one in a population-based cohort with a high (83%) proportion of high-risk children (72) and one was in children with a predisposition for type 1 diabetes mellitus (73). Delayed introduction of solids foods was a risk factor for food allergy in four studies (70-73), had no effect in one study focused on egg allergy (69) and increased the risk on food allergy at the age of 1 year but not at the age of 5 (68) (Appendix 2, Table 5).

In a Finnish study in atopic infants, the effects of early introduction of solids on food allergy were studied. All children were breastfed without any cow's milk supplements for 6 months. One group started with solid feeding at 3 months and the other at 6 months of age. At the age of 1, the history of food allergy was significantly higher in children that started at 3 months with solid foods. Almost 40% had self-reported food allergy, compared to almost 10% in the late introduction group. However, the food allergy was not confirmed clinically or supported with sensitization data. In a follow-up study at the age of 5, it was shown that there was no difference in food allergy. At this age, reported food allergy was supported with sensitization data (68).

In the German LISA birth cohort, the effects of timing of introduction of solid foods on several allergic outcomes were studied. In this cohort, effects of introduction before 4 months, between 4 and 6 months and beyond 6 months were compared. Infants with early signs of allergy were excluded from this study, to account for reverse causality. It was found, that food sensitization was more frequent at the age of 6 in children who were introduced to solids later than 4 months. Compared to introduction before 4 months, there was a 3.2- and 2.5-fold higher

risk of food sensitization, for introduction between 4-6 months and beyond 6 months, respectively (71).

In the Dutch KOALA birth cohort, the age of introduction of solid foods was compared with food and inhalant sensitization at the age of 2. In this paper, atopic sensitization was defined as sensitization for food and/or inhalant allergens. After adjustment for confounding factors and exclusion of children with early allergy symptoms, it was shown that delayed introduction was a risk factor for food and inhalant sensitization at the age of 2. Compared to introduction before 4 months, a 3.7- and 4.3-fold higher risk were found for introduction between 4-6 months and after 7 months, respectively. Delaying solid food introduction also increased sensitization to individual food allergens (cow's milk, egg and peanut) but these increases were not statistically significant (70).

In a prospective birth cohort study from the UK, the effects of age of introduction of solid foods on the development of food allergy were investigated. The birth cohort was skewed towards children with a family history of atopy, 83% had a parent or sibling with an allergy. The children were followed up to the age of 3. It was shown that early introduction of solid foods (before the age of 16 weeks) significantly reduced the risk on food sensitization and allergy at the ages of 1 and 3 (72).

In a Finnish prospective birth cohort with children with genetic susceptibility for type 1 diabetes mellitus, but not for allergy, the association between age of introduction of solid foods and food sensitization was analyzed. It was shown that late introduction of egg (>10.5 mo), oats (>5 mo) and wheat (> 6 mo) were associated significantly with increased food sensitization. In this study potential confounders, such as parental allergies were taken into account (73).

In a large population-based cross-sectional study, in children aged 10 to 15 months, associations between timing of introduction of solid foods and egg allergy were determined. Information on infant feeding was retrieved before assessment of egg allergy in this cohort. Egg allergy was assessed with a skin prick test, followed by an open egg challenge when positive. It was shown that the age of introduction of any solid food was not associated with egg allergy (69).

There is limited evidence that delaying the introduction of solid foods for beyond 6 months of age reduces the risk on food allergy. In contrast, four studies described in this report provide evidence that delayed introduction may be a risk factor for food sensitization or allergy.

4.4 Maternal and infant food allergen avoidance

In the past, the UK recommended to avoid peanut exposure as a primary prevention strategy in families with an increased risk of atopy. It was advised not to consume peanuts during pregnancy and lactation. Furthermore, children should not be exposed to peanuts up to the age of 3. Similar recommendations were given in the USA and Australia. The efficacy of this primary prevention strategy has been questioned and these recommendations were abandoned because of lack of

conclusive evidence for a protective effect (74). The last years a paradigm shift took place, initiated by anecdotal reports from countries that have a high peanut ingestion early in life, but a low incidence of peanut allergy. Comparing peanut consumption and peanut allergy between Jewish children in Israel and the UK, has shown that the incidence in Israel is 10-fold lower, while peanuts are regularly consumed in the first year of life (75). This has led to the hypothesis that early introduction of peanut, but probably also other food allergens, during the critical window of immune tolerance development, could prevent allergy development. In experimental animal studies evidence for this hypothesis has been found. In mice it was shown that low-dose peanut exposure during pregnancy and lactation reduced the risk on peanut allergy (76).

The effects of maternal and infant avoidance of peanut but also other food allergens on food allergy were studied in 13 studies, summarized in Appendix 2, Table 6. It should be noted that the period of food allergen avoidance differs between the studies. In some studies only effects of maternal avoidance were studied, in others only infant avoidance, while some studied both. It is important to distinguish between these different interventions; since it is unknown which period in life is the most susceptible for allergy preventive measures.

4.4.1 *Avoidance of multiple food allergens*

Four studies have investigated effects of avoidance of multiple food allergens on food allergy. Three studies found no effect of maternal and infant food allergen avoidance (72, 77, 78). One study found a protective effect on cow's milk allergy, but not on other food allergies (79-81).

In a prospective birth cohort study maternal and infant food allergen intake were based on information from food frequency questionnaires. The birth cohort was skewed towards children with a family history of atopy, 83% had a parent or sibling with an allergy. The children were followed up to the age of 3. Maternal dietary intake of food allergens during pregnancy and lactation was not associated with food allergy. In contrast, exposure to a certain food allergen before the age of 3-6 months increased the risk on becoming allergic to this specific food allergen. However, these associations were not statistically analyzed. From the paper it is unclear if the data were adjusted for potential confounders. Therefore, the association between infant food allergen intake is judged as inconclusive (72).

In a small prospective intervention trial in infants with a family history of atopy the effects of allergen avoidance on allergy development were assessed. In the group randomized to allergen avoidance, mothers were advised to avoid cow's milk, egg, fish, peanuts and soy during breastfeeding and in the first 9 months of life. In addition, house dust mite exposure should be reduced, pets were not allowed and smoking was prohibited. It was shown that the prevalence of food allergy at the age of 8 was higher in the allergen avoidance group. However, after adjustment for confounding factors, this difference was not statistically significant (77).

In a randomized cohort study in pregnant women with respiratory allergy, effects of reduced or high intake of milk and egg during pregnancy and breastfeeding on milk and egg sensitization were compared. It was shown that a higher intake of these food allergens did not increase the risk on sensitization, suggesting that a higher exposure to these food allergens does not increase the risk on allergy development (78).

In a small prospective intervention study in infants with a family history of atopy pregnant women were randomized to a prophylactic or a control group. Women in the prophylactic group were advised to avoid cow's milk, egg, and peanut during the last trimester of pregnancy and during breastfeeding. The infants should avoid cow's milk until the age of 1 year, egg until the age of 2 and peanut and fish until the age of 3. The control group was advised to follow standard feeding practices and not to avoid food allergens. The children were followed until the age of 7 and the prevalence of food sensitization, food allergy related symptoms (hives, gastrointestinal symptoms), and food allergy (confirmed with food challenges) were assessed at ages at the ages of 1, 2, 4 and 7. At the ages of 1 and 2 the prevalence of cow's milk allergy and confirmed food allergy was significantly lower in the prophylactic group. At the ages of 4 and 7, the rates of food sensitization and confirmed food allergy were not different between the two groups. These data show that maternal and infant food allergen avoidance had a protective effect on cow's milk allergy and not on other food allergies (79-81).

4.4.2

Peanut

Four studies have investigated the effects of peanut avoidance on peanut and other food allergies. Two studies showed that maternal peanut avoidance was not associated with peanut allergy (82, 83), one study showed that delaying the introduction of peanut in the infants diet might be a risk factor for peanut, sesame and tree nut allergy (75) and the results of one study were inconclusive (84).

In a small case-control study from South Africa, maternal and infant peanut consumption was compared between children sensitized to peanuts (cases) and those sensitized to egg or milk (controls). Maternal peanut consumption during pregnancy was almost 4 times more frequent in cases compared to controls, suggesting that maternal peanut consumption was a risk factor. However, this difference was not statistically significant and the results were not adjusted for confounders. In this study it was also found that the mean age of introduction of peanuts was significantly earlier in the cases compared to the controls. Hence, peanut allergic children introduced peanuts earlier in their diets. The results should be interpreted with caution, since the sample size was small, there was no adjustment for confounding factors and there was no non-atopic control group included (84).

In a small case-control study from the UK, maternal peanut intake was compared between children with clinically confirmed peanut allergy, atopic controls and non-atopic controls. The percentage of mothers that consumed peanuts during pregnancy was similar between the three

groups. A higher percentage of mothers with peanut allergic children consumed peanuts at least seven times per week compared during breastfeeding. This difference, however, was not statistically significant after adjustment for confounders. Hence, this small study did not show any association between maternal peanut consumption during pregnancy and lactation and a higher risk on peanut allergy (83).

In a larger case-control study, maternal and household peanut consumption were compared between children with peanut allergy (cases), high-risk controls (with egg allergy) and low-risk controls. Cases were selected from a group of children with eczema, who underwent clinical examinations to assess peanut allergy. In this study, families who did suspect peanut allergy in their child were excluded, because this would have skewed their recollection of previous peanut consumption. There were no differences in infant peanut consumption between the groups. Maternal peanut consumption during pregnancy and lactation were significantly higher in cases compared to atopic controls, but not different from non-atopic controls. After adjustment for confounding factors, this was no longer significant. The biggest difference between the cases and controls was the median weekly household peanut consumption by all family members. This is a measure for environmental peanut exposure. The relative risk of peanut allergy increased significantly with higher environmental concentrations of peanut. When cases were compared to high-risk controls an increased risk of 23 was found for the highest environmental exposure. The risk increased 6-fold when cases were compared to the low-risk controls. The environmental exposure to peanuts was identified as the most important risk factor for peanut allergy and differences in maternal peanut consumption became non-significant after adjusting for environmental exposure. It was hypothesized that other routes of exposure, i.e. skin or inhalation exposure might increase the risk on peanut sensitization, whereas oral exposure would promote tolerance development (82).

In a large cross-sectional study, self-reported food allergies were compared between Jewish children living in Israel and those living in the UK. The prevalence of food allergy was associated with the age of introduction of food allergens and the frequency of consumption in the first year. It is important to note that the information on the dietary intake early in life was obtained in a different cohort of Jewish children aged 4 to 24 months. The prevalence of peanut allergy was, after adjustment for confounding factors, 5.8 times higher in the UK compared to Israel. The prevalence rates of sesame and tree nut allergy were also higher: 2.7 and 15.2, respectively. There was no difference in prevalence of egg and milk allergy between the two countries. The timing of introduction of egg, wheat, soy and tree nuts, was not different in the UK and Israel. Introduction of cow's milk and sesame was slightly earlier in Israel. The largest difference in consumption of solid foods in the first year of life was observed for peanut. In Israel, peanuts are introduced earlier in the diet and are consumed more frequently at higher quantities. Possibly, the early introduction of peanut in the diet can explain the lower prevalence of peanut allergy. Furthermore, sesame and tree nut allergy were more prevalent in the UK. For sesame, this could be associated as well with a higher consumption in Israel, but for tree nut this was not the case. The

strong association between peanut, tree nut and sesame allergy might explain the difference in tree nut allergy. It is possible that cross-sensitization can explain the occurrence of multiple allergies in the UK, whereas cross-tolerance for peanut might explain the low prevalence of tree nut allergy in Israel (75). A limitation of this study is that it is not possible to directly associate timing of introduction of food allergens with food allergy, since dietary exposure and prevalence of food allergy were measured in different cohorts.

4.4.3 *Cow's milk*

In three studies associations between timing of introduction of cow's milk in the infants' diet on cow's milk or other food allergies were investigated. An intervention study showed that cow's milk exposure early in life had no effect on the incidence of cow's milk allergy (85, 86). One study showed that there appeared to be a critical period in which cow's milk introduction increased the risk of cow's milk allergy (87) In contrast, one study found no association between timing of introduction and cow's milk sensitization (70).

In a Dutch birth cohort, the effects of brief neonatal exposure to cow's milk on allergy development were studied in a double blind placebo controlled intervention trial (BOKAAL study). Infants that were exclusively breastfed were randomized to receive either cow's milk free formula (placebo group) or cow's milk based formula in the first three days of life. It was shown that exposure to cow's milk early in life did not increase the frequency of milk and egg sensitization up to the age of 5 (85, 86).

In a large prospective study from Israel, it was shown that the incidence of cow's milk allergy was influenced by the timing of exposure to cow's milk. In this prospective study, more than 13,000 infants were followed in the first year of life. Infants that were exposed to cow's milk for the first time in the period of 3.5 months to 6 months of age had the highest incidence of cow's milk allergy (1.75%). A very low incidence of 0.05% was found in children that received cow's milk in the first 2 weeks of life. An incidence of 0.5% was found in children that were exposed before the age of 3.5 months or after the age of 6 months (87). The authors conclude that exposure to cow's milk early in life appears to induce tolerance and prevent allergy development. Furthermore, the time of introduction of cow's milk appears to be an important determinant and the data suggest that cow's milk should be introduced before the age of 3.5 months or after 6 months.

In the Dutch KOALA birth cohort, the effect of age of introduction of cow's milk was compared with food sensitization. There was a trend towards a lower cow's milk sensitization, but this was not statistically significant. There was no association between cow's milk introduction and peanut and egg sensitization (70).

4.4.4 *Other food allergens: egg, fish and wheat*

Three studies were published that have investigated the effects of timing of introduction of other food allergens. It was shown that delaying the introduction of egg (69), fish (88) or wheat (89) was a risk factor for egg, fish or wheat allergy, respectively.

In a large population-based cross-sectional study, in children aged 10 to 15 months, associations between egg allergy and timing of introduction of egg were determined. Information on infant feeding was retrieved before assessment of egg allergy in this cohort. Egg sensitization was assessed with a skin prick test and positive results were confirmed with an open egg challenge. It was shown that delaying egg introduction in the diet was a risk factor for egg allergy. The lowest prevalence of egg allergy was found in children who first consumed eggs between 4 to 6 months. Higher risks were found in children that were exposed to eggs later. After adjustment for confounders, a 3.4-fold increase of egg allergy was found when egg was introduced after the age of 12 months. The influence of the type of egg was also studied and it was shown that introduction of cooked egg into the diet at 4 to 6 months, was associated with the lowest risk (69).

In a Swedish population-based birth cohort, effects of frequency of fish consumption on allergic diseases was studied. In this study, age of introduction of fish was associated with the frequency of fish sensitization at the age of 4. The average age for introduction of fish was 8.3 months, but children from atopic families and children who developed wheeze or atopic eczema introduced fish later. To avoid bias children with eczema and wheeze during first year of life were excluded. Furthermore, odds ratios (OR) were adjusted for atopic heredity, and other confounding factors. It was shown that children who consumed fish before the age of 8 months had a lower prevalence of fish sensitization compared to children who started with fish after this age. It should be noted that the results should be interpreted with caution, since only a small number of children were sensitized to fish (0.7%) (88).

It can be concluded that strict maternal food allergen avoidance during pregnancy and breastfeeding has no protective effect on food allergy development. Pregnant women should therefore not be advised to eliminate food allergens from their diet. Delaying the introduction of food allergens in the infants' diet seems not to be protective either. On the contrary, the new paradigm is that delaying introduction might be a risk factor for food allergy. There is limited evidence that this might be true for peanut, egg, fish and wheat. For cow's milk the available data were limited and conflicting. The optimal timing of introduction of food allergens for allergy prevention is currently unknown.

4.4.5 *Future perspectives on food allergen avoidance*

The drawback of prospective cohorts is that recall bias is possible, i.e. parents might not know exactly the timing of food allergen introduction. Furthermore, reverse causation is possible, since parents with allergies might be more careful and delay introduction of food allergens in the diet of their child. In the most recent studies, this has been taken into account by adjusting for confounding factors and by exclusion of children with early allergies. More substantial evidence would be provided by investigating the role of timing of food allergen introduction in randomized intervention studies, preferably with a placebo group. Currently, a number of such studies have been initiated and are in progress. These studies are summarized below.

- **The LEAP study** (Learning Early About Peanut Allergy) started in 2007 in the UK. This is a randomized clinical trial in which 640 children were enrolled from 4 to 10 months of age. Children were randomly assigned to receive either 6 grams of peanut protein per week or to avoid peanuts until the age of 3. The main outcome is the number of children that have developed peanut allergy at the age of 5. Development of other atopic diseases will be recorded as well. The results are expected in 2013. <http://www.leapstudy.co.uk>.
- **The EAT study** (Enquiring About Tolerance) is a second UK study, which is currently recruiting infants. The aim is to enrol 1300 infants, but recruitment goes slow. In August 2010, 350 children were recruited. This study is a randomized controlled trial of early introduction of allergenic foods in a population-based cohort. The infants will be placed at random in one of the two groups. One group will introduce six allergenic foods from 3 months of age alongside continued breastfeeding. At the age of 3 months cow's milk is introduced and between 4 to 5 months peanut butter, fish, wheat, eggs and sesame are included in the diet (Early Introduction Group). The other group will follow present UK government weaning advice i.e. aim for exclusive breastfeeding for around six months and will not introduce the food allergens before this age (Standard Weaning Group). The prevalence of food allergies and other allergies will be monitored up to the age of 3. <http://www.eatstudy.co.uk>.
- **The HEAP study** (Hen's Egg Allergy Prevention) in Germany is a randomized placebo controlled study. A total of 800 children are enrolled in this study and at the age of 4 to 6 months they are exposed to either hen's egg or a placebo. The development of egg allergy and other allergies will be monitored. Results are expected in 2012.

The STAR and STEP trials in Australia are two randomized placebo controlled trials on egg allergy prevention. In both studies egg is introduced in the form of whole egg powder mixed into an infant's solid foods commencing from 4-6.5 months of age. The placebo group receives rice powder. Both trials are in the recruitment phase and will be completed in 2012-2013.

 - The STAR Trial will involve 200 infants with moderate to severe eczema.
 - The STEP Trial will involve 1500 infants without eczema but with atopic mothers.

4.5 Pre- and probiotics

The gut microflora plays an important role in the maintenance of the gut barrier function and modulation of the immune response. The composition of the gut microflora differs between healthy and allergic children and in countries with a low and high prevalence of allergies (90-93). These differences point towards the importance of the gut microbiota in the development of allergies and modification of this microflora might be used in primary prevention. Furthermore, it has been shown that the gut microflora differs between breastfed and formula-fed children. Breastfeeding promoted the colonization with bifidobacteria and lactobacilli, which are considered to be beneficial bacteria. The addition of 'pre- or probiotics' to infant formulas is intended to modify the infants gut microflora, thereby reducing the risk on allergies.

Prebiotics are nondigestible food components that selectively stimulate the growth or activity of bacteria in the colon and convey a health benefit to the host. The most commonly used prebiotics in infant food

are oligosaccharides (94). Probiotics are defined as live microorganisms that provide health benefits to the host by altering the microflora. This definition can only be used when there is scientific evidence for a health benefit. Effects on allergies by pre- and/or postnatal supplementation with different micro-organisms with intended probiotic activity have been widely studied. The reason for this is that some of these micro-organisms have immunomodulatory properties, including stimulation of Th1 immunity which could inhibit the development of allergies. In addition, effects on regulatory T cells have been found for some probiotics, which could also reduce the risk on allergies (95, 96).

No studies were found that have investigated effects of prebiotics on food allergy. Five studies were found that have assessed effects of supplementation with micro-organisms with an intended probiotic activity on food allergy. All studies were performed in children with a family history of atopy (Appendix 2, Table 7).

The micro-organisms used differed between the studies, only the studies from Kalliomaki et al. (2001, 2003, 2007) and Rautava et al. (2002) used the same strain. All studies were randomized double blind placebo controlled trials (RDBPCT) and treatment with the 'probiotics' started either at the last 2-4 weeks of pregnancy or directly after birth. In only one study a beneficial effect of supplementation with *Lactobacillus reuteri* during pregnancy and the first year of life was found. The beneficial effect, a lower prevalence of food sensitization, was only shown in a subgroup of children with allergic mothers, not in the complete cohort (97). Taylor et al. (2007) show that supplementation with *L. acidophilus* from in the first 6 months of life was a risk factor for food sensitization at 12 months, but not on the incidence of food allergy at 6 and 12 months (98). The other studies showed no effect of probiotics on cow's milk allergy (99-102) or food sensitization (103).

There is currently no scientific evidence to recommend the addition of prebiotics or micro-organisms with intended probiotic activity to infant formulas or supplements for pregnant women for the prevention of food allergy.

4.6 Fish oil supplements

Changes in our western diet during the last century have been linked to the increase in allergic diseases. Our modern diet differs in many ways from more traditional diets, with more processed and synthetic foods and less fresh fish, fruits and vegetables. One change during this period was the intake of polyunsaturated fatty acids (PUFA), which are essential fatty acids that cannot be produced in humans. PUFA are classified in two families: the omega-6 (n-6) and n-3 families. During the last decades the intake of the anti-inflammatory n-3 PUFA has decreased, whereas the intake of n-6 PUFA has increased (104, 105). It is hypothesized that the declining n-3/n-6 PUFA ratio in modern diets has an effect on early immune programming and subsequent development of allergic diseases. Different foods contain 3-PUFA, but especially fatty fish is rich in these compounds.

The effects of n-3 PUFA have been studied in two intervention studies with fish oil supplementation during pregnancy (106, 107). In addition,

in a birth cohort frequent fish consumption in first year of life was associated with the age of 4 years (88) and in a birth cohort associations between higher concentrations of n-3 PUFA in breast milk food sensitization were studied {Thijs, 2011 #537} (summarized in Appendix 2, Table 8).

In a small randomized placebo-controlled intervention trial, it was shown that fish oil supplementation during pregnancy reduced the rate of egg sensitization at the age of 1 compared to the placebo group. There were no changes in sensitization to cow's milk or peanut. The study population was relatively small and clinical allergy was not assessed. In addition, immunological changes measured in the cord blood were in line with effects on egg sensitization. Fish oil supplementation reduced neonatal cytokine responses directed towards ovalbumin, an egg allergen (106).

Beneficial effects of fish oil supplementation during pregnancy on egg allergy were also found in another double-blind placebo controlled intervention trial. Fish oil supplementation during the last seven weeks of pregnancy significantly decreased the prevalence of food allergy in the first year of life. The effects were significant for egg allergy at 6 and 12 months. There was a non-significant trend in a lower prevalence of cow's milk allergy (107).

In a Swedish population-based birth cohort, it was shown that regular fish consumption in the first year of life reduced the frequency of food sensitization at the age of 4. In this study questionnaires were used to determine the frequency of fish consumption. The age for introduction of fish was 8.3 months, but children from atopic families and children who developed wheeze or atopic eczema introduced fish later. To avoid bias children with eczema and wheeze during first year of life were excluded. Furthermore, odds ratios (OR) were adjusted for atopic heredity, and other confounding factors. It was shown that regular fish consumption reduced the frequency of food sensitization significantly compared to children who never consumed fish (88).

The concentration of fatty acids in breast milk was measured in a subgroup of the KOALA birth cohort study. In this study, the levels of n-3 PUFA and of ruminant fatty acids were measured. Ruminant fatty acids are present in human breast milk and the main source of these fatty acids is fat from dairy products. Higher levels of n-3 PUFA or ruminant fatty acids were both associated with a significantly lower rate of sensitization to milk, egg and peanut. At the age of 2, this beneficial effect disappeared {Thijs, 2011 #537}.

There is limited evidence from two intervention studies that n-3 PUFA supplementation during pregnancy reduces the prevalence of food (predominantly egg) allergy in the first year of life. These findings should be confirmed in larger intervention trials with a longer follow-up period to assess effects on other food allergies. There is also limited evidence that frequent fish consumption in the first year of life appeared to be associated with less food sensitization at the age of 4. These associations should be confirmed in more than one epidemiological study.

4.7 Vitamins

Not much is currently known about the effects of vitamins on food allergy development and only three studies were found, two on multivitamin intake and one on vitamin D intake.

In a large prospective population-based birth cohort associations between early vitamin use and asthma and food allergy were assessed. It was shown that in children that were not breastfed, the use of multivitamins before the age of 6 months was a risk factor for parental reported food allergy. In addition, the use of multivitamins at the age of 3 was a risk factor for food allergy both in breastfed and formula-fed children.

In a large prospective birth cohort intake of multivitamins was derived from questionnaires. An association between intake of multivitamins before 4 years, reduced the frequency of food sensitization significantly. It was speculated that antioxidant and immunomodulatory properties of some vitamins might be involved in this beneficial effect (109)

In a prospective birth cohort in children with a genetic susceptibility for type 1 diabetes, it was shown that increasing maternal intake of vitamin D was associated with a lower risk on food sensitization (110) (Appendix 2, Table 9).

The effects of use of multivitamins in childhood on food allergy are conflicting and it is not possible to draw any conclusions. There are insufficient data to draw conclusions on maternal vitamin D use and food allergy.

4.8 Organic food

In the Dutch KOALA study, the effects of consumption of organic foods on allergic diseases, including food sensitization were assessed in children aged 2 years (n=2764). The cohort was divided into three groups: conventional diet, moderately organic and strictly organic. There were no differences in food sensitization between the three different groups (111) (Appendix 2, Table 9).

5 Lifestyle factors

5.1 Anthroposophic lifestyle

The anthroposophic way of living comprises a characteristic lifestyle that is different from the general population. This way of life has much resemblance with lifestyles that were more common a few decades ago. The most important characteristics are restricted use of antibiotics, antipyretics and vaccinations and specific dietary habits, such as more consumption of organic or biodynamic foods and fermented vegetables. It has been speculated that growing up according to this lifestyle might reduce the risk on allergies (112). It has been shown that the microflora of anthroposophic children is different from children with a more conventional lifestyle, which could have an influence on the development of immunological tolerance to food allergens (113).

The literature search revealed that most studies have investigated the effects of this lifestyle on inhalation allergies or on atopic sensitization. In the latter sensitization to both inhalant and food allergens was measured and these studies were excluded from this review. The effects of anthroposophic lifestyle on food allergy were assessed in one study. In this cross-sectional study prevalence of food allergy was compared between children from anthroposophic schools and those attending control schools. The frequency of food sensitization, based on specific IgE levels, was significantly lower in children from the anthroposophic schools, 9% was sensitized, compared to 16% in the control school children. In contrast, the prevalence of positive SPT for food allergens and confirmed food allergy based was not different between these children (113). In this study, no adjustments were made for confounding factors. The only difference that was found was a higher prevalence of specific IgE for food allergens, but this was not supported by the SPT data, making the results of this study inconclusive.

There is no evidence for a possible role of anthroposophic lifestyle on food allergy.

5.2 Tobacco smoke exposure

There are indications that tobacco smoke exposure during pregnancy or early in life is a risk factor for respiratory allergic diseases. Possible associations with food allergens have been explored in two studies. In a prospective population-based birth cohort, the effects of pre- and postnatal tobacco smoke exposure on food sensitization at the age of 3 were assessed. It was shown that environmental tobacco smoke exposure was a risk factor: the prevalence of food sensitization was significantly higher in exposed children. Postnatal tobacco smoke exposure alone was not a risk factor. In this study no adjustments were made for confounding factors (114).

In a prospective population-based birth cohort, it was shown that maternal smoking during pregnancy was not associated with food sensitization. Environmental tobacco smoke exposure in the first 2 months of life, however, significantly increased the risk on food sensitization at the age of 4 (115).

There are insufficient data available on the effects of pre- and/or postnatal tobacco smoke exposure on food allergy.

5.3 Other lifestyle and environmental factors

In the literature databases no studies were found about associations between food allergy and vaccinations, use of antibiotics, use of other medicines and exposure to environmental toxicants or natural toxins.

6 Conclusion and recommendations

Prevention of allergic diseases, including food allergy, is an area of interest for parents, pediatricians, allergists, health care professionals, and policy makers. The complexity of atopic diseases, involving both genetic and environmental components, makes research in this field difficult. The outcomes of epidemiological studies are not always easily translated into recommendations for primary prevention due to conflicting or inconclusive data. Epidemiological studies are often hampered by limitations in the study design and the outcome can be confounded by several factors including family history of atopy. Especially breastfeeding is difficult to study since it is unethical to randomize infants at birth to either breastfeeding or artificial feeding. The currently ongoing clinical studies that are investigating timing of introduction of food allergens might provide more insight into this complex area, since they are randomized and use an intervention strategy. It is to be expected that the current recommendations of allergy experts will evolve according to progress made in the field of allergy research.

This literature review provides a state-of-the-art overview of risk factors associated with food allergy. The results of this review should be related to risk factors related to other allergies, since strategies for primary prevention will be formulated for allergy in general. Also for other allergies, the results from epidemiological studies are for many environmental exposures conflicting or inconclusive. Different expert committees, i.e. the American Academy of Pediatrics (AAP), European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and others, regularly update their recommendations on early life dietary factors for allergy prevention, in order to keep these up-to-date with progress made in the scientific field. The most recent dietary advises are summarized below (116-120). The findings for microbial, dietary and lifestyle factors for food allergy retrieved in this systematic review are included in this summary as well.

Microbial factors

- This review did not find evidence for a protective role of early life infections on food allergy.
- There are insufficient data to support an association between pet exposure early in life and food allergy.
- There is insufficient evidence to support that day care attendance is a risk factor for food allergy.
- The data on effects of mode of delivery on clinically diagnosed food allergy are conflicting.

Dietary factors

- The WHO recommendations of 6 months exclusive breastfeeding are not advised by AAP and ESPGHAN. They recommend exclusive breastfeeding for 4-6 months. This recommendation takes into

account multiple benefits of breastfeeding, including prevention of gastrointestinal infections. For prevention of atopic eczema, wheeze and asthma, exclusive breastfeeding for 4 months is possibly preventive (47, 116). The preventive effect of exclusive breastfeeding on food allergy is unknown. This literature review shows that results from different studies are conflicting, with studies showing protection, no effect or increased risk.

- When breastfeeding fails or is insufficient, most allergy experts recommend the use of hypoallergenic (partially hydrolyzed) infant formulas for high-risk children. Studies that have investigated the effects of partially or extensively hydrolyzed formulas found no effect on asthma. There is limited evidence for a protective effect of partially and extensive hydrolyzed formulas in the prevention of atopic eczema. In this study some conflicting results were obtained for two different types of extensive hydrolyzed formulas (based on whey or casein). Only the extensive hydrolyzed casein formula and the partially hydrolyzed whey formula reduced the risk on atopic eczema (121). In this review one study showed that extensive hydrolyzed infant formulas were protective for food allergy. There were no studies that specifically studied effects of partially hydrolyzed infant formulas on the prevalence of food allergy. There are currently insufficient data to support the protective role of partially hydrolyzed infant formulas in food allergy prevention.
- Maternal avoidance of food allergens during pregnancy and breastfeeding has no preventive effect on food allergy.
- There is limited evidence that delaying the introduction of solid foods beyond 6 months is a risk factor for food allergy. The ESPGHAN recommends not to introduce solid foods before 4 months of age and not to delay introduction beyond 6 months.
- Delayed introduction of food allergens does not prevent food allergy development and recent studies indicate that it might be a risk factor for food allergy. The optimal timing of introduction of food allergens is not known. Both ESPGHAN and AAP recommend not delaying the introduction of food allergens and introducing them together with other solid food at 4 to 6 months. Information from currently ongoing randomized intervention trials might provide substantial evidence that can be used for new recommendations on timing of food allergen introduction.
- There is no evidence that supplementation of infant formulas with micro-organisms with intended probiotic activity reduces the risk of food allergy.
- There is limited evidence for a protective role of fish oil (n-3 PUFA) supplementation during pregnancy on reduction of the prevalence of egg allergy. These findings should be confirmed in larger epidemiological studies and require a longer follow-up period.

- There is insufficient evidence to support a protective role for maternal vitamin D intake during pregnancy on food allergy.
- The data on the use of multivitamins early in life on food allergy are conflicting and cannot be used in terms of allergy prevention.
- There is no evidence for a protective effect of consumption of organic foods on food allergy.

Lifestyle factors

- There is insufficient evidence for a protective role of anthroposophic lifestyle on food allergy.
- There are insufficient data available on the effects of pre- and/or postnatal tobacco smoke exposure on food allergy. However, maternal cigarette smoking and smoking around children should be discouraged in view of all other adverse effects.

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Appendix 1: Microbial exposure

Table 1 Early life infections

Study design	Assessment of food allergy	Results	Outcome	Reference
Case-control study in 5-15 yr old children: <ul style="list-style-type: none"> • <i>Helicobacter pylori</i> infection, n=51 • Controls, n=23 	sIgE (wheat, fish, milk, egg, soybean, peanut)	Food sensitization frequency was not different between children with and without a <i>H. pylori</i> infection	<i>H. pylori</i> infection has no effect on food sensitization	Kolho et al., 2005
Prospective population-based birth cohort, n=612; seropositivity for rotavirus and norovirus (IgG, IgA)	sIgE (milk, egg, peanut) at 1 yr	A lower prevalence of food sensitization was found in children who have been infected with norovirus. This difference was not significant.	Norovirus or rotavirus infection have no effect on food sensitization	Reimerink et al., 2009
Prospective birth cohort, skewed towards parental allergy, seropositivity for Epstein-Barr virus (EBV) or cytomegaly virus; n=219	SPT and sIgE (egg, peanut, cod, milk, soybean) at 2 and 5 yr	Infection with EBV before the age of 2 yr significantly reduced the prevalence of food sensitization at 5 yr. After adjustment for confounding factors the OR was 0.34 (0.12-0.94). Infection with EBV between 2 to 5 year significantly increased the prevalence of food sensitization at 5 yr. Adjusted OR 4.64 (1.57-13.9)	Early life (<2 yr) EBV infection is a protective factor. Late (2-5 yr) EBV infection is a risk factor	Saghafian-Hedengren et al., 2010
Cross-sectional study in school children (5-15 yr) comparing seropositivity for foodborne-, airborne- and bloodborne infections between Roma (n=118) and non-Roma (n=98) children	sIgE (egg, milk, fish, wheat, peanuts, soybean)	Roma children were significantly more seropositive for <i>Hepatitis A</i> and <i>B</i> , <i>T. gondii</i> , <i>H. pylori</i> , cytomegalovirus, <i>herpes simplex</i> . Non-Roma children were significantly more seropositive for <i>M. pneumonia</i> and <i>respiratory syncytial virus</i> . Food sensitization prevalence was not different between Roma and non-Roma	No protective effect	Michos et al., 2010

Abbreviations: yr: years; n: number; sIgE: serum specific IgE levels; OR: odds ratio; EBV: Epstein-Barr virus

Table 2 Other microbial exposures

Study design	Assessment of food allergy	Results	Outcome	Reference
<i>Pet exposure</i>				
Prospective birth cohort, one parent with asthma or rhinitis; n=283	Parent-reported physicians diagnosed food allergy and sIgE (egg, milk, peanut) at 1 yr	Having a cat or a dog in the house was not associated with food allergy.	No effect	Gern et al., 2004
Prospective population-based birth cohort, n=835	sIgE (peanut) at 18 yr	Having a cat or dog in the house was not associated with peanut sensitization at 18 yr	No effect	Wegienka et al., 2010
<i>Day-care attendance</i>				
Cross-sectional questionnaire study in children aged 1-6 yr, n=10,851	Parent-reported physicians diagnosed food allergy	Children in day care had a significantly higher risk of food allergy compared to those that stayed at home. OR after adjustment for confounding factors: <ul style="list-style-type: none"> • Home: 1.00 • >20 h/week: 1.27 (1.07-1.52) • <20 hr/week: 1.22 (1.00-1.49) 	Day care attendance may be a risk factor for food allergy	Hagerhed-Engman et al., 2006

Abbreviations: yr: years; n: number; sIgE: serum specific IgE levels; h: hours; OR: odds ratio

Table 3 Mode of delivery

Study design	Assessment of food allergy	Results	Outcome	Reference
Prospective birth cohort, family history of atopy, n=865	sIgE (egg, milk, soybean) at 1 yr	Children born by caesarean section had a significant higher prevalence of food sensitization compared to those born by vaginal delivery. After adjustment for confounders the OR was 2.06 (1.2-3.8)	Risk factor for food sensitization	Laubereau et al., 2004
Prospective population-based birth cohort, n=2803	1. Parent-reported food allergy at 12, 18, 24 mo; 2. Egg allergy (sIgE to egg, food challenges (open or DBPCFC)	Infants who were born by caesarean section had a significant higher prevalence of parent-reported food allergy. OR after adjustment for confounding factors: 3.2 (1.4-7.3). After stratification for maternal allergy, it was found that the risk was higher in children of allergic mothers: OR of 7.0 (1.8-28). In children of allergic mothers caesarean delivery was associated with an increased risk of confirmed egg allergy. The adjusted OR was 4.1 (0.9-9.1, p=0.08).	Risk factor for parent-reported food allergy, especially in children of allergic mothers.	Eggesbø et al., 2003
Prospective population-based birth cohort, n=2500	sIgE (egg, milk, wheat, peanut, soybean, cod) at 2 yr	Food sensitization was significantly more frequent in children born by caesarean delivery. After adjustment for confounding factors the OR was 1.64 (1.03-2.63).	Risk factor for food sensitization	Negele et al., 2004
Prospective population-based birth cohort, n=609	sIgE (milk, egg, soy, fish, peanut, hazelnut, wheat), SPT (milk, egg, cod, hazelnut, peanut, wheat, soybean), food challenge (open or DBPCFC)	The prevalence of food allergy was not different between children born by a caesarean section and those born by vaginal delivery	No effect	Kvenshagen et al., 2009
Retrospective cohort study in 3-10 yr old children, n=8953	Information from electronic medical records	The mode of delivery was not associated with food allergy	No effect	Renz-Polster et al., 2005

Study design	Assessment of food allergy	Results	Outcome	Reference
Cross-sectional study in children with IgE-mediated CMA (n=119) and with non-IgE-mediated (n=206) CMA	sIgE (milk), elimination diet and provocation test	The prevalence of IgE-mediated CMA was significantly higher in children born by a caesarean section. The OR was not adjusted for confounding factors: 2.15 (1.02-4.49). The results might be confounded by another identified risk factor: feeding with infant formula in the first days of life. This was significantly different in children born by caesarean section (93%) compared to those born by vaginal delivery (50%). The mode of delivery had no effect on non-IgE mediated CMA.	Inconclusive, no corrections for possible confounding factors	Sánchez-Valverde et al., 2009
Nested case-control study, data of children born in 1996-2004 was obtained from national registers 1. Cases: IgE-CMA, n=16,237 2. Matched controls, n= 16,237	CMA diagnosis was based on special reimbursement of the costs for extensive hydrolyzed infant formulas. Exclusion of infants that occasionally used these formulas and those that used it for less than 6 mo. This special reimbursement is only provided after clinically diagnosed CMA	A moderate but significant increased risk was found for CMA in children born by caesarean section. OR was not adjusted for confounding factors: 1.18 ((1.10-1.27).	Inconclusive, no corrections for possible confounding factors	Metsala et al., 2010

Abbreviations: yr: years; mo: months; n: number; sIgE: serum specific IgE levels; SPT: skin prick test; DBPCFC: double blind placebo controlled food challenge; OR: odds ratio; CMA: cow's milk allergy

Appendix 2: Dietary factors

Table 4 Breastfeeding and hypoallergenic infant formulas

Study design	Assessment of food allergy	Results	Outcome	Reference
Population-based¹				
Birth cohort, , n=236	Clinical anamnesis in 3 groups: I) Short or no BF (<1 mo) II) Intermediate BF (1-6 mo) III) Prolonged BF (>6 mo)	At ages 1 and 3 yr significantly less food allergy in children that were not BF or less than 1 mo compared to those that were BF for 1-6 mo or > 6 mo.	Protective	Saarinen and Kajosaari, 1995
Birth cohort; n=3825	sIgE levels at 8 yr (milk, egg, fish, soy bean, peanut, wheat)	Exclusive BF \geq 4 mo reduced the risk of sensitization to milk and fish significantly at the age of 8. Adjusted OR of 0.79 (0.64-0.99).	Protective for milk and fish sensitization	Kull et al., 2010
Prospective cohort, n=8280	Questionnaire at 7 and 44 yr	Exclusive BF \geq 3 mo reduced the risk of food allergies at age 7 significantly from 8% in children not exclusively BF to 5.7%. At the age of 44 a significant increase in prevalence was found: 10.1% in those not BF compared to 12.3% in those exclusively BF.	Protective at age 7 Risk factor at age 44	Matheson et al., 2007
Prospective birth cohort, family history of allergy, 1. Exclusive BF 6 mo; n=20 2. BF and casein extensive hydrolysate; n=59 3. BF and whey extensive hydrolysate; n=62 4. No dietary restrictions; n=75	Physical examination at 6, 12 and 18 mo, when cow's milk allergy was suspected this was confirmed with controlled elimination- challenge studies	At 18 mo cow's milk allergy was significantly less prevalent in children that were BF or received one of the extensive hydrolyzed formulas compared to the children that had no dietary restrictions. Prevalence of cow's milk allergy: Group 1.: 5% Group 2: 1.7% Group 3: 4.8% Group 4: 20%	BF and extensive hydrolyzed FF are protective for cow's milk allergy	Halken et al., 1993

Study design	Assessment of food allergy	Results	Outcome	Reference
Prospective population-based intervention study in preterm infants 1) Exclusive BF for at least 5 wk, n=227 2) BF combined with cow's milk formula, n=219	Clinical anamnesis and controlled rechallenges at 9 and 18 mo	No difference between the frequencies of cow's milk allergy between the two groups	No effect	Lucas et al., 1990
Questionnaire survey, n=13,110	Questionnaire filled in by the parents of children aged 7-15	Prevalence was not different between children exclusively BF for 6 mo and those receiving FF	No effect	Kusunoki et al., 2010
High-risk children²				
Prospective birth cohort, family history of atopy and/or elevated cord blood IgE, n=475	sIgE levels at 1 and 2 yr (egg)	Exclusive BF \geq 5 mo increased sensitization to egg white in children with elevated cord blood IgE. OR = 4.9 (1.2-20.4) at age 1. No effects at age 2	Risk factor for egg sensitization at age 1 yr	Wetzig et al., 2000
Cross-sectional study in infants \leq 6 mo with atopic dermatitis, n=143	sIgE levels (milk, egg, soy) at 6 mo	The rate of sensitization to egg was 40% in children exclusively BF and this was significantly higher than in the group that received exclusively infant formula (6.2%). In children that received both BF and formula feeding the rate of sensitization was also significantly higher (40.4%). No differences were found for milk and soy sensitization	Risk factor egg sensitization No effect milk and soy sensitization	Han et al., 2009
Prospective birth cohort, family history of atopy, n=174	Clinical history and DBPCFC at 6, 12, 24, 36 and 52 mo	Exclusive BF for more than 6 mo had no effect on food allergy	No effect	Bruno et al., 1993
Prospective birth cohort, family history of atopy, n=1121	sIgE levels at 4 mo (milk) and 12 mo (milk and egg)	The rate of sensitization to cow's milk at 4 mo and to egg and milk at 12 mo was not different between children BF exclusively for at least 4 mo and those that received FF	No effect	Schoetzau et al., 2002

Abbreviations: BF: breastfeeding; FF; formula feeding; yr: years; mo: months, n: number; sIgE: serum specific IgE levels; ¹ Population-based studies aim at inclusion of children that reflect the general population. ² High-risk children are defined as children with at least one first-degree relative (parent or sibling) with atopic disease or children with atopic eczema.

Table 5 Introduction of solid foods

Study design	Assessment of food allergy	Results	Outcome	Reference
Prospective intervention study in children with atopic parents, BF for 6 mo 1. Solid foods from 3 mo of age, n=62 2. Solid foods from 6 mo of age, n=51	History of food allergy at 1 and 5 yr. SPT (milk and wheat) at 5 yr	At the age of 1 yr the history of food allergy was significantly higher in children that started early with solid foods. Almost 40% had a history of food allergy, compared to almost 10% in the late introduction group. Data were not confirmed with SPT or challenge. No adjustment for confounders. At the age of 5 yr the frequency of food allergy confirmed with SPT was not different.	Early introduction is a risk factor at age 1 but not at age 5.	Kajosaari, 1991
Prospective population-based birth cohort, n=2073 1. Solids < 4 mo 2. Solids: 4-6 mo 3. Solids 6 mo	sIgE (egg, milk, soy, wheat, peanut, fish) at 2 and 6 yr	After adjustment for potential confounders (exclusion children with early allergies) late introduction of solids (> 4 mo) increased food sensitization at age 6: Adjusted OR: 1. < 4 mo: 1.00 2. 4-6 mo: 3.2 (1.5-6.9) 3. > 6 mo: 2.5 (1.03-6.3)	Delayed introduction of solids is a risk factor for food sensitization at 6 yr	Zutavern et al., 2008
Prospective population-based birth cohort. High percentage of family history of atopy (83%). Maternal and infant dietary intake was obtained with a food frequency questionnaire.	Questionnaires, SPT (milk, egg, wheat, cod, peanut, sesame) and open challenges at 1, 2 and 3 yr	Introduction of solid foods before age 16 wk significantly reduced the risk of food sensitization and allergy at ages 1 and 3 yr. OR in children exposed < 16 wk 1 yr: 0.41 (0.18-0.89) 2 yr: 0.51 (0.28-0.92)	Delayed introduction is a risk factor for food sensitization at 1 and 3 yr	Venter et al., 2009b
Prospective population-based birth cohort, n=2558 1. Solids < 4 mo 2. Solids 4-6 mo 3. Solids >7 mo	sIgE (egg, milk, peanut) at 2 yr	Delayed introduction of solid foods increased risk of sensitization to foods and inhalant allergens. OR after adjustment for confounding factors. 1. 1.00 2. 3.7 (1.4-9.6) 3. 4.3 (1.1-16.2) Sensitization to the separate food allergens was increased after delayed introduction of solid foods, but these effects were not significant.	Delayed introduction of solids is a risk factor for food sensitization at 2 yr	Snijders et al., 2008

Study design	Assessment of food allergy	Results	Outcome	Reference
Prospective birth cohort in children with genetic susceptibility for type 1 diabetes, n=931	sIgE (egg, milk, wheat, fish) at 5 yr	After adjustment for potential confounders late introduction of egg (>10.5 mo), oats (>5 mo) and wheat (> 6 mo) were statistically significant associated with a higher rate of food sensitization.	Delayed introduction is a risk factor for food sensitization at 5 yr	Nwaru et al., 2010
Population-based cross-sectional study, children aged 11-15 mo, n=2589. Age of introduction of solids was compared between children with and without egg allergy	SPT (egg) and food challenge at inclusion	Age of introduction of solid foods was not associated with egg allergy.	No effect on egg allergy	Koplin et al., 2010

Abbreviations: yr: years; mo: months, n: number; sIgE: serum specific IgE levels; SPT; skin prick test

Table 6 Maternal and/or infant food allergen avoidance

Study design	Food allergen	Assessment of food allergy	Results	Outcome	Reference
Prospective population-based birth cohort. High percentage of family history of atopy (83%). Maternal and infant dietary intake was obtained with a food frequency questionnaire.	Several food allergens	Questionnaires, SPT (milk, egg, wheat, cod, peanut, sesame) and open challenges at 1, 2 and 3 yr	Maternal dietary intake of food allergens during pregnancy and lactation had no effect on food allergy. Exposure to a certain food allergen before the age of 3-6 mo increased the risk of becoming allergic to this specific food allergen. No statistical analysis was described. No adjustments for possible confounders were described.	Maternal food allergen intake has no effect. Results on infant allergen intake are inconclusive	Venter et al., 2009b
Prospective birth cohort, family history of atopy. Randomized to: 1. Prophylactic group: maternal and infant food allergen and house dust mite avoidance in the first 9 mo of life; n=58 2. Control group, n=62	Milk, egg, fish, peanuts, soy nuts, soy	SPT together with food allergic reactions within 2 hours after ingestion at 1, 2, 4 and 8 yr	At the age of 8 yr the prevalence of food allergy was significantly lower in the prophylactic group. After adjustment for confounding factors this was no longer statistically significant.	No effect	Arshad et al., 2007
Prospective intervention study, family history of atopy, 1. <i>Prophylactic group</i> , n=59. Maternal avoidance of milk, egg, peanut during last trimester pregnancy and lactation. Infant avoidance of milk until age 1 yr, egg until age 2 yr and peanut and fish until 3 yr. 2. <i>Control group</i> , n=106. Standard feeding practices	milk, egg, peanut, fish	SPT (milk, egg, peanut, cod, shrimp, walnut) with symptoms consistent of food allergy and DBPCFC at ages 2, 4 and 7 yr	At 1 and 2 yr the prevalence of cow's milk sensitization and the prevalence of confirmed food allergy were significantly higher in the control group. At 4 and 7 yr there was no difference in food allergy between the groups.	Maternal and infant avoidance of food allergens were protective for cow's milk allergy at ages 1 and 2 yr	Zeiger et al., 1989, 1992, 1995

Study design	Food allergen	Assessment of food allergy	Results	Outcome	Reference
Randomized cohort study in pregnant women with respiratory allergy. Intake egg and milk during pregnancy and breastfeeding 1. Low maternal intake of milk and egg, n=81 2. High maternal intake of milk and egg, n=82	Milk and egg	sIgE (milk and egg) and SPT at 18 mo	No difference in milk and egg sensitization between the two groups	No effect	Lilja et al., 1991
Case-controls study in children aged 0-3 yr. Maternal and infant food allergen intake was compared between peanut sensitized (n=43) and egg and/or milk sensitized (n=18) children.	Peanut	sIgE (peanut, milk, egg, soy, wheat, fish) at inclusion	Mothers who consumed peanuts more than once a week had a 4-fold higher risk of having a peanut allergic child. This increase was not significant and the results were not adjusted for confounders. Age of introduction of peanuts: Cases: 12.5 ± 6.4 mo Controls: 17.3 ± 5.5 mo (p value = 0.03) Not adjusted for confounders	Maternal food allergen intake: inconclusive due to small sample size Peanut allergic children introduced peanuts earlier in diet.	Frank et al., 1999
Case-control study comparing maternal peanut intake in children with confirmed peanut allergy (n=23) with controls: atopic children (n=70) and non-atopic children (n=140)	Peanut	Peanut challenge	Percentage that consumed peanuts during pregnancy (not adjusted for confounders): 1. Cases: 65% 2. Atopic controls: 71% 3. Non-atopic controls: 61% Percentage that consumed peanuts at least 7 times per wk: 1. Cases: 17% 2. Atopic controls: 5% 3. Non-atopic controls: 5% Difference was not significant.	No effect of maternal peanut intake on peanut allergy	Lack et al., 2003

Study design	Food allergen	Assessment of food allergy	Results	Outcome	Reference
Case-control study comparing peanut consumption by all family members with peanut allergy in children 2-4 yr 1. Cases (clinically confirmed peanut allergy), n=133 2. High-risk controls (egg allergy), n=160 3. Low-risk controls (no allergies), n=150	Peanut	Clinically confirmed with SPT and DBPCFC	Maternal consumption during pregnancy and lactation was significantly higher in cases compared to atopic controls, but not different from non-atopic controls. After adjustment for confounding factors, the RR was not significant between the cases and atopic controls. The median weekly household peanut consumption (in gram per wk) was the most important risk factor for peanut allergy: RR vs high-risk vs low-risk controls - 0 g/wk: 1.00 - 1.00 - 0.1-3.8: 1.23 (0.4-3.7) - 1.57 (0.5-4.6) - 3.8-15: 5.8 (2.3-14.3) - 2.77 (1.2-6.5) - >15: 22.8 (8.9-59) - 6.09 (2.7-13.8)	Maternal peanut exposure was not a risk factor after adjustment for confounders. Most important risk factor was household peanut consumption	Fox et al., 2009

Study design	Food allergen	Assessment of food allergy	Results	Outcome	Reference
Cross-sectional cohort study in Jewish children 4-12 yr from Israel (n=4657) or the UK (n=3943). Consumption of peanut, sesame and other solids during weaning was assessed in 176 infants aged 4-24 mo with a Food Frequency Questionnaire	Peanut or sesame	Questionnaires	After adjustment for confounding factors the prevalences of peanut, sesame and tree nut allergy were significantly higher in the UK compared to Israel. There were no differences in prevalences of milk and egg allergy. Age of introduction of egg, wheat, soy, tree nuts was similar in both countries. Introduction of cow's milk and sesame was slightly earlier in Israel. The largest difference was found in peanut consumption: earlier introduction in Israel and higher median monthly consumption in first year of life.	Avoidance of peanut early in life might be a risk factor for peanut, sesame and tree nut allergy	Du Toit et al., 2008
Double blind placebo controlled intervention trial, intervention on first 3 days of life in BF children 1. Cow's milk free formula, n=775 2. Cow's milk formula, n=758	Milk	sIgE (milk, egg) at ages 1, 2 and 5 yr	No difference in milk or egg sensitization	No effect	de Jong et al., 1998, 2002
Prospective population-based birth cohort, n=2558. Milk introduced at: • 0-3 mo • 4-6 mo • 7-9 mo • > 9 mo	Milk	sIgE (milk, egg, peanut) at 2 yr	Delaying the introduction of cow milk products tended to be associated with a lower sensitization for cow's milk but this was not statistically significant. There was no effect on sensitization to egg or peanut	No effect on food sensitization	Snijders et al. 2008

Study design	Food allergen	Assessment of food allergy	Results	Outcome	Reference
Prospective population-based study including all newborns between June 2004 to June 2006, n=13019 comparing mean age of introduction of cow's milk with incidence of cow's milk allergy	milk	SPT (milk, soy) , open oral milk challenge when allergy was suspected	A significant association was found between the age of introduction of milk and development of cow's milk allergy. 1. First 2 wk: incidence 0.05% 2. 0.5 – 3.5 mo: incidence: 0.6% 3. 3.5 – 6 mo: 1.75% 4. > 6 mo: 0.5%	Critical window: 3.5-6 mo of age: increased risk of cow's milk allergy	Katz et al., 2010
Prospective population-based birth cohort, n=2614, questionnaires at 1 yr used for age of introduction fish	Fish	sIgE (milk, egg, fish, soy, peanut, wheat) at 4 yr	At 4 yr 18/2614 (0.7%) were sensitized to fish. Introduction of fish before 8 mo of age reduced risk of fish sensitization compared to those who started after 8 mo. After exclusion of children with eczema and wheeze this was not statistically significant (ORadj 0.27 (0.04-1.47))	Delayed introduction of fish may be a risk factor for fish sensitization	Kull et al., 2006
Population-based cross-sectional study, children aged 11-15 mo, n=2589. Age of introduction of egg: was compared between children with and without egg allergy	Egg	SPT (egg) and food challenge at inclusion	Late introduction of eggs was associated with a higher risk of egg allergy. Adjusted ORs: – 4-6 mo: 1.00 – 7-9 mo: 1.3 (0.8-2.1) – 10-12 mo: 1.6 (1.0-2.6) – > 12 mo: 3.4 (1.8-6.5) Type of egg has an effect on the risk. Introduction of cooked egg first at 4 to 6 months was associated with a lower risk compared to introduction of baked egg. .	Delayed introduction of egg is a risk factor for egg allergy.	(69)

Study design	Food allergen	Assessment of food allergy	Results	Outcome	Reference
Prospective birth cohort in children with a genetic susceptibility for diabetes, n=1612, children with celiac diseases were excluded	Wheat	Parent-reported wheat allergy at 3, 6, 9, 15, 24, 36 and 48 mo	Prevalence of parent-reported wheat allergy was significantly lower in children that first were exposed to cereals in the first 6 mo of life compared to those that were exposed after the age of 7 months. OR after adjustment for confounding factors compared to 0-6 mo: ≥ 7 mo: 3.8 (1.18-12.3)	Delayed introduction of cereals is a risk factor	Poole et al., 2006

Abbreviations: BF: breastfeeding; yr: years; wk: weeks, mo: months, n: number; sIgE: serum specific IgE levels; SPT: skin prick test; DBPCFC: double blind placebo controlled food challenge

Table 7 Probiotics

Study design	Assessment of food allergy	Results	Outcome	Reference
RDBPCT, 188 pregnant mothers, family history of atopy 1. Placebo n=93 2. <i>L. reuteri</i> n=95 Treatment: mothers from week 36 until delivery; infants until age of 12 mo	SPT (milk, egg) and sIgE (milk, egg, cod, wheat, peanut, soybean) at 6, 12, 24 mo	No effects of food sensitization Subgroup analysis showed a significantly lower prevalence of food sensitization at age 2 in children from allergic mothers. In the probiotic group 5% was sensitized, compared to 14% in the placebo group	Protective for food sensitization in subgroup children from allergic mothers	Abrahamsson et al., 2007
RDBPCT, pregnant mothers, family history of atopy 1. Placebo n=68 2. LGG n=64 Treatment: mothers 2-4 wk before delivery; infants until 6 mo. BF: mothers took probiotics	Cow's milk challenge when allergy was suspected SPT (milk, wheat, rye flour, carrot, banana, peanut, hazelnut, potato, egg, cod, soybean) and sIgE (milk, egg) at 6, 12, 24, 48 mo	No effects on cow's milk allergy at 4 and 7 yr and no effect on food sensitization at 2, 4 and 7 yr	No effect	Kalliomaki et al., 2001, 2003, 2007
RDBPCT, pregnant women, family history of atopy 1. Placebo n=89 2. <i>L. acidophilus</i> n=89 Treatment: infants from birth until 6 mo	History of immediate symptoms after ingestion of food and positive SPT at 6 and 12 mo SPT (milk, peanut, egg) at 12 mo	No effect on incidence food allergy at 6 and 12 mo Higher sensitization rate at 12 mo in probiotic group (36% vs 23% (p=0.059))	Risk factor for food sensitization	Taylor et al., 2007
RDBPCT, pregnant women, family history of atopy, exclusively BF infants 1. Placebo n=32 2. LGG n=30 Treatment: 2-4 wk before delivery until infant was 3 mo	Cow's milk allergy was confirmed in DBPCFC when allergy was suspected	No difference in cow's milk allergy at 24 mo	No effect	Rautava et al., 2002

Study design	Assessment of food allergy	Results	Outcome	Reference
RDBPCT, pregnant women, family history of atopy 1. Placebo n=121 2. <i>B. longum</i> BL999 and <i>L. rhamnosus</i> LPR n=124 Treatment: infants from birth until 6 mo	SPT (soy, milk, egg) at 12 mo	No effect on food sensitization frequency	No effect	Soh et al., 2009

Abbreviations: mo: months, wk: weeks; n: number; sIgE: serum specific IgE levels; SPT: skin prick test; DBPCFC: double blind placebo controlled food challenge

Table 8 Fish oil supplements, fatty acids

Study design	Assessment of food allergy	Results	Outcome	Reference
Randomized trial, pregnant women with family history of atopy, fish oil capsules (n=40) or placebo capsules (n=43) during pregnancy	Skin prick test (peanut, cow's milk, egg) at age of 1 yr	Fish oil supplementation decreased the rate of egg sensitization 3-fold. OR = 0.34 (0.11-1.02). This effect was almost statistically significant. No effect on peanut and milk sensitization	Protective for egg sensitization	Dunstan et al., 2003
Randomized trial, pregnant women with family history of atopy, fish oil supplementation (n=52) or placebo capsules (n=63) in the last 7 wks of pregnancy	Clinical anamnesis, sIgE and SPT at 3, 6 and 12 mo	Fish oil supplementation significantly decreased the prevalence of food allergy in the first year of life. Adjusted OR=0.11 (0.01-0.87; p<0.05). Fish oil significantly reduced the frequency of egg sensitization and allergy at 6 and 12 mo. Adjusted OR=0.31 (0.11-0.89, p<0.05). There was a non-significant trend in a lower prevalence of cow's milk allergy. Adjusted OR	Protective for food allergy, especially egg allergy	Furuhjelm et al., 2009
Prospective birth cohort, n=4089, questionnaires at age 1 used for frequency fish consumption	sIgE (milk, egg, fish, soy, peanut, wheat) at 4 yr	Frequent fish consumption reduced frequency of food sensitization at 4 yr. Adjusted OR: 1. Never: 1.00 2. Once a mo: 0.69 (0.45-1.05) 3. 2-3 x per mo: 0.61 (0.41-0.88) 4. Once a wk: 0.48 (0.43-0.68) 5. ≥ once a wk: 0.47 (0.33-0.69)	Frequent fish consumption in first year reduced risk of food sensitization at 4 yr	Kull et al., 2006
Population-based birth cohort, n=312, n-3 PUFA measured in breast milk 1 mo postpartum	sIgE levels in serum (milk, egg, peanut) at 1 and 2 yr	Higher concentrations of n-3 PUFA or ruminant fatty acids in breast milk were significantly associated with a lower rate of sensitization at 1 yr but not at 2 yr	Protective for food sensitization at 1 yr	Thijs et al., 2010

Abbreviations: mo: months, wk: weeks; yr: years; n: number; sIgE: serum specific IgE levels; SPT: skin prick test; OR: odds ratio

Table 9 Other dietary factors

Study design	Assessment of food allergy	Results	Outcome	Reference
Intake of multivitamins				
Prospective population-based birth cohort, n=8285	Parental report of physicians diagnosed food allergy at 3 yr	Early vitamin use (before 6 mo) was associated with a higher risk of food allergy in exclusively formula-fed children. After adjustment for confounders: OR = 1.63 (1.21-2.20) Vitamin use at 3 yr was associated with increased risk of food allergy in all children. Adjusted OR: 1.39 (1.03-1.88)	Risk factor	Milner et al., 2004
Prospective population-based birth cohort, n=2423	sIgE levels in serum (milk, egg, fish, soy, peanut, wheat) at 8 yr	Intake of multivitamins before the age of 4 reduced the frequency of food sensitization significantly. OR for first use of multivitamins after adjustment for confounders: <ul style="list-style-type: none"> • Never: 1.00 • ≤ 4 yr: 0.61 (0.39-0.97) • ≥ 5 yr: 1.09 (0.84-1.41) 	Intake before 4 yr: prevention of food sensitization	Marmsjo et al., 2009
Maternal vitamin D intake				
Prospective birth cohort in children with genetic susceptibility for type 1 diabetes, n=931	sIgE (egg, milk, wheat, fish) at 5 yr	Increasing maternal intake of vitamin D significantly reduced the risk of food sensitization. Adjusted OR was 0.56 (0.37-0.86)	Prevention of food sensitization	Nwaru et al., 2010a
Organic diet				
Prospective population-based birth cohort, n=2764 1. Conventional diet 2. Moderately organic 3. Strictly organic	sIgE levels (egg, peanut, milk) at 2 yr	Moderately or strictly organic diets did not affect food sensitization	No effect	Kummeling et al., 2008

Abbreviations: yr: years; n: number; sIgE: serum specific IgE levels; OR: odds ratio

Appendix 3: Lifestyle and environmental factors

Table 10 Anthroposophic lifestyle

Study design	Assessment of food allergy	Results	Outcome	Reference
Cross-sectional study in children of 5-13 yr comparing children from anthroposophic (Steiner) schools (n=295) and children from control schools (n=380)	Food allergy was diagnosed as acute onset of symptoms on more than one occasion after ingestion of the food allergen; sIgE and SPT (egg, milk, peanut, cod, soybean)	The prevalence of food allergy was similar in children from Steiner and control schools. The rate of food sensitization (sIgE) was significantly lower in children from Steiner schools: 9.2% compared to 16% in control school children. The frequency of SPT positive children was not different The data were not adjusted for confounding factors	Inconclusive, data not adjusted for confounding. Data suggest that this lifestyle is protective factor for food sensitization (sIgE). There is no effect on sensitization assessed with SPT and on food allergy	Alm et al., 1999

Abbreviations: yr: years; n: number; sIgE: serum specific IgE levels; SPT: skin prick test

Table 11 Tobacco smoke exposure

Study design	Assessment of food allergy	Results	Outcome	Reference
Prospective population-based birth cohort, n=342	sIgE (milk, egg, soybean, wheat) at 3 yr	Prevalence of food sensitization was significantly higher in children that were pre- and postnatally exposed to tobacco smoke. OR of 2.3 (1.1-4.6). No adjustments were made for possible confounding factors.	Inconclusive: no adjustment for confounding. Data suggest that pre- and postnatal tobacco smoke exposure may be a risk factor for food sensitization.	Kulig et al., 1999
Prospective population-based birth cohort, n=4089	sIgE (milk, egg, peanut, soybean, wheat, cod fish) at 4 yr	The prevalence of food sensitization at 4 yr was significantly higher in children exposed to tobacco smoke in the first 2 mo of life. Effects of maternal smoking during pregnancy or during pregnancy and in first 2 mo were not significant. After adjustment for confounding factors the Ors compared to no exposure were: <ul style="list-style-type: none"> • During pregnancy: 1.28 (0.72-2.26) • In first 2 mo of life: 1.61 (1.116-2.24) • During pregnancy and in first 2 mo of life 1.24 (0.82-1.89) 	Smoking of one or both parents in first mo of life is risk factor for food sensitization.	Lannero et al., 2008

Abbreviations: yr: years; n: number; sIgE: serum specific IgE levels; SPT: skin prick test

**National Insitute for Public Health
and the Environment**

P.O. Box 1 | 3720 BA Bilthoven

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