



National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Are common intervention strategies to prevent a range of allergic conditions feasible?

RIVM letter report 340007003/2011

C.M. Janssen et al.



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Abstract

Are common intervention strategies to prevent a range of allergic conditions feasible?

Allergic conditions comprise food allergy, rhinitis, atopic dermatitis and asthma. These allergic conditions present at various stages in life and may influence each other. Different allergens are involved at different stages in life. It is still unclear if the different allergic conditions have a common or distinct etiology. If food allergy and respiratory allergy have a common aetiology or if risk factors are overlapping, common intervention strategies may be possible. In a previous study (putative) risk factors for food allergy were identified. In the current literature study breast-feeding, allergen avoidance, introduction of solid foods, pre- and probiotics intake, and (poly unsaturated fatty acid (PUFA) intake were studied in relation to development of respiratory allergy. These factors were selected based on their (possible) effect on development of food allergy. In addition, the impact of currently promoted intervention strategies was discussed. The main conclusions are that:

- Breast feeding is a protective factor in the development of respiratory allergy. For food allergy data are conflicting.
- There is limited evidence to suggest that intake of PUFA is associated with development of respiratory allergy. There is also limited evidence that PUFA intake is associated with development of food allergy.
- Other studied risk factors for food allergy did not affect development of respiratory allergy.
- One of the strategies to prevent development of allergy is allergen avoidance or delayed introduction of solid foods. Data described in the literature indicate that this does not prevent allergy and may even be a risk factor.

Promising areas of research that will help develop intervention strategies in the future are: vitamin D- , PUFA and antioxidant-intake, modulation of intestinal flora, and developmental programming of food allergy. In addition, ongoing studies on possible detrimental effects of delayed introduction of solid foods, need to be monitored closely.

Keywords:

food allergy, risk factors, intervention, respiratory allergy

Samenvatting

Voedselallergie, hooikoorts, eczeem en astma zijn allemaal allergische aandoeningen. Deze aandoeningen ontstaan in verschillende stadia van het leven en zouden elkaar kunnen beïnvloeden. De betrokken allergenen zijn ook anders in de verschillende levensstadia. Of deze allergische aandoeningen een gemeenschappelijke etiologie hebben is tot op heden onopgehelderd. Als de etiologie hetzelfde is, of als risicofactoren voor deze aandoeningen overlappen, zou het wellicht mogelijk zijn om interventiestrategieën te ontwikkelen die het hele spectrum van allergische aandoeningen kunnen beïnvloeden. In een recente literatuurstudie zijn mogelijke risicofactoren voor voedselallergie onderzocht. In de huidige studie wordt geanalyseerd of borstvoeding, allergeenvermijding, introductie van vaste voeding, pre- en probioticagebruik, en meervoudig onverzadigde vetzuren (PUFA) inname een rol spelen bij de ontwikkeling van luchtwegallergieën. Deze factoren zijn geselecteerd op basis van hun mogelijke effect op ontwikkeling van voedselallergie. Daarnaast wordt de impact van geadviseerde interventiestrategieën bediscussieerd. De belangrijkste conclusies zijn:

- Borstvoeding is een beschermende factor in de ontwikkeling van luchtwegallergie. Voor voedselallergie zijn de effecten minder consistent.
- Er is enig bewijs dat inname van PUFA geassocieerd is met de ontwikkeling van luchtwegallergie en voedselallergie.
- De andere bestudeerde risicofactoren hebben geen effect op ontwikkeling van luchtwegallergie.
- Een strategie om ontwikkeling van allergie bij baby's te remmen is het uitstellen van de introductie van vaste voeding. De data in de literatuur geven aan dat dit de ontwikkeling van allergie niet kan voorkomen en mogelijk, zelfs een risicofactor is.

Veelbelovende onderzoeksgebieden die wellicht zouden kunnen leiden tot de ontwikkeling van nieuwe interventiestrategieën zijn: vitamine D-, PUFA- en anti-oxidant-inname, beïnvloeding van de darmflora, en programmering van voedselallergie tijdens de ontwikkeling. Daarnaast moeten lopende studies over mogelijke nadelige effecten van het uitstellen van de introductie van vast voedsel, nauwkeurig gevolgd worden.

Contents

1	Etiology of allergic disease—6
2	Questions addressed in this study—8
3	How large is the problem—9
4	Effect of risk factors for food allergy on development of respiratory allergy—13
4.1	Breastfeeding—13
4.2	Allergen avoidance—13
4.3	Introduction of solid foods.—14
4.4	Pre- and probiotics—14
4.5	Consumption of poly-unsaturated fatty acids (PUFA)—15
5	Recommendations on intervention strategies—16
5.1	Recommendation from the Netherlands Nutrition Centre Foundation—16
5.2	Conclusions from the current literature study—16
6	Future directives—18
7	References—19

1 Etiology of allergic disease

Allergic conditions comprise food allergy, rhinitis, atopic dermatitis and asthma. These allergic conditions present at various stages in life and may influence each other. Different allergens are involved at different stages in life. It is still unclear if the different allergic conditions have a common or distinct etiology. For instance, children with IgE-mediated cow milk allergy early in life are more likely to develop respiratory allergies later in life, suggesting a common etiology. The incidence of respiratory allergy is higher than that of food allergy implying that a proportion of children with respiratory allergy develop this allergy without a history of food allergy. It is still unclear which environmental and genetic factors are most important in determining development of allergy and which intervention strategies would be most promising in reducing the risk of developing allergy.

Common etiology would imply common risk factors and would enable development of common intervention strategies to reduce the risk of developing a range of allergic conditions. Distinct etiology would imply distinct risk factors and distinct prevention strategies for each allergic disorder.

The 'atopic' march

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 (reviewed in, (1)). 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.

Genes or environment?

Parental atopy predisposes children to develop atopy indicating a strong genetic component in the development of allergic disorders. However, a large number of studies show that maternal atopy is a stronger predisposing factor than paternal allergy. If only genetic susceptibility was involved paternal and maternal atopy would have exactly the same effect on predisposition. Apparently environment factors also play an important role in determining development of allergy (2). Various maternal factors, such as breast-feeding, maternal-and child-diet, have been implicated in determining the development of allergic disease in the child. Some of these factors operate in utero and others during lactation. Taken together these observations indicate that development of allergic conditions in infants and children are determined by the complex interplay between host-genetic and environmental factors (reviewed in (3)). Since environmental factors that operate in utero, during lactation and early in life can potentially be influenced, this opens up possibilities for development of intervention strategies aimed at decreasing the risks of development of allergic disease in children.

Common or distinct etiology?

The majority of children that suffer from food allergy to cow's milk and egg early in life recover from this condition by the age of five years. A proportion of

children with food allergy will go on to develop respiratory allergy and possibly asthma later in life. Both respiratory allergy and asthma are life-long conditions with a considerable burden of disease. If intervention strategies aimed at reducing the incidence and severity of food allergy would stop the atopic march altogether this would also lead to a reduced number of children and adults with respiratory allergy or asthma. A prerequisite for this would be that there is a common etiology for development of food-allergy and respiratory allergy in these children. Although the 'atopic march' indicates such a common etiology there are also several observations that point to distinct etiology:

- Both asthma and food allergy have shown a steady increase over the last decades. However, recent data suggest that the asthma epidemic preceded the food allergy epidemic pointing to different risk factors. This would point to a distinct etiology (4).
- Although parental allergic disease predisposes children to develop allergic diseases there seems to be allergy specificity: parental asthma especially predisposes to asthma in the child, parental AD to AD, and parental rhinitis to rhinitis. This suggests that the etiology of asthma, rhinitis and AD are different (5). Similarly, parental peanut allergy increases the risk of peanut allergy in children (6).
- Genetic factors have been identified that are associated with more than one allergic condition. However, distinct genetic factors have also been identified for different allergic conditions (7).

Taken together these data suggest that a subgroup of infants that develop food allergy is at risk of developing respiratory allergy, and that in this subgroup both conditions arise because of a common etiology. Whether common etiology is also present in the rest of the population is unclear. It should however be taken into account that distinct etiology does not rule out the presence of common risk factors.

2 Questions addressed in this study

In a previous study risk factors for development of allergic disease have been reviewed and the weight of evidence of these individual risk factors has been evaluated (RIVM rapport risk factors food allergy 340007001). In addition, in the Netherlands the Nutrition Centre Foundation (Voedingscentrum) has made recommendations for infant nutrition in the first year of life. In this study these risk factors will be evaluated in the context of development of respiratory allergy. In addition the impact of recommendations will be evaluated. The specific questions that will be addressed are:

- What is the proportion of food allergic children that go on to develop other allergies, how large is this group of children, and, is this proportion different for various food allergens?
- Which risk factors for food allergy also affect development of respiratory allergy?
- What is the expected impact of intervention strategies that are currently employed

3 How large is the problem

The 'atopic march' refers to a certain sequence of presentation of allergies in an individual. First patients present with food allergy and atopic dermatitis and then they progress to asthma and later hay fever. However, only a small proportion of food allergic children have persistent food allergy. In addition, the prevalence of respiratory allergy and asthma is much higher than that of food allergy suggesting that a large proportion of children with respiratory allergy have not suffered from food allergy early in life. Rough estimated indicate that up to 5% of children and 1- 2% of adults suffer from food allergy. Rhinitis is present in up to 30% of children and adults and asthma in up to 10%. However, prevalence data differ between countries and are difficult to interpret. For instance, prevalence of self-reported allergic conditions and doctor's diagnosed allergic conditions are different.

The golden standard for diagnosing true food allergy is double blind placebo controlled food challenge (DBPCFC). Very few studies use this method to determine prevalence of food allergy. In general, studies that use DBPCFC to determine prevalence of food allergy, use data on self-reported respiratory allergy. Conversely, studies on asthma, use sound methods to determine prevalence of asthma, but rely on self-reported food allergy or food sensitization.

Long term follow up studies dealing with food allergy and respiratory allergy are lacking and estimates on the proportion of children that display food allergy early in life and respiratory allergy later in life are not available.

To gain some insight in this group, data from several lines of investigation were studied:

1. Food allergy incidence and respiratory sensitization data from the Isle of Wight studies in the United Kingdom (8-10).
2. Birth cohort studies from Finland in which children with cow's milk allergy (CMA) were followed up until the age of 8.6 (11, 12).
3. Food allergy cohorts from the USA (13).
4. A prospective birth cohort from Norway in which at the age of 10, food sensitization was measured in asthma patients (14).
5. Data from the Dutch PIAMA cohort.

The conclusions of these studies are summarized below.

Table I gives some indications about the prevalence of food allergy from the Isle of Wight study. Although good follow-up data on respiratory allergy are lacking, the first impression these data give is that respiratory allergy is much more common than food allergy. This implies that the proportion of children that through the atopic march is small. In addition, it is clear that parent-reported food allergy is an overestimation of true food allergy, especially in the first 3 years of life.

Table I. Proportion of children with food sensitization and food allergy in the Isle of Wight study

Age (years)	Reported food-related problem (%)	Sensitization to food allergens (%)	Food allergy (DBPCFC) (%)	Sensitization to aero allergens (%)
1	33.7	2.2	3.2	1.1
2	33.7	3.8	3.5	6.4
3	33.7	4.5	5.0	10.9

6	11.8	3.6	1.6	16.9
11	11.6	5.1*	0.1	22.9
15	12.4	4.9*	0.5	26.9

*wheat was excluded because of cross-reactivity with grass

Conclusion from the Isle Wight studies (8-10) and American food allergy cohorts . (13)

- *The number of children that suffer(ed) from food allergy and go on to develop respiratory allergy is not known but is only a proportion of the 4-5% of children that suffer from food allergy.*

Conclusions from the Finnish birth cohort studies on CMA (11, 12) .

- *Children with IgE-mediated CMA have an increased risk of developing respiratory allergies later in life.*
- *Within this group children with persistent CMA (15%) have the highest risk.*
- *Proven CMA is probably an early manifestation of the atopic march*
- *Severe or persistent food allergy is associated with the highest asthma risk.*
- *IgE sensitization without clinical symptoms is not a strong risk factor for development fo asthma.*
- *Early wheeze is more likely to occur in high risk children (i.e. in children with an atopic family history).*

Conclusion from the Norwegian birth cohort study (14) :

- *Approximately 25% of children with asthma at age 10 displayed sensitization to food allergens, as compared to 5% of control children. Sensitization to food allergens is not the same as clinical food allergy, but data on clinical food allergy are not available in this study.*



The Dutch PIAMA cohort

Dutch prevalence data are available from the PIAMA cohort. In the PIAMA cohort data on food allergy were not established via DBPCFC. To compare data from the PIAMA cohort with other literature data described above it is therefore important to first describe the methods used in the PIAMA cohort.

Parents of children that participated in the PIAMA cohort received questionnaires. One of the questions asked was: "Did a doctor ever diagnose allergy in your child using a blood or skin-prick test?" If yes the parents were asked to report to which allergens their children responded to in this test and at what age they responded. It is clear that reported allergy in PIAMA is true allergy. However, hese data have to be interpreted with caution because: (i) it is not known if children were tested for allergy based on symptoms related to food- or respiratory allergens. As a result the dataset includes children with clinical respiratory allergy and food sensitization without symptoms, children with clinical food allergy and respiratory sensitization and symptoms, and children with clinical food and reparatory allergy, (ii) the data show cumulative numbers over time and (iii) the sequence of developing a reaction to the tested allergens is not know, and (iv) follow up data after the age of 7 are not available so respiratory allergy probably means asthma and not rhinitis, which is usually diagnosed at later ages.

Because PIAMA data are highly relevant for the Dutch prevalence of allergy we will show a summary some of the available data. In line with other data food

allergy is generally diagnosed in the first 5 years of life. Similar to other studies prevalence in age groups up to 7 years olds is 2.4-4.4% (see Table1)

Tabel 1: Prevalence of 'ever allergy' and a positive test to a food allergen by age.

Age	Number of participants	Doctor's diagnosed "ever allergy" %	Positive test to food allergen %
2	3705	3.2	2.4
3	3670	4.8	3.3
4	3542	5.5	3.5
5	3463	7.4	4.1
6	3450	8.7	4.4
7	3360	9.3	4.4

In Table 2 the prevalence of respiratory allergy is stratified for presence of food allergy. As outlined above, the methodology of this subset of PIAMA data does not allow assessment of the sequence of food allergy and respiratory allergy, and it is not known if food allergic or respiratory allergic symptoms present when the children underwent allergy testing. As a result the data in table 2 include data on true allergy and on sensitization to allergens, and it is not possible to separate the two. Therefore, the proportion of children with true food allergy and true respiratory allergy cannot be deduced from these data.

Table 2: Prevalence 'positive test to respiratory allergen' in children that with and without a positive test to food allergens in the first 7 years of life

Age (years)	Prevalence (%) "positive test to respiratory allergens"	
	No positive test to food allergens n=3215	Positive test to food allergens n=147
3	1.0	28.7
4	1.5	32.6
5	2.7	44.1
6	3.5	53.2
7	4.3	59.9

* The test used was a blood test or skin prick test.

Conclusions of the PIAMA data

- The prevalence of food allergy reported in the PIAMA cohort is in line with other literature data.
- A positive test to food allergens during the first 7 years of life is a strong risk factor for a positive test to respiratory allergen during the same period.

Overall interpretation of the data

The number of children that go through the atopic march is small and constitutes a proportion of the 4-5% of children that suffer from food allergy. Although food allergy may be one of the first manifestations of the atopic march it is unlikely to cause the atopic march. A more likely explanation of all these data is that a subgroup of children is predisposed to develop a large range of allergies, and that this subgroup goes through the atopic march.

Data from the Dutch PIAMA cohort indicate that the problem of food allergy in the Netherlands is similar to that in the other Western countries.

4 Effect of risk factors for food allergy on development of respiratory allergy

The risk factors investigated in this study were selected based on two criteria:

1. The possibility of modulating the risk factor by intervention strategies.
2. Some evidence that the risk factor affects the development of food allergy even if evidence is conflicting.

The following risk factors met these criteria: breast feeding, allergen avoidance, introduction of solid foods, pre-and probiotics and fatty acids.

Risk factors associated with microbial exposure and life-style were not part of this study. Food-related risk factors that were excluded because they did not affect food allergy or because insufficient data were available for establishing effects on food allergy were: hypoallergenic infant formulas, vitamins and organic foods.

For the selected risk factors we briefly reviewed the evidence that points to the role of these risk factors in development of respiratory allergy.

4.1 Breastfeeding

Many positive effects of breastfeeding on the health of children have been observed. Protective effects have been observed against gastro-intestinal infections, respiratory tract infections and otitis media. Evidence on the effects of breastfeeding on occurrence of respiratory allergy has been conflicting. Like for food allergy, sensitization to allergens does not always mean clinical disease. Diagnosis of asthma at ages younger than 6 years is difficult and therefore studies on effects of breastfeeding on development of asthma have been confounded by effects on early wheezing due to respiratory infections. Recently Oddy reviewed the evidence on the effects of breastfeeding on development of asthma and atopic disease using very strict criteria (15). Studies that met these strict criteria all showed a protective effect of breast feeding resulting in a 20-30% reduction of the probability of developing asthma and other allergic conditions. These protective effects are found in children from both allergic and non-allergic parents. Although observed effects are small they are relevant at the population level due to the high incidence of asthma and atopic disease. However, the continuation of this protective effect into adulthood still needs to be confirmed in large prospective studies that meet very strict criteria.

Conclusion: breast feeding has a number of positive effects on health and should be promoted. Although effects of breast feeding on development of food allergy are conflicting (RIVM report 340007001), the protective effects on development of respiratory allergy are more consistent.

4.2 Allergen avoidance

Of course avoidance of food allergens prevents the occurrence of allergic symptoms in individuals with established allergies. However, allergen avoidance has also been promoted as a strategy to prevent food allergy. Recent data suggest that there is no beneficial effect of allergen avoidance on the development of food allergy and that allergen avoidance may in fact be detrimental (RIVM report 340007001).

Also in respiratory allergy, allergen avoidance has been promoted for instance through the use of mite-impermeable mattress and pillow covers (16). The Dutch PIAMA study has however shown that house dust mite avoidance

strategies using HDM impermeable mattress covers, does not affect the risk of developing respiratory allergy (17, 18). Combined avoidance of food allergens and respiratory allergens has also been studied in the Isle of Wight cohort of high risk children (19). In addition, a Canadian study combined all known risk factors for respiratory and food allergy, allergen avoidance, tobacco smoke avoidance, promotion of breast feeding, late introduction of solid foods (20-22). The Canadian study showed protective effects on development of asthma resulting in a 2 fold reduction in the intervention group. The Isle of Wight study showed 2-5 fold reduction but due to small study groups (n=40-70) the level of uncertainty around these levels was large. Due to combined intervention it is unclear if the combination of intervention measures or one of the separate interventions was responsible for this effect.

Conclusion: Effects of allergen avoidance in both food allergy and respiratory allergy are questionable. Since the allergens that are avoided to prevent food allergy and respiratory allergy are different a common intervention study aimed at preventing both conditions will prove difficult.

4.3 Introduction of solid foods.

Delayed introduction of solid foods was studied to prevent food allergy. However, recent studies have shown that this is not effective and may even be detrimental (RIVM report 340007001). Apparently, introduction of solid foods between 4 and 6 months can lead to development of tolerance to these food allergens. Currently, there is no evidence that delaying the introduction of solid foods, including food allergens, is a determinant in the development of respiratory allergies.

4.4 Pre- and probiotics

The intestinal flora is important for the development and maturation of the immune system and in that way could also have impact on the development of respiratory allergy (23-25). Comparison of the intestinal flora of allergic and non-allergic children revealed that there were differences in the composition of the flora (26). In addition, the use of antibiotics in the first 6 months of life is associated with a higher risk of developing allergy (27). The mechanism underlying this finding is that disturbance of the commensal flora early in life affects the development of a balanced immune response. Strategies aimed at modulating the early intestinal flora may therefore be beneficial. Since the intestinal flora is very complex and understanding of this complexity is just beginning to emerge, further studies are needed to study its relationship with development of allergy. Studies on the effect of pre- and probiotics on development of allergy were boosted by the observations described above. Pre- and probiotics are believed to alter the intestinal flora thereby promoting the development of tolerance to allergens. However, effects of pre- and probiotics on development of both food and respiratory allergy have been conflicting (reviewed in (28, 29). Since the composition of the intestinal flora is rather stable it may be difficult to induce alteration with poorly colonizing probiotics. Prebiotics are believed to alter the intestinal environment in such a way that certain commensals grow faster than others. Stable alterations in the commensal flora that are beneficial for protection against allergies may be difficult to accomplish without a more complete understanding of an intestinal flora that may protect against development of allergy. Another observation that deserves attention is that probiotics accelerate the development of autoimmune disease in an animal model indicating that probiotics may also lead to unwanted side-effects (30).

Conclusion: Data on the effects of pre- and probiotics on development of food- and respiratory allergy are inconsistent. Before recommending supplementation of infant formulas with pre-or probiotics, and recommending supplements for pregnant women both efficacy and safety of these probiotics should be investigated.

4.5 Consumption of poly-unsaturated fatty acids (PUFA)

Changes in fatty acid consumption have been hypothesized to play a role in development of asthma and respiratory allergy. Changes in fatty acid consumption also lead to an altered composition in breast-milk. Therefore, such changes could influence the intake of fatty acids at a very early age. The evidence that such changes indeed lead to development of asthma have recently been reviewed (31). In Westernized countries the diet has changed over the last decades. Increased intake of n-6 PUFA mainly linoleic acid (LA), present in margarine and oils sourced from vegetables, and decreased intake of n-3 PUFA such as alpha linoleic acid (ALA), present in some vegetable oils, and DHA and EPA present in fish, have been observed. A changed ratio in n-6 PUFA and n-3 PUFA can modulate the inflammatory response and is believed to promote Th2 and allergy development. However, most of the data that show these effects come from in vitro studies. Observational studies are limited. A systematic review was conducted to establish the relationship between increased n-6 PUFA consumption and development of asthma (32). No evidence was found to support the hypothesis that increased n-6 PUFA was associated with development of allergy. In contrast the authors concluded that if anything, the data suggested that decreased n-6 PUFA was associated with allergy and asthma. With respect to lower n-3 PUFA consumption the authors concluded that published data were inconsistent and they indicated that PUFA metabolism needs to be better understood in order to draw conclusions on effect of PUFA on development of allergy.

Intervention studies aimed at increasing EPA and DHA intake either during pregnancy or very early in life were also reviewed (32). These data show some improvement of wheeze in children by age 1 but it is unclear if these differences persist later in childhood. Studies performed after the systematic review was conducted yielded conflicting results (reviewed in(31)). New intervention studies are needed to make recommendations on EPA and DHA intake during pregnancy or very early in life.

Studies on intake of PUFA are complicated by the fact that the ratio of n-3 PUFA (ALA) and n-6 PUFA (LA) is important for the enzymatic conversion of these PUFA to longer-chain PUFA. The same enzymes convert n-3 and n-6 PUFA and as a result competition for conversion occurs. Therefore, it is important that studies aimed at measuring effects of one of the two classes should always take into account, intake of the other class of PUFA. In fact data from the Dutch PIAMA cohort indicate that in allergic mothers, breast milk n-3 PUFA and the ratio between n3-/n-6 PUFA was inversely associated with asthma in their child at 4 years (33).

5 Recommendations on intervention strategies

5.1 Recommendation from the Netherlands Nutrition Centre Foundation

The current recommendations of the Netherlands Nutrition Centre Foundation are listed below. They advise on breast-feeding, introduction of solid foods, introduction of solid foods in allergic individuals, and on vitamin intake. Especially vitamin D intake is interesting in this respect. Because insufficient data were available to assess the effects of vitamin D intake on development of food allergy it was also not part of the current study. Recently, vitamin D has attracted a lot of attention in relation to development of various chronic disease, including asthma.

Recommendations of the Netherlands Nutrition Centre Foundation (Voedingscentrum) for the infants' diet:

- First six months, only milk, preferably breastfeeding.
- Introduction of solid foods between 4-6 months. Solid foods are essential in the diet from 6 months on.
- Supplementation with vitamin K and D when breastfeeding.
- Supplementation with vitamin D until the age of 4.
- Atopic families: delay introduction of solid foods until after 6 months

5.2 Conclusions from the current literature study

Breast feeding.

Currently, exclusive breast-feeding is promoted until the age of 4-6 months. Because breast-feeding has shown beneficial effects on development of respiratory allergy this should continue to be promoted. In addition, breastfeeding has beneficial effects on development of gastro-intestinal infections, respiratory tract infection and ear infections. The effects of breastfeeding on food allergy are less clear and studies show conflicting outcomes.

Allergen avoidance.

Avoidance of allergens as a strategy to prevent development of respiratory allergy has been disappointing. For foodallergens similar observations have been made. Data even suggest that exposure to food allergens between 4 and 6 months may lead to tolerance induction to these allergens. Avoidance of allergens will therefore probably not be a good strategy to prevent development of food allergy. Data of ongoing studies in this field should shed further light on this issue.

Introduction of solid foods.

For food allergy, available data indicate that delaying exposure to allergens beyond 6 months is not beneficial to prevent food allergy and may even be detrimental. Since food allergy is a risk factor for development of respiratory allergy one could reason that delayed introduction of solid foods may also be detrimental to development of respiratory allergy. No studies are conducted to address this issue. In addition, as outlined above, the highest risk of respiratory allergy in children with food allergy is present in a subgroup of children.

Identification of this high risk population is difficult but could partly be done based on family history. A problem with this high risk groups is that they may be predisposed to development of any allergy and it is currently unknown if development of any allergy can be modulated in this subgroup. For the children with food allergy that do not belong to the group with the highest risk, intervention studies are needed before recommendations can be made.

Pre-and probiotics.

There is insufficient evidence to suggest that intake of pre- and probiotics have an impact on development of both food-allergy and respiratory allergy. However, the intestinal flora has been shown to be an important factor in development of immune responses. It is not inconceivable that strategies to modulate intestinal flora could be beneficial for prevention of allergy. Further research on the composition of the intestinal flora and its impact on development of balanced immune responses is needed. Currently, no recommendations are made to pregnant women or children to consume pre-and probiotics.

Intake of PUFA

There is limited evidence that increased intake of n-3 PUFA prevents development of food allergy. For respiratory allergy some data are available that indicate a beneficial effect on early wheeze in children. However, data are conflicting and some data suggest that a beneficial effect subsides after the age of 1 year. Currently, no recommendations are made to pregnant women and children to alter their intake of PUFA

6 Future directives

This literature study was limited to intervention strategies that were previously investigated in the context of development of food allergy. Novel insights into the etiology of allergic disease are continuously reported. Some of these issues are discussed here.

- *Vitamin D intake.* Vitamin D intake was not part of the current literature study. Over the past year an increasing number of studies have reported effects of vitamin D on development of a whole range of diseases. Although there were insufficient data to conclude that vitamin D affects development of food allergy (RIVM report 340007001) or asthma (34), more studies are becoming available (35). Effects of vitamin D include modulation of both innate and adaptive immune responses, and modulation of gut homeostasis (36). Studies on vitamin D intake and development of allergy should therefore be closely followed in the future.
- *Introduction of solid foods/allergens.* Several studies are ongoing to investigate the effect of delaying introduction of solid foods/allergens on development of food allergy. Preliminary data have already led to responses from the field to inform parents that benefits of delaying introduction of solid foods/allergens may not be beneficial and may in fact increase the risk of food allergy. These studies should be monitored closely in order to update advice given to pregnant women and parents of infants.
- *PIAMA study.* The PIAMA cohort was established to study development of respiratory allergy early in life. In the current literature review some data on food allergy are presented for the PIAMA cohort. As outlined in chapter 3 there are some limitations to the PIAMA data used for this literature review. Follow up data after the age of 7 are available and also information on clinical symptoms of the children at different ages is available. However, these data were not part of the analysis shown in this report. Careful evaluation the data on clinical symptoms at the individual level, may allow calculation of the proportion of children with food allergy that develop respiratory allergy.
- *Anti-oxidant intake.* Anti-oxidant intake was not part of this study. The interest in the use of anti-oxidants to prevent or modulate a range of diseases, including allergic diseases (37), has recently increased considerably. Anti-oxidants are believed to modulate inflammatory processes and studies on anti-oxidants should be followed in the future.
- *Intestinal flora.* An increasing amount of insight into the composition of the intestinal flora is currently becoming available, including the effects of intestinal flora on development of a balanced immune response (36, 38). Also this field of research should be followed closely.
- *Epigenetics.* Genes are known to play a role in development of many chronic diseases. Recently, it has become apparent that genes can also be modified during development and early in life leading to the *Developmental Origins of Health and Disease hypothesis*. This hypothesis states that stable programming of sets of genes during development affects the occurrence of chronic diseases later in life (39). Programming can be influenced by external factor such as diet. Also for development of allergy these epigenetic modifications are believed to be very important (40, 41). This idea would fit with the finding that risk factors for development of (food) allergy, operate during pregnancy and very early in life. Therefore, studies on the role of epigenetic programming and development of allergy should be followed closely.


7

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