



Effective Ways to Prevent Allergic Diseases: Where Do We Stand?

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Abstract

Since allergic diseases are of great public health relevance, effective primary prevention strategies are urgently needed. This chapter gives an overview of existing primary prevention programs on environmental exposures and dietary strategies based on epidemiological studies which have defined risk- and protective factors for the development of allergic diseases.

The allergy protective effect mediated by growing up on a traditional farm environment is well studied. But the exact underlying mechanisms have still not been fully clarified and have not yet led to concrete prevention strategies. The beneficial effect of avoiding cigarette smoke exposure, indoor moisture and molds in pregnancy and childhood on the development of asthma is well documented. Whereas the avoidance of house dust mite exposure is not recommended to prevent eczema or allergy. Dietary supplementation with vitamins, pre- and probiotics in pregnant woman and their offspring is not harmful but evidence for the prevention of allergic diseases is still lacking. Fish oil consumption was shown to be asthma protective. The early introduction of peanuts and egg protein to prevent peanut and egg allergy in children with atopic dermatitis is promising. Further studies are needed to increase the overall evidence in allergy prevention. Most studies lack methodological standards such as randomization and blinding. More evidence is in demand on the potential beneficial impact of multifaceted interventional studies. The future of allergy prevention strategies might be based on individual risk assessment. Therefore, research in the immunological and molecular basis of allergic diseases needs to be promoted.

Keywords

Allergy · Eczema · Primary prevention

1 Introduction

With a high prevalence in developed countries allergic diseases are a major burden of public health relevance in all age groups. Allergic diseases include allergic asthma; allergic rhinitis; anaphylaxis; drug-, food-, and insect- allergy and eczema with highest level of suffering in children (Pawankar et al. 2013). The different forms of allergy are caused by complex and multiple pathophysiological changes in different organs, which cause manifold symptoms. Therefore, a “one size fits all” approach to prevent the different forms of allergic diseases is likely unrealistic. Nevertheless, there are promising findings from epidemiologic studies which detected distinct risk factors and also environmental and nutritional components decreasing the risk to develop allergic diseases. This chapter gives a brief overview of existing insights into promising intervention strategies and reveals gaps in evidence. Most atopic diseases are known to have its origin in the childhood. For this reason, we focus on interventional strategies in pregnancy and childhood.

2 Environmental Exposure in Interventions

Environmental exposure describes all particles and substances of different size which are in contact with the human body and might enter it through different barriers like the skin, the lung, the nose, and the digestive system. Environmental components have been associated with not only protective but also harmful effects on allergy development.

2.1 The More Microbes, the Better?!

2.1.1 Hygiene Hypothesis and Farm Environment

After David Strachan associated increased microbial exposure with decreased prevalence of hay fever in developed countries in 1989 (Strachan 1989), the “hygiene hypothesis” was born. Several following studies showed that microbes play an important role in tolerance induction by activating regulatory immune cells like regulatory T and B cells (Smits et al. 2016). In addition to the observation of Strachan, rural living such as “traditional” farming was shown to be associated with a decreased risk of allergy development. Numerous “farm studies” confirmed the protective effect and associated it with being exposed to cattle, their sheds and by the consumption of unprocessed cow’s milk since early childhood. These effects were traced back to an increased diversity and richness of bacteria and fungi in the farm environment (Ober et al. 2017; von Mutius and Vercelli 2010; von Mutius and Smits 2020). Latest results of the Finnish birth cohort study LUKAS showed that microbiota composition in non-farm houses which are comparable to those of traditional farms also have allergy protective effects (Kirjavainen et al. 2019). These studies showed the influence of environmental microbes on the development of allergic diseases, but have not yet led to concrete guidelines or intervention studies.

2.1.2 Dogs and Cats

The influence of intense contact to dogs and cats in the development of allergies is still under debate. Observational studies on pet ownership and its association with allergy protection may be biased as dog/cat owners are unlikely to be allergic to their animals and keep them whereas allergic persons do not have cats or dogs in their home (Konradsen et al. 2015). Nevertheless dog ownership was associated with allergy protection. Marrs et al. showed that children growing up with more than one dog are likely to be protected from food allergy and house dust mite (HDM) sensitization until their 3rd year of life (Marrs et al. 2019). This effect was traced back to increased microbial diversity. Kettleleson et al. revealed that homes with dogs contained four times more putative bacterial species compared to homes without a dog (Kettleleson et al. 2015). In different studies, cat ownership was associated not only with protective but also with harmful effects on allergy development in the past. Discussion on the influence of cats in allergy development is still ongoing (Konradsen et al. 2015; Pawankar et al. 2013).

2.1.3 C-Section

The contact to maternal bacteria through natural birth seems to be important in the development of child's own gut microbiome. It has been shown that delivery by cesarean section (CS) is predisposed to the development of food allergy but not to atopic dermatitis in early childhood (Papathoma et al. 2016; Chernikova et al. 2019). CS without medical indication was also associated with an increased risk of childhood asthma (Chu et al. 2017). Highly standardized interventional studies with randomization are unfeasible but pregnant women should be encouraged to give birth naturally.

2.1.4 Day Care

Attending day care in early life was associated with a reduced risk to develop atopic dermatitis (Kantor and Silverberg 2017) to be sensitized against food- and aero-allergen (Gabet et al. 2016) and asthma development in high-risk children (Grabenhenrich et al. 2014). These results are consistent with Strachan's original hygiene theory. But these observational studies do not lead to evidence in allergy prevention.

3 Potentially Harmful Environmental Factors

3.1 Exposure to Molds

As children more and more spend time indoors than outdoors, indoor exposure plays an increasingly important role in allergy prevention. Indoor mold exposure is known to be a risk factor for respiratory diseases like asthma especially in moist homes (Casas et al. 2016). An intervention study in European schools reducing indoor mold exposition showed beneficial effects in asthma symptoms (Hauptman and Phipatanakul 2016). The mold free environment in schools and households might also be important for primary prevention of allergic and also other respiratory diseases. Of note a recently published review pointed out that indoor fungal diversity is associated with atopy protection. The harmful effect has been attributed to indoor moisture rather than molds by the author (Barnes 2019).

3.2 Exposure to Cigarette Smoke

The negative health effect of active and passive smoking is well studied. The risk of wheezing and asthma is increased by at least 20% in the offspring of active and passive smoking parents (Burke et al. 2012; Neuman et al. 2012; Hollams et al. 2014). The benefits of avoiding tobacco smoke during pregnancy, childhood, and ideally during the whole life is one of the best studied health promotion strategies, not exclusively for atopic diseases. Reduced asthma-associated hospital stays have already been reported after the smoke free legislation in the USA (Been et al. 2014). National anti-smoking campaigns, e.g. in Germany, are already showing signs of success. The frequency of smoking, especially among adolescents, is decreasing

(Zeihner et al. 2018). Encouraging pregnant women to raise their children in a smoke free environment needs to be the task for gynecologists and pediatricians.

The effects of the more and more upcoming “e-cigarettes” on allergy development are poorly studied and prevention strategies are not published yet.

3.3 House Dust Mite Exposure

One of the best studied environmental indoor allergens is the house dust mite (HDM). Numerous studies investigated the effects of reducing HDM at home, e.g. with special bed covers or chemical removal strategies. HDM avoidance strategies alone or in combination with additional allergen avoidance did not decrease the risk of atopic dermatitis (Bremmer and Simpson 2015) or allergy development (Arroyave et al. 2014) and should therefore not be recommended as it was in former years.

4 Climate Change and Air Pollution

The world allergy organization (WOA) summarized the influences of climate changes on allergy and asthma risk and development in one publication (D’amato et al. 2015). The most important changes which are relevant in allergic diseases are the extension of the pollen season as the global temperature increases and the spread of non-indigenous plants and their pollen like *Ambrosia* in middle Europe. Climate change will also lead to global wind changes affecting the distribution of pollen.

Air pollution is mostly referred to traffic-related air pollutants (TRAP), including elemental carbon, black soot, nitrogen dioxide (NO₂), nitric oxide (NO), sulfur dioxide (SO₂), carbon monoxide (CO), and carbon dioxide (CO₂). It is uncontroversial that the concentration of these pollutants increased during the last century. A recently published review of air pollution effects on asthma, rhinitis, and atopic dermatitis concluded growing evidence for a significant association. But the authors pointed out that observational studies often lack standardized methodology (Hassoun et al. 2019). Climate changes and increase in TRAP have influences on the global burden of allergic diseases. For this reason, global programs against climate change might also have a positive impact on allergy prevalence.

5 Dietary Intervention Strategies

5.1 Supplements

Dietary supplements to prevent allergic diseases have been studied for years. This chapter will summarize the evidence of the supplementation with pro- and prebiotics, long chain polyunsaturated fatty acids (LC-PFUAs), and vitamins.

A systematic review summarized the effect of probiotics on the prevention of allergies and showed positive effects in the prevention of eczema in childhood when probiotics are taken in pregnancy and/or given to infants. But the authors found no

beneficial effects in the prevention of any allergy. They emphasize the lack of highly standardized RCTs and objective outcomes in the studies (Cuello-Garcia et al. 2015). Also other studies found some evidence for the eczema preventive effect of supplementation with *Bifidobacterium lactis* and *Lactobacillus rhamnosus* in pregnant women and their children. The evidence for allergy and asthma prophylaxis with pro- and prebiotics is still unclear, but could be advantageous in high-risk children (Mennini et al. 2017; Krzych-Falta et al. 2018). Research is needed to define the period, dose and composition of pre- and probiotic supplementation to prevent allergic diseases. Although the beneficial effect of prebiotics is still under debate, the WAO recommends prebiotic supplementation for all infants who are not breastfeed (Cuello-Garcia et al. 2016) and probiotics in pregnancy and early childhood for children at high risk to develop allergy. But the WAO has also highlighted the poor quality of the evidence (Fiocchi et al. 2015).

A systematic review on the effect of vitamin D supplementation did not conclude evidence for the prevention of allergy. The authors criticize the poor study quality of their included studies (Yepes-Nunez et al. 2018). Studies which investigated the effect of vitamin D supplementation in the development of asthma did also find no clear beneficial effect (Brustad et al. 2019; Shen et al. 2018). Therefore, supplementation with vitamin D is not recommended for the prevention of allergic diseases.

N-3 long chain polyunsaturated fatty acids (LCPFUs), most importantly omega-3 and omega-6 fatty acids were shown to influence immunological cells and act immunosuppressive in different cell culture and animal models. They modulate T-cell proliferation, decrease pro-inflammatory cytokine production, and can increase IL-10 secretion in vitro (Hoppenbrouwers et al. 2019). Although these effects were striking, consumption of LCPFUs in pregnancy during breastfeeding periods and in early childhood did not show evidence in the prevention of allergy or dermatitis/eczema and insufficient evidence for the prevention of allergic rhinitis (Schindler et al. 2016; Gunaratne et al. 2015). The Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) showed promising results in the prevention of wheezing and asthma development in the offspring with fish oil supplementation in pregnancy. The study consortium detected reduced wheezing and asthma prevalence in 5-year-old children whose mothers took 2.4 g of fish oil capsules daily from the 24th pregnancy week until 1 week after birth, compared to the control group supplemented with olive oil. They did not observe a reduced risk for allergic sensitization, rhinoconjunctivitis, or eczema (Bisgaard et al. 2016). A recently published study associated the consumption of fish or cod liver oil in the first year of life with a reduced risk for eczema, asthma, and wheeze at 6 years of age using data from the PACT study in Norway (Oien et al. 2019). Whereas evidence for asthma prevention with fish oil consumption is increasing, it is still lacking for other allergic diseases.

5.2 Solid Food Introduction

Recommendations on solid food introduction in young children are manifold and emotionally discussed. The current practice of gradually introducing solid foods in children and avoiding potentially allergenic foods is likely to be outdated.

Different studies showed an association between the avoidance of egg, fish, milk, and tree nuts in pregnancy and early life on decreased rates of asthma, rhinitis, and atopy but not for food allergy (Zeiger and Heller 1995; Arshad et al. 2007). Whereas the Cochrane review of Kramer and Kakuma did not find evidence for positive effects of antigen avoidance in pregnancy for the offspring's eczema or food allergy risk. They concluded that avoiding potentially antigenic foods during pregnancy is not recommended to prevent eczema or food allergies in the offspring (Kramer and Kakuma 2012). In more recent studies the early introduction of potentially allergenic food was studied. The early introduction of peanut- and egg-protein to avoid peanut and egg allergy was shown to be successful in children being at risk to develop food allergy in the Learning Early About Peanut (LEAP) and Enquiring About Tolerance (EAT) studies. The authors did not show reduction or increase of other food allergies or eczema (Fisher et al. 2018). These results go along with a recently published multicenter cluster randomized prevention study which concluded not only no beneficial but also no harmful effect of early introduction (starting 3 month after birth) of peanut, cow's milk, wheat, and egg on the prevention of eczema at 12 months of age. The assessment of food allergy will be a primary outcome of the follow-up protocol after 36 months (Skjerven et al. 2020). These results were striking because they brought about a paradigm shift, which is also supported by the biodiversity hypothesis which recommends as much diverse contact to natural environment early in life as possible which includes exposure to various food products (Haahtela 2019). "The Guidelines for the Diagnosis and Management of Peanut and Tree Nut Allergy in the United Kingdom" thereupon recommends the early introduction of peanuts (at least 2 g of peanut protein three times a week) for children at risk to develop peanut allergy. High risk is defined by severe eczema or egg allergy. Non-risk children consuming peanuts do not have any increased risk to develop peanut allergy (Stiefel et al. 2017). The American Academy of Allergy guidelines also recommends the consumption of potentially allergenic food in young age and highlights that avoidance of egg, dairy, peanut, tree nuts, fish, and shellfish might even increase the child's risk to become food allergic (American Academy of Allergy, Asthma, and Immunology 2019).

5.3 Breastfeeding

The positive effects of breastfeeding for mother and child are well studied. But the protective effects on allergy and asthma development are still under debate. RTC studies are not feasible as well as blinding. Although no evidence for allergy and asthma prevention exists, breast feeding is highly recommended for the first 4 months of life (Heinrich 2017; Victora et al. 2016).

6 Conclusion

Many attempts to prevent allergic diseases have been taken, but so far no conclusive evidence for general allergy prevention recommendations exists. Avoidance of passive and active cigarette smoke exposure for pregnant women and children and avoidance of indoor moisture and mold is beneficial for the prevention of wheezing and asthma. Whereas the avoidance of HDM allergens to prevent HDM allergy is not recommended anymore. There are epidemiological studies which associated the traditional farm environment with allergy reduction but primary prevention studies are not published yet. Supplementation with vitamins, pre- and probiotics is not harmful but evidence for the prevention of allergic diseases is still lacking. Supplementation with LCPFUAs was shown to be asthma but not allergy protective. Best evidence was shown in the early introduction of peanuts in children with egg sensitization or eczema to prevent peanut allergy.

The evidence for allergy prevention in total can be classified as low. The lack of RCTs has a major impact on evidence generation. With regard to behavioral studies, blinding or randomization is hardly feasible, which makes the evaluation of evidence more difficult. Most of the prevention strategies are based on observational studies which are less meaningful than RCTs and very hard to compare. Another factor associated with observational and intervention studies is a large influence of bias, especially when it comes to parents filling out questionnaires and describing their children's symptoms. Outcome assessment was mostly based on observation instead of evaluated objective measures like the skin prick tests, blood IgE levels, and/or lung function tests, just to mention a few. Research on reliable, easy-to-use and inexpensive biomarkers that can be used in various body fluids, ideally non-invasive, is ongoing and will increase the quality and comparability of study results in future studies. Figure 1 summarizes beneficial strategies and research needs in allergy prevention.

	Beneficial allergy prevention strategies	Research needs
Global environment	Reduction in traffic related air pollution	Impact assessment of air pollution and climate change on allergic diseases
Local environment	- Environment of rich and diverse bacteria species - Cigarette-smoke free environment - Less indoor moisture and molds	Exact definition of protective microbial composition
Individual behavior	- Dietary supplements in pregnancy might be beneficial - Natural birth might be beneficial - Early introduction of diverse solid food	Prevention studies based on individual risk assessment with novel biomarkers

Fig. 1 An overview of prevention strategies and research needs to reduce allergic diseases in three dimensions, including individual behavior, local and global environment

Targeted prevention based on individual risk assessment with the help of evaluated biomarkers could be one future strategy to overcome the burden of allergic diseases. With profound knowledge in cellular and molecular signal processing in allergy sufferers, these strategies will be improved. Although all quoted studies in this chapter focusing on one intervention strategy or one outcome, the future in prevention of allergy and atopic diseases may also lie in multifaceted allergy prevention programs. They can combine best evidence studies in a national program where forces are bundled and which includes stakeholders, communities, patients, and their parents already in the conceptual stage to develop prevention strategies on a population level like the Finnish allergy program (Pelkonen et al. 2012).

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