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Allergy and asthma prevention 2014

Antonio Nieto[1], Ulrich Wahn[2], Albrecht Bufe[3], Philippe Eigenmann[4], Susanne Halken[5], Gunilla Hedlin[6], Arne Høst[5], Jonathan Hourihane[7], Jocelyne Just[8], Gideon Lack[9], Susanne Lau[2], Paolo Maria Matricardi[2], Antonella Muraro[10], Nikos Papadopoulos[11], Graham Roberts[12], Angela Simpson[13], Erkka Valovirta[14], Stephan Weidinger[15], Magnus Wickman[16], Angel Mazon[1]

[1]Unit of Pediatric Allergy & Pulmonology, Children's Hospital La Fe, and Instituto de Investigacion La Fe,Valencia, Spain; [2]Depatment of Pediatric Pneumology and Immunology.,Charité Universitatsmedizin,, Berlin, Germany; [3]Experimental Pneumology, BGFA-XU18, Ruhr-University Bochum, Germany; [4]Pediatric Allergy Unit, University Hospitals of Geneva, Geneva, Switzerland; [5]Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark; [6]Astrid Lindgren Children's Hospital and Centre for Allergy Research, Karolinska University Hospital, Stockholm, Sweden;; [7]Paediatrics and Child Health, University College Cork, Cork, Ireland; [8]Allergology Department, Centre de l'Asthme et des Allergies, Hôpital d'Enfants Armand-Trousseau - INSERM, UMR_S 1136, Sorbonne Universités, UPMC Univ Paris 06, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Equipe EPAR, Paris, France; [9]King's College London, King's Health Partners, MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, and the Department of Paediatric Allergy, Guy's and St Thomas' NHS Foundation Trust, London, UK; [10]The Food Allergy Referral Centre Veneto Region, Department of Women and Child Health, University of Padua, Padua, Italy; [11]Allergy Department, 2nd Pediatric Clinic, National & Kapodistrian University of Athens, Athens, Greece, and Centre for Paediatrics and Child Health, Institute of Human Development
University of Manchester, Manchester, UK; [12]University of Southampton, Southampton; David Hide Asthma and Allergy Research Centre, Isle of Wight; and NIHR Respiratory Biomedical Resaerch Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK; [13]Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, University of Manchester & University Hospital of South Manchester, Manchester, UK; [14]Terveystalo Turku, Allergy Clinic, University of Turku, Turku, Finland; [15]Department of Dermatology, Venereology and Allergy, University Hospital Schleswig-Holstein, Kiel, Germany; [16]Sachs' Children's Hospital, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

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Correspondence:

Dr. Angel Mazon

Unit of Pediatric Allergy & Pulmonology, Children's Hospital La Fe

Bulevar Sur s/n

46026-Valencia, Spain

Tel: 00 34 961 244 378

E-mail: amazon@comv.es

Abstract

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Asthma and allergic diseases have become one of the epidemics of the 21st century in developed countries. Much of the success of other areas of Medicine, such as infectious diseases, lies on preventive measures. Thus, much effort is also being placed lately in the prevention of asthma and allergy. This manuscript reviews the current evidence, divided in four areas of activity. Interventions modifying environmental exposure to allergens have provided inconsistent results, with multifaceted interventions being more effective in the prevention of asthma. Regarding nutrition, the use of hydrolysed formulas in high risk infants reduces the incidence of atopic dermatitis, while there is for now not enough evidence to recommend other dietary modifications, prebiotics, probiotics, or other microbial products. Pharmacologic agents used until now for prevention have not proved useful, while there is hope that antiviral vaccines could be useful in the future. Allergen-specific immunotherapy is effective for the treatment of allergic patients with symptoms; the study of its value for primary and secondary prevention of

asthma and allergy is in its very preliminary phases. The lack of success in the prevention of these disorders lies on their complexity, which involves many genetic, epigenetic and environmental interactions. There is a need to identify target populations, involved mechanisms and interactions, and the best interventions. These must be effective, feasible, implementable and affordable.

1- INTRODUCTION

Allergic conditions in childhood are associated more with an affluent life style than poverty. Migration from rural to urban settings is associated with a generational transition from non-allergic to allergic disorders. Non-farming families residing in a rural setting have intermediate rates of asthma and allergy compared to their farming neighbours and urban families. Certain populations, such as anthroposophic families, in developed countries have lower rates of allergic disorders than families who live in a "conventional" way (1, 2). The underlying reasons are not completely understood.

Not all symptoms seen in a child predisposed to allergy will have an allergic cause. Only a small proportion of infants who wheeze develop asthma by 5 years of age. Some infants have airway hyper-responsiveness and allergic features from a very early age and could possibly be considered to have asthma, if an accurate diagnostic test was available (3). Thus, the recognition and accurate diagnosis of allergic diseases in early life can be difficult and phenotypes, including biomarkers, comorbidity, and natural history, need to be well defined.

It has become obvious that allergy and asthma represent a pattern of disorders related to a multigene-environmental interaction. While twin studies suggest significant concordance between

monozygotic twins this is not 100% penetrant so identical twins can be discordant for an allergic disorder despite almost identical exposures to environmental triggers (4).

Preventive strategies for asthma and allergic disorders targeting different groups of children have been proposed:

1. General health education. The target group comprises a non-selected part of the population, such as all newborns or all pregnant women. For example, avoidance of tobacco smoke exposure during pregnancy and after birth is strongly recommended (5-8). There should be minimal or no risk associated with implementation on a population level.

2. Primary prevention for infants at higher risk. Several longitudinal birth cohort studies have clearly demonstrated an increased risk of allergic manifestations if one or two parents are or have been affected themselves (9). Some strategies involving relevant resources may only be justified in children at risk and not in whole populations. These strategies may also represent a burden to the family or there may be potential negative side effects. Evaluation is required in families with elevated risk.

3. Secondary prevention strategies are aiming at children who have already developed allergic sensitization or the first manifestations of allergic diseases (e.g. eczema, wheeze); such strategies aim to reduce the incidence of clinical manifestations such as food allergy, rhinitis or asthma (10).

Single–factor interventions may be ineffective in certain genotypic profiles (11) Some interventions may be too late (e.g. eliminating pets although their allergens may persist for years in a house) in that the disease may already be certain to occur. Other early life interventions may be beneficial, although it remains to be shown if they successfully prevent the onset of asthma or just delay it to later adult life (12). Major complex interventions may be effective (e.g. house dust mites (HDM)

reduction in the Isle of Wight study) but may not be affordable or practical in large populations (12). In contrast, simple, single interventions may be ineffective in adequately reducing the relevant exposure.

Many people with allergic disorders tolerate their symptoms and need for medication, while relatively few have severe disease. How can these subjects be protected from the burden of ill health at a price that the population/ policy makers are prepared to pay? What is the social and financial cost that both affected and unaffected people must pay to prevent allergic conditions in a proportion of citizens? Should preventive measures be directed to severe disease only or, given the high burden of allergic diseases for patients and society, would a more global preventive strategy be cost-effective? To answer to these and other questions, we need to improve our understanding of the genetic basis of asthma and allergy (genomics), the DNA modifications that affect gene expression (epigenomics), the environmental factors interacting with those genes ("environomics") (13), the structure and function of involved proteins (proteomics), and the intermediate and final products of metabolism (metabolomics). The use of highly powered informatics tools would allow analyzing and integrating the huge amount of information already available (14-16) and to take significant steps forward in the field of prevention of asthma and allergy.

Much of our understanding of preventive interventions early in life derives from epidemiological studies. There is a clear hierarchy of evidence:

1. Cross sectional studies generating hypotheses. They describe associations, but they will not prove causal relationship between a protective or a risk factor and the outcome nor even the direction of any relationship.

2. Longitudinal, non-interventional studies, like prospectively-followed birth cohorts, are able to describe time courses with incidence, remission and persistence in relation to risk and protective factors. They are considered to deliver more definite information but again can

not provide evidence of causality.

3. Longitudinal randomized interventional studies can provide evidence of a causal relationship between an intervention and outcome. If consistent results are found in multiple studies, the overall effectiveness of an intervention and associated health economic can be estimated.

This manuscript reviews the evidence for the prevention of asthma and allergy obtained from observational and interventional studies and, where appropriate, animal model data. Both single and multifaceted interventions are included. Aims range from the prevention of a specific allergic disorder to the induction of a wider "healthy" immune status to prevent all allergic conditions. A summary of current knowledge and the needs for future research are presented.

2- LIFESTYLE AND ENVIRONMENT AS RISK FACTORS FOR ALLERGY AND ASTHMA

Very few environmental exposures have been consistently and reproducibly associated with allergy and asthma. Asthma is an umbrella term encompassing many different diseases which present with the same or similar symptoms – each of these may have its own causal factors (17). Additionally the inherited predisposition determines whether or not an environmental exposure is hazardous for an individual mediated through gene-environment interactions (18) or epigenetic mechanisms (19).

INDOOR ALLERGEN EXPOSURE

Results from observational studies

Many studies have reported on the association between cat and dog ownership and asthma although results are heterogeneous (20-23). A recent pooled analysis of 11 birth cohorts found a weak association of early dog or rodent ownership and reduced likelihood of allergic sensitisation, but no

association with asthma or rhinitis (24). It is likely that genetic susceptibility in combination with a possible dose-response relationship is relevant as has been shown for eczema and cat ownership (25).

Cat and dog ownership is confounded by family history of allergy meaning that the effects of exposure are difficult to evaluate due to reverse causation with allergy in the family being a reason to avoid pets (26-28). Furthermore, dog and cat allergens are airborne and are found in significant amounts in schools and public places (29-31), so community exposure is important. This issue is not amenable to randomised interventional studies; we therefore need to focus on a mechanistic approach to understanding why some children become allergic to domestic animals while others do not.

For mite exposure, some studies have shown a linear association between exposure and sensitization (23, 32-34), but several have shown different patterns of association (35) or none(36). It is not clear what the best level of exposure is and emerging data suggest significant exposure may also occur outside the home (37). The evidence linking mite allergen exposure and asthma is weak and needs further evaluation (38).

Children of farmers have been shown to be at reduced risk of allergic sensitization and asthma (39), especially in Alpine regions of Europe. Recent results from the International Study of Asthma and Allergies in Childhood indicate that children of farmers were more likely to have asthma, especially if they were from non-affluent countries (with no effect seen in children from affluent countries) (40). Even in these regions, the protective factor remains elusive, possibly unpasteurized milk (41) or the diversity of microbial exposures (42). It is likely that gene-environment interactions and epigenetic effects are also important.

Results from interventional studies

Six studies that aimed to decrease HDM exposure to reduce allergic sensitisation (Table 1) were identified. Most used a number of interventions, in particular mattress covers, acaricides and education, to reduce HDM exposure. Four studies recruited prenatally (43-46). They followed participants for 2-5 years. The other two (47, 48), recruited pre-school children and young school children respectively and followed them for one year. Allergic sensitisation was measured by skin prick testing to HDM and, in the case of some studies, to other allergens.

The study results are mixed. The two SPACE studies, recruiting pre-school and school children, demonstrated more than a 50% reduction in HDM sensitisation, one also documented reduced HDM exposure in the intervention group (47, 48). Three studies, recruiting prenatally, all failed to show any difference between the intervention and control groups after 2-5 years of follow up for either HDM or any sensitisation, despite two providing data to show they managed to reduce HDM exposure (43, 45, 46). The other study, which again recruited prenatally and had the most extensive measures for reducing HDM exposure, reported more than a 50% increase in HDM and any sensitisation to common allergens in the intervention group, despite demonstrating large reductions in all allergen exposure in the intervention group (44). The authors have speculated that their intervention also reduced endotoxin exposure and, because of the genetic characteristics of their population, this was associated with increasing sensitisation. In summary, strategies to reduce HDM exposure do not seem to consistently be associated with reduced HDM sensitisation or sensitisation to any allergen.

Two other studies have taken a multifaceted approach to allergen avoidance with both HDM reduction measures and dietary advice. Breast feeding was encouraged, with extensively or partially hydrolysed formulas used where this was not possible, and the introduction of solid foods was delayed. Both studies recruited ante-natally and had a seven and 18 year follow up respectively (12, 49). Only the small Isle of Wight study demonstrated a significant reduction in sensitisation up to eight years of age, reduced persistent HDM sensitisation until 18 years, but at 18 years the

overall effect on current sensitisation was lost, despite reduction in HDM exposure. There was no significant difference in sensitization in the Canadian study.

Four of the single intervention HDM reduction strategy studies also looked at asthma (43-46). In one of these (44) the number with asthma was only reduced in the intervention group at one year of age. Otherwise, there were no difference in current wheeze, current asthma or physician diagnosed asthma, despite reduced HDM exposure in three studies. In these studies follow-up was until the age of 2-5 years, age group in which the diagnosis of asthma is difficult, as most children have transient wheeze related to infections only. Therefore, a longer-term follow-up is necessary.

Three multifaceted intervention studies have looked at asthma. These include the two previously mentioned (12, 49) plus another one recruiting prenatally with a similar intervention strategy and a follow up to six years of age (50). Only the first two studies demonstrated a difference, with current asthma being reduced by over 50% at 18 years of age and wheeze without colds and bronchial hyper responsiveness at seven years of age being reduced by around 50% in the intervention group respectively. The third study showed no difference in allergic asthma between the two groups, although HDM exposure was reduced in the intervention group. The Cochrane meta-analysis focusing on this area concluded that only multifaceted interventions are effective in preventing asthma (51). In summary, there are some data suggesting that a multifaceted allergen reduction measure does prevent the development of asthma but the data are not consistent for all studies and the duration of the follow up varies.

While in some studies allergen reduction measures seem to be associated with reduced sensitisation and reduced levels of asthma, this is far from consistent. It may be partly explained by the sub-optimal intervention strategies previously used, but also by difference in age for follow-up, with more unspecific asthma outcome measures for young children, and by a high geographical and

climate determined variability in the exposure. In some regions, e.g. Australia, exposure to HDM is very high and, therefore, even an efficient reduction in exposure still is equivalent to a high exposure in northern European countries. New data suggest that there may be significant exposure to HDM during the day time and so this needs to be taken into account (37). Additionally, we know that aeroallergens are widespread in the community with, for example, cat allergen even being found in what might be regarded as safe environments, such as schools (29-31, 52). The second likely reason for variable results between studies is the failure to take into account modifying factors. An example is the CD14 gene polymorphism that is associated with susceptibility to endotoxin, with children having the CD polymorphism being much less likely to become sensitised on exposure to endotoxin (11). This suggests it is critical to understand the target population and other important environmental factors before intervening. This can only really be explored within a large randomised control trial of allergen reduction measures where participants are genotyped, phenotyped, and other key environmental exposures are monitored (Table E-1 online).

POLLUTANTS AND TOBACCO SMOKE

Pollutants are a key cause of airway inflammation. High exposures in patients with asthma may increase the risk of an exacerbation (53) and impair lung function in children with asthma (54). An association between traffic related air pollution and asthma prevalence has also been demonstrated (55, 56). Other studies have not found significant associations (57-59).

Prenatal and passive smoke exposures have been associated with early life wheeze and asthma in childhood, increasing the incidence by an estimated 20% (5). Children exposed only during pregnancy were at an increased risk (7, 60), and exposure during the first year of life was more strongly associated than current exposure (6), indicating that the perinatal period is a particularly high risk time (8). A dose response relationship can be demonstrated (6, 7), adding strength to the

association. Unfortunately, too many young children continue to be exposed to smoking. This represents a public health issue that needs to be addressed. For example, it would be useful to run a cluster randomised control trial of a smoking cessation campaign specifically directed at women who are likely to become pregnant or who are in early pregnancy, to see whether such a strategy would impact on their levels of smoking and improve the health of their children.

Indoor and outdoor air quality is also an issue, particularly in the developing world. The relation between pollution and asthma is well established (61). Although several pollutants have been linked to new-onset asthma, the strength of the evidence is variable. Epigenetic mechanisms (such as hypermethylation of CpG islands in Foxp3) are associated with chronic exposure to diesel-exhaust particles and with suppression of Treg function and increased asthma severity in children (62). This deserves further attention and, if associations are consistent, development of potential interventional strategies.

OBESITY

There is increasing evidence that obesity is associated with the development of asthma (63-65) although there is no recent meta-analysis of these data (66). The association may differ between boys and girls and body mass index is probably not the best measure (67). Associations between measures of body fat and asthma should be jointly modeled longitudinally in prospective cohort studies with measures of activity (68). There is a need to study whether weight reduction will impact on the risk of developing asthma, both in terms of the concept and whether it would be an effective public health interventional strategy (Fig. 1).

Box 1. Messages for the pediatric allergist: life style and environmental exposures

- There is no clear evidence that preventive strategies just based on reducing indoor allergen exposure are effective.
- Multifaceted interventions (environment and diet) may be effective in preventing asthma.
- Prenatal and passive tobacco smoke exposure is an important risk factor for the development of asthma.
- Tobacco smoke and exposure to other pollutants are important risk factors for exacerbations of asthma.
- Obesity in infancy may be associated with later asthma.

3- NUTRITIONAL AND MICROBIAL FACTORS AS POTENTIAL PROTECTIVE FACTORS FOR ALLERGY AND ASTHMA

BREAST FEEDING AND INFANT FORMULAS

There is general consensus that breast milk is the best option for all children regardless of any atopic heredity. Whether duration of breastfeeding influences the development of allergy related diseases remains debated (69-71). So far conflicting results have been presented, which might be explained by methodological differences of studies, as well as structural diversity of different fatty acids, differences of immune competent cells in human milk, etc. In addition, selection bias and reverse causation is a problem since it is not possible to randomize to breastfeeding. However, recently in the EAACI systematic review (72)and guidelines (73) on prevention of food allergy it was concluded that, despite controversial results, there is evidence to recommend exclusive breastfeeding to all children for the first 4-6 months to reduce the risk of food allergy. There is no

evidence for the restriction of allergenic foods in the diet of lactating mothers or during pregnancy to prevent allergic disease in their offspring (74).

If breastfeeding is insufficient or not possible, high-risk infants should receive a hydrolysed formula with documented preventive effect for the first 4 months, whereas other infants should receive a standard formula. Recent guidelines support the use of some hydrolyzed cow's milk based formulas to prevent cows' milk allergy in high risk infants (72, 73) although the evidence is not strong (75, 76). Some cow's milk based hydrolysates have demonstrated long term effect, up to 10 years, in preventing atopic dermatitis, with no effect on asthma or allergic rhinitis (77). After the age of 4 months, a standard cows' milk based formula is recommended according to standard nutrition recommendations also in children at risk (10, 72, 73, 78).

TIMING OF SOLID FOOD INTRODUCTION

Regarding the age of introduction of solid foods, there is data indicating that special dietary restrictions after the age of 4 months for infants with high risk for development of allergic disease are not useful for preventing food allergy and that may even contribute to increase the risk for food sensitization and promote allergic diseases (79-81). The pattern of foods in the infant diet may though be important in the development of food allergy (82, 83). In the EAACI Primary Prevention of Food Allergy Systematic Review and Guidelines it has been highlighted that there is not enough evidence to provide recommendations about the timing of the introduction of complementary foods (72, 73). However, a few studies suggest that it might be an advantage not to introduce solids before 4 months of age. Therefore, it is currently recommended that complementary foods should be introduced after the age of 4 months for all children irrespective of atopic heredity, according to normal standard weaning practices and nutrition recommendations as well as to the child's specific needs. In addition it is recommended that "highly allergenic" foods such as cow's milk, hen's egg and peanuts, should not be withheld irrespective of atopic heredity, once weaning has commenced.

PRE- AND PROBIOTIC SUPPLEMENTATIONS

Epidemiological trials identifying risk factors for later allergic diseases have suggested that birth by caesarean section may be associated with a higher risk for allergic diseases, and it is hypothesised that this might be due to an unfavourable gut microbiota (84-86). Preclinical studies have shown that modifying the microbiota modulates the global immune response of the host, reduces sensitization and allergic inflammation (87-89). These and other studies have led to the hypothesis that pre- and probiotics might be protective for allergy.

Interventional trials in infants have included prebiotics, probiotics and bacterial lysates (90-93). Positive studies (mainly on infant eczema) were mostly conducted in high risk populations and many aspects are still not clear (94, 95). Multiple and sometimes counteracting interactions between environmental factors and genes may be behind the heterogeneity in results (11).

An earlier systematic review of studies exploring prevention of atopic eczema compared the administration of probiotics versus placebo in infants (96). In populations with normal/low and high allergic risk, probiotic interventions showed no statistically significant protective effects. However, three other more recent meta-analyses found significant benefits in the reduction of eczema when probiotics were administered prenatally (97), or either pre- and postnatally (98, 99). One of these meta-analyses found a reduction for both eczema and IgE-associated eczema (98). Another meta-analysis described a reduction in atopic sensitisation and in serum total IgE, but not in asthma/wheeze symptoms (100).

Probiotics seem a promising approach but some aspects remain to be elucidated. In addition to the common heterogeneity of meta-analyses, not all strains seem equally effective. Dang found efficacy for combinations but not for single strains (99), while, conversely, Doege found lactobacilli but not mixtures to have an effect (97), and Elazab describes an increased risk of atopic sensitisation with the administration of Lactobacillus acidophilus (100). Likewise, the meta-analysis by Elazab could

find no effect on atopic sensitization when probiotics have been administered only postnatally; the combined pre- and postnatal administration seemed to be necessary for efficacy (100).

A meta-analysis explored the effect of specific prebiotics versus placebo supplementation (101), with four studies eligible for inclusion. The meta-analysis of two of them found no effect on infant asthma. The meta-analysis of the four studies found a significant reduction in eczema, although with a high number needed to treat to benefit (n=25, 95% CI: 14-100). Although individual studies found significant effects for specific risk populations, the joint analysis did not identify significant subgroup differences depending on the degree of risk for allergy or type of infant feeding. No effect on eczema by prebiotics alone was seen in the meta-analysis by Dang (99).

In summary, supplementation with probiotics may have an effect for primary prevention of eczema although clearer evidence is needed and their use is not generally recommended for this indication. Their effect could be strain-specific and further investigation is required.

BACTERIAL LYSATES

Data on allergy protective effects of bacterial lysates are mostly epidemiological or preclinical with very few interventional clinical studies. The actual interventional products are not always clearly defined. Table E-2 online differentiates between microbial products, microbes themselves, vaccines and other substances as isolated from environmental extracts such as cowshed dust.

Lipopolysaccharides (LPS)/endotoxin level in child mattresses as a microbial product was associated with a reduced prevalence of atopic asthma, suggesting that LPS induces an immunological tolerance effect in children exposed to higher levels in early life (102). Data from farming communities have suggested that early contact, i.e. *in utero* and perinatally, with bacteria

and microorganisms may be beneficial in terms of allergy and asthma prevention (42, 103-105). The immunomodulating capacity of Gram-negative bacteria, endotoxin and bacterial lysates (106-108), as well as LPS and lipopeptides (109) has been demonstrated in animals. Oral application of a bacterial lysate (Pro-Symbioflor™) in healthy newborns for at least 6 months daily demonstrated a reduction of atopic dermatitis only in a subgroup of infants with single heredity for atopy directly after the treatment and at age 7 months (91). No effect was seen on sensitization or other allergic diseases.

OTHER BACTERIA-DERIVED CANDIDATES

Other substances such as cowshed dust extracts (110), plant derivatives (arabinogalactan) (111), and small animal derivatives (serine protease from *Tenebrio molitor*) (112) have all been demonstrated to protect *animals* from allergy by different mechanisms. Importantly, they seem to act synergistically with the best results seen when multiple substances are applied. These substances still need proof of effect as allergy protective treatment in children before they can be considered for clinical use (Table E-3 online). Little is known about the significance of food compounds (immunogenetic peptides, antioxidants) and epigenetic effects (113, 114).

OTHER SUPPLEMENTATIONS

Other allergy protective effects of nutritional supplementations, in particular of vitamins, have been explored. West *et al.* have shown that a lower intake of vitamin C and copper is associated with increased eczema, wheeze and allergic diseases at 1 year of age (115). Additionally, an increased incidence of wheeze is associated with a low intake of vitamin E during pregnancy (116, 117). Likewise low cord blood selenium and iron status were associated with increased risk of wheeze (118). Some studies and a recent meta-analysis have also shown an association of maternal and/or early childhood intake of vitamins A, D, and E, zinc, magnesium, fruits and vegetables, and a Mediterranean diet, with reduced asthma (119-121). Specifically regarding vitamin D some studies

have found an association of lower intakes of vitamin D during pregnancy or low levels of maternal or cord blood vitamin D with higher risk of eczema (122), food sensitization (123), or asthma (124) in the offspring, while other studies have found opposite results with a higher risk of food allergy (125) or atopic eczema (126). On the other hand, many other results have not found an association in any direction (122, 126-128), nor effect of prenatal supplementation on several wheezing and allergy outcomes (129). In view of the conflicting results, no recommendation can be done. Finally, dietary interventions aimed at increasing polyunsaturated fatty acids with or without reduced omega-6 fatty acid intake have been associated with decreased incidence of eczema in one trial (130) and no effect in others (46, 131). The fact that the first study was a prenatal intervention, compared to the other postnatal two studies, further raises the question of whether there could be a window of opportunity for intervention.

In summary, the variety of administration protocols (pre- and postnatal), and of intervention options chosen (e.g. type of prebiotics and strain(s) of probiotics) prevents the generalization of recommendations to all types of pre- and probiotics. The available evidence suggests that in order to be most effective, primary prevention strategies may have to combine various interventions and define target populations (Fig. 2). A better understanding of allergy phenotypes and the discovery of markers that can identify them in early life may help defining these populations. No recommendations can be currently made concerning other supplementations.

Box 2. Messages for the pediatric allergist: nutritional and microbial factors

- The use of cow's milk based hydrolysates for the first 4 months, when breast milk is insufficient, can reduce the development of eczema in high risk infants
- Delayed introduction of solids after the fourth month of life has no preventive effect on

allergy.

- Probiotics can to some extent prevent atopic eczema; bacterial strains and timing for administration need investigation. So far no preventive effects on food allergy, asthma or allergic rhinitis have been documented.
- The available information on bacterial lysates is insufficient for recommendation.
- Dietary modifications not accompanied by environmental measures have to prove their efficacy to prevent respiratory symptoms.
- Until more definite information on specific supplementations is available, the recommendation stands for a healthy balanced diet both for pregnant women, nursing mothers, infants and children.

4- PHARMACOTHERAPY AND VACCINES AS POTENTIAL PROTECTIVE INTERVENTIONS FOR ALLERGY AND ASTHMA

Viral infections, particularly respiratory syncytial virus (RSV), are often the first cause of acute bronchial obstruction. By age two years, the majority of children have had their first RSV infection. Children with early wheeze may have an impaired response to viral infections (132, 133) due to an impaired interferon response to viral invasion(134). There are conflicting reports on the risk of early bronchial wheeze and later development of asthma after an early RSV infection (135). A Swedish long-term follow-up of infants hospitalized for RSV bronchiolitis has shown both an increased risk of allergic sensitization and persistent asthma (136); this has not been confirmed in other studies (137, 138). Recently, viral wheezing due to rhinovirus has been reported to increase the risk of developing asthma; this risk may correspond to a particular genotype (139).

RSV AND PALIVIZUMAB

Palivizumab is a monoclonal antibody for prevention of RSV infections. It is used for high risk children, for example children born prematurely with bronchopulmonary dysplasia, children with severe congenital heart problems and children with severe lung diseases (140). It is effective in the prevention of recurrent wheezing during the first year of life in otherwise healthy premature infants (141). Its impact on the development of asthma has not been studied in long term studies of children with high risk of asthma by heredity and/or early signs of severe allergic disease. One small study indicates a possible asthma-preventive effect in children with no family history of asthma or allergy (142). The lack of studies, the cost of the drug and the mode of administration mean that palivizumab is not currently indicated either for preventing the development of asthma nor for exacerbations (143).

RHINOVIRUS AND ASTHMA

Rhinovirus infections have been shown to increase the risk of asthma development (144). There are also indications that the combination of rhinovirus infection and allergic sensitization could, synergistically, increase the risk of asthma development and of acute exacerbations (145, 146). Vaccination towards rhinovirus could potentially decrease the risk but this is complicated by the multiple strains of rhinovirus. So far there has not been any successful trial of rhinovirus vaccination although an *in vitro* study has indicated some promise in preventing allergic asthma (147, 148). For example, a combination of grass pollen allergen and a rhinovirus surface antigen (VP1) can induce the development of biologically active grass pollen and rhinovirus specific IgG antibodies in animal models (148).

INFLUENZA AND ASTHMA

Influenza vaccination is recommended for children with airway conditions like severe asthma and/or other lung diseases. So far there are no studies showing any primary preventive effect of influenza vaccination, although a secondary partly preventive effect on asthma deterioration is possible (149).

BACTERIAL INFECTIONS AND ASTHMA

The role of antibiotics for bacterial infections or colonization and risk of asthma has been studied in retrospective cohort studies. Some have found an increased risk of asthma after early use of antibiotics (150) or maternal use during pregnancy (151), but there is a chance of reverse causation (152). For example, children with early wheeze may have an impaired response to viral infections (134), which might make them more prone to infections and therefore more likely to receive antibiotics. There have also been recent suggestions that bacterial colonization may have a role in the pathogenesis of asthma or expression of symptoms (153-155).

EARLY ANTI-INFLAMMATORY TREATMENT FOR PRE-SCHOOL WHEEZE AND MILD CHILDHOOD ASTHMA

The ERS Task Force (156) proposed that pre-school children with episodic viral wheeze should be treated with intermittent therapy. This is supported by three studies that show that early initiation of either continuous (157, 158) or intermittent (159) inhaled corticosteroids (ICS) attenuates progression of episodic viral wheezing to school age asthma. There is no evidence of a preventive effect though. The TREXA study assigned 288 children aged 5-18 years to one of four regimes in a 44 week study (160). The children had well controlled mild persistent asthma and the study focused on a tertiary preventive effect on risk of exacerbation and or persistent deterioration. The frequency of exacerbations was lower in the all three beclomethasone groups compared with the placebo

group. This study suggests that ICS at the time of viral infections may be beneficial in children with asthma. Other studies confirm beneficial effects in mild asthma and risk of deterioration when treatment is stopped (161).

TREATMENT FOR ALLERGIC DISEASES OTHER THAN ASTHMA TO PREVENT ASTHMA IN SECONDARY PREVENTION

Nasal corticosteroids for allergic rhinitis.

Treatment of allergic rhinitis in order to prevent asthma has been studied in a few open randomized studies of pollen-allergic children receiving immunotherapy or just pharmacotherapy (162). There are also several studies with intranasal corticosteroid for treatment of rhinitis and prevention of asthma. So far these studies have, at best, reported positive effect on bronchial hyper-responsiveness (BHR) but uncertain effects on asthma prevention (163, 164).

Antihistamines for atopic eczema and/or food allergy.

In the 1990s some studies of early anti-allergic treatment with the antihistamine ketotifen showed some preventive effect on the development of asthma (165, 166) in children with signs of atopy but without symptoms of asthma; these findings have not been confirmed. Another prospective study with cetirizine had negative results for asthma prevention although there were some signs of a preventive effect on sensitization to grass and HDM and allergic asthma (167); this was not confirmed in a similar randomised clinical trial (RCT) using levocetirizine (168).

Emollients to prevent atopic eczema and allergic sensitization towards asthma.

Prevention strategies in atopic eczema using allergen avoidance have not been consistently effective. Given the new hypothesis that the skin barrier may be important in the development of atopic eczema and possibly food allergy and asthma, optimising skin barrier function may be helpful. A pilot study suggests that emollient therapy may have a protective effect compared with historical controls for the primary prevention of atopic eczema (169).

IMMUNE MODULATORS TO PREVENT ASTHMA

Anti-IgE monoclonal antibodies

The anti-IgE antibody omalizumab has so far only been studied as a treatment for severe allergic asthma. There are well documented effects on risk of asthma exacerbation (170). The drug is expensive and requires injections at monthly or bi-weekly intervals. A reduction of free IgE levels following the anti-IgE therapy could lead to reduction in high affinity receptor for IgE (Fc RI) expression on mast cells, basophils and dendritic cells (171). One could speculate that treatment with anti-IgE in high risk children could prevent allergic sensitization and delay or prevent development of allergic asthma. On this premise an observational study has shown that after stopping prolonged treatment with omalizumab, asthma control can persist as a residual effect, possibly indicating a modifying effect on the natural history of asthma (172); a specific study to evaluate this is currently ongoing. Furthermore, omalizumab reduces airway remodelling by modulating bronchial reticular basement membrane thickness and eosinophil infiltration (173).

New immune modulators

Interventions are being developed to improve the immune response to viral infections in children with impaired innate immunity, as shown by decreased levels of gamma-interferon (IFN) or

impaired function of Toll-like receptors (TLR) (174). Examples are inhaled IFN- beta and a TLR agonist. They are being evaluated for treatment, but they may potentially have a preventive activity.

In summary there are still no drugs to be used for primary prevention of asthma (Fig. 3). There are however treatment possibilities for tertiary prevention of deterioration and exacerbations although effects on the long term prognosis are still uncertain. Prevention of rhinovirus infections may provide a major step forward in primary prevention; immune modulators improve the innate immunity and response to virus infections and are other potential approaches (Table E-4 online).

Box 3. Messages for the pediatric allergist: pharmacotherapy and vaccines

- All drugs which have been studied so far for primary or secondary prevention have failed to demonstrate efficacy
- Antiviral vaccines (RSV, Rhinovirus, etc) are not available but might become important in the future

5. ALLERGEN-SPECIFIC IMMUNOTHERAPY

Allergen-specific immunotherapy (AIT) by the subcutaneous route (SCIT) has been studied for more than 100 years and, during the last decade, interesting results for sublingual administration (SLIT) by drops or tablets have been achieved. AIT has proved its efficacy for the treatment of symptoms in children who have already developed disease (tertiary prevention) (175-179). Due to its long-term immunomodulatory effects (180-182), AIT might be an effective intervention for primary and secondary prevention.

PRIMARY PREVENTION OF ASTHMA

The sublingual administration of AIT would give a possibility to prevent the development of asthma in children, especially in youngest ones although the results of initial pilot studies are mixed (183, 184).

SECONDARY PREVENTION OF ALLERGY AND ASTHMA

Development of asthma in patients with allergic rhinitis

Allergic rhinitis (AR) and asthma often co-exist; up to 50% of patients with AR have BHR and children with AR have an increased risk for development of asthma, especially those with bronchial hyperreactivity (185). Studies have shown that SCIT resulted in a reduced risk for developing BHR and asthma in children with AR and pollen or HDM allergy (162, 186-188). One study with long-term follow up (162, 188) was randomised but was not blinded to birch/grass SCIT and the other one, with HDM allergen, was double-blind, placebo-controlled, but had a low number of children with follow up only during two years of treatment (187). In addition, some open randomised studies indicated an asthma-preventive effect of SLIT, though the evidence is weaker than for SCIT and there are no long-term data. Thus, in one open randomised study with grass pollen SLIT in children with AR, SLIT was associated with a lower prevalence of asthmatic symptoms during three years of treatment (189). In another open randomised study of three years treatment, SLIT was associated with reduced onset of mild persistent asthma and reduced BHR in children with AR +/- mild intermittent asthma (190). The sublingual administration increases the possibility to perform high quality double-blind placebo-controlled trials, and at present there is an ongoing double-blind placebo-controlled long-term study in children with AR, examining a preventive effect on development of asthma (191).

Development of new sensitisations

Most studies on the possible asthma-preventive capacity of AIT do not report whether it is allergic asthma, but others do indicate that AIT may prevent development of new allergic sensitisations. However, the evidence is weak and based on just two prospective non-randomised studies(192, 193) and one retrospective study (194) on SCIT, and two open randomised controlled on SLIT for respiratory allergy (190, 195).

Allergen-specific secondary prevention of allergic rhinitis

The evidence of a molecular-spreading process in allergic rhinitis (196) calls for an earlier immunological intervention targeted to prevent its clinical consequences. In this perspective, 'secondary' allergen-specific immunoprophylaxis, targeted to children already sensitized to grass pollen but still healthy, has been recently proposed (197).

In summary (Table E-5 Online), there is some data to suggest that AIT may prevent the development of asthma in patients with AR (186, 198). At present we do not have evidence but ongoing studies may contribute more information (191). The evidence so far is weak regarding a possible preventive effect on development of new sensitisations and firm conclusions can not be made (Fig. 4). A recent call has been made to support research in the field of immunotherapy, due to its current value for treatment and its potential for prevention (199).

Box 4. Messages for the pediatric allergist: allergen specific immunotherapy

- Both subcutaneous and sublingual immunotherapy are effective in improving symptoms of respiratory allergies

- AIT is currently the only treatment that may affect the natural history of respiratory allergy; data from better designed studies are required.
- AIT with different application routes remains a candidate for primary or secondary prevention

6. CONCLUSIONS AND OUTLOOK FOR THE NEXT DECADE

The considerable efforts that have gone into the prevention of allergy and asthma over the last decades have helped us to better understand how these diseases develop in childhood. Evidence from different type of studies has highlighted the key importance of genetic inheritance, epigenetic factors as well as allergen and other environmental exposures such as cigarette smoke. We know that multifaceted interventions to reduce allergen exposure can be successful preventive strategies, although they may be challenging to implement. Breastfeeding for all and cows' milk hydrolysates for high-risk children for the first 4-6 months seem to be an effective preventive strategy for food allergy although modifying the diet in other ways seems to be unhelpful. Pharmacotherapy has not been found to be effective but immunotherapy may have secondary preventive activity on the development of new allergic sensitisations and the development of asthma.

There are many remaining questions in this area (Tables E-1, E-3, E-4, and E-6 online).. These need to be addressed primarily by interventional trials which require considerable thought, time, energy and financial resources (200). Regulators should be aware of this to avoid wasting resources, both human and financial. The responsibility towards research participants and funders should demand that trial results are accepted even if in the time course regulations may change. Meta-analyses can be helpful; however, they can be misleading in their conclusion, especially if study populations,

definition of outcomes and interventions are not identical or if multiple approaches are implemented making them not comparable. To facilitate the synthesis of different trial data, an "ideal study design" of preventive trials should be created in collaboration with international societies and experts (201). Ideally, studies should also include promising synergistic approaches. Future interventional studies should be informed by a better understanding of tolerance induction and immunomodulatory effects of nutritional compounds and other possible factors.

Despite limited results so far, we should still aim for developing measures to prevent allergy and asthma, especially the most severe cases. The feasibility, effects and costs of any potential preventive measure should be very carefully evaluated. Other approaches, including early diagnosis and treatment to avoid further progression, should also not be forgotten. It is of utmost importance that all children with possible allergic symptoms have access to a proper and relevant diagnosis and treatment, as exemplified by the Finnish Allergy Programme. This has taken a more practical and holistic health-promoting based approach, promoting "Health" and tolerance of ill-health in a population (202, 203), rather than hoping to implement possibly stigmatising recommendations, which could be based on inadequate evidence and could represent an important burden on health care systems.

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Table 1. Summary of preventive effects of environmental interventions. (HDM: House dust mites. SPT: skin prick tests. ETS: Exposure to tobacco smoke. pHF: Partially hydrolysed formula. RR: Relative risk. OR: Odds ratio.

		OUTCOME										
		ALLERGIC SENSITIZATION					ASTHMA					
		A					C					
		Study	No	Selection criteria	Intervention	Age last seen (y)	Sensitisation control vs intervention	Study	No	Selection criteria	Intervention	Age last seen (y)	Asthma in control vs intervention
INTERVENTION	SINGLE	Horak 2004 (Europe, SPACE)(43)	696	Prenatal recruitment; Atopic disease parents or sibs	HDM reduction: cover & education	2	HDM sensitisation: 8.4 vs 6.1%, p=0.33	Horak 2004 (SPACE)(43)	696	Atopic disease parents / sibs	HDM reduction: cover & education	2	Asthma: 3.5 vs. 5.1%, p=0.377
		Woodcock 2004 (UK, MAAS)(44)	291	Prenatal, both parents atopic	HDM reduction: cover, vacuum, floor boards	3	Dp SPT positive: 12 vs 20% RR=1.67 (0.88–3.15, p =0.15) SPT positive: 21.5 vs 34.7% RR=1.61 (1.02–2.55, p=0.04 (allergen levels reduced)	Woodcock 2004 (UK, MAAS)(44)	291	Prenatal, both parents atopic	HDM reduction: cover, vacuum, floor boards	3	Physician diagnosed asthma: 11.7 vs 11.7% RR= 1.00 (0.50–2.01, p =1.0) (allergen levels reduced) Reduced asthma at 1 year
		Corver 2006 (Neth., PIAMA)(45)	1272	Maternal allergic disease	HDM reduction: covers vs. placebo vs. none	4	No difference in HDM sensitisation nor atopy (HDM levels reduced)	Corver 2006 (PIAMA)(45)	1272	Maternal allergic disease	HDM reduction: covers vs placebo vs none	4	Current wheeze: 5.7 vs 5.2% RR 1.2 (0.7–2.0) (HDM levels reduced)
		Marks 2006 (Australia)(46)	616	At least 1 parent with asthma	HDM reduction: cover & arachnicide	5	HDM positive: 36.4 vs 31.5% RR 0.87 (0.67 - 1.11, p=0.3) Atopic: 46.8 vs 42.0% RR 0.90 (0.74-1.10, p=0.3) (Reduced HDM levels)	Marks 2006 (Australia)(46)	616	At least 1 parent with asthma	HDM reduction: cover & acaricide	5	Probably current asthma: 23.1 vs 20.7% RR= 0.90 (0.65 to 1.24), p=0.6 (reduced HDM levels)
		Arshad 2002 (Europe,	242	5-7y. FHx, positive	HDM avoidance: impermeable	6-8	HDM sensitisation 9.4 vs 2.6%						

		SPACE)(47)		SPT (not HDM)	mattresses		OR 0.14 (0.03-0.79, p=0.03). NNT 15. (HDM levels reduced)						
		Tsitoura 2002 (Europe, SPACE)(48)	636	<5y. 1 parent with atopic symptoms & sensitisation	HDM avoidance: impermeable mattresses & education	1y follow up (mean age 3y)	HDM sensitisation 6.5 vs 3.0% Adj RR 0.36 (0.16-0.83)						
	MULTIFACETED	B						D					
		Scott 2012 (UK, IoW)(12)	120	2x 1st relative with allergic disease or 1 plus ↑ cord IgE, prenatal recruitment	↓ HDM breast/ eHF & delayed solids	18	HDM sensitisation: 41.8 vs 29.2%, p=0.18 Atopic: 50.9 vs 43.8%, p=0.47 (significantly reduced up to 8y) (HDM levels reduced) Persistent HDM sensitization reduced: 30.9 vs 12.5 %, p=0.02	Scott 2012 (UK, IoW)(12)	120	2x 1st relative with allergic disease or 1 plus ↑ cord IgE, prenatal recruitment	↓ HDM Diet & breast/ eHF	18	Current asthma: 25.9 vs 10.7% P=0.04 (reduced HDM levels) Atopic asthma: 23.6 % vs 8.3 %, p=0.04
		Chan-Yeung2005 (Canada, CAPS)(49)	616	1 parent or sib with asthma	↓HDM, pets, ETS Breast feeding encouraged, pHF, solids delayed	7	Atopic: 41.6 vs 49.0% RR 1.23 (0.80-1.90, p=0.35) (similar results at 1 year)	Chan-Yeung 2005 (Canada)(49)	616	1 parent or sib with asthma.	↓HDM, pet allergen, ETS Breast feeding encouraged, pHF, solids delayed	7	Wheeze without colds & BHR: 25.0 vs 12.9% RR 0.39 (0.22-0.71, p=0.002)
								Maas 2011 (PREVASC) (50)	476	1st relative with asthma, prenatal recruitment	HDM (covers), pet, ETS Breast / hypoallergenic formula 6m	6	No difference in allergic asthma (OR 1.01, 0.58-1.76) (reduced allergen levels)