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Primary prevention of asthma and allergy

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The relentless increase in the prevalence of asthma and allergic diseases highlights the need for devising effective preventive strategies. Although the genetics of these disorders are being investigated, manipulation of known environmental risk factors remains the best available approach to this problem. However, the large number of potential environmental risk factors and our inability to accurately predict the development of asthma and allergy has led to conflicting data from recent prevention studies. Nonetheless, some useful recommendations can be made. Exclusive breast-feeding and avoidance of exposure to environmental tobacco smoke exposure can be safely recommended for the whole population, not only for prevention of allergy but also for other known benefits. Additionally, for children at high risk of allergy, maternal exclusion diet during lactation and protein hydrolysate as a supplement or alternative for children who could not be breast-fed seems to provide further protection. The preventive effect of avoidance of house dust mite allergen alone during pregnancy or after birth is disappointing. However, prospective randomized studies evaluating a combined food and house dust mite allergen avoidance regimen show some protection against atopic dermatitis in infancy and asthma in later childhood. Urgent research is needed to accurately identify children at high risk and to test novel preventative measures with the potential for immunomodulation. Further randomized controlled trials are also needed with long-term follow up to evaluate combined approaches that might provide maximum benefit. (*J Allergy Clin Immunol* 2005;116:3-14.)

Key words: *Asthma, allergy, atopy, prevention, allergen avoidance, house dust mite*

There has been a dramatic increase in the prevalence of asthma and other allergic diseases over the last few decades. They are now major public health problems¹ and are an enormous burden on health care resources.² Importantly, severe asthma and systemic allergic reactions are potentially life-threatening conditions. Additionally, these diseases adversely affect the quality of life of millions of children and adults. There is an urgent need

Abbreviations used

ETS: Environmental tobacco smoke
HDM: House dust mite
PUFA: Polyunsaturated fatty acid
RCT: Randomized controlled trial

to formulate strategies leading to a reduction in morbidity and mortality from asthma and allergy. This can be achieved through either primary or secondary prevention, and improved efforts in both these areas are essential (Table I).

Common clinical manifestations of allergy include asthma, allergic rhinitis, atopic dermatitis, and food allergy. Subjects with allergic diseases are often atopic, manifested by sensitization to common allergens. However, atopy is only one of many factors involved in the pathogenesis of these disorders. The contribution of atopy and atopy-related genes might vary with the disease in question. For example, atopy plays a dominant role in IgE-mediated food allergy, such as peanut allergy, but alternate immunologic pathways, driven directly by T lymphocytes, assume significance in conditions such as nonatopic asthma. Allergic diseases are polygenic, with several genes on different chromosomes involved in the genesis of these disorders. However, the phenotypic expressions, manifesting in clinical disorders, require an interaction of genes with environmental factors. Genetic manipulation to prevent these disorders is not yet in sight, and recent increases in prevalence argue strongly for a significant role of environmental factors. These factors might increase or decrease the risk of allergy development, and some might be amenable to manipulation. We thus have to rely on identification and removal of environmental risk factors in an attempt to stem and reverse the rising trends in allergy. A number of risk factors have been identified, including early feeding, diet, infections, allergens, pollutants, and tobacco smoke.

RISK FACTORS

During early infancy, the child is exposed to small quantities of a variety of food proteins through breast milk and larger quantities of cow's milk protein if formula fed. The normal response to the initial introduction of these

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TABLE I. Definitions

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- **Allergy:** Clinical manifestations of immunologically mediated reactions to foreign substances, usually proteins.
 - **Atopy:** The genetic propensity to produce IgE antibodies after exposure to allergen. This can be confirmed by means of skin prick test or measurement of specific IgE antibodies in the serum (allergic sensitization).
 - **At-risk population:** Those who have a genetic predisposition and are at higher risk of development of allergic diseases. At present, this is usually assessed through family history of allergy, presence of other allergic diseases, or allergic sensitization.
 - **Primary prevention:** Preventing the development of allergic manifestations, such as asthma, allergic rhinitis, or atopic dermatitis.
 - **Secondary prevention:** Prevention of symptoms, exacerbation, or lung function deteriorations in those who already have an allergic disease.
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proteins is immune tolerance. However, in children with atopic predisposition, this immune tolerance breaks down. Thus sensitization to foods such as cow's milk and egg is common in infancy, and in a subset of these children, clinical allergic reactions occur that manifest in the form of skin rash—urticaria, gastrointestinal manifestations, atopic dermatitis, and occasionally systemic allergic reactions. It has been proposed that early introduction of allergenic foods might promote the development of allergy, whereas later introduction might induce tolerance.³ Thus prevention of food allergy could be achieved by altering the dietary pattern of the at-risk infant.

Exposure to aeroallergens might be relevant to the development of respiratory allergy.^{4,5} The specific type of aeroallergens varies according to the socioeconomic situation. For example, house dust mite (HDM) is the most important allergen in humid climates, pet allergens might be more relevant in cold countries, *Alternaria* species assume significance in dry climates, and cockroach might be the dominant allergen in inner-city areas. Previous efforts at primary prevention have largely focused on reduction of exposure to HDM allergen.

The hygiene hypothesis proposes that exposure to certain infections and vaccines might influence the direction of immune responses and protect against the development of atopy.⁶⁻⁸ However, not all infections are protective. Recurrent lower respiratory tract infections in early childhood are a recognized risk factor for asthma in later childhood.⁹ The most common respiratory pathogen in infancy is respiratory syncytial virus, and this has been linked to later development of wheeze, asthma, and airways obstruction.¹⁰⁻¹²

Maternal smoking during and after pregnancy promotes sensitization and the development of asthma.¹³ However, Tariq et al¹⁴ suggested that maternal smoking is predominantly a risk factor for early childhood wheeze and nonatopic asthma. A number of studies have supported the link between exposure to environmental tobacco smoke (ETS) and development of wheeze and asthma during childhood.¹³⁻¹⁵ Similarly, dietary factors, such as antioxidants (vitamin C and E and selenium), magnesium,

sodium, and omega-3 fatty acids, might affect the development of allergic diseases.¹⁶⁻¹⁸

WHAT ARE WE TRYING TO PREVENT?

Allergic manifestations are protean, and there is a lack of uniformity in definitions of outcome measures used in various studies. The definition and diagnosis of asthma and rhinitis in early childhood is most challenging in view of the lack of uniform criteria and availability of objective tests to support the diagnosis. Another complication is that early childhood allergic manifestations are often transient, and yet many studies report short-term (<5 years) follow-up periods. Most studies suggests that an intervention such as exclusive breast-feeding prevents wheeze in early childhood,¹⁹ but recently, it has been reported that it might increase the risk of asthma in early adult life.²⁰ Thus if short-term follow-up studies defined early childhood wheeze as asthma, the same intervention can have positive or negative outcomes. Further confusion arises when there is a discrepancy between the effects of preventive measures on subjective (symptoms and diagnosis) and objective (allergic sensitization, airway obstruction on lung function, and bronchial hyperresponsiveness) manifestations of asthma and allergy. Some studies have attempted to prevent allergic sensitization as the principal outcome, but this might not necessarily have the desired effect of reducing clinical allergic disorders. There might also be a differential effect of the chosen intervention on the type of allergic manifestation. For example, dietary modifications, such as avoidance of cow's milk, might prevent cow's milk allergy and perhaps atopic dermatitis but might not influence allergic rhinitis or asthma, and the reverse might be true for aeroallergen avoidance. It is therefore important that each randomized controlled trial (RCT) in primary prevention should have predefined specific outcomes, use standardized definitions as far as possible, and plan to follow-up children for an appropriate period depending on the outcome being tested.

PREVENTIVE STRATEGIES: ALLERGEN AVOIDANCE, DIETARY MANIPULATION, INFECTIONS-ENDOTOXIN, IMMUNOTHERAPY, AND DRUGS

Although there is good evidence that allergen exposure leads to sensitization^{21,22} and that sensitization is an important risk factor for the development of allergic disease,^{23,24} the direct relationship of allergen exposure in the causation of allergic disease is still questioned.²⁵ The effect of exposure to allergen might depend on the nature of allergenic protein. Exposure to HDM is reported to cause asthma,^{26,27} whereas dog or cat allergen exposure might be protective,²⁸⁻³⁰ although there remains some controversy regarding this issue.³¹ It is also not

clear whether any protective effect of pet exposure is due to induction of tolerance mechanisms (eg, modified T_H2 response) or a concomitant increased exposure to infections or endotoxin.³² In view of these conflicting reports, should we even be attempting to use allergen reduction as a strategy for primary prevention? That reduction in allergen exposure can lead to primary prevention of a specific allergy is exemplified by latex allergy. During the last decade, the incidence of latex allergy has decreased sharply with the increase in the use of latex-free gloves.³³

WHOLE POPULATION OR AT-RISK INDIVIDUALS

Because primary prevention measures require motivation, effort, and expense, most studies have targeted infants at high risk of allergy to maximize the benefit.³⁴⁻³⁷ Until children can be screened for specific genes with more accurate prediction for future development of asthma and allergy, family history of allergy is often relied on to identify children at high risk. Although family history of allergy is a well-known risk factor, it remains true that the majority of asthmatic children are from families with no asthma, and the same is true for atopic dermatitis and allergic rhinitis.^{38,39} During the 1980s, it was proposed that the level of IgE at birth (cord blood IgE) could more precisely indicate the risk of future allergic disease. However, cord blood IgE has low sensitivity for prediction of allergy in general,⁴⁰ and it might predict allergic sensitization but not clinical allergic disease.^{38,41} Despite these observations, in an attempt to include children at very high risk of allergy, some studies have combined high cord IgE levels and family history of allergy in selecting children suitable for preventive measures.⁴² Egg sensitization in early childhood has been shown to predict respiratory allergy. However, its sensitivity as a predictive marker is poor, and it cannot be usefully used to identify children at high risk.⁴³ Other biomarkers, such as serum eosinophil cationic protein, urinary eosinophil protein X, and various cytokines, have not proved to be reliable predictive markers.⁴⁴

The Study on Prevention of Allergy in Children in Europe selected school-aged (6-8 years old) children for primary prevention of HDM sensitization and asthma on the basis of a positive family history of atopy plus sensitization to other allergens but not HDM. Children can also be selected on the basis of having one allergic disease and are thus at a higher risk of having another. For example, children with atopic dermatitis in early childhood and allergic rhinitis in later childhood are at increased risk of asthma.⁴⁵

For any prevention program, the population to be targeted would eventually depend on the safety and cost of the measure being recommended and whether there are any advantages for the low-risk population. For example, breast-feeding and avoidance of ETS are safe and inexpensive and have other advantages apart from possible

prevention of allergic diseases. Therefore these measures can and should be recommended for the whole population, even in the absence of convincing evidence for allergy prevention from RCTs. Other measures, such as maternal avoidance of allergenic foods, might not be completely safe, require convincing evidence, and might be suitable for only the high-risk population.

WHEN: PREGNANCY, INFANCY, LATER CHILDHOOD, OR ADULT

The onset of allergic manifestations is usually during early childhood. Hence primary prevention efforts have to commence soon after birth or preferably during pregnancy. Animal models support the hypothesis that contact with an allergen early in life induces a state of general immune hyperresponsiveness, with increased production of specific IgE antibodies.⁴⁶ Pregnancy is a T_H2 environment with predominance of T_H2 -type cytokines. After birth, the immune system matures to achieve a balance between T_H1 and T_H2 cytokine responses.⁴⁷ However, in children with atopic heredity, this balance might never be achieved, and a T_H2 predominance persists, leading to sensitization and allergic diseases. Thus a window of opportunity exists in early life (infancy and early childhood), when manipulation of the environment in children with atopic heredity might restore the balance. The T_H1/T_H2 hypothesis has recently been challenged, and immune tolerance-suppression might involve regulatory T cells.⁴⁸ Whatever the precise mechanism, it is generally agreed that primary prevention strategies have to focus on early childhood, before the immune system matures and exposure to allergens leads to sensitization.

Observational studies have suggested that an intense exposure to a particular allergen, such as birch pollen, during pregnancy could increase the risk of offspring being sensitized to that allergen and having allergic asthma.⁴⁹ It is now known that allergens can pass through the placenta and sensitize the fetus.^{50,51} A number of studies have shown that cord blood mononuclear cells recognized food and inhalant allergenic epitopes and respond to stimulation by proliferation.⁵² It has been suggested that exposure to β -lactoglobulin and ovalbumin during fetal life might influence the direction of immune responses such that there will be reduced T_H1 -type cytokine releases, such as IFN- γ , in turn increasing the risk of allergic diseases.⁵³ It is therefore argued that fetal exposure to allergens should be minimized to protect the developing immune system. This begs the question of whether preventive measures should be instituted before birth. However, in the Childhood Asthma Prevention Study investigators were unable to demonstrate a correlation between maternal exposure to HDM allergen and cord blood mononuclear cell cytokine responses, arguing against a beneficial effect of maternal HDM allergen avoidance.⁵⁴ Indeed, in a rat model Melkild et al⁵⁵ argue that exposure to allergen early in pregnancy might favor the development of tolerance, with increased production of IgG2a antibodies and suppression of specific

IgE antibodies. However, there is good evidence that smoking during pregnancy increases the risk of childhood asthma and adversely affects lung function.^{56,57} Use of drugs, such as paracetamol and dietary constituents, during pregnancy might also influence the development of asthma in the offspring.^{58,59} Thus in principal primary prevention should start as early as possible during pregnancy. The specific recommendations, however, should not be made until the evidence and risk/benefit ratio have been carefully considered.

PREVENTATIVE STRATEGIES

The identification of risk factors, such as allergen exposure, has led to evaluation of various strategies for primary prevention. The conclusive proof of effectiveness requires well-designed double-blind RCTs. However, this is not always possible. For example, the effect of breast-feeding or maternal smoking cannot be tested by means of RCTs for ethical reasons. Blinding might not be possible for practical reasons (eg, when testing the effect of exposure to pet allergens).

Food allergen avoidance

Avoidance of cow's milk protein with exclusive breast-feeding (with or without maternal avoidance of allergenic foods) or hydrolyzed formula has been suggested for infants at risk of allergy. It has also been proposed that introduction of other highly allergenic foods, such as eggs and nuts, to the infant is delayed.

Exclusive breast-feeding. The extent of the preventive effect of breast-feeding on allergic diseases remains controversial. Exclusive breast-feeding does seem to prevent wheeze and atopic dermatitis during early childhood.^{19,60} However, long-term prospective studies have produced conflicting data. A relatively small study of at-risk children with 15 years' prospective follow-up did show a reduction in allergic manifestations in the breast-fed children compared with those fed cow's milk or soya milk.⁶¹ However, several large observational studies failed to show a long-term protective effect of exclusive breast-feeding on asthma or other allergic manifestations.^{9,20,62} Two systematic reviews on this subject reached the conclusion that exclusive breast-feeding does seem to have some protective effect on the development of allergy.^{63,64} This effect might be due to avoidance of cow's milk protein allergen, other dietary constituents of breast milk, an immunomodulatory effect, or a combination of these. It was recently suggested that the effect of exclusive breast-feeding might be dependent on atopic heredity. Those with a genetic predisposition had a lower incidence of sensitization and allergic rhinitis, whereas children without such a predisposition had an increased risk.⁶⁵ In this issue of the Journal, another article discusses this subject in more detail.⁶⁶

Hydrolyzed milk formulae. In an attempt to avoid exposure to cow's milk protein early in life, hydrolyzed (casein or whey) formulae are suggested as a replacement for or supplement to breast-feeding. A number of RCTs

have been done over the last 2 decades to assess the preventive effect of replacing cow's milk formula with hydrolysate or soy milk formulae. Chandra et al^{67,68} compared the development of allergic diseases (asthma, atopic dermatitis, and food allergy) in groups of children fed breast milk, hydrolyzed formula, cow's milk formula, and soy formula. A significant preventive effect of breast milk and partially hydrolyzed formula was shown consistently up to the age of 5 years. Another study, this one comparing cow's milk formula and whey hydrolysate, shows a reduction in cow's milk allergy and atopic dermatitis in the first year.⁶⁹ In a study by Marini et al,⁷⁰ exclusive breast-feeding combined with hydrolysate supplementation led to a significant reduction in various allergic manifestations up to the age of 3 years. Another RCT showed prevention of atopic dermatitis, but not asthma, with the use of hydrolysate formula.⁷¹

Proteins can be extensively or partially hydrolyzed in the infant formulae. For secondary prevention, in children with cow's milk allergy, it is generally agreed that only extensive hydrolysate should be used to avoid any reaction in highly sensitized infants. There is some controversy regarding the extent of hydrolysis needed for primary prevention. In an RCT use of partially hydrolyzed formula during the first few months of life in genetically at-risk infants reduced the prevalence of atopic dermatitis, but not wheeze, in the first 2 to 3 years of life.⁷² The German Infant Nutritional Intervention Study compared the preventive effect of 3 hydrolyzed formulas (partially hydrolyzed whey formula, extensively hydrolyzed whey formula, and extensively hydrolyzed casein formula), with cow's milk formula-fed children as control subjects. The incidence of allergic manifestations, such as atopic dermatitis, food allergy, or allergic urticaria, was significantly reduced by using an extensively hydrolyzed casein formula compared with a cow's milk formula. There was also some protective effect of partial (but not extensive) whey hydrolysate on reduction of atopic dermatitis.⁷³ However, other RCTs indicate a greater preventive effect of extensively hydrolyzed milk compared with partially hydrolyzed formula on allergic manifestations, particularly cow's milk allergy.^{74,75} Overall, it seems that protein hydrolysate reduces allergic manifestations during the first 2 to 3 years of life in children at high risk of atopy, as a supplement or alternative to breast-feeding.⁷⁶ These hydrolysates have been shown to be nutritionally adequate of the needs of the infant.⁷⁷ However, these have not been shown to be superior to exclusive breast-feeding. There remains some uncertainty as to the superiority of extensive versus partial hydrolysate in primary prevention.⁷⁸ Most studies found that soy formula do not protect against allergy in high-risk infants.⁷⁹

Maternal avoidance diet during pregnancy. Several studies have investigated the preventive effect of maternal avoidance of highly allergenic foods, such as cow's milk, egg, and nuts, during pregnancy to protect the fetus from the effect of food allergens ingested by the mother. An RCT showed that maternal diet (excluding cow's milk and egg) during late pregnancy does not protect against the

development of allergic manifestation in genetically predisposed children.^{80,81} Additionally, there was some concern regarding maternal and fetal weight gain. Zeiger et al⁸² evaluated the effect of maternal avoidance of allergenic food (cow's milk, egg, nuts, fish, and soy) during late pregnancy and lactation, supplementation with extensive hydrolysate, and avoidance of solids up to 6 months. There was a reduction in food sensitization on skin prick tests, food allergic manifestations, and atopic dermatitis at the age of 2 years. However, no long-term benefit beyond early childhood was observed.⁸³ Weight gain during the third trimester was again a concern in mothers who practiced an avoidance diet.

Maternal avoidance diet during lactation. In an RCT maternal avoidance of highly allergenic food (dairy produce, egg, fish, peanut, and soy) during lactation led to a reduction in the prevalence of atopic dermatitis at 18 months in high-risk infants.⁸⁴ In a Japanese study infants in the intervention group were exclusively breast-fed or given whey hydrolysate, whereas the lactating mothers were given the same whey hydrolysate as the only source of protein. These infants were compared for the development of allergy with 2 other groups of children. One group was breast-fed with the mother consuming cow's milk, whereas in the third group infants were given cow's milk formula. The active group infants showed lower incidence of atopic dermatitis and cow's milk allergy.⁸⁵ In another RCT maternal avoidance diet (cow's milk, egg, and fish) during the first 3 months of lactation reduced atopic dermatitis in early childhood, but there was no long-term benefit.^{86,87} Herrmann et al,⁸⁸ however, failed to show a protective effect of maternal avoidance diet (cow's milk and egg) during late pregnancy and lactation. Although a maternal avoidance diet during lactation is difficult to adhere to, none of the studies reported any adverse nutritional effects for mother or child. A Cochrane database review concluded that restricting maternal diet during pregnancy does not prevent allergy and might have adverse consequences for maternal nutrition, fetal nutrition, or both. However, maternal food allergen avoidance during lactation might be of some benefit.⁸⁹

Late introduction of solid foods. Some observational studies have supported the concept that introduction of solid foods before the age of 4 months might increase the risk of atopic dermatitis in genetically predisposed children.⁹⁰ However, other studies could not find a beneficial effect of late introduction of solid foods.^{60,91} Most intervention studies have combined late introduction of solids with other intervention measures, and thus it is difficult to know whether this strategy alone has any protective effect.^{42,82}

HDM avoidance

In view of the link between exposure to HDM and development of asthma suggested by several cross-sectional and prospective studies, there has been an attempt to reduce at-risk children's exposure to HDM allergen.^{5,26,27} Three large prospective studies have instituted HDM avoidance measures during pregnancy, at birth, and later

in childhood and assessed children for asthma and allergic manifestations (Table II).

Study of Prevention of Allergy in Children in Europe. The Study of Prevention of Allergy in Children in Europe was designed to assess the effect of simple HDM avoidance measures, such as mattress covers, and a set of environmental educational advice on the development of sensitization to HDM and allergy manifestations. The researchers recruited 3 cohorts of children (newborns, toddlers [2-4 years], and school-aged children [5-7 years]) at high risk of sensitization to HDM. In the newborn cohort, sensitization, particularly to HDM, was reduced in the intervention group children at 1 year, but this effect was lost by the age of 2 years. Moreover, no difference was observed in clinical allergic manifestation between the 2 groups.^{37,92} In the toddler⁹³ and school-aged children cohorts,⁹⁴ a reduction in the incidence of sensitization to HDM was observed at 1 year but not in the occurrence of allergic manifestations. This study provides evidence that allergen avoidance could protect at-risk children against sensitization to that allergen, even in later childhood. However, this might not protect children from clinical allergic manifestations. Further follow-up of the toddler and school-aged children will determine whether reduction in allergen sensitization is sustained and whether this translates into reduced occurrence of clinical allergy.

Manchester Asthma and Allergy Study. The Manchester Asthma and Allergy Study used extensive environmental control measures during pregnancy and infancy. These included impermeable mattress covers on parental beds from the second trimester of pregnancy, mattress covers for children's beds, hardwood flooring in bedrooms, use of high-efficiency particulate air filter vacuum cleaners, and application of antimite foam, benzyl benzoate (Allergopharma, Reinbek, Germany), on soft furnishings to reduce dust mite numbers and allergen. A highly significant reduction in exposure to dust mite, cat, and dog allergens was achieved.^{36,95} At age 1 year, there was no difference in mite sensitization, mild wheeze, or cough or atopic dermatitis. There was, however, a significant reduction in the occurrence of severe wheeze in the intervention group infants.⁹⁶ Further follow-up of this cohort will provide useful information.

Prevention and Incidence of Asthma and Mite Allergy. The Prevention and Incidence of Asthma and Mite Allergy study evaluated the effectiveness of HDM avoidance measures, including allergen-impermeable (intervention group) and placebo (control group) mattress encasings, in the children's and parent's beds before birth and during the first year of life. Although HDM allergen levels were reduced in the intervention group,⁹⁷ there was no difference in the development of atopy or asthma. At age 2 years, the only difference seen was a slight but significant reduction in nighttime cough in children in the active group.^{98,99}

Multiple interventions

The Isle of Wight prevention study. This RCT evaluated the effect of a combined food and HDM allergen avoidance regimen implemented from birth up to the age

TABLE II. Cohort intervention studies (RCTs) with HDM allergen avoidance alone or in combination with dietary measures

Study	Number	Intervention started at:	Intervention	Main outcome measures	Reported follow-up and outcome showing significant reduction in:
Study of Prevention of Allergy in Children of Europe, 3 cohorts: newborn, toddler, school children ^{37,92-94}	Newborn: 696	Birth	HDM avoidance measures: mattress covers (infant and parent's beds) and general advice	• Allergic sensitization	• 1 y: allergic sensitization • 2 y: no effect
	Toddler: 636	2-4 y	Mattress covers and general advice	• Allergic sensitization	• 1 y: allergic sensitization
	School children: 242	5-7 y	Mattress covers and general advice	• Allergic sensitization	• 1 y: allergic sensitization
Manchester Asthma and Allergy Study ^{36,95,96}	620	Prenatal	Extensive HDM avoidance measures included mattresses covers, HEPA filter, hardwood flooring, and use of Acarosan	• Allergic sensitization • Wheeze • Airway resistance (sRaw)	• HDM allergen levels • 1 y: only severe wheeze
Prevention and Incidence of Asthma and Mite Allergy ⁹⁷⁻⁹⁹	810	Prenatal	HDM avoidance measures: mattress covers and general advice	• Total IgE • Specific IgE • Cough, wheeze • Atopic dermatitis	• HDM allergen levels • 2 y: nocturnal cough
Isle of Wight prevention study ^{34,42,100,101}	120	Birth	Food and HDM mite allergen avoidance	• Allergic sensitization • Asthma • Allergic rhinitis • Atopic dermatitis • Food allergy	• HDM allergen levels • 1 y: asthma, atopic dermatitis, and allergic sensitization • 2 y: atopic dermatitis and allergic sensitization • 4 y: atopic dermatitis and allergic sensitization • 8 y: asthma and allergic sensitization
Canadian Asthma Primary Prevention Study ^{35,103}	545	Prenatal	Dietary and environmental avoidance	• Allergic sensitization • Asthma • Allergic rhinitis	• HDM allergen levels • 1 y: asthma and allergic rhinitis • 2 y: asthma
Prevention of Atopic Allergy ¹⁰²	531	Birth	Dietary and environmental avoidance	• Asthma • Atopic dermatitis • Rhinitis • Urticaria	• 4 y: any allergy (including asthma, atopic dermatitis, rhinitis, and urticaria)
Childhood Asthma Prevention Study ^{104,105}	616	Prenatal	• HDM avoidance group • Diet (omega-3 fatty acid supplementation) group • Combined intervention	• Cough, wheeze • Asthma • Allergic sensitization • Total IgE	• 1.5 y: Diet group: wheeze; HDM group: no effect • 3 y: Diet group: cough; HDM group: sensitization to HDM

HEPA, High-efficiency particulate air.

of 1 year in at-risk children (on the basis of family history and high cord IgE levels). Children were exclusively breast-fed, with maternal avoidance of highly allergenic foods, extensive hydrolysate used as a supplement or alternative to breast milk, and delayed introduction of

solid foods. Environmental control measures included polyvinyl mattress covers and antidust mite spray, resulting in significant reduction of dust mite allergen in the intervention group. There was a sustained reduction in sensitization to most allergens, including HDM, up to the

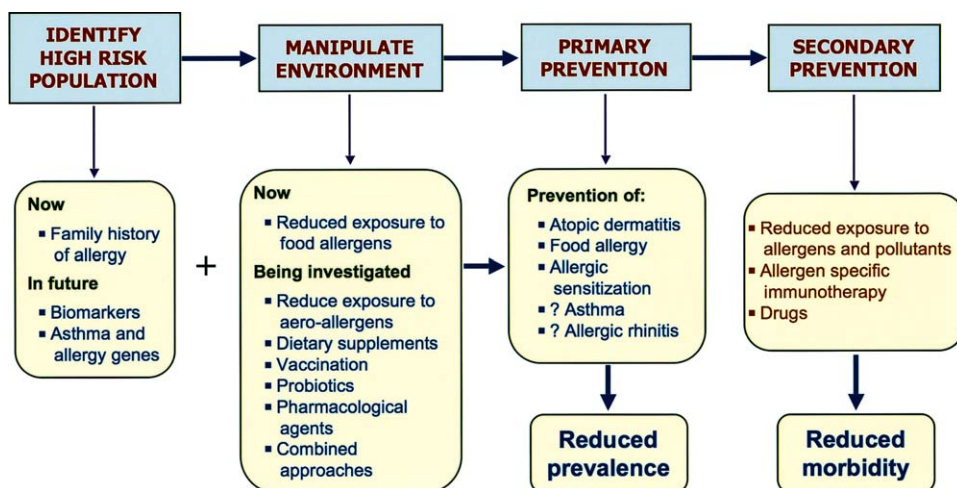


FIG 1. Schematic diagram of steps for primary and secondary prevention.

reported last follow-up at the age of 8 years. The intervention group children also showed a significant reduction in the prevalence of asthma and atopic dermatitis at 1 year,⁴² atopic dermatitis at 2 and 4 years,^{100,101} and asthma at 8 years.³⁴ This study supports the hypothesis that strict food and aeroallergen avoidance in infancy in high-risk children might reduce the development of allergic sensitization, leading to less atopic dermatitis in infancy and asthma in later childhood.

Prevention of atopic allergy. Bruno et al¹⁰² reported 48-month follow-up of a multicenter study of allergy prevention in 513 at-risk children (on the basis of family history). The intervention group children, after a program of reduction in food allergen (exclusive breast-feeding or soya formula) and environmental exposure (house dust and ETS), were found to have significantly less cumulative prevalence of allergic manifestations (asthma, rhinitis, atopic dermatitis, and urticaria).

The Canadian Asthma Primary Prevention Study. This study used a multifaceted program of intervention, including breast-feeding, delayed introduction of solids, reduction of HDM and pet allergen exposure, and ETS in at-risk infants (on the basis of family history). This RCT showed a reduction in asthma and wheeze, but not atopy, up to the age of 2 years.^{35,103} However, the follow-up at present is too short to say whether it is early transient wheeze or asthma that is being prevented.

Childhood Asthma Prevention Study. The Childhood Asthma Prevention Study was designed to assess the benefit of omega-3 polyunsaturated fatty acid (PUFA) supplementation, HDM allergen avoidance, or a combination of these strategies. Outcome data at the age of 18 months indicate a possible protective effect of dietary supplementation on wheeze, but not atopy. No benefit of HDM allergen avoidance was demonstrated at this age, and there was no synergistic effect with dietary supplementation.¹⁰⁴ At 3 years of age, a modest reduction was seen for cough, but not wheeze, in the diet group and HDM sensitization in the allergen avoidance group.¹⁰⁵

Although the study was reported as showing benefit, the outcome is disappointing. For example, 14 children needed to avoid HDM allergen to prevent sensitization in 1 child, and 10 children should be given dietary supplement of omega-3 fatty acid to prevent cough in 1 child.

Other strategies for primary prevention

Diet. Some observational studies link intake of antioxidants, such as vitamins C and E and selenium, and vitamin A with the occurrence of atopy and asthma.⁵⁹ However, RCTs fail to show a benefit of supplementation with these vitamins in asthmatic patients.¹⁸ The primary preventive effect of antioxidant supplementation with RCT has not been studied. Observational studies consistently show a protective effect of omega-3 polyunsaturated fatty acids (omega-3 PUFAs) and an increased risk with high intake of omega-6 PUFAs.⁵⁹ Thus dietary modifications of supplementation with fish oil, rich in omega-3 PUFAs, might be of some benefit. A prospective observational study indicated that introduction of fish into the infant's diet reduces occurrence of rhinitis but not asthma.¹⁰⁶ An RCT of fish supplementation during pregnancy indicated possible reduction in cytokine responses and allergic manifestations (skin test positivity and severity of atopic dermatitis).¹⁰⁷ Supplementation with gamma-linolenic acids during the first 6 months of life might reduce the severity of atopic dermatitis, but no effect on incidence of atopic dermatitis or serum IgE was observed.¹⁰⁸ This subject is dealt with in more detail elsewhere in this issue of the Journal.¹⁰⁹

Exposure to endotoxin. Atopy is mediated by T_H2-type immune responses. The hygiene hypothesis proposes that stimulation of T_H1 cells by infections, vaccinations, or endotoxin exposure early in life redresses the T_H1/T_H2 balance and thus protects against atopy and allergic manifestations. Several epidemiologic studies provide evidence to support this notion,^{110,111} but others could not find a protective effect of recurrent infections¹¹² or

endotoxin exposure.¹¹³ Moreover, randomized clinical trials to prove the effectiveness of this approach are lacking.

Probiotics. In an RCT *Lactobacillus* GG given during pregnancy to mothers with a family history of atopy and for 6 months to their infants resulted in significant reduction in the occurrence of atopic dermatitis up to the age of 2 years.^{114,115} Further details of this important strategy are provided in a separate article in this issue of the Journal.¹¹⁶

Vaccination. Vaccination against bacterial and viral diseases is often given in early childhood. There is some evidence to suggest that it might influence the development of allergy. For example, BCG vaccination, by stimulating T_H1 immune responses and altering the T_H1/T_H2 balance, might reduce the development of allergic sensitization in developing countries.¹¹⁷ However, this might not be true for western populations.¹¹⁸ No clinical trials have been done to assess the immunomodulatory effect of vaccination in primary prevention of allergy.

Allergen Immunotherapy. Specific allergen immunotherapy in children with respiratory symptoms and mono-sensitization (sensitized to only one allergen) reduces the development of new sensitization compared with those who are treated with medications only.^{119,120} Whether this would protect children from having other allergic manifestations is not known. Subjects with allergic rhinitis are at a higher risk of asthma development. There is some evidence to suggest that subsequent development of asthma in those with allergic rhinitis can be prevented by using allergen immunotherapy at an early stage.¹²¹⁻¹²³

Drugs. In an RCT ketotifen was reported to significantly reduce the development of asthma in children with atopic dermatitis.¹²⁴ More recently, cetirizine was reported to reduce the development of asthma in children with atopic dermatitis who were sensitized to HDM or grass pollen.¹²⁵

Occupational asthma. We should keep in mind that the best approach to manage occupational asthma is primary prevention (ie, reduction in exposure to occupational allergens in all susceptible individuals).¹²⁶ Problems in this area include measurement of airborne allergens in the workplace and defining the safe level of exposure. However, reduction in exposure can be achieved through the use of alternative and less-sensitizing agents, automation or modification of a process known to cause sensitization, and use of personal protective devices.

Secondary prevention of asthma and allergy

Secondary prevention of asthma and allergy with HDM avoidance measures remains a contentious issue. Studies showing a beneficial effect and those unable to find a benefit continue to appear in the literature.^{127,128} A number of RCTs have shown that HDM avoidance is effective in the secondary prevention of atopic dermatitis.¹²⁹ Allergen avoidance should remain an essential part of the management of allergic diseases, even if the

benefit of mattress covers is in doubt.¹²⁸ A separate article in this issue of the Journal deals with this subject.¹³⁰

SUMMARY (FIG 1)

What we do know

- Exposure to ETS, especially during pregnancy and early childhood, increases the risk of childhood wheeze and asthma, and avoidance of exposure to ETS must be included in all preventive advice.
- Maternal avoidance of allergenic foods during pregnancy does not work and could be harmful.
- Breast-feeding for 4 to 6 months protects against the development of early childhood wheeze and atopic dermatitis, but there is no evidence of a long-term benefit.
- Maternal avoidance of allergenic foods during lactation might have some additional protective effect on reduction of cow's milk allergy and atopic dermatitis. However, this should only be undertaken by highly motivated mothers with a high risk of allergy in the offspring and under strict dietary supervision.
- Convincing proof for the preventive effects of the delayed introduction of solid foods is lacking.
- Use of hydrolyzed milk formula shows a preventive effect on cow's milk allergy and atopic dermatitis.
- The evidence to support a preventive effect of HDM allergen avoidance for the development of sensitization to HDM or respiratory allergy is not compelling. It might be that current methods of allergen reduction are not effective, that reduction in HDM allergen exposure alone is not sufficient, or that allergen-induced inflammation is only one of many different pathways for allergy development. Results from further follow-up of the current large RCT are awaited.
- A strategy of combining food and aeroallergen avoidance seems effective in reducing early childhood wheeze and atopic dermatitis and later childhood asthma. Further follow-up of current RCTs might provide more definitive information.
- There is some evidence that probiotics might be useful in preventing atopic dermatitis.

What we need to know

- We do not know how best to identify the at-risk population, which would include most children destined to become allergic. Further research in the genetics of asthma and allergy hold promise.
- More evidence for the optimal time-age to implement preventive measures is required. Thus far, a clear benefit of prenatal intervention is not forthcoming (except smoking). Most prevention studies have focused on early childhood. However, new onset of asthma and allergic rhinitis is common in later childhood and early adult life. Prevention might still be possible in this age group, with the added advantage of more accurate identification of at-risk individuals

(eg, those with transient early childhood wheeze, atopic dermatitis, or allergic sensitization).

- Further research to evaluate the influence of exposure to pet allergens on the development of the immune system in early childhood is needed. Until then, no advice can be given regarding exposure to animal allergen for primary prevention.
- No RCTs have yet been done on the primary preventive effect of specific reduction in cockroach or mold allergen.
- Although there is evidence from epidemiologic and cross-sectional studies of a link between various dietary constituents and asthma, RCTs to assess the preventive effect are either not available or fail to show a convincing benefit.
- More research is needed to develop and test novel immunomodulatory agents, such as probiotics, vaccination, and pharmacologic agents.
- Combined strategies, such as allergen avoidance with dietary manipulation or pharmacologic intervention, need further evaluation.
- It might be that individuals with different risk profiles require different preventive strategies. Thus in the future, a child could be screened for identification of his or her risk profile (genetic and likely environmental factors), and an appropriate preventive strategy could be recommended.

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