

Possible Reasons for Lack of Effect of Allergen Avoidance in Atopy-Prone Infants and Sensitive Asthmatic Patients

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Abstract

The basic paradigm that allergen exposure produces atopic sensitization, and that continued exposure leads to clinical asthma throughout the development of airway inflammation and bronchial hyperreactivity has been challenged. However, because it was observed that epidemiological evidence suggests that around 40% of asthma cases are attributable to atopy (even using restrictive criteria), the obvious corollary is that if allergen avoidance begins before the onset of sensitization (primary prevention), then it should be associated with a reduced number of new cases of the disease. However, there are conflicting results regarding the effect of allergen avoidance on primary prevention of atopic sensitization and asthma onset. Instead, more uniform and positive results are available from secondary prevention studies. Secondary prevention obviously is an attractive opportunity for pediatricians who may recognize the patients who might benefit from these interventions simply by screening for food allergy in young children with atopic dermatitis. The conflicting results of tertiary prevention are most frequently observed in adult patients and sometimes result from incomplete avoidance of allergens responsible for the sensitization.

Index Entries

Atopy; environmental avoidance; allergy prevention; IgE.

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Introduction

The basic paradigm that allergen exposure produces atopic sensitization, and that continued exposure leads to clinical asthma throughout the development of airway inflammation and bronchial hyperreactivity (BHR) has recently been challenged (1). More precisely, it has been observed that epidemiological studies on asthma that used the term "atopy" or "bronchial hyperresponsiveness" in the definition of cases obviously are biased toward the association of sensitivity to allergens and airflow obstruction, thereby automatically excluding a significant proportion of asthmatics. It has been proposed that asthmatics may have a nonspecific predisposition to become sensitized to certain aeroallergens in relation to the density and timing of exposure and, therefore, that sensitization is not the cause, but rather the consequence, of the asthmatic predisposition (2).

Atopy and Asthma: A Causal Relationship or a Simple Association?

The cause–effect relationship between sensitization and asthma has been repeatedly proposed—particularly for house dust mites (HDMs; refs. 3 and 4). Additionally, the observation that in certain geographical areas, such as the desert regions and regions at high altitude (5) (where HDM exposure is very low or absent), the prevalence of asthma is as high or even higher than in regions where subjects are exposed to HDM was used to challenge the cause–effect relationship between exposure–sensitization and asthma onset. However, other allergens (cat, dog, cockroach, *Alternaria*) are also important. *Alternaria* is the major allergen for asthma in children raised in a desert environment (6); cockroach sensitivity is most often associated with an increased asthma morbidity in inner-city children (7,8); and cat and dog sensitization is most associated with asthma in children living at high altitude (5). Thus, many studies have demonstrated a strong relation-

ship between atopy, exposure to allergens, and asthma (3,6,9–12). Obviously, different allergens are involved in different regions with different climatic conditions (13).

Additionally, the dose–response relationship between exposure and sensitization and development of asthma may be very complex. It is plausible that atopy is one factor involved in the pathogenesis of the disease, which becomes manifest in individuals who lack additive protective factors or who are exposed to additional inductive factors. Therefore, the single evaluation of atopy in a population study may dilute the association between level of sensitization, exposure to allergen, and disease (13,14). Individual patients may have different thresholds of allergen exposure for production of immunoglobulin E (IgE), and sensitized subjects with asthma may have different thresholds of allergen exposure for onset asthma attacks (15); it is possible that subjects with a low threshold for sensitization also have a low threshold of allergen exposure for the onset of symptoms. In fact, even low-dose, repeated allergen exposure may increase BHR in asthmatics and induce permanent symptoms (16–20). This may partially explain the observed lack of a correlation between the dose of allergen exposure and asthma, despite the association that the disease with atopy (21). It is tempting to speculate that once a subject is sensitized and has, under the influence of other additive and still unknown factors, developed the disease then even mild allergen exposure is sufficient to build up the appearance of a complex of symptoms. This is usually observed in cross-sectional studies during the pollen season, in which only sensitization to the pollen is useful in predicting which individuals will have symptoms (15). Local variations in exposure are irrelevant compared with the effects of sensitization (22,23). The importance of allergens in the development of asthma and persistence of symptoms is also suggested by the appearance of asthma in the occupational setting, where atopy plays an important role in the development of a sig-

nificant proportion of asthma cases (24,25). Similarly, the appearance of asthma and sensitization to pollens of horticultural plants imported for the purpose of "greening" desert areas of Kuwait further support the causal relationship between allergen exposure and asthma (26). Furthermore, Inuit schoolchildren living in northern Quebec, Canada (where allergen exposure is limited) have been found to have a very low prevalence of positive skin-prick test (SPT; 5.3%) and also a low prevalence of exercise-induced asthma (27).

Allergen Exposure and Exacerbations

If a dispute exists regarding the effects of allergens in increasing the risk of asthma development (primary causation) (1,13,14), then it is well-established and accepted that allergen exposure is a secondary cause of asthma in that it can trigger asthma exacerbations in sensitized patients and that continuous exposure can lead to worsening of BHR, as well as to the persistence of symptoms (1,13,14,28,29). In sensitized inner-city children, asthma exposure to cockroaches was found to be associated with an increased number of hospital days, unscheduled physician visits, asthma symptoms, and number of days missed from school (30). The same was repeatedly observed in asthmatic children sensitized and exposed to mite allergens (31,32). The corollary is that allergen avoidance should always be associated with a reduction of symptoms, as well as BHR and improved lung function in asthmatic subjects (tertiary prevention).

Because, even using restrictive criteria (i.e., excluding the studies in which asthma was defined in terms of bronchial hyperresponsiveness) it was demonstrated that epidemiological evidence suggests that around 40% of asthma cases are attributable to atopy (1), then if allergen avoidance starts before the onset of sensitization (primary prevention), it should be associated with a reduced number of new cases of the disease (12). This was clearly observed for diseases associated with natural rubber

latex allergy when powder-free, low-protein natural rubber latex was introduced in an acute care hospital in Germany (33). When allergen avoidance measures are performed when the disease has already started (tertiary prevention), they should reduce the severity of asthma or, at least, prevent further deterioration of the disease.

Level of Prevention

In a recent review of allergen avoidance, *primary prevention* was defined as elimination of any risk/etiological factor before it causes the disease; *secondary prevention* was defined as the diagnosis and therapy at the earliest possible point in disease development; and *tertiary prevention* was defined as the limitation of the disease effect (34).

Using HDM sensitization as a major risk factor for the development of asthma, we can consider primary prevention as the prevention of sensitization to mite. Secondary prevention can be considered as the prevention of clinical asthma in those already sensitized to mite who do not have clinical symptoms or as the prevention of mite sensitization in those already sensitized to other allergens (i.e., the prevention of asthma in children with atopic dermatitis and food allergy). Tertiary prevention can be defined as the reduction in severity of asthma caused by mite sensitivity and exposure as a consequence of mite avoidance measures (35).

Effect of Allergen Avoidance in Primary Prevention

There are several placebo-controlled, longitudinal, primary prevention studies performed in high-risk subjects with a family history of atopy (refs. 36–48 and Table 1). The study, performed in the Isle of Wight, showed a reduction in the incidence of both positive SPT to HDMs and atopic dermatitis at ages 1, 2, and 4 yr in the intervention group (36–38). Significantly less wheezing was observed at the first year (36). This difference progressively weak-

Table 1
Primary Prevention Studies on Allergen Avoidance

Study center, number involved, references	Age at start	Follow-up	Intervention	Outcome
Isle of Wight (United Kingdom) <i>n</i> = 120 Arshad (36) Hide (37) Hide (38) Arshad (39)	Birth	1, 2, 4, 8 yr	No allergenic foods before 12 mo Mattress encased Acaricide	Der p 1 was significantly reduced. Age 1 active group showed significantly less asthma, eczema (+)SPT. Age 2–4 yr active group showed signifi- cantly less eczema and less atopy ($p < 0.05$). Age 8 yr active group showed significantly less risk factor for: current wheeze (OR = 0.22) wheeze and BHR (OR = 0.4)
Canada <i>n</i> = 545 Chang-Yeung (40)	Prenatal	1 yr	No allergenic foods before 6 mo Mattress encased Acaricide Pets avoidance	Der p 1 was significantly reduced. In active group, there was reduced risk of possible asthma (RR = 0.66; $p = 0.04$). Reduced risk of rhinitis (RR = 0.51; $p < 0.01$). Der p 1 was significantly reduced at age 1 yr in active group:
Manchester (United Kingdom) <i>n</i> = 620 Custovic (41) Lowe (42)	Prenatal	1, 3 yr	Parental and infant mattress, pillow, and duvet encased HEPA filter vacuum cleaner Acaricide	reduced risk for severe wheeze (OR = 0.44; $p < 0.05$) reduced use of medication for wheezing attacks (RR = 0.58; $p < 0.05$) reduced risk of wheezing after vigorous crying or exertion (RR = 0.18; $p < 0.05$) At age 3 yr: atopics higher sRAW than nonatopics
The Netherlands <i>n</i> = 810 Koopman (43) Von Strien (44)	Prenatal	1, 2 yr	Parental and infants mattress and pillows encased	Mite allergen levels low in general and treatment effect modest At age 1 yr: no effect on recurrent wheezing no effect on atopic dermatitis At age 2 yr: active group less night cough without a cold (OR = 0.65), no difference in wheezing and atopic dermatitis

ened; however, at age 8 yr, current wheeze was observed in 13.8% of the active group compared with 27.4% of the control group ($p = 0.08$), and atopy was still less prevalent (20.0 vs 46.8%; $p = 0.03$) in the active compared with the control group (39).

In the study performed in Canada at a 1-yr follow-up, wheezing was observed in 15.1 and 20.2% in the active-treated and placebo groups, respectively (relative risk [RR] = 0.66); the respective values of rhinitis without colds were 16.7 and 27.3% (RR = 0.51). There was no difference in the prevalence of sensitization between

the two groups (4.4 vs 4.6%) (40). A follow-up report from this population is needed because differentiation between asthma and transient wheezing is difficult at age 1 yr (49).

In the Manchester cohort at a 1-yr follow-up, the sensitization to mite was low (1–2%) in both groups, but severe wheeze with shortness of breath was present in 6% of the active group and 14% of the control group (RR = 0.44). The active group also showed a reduced prevalence of wheezing after vigorous playing, crying, or exertion (RR = 0.18), as well as a reduced use of medication for the treatment of wheezing attacks

Table 1 (Continued)

Study center, number involved, references	Age at start	Follow-up	Intervention	Outcome
Australia <i>n</i> = 616 Mihirshahi (45,46)	Antenatal	18 mo	Supplementation with ω -3 fatty acids Infants mattress encasing Acaricide washes laundry Group A = placebo diet, no HDM avoidance Group B = placebo diet plus HDM avoidance Group C = active diet, no HDM avoidance Group D = active diet, plus HDM avoidance	Reduced mite allergen exposure that remained high by international standard No reduction in sensitization No effect on eczema Prevalence of wheeze-ever 9.8% lower in the ω -3 supplemented group ($p = 0.02$). A significantly lower prevalence of use of oral steroid in HDM avoidance ($p = 0.04$).
Europe (England, Greece, Lithuania) <i>n</i> = 696 Holmerbouner (47) <i>n</i> = 636 Tsitoura (48)	Newborn, toddlers, and Newborn, preschool toddlers or preschoolers not sensi- tized to mite	1 yr	Mattress encasement	Newborn cohort at age 1 yr less sensitization to HDM (OR = 0.5) Toddlers and preschooler after 1 yr showed significantly less sensitization to mite (RR = 0.36; $p = 0.04$). Prevalence of doctor-diagnosed asthma and eczema significantly higher in sensitized children ($p < 0.05$).

SPT, skin-prick-test; OR, odds ratio; BHR, bronchial hyperactivity; RR, relative risk; SRAW, airway resistance; HDM, house dust mites.

(RR = 0.58) (41). However, the results of a longer follow-up are needed to determine the effect on asthma prevalence. However, in this study population at age 3 yr, an increased specific airway resistance was observed in children of atopic parents and in those with personal atopy (42).

In Prevention of the Incidence of Asthma and Mite Allergy (PIAMA) study in the Netherlands, avoidance had no effect on HDM sensitivity, wheezing, and eczema at a 2-yr follow-up (43). The avoidance group only showed a significant reduction in nighttime cough without a cold (odds ratio [OR] = 0.65). In the Children's Asthma Prevention Study (CAPS)

in Australia, the diet intervention (i.e., ω -3 supplementation to the mother and the child) resulted in a 9.8% absolute reduction ($p = 0.02$) in the prevalence of any wheeze but had no effect on serum IgE, atopy, or doctor's diagnosis of asthma at age 18 mo. The HDM avoidance intervention did not affect these outcomes but was associated with a lower use of oral steroids (8.1 vs 13.7%; $p = 0.04$), which might indicate a trend toward a lower prevalence of severe disease in this group (46).

In collaborative studies performed in Europe (Study of Prevention of Allergy in Children in Europe [SPACE]), HDM avoidance in a birth cohort measures resulted in less sensi-

zation to HDM (1.86 vs 5%; OR = 0.5) at age 1 yr (47). In the toddlers and preschool cohorts, sensitization to mite allergens was less prevalent in the HDM-avoidance group compared with controls (3 vs 6.5%). Furthermore, the frequency of asthma symptoms and atopic dermatitis symptoms was greater among the children who became sensitized to HDMs during the study year (48).

Clearly, there are conflicting results regarding the effect of allergen avoidance on primary prevention of atopic sensitization and asthma onset, and this article attempts to provide possible explanations for this.

Secondary Prevention Studies

There are very few secondary prevention studies with the use of HDM allergen avoidance measures. In one study, 57 infants with atopic dermatitis who had high levels of IgE antibodies for egg, cow's milk, or soybean, but not against HDMs, were randomly allocated to encasing of quilts and mattresses of all family members or only to cleaning instruction (50). In the 1-yr follow-up, HDM avoidance (by the use of covers), was associated with a significantly reduced HDM allergen exposure in infant beds (0.77 $\mu\text{g/g}$ vs 3 $\mu\text{g/g}$ of dust; $p < 0.01$), a reduced prevalence of SPT positivity for mites (31 vs 63%; $p < 0.02$), and, most importantly, a reduced prevalence of wheezing infants (11 vs 37%; $p < 0.05$) (50).

In another study, 242 children (ages 5–7 yr) with a family history of atopy and with a positive skin test to an aero-allergen, but not to HDM, were randomized to impermeable mattress covers or to nonspecific advices (51). After 12 mo, 2.56% of children in the prophylactic group and 9.38% in the control group developed sensitization to dust mites ($p = 0.03$; OR = 0.14). Because children sensitized to pollens are likely to become sensitized to HDM in following years (52), the possibility to reduce the progression to HDM sensitivity by simple avoidance measures is very attractive—particularly if a longer follow-up will demonstrate

a greater further increase in HDM sensitivity in the control group compared with the active treated group (as expected).

Another study, which can somewhere be considered between secondary and tertiary prevention, was performed in a small number of adults with HDM sensitivity but not yet asthma (53). Patients with allergy but not yet asthma (forced expiratory volume after 1 s $99.1 \pm 10.6\%$ predicted, PEFR variability = $5.21 \pm 3.41\%$, reversibility of forced expiratory volume after 1 s after salbutamol of $3.92 \pm 3.75\%$) were randomly allocated to the use of covers for mattress and bedding or placebo. A significant improvement in peak expiratory flow (PEF) was observed in the active-treated group in the 6-wk follow-up ($p = 0.03$), and this was associated with a reduction in the Borg Score for disturbed sleep and breathlessness ($p < 0.05$), which was not observed in the placebo group. Although the study is not long enough to evaluate the development of asthma, the results may indicate that there may be room for intervention in HDM-sensitive subjects before the onset of clear symptoms of respiratory diseases. This study is particularly important for the potential consequences of mite allergen-avoidance when it is performed early in life. HDM sensitivity can be lost in young patients as a consequence of environmental changes: of 115 young children with positive SPTs to mites, 66 of 67 whose skin responses become negative over a period of 2 yr were exposed to a concentration of mite allergen less than 2 $\mu\text{g/g}$, whereas 15 of 48 who remained positive on SPTs had a level of exposure greater than 2 $\mu\text{g/g}$ (54).

Therefore, more uniform and positive results are available from secondary prevention studies. Secondary prevention is obviously an attractive opportunity for pediatricians who can recognize the patients who might benefit from these interventions simply by screening for food allergy in young children with atopic dermatitis.

Tertiary Prevention

A meta-analysis by Goetsche et al. (55) suggested that current chemical and physical methods aimed at reducing exposure to allergens from HDMs might be ineffective. This meta-analysis was an agglomerate of different studies, the majority of which used techniques that are now known to have little effect on mite levels (35,56). Therefore, it is not surprising that interventions lacking efficacy are clinically ineffective (57). It was thus suggested that the conclusions of the meta-analysis were wrong (58). Another meta-analysis performed by the same group observed that for chemical methods used alone, there was a statistically significant adverse effect on symptoms ($p = 0.03$), whereas for physical methods used alone, there was a statistically significant beneficial effect ($p = 0.02$). However, more trials are needed (59). After this second meta-analysis, other controlled studies have been performed in adults (60–64) and in children with asthma (65,66) with both negative (60–62,66) and positive results (63–65), further increasing the controversy on the efficacy of mite avoidance measures.

However, in one negative study, the drop-out caused by disease instability was higher in the placebo group compared to active-treated subjects, and all the patients had severe BHR, despite receiving relatively high doses of intracortico steroids ($>800 \mu\text{g}$) for years before the study (60). Once airway remodeling is established, it is very likely to persist even if allergen is avoided (67); therefore, in these patients, it is more correct to look for no further deterioration of the disease rather than for an improvement, as was observed in a similar study population (64). In another negative study at the end of the 12-mo study period, there was no significant difference in the level of mite allergens between the active-treated and the placebo groups ($1.05 \mu\text{g/g}$ vs $1.64 \mu\text{g/g}$ of dust; $p = 0.74$). This very likely resulted from the fact that no specific washing instructions for bed covers were given (61). It is well-established that if covers are not

regularly hot-washed then mites can grow on them (68). In the two other negative studies—one in adults (62) and the other in children (66)—there was a progressive improvement in mean peak flow readings in both the active- and placebo-treated groups, indicating a possible barrier effect of the placebo covers (47), as demonstrated by the decrease in mite allergen levels in the placebo arm of the study (62).

In the positive trial in children after 12 mo, it was possible to reduce the dose of inhaled steroids by at least 50% in significantly more children in the active-treated group than in the placebo-treated group (73 vs 24%; $p < 0.01$) (65). If the results of this study can be confirmed in a larger number of patients, then this would be associated with a significant reduction in health care expenditure and with the further advantage of a reduction in the risk of side effects related to the use of corticosteroids (69–70). The results of these studies demonstrate that when properly performed and when suggested to the right patients, allergen avoidance is associated with a reduction of symptoms, BHR, and consumption of drugs.

Why Indoor Allergen Avoidance May Not Work

There are several reasons for failure of allergen avoidance in improving clinical symptoms (Table 2).

If the allergen selected for avoidance is not relevant to the development and progression of the disease and sensitization is only an epiphenomenon, there is no reason for improvement evident with appropriate avoidance. For example, asthmatic subjects sensitive to HDM may not react to a specific bronchial provocation with HDM antigen (71,72), and some patients do not present with a late asthmatic reaction (73), and a positive reaction to the specific bronchial challenge is not always associated to an increase in nonspecific BHR (74). Consequently, some patients may not improve after mite allergen-avoidance simply because other causes are involved in the pathogenesis

Table 2
Possible Causes of Allergen Avoidance Failure

1.	The allergen that is avoided is not relevant to the etiopathogenesis of the disease.
2.	Multiple allergens are involved in the etiopathogenesis of the disease.
3.	Nonefficacious measures have been suggested.
4.	Low adherence to the suggested measures.
5.	Inadequate or incomplete use of the measures.
6.	Exposure to the responsible allergen outside the home.
7.	Some obvious parts of the house that exert should be treated but are not or cannot be treated.
8.	Short period of observation or short period of low allergen exposure.
9.	Comparison with placebo mattress—covers with a significant protection.
10.	Long-term duration of the disease with irreversible pathological changes in the target organ.

of the disease. However, the importance of HDM avoidance remains, because increasing titers of specific IgE to *Dermatophagoides pteronyssinus* are usually associated with increasing bronchial responsiveness (75).

Furthermore, sensitization to multiple allergens is common in atopic patients, and children tend to develop multiple sensitivities within a few years of exposure (52). Obviously, avoidance of multiple allergens is a more difficult task.

Sometimes, nonefficacious measures have been offered to patients. For example, studies with acaricides have shown that even the use of a good active compound does not necessarily equate with good mite allergen control and subsequent improvement of symptoms (76–78). Vacuum cleaning alone, not combined with steam cleaning (79), does not remove deeply embedded allergens and does not reduce the number of live mites in carpets (76). Air filtration is not effective for mite allergen avoidance and also has a limited efficacy for pet allergen control (80). Air filtration is only effective in cat-sensitive children who also do not have the cat in the house (81). Furthermore, lay advertising advocating the use of foam mattresses and pillows in patients with allergies should be the object of careful revision by the scientific community. There are numerous demonstrations that the use of synthetic bedding is a risk factor for severe atopic disease (82,83) and that there are higher contents of

mite and pet allergens in foam mattresses compared with spring mattresses (84) and in synthetic pillows compared with feather ones (85,86). However, it has become a routine for a mite-sensitive patient to use foam mattresses and synthetic pillows and quilts. In contrast, more traditional mite-avoidance measures, such as encasement of mattresses and box springs, removal of carpeting, and replacing upholstered furniture, which can reduce allergen burden and alleviate mite-induced atopic disease are poorly adhered to (87–89). With usual clinically based education efforts, only 17% of patients completely adhere to the prescribed avoidance plan (90), and this percentage rises to only 39% with the use of computer education program (91). Reasons for nonadherence include lack of understanding of the role of allergen in allergic disease, lack of spousal support, the time required, and the necessity to alter lifestyle (91). Low socioeconomic status may be another reason (92), although 10 to 20% of the patients do not use dust-mite-proof bedding covers, even when they are provided without cost in clinical trials (45,93). The failure to use a simple measure such as hot-washing of the covers may also be a common cause of reduced efficacy, because it is well-known that hot water is a requirement for an acaricidal effect. When first introduced, it was clear that covered mattresses could reduce mite allergen levels up to 100 times, but it was also clear that after 6 wk of use, mite allergen levels began to

rise on the cover again (68). In this regard, a recent trial evaluating the use of allergen-impermeable bed covers for adult asthmatics was not effective (61). However, in this study, the concentration of Der p 1 in mattress dust was significantly lower in the active intervention group at 6 mo (geometric mean: 0.58 vs 1.71 $\mu\text{g/g}$ in the control group; $p = 0.01$) but not at 12 mo (1.05 vs 1.64 $\mu\text{g/g}$; $p = 0.74$), as could be expected when no washing instructions were provided and, consequently, no regular hot-washing of the covers was performed.

Despite adherence to allergen avoidance at home, there are other reasons for failure, including exposure to allergens in public places (94–96), to pet allergens (97–101), and in private cars (102). There are some houses in which it is practically impossible to avoid allergen exposure because of the type and amount of furniture they possess. For example, the mattress base has been demonstrated to be a major reservoir for domestic mite allergens, because the allergen content is higher in bases than in mattresses themselves (103,104). Encasement of mattresses in such situations appears inadequate and certainly would not reduce allergen loads in bedrooms.

Because of the adherence problems with allergen avoidance as well as with the type of furnishings of the house, a new measure has been proposed: the medical indoor environment counselor (MIEC) (105). It has been shown that home visits by a MIEC increased the compliance to mite reduction methods advised, induced a significant difference in mite reduction levels on mattresses and carpets, and avoided nonestablished avoidance advices. Very likely, the MIEC will also advise when avoidance measures are unlikely to work in a particular infestation-prone environments.

The short period of observation may also be a reason for failure to show an effect—particularly in primary prevention studies. It has been demonstrated that the type of positive or negative effects that have been produced by early life events may not be evident until ado-

lescence or early adulthood (29,106,107). Obviously, to have an effect a low-allergen exposure should be maintained for a long period of time, which was accomplished in the Manchester study (108) but not in the PIAMA study (109). Because there are new cases of onset of atopy and asthma during adolescence and really new cases exceed those who go on remission (110) and because mite exposure and sensitization is a strong risk factor for asthma onset (110,111) as well as for its persistence (106), mite allergen avoidance should become a lifestyle, and the problem should be addressed when planning housing construction (112). Furthermore, conducting a double-blind, controlled trial with allergen avoidance is difficult (113) because the knowledge of sensitivity (skin wheal) may be a stimulus for changing behaviors (such as an increase in cleaning) and also because, sometimes, placebo covers may be as effective as active covers (47,62).

Finally, long-term established disease is also less likely to respond to allergen avoidance (60). In longlasting asthma, irreversible pathological changes in the airways may be more difficult to reverse. In fact, the majority of negative studies regarding the effect of allergen avoidance have been observed in adult asthmatics. In this regard, occupational asthma may be a useful model to explain the different results between young and adult patients: although early diagnosis and removal from the workplace (where exposure has occurred) are associated with recovery, a long duration of exposure in sensitized subjects leads to persistent and sometimes progressive deterioration of asthma control, even if the exposure has ceased (114,115).

Conclusion

Environmental factors seem to be at least as important as genetic factors in determining the expression of asthma (1–32). The challenge now is to find effective public health interventions capable of reducing the burden of atopic disease—especially those involving avoiding

exposure to factors, such as indoor allergens, for which there is good evidence for a causal relationship (116–118). The information and education process should be part of a public health policy. Parental history of atopic disease is a strong risk factor for atopic outcome in the offspring, but the majority of infants who develop an atopic phenotype and sensitization do not have atopic parents (119). Therefore, to be effective, interventions aimed at reducing the onset of atopic diseases (primary prevention) should be directed at a population level. The same is partially true for most of the cases of secondary and tertiary prevention, because exposure to allergens outside the house does not depend on, and cannot be controlled by, the individual patient. Identification of risk factors is the first point education needs to follow. Unfortunately, this is still limited, even in the parents of atopic children (120–122).

Furthermore, there is a great deal of conflicting information, with no clear data regarding the precise measures that most effectively prevent asthma (123). Clearly, there is room for improvement (122,123) because it has been recently shown in Sweden that asthma can be prevented in real life (124) by simple measures such as breastfeeding, avoiding tobacco smoke during pregnancy, and maintaining good ventilation of the house (125). Obviously, the complex effect of these three suggestions is difficult to separate; however, very likely, increased ventilation with consequent reduced home dampness is associated with reduced allergen exposure (particularly mold and mites, which also have been shown to be a problem in the cool, dry climate of Scandinavia) (125–127). In cool, dry regions, mite exposure can be significantly reduced by increasing room ventilation and thus reducing indoor humidity (128,129). Because of the complexity of the pathogenesis of asthma and the different phenotypes of the disease, a prevention strategy limited at allergen avoidance will have only a partial impact on the prevalence of the disease. Future successful strategy would likely include both

“prohibitionist” advice, such as reducing allergen exposure and other environmental triggering factors, and “pro-active” advice aimed at the implementation of protective factors (130). Instead, the importance of mite allergen avoidance in sensitive asthmatic children (tertiary prevention) with the aim to reduce the severity of the disease is well-documented by several double-blind, placebo-controlled studies.

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