

Original article

The role of house dust mite elimination in the management of childhood asthma: an unresolved issue

Indoor allergens are likely to be direct environmental causes of asthma and mite exposure, and sensitization is the most important environmental risk factor for childhood asthma in temperate zones. Analogous to occupational asthma, allergen avoidance in asthmatic children sensitized and exposed to mite allergens is associated with a reduction in airway hyperresponsiveness and symptoms associated with improvement in lung function. The long-term effect of this strategy needs to be prospectively evaluated considering both the timing and duration of exposure, as well as the timing and duration of removal. In order to be successful, it is important to achieve and maintain a major reduction on allergen levels, for a long period of time.

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Key words: allergen avoidance; house dust mite; avoidance; atopic diseases; prevention.

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Introduction

Several studies have documented an increasing prevalence of childhood asthma and other allergic diseases in the past three decades, both in industrialized and in developing countries (1–7). Where different ethnic groups share similar lifestyles, prevalence rates are similar, suggesting that the prevalence of asthma and other allergic diseases may be increased by aspects of the “Western” lifestyle (8). Studies in Africa have shown that asthma prevalence increases as indigenous populations move from rural communities to the cities, suggesting a dose–response relation between the degree of affluence and asthma (9). Similarly, studies in Papua New Guinea have revealed a substantial increase in the prevalence of asthma at a time of increasing Western influence (10). It has been argued that part of the increase may be explained by changes in diagnostic labels and in diagnostic methods used over the years (11). However, the real increase is validated by observations that have been made with objective markers such as the increase in hospital admission for asthma (12, 13) and the increase in bronchial hyperresponsiveness in the population (6), and an increase in atopic sensitization (14). For this reason, it has been recently claimed that: “It is time to take steps to reduce the prevalence of asthma in the many countries in which it is now unacceptably high. It is also important to develop strategies to ensure that developing

countries do not attain such high rates of asthma in their children in the coming years” (15).

Indoor allergens

The progressive increase in the prevalence and morbidity of asthma has been observed in perennial rather than seasonal disease, and the vast majority of the patients are sensitized to one or more of the indoor allergens (16). In a study examining possible risk factors for the development of wheezing and bronchial hyperresponsiveness in a cotwin-control study, it was observed that, in 62 monozygotic twin pairs discordant for a history of wheezing, a positive skin prick test response to house dust mites (HDMs) was the most important discriminator followed by sensitization to cat and cockroach allergens (17). In contrast, dizygotic discordant twin pairs differed additionally in sensitization to grass pollen and fungi. This monozygotic–dizygotic difference suggests that pollen allergy in asthmatics is more an epiphenomenon, whereas indoor allergens are likely to be direct environmental causes of asthma (17). The most important environmental risk factor for childhood asthma in many temperate zone countries is mite sensitization (18). There is strong evidence that exposure to dust mites early in childhood leads to sensitization (19). In populations at high risk of asthma, dust mite levels in infancy predict early

sensitization, later childhood asthma and bronchial hyperresponsiveness (20). The situation in a general population sample (most of whom will be at low risk) may be quite different. In such a population, HDM exposure in infancy bears no relation to subsequent childhood asthma (21). In environments where HDM prevalence is low, other aero-allergens (such as *Alternaria* in the desert conditions of Tucson, AZ) predominate.

The role of other allergens, such as those derived from cats and dogs, in the initiation of asthma is also complex. Here again, evidence suggests that the risk of sensitization depends on the risk group. Ownership of a family dog had no effect on the prevalence of frequent wheeze at 12 years, in the young children of high risk (atopic) patients, whereas for the children of low risk families, the presence of a dog diminished the likelihood of frequent wheeze (22). Removal of the dog by the age of 3 years cancelled this protective effect. This could be explained by two opposing effects of dog ownership: a (environmental) protective effect, which is seen in low risk populations and which is cancelled out by the (genetically potentiated) increased likelihood of sensitization in the high risk group. Recent evidence also casts doubt on the suggestion that early cat exposure leads to asthma (23).

Epidemiological evidence linking HDM exposure to asthma

Even if there is strong evidence that sensitization to HDMs is associated with an increased prevalence of airway hyperresponsiveness (AHR), it could be argued that mite sensitization does not cause asthma but just has a close association with the disease. The criteria for proving a causal relationship between an environmental exposure and a noninfectious illness have been defined by Bradford Hill (24) and are as follows: (i) biologically plausible, (ii) analogous associations, (iii) temporality, (iv) dose-response effect, (v) consistency, and (vi) decrease in effect when exposure ceases. These criteria have been applied to the association between dust mites and asthma (25–27).

(i) There is good *plausibility*, because mite allergens occur commonly in houses, and Der p 1 concentration in broncheolalveolar lavage of asthmatic patients has been demonstrated to correlate with allergen levels in the environment (28). Effectively, it was recently demonstrated that mite allergen (Der p 1) is not only carried on mite faeces (mean diameter of $22 \pm 6 \mu\text{m}$; range, 10–40 μm) (29). Some allergen is carried on smaller particles and on heterologous particles. These particles could be inhaled more readily into the lungs, causing sensitization and, with repeated exposure, airway inflammation, AHR and asthma.

(ii) A good *analogy* comes from occupational asthma, where novel repeated exposure is associated with the development of sensitization and with the appearance of

bronchial hyperresponsiveness and asthma after repeated exposure (30, 31). The treatment of choice is removal from the work place, by analogy with allergen avoidance in asthmatic children sensitized and exposed to mite allergens, by removal to high altitudes, where HDM concentrations are low. If removed from the industry while their asthma is mild, these workers may lose their symptoms but, if they remain in the industry and are repeatedly exposed, then they develop chronic asthma that does not go into remission following avoidance of exposure. Timing of removal from exposure is a predictor of outcome in occupational asthma and this information may have important implications for the effectiveness of allergen avoidance strategies in the population in general. Another good example of analogy comes from the soybean epidemics in Barcelona (32), where many people developed sensitization to soybean allergens following low level exposure to soybean dust. However, intermittent high exposures following the loading of soybeans into a dock-side silo led to acute exacerbation and hospitalization of sensitized subjects. The repair of the ineffective silo filters eliminated further outbreaks. One important implication of adult (occupational) sensitization is that sensitization is not confined to infancy. Primary HDM sensitization can certainly occur in school children (33). Avoidance of allergen exposure in infancy may, therefore, delay rather than prevent sensitization and its possible consequences.

(iii) *Temporality* has been shown, because exposure precedes the clinical effect. In a birth cohort of high risk infants, the onset of wheeze had a linear relationship to the amount of Der p 1 in beds (20). The infants who were exposed to high Der p 1 levels following birth developed wheeze at an earlier age than did infants exposed to lower allergen levels. Furthermore, in a population study from Papua New Guinea, it was demonstrated that contact with Western civilization – in particular, changes in sleeping habits as a result of the use of blankets which become mite infested – was followed by an increase in mite sensitization and an epidemic of asthma. In this community until the early 1970s, asthma was almost nonexistent, having a prevalence of 0.1%. The introduction of blankets was followed by an asthma epidemic with a prevalence of the disease of 7.3% in the adult population (34).

(iv) There is a *dose-response* relationship between exposure and sensitization, and between exposure and severity of asthma. In Australian regions where Der p 1 levels were high, more children were sensitized to HDMs and the risk of house-mite-sensitized children having current asthma approximately doubled with every doubling of Der p 1 levels (35). In Germany, children who were sensitized during the first 3 years of life had been exposed to significantly higher levels of HDM allergen at home than those without sensitization (19). The relative risk for sensitization in the high-exposure group was 7–32. In another study performed in HDM-sensitive children, seasonal differences in peak flow amplitudes

could be explained by seasonal differences of mattress HDM concentrations (36). Furthermore, a significant correlation was observed between Der p 1 concentrations in beds and FEV₁ ($P < 0.02$) and PD₂₀ methacholine ($P < 0.01$) (37), and with medication requirements (38) in adult asthmatics sensitive to mites. Sensitization to mites also correlates with the risk of hospital admission for asthma exacerbations (39).

(v) The data are fairly *consistent* in showing that exposure to mite allergens leads to sensitization and that asthma is strongly associated (in some parts of the world) with sensitization. This is true even in urbanized African communities (40). There is a correlation between the degree of sensitization to mites, measured as the SPT wheal diameter, and the prevalence of diagnosed asthma in the population (41, 42), demonstrating that the strength of the association is considerable. Epidemiological studies have consistently demonstrated that up to 85% of patients with asthma have specific IgE to HDM as compared with only 5–30% of the general population (27).

However, almost all the previous data have either been observational, cross-sectional epidemiology or cohort studies in high risk populations. Recent data in complete population samples do not show such a strong effect. In fact, asthma and AHR in middle childhood were unrelated to HDM allergen levels in the home in the first 3 years of life in one recent birth-cohort study (21), although the risk of sensitization was clear (19).

Most childhood asthma, even in temperate zone environments, is not attributable to atopy in general or HDM sensitivity in particular (Table 1). In fact, the population attributable risk declines with increasing “degree” of atopy (43).

(vi) The evidence of a *decrease in effect when exposure ceases* will be discussed in the following section. The objectives of HDM avoidance measures are three-fold (Table 2).

Mite allergen avoidance

Tertiary intervention

There are different *models* which demonstrate that the avoidance of a relevant mite allergen exposure can reduce asthma morbidity. Studies performed at *high altitude* (> 1500 m), where humidity is too low to support mite populations, have clearly demonstrated a decrease in

Table 2. Objectives of HDM avoidance

Primary prevention:	prevention of HDM sensitization
Secondary prevention:	prevention of clinical asthma in HDM-sensitive children
Tertiary intervention:	reduction in severity of asthma due to HDM

different inflammatory parameters, a reduction in AHR and symptoms associated with an improvement in lung function in asthmatic children sensitive to mites taken from their homes to the Alps (see 44, for review). The high altitude studies have suggested that, in order to be successful, it is important to achieve and maintain a major reduction in allergen levels. These studies include no control (non-HDM-sensitive) severe asthmatics, so that alternative explanations for improved illness cannot be excluded. Moreover, on return to sea level, symptoms and associated inflammation quickly return (45). This effect is analogous to the well-known recurrence and persistence of symptoms and BHR in pollen-sensitive, quiescent asthmatics given a pollen challenge outside the pollen season (46).

The *public place* model has repeatedly shown that low levels of Der p 1 can be achieved in public building in regions where domestic levels are high, endorsing the feasibility of attaining low allergens levels in humid climates by good housekeeping (47–49). With the “*healthy homes*” model in Denmark, it has been shown that, in specially designed, mechanically ventilated houses, reduced HDM exposure can be achieved; the removal of asthmatic patients into these buildings results in an overall clinical improvement in an uncontrolled, observational study (50).

The efficacy of mite antigen reduction in houses is controversial (44, 51). An independent Cochrane Collaboration analysis of house dust control measures in the management of asthma reported that “current chemical and physical methods aimed at reducing exposure to allergens from house dust mites seem to be ineffective and cannot be recommended as prophylactic treatment for asthma patients sensitive to mites” (51). The meta-analysis, however, comprised a “soup” of 23 studies, the majority of which used techniques that probably had little effect on mite allergen levels. In 12 of the 23 studies, the avoidance measures did not decrease mite allergen concentrations. For example, one study included in the meta-analysis (by one of the authors of the meta-analysis) was an ineffective programme, which included, among other ineffective procedures, the replacement of feather pillow with pillows of synthetic filling (52) – a manoeuvre that is associated with an increased risk of severe childhood asthma (53). In fact, the increased use of nonfeather pillows was the main indoor exposure associated with increased prevalence of asthma over a 13-year period (54). Synthetic pillows contain significantly greater amounts of Der p 1 than do feather pillows (55), and accumulate Der p 1, Fel d 1 and Can f 1 more rapidly (56, 57).

Table 1. Prevalence of childhood atopy and dust mite sensitivity and population risk of asthma attributable to sensitization

	Prevalence in children (%)		Population attributable risk (%)
	Asthma	All children	
Any atopy by SPT	58	29	38
HDM sensitivity by SPT	44	19	30

SPT skin prick tests; HDMs. From Pearce et al. (43).

Of the other manoeuvres used, vacuum cleaning of mattresses does not affect the Der p 1 concentration in the mattress itself (58) and vacuum cleaning of carpets results in an increased aerodispersal of the allergens (59–61). Therefore, it is not surprising that interventions that lack efficacy (no reduction in allergen exposure) are clinically ineffective (62).

In the subgroup of five trials which reported a successful reduction in mite populations, the results were “similar to the overall results” (51), although statistics are given only for peak flow rate as an outcome. The enormous heterogeneity of PEFR values, however, makes them poor measures of asthma severity when studying population (63). The negative conclusions of this meta-analysis are still controversial and others examining the same data set have reached different conclusions (44). The subjects in most of the clinical trials had moderate or severe asthma. A trial of dust mite reduction in mild asthma could be important, especially because it could have implications for early intervention in children. A recent, well-conducted study in mild, nonsteroid-using dust-mite-sensitive adult asthmatics showed no benefit over a period of 5 months (64).

For more than 400 years we have been giving our patients wrong information concerning HDM antigen avoidance. This is evident from the case of Gerolamo Cardano, who in 1542 was called from Italy to Scotland to look after a severe and famous asthmatic patient, John Hamilton, Bishop of St. Andrews. Cardano observed the bishop for 40 days and then he prescribed the following: a light diet, to be at rest, to ride, frequent cold baths and to change a feather mattress with one of raw silk. Cardano was successful but only because the bishop was killed a few months later by the Scots, before his bed had become re-infested with mites (65). Furthermore, a warm bath and not a cold one should have been suggested. It has recently been demonstrated that warming the feet elevates nasal mucosal surface temperature and reduces the severity of the response to specific allergen nasal challenge (66).

If we give the right advice (Table 3), allergen reduction can be achieved (67). Only five published controlled trials in children have achieved a decrease in allergen exposure (68–72) – three with an adequate duration (6 months) (68, 69, 72), of which one had only about eight appropriate

subjects (69) and one is only reported in abstract (68). We are left with a single pediatric study of adequate power using an effective intervention, and with a significant outcome (72). The reasons for the previously unfortunate outcome of all this complex and expensive clinical trial work are many (Table 4).

Primary prevention

The possibility of preventing sensitization to inhalant allergens (primary prevention) has been reported in one prospective study on three occasions (73–75): high risk infants in the intervention group, reduced exposure to food antigens, and HDM contact in the first year of life. This trial, together with another of similar design, claimed reductions in wheeze of 11% (75) and 5% (76), although in neither was the effect significant. The problems of interpretation of these confusing studies are legion. First, high risk infants were chosen. They represent a very small (but important) subset of the total population (77), and are the most sensitive to dust mite exposure, making them the least likely group in which to demonstrate a reduction in HDM sensitization (33). Second, wheeze in the first 2–3 years of life is largely a nonatopic, transient, viral illness (78, 79) unrelated (even in high risk infants) to later asthma (20). If atopic asthma is the outcome of interest, then early wheeze cannot be used as an appropriate endpoint. Third, a number of initiatives were introduced simultaneously, so that the effect of any one of these (HDM in the present case) cannot be separately identified.

In another study, 57 infants with atopic dermatitis, who had high levels of IgE antibodies against either egg white, cow’s milk, or soybean but none against HDMs, were randomly divided in two groups: one which received conventional instruction for cleaning the house and one in which microfine fiber encasing for quilts and mattresses was suggested for all family members (80). After 1 year, the mite-blocking encasing significantly reduced the level of mite allergens and it also prevented sensitization.

The possibility of preventing sensitization to mites and the subsequent onset of asthma is now under evaluation with five long-term studies in high risk infants in Europe, USA and Australia.

Table 3. Recommended avoidance measures for mite allergens

Definitely useful
decrease clutter
bedding: mattress and pillow encasement
laundry: washing blankets every week (> 55°C)
no carpets
Probably useful
surface cleaning once a week with a moist cloth
vacuuming with appropriate filter
steam-cleaning

From (67).

Table 4. Controlled trials of dust mite avoidance have been uninformative so far, for many reasons

Patient selection criteria vary (“high risk” groups, for example)
Methods of control vary in efficiency
Trial size is often inadequate
Inappropriate control groups recruited
Confounding (by furry pets, for example)
Interaction with other factors (pets for example)
Inadequate measures to ensure no “contamination” of control group
Inadequate duration
Inappropriate clinical outcomes (preschool wheeze, for example)
Inappropriate physiological outcomes (PEF or PC ₂₀)

Secondary prevention

HDM sensitivity can be lost as well as acquired by environmental change. Of 115 children with positive skin prick test to mite allergens, 66 of 67 whose skin responses became negative over a period of 2 years were exposed to a concentration of mite allergen less than 2 µg/g, whereas 15 of 48 who remained skin prick test positive had a level of exposure greater than 2 µg/g (81). The possibility that this outcome could be associated with the prevention or remission of asthma, in analogy with occupational asthma, needs to be tested in long-term randomized controlled studies.

There is only one study that evaluated the effect of mite antigen manoeuvres in subjects with specific IgE for mites but not yet diagnosed as asthmatic. In these adult subjects (82), the use of mattress covers for 6 weeks was associated with a significant improvement in symptoms scores for disturbed sleep, breathlessness and wheeze compared with the placebo group (80). These findings are at variance with others in the same group, in very mild asthma (64). Larger studies with a longer follow-up period are necessary.

Compliance with mite avoidance measures

To be effective in real life, adherence to allergen avoidance measures has to be strictly maintained for long periods. For this reason, only interventions which have been proven to be effective should be given to the patients (Table 3), and behavior modification techniques should be used to teach the patients (83) and the primary-care physicians (84). A study showed that, without formal education programs, compliance in using mattress covers was nil (85). Adherence to advice was 17% following the usual clinic-based educational efforts (86), 27% with repetitive clinic-based education and 39% with a computer-based education program (85). More recently, daily compliance with keeping bed covers was 73% (87). In the same study, the adherence with keeping the dehumidifier running was as low as 11%. This can, however, be considered a form of intelligent noncompliance, because the effect of dehumidification on the mite allergen level in humid regions is controversial (67) and probably trivial in relation to the effects of outdoor humidity. Deterrents to implementing allergen avoidance measures have been shown to be cost, altered life style and lack of spouse support (85, 88). Better education, simplifying recommendations and developing a partnership between physician and patients, as well as access to free or low cost mattress covers and pillow covers would improve compliance (89). If obsessively implemented, the measures suggested by Custovic et al. (44) would keep a housewife (or her partner) fully occupied (Table 5)!

Table 5. Measures for reducing HDM allergen exposure

Encase mattress, pillow and quilt in impermeable covers
Wash all bedding in the hot cycle (55–60°) weekly
Replace carpets with linoleum or wood flooring
If carpets cannot be removed, treat with acaricides and/or tannic acid
Minimize upholstered furniture/replace with leather furniture
Keep dust accumulating objects in closed cupboards
Use a vacuum cleaner with integral HEPA filter and double thickness bags
Replace curtains with blinds or easily washable (hot cycle) curtains hot wash/freezer soft toys

From Custovic et al. (44).

Avoiding the nonallergenic properties of HDMs

At least five mite allergens have enzymatic activity. In mixed house dust, the following enzyme activities can be detected: trypsin, chymotrypsin, collagenase, amylase, glucoamylase, chitinase, cellulase, lipase, elastase, lysozyme and alkaline phosphatase. It is now evident that the proteolytic activity might contribute to the pathogenic effects of dust mites and mixed dust, and therefore to the pathogenesis of airway disease, including asthma. It is possible that focal deposition of proteinase allergens results in disruption of intercellular adhesion and intercellular communication. Histologically, such disruption is characterized by loss of lateral and basalateral adhesion between cells, suggesting that the enzymes disrupt intercellular junctions (90). At the site of disruption, the allergen may gain easier access to antigen presenting cells. It has been recently shown that Der p 1 impairs adhesion in epithelial cells and detaches cultured epithelial cell monolayers from both artificial and natural biopolymer substrata (91). This can elicit an increase in the permeability of the bronchial mucosa to macromolecules such as serum albumin (91) and possibility to other proteins with allergenic activity. This may in part explain the tendency of children sensitive to HDMs to become sensitive to other allergens.

Furthermore, allergens from HDMs are capable of activating inflammatory pathways independently of a specific IgE response. Der p 1 and Der p 9 have been shown to induce expression of ICAM I and HLA class II (92). Der p 1 induces mast cell and basophil degranulation, and stimulates IL-4 synthesis and secretion independently of IgE (93). Der p 1 was shown to cleave CD23 (e.g. IgE low affinity receptor *FcεRII*) from the surface of B cells (94). The binding of IgE to membrane CD23 delivers a negative IgE regulatory signal to the B cell; therefore, exogenous cleavage of CD23 may disrupt important IgE regulatory mechanisms. Der p 1 also cleaves human CD25, i.e. the α subunit of the receptor for the TH1 cytokine IL-2 (95), with consequent markedly diminished secretion of INF-γ. This may further compromise the TH1/TH2 subset distribution in favor of the TH2 line (96). Moreover, Der p 1-induced CD25 cleavage has a strong antiproliferative effect on CD8⁺ T cells which are

responsible for the suppression of IgE production (97). Thus, the proteolytic activity of HDM allergens may destabilize the microenvironment in the lungs to one which is proallergic, and may favor the allergic inflammation (98), or even cause inflammation in its own right. Dust mite avoidance may therefore have important modulating effects on sensitization to other aeroallergens and on inflammatory symptoms induced by its own proteolytic activity. These benefits remain theoretical.

Mite antigen avoidance as a life style

It is often stated that the majority of mild-to-moderate childhood asthmatics, whether or not sensitive to HDMs, improve with time, even in the absence of HDM avoidance. However, although respiratory symptoms disappear in half the children with asthma and although adults may believe that they have outgrown their disease, they probably retain the possibility of responding adversely to inhaled mite allergens. In a study in which specific bronchial challenges with HDM allergen were performed during childhood and again in adulthood, it was shown that 61% of adults, although symptom free, had a positive response to challenge (99). This suggests that the mite sensitivity is not sufficient for continued clinical asthma and that any lapse in the mite avoidance regime could lead to a relapse in asthma (as implied by the challenge studies themselves). Mite sensitization is a risk factor for asthma in children, in adolescents (100) and in adult asthmatics. Several studies have documented that sensitization to mites is associated with smaller growth in lung function (101–103). These physiological outcome studies, however, often confuse improved lung growth with active (if mild) asthma, by failing to report postbronchodilator lung function. Because a number of studies have documented that the level of childhood pulmonary function is indeed predictive of persistent asthma symptoms in adulthood (104–107), it is obvious that, if mite antigen avoidance is

effective, it must be maintained life-long – an unlikely scenario, given what we know of short-term compliance with dust control measures.

Conclusion

There is strong evidence that mite sensitization and exposure are associated with asthma as well as with severity of symptoms and bronchial hyperresponsiveness. The application of strict measures can result in a drastic reduction in mite allergen levels in houses, even in humid regions where mite growth is particularly evident. Whether these reductions can lead to improvements in lung function, reduction in AHR, decrease in symptoms and reduced healthcare costs has yet to be proved beyond doubt, especially in children. Nevertheless, antigen avoidance is often recommended for dust-mite-sensitive asthmatic children, as part of an overall therapeutic strategy (tertiary intervention). We need more studies in primary and secondary prevention. In particular, we need to know if mite antigen avoidance will lead to a reduction in the prevalence of asthma. Because epidemiological studies have documented that, in absolute numbers, the majority of asthmatic patients do not come from high risk families but from those with little or no history of atopic diseases (77), it will be important to evaluate the effect of primary prevention on the whole population. This strategy is particularly attractive, because it has been shown that the levels of mite allergens necessary to sensitize children with a negative parental history of atopy were 20 times higher than those able to sensitize children with a positive family history (33). Moreover, epidemiological studies suggest that a two-fold reduction of allergen exposure at community level would significantly reduce sensitization rates in early childhood (19, 108). Whether this will reduce the risk of subsequent asthma or its severity remains to be proved, but preliminary results from early interventions are not promising (21).

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