

House dust mite exposure as a risk factor for asthma: benefits of avoidance

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There is a dose-response relation between the level of exposure to house dust mite allergen and the risk of acquiring sensitization to this allergen as well as the risk of developing asthma. This relation is apparent at levels of exposure below 10 $\mu\text{g/g}$. In communities where nearly all houses have house dust mite allergen levels above this threshold, all susceptible individuals will be affected, and the relation to house dust mite exposure will not be apparent. Although these observational data would suggest that reducing exposure to house dust mite allergen should lessen the risk of developing sensitization and asthma, definitive evidence from randomized controlled trials is not yet available. Of the many clinical trials of house dust mite avoidance as therapy for asthma, only a few have produced sustained, substantial reductions in allergen levels in the bed. These effective interventions all included allergen-impermeable encasement of mattresses along with other strategies. In most trials where allergens levels were successfully reduced, there were clinical benefits for patients with asthma.

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Asthma is a complex disorder usually characterized by a prolonged and often fluctuating course which is punctuated by acute exacerbation. Remissions and relapses may occur (1–3), and, in those in whom the disease persists, outcomes vary from mild to severe effects on lifestyle (4), with occasional deaths attributable to asthma. Environmental factors such as house dust mite (HDM) exposure may have important effects on asthma at any of these stages in the course of the illness.

The potential benefits of avoiding exposure to HDM allergen start with the possibility of preventing the onset of asthma: either by preventing sensitization or by preventing the onset of symptoms, airway hyperresponsiveness, and asthma after sensitization is acquired. If the disease is already established, then the benefits of HDM avoidance relate to altering the course of the illness and improving disease outcomes.

HDM exposure and allergic sensitization

Ecologic evidence supports the hypothesis of an aetiological association between HDM exposure and sensitization (5–7). For example, among six regions of New South Wales, Australia, where the average

levels of HDM allergen in children's beds ranged from 0.7 to 47.8 $\mu\text{g/g}$ dust, the prevalence of sensitization to HDM among children ranged from 12.7% to 34.4% (Fig. 1) (7). The three centres with average HDM levels below 10 $\mu\text{g/g}$ had a lower prevalence of sensitization than the centres with higher levels of HDM exposure.

Studies linking the presence of allergic sensitization with individuals' own HDM exposure have yielded apparently conflicting results. In a group of 68 atopic schoolchildren attending an asthma clinic, the presence of skin test reactivity to HDM was strongly associated with the presence of detectable airborne Der p 1 (odds ratio 8.3, $P < 0.001$) or the presence, in dust collected from the floor, of Der p 1 concentrations of $> 0.5 \mu\text{g/g}$ (OR 5.4, $P < 0.005$) (8). Similarly, in Stockholm, where HDM-allergen levels are generally low, HDM-sensitized children had higher concentrations of HDM allergen in mattress dust than atopic subjects who were not allergic to HDM and nonatopic subjects (9). This observation was confirmed in a study of children with asthma in three regions of Sweden: sensitization to HDM was more common in children living in houses where household dust specimens contained $> 2 \mu\text{g/g}$ Der p 1 allergen (10). The dose-

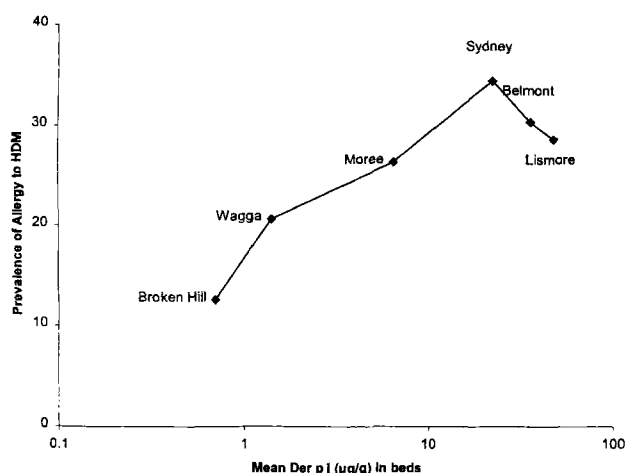


Fig. 1. Relation between exposure and sensitization to house dust mite allergen in children in six regions of New South Wales, Australia (data from Peat et al. [7]).

response relation between exposure and risk of sensitization was apparent at levels below 2 µg/g (11). Among a group of atopic children in Germany, the level of sensitization to HDM allergen was correlated with the concentration of Der p 1 allergen in dust from their mattress (12). In northern Norway, a study comparing HDM-allergic and nonallergic children found that Der p 1 concentrations of >25 ng/m² were found only in mattresses belonging to HDM-sensitive children (13). In these generally low-HDM environments, a dose-response relation between exposure and sensitization to HDM has been observed.

However, additional factors must be involved in the induction of mite allergy, since several other studies have failed to confirm any relation between HDM-allergen exposure and the presence of allergy to HDM. Among children and adults attending general and allergy clinics in Baltimore (USA), there was no significant difference in the HDM-allergen content of vacuum-cleaner dust collected from 42 HDM-allergic subjects (mean 1.32 µg/g) and 49 non-HDM-allergic subjects (mean 0.68 µg/g, $P=0.64$) (14). In both groups, the allergen levels were very low. Among school-children in Sydney, where HDM-allergen levels are very high, we found higher levels in the beds of children who were not allergic to HDM than in the HDM-allergic children (64 µg/g vs 41 µg/g, $P=0.006$) (15). This raised the possibility that families with allergic children had taken some avoidance measures, but we could find no evidence to support this.

There are many problems in identifying risk factors with data from cross-sectional or case-control studies. Data on the incidence of sensitization to HDM allergen in initially nonsensitized 7-year-old children in Germany have helped to

clarify the issues (16). Over a 2-year period of follow-up, the incidence of new cases of sensitization to HDM allergen was 3.2–6.7%, depending on the definition applied. In the subgroup who were sensitive to other allergens at baseline, and hence were genetically or otherwise at greatest risk of acquiring sensitization to new allergens, the risk of incidence of new HDM allergy was increased if they had >2 µg/g Der p 1 in dust collected from their mattress. If the Der p 1 level was >10 µg/g, the odds ratio for incidence of sensitization in this subgroup was 4.7 (95% confidence interval 1.7–10.4).

The benefits of HDM avoidance for prevention of sensitization have not been adequately evaluated. A clinical trial of HDM avoidance and food-allergen avoidance, conducted on the Isle of Wight, UK, showed a reduction in the prevalence of both positive skin prick tests to HDM and eczema at ages 1, 2, and 4 years in the intervention group (17–19). It is not possible to be certain of the relative importance of HDM avoidance and food-allergen avoidance in achieving this. However, another trial of food-allergen avoidance for prevention of atopic disease had a negative outcome (20); therefore, it might be inferred that the HDM avoidance was responsible for the positive outcome in the Isle of Wight study.

Some years ago it was proposed that exposure to Der p 1 at a level of >2 µg/g was associated with an increased risk of sensitization to HDM allergen (21). It now seems likely that a threshold, below which sensitization does not occur, is either much lower than 2 µg/g or does not exist (8, 11). Over a wide range of exposure levels, there is a dose-response relation between the level of exposure and the risk of sensitization. On the other hand, there does appear to be an upper limit on the dose-response relationship: that is, a level above which further increases in exposure do not cause any further increase in risk of sensitization. This upper limit is probably around 10 µg/g. In populations such as children living in Sydney, where virtually everyone is exposed to HDM levels of >10 µg/g, other factors influence the risk of developing allergy. In these settings, all predisposed individuals are exposed to sufficient HDM allergen to cause them to become sensitized. In summary, HDM exposure is a necessary, but not sufficient, factor in the development of HDM sensitization.

HDM exposure and the prevalence of asthma

The degree of increased risk of asthma associated with exposure to HDM was first measured by Korsgaard (22). The mite density in dust collected

from the mattresses and floor coverings of 25 mite-allergic subjects with newly diagnosed asthma was significantly ($P < 0.02$) higher than the mite density in dust from control subjects. The odds ratio for asthma if exposed to > 100 mites/g of mattress dust was 6.8. The relevance of early childhood exposure to HDM for the subsequent development of asthma was investigated in the UK (23). In children born to atopic parents, the risk of having asthma at age 11 years was 4.8 times higher in children who, at age 1, were exposed to > 10 $\mu\text{g/g}$ Der p 1 than those exposed to lower concentrations ($P = 0.05$). Indeed, only one subject who was exposed to < 10 $\mu\text{g/g}$ at age 1 year had asthma at age 11.

The impact on a population of changes in HDM levels was dramatically observed in Papua New Guinea. Here the accidental introduction of this exposure with blankets led to an epidemic of asthma associated with allergy to HDM (24, 25).

However, as for sensitization, there are conflicting findings in some settings. Among HDM-allergic Sydney schoolchildren, who were all exposed to high levels of HDM allergen, there was no difference in the level of exposure between those with and without asthma (15). Similarly, in Strasbourg, France, HDM-allergic patients with asthma and matched controls did not differ in the levels of HDM allergen in mattress dust (26); in Taiwan, during winter, HDM-allergen levels were lower in the homes of children with asthma than in those of allergic and nonallergic asymptomatic controls (27). As in Sydney, allergen levels were high: in Strasbourg, 69% of samples had levels of > 10 $\mu\text{g/g}$. As noted above, it seems likely there is an upper limit on the dose-response relation between exposure and risk of disease.

Peat et al. gathered data over a very wide range of exposure levels by using a mixed ecologic and cross-sectional design in studying children in six centres in New South Wales with varying climates. Mean levels of Der p 1 in beds in a sample of houses ranged from 0.7 $\mu\text{g/g}$ in Broken Hill in the dry hinterland to a mean of 47.8 $\mu\text{g/g}$ in Lismore on the coast. They found that the risk of asthma associated with HDM allergy correlated with the mean Der p 1 level in each centre (7). The risk approximately doubled with each doubling of HDM-allergen levels. Exposure to HDM allergen is an important risk factor for asthma: both as a cause of sensitization and as a cause of disease in sensitized subjects. It follows that one important potential benefit of HDM avoidance is the primary prevention of asthma. This benefit has not yet been established in a clinical trial. However, randomized controlled trials of HDM-allergen avoidance initiated from birth for the prevention of allergic

sensitization and asthma are in progress in several countries.

The effect of HDM-allergen exposure on the severity of asthma

Observational and experimental studies have been conducted to examine the influence of mite-allergen exposure on the severity of asthma, and hence the potential benefits which may arise from interventions which reduce exposure. Experimental studies (randomized controlled trials) provide the highest level of evidence, but, in this field, many such studies have been limited by the ineffectiveness of the trial intervention in substantially changing the level of HDM allergen. For this reason much of the evidence relies on observational studies: uncontrolled before and after studies or cross-sectional surveys.

Observational studies

Some cross-sectional studies among patients with asthma have demonstrated a relation between exposure to allergen and the severity of asthma. In HDM-allergic children with asthma in The Netherlands, the level of HDM allergen in dust collected from the floor was related to the severity of asthma measured as variability in peak expiratory flow rate and frequency of attacks of shortness of breath over a 4-week study period (28). Similarly, among patients with asthma and allergy to HDM who were recruited from general practices in Manchester, UK, those with airway hyper-responsiveness (AHR) were exposed to higher levels of HDM allergen in the bed (geometric mean 13.2 $\mu\text{g/g}$) than those who did not have AHR (1.5 $\mu\text{g/g}$, $P < 0.02$) (29). Furthermore, the level of HDM allergen in the bed was correlated with several measures of severity of asthma: degree of AHR, lung function, and peak flow variability.

A number of studies have taken advantage of natural variation in the level of HDM exposure to examine the relation to the manifestations of asthma. Seasonal fluctuations in mite-allergen levels are associated with changes in the risk of exacerbation of asthma in the USA (30) and with variation in the severity of AHR in The Netherlands (31).

In Israel, where HDM counts were high, no correlation was found between change in mite counts and symptoms, lung function, or AHR (32). This study relied on mite counts and included only 17 subjects. In our study among adults with asthma, who also lived in a high HDM environment in Sydney, changes in HDM-allergen levels in the bed,

measured at 3-month intervals, did correlate with changes in the severity of AHR and symptom scores recorded by diary cards (Fig. 2) (33). However, the strength of association was only modest: large changes in HDM levels were associated with small changes in measures of asthma. In a generally low-HDM-allergen environment in Vancouver and Winnipeg, Canada, the severity of symptoms and impairment of peak expiratory flow, both recorded daily over a year, among children (but not adults) with asthma was correlated with the level of HDM allergen in their beds (34).

A number of uncontrolled, before and after studies have demonstrated improvements which

may well be attributed to reduction in HDM exposure. Admission to a hospital room in which allergen levels were very low resulted in substantial improvements in symptoms, lung function, medication requirement, and AHR in some, but not all, subjects (35). Similarly, moving from the humid Mediterranean coast of France, where HDM-allergen levels are high, to a low-mite environment in the French Alps (36) or from the plains of Italy to the Alps (37) has resulted in impressive reductions in the severity of asthma and levels of anti-HDM IgE. These improvements are reversed on returning to the high-HDM environment. In The Netherlands, children admitted to a high-altitude asthma

Table 1. Placebo-controlled trials of allergen avoidance in HDM-allergic subjects with asthma

Age group	City	Intervention(s)	n (intervention/ control)	Length of follow-up	Reduction in HDM (compared with control)	Clinical benefit (compared with control)	Year	Citation
Adults	Cardiff (UK)	Washing, vacuuming, encasing mattress	32 (crossover)	6 weeks	Not measured	none	1976	(57)
Children	Cardiff (UK)	Washing and vacuuming	26/27	8 weeks	No	None	1980	(58)
Adults	Aarhus (Denmark)	New bedding, vacuuming, washing, reduce indoor humidity, remove carpets	23/23	6 months	Floor but not mattress	Symptoms	1983	(39)
Children	Vancouver (Canada)	Encasing, washing, dusting, remove soft furnishings and carpets	10/10 ¹	4 weeks	Not measured	Symptoms, medication, lung function, AHR	1983	(40)
Adults	Liverpool (UK)	Encase mattress, synthetic and cotton bedding, bedding washed weekly, remove carpets, reduce indoor humidity	15/20	12 months	Yes	Lung function, symptoms, medication, IgE, AHR	1986	(41)
Children	Harrogate (UK)	Encasing mattress and pillow; vacuuming	13/12	6 weeks	Yes	None (except IgE)	1987	(42)
Adults	Glasgow (UK)	Liquid nitrogen to mattress and carpets	9/9	8 weeks	Yes	Wheezing, AHR	1988	(43)
Children	Berlin (Germany)	(1) BB ² to mattress and carpets (2) Encase mattress and pillows; TA to carpets	8/8/8	12 months	(1) No (2) Yes	(1) None (2) AHR	1992	(44)
Adults	Washington, DC (USA)	Encasing mattress and pillows, removing carpets and upholstered furniture, hot washing bedding, reducing indoor humidity	26/26	12 weeks	No ³	Symptoms	1992	(45)
Adults	Strasbourg (France)	BB to mattress, bedding and furniture	11/12	12 months	No	None	1993	(46)
Children	London (UK)	Ionisers	20 (crossover)	6 weeks	Yes (aeroallergen)	None	1993	(47)
Adults	Sydney (Australia)	BB/TA ⁴ to bedding, furniture and carpets; encase mattress	17/18	6 months	Transient only	None	1994	(48)
Adults	Baltimore (US)	BB to carpets	6/6	12 months	No	None	1994	(49)
Children	Italy	BB to mattress	14/10	Short term	No	None	1994	(50)
Children	Bristol (UK)	BB to bedding, furniture and carpet; encase bedding; hot wash bedding	23/26	6 months	Yes	Symptoms, bronchodilator usage	1996	(51)
Children	Southampton (UK)	Encase mattress	31 (crossover)	3 months	Yes	Essentially none ⁵	1997	(52)
Adults	Groningen (The Netherlands)	(1) Air filter (2) encase mattress (3) air filter and encase mattress	15/15/15	6 months	Yes (in mattress in groups 2 and 3)	AHR in group 3 compared with groups 1 and 2	1997	(53)

¹Possibly nonrandom assignment.

²BB: Benzyl benzoate (an acaricide).

³Significant reduction in both active and control groups but no difference between groups.

⁴TA: tannic acid, which denatures allergen.

⁵Reduction in one of three eosinophil markers (possibly represents Type 1 error due to multiple comparisons)

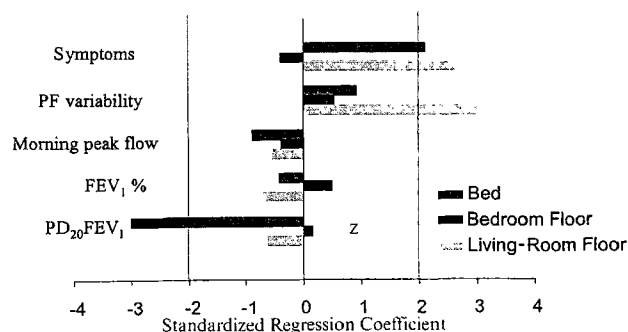


Fig. 2. Effect of changes in house dust mite allergen levels on outcomes of asthma (data from Marks et al. [33]).

centre showed reduction in blood eosinophilia, reduced peak flow variability, and improved airway responsiveness to adenosine (but not to methacholine) (38).

Data from these uncontrolled studies support the view that substantial reductions in exposure to HDM allergen result in clinically significant improvements in outcomes of asthma. Furthermore, there is consistent evidence that the bed is the household site where HDM exposure is most important in relation to outcomes of asthma.

Randomized controlled trials

A number of randomized controlled trials, using various methods of HDM avoidance, have assessed the role of this modality in the treatment of asthma. These are summarized in Table 1. In nine studies, active avoidance intervention resulted in a reduction in HDM-allergen levels which was significantly greater than that observed in the control group (39, 41–44, 47, 51–53). However, in one of these, mite numbers were reduced only in the floor, not the bed (39); in another, only aeroallergen results were reported (47). The period of observation in two other studies (42, 43) was probably too short to cause any clinical benefit. In the remaining five studies, in which sustained reductions in HDM levels in the bed were observed, clinically relevant benefits were observed in four (41, 44, 51, 53). In addition, a nonrandomized controlled trial of “healthy homes” in Denmark (54) demonstrated substantial improvements in lung function, medication use, and symptoms of asthma.

Where HDM-avoidance interventions have been successful in producing a measurable, sustained reduction in HDM levels, particularly in the bed, this has been associated with evidence of clinical benefit. This has usually involved mattress encasement or similar intensive efforts directed at the bed. Where no sustained reduction in exposure was achieved, no clinical benefit was observed.

There is substantial evidence that effective

HDM-avoidance strategies which focus on the bed will produce improvements in outcomes for adults and children with asthma.

Conclusion

Exposure to HDM allergen plays a key role in the causation and persistence of asthma. Avoidance of exposure, particularly in early life (55, 56), may have a role in the primary prevention of asthma. This potentially important intervention requires further evaluation. There is little doubt that effective HDM-avoidance strategies will reduce the severity of established asthma. However, in many settings, it is difficult to achieve the substantial and sustained reductions in HDM exposure that are required for clinical benefit. The role of an allergen-avoidance strategy, alongside safe and effective pharmacologic interventions, in the management of asthma remains uncertain.

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