

The importance of allergens in the development of asthma and the persistence of symptoms

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The importance of allergies and allergens in the development and persistence of asthma is suggested by 3 lines of evidence. First, a number of epidemiologic studies demonstrate that sensitization to indoor allergens and the spores of the outdoor seasonal fungus *Alternaria* is a risk factor for the development of asthma in both children and adults. Sensitivity to pollens, on the other hand, rarely constitutes a risk for asthma but does constitute a risk for seasonal allergic rhinitis. Second, several studies, again in both children and adults, have demonstrated that, in persons sensitive to indoor allergens, the severity of asthma symptoms will vary with the level of exposure. Third, the elimination of exposure to house-dust mites has produced a remarkable reversal of asthma in sensitive children and adults. Not only have symptoms and pulmonary function improved, but there has also been evidence of a reduction in airway inflammation and hyperresponsiveness. Taken together, these studies make a strong argument for the importance of allergy and allergen exposure as aggravating factors in asthma in both children and adults and reinforce the importance of the identification and treatment of these allergen sensitivities. (*J Allergy Clin Immunol* 2000;105:S628-32.)

Key words: Allergic rhinitis, asthma, indoor allergens, pollen

Three lines of evidence support the importance of allergens in bronchial asthma. Investigators have linked allergen sensitization to the risk of asthma, have correlated asthma severity to allergen exposure, and have demonstrated improvement in asthma when the allergen exposure is reduced.

ALLERGEN SENSITIZATION AS A RISK FACTOR FOR BRONCHIAL ASTHMA

Allergen sensitization is a risk factor for the development of bronchial asthma in both children and adults. Sensitivity to indoor allergens and certain outdoor mold spores has been found to increase the risk of bronchial hyperresponsiveness and asthma symptoms in children. On the other hand, the data are fairly consistent that exposure to grass pollen, ragweed, or other geographically relevant pollen does not constitute a risk for asthma.

For example, a study by Sears et al¹ of children in New Zealand demonstrated that sensitivities to house dust

Abbreviation used

HDM: House dust mite

mite (HDM), cat, dog, and/or indoor mold spores were associated with an increased risk of the occurrence of asthma. However, this was not true for sensitivity to grass pollen. A group of children were followed up from birth until 13 years of age. They underwent skin testing for 11 allergens and responded to questionnaires about a history of wheezing episodes. The children were also tested for bronchial hyperresponsiveness. The most common sensitization in New Zealand is to grass pollen. Yet, children in this unselected group who were sensitized to grass pollen were not at significantly increased risk for the development of asthma symptoms with concurrent airway hyperresponsiveness. However, sensitivity to HDM, cat, dog, or an indoor mold spore (*Aspergillus fumigatus*) conveyed an increased risk of current asthma. Because HDM sensitivity so greatly exceeded the other sensitivities, it was clearly the most important risk factor in these New Zealand children.

Other supporting studies include those from Japan,² Africa,³ and the United States.^{4,5} Shibasaki et al² measured HDM-specific IgE levels in 419 school-aged children in Japan. The incidence of asthma correlated with the concentrations of IgE for HDM but not grass pollen. Cookson et al³ found that the risk for bronchial hyperresponsiveness in young subjects increased 4-fold for those who were skin-prick test positive to HDM and nearly 6-fold for those who were sensitive to a mix of indoor and outdoor molds but that there was no significantly increased risk for those subjects who were sensitive to grass.

In the United States, Henderson et al⁴ examined factors linked to recurrent wheezing in a case-control study of 343 children 7 to 12 years of age who had been recruited from a general pediatric practice. Positive skin test results were observed in 77% of children with a history of 2 to 4 episodes of wheezing and in 90% of children with 5 or more episodes but in only 35% of those children with no recurrent wheezing. The antigens most frequently associated with wheezing were HDM, cat, and *Alternaria*. However, sensitization to pollen was not associated with recurrent wheezing. The second National Health and Nutrition Examination Survey also evaluated the association of individual allergen sensitivity with asthma and allergic rhinitis in the United States. Gergen and Turkeltaub⁵ studied 4295 children and young

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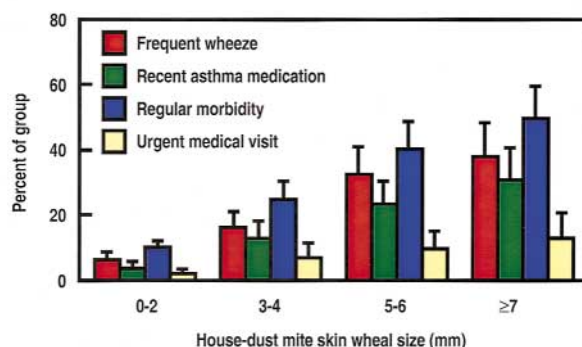


FIG 1. Childhood asthma and HDM sensitivity. (Adapted from Peat JK, Tovey E, Gray EJ, Mellis CM, Woolcock AJ. Asthma severity and morbidity in a population sample of Sydney school children: part II: importance of house dust mite allergens. *Aust NZ J Med* 1994;24:270-6. With permission.)

adults 6 to 24 years of age and measured allergen reactivity by skin-prick test. Asthma without allergic rhinitis was associated with sensitivity to house dust and *Alternaria*, whereas allergic rhinitis without asthma was associated with reactivity to ryegrass, ragweed, and house dust.

Similar data have been reported for adults. In Australia, Duffy et al⁶ compared risk factors for the development of wheezing and bronchial hyperresponsiveness in adult monozygotic twin pairs. A positive skin-prick test result to HDM was the most important risk factor in the monozygotic twins, followed by sensitivity to cat and cockroach allergens but not to grass pollens and fungi. The Veterans Administration Normative Aging Study⁷ found that sensitivity to cat was a risk factor for new onset of bronchial hyperresponsiveness in the middle-aged male population in the United States, although ragweed sensitivity was not. A group of adults in France with allergic rhinitis, almost one half of whom had asthma, was evaluated to identify factors associated with asthma.⁸ Several factors were found: atopy, high total IgE levels, a maternal history of asthma, elevated blood eosinophil count, and sensitivity to indoor allergens. Sensitivity to pollen was correlated with uncomplicated seasonal allergic rhinitis and not with asthma.

In most parts of the world, sensitivity to HDM is the most consistent risk factor for the development of asthma in both children and adults. Peat et al⁹ studied an unselected group of 8- to 11-year-old children in Australia who underwent a questionnaire for asthma symptoms and measurements of bronchial hyperresponsiveness and atopy. The investigators determined that wheezing, recent asthma medication, and urgent medical visits for the treatment of asthma symptoms were correlated with a positive skin test result to HDM and were most common in the children with marked skin test reactivity to mite (Fig 1).⁹ Similarly, bronchial hyperresponsiveness was strongly correlated with the presence of a positive

skin prick test result to HDM, and the greater the size of the skin wheal formed in response to the HDM test, the greater the degree of bronchial hyperresponsiveness.⁹

Researchers also investigated the relationship of HDM sensitization and asthma in adults 18 to 73 years of age in Bergen, Norway.^{10,11} A serologic study measured the presence of specific IgE antibodies to several indoor allergens and outdoor pollens. The FEV₁ was lower in those patients who had IgE antibodies to HDM,¹⁰ and bronchial hyperresponsiveness was also more apt to be present in those patients with IgE antibodies to HDM, cat, or mold *Cladosporium herbarum*.¹¹ However, antibodies to either timothy or birch were not associated with increased risk for either lower FEV₁ or increased bronchial hyperresponsiveness.

ALLERGEN EXPOSURE AND SEVERITY OF ASTHMA

Researchers have shown in both children and adults that the severity of asthma symptoms will vary with the level of exposure in persons sensitive to indoor allergens.

Several studies support the importance of allergen exposure in persistent asthma in children. A report by Zock et al¹² from the Netherlands showed a correlation between levels of HDM allergen in children's carpets and both asthma symptoms and peak airflow variability. Chan-Yeung et al¹³ found a relationship between levels of HDM in homes of children with asthma and both daily asthma symptoms and mean daily peak airflow. Rosenstreich et al¹⁴ studied inner-city children with asthma and reported that exposure to cockroach antigen in sensitized children was associated with an increased number of hospital days, unscheduled physician visits, asthma symptoms, and number of days missed from school. Peat et al¹⁵ studied 6 different regions of Australia with different levels of humidity and concentrations of HDM. Going from lowest to highest HDM-

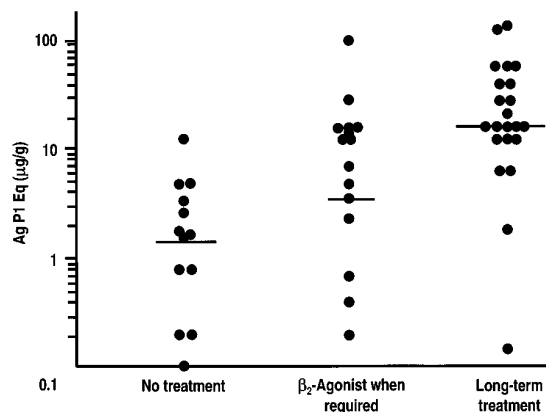


FIG 2. HDM exposure and asthma treatment required. Ag P1 Eq is the sum of major allergens Der p I and Der p II. Each patient is represented by a single dot. The horizontal bars represent the mean level computed in each group. (Adapted from Vervloet D, Charpin D, Haddi E, N'guyen A, Birnbaum J, Soler M, et al. Medication requirements and house dust mite exposure in mite-sensitive asthmatics. *Allergy* 1991;46:544-8. Copyright 1991, Munksgaard International Publishers Ltd, Copenhagen, Denmark.)

infested areas was associated with an increased prevalence of HDM-positive skin test results, ranging from 13% at the low end to 29% at the high end. Furthermore, each doubling of exposure level to HDM was associated with a doubling of the prevalence of current asthma in children with positive skin test results for HDM. (Current asthma was defined as wheezing plus bronchial hyperresponsiveness.) Sporik et al¹⁶ selected 67 children who had been identified by having 1 parent with either allergic rhinitis or asthma and followed up with them until they were 11 years of age. Exposure to greater than 10 µg Der p I (HDM) per gram of dust at 1 year of age was associated with a 5-fold greater likelihood of asthma at age 11. Also, the greater the exposure at 1 year of age, the earlier the onset of asthma.

Similar results have been reported in adults. Custovic et al¹⁷ studied a population whose mean age was 41 years. They reported a positive correlation between HDM exposure and bronchial hyperresponsiveness and a negative correlation with FEV₁. Van der Heide et al¹⁸ studied 9 adults with asthma with an isolated allergy to HDM. The researchers measured the concentration of Der p I in floor dust from living rooms and bedrooms. Both the levels of HDM and bronchial hyperresponsiveness peaked in late summer and autumn, and both were lowest in the spring.

An interesting study from the highlands of Papua, New Guinea noted that the prevalence of asthma in the South Fore area had increased from 0.1% to 7.3% over several decades.¹⁹ More than 90% of patients with asthma had a positive skin test result to HDM. However, HDMs were found almost exclusively in blankets introduced by missionaries in that area in the 1950s. Together these facts strongly implicated the HDM in the blankets as the cause for the increase in asthma. As a control

study, the investigators looked at another area in eastern New Guinea that was located at the same altitude but that had a drier climate. Blankets had been introduced there simultaneously, but no increase in asthma had been noted. The HDM levels in those blankets were only one fifth of those found in the blankets in the South Fore area, which further supported the role of allergen exposure in the development of asthma.

A study by Vervloet et al²⁰ studied 49 patients with asthma and a positive skin-prick test result to HDM. Dust samples from the patients' mattresses were analyzed for HDM, and these values were compared with the severity of asthma as indicated by the requirement for asthma medication (Fig 2).²⁰ Patients who used β_2 -agonists on an as-needed basis were exposed to a middle range of mite antigen. Those who required regular treatment with medication were exposed, on average, to well over 10 µg of HDM antigen per gram of dust, a level that is sometimes said to be the amount needed to cause active asthma.

Other data suggest that allergens can also be implicated in asthma deaths. Campbell et al²¹ studied the pattern of deaths from asthma in England and Wales and found that the pattern varies with the age of the patients. For individuals younger than 45 years of age, the peak of asthma deaths occurs during the summer (July and August). For those individuals 65 years of age or older, the peak shifts to November through March. Interestingly, both peaks for deaths from asthma are found in those individuals 45 to 64 years of age. June through early July is the grass pollen season in these areas, but outdoor molds are highest during the periods of peak asthma deaths in those individuals 44 years of age or younger.

A second analysis of seasonal variation in asthma deaths was made by Weiss,²² who studied US hospitalization and mortality statistics from 1982 through 1986. He found a similar difference in age and peak likelihood of death from asthma. In the group that was 5 to 34 years of age, the highest death rate from asthma was in the period from June to August, but in those individuals 65 years of age or older, the peak came during the winter.

Finally, Targonski et al²³ studied asthma deaths in individuals 5 to 34 years of age in Chicago from 1985 through 1989 and found that mold spore levels (but not tree, grass, or ragweed pollen levels) were high on days when asthma deaths peaked. The odds of an asthma-related death were 1.2 times higher for every increase of 1000 spores per cubic meter in the daily mold spore level.

These studies suggest that molds are implicated as a particular risk factor for death in individuals with asthma; this is consistent with the data from Weiss²² because grass peaks in most parts of the United States in June, weeds peak in late August, and mold spores peak between these 2.

Additional supporting data come from O'Hollaren et al.²⁴ Researchers from the Mayo Clinic identified 18 episodes of sudden-onset respiratory arrest in 11 adolescents and young adults. All these occurred in the summer and early fall, the typical peak period in the United States for *Alternaria* and other mold spores (Fig 3).²⁴ Ten of the

Figure available in print only.

FIG 3. Timing of episodes of respiratory arrest in young patients with asthma. Each circle corresponds to 1 episode. (Adapted with permission from O'Hollaren MT, Yunginger JW, Offord KP, Somers MJ, O'Connell EJ, Ballard DJ, et al. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. *N Engl J Med* 1991;324:359-63. Copyright © 1991, Massachusetts Medical Society. All rights reserved.)

11 patients (91%) had positive skin-prick test results for *Alternaria* compared with 31% of 99 age-matched control subjects, a significant difference ($P < .001$). After an adjustment was made for age, sensitivity to mold was associated with a 200-fold increased risk of respiratory arrest.

IMPROVEMENT IN ASTHMA WITH REDUCTION OF ALLERGEN EXPOSURE

A final line of evidence for the role of allergens in bronchial asthma comes from the improvement of asthma symptoms and bronchial hyperresponsiveness when allergen exposure is reduced. For example, several studies show that condition of children with asthma improves when these children are in dust mite-free environments and relapse when the children return to areas more prone to dust mites.^{25,26} The condition of Italian children with asthma who were sent to an hospital for the treatment of asthma in the Italian Alps (where there are no HDMs because of the elevation) improved when they were in the mite-free area and then relapsed when they returned to their homes in the more humid coast cities of Italy.^{25,26} Parameters that change when exposure to HDM is removed include reduced asthma symptoms, increased peak flow levels, decreased bronchial hyperresponsiveness, reduced HDM-specific IgE levels, and decreased numbers of eosinophils and epithelial cells in induced sputum. Concentration of inhaled histamine or methacholine required to reduce FEV₁ by 20% (PC₂₀), a negative measure of bronchial hyperresponsiveness, was measured in September when the children with asthma left home for the mountains and in December just before they left the mountains to go home for Christmas vacation (Fig 4, A).²⁵ An upward shift in PC₂₀ levels, reflecting a decrease in bronchial hyperresponsiveness, occurred by December as a result of removal from HDM exposure. A reduction in the percent of eosinophils in hypertonic saline-induced sputum also showed an improvement denoted by a reduction in cell count when HDM exposure was eliminated (Fig 4, B).²⁵

A classic study of reduction in HDM exposure was conducted in young adults with asthma by Platts-Mills et al.²⁷ These patients who were allergic to HDM slept in hospital rooms with very low levels of mite antigens for 2 months or more. HDM levels were less than 2% of those in the individuals' homes. The subjects were

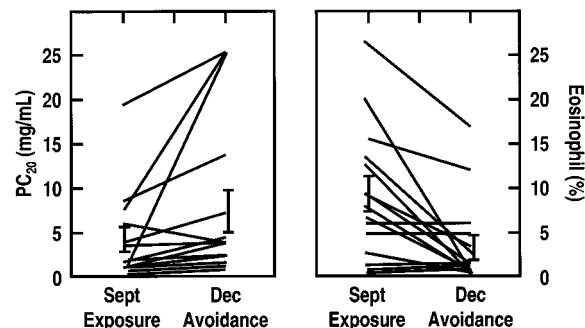


FIG 4. The effect of allergen avoidance on childhood asthma. Shaded lines show changes in the study population, which, for graphic purposes, have been expressed as means $\pm$ SEM. (Adapted from Piacentini GL, Martinati L, Mingoni S, Boner AL. Influence of allergen avoidance on the eosinophil phase of airway inflammation in children with allergic asthma. *J Allergy Clin Immunol* 1996;97:1079-84. With permission.)

allowed to leave the hospital but not to visit any homes or to have contact with animals. Further, if pollen-sensitive, the individuals were studied outside the pollen season. Five of the 9 young adults showed an 8-fold or greater improvement in bronchial hyperresponsiveness with the decrease in HDM exposure.

One factor that contributes to the increase in asthma over the last 25 years is the increase in home insulation in response to the "energy crisis." Insulation of homes causes a marked drop in the exchange rate at which outdoor air is introduced into the home. Before the mid-1970s, houses were very porous, and complete air exchanges occurred often in the average American or European house. With the advent of insulation, the number of air exchanges per hour decreased. In Denmark, the air and heat exchange systems in identical apartments were modified to restore the previous levels of air exchange, an increase from an energy-efficient 0.4 air exchange per hour to a typical older value of 1.52 exchange per hour.^{28,29} Several families who had members with asthma who were sensitive to HDM were moved into these modified apartments. The HDM count in the mattresses decreased from 110 mites per gram of dust to 20 mites per gram of dust during the first 5 months and then continued to decline.²⁸ The 14 individuals with asthma who were HDM sensitive and who were moved had improved FEV₁ levels, decreased medication scores, and decreased total IgE levels after 5 months.²⁹ After 15 months in the healthy apartments, they also experienced improvement in peak expiratory flow rates and asthma symptoms.²⁹

SUMMARY

Many studies demonstrate the important role allergens play not only in the initiation of asthma but also in its persistence. The severity of asthma in children and adults is

related to the levels of allergen exposure. Asthma symptoms and bronchial hyperresponsiveness are improved by the reduction of allergen exposure.

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