

to increasing production and accumulation of moisture in homes (frequent showers, new cooking methods, inadequate airing of bedrooms, etc.).

From 1981 to 2000, the Scientific Institute of Public Health sampled more than 500 home environments of allergic and/or asthmatic patients in urban or rural areas throughout Belgium. Results showed that more than 150 fungal species, among them *Cladosporium*, *Penicillium* and *Aspergillus*, were collected in 90–98% of the sampled environments. *Cladosporium sphaerospermum* was found in 60% of the dwellings, with the highest levels of contamination especially in bedrooms and bathrooms (hundreds of spores/m³). *C. sphaerospermum* is often associated with *Aureobasidium pullulans*, *Phoma* sp., *Acremonium strictum* and some yeast on window frames, whereas *Cladosporium herbarum*, which is an outdoor mould, does not grow in dwellings. However, its spores invade home environments through open doors and windows, mainly during the summer months.

Aspergillus versicolor, *Penicillium chrysogenum*, *Penicillium aurantiogriseum*, *Penicillium spinulosum*, *Penicillium brevicompactum*, *Chaetomium globosum*, *Stachybotrys chartarum*, *A. strictum* and *Alternaria alternata* are sometimes found in huge quantities on walls in bedrooms, living rooms and kitchens, most frequently inducing allergic asthma.

Mattresses are also often badly looked after, and the concentrations of dust are often quite important: 10³–10⁷ spores/g of dust. In temperate regions, moulds, like mites, are thriving in environments that are excessively moist because of a lack of ventilation and new living conditions. In tropical zones, the conditions that stimulate the growth of moulds are found naturally. Among the most frequent species, *C. sphaerospermum*, *A. alternata*, *Epicoccum purpurascens*, *A. pullulans*, *Aspergillus restrictus* and *A. versicolor*, various species of *Mucorales* and *Trichoderma* should be pointed out. Mould strips due to *C. sphaerospermum* can even sometimes be seen at contact point of mattresses and fixed bedslats.

It should also be noted that some Basidiomycetes grow mainly in enclosed spaces. *Serpula lacrymans* or *Merulius lacrymans* is the dreadful dry rot responsible for considerable damage in dwellings. This fungus attacks damp wood and can very rapidly grow across timber and even walls. It only develops in enclosed spaces. For about 20 years now, lack of ventilation in present dwellings has made this fungus active again, and cases of sensitization have been diagnosed.

Mycotoxins associated with moulds are secondary metabolites with low molecular weight compared with allergens. It is well known that ingestion of mycotoxins (ex. aflatoxins) can cause illness and even prove fatal for Man. According to various studies, it has been established now that inhalation of the same amounts of mycotoxins is even more toxic. Trichothecenes produced by *S. chartarum* and various *Fusa-*

rium spp., patulin, and penicillic acid produced by various *Penicillium* have shown acute toxicity. Large areas contaminated by *S. chartarum* and *A. versicolor* can sometimes be seen on damp walls in dwellings. Great care should thus be exercised with patients living in 'musty' dwellings and complaining of irritation symptoms and nausea when at home.

B1–3 glucans, components of the walls of moulds, act as potent inflammatory agents. Their role as asthma exacerbator in musty homes should not be neglected.

In summary, moulds are linked at different stages to allergic reactions and more especially asthma:

- Some moulds (*Alternaria*, for example), like pollens, are potent allergens that can cause severe asthma, calling for emergency treatment.
- A lot of moulds produce secondary metabolites that accumulate in airborne spores. Inflammatory reactions, which play an important role in asthma, are consequently exacerbated by the inhalation of these spores.
- Some moulds produce toxins that directly work on and sensitise the bronchus and lungs.

In fact, people should not be allowed to live in environments contaminated by moulds and fungi.

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Environmental allergen exposure and asthma: prospects for primary prevention

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Why are asthma and atopy increasing – relevance for prevention

The observed increase in asthma prevalence cannot be genetic in origin.¹ Many aspects of modern life

have changed and many theories advanced to explain this phenomenon.² While there is no direct evidence for the increase in allergen exposure, the indirect evidence is overwhelming. The indoor environment of homes has changed over the past three decades, making it more suitable for dust-mite population growth. The number of indoor pets has increased, resulting in increased community exposure.³⁻⁵ Houses have become better insulated, with lower air-exchange rates, resulting in exponential increases in concentration of potentially harmful substances in indoor air. At the same time as pet and mite allergens in reservoir dust have increased, personal exposure has increased even further due to the greater time now spent indoors, especially by children.

Concurrently, there could be an increased susceptibility of children, for example due to changes in diet, or the type and level of microbial stimulation. In terms of prevention, one way to modulate the immune response might be to stimulate a T helper cell (Th)1-like response in infancy (e.g. vaccination with Th1 promoting agent). Alternatively, and possibly additionally, early allergen avoidance may have an important effect. A reduction in exposure to allergens in early life may allow more time for the developing immune system to mature, so that when common inhalant allergens are encountered the predominant response to them does not resemble a foetal Th2-like profile, but more a mature Th1-like profile. Rather than stimulating a Th1 response early in life, perhaps allergen avoidance may give an immature immune system enough time to 'prepare' for the normal response to environmental allergens.

Risk factors for asthma with a potential for primary prevention

As the direct evidence of the primary risk factors that have led to the increase in asthma is lacking, the only way forward is to change the exposure to the risk factors, for which there is a good evidence of their association with asthma.²

Indoor allergens

The rising trend in asthma prevalence can be linked to a possible increase in exposure to allergens in the indoor environment. Over the past few decades, sales of pillows using synthetic fillings have increased enormously based on the concept that they are non-allergenic. However, synthetic pillows accumulate mite allergens faster and ultimately contain approximately five-fold more Der p 1⁶⁻⁸ and eight to 10 times more cat and dog allergen than feather pillows.⁹ A UK study found a moderate but significant increase by 20% in wheeze, and an increase of 16% in a 12-month period in the prevalence of wheezing attacks

between 1978 and 1991.¹⁰ The prevalence of wheeze was negatively associated with the use of feather pillows (reduction in the odds of 36% for infrequent wheeze and 61% for frequent wheeze). An observed rise in the use of non-feather pillows from 44 to 67% was large enough to explain more than one-half of the increase in wheeze.¹⁰ It is tempting to speculate that the increased use of non-feather pillows has contributed to increasing allergen exposure, which could be partly responsible for the increase in the prevalence of wheezing.

Sensitisation and exposure to indoor allergens and asthma.

Generally, individuals become sensitised to the allergens to which they are exposed. There is overwhelming evidence that sensitisation to dust mites is a major independent risk factor for asthma in all areas where climate is conducive to support mite population growth.¹¹⁻¹⁴ For allergens other than mites, the relationship depends on the climate, habits and socio-economic features of the local community.¹⁵⁻¹⁸ It was relatively straightforward to demonstrate a quantitative dose-response relationship between exposure to mite allergens and subsequent sensitisation.¹⁹⁻²¹ Early infancy has been identified as a critical period for primary sensitisation.

Pet ownership, sensitisation and asthma.

In recent years, different groups of investigators have published intriguing and often conflicting data on the effect of pet ownership in early life on the subsequent development of sensitisation and asthma. Some studies found that exposure to pets in early infancy was associated with specific immunoglobulin E (IgE) sensitisation and allergic disease later in childhood,^{22,23} while others reported the opposite finding - an apparent protective effect.^{24,25} The difficulty in interpretation relates to the retrospective nature of the studies and the possibility of selection bias (e.g. parents at risk have got rid of pets). In the only prospective study with objective measurements of exposure, Wahn *et al.* demonstrated a strong positive dose-response relationship between cat allergen exposure and specific sensitisation during the first 3 years of life.²¹

At present, it is difficult to explain these apparently irreconcilable differences between studies. First, prospective studies indicate that extremely low levels of cat allergen exposure are associated with some risk of sensitisation and that, at least in early life, there appears to be a dose-response relationship between exposure and sensitisation.²¹ Cat allergen is ubiquitous, and exposure outside the domestic environment may lead to specific IgE responses. A recent report has indirectly confirmed the potential importance of passive exposure, finding a significant correlation

between the community prevalence of cat ownership and community prevalence of sensitisation to cats, prevalence of respiratory symptoms, physician-diagnosed asthma and current asthma medication.²⁶ It is possible that later cat allergen exposure is a risk for disease, but early exposure to cats may be protective. Only the long-term prospective follow-up of well-defined cohorts, avoiding recall biases and with objective measure of exposure, will provide a definitive answer to this important question and inform a decision about appropriate public health strategies for prevention (i.e. having or not having a pet).

Primary prevention by environmental control

Occupational asthma is a useful model. Some patients develop asthma following exposure and sensitisation to a number of agents in the workplace. The treatment of choice is removal from the workplace. Early diagnosis and removal from exposure are associated with recovery, while long-term exposure in sensitised subjects can lead to persistence of symptoms and progressive deterioration of asthma, even after the sensitising agent is removed.²⁷⁻²⁹ Studies in occupational asthma indicate that it is crucially important to identify the sensitising agent as early as possible and that, if there is no exposure to the sensitising agent, the disease never develops.

Successful environmental control could be anticipated to have a greater impact on prevalence of asthma than interventions directed at other risk factors such as exposure to environmental tobacco smoke, dietary intervention and breast feeding.³⁰ So far, only one prospective, randomised study has investigated the efficacy of avoidance of indoor allergens (house-dust mites) in high-risk infants followed from birth (Isle of Wight Study).³¹⁻³³ This study has produced the first indications that even a modest reduction in mite-allergen levels in homes of infants at risk of allergy may reduce the prevalence of sensitisation to mites and recurrent wheezing during the first years of life. The trial was unfortunately complicated by the very complex nature of intervention strategy, including dietary advice to mothers during the pregnancy, as well as an attempt to reduce mite-allergen exposure by the use of benzyl benzoate (a relatively ineffective mite-allergen avoidance measure). Recently, a prospective study in Manchester has documented that mite avoidance measures can achieve and maintain a very low mite-allergen environment during pregnancy and in the first year of life in homes of infants at risk of atopy.³⁴

Several other ongoing studies are addressing this important question (Canada, Australia, The Netherlands, Southampton, UK). The results of these longitudinal studies are still awaited, as reasonable conclusions can only be drawn once the children reach at least 5 years of age.

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Allergen avoidance

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Allergen exposure and allergic diseases: allergens and relationship to allergic diseases

Exposure to allergens plays an important role in allergic diseases. It is essential for the induction of sensitisation (production of allergen-specific immunoglobulin E) and in communities with 'affluent' lifestyles that the prevalence of sensitisation to mites has been directly related to domestic mite-allergen concentrations.¹ However, the relationship of exposure to asthma occurrence and symptoms is more complex. Many factors affect this role, including genetic factors, immune/pathology patterns established in infancy, the nature and continuity of the allergen exposure, asthma phenotypes, other non-allergen factors affecting the disease (e.g. viral infections), concurrent pharmacotherapy, and time.² While events involving major increases or decreases in allergen exposure such as moving location may have parallel effects on asthma indices, the clinical effects of smaller changes in allergen exposure such as seasonal fluctuations³ or domestic interventions are often more difficult to distinguish.

While most allergen avoidance studies have focused on asthma, there is accumulating support that reducing exposure should also be applied to reducing the incidence of sensitisation (primary intervention)⁴ and in reducing the severity of atopic eczema.⁵ The role of allergen avoidance on managing perennial rhinitis is also underexplored.

Important allergens and their domestic ecology

Internationally, for asthma, the most important allergens are those from house-dust mites.⁶ In temperate regions, these are mites of the genus *Dermatophagoides*, and in tropical regions *Blomia tropicalis*. Their occurrence and distribution is largely driven by microclimate factors, which favour consistent warmth and humidity.⁷ Thus, domestic mite populations in coastal regions are greater than those in drier inland regions, and those in damper houses are greater than those in drier houses. Allergen levels > 10 µg allergen/g dust would be regarded as 'high' and those < 1 µg/g as 'low'.⁶ The mites populate reservoirs of shed human skin, particularly in beds, clothing, soft furnishings, toys and carpets. The allergens are associated with accumulated mite faeces and other dust particles, which become ubiquitously distributed throughout houses.⁸

Sources of other domestic allergens include pets, particularly cats and dogs,^{9,10} and, in some urban poorer groups, cockroaches.¹¹ When houses have a resident cat, allergen levels can exceed 10 µg allergen/g dust;^{12,13} in cat-free residences, allergens are usually present by ~300-fold less. 'Outdoor' allergens, particularly in dry regions, the spores of *Alternaria alternata* fungi and pollen grains, accumulate indoors and may be regarded as 'domestic' allergens.¹⁴ Many other domestic allergens also occur less frequently - sourced from plants, insects, rodents, foodstuffs, domestic products and furnishings. The original source of allergens may not always occur in the home - the presence of cat allergen in houses without a cat is the classic example;¹⁵ other allergens may also be introduced from occupational sources.

In addition, houses may contain additional materials that modulate the effects of allergens; these include biological materials such as endotoxin,¹⁶ chemicals in building and domestic products, and combustion products such as tobacco or wood-smoke.

Practising allergen avoidance

Numerous reviews and all comprehensive guidelines for asthma management advocate the avoidance of allergen exposure and of other airborne trigger factors.¹⁷ Such minimising of exposure is the logical extension of a causal role for allergen. It provides parents of at-risk infants and also people with asthma with an active role in long-term prevention and management of disease, and it is consistent with their anecdotal experiences and with cultural views that diseases can be controlled with greater attention to domestic hygiene.

However, the evidence base advocating avoidance of allergens in on-going symptoms is less conclusive. A recent meta-analysis of trials found no conclusive support for mite-allergen avoidance¹⁸