Allergen avoidance: does it work?

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The first recorded example of allergen avoidance in the treatment of allergic disorders dates from the 16th century. The Italian physician Gerolamo Cardano (1501–1576) was invited to Scotland by John Hamilton, Archbishop of St Andrews (and brother of the Regent), to give advice on the treatment of his asthma. Cardano recommended that the Archbishop should get rid of his feather bedding, which was followed by a ‘miraculous’ remission of otherwise troublesome symptoms. The first controlled attempts to treat asthma by environmental manipulation date to the beginning of 20th century. In 1925, the Leopold brothers treated patients with asthma and other allergic disorders by moving them into a dust free room. Storm van Leeuwen created a ‘climate’ chamber in The Netherlands in 1927 and demonstrated that asthmatic patients improved when moved from their homes into the chamber. One year later, Dekker observed that measures aimed at reducing the amount of dust in bedrooms had a beneficial effect on asthma symptoms in patients allergic to house dust. Van Leeuwen wrote: ‘In our endeavours to find the cause of the attack...we utilised the known fact that the environment of the asthmatic patient is, as a rule, of primary importance in determining the intensity and frequency of his attacks’. Nowadays, more than ever, it is essential to address the environmental influences on the increasing prevalence of asthma and allergic disorders.

The majority of people in the industrialised world spend most of their time inside one type of building or another, and the indoor environment has begun to attract deserved attention over the last several years. We are beginning to appreciate that living in a damp house may have more adverse effects on respiratory health than living next to a busy motorway. The indoor environment of modern homes contains many substances that can cause or exacerbate allergic disease in susceptible individuals. The major biological sources of allergens are acarids (e.g., house dust mites), insects (e.g., cockroaches), domestic animals (cats and dogs) and fungi, but also such sources as rodents and pollens derived from outside. In addition, environmental tobacco smoke (ETS), indoor air pollution (e.g., NO\textsubscript{2} and ozone) and endotoxin may have potential roles as the enhancers of both allergic sensitisation and disease.
Avoidance of indoor allergens

The effectiveness of allergen reduction in the treatment of asthma was first suggested by studies in which patients were removed from their homes into a low allergen environment of high altitude sanatoria. However, the real challenge is to create a low allergen environment in patients' homes. Although not easy, it is possible to achieve substantial reductions in allergen exposure. Effective control strategies should be tailored to individual allergens, flexible to suit individual needs and cost-effective.

Distribution and aerodynamic properties of indoor allergens-relevance to avoidance

Knowledge of the sources and aerodynamics of allergen-carrying particles is essential for the design of successful strategies to reduce personal exposure. Allergens from mites, cats, dogs and cockroaches have different aerodynamic properties (Table 1). Mite and cockroach allergens can be detected in the air in significant amounts only after vigorous disturbance, and are predominantly, but not exclusively, contained within relatively large particles (> 10 μm diameter). In contrast, airborne cat and dog allergens are readily measured in houses with pets (and in a quarter of the homes without pets), and ~25% of airborne Fel d 1 and Can f 1 is associated with small particles (< 5 μm diameter). This underlies the difference in the clinical presentation of the disease. Mite and cockroach sensitive asthmatics are usually unaware of the relationship between allergen exposure at home and asthma symptoms (exposure is low grade and chronic). The large particles, however, may contain a large quantity of allergen, and even small numbers may cause a significant inflammatory response when impacted in the airways. In contrast, cat or dog allergic patients often develop symptoms within minutes of entering a home with a pet due to the inhalation of large amounts of airborne allergen on

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Particle size</th>
<th>Airborne level</th>
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<tbody>
<tr>
<td>Mite:</td>
<td>Group 1 Large particles &gt; 10 μm</td>
<td>Undisturbed: Undetectable with conventional assays (&lt; 0.2 ng/m³ for mite allergens, &lt; 0.02 ng/m³ for cockroach)</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>Disturbed Detectable after vigorous disturbance</td>
</tr>
<tr>
<td>Cockroach: Blag 1 Bla g 2</td>
<td>Large particles &gt; 5 μm (-75%)</td>
<td>Homes with animal Detectable in all homes. Levels 4-5 times higher with animal in the room</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homes without animal Detectable in ~1/3 of the homes without artificial disturbance</td>
</tr>
<tr>
<td>Cat:</td>
<td>Fel d 1</td>
<td>Large particles &gt; 5 μm (-75%)</td>
</tr>
<tr>
<td>Dog:</td>
<td>Can f 1</td>
<td>Small particles &lt; 5 μm (-25%)</td>
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Table 1 Aerodynamic characteristics of house dust mite, cat, dog and cockroach allergens
small particles which can penetrate deep into respiratory tract inducing acute asthma. Application of this information in terms of avoidance strategies is important, implying, for example, that air filtration units have no place in mite or cockroach avoidance, but may be useful in removing cat and dog allergen from the air.

It is important to know where patients receive most of their exposure. The bed is the most important source of mite allergens and lowering exposure in the bedroom is the primary target of avoidance. In contrast, it is likely that the majority of exposure to allergens of domestic pets occurs in the living room area, and this must be taken into account when planning avoidance strategies.

Control of house dust mites and mite allergens

The most effective and probably most important avoidance measure is to cover mattress, pillows and duvet with covers that are impermeable to mite allergens. Development of water vapour-permeable fabrics which are both mite allergen impermeable and comfortable have considerably increased compliance. Allergen levels are dramatically reduced after the introduction of covers\textsuperscript{17}, which should be robust, easily fitted and easily cleaned, as their effectiveness is reduced if they are damaged. Mite allergens can accumulate on the covers and it is important that covers are wiped at each change of bedding. All exposed bedding should be washed at 55°C (the temperature that kills mites)\textsuperscript{18}. The cold cycle of laundry washing reduces allergen levels, but most of the mites survive. Additives for detergents providing a concentration of 0.03% benzyl benzoate, or dilute solutions of essential oils in normal and low temperature washing provide alternative methods of mite control\textsuperscript{19}.

Carpets are an important microhabitat for mite colonisation and a possible source of allergen from which beds can be re-infested\textsuperscript{20}. Fitted carpets should ideally be replaced with polished wood or vinyl flooring. Exposure of carpets to direct strong sunlight may be used in loosely fitted carpets in certain climatic areas\textsuperscript{21}. Steam cleaning may be used as a method of killing mites and reducing allergen levels in carpets\textsuperscript{22}. A number of different chemicals that kill mites (acaricides) have been identified, and shown to be effective under laboratory conditions\textsuperscript{23}. However, data on whether these chemicals can be successfully applied to carpets and upholstered furniture are still conflicting, as the method of application of the benzyl-benzoate moist powder on carpets is very important\textsuperscript{24}. The main problem of chemical treatment is not its ability to kill mites, but how to get the chemicals to penetrate deep into carpet and soft furnishing, the persistence of mite allergen until re-colonisation occurs, and the nuisance of frequent re-applications. Freezing with
liquid nitrogen can also kill mites. However, the technique can only be carried out by a trained operator, which limits its use, especially since treatment needs to be repeated regularly. When used, both acaricides and liquid nitrogen should be combined with intensive vacuum cleaning following administration.

The protein-denaturing properties of tannic acid are well recognised, and it has been recommended for the reduction of indoor allergen levels in house dust. However, high levels of proteins in dust (e.g. cat allergen in a home with a cat) block its effects.

Intensive vacuum cleaning may remove large amounts of dust from carpets, reducing the size of allergen reservoir. However, vacuum cleaners with inadequate exhaust filtration may increase airborne allergen levels during use. Thus, atopic asthmatic patients should use HEPA-filter vacuum cleaners with double thickness vacuum cleaner bags, although the benefits have not been established in a clinical trial. Ducted systems offer similar advantages.

High levels of humidity in the microhabitats are essential for mite population growth, and reducing humidity may be an effective control method. However, detailed models of the humidity profile of domestic microclimates (e.g. in relation to humans in bed) are not yet available. Reducing central humidity alone may be ineffective in reducing humidity in mite microhabitats (e.g. in the middle of a mattress). Reducing humidity by mechanical ventilation heat recovery units or dehumidifiers should be used in areas where the climate is right, i.e. where winters are dry and cold.

Due to the aerodynamic characteristics of mite allergens, it makes little sense to use air filtration units and ionisers as the only way of reducing personal exposure.

Since mites live in different sites throughout the house, it is unlikely that a single measure can solve the problem of exposure, and an integrated approach including barrier methods, dust removal and removal of mite

<table>
<thead>
<tr>
<th>Table 2 Measures for reducing house dust mite allergen exposure</th>
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<tbody>
<tr>
<td>Encase mattress, pillow and quilt in impermeable covers</td>
</tr>
<tr>
<td>Wash all bedding in the hot cycle (55–60°C) weekly</td>
</tr>
<tr>
<td>Replace carpets with linoleum or wood flooring</td>
</tr>
<tr>
<td>If carpets cannot be removed, treat with acaricides and/or tannic acid</td>
</tr>
<tr>
<td>Minimise upholstered furniture/replace with leather furniture</td>
</tr>
<tr>
<td>Keep dust accumulating objects in closed cupboards</td>
</tr>
<tr>
<td>Use a vacuum cleaner with integral HEPA filter and double thickness bags</td>
</tr>
<tr>
<td>Replace curtains with blinds or easily washable (hot cycle) curtains</td>
</tr>
<tr>
<td>Hot wash/freeze soft toys</td>
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microhabitats is needed (Table 2). One such approach was recently used and shown to be highly effective in achieving and maintaining a very low allergen environment in homes of children at high risk of allergic disease.

**Pet allergen avoidance**

Complete avoidance of pet allergens is all but impossible, as sensitised patients can be exposed to pet allergens not only in homes with pets, but also in homes without pets and in public buildings and public transport.

The major cat allergen Fel d 1 is produced primarily in the sebaceous glands and in the basal squamous epithelial cells of the skin. Its production is under hormonal control, and the castration of male cats results in a 3-5-fold reduction of Fel d 1 concentration in skin washing. Testosterone treatment restores the Fel d 1 levels to precastration values.

It has recently been suggested that Fel d 1 production is higher in male than in female cats. However, the observed gender difference in Fel d 1 secretion is too small to suggest that patients allergic to cats could benefit by getting a female rather than male cat, or by castrating their male cats.

The best way to reduce exposure to cat or dog allergen is to remove the animal from the home. Even after permanent removal of the animal, it can take many months before reservoir allergen levels decrease.

Unfortunately, despite continued symptoms many pet allergic patients insist on keeping their pet. Asthma is often severe and difficult to control in pet sensitised asthmatics who continue to be exposed to high allergen levels because they refuse to get rid of the family pet.

**Control of the airborne allergen levels with a pet in home**

Airborne pet allergen levels increase by ~5-fold when a pet is in a room, indicating that the immediate presence of a pet contributes to airborne allergen levels. Pets should be kept out of the bedroom, and preferably outdoors.

Several studies have investigated the effect of washing pets on allergen levels. Washing dogs in a bath using a hand-held shower unit and shampoo and rinsing thoroughly produced a substantial, but short-lived, fall in recovered Can f 1. Pet washing may reduce airborne allergen in an experimental room, but the effect in homes with pets is largely unknown. De Blay et al reported a reduction in airborne Fel d 1 following washing one cat weekly over a 4 week period, and a similar reduction in airborne Can f 1 was observed in homes with dogs. However, the main benefit of washing the pet regularly, probably twice...
Table 3 Measures for reducing cat/dog allergen exposure

<table>
<thead>
<tr>
<th>Measures for reducing cat/dog allergen exposure</th>
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<tbody>
<tr>
<td>Remove cat/dog from the home</td>
</tr>
<tr>
<td>If the pet cannot be removed:</td>
</tr>
<tr>
<td>Keep the pet out of the main living areas and bedrooms</td>
</tr>
<tr>
<td>Install HEPA air cleaners in the main living areas and bedrooms</td>
</tr>
<tr>
<td>Have the pet washed twice a week</td>
</tr>
<tr>
<td>Thoroughly clean upholstered furniture/replace with leather furniture</td>
</tr>
<tr>
<td>Replace carpets with linoleum or wood flooring</td>
</tr>
<tr>
<td>Fit allergen-impermeable bedding covers</td>
</tr>
<tr>
<td>Use a vacuum cleaner with integral HEPA filter and double thickness bags</td>
</tr>
</tbody>
</table>

weekly, may be the reduction in the build-up of allergen in dust reservoirs (e.g. carpets and upholstered furniture), but this too is unproven.

Airborne pet allergens in homes with pets can be reduced by the use of a HEPA air cleaner. Vacuum cleaners which contain integral HEPA filters and double thickness bags do not leak allergens into the air.

Since getting rid of the family pet is rarely a viable option, in patients who are allergic to cats or dogs and persist in keeping their pet we propose the set of measures listed in Table 3.

Avoidance of cockroach allergens

In areas where housing conditions sustain large cockroach populations, both physical and chemical control measures should be used. Reducing access to food and water is critical, thus waste food should be removed and surface water should be contained by reducing leakage through faulty taps and pipework, and reducing condensation by improved ventilation. Cockroach access should be restricted by caulking and sealing cracks and holes in the plasterwork and flooring. Several chemicals are marketed for controlling cockroach infestation, including diazinon, chlorpyrifos and boric acid. The most useful for patients with allergic disease are bait stations, where the chemical (hydramethylnon, avermectin) is retained within a plastic housing. A paste formulation of hydramethylnon may be used on cockroach runways and underneath counters, etc. Bait stations are generally effective at reducing cockroach levels for 2–3 months.

The attempts to reduce cockroach allergen exposure rely on improving patient education and concerted attempts by pest control companies and public health departments to reduce cockroach infestation.

Fungi

Airborne fungal spore concentrations have been associated with adverse health outcomes in children (e.g. respiratory symptoms were associated
with an increase in indoor Cladosporium exposure. Exposure to Cladosporium and Penicillium was found to be a risk factor for sensitisation to these genera, but also for allergy to other fungal extracts, and, in the case of Penicillium exposure, for allergy to house dust and dog. It is thus possible that fungal exposure may have an allergen-specific effect on sensitisation, but also a non-specific effect on immune system facilitating sensitisation to other allergens (perhaps via mycotoxins and β-glucans). Therefore, reducing exposure to fungi may be important. Removing or cleaning mould-laden objects and maintaining a low humidity (less than 50%) may be beneficial in reducing fungal allergens. Using a dehumidifier and/or air conditioning unit can reduce both mould and bacteria. Care should be taken to make sure that dehumidifiers or air conditioning units do not become contaminated with moulds and thus form a new source of allergens or non-specific irritants. In tropical and subtropical climates, fungi might grow on the walls of the house due to water leakage and humidity. To avoid this, the walls could be tiled or cleaned as necessary.

Avoidance of outdoor allergens

The most important outdoor allergens which often induce symptoms in susceptible individuals are pollens and mould spores. However, the threshold levels which induce sensitisation and/or clinical reaction remain to be determined. Although outdoor pollens and moulds are impossible to avoid completely, closing windows and doors and remaining indoors (particularly when pollen and fungal spore counts are high) may reduce personal exposure and works at a symptomatic level in hay fever sufferers. The information about a patient’s sensitivity to specific allergens may be useful for giving advice about the timing and location of the patient’s travel.

Allergen avoidance: does it work?

Exposure to allergens has a profound effect on the development of IgE mediated sensitisation (primary sensitisation), progression from sensitisation to allergic disease (secondary exposure) and the severity of symptoms in the established disease (tertiary exposure). The potential benefits of allergen avoidance can be assessed in terms of: (i) prevention of allergic sensitisation (primary prevention by allergen avoidance); (ii) prevention of atopic disease in sensitised individuals (secondary avoidance); and (iii) effectiveness in the treatment of established disease. There have been very few studies on primary or secondary avoidance. In contrast, there have been many studies of variable quality.
Lessons from high altitude studies

In Europe, mite allergen levels are very low at high altitude where the ambient humidity is insufficient to support mite populations. Testing the hypothesis of a cause and effect relationship between exposure to dust mite allergens and sensitisation, Charpin et al compared the prevalence of asthma and positive skin test to mites in subjects living in the Alps and those living at sea level. Briancon in the French Alps (altitude 1326 m) is the highest city in Europe, with a mean annual absolute outdoor humidity of 5.7 g/kg, thus making it unfavourable for mite population growth. Martigues (near Marseilles), on the contrary, is located on the French Mediterranean coast and has a mean annual absolute outdoor humidity of 9.3 g/kg, which is conducive for mite growth. The prevalence of mite allergy in a random sample of 18–65-year-old adults was found to be 4-fold higher in those living in Martigues (44.5%) compared to Briancon (10%). In a later study conducted by the same authors, a similar pattern of sensitisation was found in schoolchildren where the prevalence of skin test sensitivity to mite allergens was found to be 16.7% in Martigues compared with 4.1% in Briancon. House dust mite allergen level in mattresses was found to be much lower in the Alps (0.36 mg/g of dust) than at sea level (15.8 mg/g of dust). The authors appropriately subtitled their paper A paradigm of the influence of the environmental exposure on allergic sensitisation and suggested that living in a mite-free environment reduce the risk of sensitisation and development of respiratory symptoms.

There are several sanatoria built in the Alps (e.g. Davos, Switzerland and Misurina, Italy), in which long-term residence can be beneficial for asthmatic children. Dust mite sensitive asthmatic children had a progressive reduction in non-specific airway reactivity after a 1 year period spent in Davos. Several studies from Misurina reported a reduction in asthma symptoms and significant decreases in mite allergen induced basophil histamine release, mite-specific serum IgE level and methacholine and allergen-induced airway reactivity. However, further studies also observed reversal of this trend towards improvement 15 days after returning to sea level. The result of high-altitude studies suggest that mite allergen avoidance leads to a decrease of airway inflammation with consequent improvement in specific and non-specific airway reactivity and symptoms and that re-exposure results in a rapid relapse. These studies were not controlled, and there is a possibility that other domestic factors (e.g. exposure to pets, environmental tobacco
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smoke, etc.) contributed to the observed improvement in asthma control. Nevertheless, mite avoidance is the most plausible reason for clinical success.

The high altitude studies suggest that:

- With low levels of allergen exposure in high altitude residents, rates of sensitisation and allergic disease are low
- To get clinical effect in established allergic disease, it is essential to achieve and maintain a major reduction in allergen levels
- Even with such a reduction in exposure, it may take many months for the effect on symptoms, medication use, pulmonary function, non-specific and specific airway reactivity and immunological parameters to become fully apparent.

High altitude studies provide an important proof of a principle: a substantial reduction in allergen exposure over a long period of time may result in clinical improvement in allergic asthmatic patients.

Clinical trials of mite allergen avoidance in patients' homes

Having explored various methods of allergen avoidance, the important question is whether allergen avoidance in homes by these techniques improves asthma control in sensitised patients. This is an area of controversy, mainly because of the inadequacies of the clinical studies on allergen avoidance. It is very difficult to conduct a placebo-controlled trial in this area: the combination of skin wheal and home visit is a potent stimulus for a change in behaviour, resulting in increased cleaning, removal of mite habitats and reduction in allergen levels even in a non-intervention group. Virtually every controlled study has observed a significant reduction in mite allergen levels and sometimes improved clinical symptoms in both the control group as well as the active group. Furthermore, as stressed previously, a successful trial would need to achieve and maintain a major reduction in allergen levels, be sufficiently long (i.e. probably not less that a year, with at least 6 weeks run-in period) and have adequate power.

The majority of studies on allergen avoidance in patients’ homes have been small, poorly controlled and have often used measures that we now realise do not reduce mite allergen exposure. Consequently, many fail to show clinical benefits. We have recently reviewed 31 trials of mite allergen avoidance regimens in asthma in the literature. Most of the studies have been small, poorly controlled and have used measures that failed to reduce mite allergen exposure. Of the 31 studies, only 9 showed significant reduction in mite counts and/or mite allergen levels.
In 3 of these 9, the period of treatment was too short, but nonetheless showed some effect. The final 6 controlled studies, all of which used bed covers, achieved both significant reduction in mites/allergen levels and were sufficiently long to show an effect on outcomes. Although these 6 studies had different endpoints, they all showed some evidence of clinical benefit. Whilst all trials of bed coverings suggest they are clinically effective, the impact of their widespread use by asthmatics has not been determined in a public health context. The Cochrane Airways Group have also recently published a meta-analysis on the effectiveness of mite allergen avoidance. Of 23 studies, only 3 met the basic criteria of: (i) being randomised and controlled; (ii) demonstrating substantial reduction in mite allergen exposure; and (iii) lasting 6 months or longer. These 3 studies (1 in adults, 2 in children, total randomised subjects 123), although small and with diverse endpoints, again suggest some clinical benefit. Which patients benefit and whether treatment is cost-effective is unknown. Large-scale trials are underway to answer these questions. One such study on the effect of mite allergen avoidance by the use of allergen impermeable bedding on asthma control is currently being carried out in the UK. This is a randomised, parallel group, double blind, placebo controlled trial, due to randomise 1500 patients. During the first 6 months of the trial, patients will take their usual inhaled steroid therapy, and during the next 6 months patients will make a controlled reduction of inhaled steroids.

House dust mite allergen avoidance have been shown to be of some benefit in the treatment of atopic dermatitis and perennial allergic rhinitis.

**Clinical trial of pet allergen avoidance**

A recent study investigated the effectiveness of environmental allergen control using high efficiency particulate arrest (HEPA) air cleaners in the management of asthma and rhinitis in cat allergic patients who were sharing their home with one or more cats. Although a small reduction in airborne Fel d 1 was observed in the active (but not in the control group), there was no difference between the groups in any of the outcome measures during the 3 months of a study. The reduction in cat allergen exposure afforded by the measures used in this trial was modest (~50%). It seems likely that a much more complex series of measures are needed if substantial reduction in exposure to airborne cat allergen is to be achieved. As outlined before, these could include keeping the pet out of the bedrooms and main living areas, installing HEPA air filtration units in the main living areas and bedrooms, washing the pet twice a week, thorough cleaning of the upholstered furniture (or replacing it with leather
furniture), replacing carpets with linoleum or wood flooring and using a vacuum cleaner with integral HEPA filter and double thickness bags. Although such an integrated approach may have a desired clinical effect, it is essential that this is validated in a clinical trial.

Allergen avoidance in the primary prevention of atopy

Epidemiological studies suggest that in the areas with low levels of allergens in homes, the prevalence of sensitisation is low. Any primary allergen avoidance should be started early in infancy if maximum benefit is to be achieved. The Isle of Wight study has produced the first indication that even a modest reduction in house dust 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\textsuperscript{97,98}. The trial was unfortunately complicated by a multifaceted intervention strategy, including dietary advice to mothers during the pregnancy, as well as an attempt to reduce mite allergen exposure by the use of the acaricide benzyl benzoate (a relatively ineffective avoidance measure).

Recent studies have suggested that it may be necessary to start the environmental manipulation even before birth, i.e. early in pregnancy. There is an increasing body of evidence that the initial priming of the T cell system to environmental allergens may occur before birth, probably during late gestation, and that this process in infants at high risk of atopy may be skewed from Th1-like to Th2-like phenotype. This has been the subject of three recent review articles\textsuperscript{99-101}. It has recently been suggested that maternal exposure to allergens from the 22nd week of pregnancy may play an important role in fetal T-cell priming. It is possible that allergen crossing the placenta may be involved in the subsequent development of atopy. Whilst this scenario may be applicable for food allergens, which are present at relatively high concentrations in the maternal circulation, it is considerably harder to explain how minute quantities of inhalant allergens (e.g. mite allergens with typical exposure in the order of 1 µg/year) could cross the placenta and sensitise the offspring. However, it would appear advisable to implement any trials of allergen avoidance during pregnancy (probably second and third trimester) in families at high risk of developing allergic disease.

Conclusions

Minimising the impact of identified environmental risk factors is a first step to reduce the severity of asthma. Although environmental control is difficult, we predict that it will be an integral part of the overall
management of allergen sensitised patients. If the benefits attributable to allergen avoidance were instead attributed to a new drug, that drug would be the subject of trials involving thousands of patients. It is unfortunate that the perceived lack of commercial benefit has discouraged large-scale population-based trials.

The results of on-going large-scale trials of the widespread applicability of mite allergen avoidance and the effect on patient symptoms, exacerbation rate, use of medication and overall health costs study will conclusively show whether a simple intervention designed to reduce domestic mite allergen exposure can improve the clinical control of asthma, which subgroups of patients benefit, and whether the intervention is cost-effective. There is little data on benefits of primary and secondary prevention by environmental control, and several prospective studies are currently under way. The results of these trials will provide conclusive evidence of the effect of environmental control measures in prevention of sensitisation and development of allergic disease.

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