



## Dust-mite inducing asthma: what advice can be given to patients?

Adnan Custovic, Clare S Murray & Angela Simpson

To cite this article: Adnan Custovic, Clare S Murray & Angela Simpson (2019): Dust-mite inducing asthma: what advice can be given to patients?, Expert Review of Respiratory Medicine, DOI: [10.1080/17476348.2019.1651647](https://doi.org/10.1080/17476348.2019.1651647)

To link to this article: <https://doi.org/10.1080/17476348.2019.1651647>



Accepted author version posted online: 01 Aug 2019.



Submit your article to this journal [↗](#)



View Crossmark data [↗](#)

**Publisher:** Taylor & Francis & Informa UK Limited, trading as Taylor & Francis Group

**Journal:** *Expert Review of Respiratory Medicine*

**DOI:** 10.1080/17476348.2019.1651647

Article type: Perspective

**Dust-mite inducing asthma: what advice can be given to patients?**

Adnan Custovic<sup>\*1</sup>, Clare S Murray<sup>2</sup> and Angela Simpson<sup>2</sup>

<sup>1</sup>National Heart and Lung Institute, Imperial College London, UK

<sup>2</sup>Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences,  
Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic  
Health Science Centre, UK

\*Corresponding author:

Adnan Custovic

Imperial College London, UK

Email: a.custovic@imperial.ac.uk

## **Abstract**

**Introduction:** Amongst allergic asthmatics, high allergen exposure increases asthma severity. However, there is no consensus on the role of mite allergen avoidance in the management of asthma, and various guidelines differ in their recommendations.

**Areas covered:** Several systematic reviews/meta-analyses on mite avoidance in the management of asthma have been published, and their findings have been used for a call to provide a recommendation in British guidelines that dust-mite control measures should not be recommended. However, there are several problems with such analysis (such as combining studies in adults and children), and we question whether these are appropriate tools to evaluate available evidence about mite allergen avoidance, and whether it is correct to rely disproportionately on the results of meta-analyses/systematic reviews to inform clinical practice in this area. Recent evidence in children suggests that mite-impermeable bed encasings reduce emergency hospital attendance with severe asthma exacerbations.

**Expert opinion:** The practical questions include how to achieve a sufficient real-life reduction allergen exposure, and how to identify patients who will benefit from effective intervention. The intervention should start early in the natural history of asthma, and consideration for choosing patients should include using the titre of allergen-specific IgE antibodies or the size of skin test wheal as an indicator.

**Key words:** House dust mite; allergens; asthma; exposure; avoidance; exacerbations

## Article highlights

- High exposure to allergens amongst sensitized individuals may worsen inflammation and trigger symptoms of asthma.
- Allergen exposure and respiratory virus infections act synergistically to increase the risk of severe asthma attacks
- There is a diversity of opinions about the role of mite allergen control methods in the management of asthma, and conflicting advice is provided in different national and international asthma guidelines.
- House dust mite allergen-impermeable covers for mattress, pillow and quilt reduce emergency hospital attendance with severe asthma attacks in children
- A pragmatic guide to allergen avoidance:
  - Personalize the intervention to the patient's sensitization and exposure status (For example, use the size of skin test wheal or the level of mite allergen-specific IgE antibodies or as an indicator; Focus on mono-sensitized children, living in non-smoking households, requiring more controller medication)
  - Start intervention early
  - Use a comprehensive mite allergen control regime

## 1. Introduction

There is an ongoing disagreement in the respiratory and allergy communities on the effectiveness and the potential role of avoidance of house dust mite allergens in the management and prevention of asthma. This is exemplified by sometimes opposite advice provided in different national and international asthma guidelines, on which most practitioners rely for the diagnosis and management of their patients. For example, the US NHLBI Guideline (2007) recommends that the role of inhaled allergens should be assessed in both adult and paediatric asthma, and that specific advice on how to reduce exposure should be given to sensitized patients (1). Contrasting guidance is provided by the Global Initiative for Asthma (GINA) (2019), which states that “allergen avoidance is not recommended as a general strategy for asthma”, and that “for sensitized patients, there is limited evidence for clinical benefit for asthma with single-strategy indoor allergen avoidance” (2). The position of the British Guideline on the management of asthma (2019) is similar to that of the GINA, concluding that “Physical and chemical methods of reducing house dust mite levels in the home (including acaricides, mattress covers, vacuum cleaning, heating, ventilation, freezing, washing, air filtration and ionisers) should not be routinely recommended by healthcare professionals for the management of asthma” (3). However, both GINA and British guidelines agree that for mite-sensitized patients, limited evidence on multifaceted avoidance strategies (particularly in children) indicate that a multi-component approach may be clinically beneficial, but that such measures are often complicated and expensive. Another British guideline (The National Institute of Clinical Excellence guideline on asthma, 2017) puts emphasis on pharmacological treatment and does not discuss potential benefits on non-pharmacological strategies (4).

In this article, we will discuss the reasons for such discrepancies, review more recent evidence that should be considered in the future iteration of guidelines, suggest a pragmatic approach to allergen control measures, and discuss how to identify patients who may benefit from intervention. We will start with a brief overview of how we measure dust mite allergen exposure, which is important for ascertaining the relationship between exposure and asthma, and for the design of effective avoidance strategies.

## **2. House dust mite allergen exposure: myths, extrapolations and assumptions**

Euan Tovey has put a compelling case that most theories on how and where personal exposure to mite allergens occurs are made through extrapolations and assumptions, rather than solid evidence or precise measurements (5). One such assumption is that mite allergen concentration in samples from dust reservoirs (usually collected by vacuuming a square meter of carpet or mattress) is a good proxy for airborne allergen, and is representative of personal exposure. However, mite allergen levels vary considerably within the same home (6) (e.g. >100 fold differences in mite allergen levels have been observed in different parts of the same carpet (7)), and it remains uncertain whether floor or mattress samples (or a combination thereof) should be used, and whether any of these relates to the personal exposure (8, 9). The assumption that most dust mite exposure occurs in bed has been questioned by an Australian study which showed that the majority of personal mite allergen exposure in adults may occur on public transport (10). We suggest that main sources of personal exposure may differ depending on age; for example infants and young children spend more time in the bed than most adults and often play on carpeted floors. Consequently, different indices of exposure may be applicable to young children and adults.

In addition, climatic conditions and housing characteristics of a geographical area will heavily influence mite allergen exposure.

Another factor which is relevant for personal exposure, and the design of effective methods to reduce it, relates to the aerodynamic characteristics of allergen-carrying particles. The majority of mite allergens are carried by relatively large particles ( $>10\text{ }\mu\text{m}$  diameter) (11). In contrast, a significant portion of airborne pet allergens is carried on particles  $<5\text{ }\mu\text{m}$  diameter (12, 13). As a consequence, the actual dose of allergen which is inhaled may be much higher for pet compared to mite allergens (14), which may account for the difference in clinical presentation of allergic asthma: mite sensitized patients may be unaware of the relationship between exposure and symptoms, while those sensitised to cat or dog often report that they develop symptoms within minutes of entering a home with a pet.

Application of this information to the design of allergen control measures would indicate that air filtration may be useful for removing airborne pet allergens from the ambient air, but may have little effect on exposure to mite allergens. It remains unclear whether the impact on chronic airway inflammation in asthma differs between exposure to a small number of large particles with high mite allergen content, compared to a larger number of smaller particles with lower allergen content (as may be the case for pet allergens), although allergen challenge models have indicated that large particles play a role in the immediate bronchial response in asthmatics (15).

Similar to the untested assumptions on how and when exposure to dust mite occurs and how to accurately measure it, unfounded inference is often made about the effectiveness of measures to reduce exposure. For example, it is assumed that the reduction in mite allergen measured by the amount of allergen recovered from mattress or carpet equates to a

reduction in personal exposure. Most of mite allergen avoidance methods have been tested under experimental conditions, with methods aiming predominantly to differentiate between different products (such as vacuum cleaners, bed covers or air cleaners), using proxy measures of exposure (reservoir allergen concentrations or allergen recovered from air by static air samplers) (5). The effect of most of these measures on personal inhaled allergen exposure is often unknown (5). Different products are often advertised to consumers without the requirement to provide evidence about their clinical effectiveness. In an excellent review of 50 websites by various asthma foundations and consumer groups, Tovey and Marks have noted that almost one third were associated with promotion of proprietary products for allergen avoidance, some having their own “certification programmes” (5), which may introduce a degree of the conflict of interest. At present we lack experimentally based models of how and when personal mite allergen exposure occurs, and this limits the development of novel effective methods for reducing exposure. To move forward, we need to develop standardized, reliable, and reproducible methods for ascertaining personal mite allergen exposure (16).

### **3. Mite allergen exposure and the development of sensitization and asthma**

Being exposed to allergen is essential for the development of allergen-specific sensitization. However, numerous observational (17) and intervention studies (18) suggest that the relationship between mite allergen levels in homes and sensitization is complex, and influenced by the timing, dose, and route of exposure, as well as the individual genetic predisposition and other environmental exposures (16). In some studies, exposure to dust mite allergens has been shown to increase the risk of mite sensitization and later development of asthma (19-22), particularly among children with parental atopy or early



manifestations of atopic disease (23, 24). However, others have not confirmed these association (reviewed in(16)). Such heterogeneity may be a consequence of differences in the study design (birth cohorts vs. case-control) and methods for ascertaining exposure, the genetics of the study populations (high-risk vs. population-based), or different longitudinal trajectories of sensitisation through life-course between exposed and non-exposed individuals (25), making comparisons between studies difficult, if not impossible.

The general assumption is that exposure to dust mite allergens occurs via inhalation.

However, the potential relevance of other routes of exposure is unknown. For example, due to their inclination to put the toys (or their hands) into their mouth, young children may ingest house dust whilst they play on the floor indoors, but the relevance of oral exposure is unknown (16). Sensitization may also be a consequence of mite allergen presentation through an impaired skin barrier. This may be of particular importance within the context of *filaggrin* genotype; for example, it has been shown that environmental exposure to peanut allergen in house dust increases the risk of peanut allergy in children with *filaggrin* loss-of-function mutations, but not in those without (26). Recent longitudinal analysis from infancy to adolescence in a population-based birth cohort has shown that Der p 1 exposure was associated with increased risk of mite sensitization throughout childhood (with the effect size being higher in early childhood); however, at age one year, the impact of mite allergen exposure was much higher in children with *FLG* mutations (OR 6.66, 95% CI 1.15-38.58), but this modifying effect of *FLG* mutations gradually reduced over time (27). These data indicate that transcutaneous exposure may be important for house dust mite allergens, which are considered as primarily inhaled.

Another study has shown different responses to mite exposure in relation to mite-specific sensitization amongst individuals with different variants in *IL4* gene; amongst those carrying the T-590 allele, the risk of mite sensitization differed between those exposed to high (OR, 3.76; 95% CI, 1.42-9.77) and low (OR, 0.74; 95% CI, 0.40-1.34] Der p 1 concentrations (28). Taken together, these studies suggest that susceptibility to mite allergen exposure differs between individuals with different genetic predispositions, but the precise nature of these complex relationships is unclear. Adding further complexity, in real life situations individuals are not exposed only to allergens, but also to a range of other environmental exposures. One example of an interaction between exposures is the observation that high allergen levels combined with an environment rich in specific bacterial families may protect against atopy (29). We have observed a complex relationship between host genetics and exposures to mite allergens and endotoxin in a population-based birth cohort, which suggested that the magnitude of the effect of early-life mite allergen exposure on mite sensitization was significantly modulated by endotoxin exposure, but only among children with specific genotype in *CD14* (CC homozygotes at *CD14/-159*) (30). These findings suggest that the development of sensitization is influenced by allergen exposure, but also by other environmental exposures, and genetic predisposition. This may imply that the effects of allergen control could differ between individuals with different genetic predispositions (31), and within different environments and only certain individuals with a particular susceptibility may benefit from a specific intervention.

Finally, the effect of allergen exposure may differ for different clinical outcomes. For example, a previously mentioned US cohort reported the opposite effect of allergen exposure on sensitisation compared to recurrent wheezing (29), and in a cross-sectional study of ~3000 adults, dust mite allergen exposure was associated with mite sensitization,

but there was no evidence of the association between exposure and respiratory symptoms (32).

#### **4. Mite allergen exposure and asthma severity**

Amongst some mite allergic asthmatics, asthma severity is associated with high exposure to mite allergens (33-35). Some studies have also reported an adverse impact of mite exposure on asthma control amongst non-atopic asthmatic patients (36). On the other hand, viral infections are deemed to be the main cause of asthma exacerbations, and viruses rather than allergens may be a major determinant of asthma attacks. However, most patients are exposed to viruses and allergens at the same time, and rather than operating in isolation, virus infections and high allergen exposure may interact to increase the risk of severe exacerbations leading to hospital admissions in both children over the age of three years (37) and adult asthma (38). Further indirect evidence of the interaction between allergic and virus pathways has been suggested by a study which showed that anti-IgE (omalizumab) treatment reduces seasonal asthma exacerbations occurring during the fall, which are caused by viral infections (39). The evidence that high mite exposure can worsen airway inflammation and trigger asthma symptoms provides the rationale for the use of mite allergen avoidance in asthma management.

#### **5. Mite allergen avoidance in the management of asthma**

##### **5.1. Measures to reduce dust mite allergens**

Major reduction in mite allergen levels in homes can be achieved and maintained over the prolonged period of time using a comprehensive allergen control regime (40), which includes a number of measures discussed below (for review see (41, 42)). Covering the mattress, duvet and pillows with encasings that are impermeable to allergens is the most

common approach to reduce mite exposure in bed. Feather pillows have been shown to contain less mite allergens than synthetic ones (43), and any bedding should be washed regularly (optimally, in a hot cycle above 55°C to kill the mites). The replacement of carpet with hard flooring may minimise the size of the dust reservoir, but the effect on airborne allergens is debatable, and is likely to be affected by factors related to particle aerosolization (including electrostatic charge, type of floor, etc). If carpets remain in place, several measures have been suggested to reduce mite allergen levels (e.g. steam cleaning, exposing to direct sunlight, use of acaricides, freezing with liquid nitrogen etc.). The use of vacuum cleaners with built-in high efficiency particulate arrest (HEPA) filters is often recommended, but real-life studies have demonstrated an increase in the amount of allergens inhaled while vacuum-cleaning or changing the bag (44), suggesting that experimental chamber studies alone are insufficient to justify the recommendations or certification of “allergy-friendly” vacuum cleaners (45). Reducing humidity is recommended for control of mite population, but the choice of methods to achieve sufficient reduction in humidity depend on the local climate and housing design (46, 47).

## **5.2. Clinical effectiveness of mite allergen control measures**

Clinical benefits reported in studies at high altitude sanatoria (48) are often attributed to allergen avoidance, but studies using allergen control in patients’ homes have provided conflicting results (49). The real question is not whether allergen avoidance is effective, but how to achieve a sufficient reduction in personal allergen exposure in real-life, and how to identify patients who will benefit from intervention.

### **5.2.1. Systematic reviews**

Several systematic reviews and meta-analyses have been published on the role of allergen avoidance in the management of asthma (50-54), and this type of evidence has been used to provide an unambiguous recommendation in asthma guidelines that “dust-mite control measures should not be recommended in the management of asthma” (55). The reality is that this question is much more complex, and that there are several potential problems with meta-analyses and systematic reviews of mite avoidance. Based on the data from 54 trials with >3000 patients (of which 26 assessed mattress covers, 10 chemical methods and eight a combination of chemical and physical methods), the most recent in the series of Cochrane meta-analyses concluded that there was no beneficial effect of chemical and physical methods and that these interventions cannot be recommended (53). More recent systematic review of 59 randomized and eight non-randomized trials of different interventions of which five were relevant for dust mite avoidance (mattress covers, acaricide, air purification, carpet removal, HEPA vacuum cleaners) reported that for most interventions and outcomes, the evidence base was inconclusive or showed no effect, and that no interventions demonstrated an improvement in validated asthma control measures or lung function (54). A Cochrane review of mite avoidance measures for rhinitis reported that trials have been small and of poor methodological quality, thereby not providing enough evidence to offer any definitive recommendations (56). A key question is whether meta-analyses and systematic reviews are appropriate tools to evaluate available evidence about dust mite allergen avoidance, and whether it is correct to rely disproportionately on the results of meta-analyses and systematic reviews to inform clinical practice in this area. This issue has been addressed in an excellent article by Platts-Mills (57), who summarised the flaws of the Cochrane systematic review from 2008 (53). Potential problems with meta-analyses and systematic reviews of mite avoidance include (but are not limited to) the

following: (1) Data from studies of adults and children were combined (this approach of combining data from adults and children is not used in any other section of any asthma guidelines); (2) Blinding in studies of mite avoidance is difficult, and interventions are not easy to maintain without extensive education; (3) Many studies were too short to have a realistic chance of showing a clinical effect (based on data from studies of allergen avoidance at high altitude); (4) Studies of multifaceted avoidance were excluded; (5) A number of studies included in meta-analyses used methods which had not been shown to reduce exposure to house dust mite and indeed in some studies where mite allergen levels were measured no reduction in the intervention group was found; (6) Some older studies were excluded because of the way the methods were reported – satisfactory in their time, but not “rigorous” in the way that modern RCTs are; (7) Many studies allowed changes in asthma medication such as inhaled corticosteroids (at the discretion of the patient’s own physician) but used measures of lung function such as bronchial hyper-responsiveness as an outcome, (and reported these clinical outcomes separately). We would argue that it is unlikely that one would see an improvement in bronchial hyper-responsiveness as a consequence of an environmental intervention, if reduction in inhaled corticosteroid dose occurs at the same time; the dose of ‘preventer’ medication should be fixed for the duration of the study.

A recent systematic review published in 2018 (54), covering avoidance of dust mite and other allergens, has potentially similar methodological problems. For example, studies of adults and children were combined. When summarising evidence for allergen-impermeable mattress covers compared with placebo covers or no intervention as a single measure in relation to exacerbations, three studies are quoted (one paediatric and two adult studies), whereas exacerbation was the primary outcome measure in only one of these studies (58).

Data from two studies in adults were included in the exacerbation category, despite the fact that in one of these studies this outcome is not listed in the methods, does not form part of the power calculation and is not fully reported in the results (59); in the second study exacerbation was a secondary outcome not included in the power calculation, and was a rare event in the unselected group of relatively mild patients from primary care (60). That there has been no attempt to comment on this or adjust the analysis for underpowered secondary outcomes raises concerns about the validity of the conclusions. Given these issues, it is important to recognise the limitations of the systematic reviews conducted. We wish to emphasise that data for adults and children should be assessed separately, rather than combined together, and that focus should be only on outcome measures for which appropriate power calculation has been provided.

### ***5.2.2. Studies of single interventions***

Several studies which tested single interventions aimed at reducing mite allergen exposure are worth discussing in more detail. The largest randomised double-blind, placebo-controlled trial assessing the effectiveness of mite-impermeable bed covers recruited over 1000 adults with asthma, and found no benefits in the primary (morning PEFr during the first 6 months, the proportion of patients able to discontinue inhaled corticosteroids during the second six months of the study) or secondary outcomes (symptoms scores, and quality of life) (60). The results of the largest randomised, double-blind placebo-controlled study of bed encasings in adults with perennial allergic rhinitis with positive mite nasal challenge demonstrated no beneficial effect of the intervention (61). These results are often used as a conclusive proof that physical methods for reducing dust mite levels in the home are ineffective. However, failure to demonstrate benefit in some domains of the disease (e.g.

lung function or symptoms) does not exclude the possibility of benefits in other domains (such as prevention of exacerbations). Indeed recent studies of biologicals in asthma provide useful insights into the importance of outcome selection; for example, mepolizumab had no effect on late-phase allergic reaction, but reduced exacerbations, and omalizumab has much larger effect on exacerbation rate than on symptoms or lung function.

One important question is in which asthma domain does allergen exposure have the most pronounced effect. As outlined previously, amongst children who are sensitised, virus infection and high allergen exposure act synergistically to increase the risk of hospital admission due to asthma exacerbation (37), and therefore effective reduction in allergen exposure may reduce the risk of exacerbations. This question has been addressed in a recent randomised double-blind placebo-controlled trial (Preventing asthma exacerbations by avoiding mite allergen - PAXAMA) (58), in which number of children experiencing exacerbations during the treatment period was the primary outcome. The study team randomized 284 mite-sensitized asthmatic children aged 3-17 years, following a hospital attendance with asthma exacerbation, to receive either mite-impermeable or placebo bed covers. Over the 12-months follow-up, significantly fewer children in the active group attended hospital with asthma exacerbation (36/123 [29.3%] vs. 49/118 [41.5%],  $p=0.047$ ), and the risk of hospital presentation was 45% lower in the active group (Hazard Ratio 0.55 [95%CI, 0.36-0.85],  $p=0.006$ ). The study concluded that this simple and relatively inexpensive intervention (costing ~\$200) halved emergency hospital attendance with severe asthma exacerbations. A subgroup analysis has shown that the benefit was most marked in children younger than 11 years, and a stratified post-hoc analysis has suggested that reduction in exacerbations was greatest in children mono-sensitized to mite, living in non-smoking households, and requiring more controller medication at baseline.



An intervention using the nocturnal temperature-controlled laminar airflow (TLA) device, which distributes a filtered cooled laminar airflow descending from an overhead position and displaces aeroallergens from the breathing zone (62), has been shown to improve quality of life and reduce airway inflammation in adults and children with allergic asthma (63). A real-life observational study which evaluated the effects of night-time TLA when used for 12 consecutive months in addition to the patients' regular medication has reported a significant reduction in asthma exacerbations (from 3.6 to 1.3) and asthma-related emergency room visits (72.4 to 23.3%) and hospitalizations (44.8 to 20.0%) (64). Recent open-label, proof-of-concept study in children with difficult-to-control atopic dermatitis has shown that addition of TLA device to standard pharmacological treatment may be an effective add-on to the management of severe eczema (65).

### **5.2.3. Multifaceted interventions**

The largest study to date of the multifaceted intervention in children (The US Inner-City Asthma Study) adopted a comprehensive set of measures tailored to the child's allergen sensitization and exposure status (66), and included the education of the parent/carer, and advice on the reduction of passive smoke exposure when appropriate. Mattress and pillow encasings and HEPA vacuum cleaner were supplied to all homes, and further tailored intervention (e.g. a HEPA air filter for the reduction in tobacco smoke exposure) were also provided as appropriate. Children in the intervention group had significantly fewer days with asthma symptoms, and the benefit was sustained throughout the two-year period. The number of emergency room visits was also reduced. This important study estimated that a multi-faceted intervention costing ~\$2000 per child was associated with an additional 34 symptom free days over a two-year period.

## **6. Identification of patients who are likely to benefit from an effective intervention**

The post-hoc analysis of the PAXAMA study suggested that intervention with mite allergen impermeable covers may be more beneficial among younger (10 years and below), mono-sensitised children living in non-smoking households (58). In most studies of allergen control (and in clinical practice), individuals are assigned as either sensitized or not based on arbitrary cut-off points on skin tests or measurement of specific serum IgE. However, a sizeable proportion of such defined “atopic” individuals have no evidence of symptoms upon exposure, and it has been suggested that sensitization may include several different subtypes (benign and pathologic (67)), which differ in their association with asthma (68, 69). Application of these findings to the selection of patients for mite allergen avoidance is unclear. However, it is clear that better biomarkers are needed to help us to accurately identify asthmatic patients in whom mite allergy is contributing to the disease severity, and who are likely to benefit from allergen avoidance. Until such tests are developed, quantification of mite-specific IgE antibody or the size of the skin test response may help predict which patients with asthma are likely to benefit from allergen control (70).

## **7. Expert opinion**

High exposure to house dust mite allergens can worsen inflammation and trigger asthma symptoms in mite sensitized individuals. Different guidelines on the management of asthma provide contradictory recommendations on the role of house dust mite avoidance in the treatment of the disease. Guidelines which suggest that dust mite control measures should not be recommended (such as GINA or British guidelines) usually justify their recommendations based on the evidence from several published systematic reviews and meta-analyses. However, it is important to recognise the limitations of the systematic

reviews and meta-analyses for combining the data from multiple studies which used house dust mite avoidance in asthma management. These statistical procedures in their current form may not be the correct way to evaluate the effectiveness of dust mite allergen avoidance and inform clinical practice. For any future systematic reviews, we would suggest that data from studies of adults and children should not be combined, but should be analysed separately. Similarly, studies using different interventions should not be combined together, and those studies which used intervention which have not been shown to reduce mite exposure should be excluded. Careful attention should be paid to the choice of outcome measures, and only those for which there is appropriate power calculation should be reported, thereby avoiding potentially misleading analysis on underpowered secondary outcomes. We would argue that future guidelines should take into account results of the studies which used comprehensive multifaceted interventions when making recommendation on mite avoidance in the treatment of asthma, rather than concentrate on potentially flawed systematic reviews.

In occupational asthma, strict allergen avoidance is a key component of the management of affected patients. Evidence however indicates that only a complete cessation of exposure started soon after the onset of symptoms results in improvement - if high exposure continues for a prolonged period, even complete avoidance of the causal allergen may not impact upon the progression or severity of asthma. These observations from occupational asthma extended to dust mite avoidance in allergic asthma indirectly suggest that we should aim to achieve as complete cessation of allergen exposure as possible, and commence the intervention early in the natural history of the disease; indeed differences seen in results of allergen avoidance between adults and children may reflect time between onset of disease and reduction in exposure. Our opinion is that based on the currently available evidence,

the pragmatic approach to house dust mite allergen avoidance in clinical practice should be to use a multifaceted set of measures aiming to achieve as great a reduction in personal exposure as possible (Table 1). Such interventions require more than a simple focus on actual physical measures to reduce exposure (such as mattress, pillow and duvet covers), and require patient education, regular removal of accumulating allergen by routine cleaning, frequent laundry etc. Any intervention should be tailored to patient's dust mite sensitization and exposure status. Practically, as assessment of exposure is not feasible in most health care settings, health care professionals making decision on whether to commence mite avoidance should use the titre of allergen specific IgE antibodies or the size of skin test wheal as an indicator(71). Generally, the higher the level of mite-specific IgE or the size of skin test wheal, the more likely it is that mite sensitisation and exposure are contributing to patient's symptoms. Finally, any intervention should be started as soon as possible after asthma diagnosis has been made.

#### **Funding**

This paper was not funded.

#### **Declaration of interest**

A Custovic has received consultancy fees from Novartis, Regeneron / Sanofi, Boehringer Ingelheim and Philips; Lecture fees from Thermo Fisher Scientific and Novartis, outside the submitted work. A Simpson has received lecture fees from Thermo Fisher Scientific. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed

#### **Reviewer disclosures**

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Table 1. Mite allergen avoidance measures in adults and children – pragmatic view of the authors

Single measure	Reduces mite allergen	Benefit in adults	Benefit in children
Allergen proof encasing of mattress pillow and duvet	yes	No effect on PEF or ICS use. Not tested for exacerbations	Reduces exacerbations in children, but no improvement in PEF
Air cleaner	no	Small benefit to quality of life, but not lung function	Small benefit to quality of life, but not lung function
HEPA Vacuum cleaner	no	Small benefit to lung function (but mostly seen in cat allergic subjects)	Small benefit to lung function (but mostly seen in cat allergic subjects)
Removal of carpets		Not tested	Not tested
Acaricides/tannic acid	Yes, have to be repeated frequently	No evidence of benefit on lung function as a single intervention	No evidence of benefit as a single intervention
Combination			
Encasings plus tannic acid/acaricide	yes	No evidence of benefit	Improvement in airway reactivity and symptoms
Encasings, Acaricides, HEPA vacuum, pest control, education	yes	Not tested	Fewer symptom days

## References

Papers of special note have been highlighted as:

\* of interest

\*\* of considerable interest

1. Guidelines for the Diagnosis and Management of Asthma (EPR-3) 2007 [Available from: <https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma>]
2. Global strategy for asthma management and prevention 2019 [Available from: <https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf>.]
3. British guideline on the management of asthma 2019 [Available from: <https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/>.]
4. Asthma: diagnosis, monitoring and chronic asthma management 2017 [Available from: <https://www.nice.org.uk/guidance/ng80/chapter/recommendations>.]
5. Tovey ER, Marks GB. It's time to rethink mite allergen avoidance. *J Allergy Clin Immunol*. 2011;128(4):723-7 e6.\*  
A comprehensive review of the evidence-based framework for effective domestic allergen avoidance interventions
6. Simpson A, Simpson B, Custovic A, Cain G, Craven M, Woodcock A. Household characteristics and mite allergen levels in Manchester, UK. *Clin Exp Allergy*. 2002;32(10):1413-9.
7. Simpson A, Hassall R, Custovic A, Woodcock A. Variability of house-dust-mite allergen levels within carpets. *Allergy*. 1998;53(6):602-7.
8. Gore RB, Hadi EA, Craven M, Smillie FI, O'Meara TJ, Tovey ER, et al. Personal exposure to house dust mite allergen in bed: nasal air sampling and reservoir allergen levels. *Clin Exp Allergy*. 2002;32(6):856-9.
9. Gore RB, Curbishley L, Truman N, Hadley E, Woodcock A, Langley SJ, et al. Intranasal air sampling in homes: relationships among reservoir allergen concentrations and asthma severity. *J Allergy Clin Immunol*. 2006;117(3):649-55.
10. Tovey ER, Willenborg CM, Crisafulli DA, Rimmer J, Marks GB. Most personal exposure to house dust mite aeroallergen occurs during the day. *PloS one*. 2013;8(7):e69900.
11. Custovic A, Woodcock H, Craven M, Hassall R, Hadley E, Simpson A, et al. Dust mite allergens are carried on not only large particles. *Pediatr Allergy Immunol*. 1999;10(4):258-60.
12. Custovic A, Simpson A, Pahdi H, Green RM, Chapman MD, Woodcock A. Distribution, aerodynamic characteristics, and removal of the major cat allergen Fel d 1 in British homes. *Thorax*. 1998;53(1):33-8.
13. Custovic A, Simpson B, Simpson A, Hallam C, Craven M, Woodcock A. Relationship between mite, cat, and dog allergens in reservoir dust and ambient air. *Allergy*. 1999;54(6):612-6.
14. Marinho S, Custovic A, Marsden P, Smith JA, Simpson A. 17q12-21 variants are associated with asthma and interact with active smoking in an adult population from the United Kingdom. *Ann Allergy Asthma Immunol*. 2012;108(6):402-11 e9.
15. Casset A, Purohit A, Birba E, Chenard MP, Uring Lambert B, Bahram S, et al. Bronchial challenge test in asthmatics sensitized to mites: role of particle size in bronchial response. *J Aerosol Med*. 2007;20(4):509-18.
16. Custovic A. To what extent is allergen exposure a risk factor for the development of allergic disease? *Clin Exp Allergy*. 2015;45(1):54-62.

17. Tunnicliffe WS, Fletcher TJ, Hammond K, Roberts K, Custovic A, Simpson A, et al. Sensitivity and exposure to indoor allergens in adults with differing asthma severity. *Eur Respir J*. 1999;13(3):654-9.
18. Custovic A, Simpson BM, Simpson A, Kissen P, Woodcock A, Asthma NACM, et al. Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during first year of life: a randomised trial. *Lancet*. 2001;358(9277):188-93.
19. Kuehr J, Frischer T, Meinert R, Barth R, Forster J, Schraub S, et al. Mite allergen exposure is a risk for the incidence of specific sensitization. *J Allergy Clin Immunol*. 1994(1):44-52.
20. Lau S, Illi S, Sommerfeld C, Niggemann B, Bergmann R, von ME, et al. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Multicentre Allergy Study Group. *Lancet*. 2000;356(9239):1392-7.
21. Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. *N Engl J Med*. 1990;323(8):502-7.
22. Wahn U, Lau S, Bergmann R, Kulig M, Forster J, Bergmann K, et al. Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol*. 1997;6(Pt 1):763-9.
23. Cole JC, Ownby DR, Havstad SL, Peterson EL. Family history, dust mite exposure in early childhood, and risk for pediatric atopy and asthma. *J Allergy Clin Immunol*. 2004;114(1):105-10.
24. Halken S. Early sensitisation and development of allergic airway disease - Risk factors and predictors. *Paediatr Respir Rev*. 2003(2):128-34.
25. Ihuoma H, Belgrave DC, Murray CS, Foden P, Simpson A, Custovic A. Cat ownership, cat allergen exposure, and trajectories of sensitization and asthma throughout childhood. *J Allergy Clin Immunol*. 2018;141(2):820-2 e7.
26. Brough HA, Simpson A, Makinson K, Hankinson J, Brown S, Douiri A, et al. Peanut allergy: effect of environmental peanut exposure in children with filaggrin loss-of-function mutations. *J Allergy Clin Immunol*. 2014;134(4):867-75 e1.
27. Simpson A, Brough HA, Haider S, Belgrave D, Murray CS, Custovic A. Early-life inhalant allergen exposure, filaggrin genotype and the development of sensitization from infancy to adolescence. *J Allergy Clin Immunol*. 2019.
28. Liu X, Beaty TH, Deindl P, Huang SK, Lau S, Sommerfeld C, et al. Associations between specific serum IgE response and 6 variants within the genes IL4, IL13, and IL4RA in German children: the German Multicenter Atopy Study. *J Allergy Clin Immunol*. 2004;113(3):489-95.
29. Lynch SV, Wood RA, Boushey H, Bacharier LB, Bloomberg GR, Kattan M, et al. Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children. *J Allergy Clin Immunol*. 2014;134(3):593-601 e12.
30. Simpson A, John SL, Jury F, Niven R, Woodcock A, Ollier WE, et al. Endotoxin exposure, CD14, and allergic disease: an interaction between genes and the environment. *Am J Respir Crit Care Med*. 2006;174(4):386-92.
31. Kerkhof M, Daley D, Postma DS, Park JE, Chan Yeung M, Wijga AH, et al. Opposite effects of allergy prevention depending on CD14 rs2569190 genotype in 3 intervention studies. *J Allergy Clin Immunol*. 2012;129(1):256-9.
32. Bakolis I, Heinrich J, Zock JP, Norback D, Svanes C, Chen CM, et al. House dust-mite allergen exposure is associated with serum specific IgE but not with respiratory outcomes. *Indoor air*. 2014.

33. Langley SJ, Goldthorpe S, Craven M, Morris J, Woodcock A, Custovic A. Exposure and sensitization to indoor allergens: association with lung function, bronchial reactivity, and exhaled nitric oxide measures in asthma. *J Allergy Clin Immunol*. 2003;112(2):362-8.
34. Rosenstreich DL, Eggleston P, Kattan M, Baker D, Slavin RG, Gergen P, et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *N Engl J Med*. 1997;336(19):1356-63.
35. Custovic A, Taggart SC, Francis HC, Chapman MD, Woodcock A. Exposure to house dust mite allergens and the clinical activity of asthma. *J Allergy Clin Immunol*. 1996;98(1):64-72.
36. Langley SJ, Goldthorpe S, Craven M, Woodcock A, Custovic A. Relationship between exposure to domestic allergens and bronchial hyperresponsiveness in non-sensitised, atopic asthmatic subjects. *Thorax*. 2005;60(1):17-21.
37. Murray CS, Poletti G, Kebabdz T, Morris J, Woodcock A, Johnston SL, et al. Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax*. 2006;61(5):376-82.\*  
Important study demonstrating the synergistic effect of allergen exposure and respiratory virus infections in causing severe asthma attacks resulting in hospital admissions
38. Green RM, Custovic A, Sanderson G, Hunter J, Johnston SL, Woodcock A. Synergism between allergens and viruses and risk of hospital admission with asthma: case-control study. *BMJ*. 2002;324(7340):763.
39. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med*. 2011;364(11):1005-15.
40. Custovic A, Simpson BM, Simpson A, Hallam C, Craven M, Brutsche M, et al. Manchester Asthma and Allergy Study: low-allergen environment can be achieved and maintained during pregnancy and in early life. *J Allergy Clin Immunol*. 2000;105(2 Pt 1):252-8.
41. Tovey E, Ferro A. Time for new methods for avoidance of house dust mite and other allergens. *Current allergy and asthma reports*. 2012;12(5):465-77.
42. Wilson JM, Platts-Mills TAE. Home Environmental Interventions for House Dust Mite. *J Allergy Clin Immunol Pract*. 2018;6(1):1-7. .\*  
Comprehensive review of dust mite avoidance measures
43. Hallam C, Custovic A, Simpson B, Houghton N, Simpson A, Woodcock A. Mite allergens in feather and synthetic pillows. *Allergy*. 1999;54(4):407-8.
44. Gore RB, Durrell B, Bishop S, Curbishley L, Woodcock A, Custovic A. High-efficiency vacuum cleaners increase personal mite allergen exposure, but only slightly. *Allergy*. 2006;61(1):119-23.
45. Green R, Simpson A, Custovic A, Woodcock A. Vacuum cleaners and airborne dog allergen. *Allergy*. 1999;54(4):403-5.
46. Simpson A, Woodcock A, Custovic A. Housing characteristics and mite allergen levels: to humidity and beyond. *Clin Exp Allergy*. 2001;31(6):803-5.
47. Custovic A, Taggart SC, Kennaugh JH, Woodcock A. Portable dehumidifiers in the control of house dust mites and mite allergens. *Clin Exp Allergy*. 1995;25(4):312-6.
48. Vinnikov D, Khafagy A, Blanc PD, Brimkulov N, Steinmaus C. High-altitude alpine therapy and lung function in asthma: systematic review and meta-analysis. *ERJ Open Res*. 2016;2(2).
49. Cipriani F, Calamelli E, Ricci G. Allergen Avoidance in Allergic Asthma. *Front Pediatr*. 2017;5:103.
50. Gotzsche PC, Hammarquist C, Burr M. House dust mite control measures in the management of asthma: meta-analysis. *BMJ*. 1998;317(7166):1105-10; discussion 10.



51. Gotzsche PC, Johansen HK, Burr ML, Hammarquist C. House dust mite control measures for asthma. *Nurs Times*. 2001;97(33):37.
52. Gotzsche PC, Johansen HK, Schmidt LM, Burr ML. House dust mite control measures for asthma. *Cochrane Database Syst Rev*. 2004(4):CD001187.
53. Gotzsche PC, Johansen HK. House dust mite control measures for asthma: systematic review. *Allergy*. 2008;63(6):646-59.
54. Leas BF, D'Anci KE, Apter AJ, Bryant-Stephens T, Lynch MP, Kaczmarek JL, et al. Effectiveness of indoor allergen reduction in asthma management: A systematic review. *J Allergy Clin Immunol*. 2018;141(5):1854-69.
55. Dust-mite control measures of no use. *Lancet*. 2008;371(9622):1390.
56. Nurmatov U, van Schayck CP, Hurwitz B, Sheikh A. House dust mite avoidance measures for perennial allergic rhinitis: an updated Cochrane systematic review. *Allergy*. 2012;67(2):158-65.
57. Platts-Mills TAE. Allergen avoidance in the treatment of asthma: problems with the meta-analyses. *J Allergy Clin Immunol*. 2008;122(4):694-6.\*\*  
Important article summarising potential problems with meta-analyses and systematic reviews of mite avoidance
58. Murray CS, Foden P, Sumner H, Shepley E, Custovic A, Simpson A. Preventing Severe Asthma Exacerbations in Children. A Randomized Trial of Mite-Impermeable Bedcovers. *Am J Respir Crit Care Med*. 2017;196(2):150-8. \*\*  
The first study to demonstrate the effect mite allergen impermeable bed covers on acute attacks of asthma, which is the primary outcome measure used to evaluate monoclonal antibodies today
59. Luczynska C, Tredwell E, Smeeton N, Burney P. A randomized controlled trial of mite allergen-impermeable bed covers in adult mite-sensitized asthmatics. *Clin Exp Allergy*. 2003;33(12):1648-53.
60. Woodcock A, Forster L, Matthews E, Martin J, Letley L, Vickers M, et al. Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. *N Engl J Med*. 2003;349(3):225-36.
61. Terreehorst I, Hak E, Oosting AJ, Tempels-Pavlica Z, de Monchy JG, Bruijnzeel-Koomen CA, et al. Evaluation of impermeable covers for bedding in patients with allergic rhinitis. *N Engl J Med*. 2003;349(3):237-46.
62. Gore RB, Boyle RJ, Gore C, Custovic A, Hanna H, Svensson P, et al. Effect of a novel temperature-controlled laminar airflow device on personal breathing zone aeroallergen exposure. *Indoor air*. 2015;25(1):36-44.
63. Boyle RJ, Pedroletti C, Wickman M, Bjerner L, Valovirta E, Dahl R, et al. Nocturnal temperature controlled laminar airflow for treating atopic asthma: a randomised controlled trial. *Thorax*. 2012;67(3):215-21.
64. Schauer U, Bergmann KC, Gerstlauer M, Lehmann S, Gappa M, Brenneken A, et al. Improved asthma control in patients with severe, persistent allergic asthma after 12 months of nightly temperature-controlled laminar airflow: an observational study with retrospective comparisons. *Eur Clin Respir J*. 2015;2.
65. Gore C, Gore RB, Fontanella S, Haider S, Custovic A. Temperature-controlled laminar airflow (TLA) device in the treatment of children with severe atopic eczema: Open-label, proof-of-concept study. *Clin Exp Allergy*. 2018;48(5):594-603.
66. Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R, 3rd, et al. Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med*. 2004;351(11):1068-80.\*\*  
The largest study to date of the multifaceted intervention in children which demonstrates the importance of addressing complex sensitization and exposure patterns

67. Holt PG, Strickland D, Bosco A, Belgrave D, Hales B, Simpson A, et al. Distinguishing benign from pathologic TH2 immunity in atopic children. *J Allergy Clin Immunol*. 2016;137(2):379-87.
68. Simpson A, Tan VY, Winn J, Svensen M, Bishop CM, Heckerman DE, et al. Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth cohort study. *Am J Respir Crit Care Med*. 2010;181(11):1200-6.
69. Fontanella S, Frainay C, Murray CS, Simpson A, Custovic A. Machine learning to identify pairwise interactions between specific IgE antibodies and their association with asthma: A cross-sectional analysis within a population-based birth cohort. *PLoS Med*. 2018;15(11):e1002691.
70. Simpson A, Soderstrom L, Ahlstedt S, Murray CS, Woodcock A, Custovic A. IgE antibody quantification and the probability of wheeze in preschool children. *J Allergy Clin Immunol*. 2005;116(4):744-9.
71. Soto-Quiros M, Avila L, Platts-Mills TA, Hunt JF, Erdman DD, Carper H, et al. High titers of IgE antibody to dust mite allergen and risk for wheezing among asthmatic children infected with rhinovirus. *J Allergy Clin Immunol*. 2012;129(6):1499-505 e5.