Received: 10 January 2023 | Accepted: 19 January 2023

DOI: 10.1111/pai.13915

REVIEW ARTICLE

WILEY

Environmental influences on childhood asthma: Allergens

Adnan Custovic[1] | Angela Pinot de Moira[1] | Clare S. Murray[2] | Angela Simpson[2]

[1]National Heart and Lung Institute, Imperial College London, London, UK

[2]NIHR Manchester Biomedical Research Unit, Division of Immunology, Immunity to Infection, and Respiratory Medicine, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester University NHS Foundation Trust, Manchester, UK

Correspondence
Adnan Custovic, Imperial College London, London, UK.
Email: a.custovic@imperial.ac.uk

Editor: Ömer KALAYCI

Abstract

Allergen exposure is associated with the development of allergen-specific sensitization, but their relationship is influenced by other contemporaneous exposures (such as microbial exposure) and the genetic predisposition of the host. Clinical outcomes of the primary prevention studies that tested the effectiveness of allergen avoidance in pregnancy and early life on the subsequent development of sensitization and asthma published to date are inconsistent. Therefore, we cannot provide any evidence-based advice on the use of allergen avoidance for the primary prevention of these conditions. The evidence about the impact of allergen exposure among and among sensitized children with asthma is more consistent, and the combination of sensitization and high exposure to sensitizing allergen increases airway inflammation, triggers symptoms, adversely impacts upon disease control, and is associated with poorer lung function in preschool age. However, there are differing opinions about the role of inhalant allergen avoidance in asthma management, and recommendations differ in different guidelines. Evidence from more recent high-quality trials suggests that mite allergen-impermeable bed encasings reduce hospital attendance with asthma attacks and that multifaceted targeted environmental control improves asthma control in children. We therefore suggest a pragmatic approach to allergen avoidance in the management of childhood asthma for clinical practice, including the recommendations to: (1) tailor the intervention to the patient's sensitization and exposure status by using titer of allergen-specific IgE antibodies and/or the size of the skin test as indicators of potential response; (2) use a multifaceted allergen control regime to reduce exposure as much as possible; and (3) start intervention as early as possible upon diagnosis.

KEYWORDS
allergen avoidance, allergens, asthma, cat, dog, dust mite, gene–environment interactions, primary prevention, sensitization

1 | INTRODUCTION

Exposure to inhalant allergens (primarily house-dust mites, cat and dog allergens) is important in the development of allergen-specific sensitization, and if asthma has developed, further allergen exposure may contribute to ongoing symptoms. However, the relationship between allergen exposure and sensitization is complex. To develop allergen-specific sensitization, one needs to be exposed to that allergen. The absence of a consistent, linear dose–response relationship between specific allergen exposures and sensitization has necessitated the application of more complex approaches to attempt to understand these inter-relationships—an essential step in would-be disease prevention. In real life, humans are simultaneously exposed to a mixture of allergens, together with a range of other

environmental factors. Studies suggest that interactions between environmental exposures, in addition to route and timing of exposure, together with the genetic predisposition of the host, contribute additional layers of complexity to the relationships (reviewed in[1]).

The evidence about the adverse effects of allergen exposure on asthma control, severity, and acute attacks among sensitized children with asthma diagnosis is more consistent. In general, among allergic asthmatics (i.e., those in whom sensitization is relevant to the disease process), asthma severity and exacerbation risk increase with high domestic exposure to sensitizing allergens (reviewed in[2]).

In this review, we will address the role of indoor allergens in the development of allergic sensitization and asthma and then explore the role of allergen avoidance in the primary prevention of asthma and allergies. In the second section, we will examine the impact of indoor allergens on asthma severity in children and explore the evidence for allergen avoidance in the treatment of asthma.

Key Messages

The development of allergen-specific sensitization is influenced by allergen exposure but also impacted by other exposures (e.g., microbial) and the child's genetic predisposition. We cannot provide any evidence-based advice on the effectiveness of allergen avoidance during pregnancy and early life in the primary prevention of sensitization and asthma. High allergen exposure among sensitized patients with asthma diagnosis can increase airway inflammation, trigger symptoms, and increase the risk of asthma attacks. There is a range of opinions about the role of inhalant allergen avoidance in asthma management, and international guidelines differ in their recommendations. Mite allergen-impermeable bed encasings can reduce the risk of hospital attendance with asthma attacks in children sensitized to mites. We suggest a following pragmatic approach to allergen avoidance in clinical practice: (1) Tailor the intervention to the patient's sensitization and exposure status; (2) Use high titer of allergen-specific IgE antibodies and/or the size of the skin test mean wheal diameter as an indicator; (3) For mite avoidance, mite monosensitized younger children (pre-, early-, and mid-school age) living in nonsmoking households who require a high dose of controller medication are more likely to benefit; (4) Start intervention as early upon diagnosis as possible; (5) Use a multifaceted allergen control regime to achieve as great a reduction in exposure as possible.

2 | ALLERGEN EXPOSURE AND THE DEVELOPMENT OF SENSITIZATION AND ASTHMA

For more than three decades, conflicting evidence has been reported about the role of exposure to indoor allergens in early life in relation to the development of allergen-specific sensitization and asthma. This heterogeneity is likely in part a consequence of the differences in study design (including definition and age of assessment of clinical outcomes), genetics of study populations, and methods of the assessment of exposure, making it challenging to summarize the findings to draw firm conclusions. In some studies, early-life dust mite allergen exposure increased the risk of the development of mite sensitization and asthma,[3–8] particularly among children at genetic high risk or with early manifestations of atopic disease.[9,10] However, others have not confirmed these associations (reviewed in[1]).

The impact of exposure to cat and dog allergens has been extensively investigated, also with inconsistent results.[11–13] For example, several birth cohorts observed a linear dose–response relationship between cat allergen levels measured in homes in early life and increased risk of sensitization to cat in preschool/early-school age.[14–16] By contrast, cross-sectional studies in older children and young adults reported that very high Fel d 1 levels may protect against cat sensitization and suggested a bell-shaped rather than linear relationship.[17–19] Such effect may be explained by the development of an allergen-specific tolerance consequent to the high-dose natural exposure,[20] possibly in part through increased allergen-specific IgG production,[17,21] which has been shown to downregulate IgE by uncoupling IgE from its effector mechanisms in allergen-specific immunotherapy (AIT; reviewed in[22]).

Since there is a strong association between pet ownership and high levels of cat/dog allergens in homes, it is difficult to differentiate between the effect of exposure to allergen to that of the animal more broadly. It is thus not surprising that similar discrepancies to the studies, which ascertained the impact of allergen exposure have been reported in analyses using cat ownership, with some studies showing increased cat sensitization among cat owners,[14,23] others finding that cat ownership protects against cat sensitization,[24–27] and some studies observing no association.[28,29] The nature and the direction of these associations may also be influenced by the geographical area and customs of the studied populations. For example, in areas with low frequency of cat ownership and low cat allergen exposure at a population level,[30,31] the relationship between Fel d 1 exposure and cat sensitization appears linear[32–34]; in such areas, individual exposure may rarely be high enough to induce tolerance.[1] In line with this, the relationship between early-life cat exposure and odds of asthma symptoms in childhood has also been observed to vary depending on the prevalence of cat keeping in the community.[35]

Compared with the inconsistent findings for cat, data on the effect of dog ownership are more consistent, with most studies[26,36] (although not all[13,14]) suggesting that having a dog in early life is protective against sensitization to dog. Moreover, many studies reported a protective effect of dog ownership on sensitization to other allergens, as well as asthma.[13,36] Some reported similar, albeit weaker, nonspecific effects for cat ownership.[13,36] The generally observed protective effect of dog ownership on outcomes not confined to specific dog sensitization suggests that the protection is likely due to an environmental exposure for which dog ownership

is a proxy (e.g., microbial exposure, higher endotoxin, more diverse external microbiome[37]), and that the observed effects for dog may be similar to that previously reported for growing up on farms.[38] This is consistent with the observation that dog ownership increases microbial diversity inside the house, particularly on pillowcases.[39] There is some evidence that effects on household microbial diversity may be greater for dogs than cats[40] (though studies have been small and underpowered). There is also evidence of pet ownership influencing the microbiota of their owners, although shared environment and lifestyle factors are also likely to play a role. For example, a Canadian birth cohort reported that early exposure to pets (both pre- and postnatal) was associated with increased diversity of the infants' gut microbiome,[41] whilst others have observed that dog and cat ownership increases the skin and/or gut microbial diversity of their adult owners, with a stronger effect in females.[42,43] Several factors have been found to influence the microbiome of cats and dogs, including to some extent outdoor exposure.[40,44] Regional variations in the proportion of households with indoor cats and notably higher frequency in North America compared with Europe[45] (81% vs. 30%, respectively, in one study[46]), may partly explain the weaker nonspecific effects and more inconsistent results observed for cat ownership.

2.1 | Allergen exposure and the development of specific sensitization: The impact of time

Interesting findings that may explain some of the inconsistencies in the literature related to cat allergen exposure were reported in a birth cohort that used longitudinal analyses to investigate the effect of early-life exposure to cat and its major allergen Fel d 1 on the development of cat sensitization from early childhood through to adolescence.[47] The trajectory of the development of cat sensitization differed between children exposed to cat (and high Fel d 1 levels) in pregnancy and infancy compared with those not exposed. When children were aged 1 year, the frequency of cat sensitization was much higher among cat owners. However, after age 1 year, the increase in sensitization rate was 6% lower per year among cat owners compared to children without a cat, so that by adolescence, the prevalence of cat sensitization was the same in both groups (Figure 1). No association was observed between early-life cat exposure and sensitization to allergens other than cat or asthma. Trajectories of cat sensitization in Figure 1 suggest that analyses of the impact of exposure to cat can reveal either an increase in risk, no effect, or even protection, depending on the age of the studied population. Therefore, in order to understand the impact of early-life exposures, more useful information can be gained through the analysis of longitudinal trajectories than in cross-sectional studies.[47] Furthermore, the apparent contradictions in different studies may be a consequence of the different longitudinal trajectories of cat sensitization between individuals who lived in a home with a cat in early life compared with those without a cat, and all conflicting results may be correct.

This finding is likely to also be relevant for associations with asthma, since different temporal patterns of allergic sensitization differentially impact upon asthma risk, with multiple early sensitization phenotypes being by far the strongest associate.[48–50]

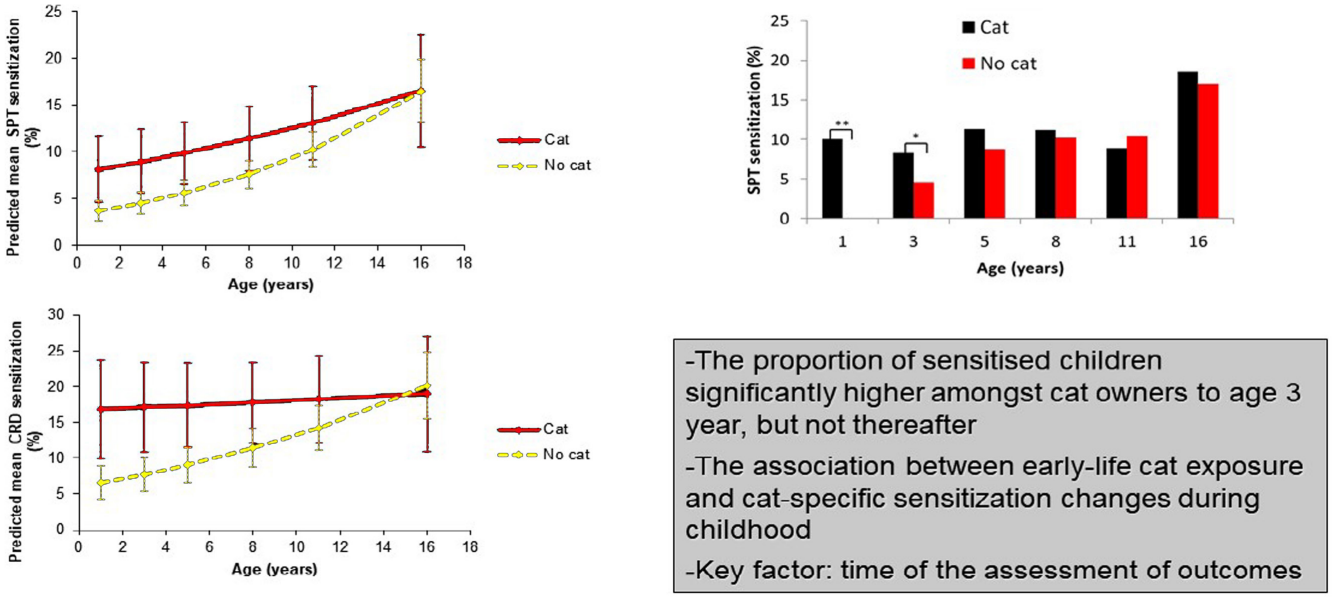

FIGURE 1 Cat ownership in the first year of life and longitudinal trajectories of cat sensitization through childhood; modified from[47] (with permission). SPT-skin prick test; CRD—component-resolved diagnostics; sensitization to Fel d 1. Left-hand panels—Longitudinal trajectories of cat sensitization (SPT) and sensitization to Fel d 1 (CRD) among children who lived in a home with a cat in early life and those who did not. Predicted value of mean response is shown in the graphical format along with 95% CIs. Right-hand panel: Cross-sectional association between cat ownership during pregnancy and point prevalence of cat-specific sensitization from infancy to adolescence (SPT).

2.2 | Is exposure to indoor allergens *in utero* important?

There is a possibility that *in utero* allergen exposure may influence sensitization in a child.[51] As early as 22 weeks gestation, peripheral blood mononuclear cells may have positive proliferative responses when stimulated with multiple indoor allergens.[52] There is also evidence that allergen-specific IgG antibodies are transferred across the placenta to the fetus.[53] Interestingly, Jenmalm and Björkstén observed higher cord blood IgG and IgG1 levels to cat in children born to atopic mothers who had a cat in the home compared to those without a cat, with lower cord blood IgG to cat associated with subsequent development of allergic symptoms in the child.[54] In a more recent study, high maternal allergen-specific IgG in the third trimester was associated with a lack of allergen-specific IgE sensitization in children at 5 years.[55] However, studies examining the effects of AIT during pregnancy have failed to provide strong evidence for a protective effect against allergic disease in offspring.[56] Further, the relative importance of *in utero* vs. postnatal allergen exposure is difficult to study, since pre- and postnatal allergen exposures (including pet ownership) are usually highly correlated.[47]

3 | INTERACTIONS BETWEEN ALLERGEN EXPOSURE AND GENETICS OF THE HOST

The concept that the same environmental exposure may have different effects among individuals with different genetic predisposition has been tested in studies which assessed the interaction between genes and the susceptibility to environmental factors (reviewed in[57,58]). One example is the reported variability in the impact of household exposure to mite allergen Der p 1 level (measured in in carpet dust) on the risk of development of mite sensitization in individuals with different C-590T promoter polymorphisms of the IL4 gene.[59]

3.1 | Filaggrin (FLG) loss-of-function mutations and allergen exposure

Whilst a common assumption is that most exposure to indoor allergens (such as mite, cat, and dog) occurs via inhalation (and to food allergens via ingestion), sensitization may also develop because of allergen presentation through impaired skin. Allergenic proteins from indoor environment could penetrate weakened skin, which may lead to IgE production. *FLG* loss-of-function mutations predispose toward an impaired skin barrier and are associated with eczema and other atopic conditions, and inhalant allergen sensitization.[60] Children with *FLG* mutations may have an increased risk of eczema if they were exposed to cat in early life,[61] but the association is inconsistent.[8] In children with *FLG* mutations, high levels of peanut allergens in house dust increase the risk of peanut sensitization and allergy, with no impact of exposure in those without *FLG* mutations.[62] Similarly, household exposure to mite allergen Der p 1 in infancy increases the risk of mite sensitization in children with *FLG* mutations and not in those without, but the modifying effect of *FLG* mutations is higher in early childhood, and gradually reduces over time.[63] The same study revealed a significant interaction between early-life Fel d 1 exposure and *FLG* genotype on the trajectory of cat sensitization during childhood, with the effect of early-life exposure being much greater among those with *FLG* mutations compared to those with the wildtype.[63] By contrast, in children with *FLG* mutations who were exposed to dog in pregnancy/early life, the risk of sensitization to any allergen was on average 5-fold lower than in those not exposed (and the protective effect of dogs was much lower in children without *FLG* mutations).[63]

3.2 | Interaction between 17q12-q21 SNPs and pet ownership in asthma development

Even for the most highly replicated and significant childhood asthma locus (17q21), evidence suggests interactions with pet ownership in modifying the risk of asthma development. Five studies (mostly in populations of European ancestry) investigated these interactions. A case–control study in children from Croatia reported a significant interaction between cat and dog ownership in the first year of life and a single nucleotide polymorphism (SNP) rs921651 in *GSDMA* in relation to school age asthma diagnosis, with pet ownership being protective among AA homozygotes but not in other genotype groups.[64] No such interaction was observed for the SNPS most associated with increased asthma risk (rs2305480 and rs7216389).[64] In a nested case–control analysis in the Danish National Birth Cohort, there was no significant impact of pet ownership in pregnancy on recurrent wheeze by age 18 months in the whole population, but among asthma risk allele homozygotes (TT) in SNP rs7216389, the current furred pets ownership decreased the risk of wheeze at 18 months, with the opposite effect in C-allele homozygotes.[65]

Several analyses were carried out in birth cohort studies. Analysis among 377 children recruited in the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC), who were at high risk of allergic diseases, reported a trend for a lower risk of asthma diagnosis at age 12 years among those exposed to pets from birth.[66] Analyses stratified by the genotype in 17q21 SNP rs7216389 suggested an interaction between pet exposure and this variant, in that pet ownership was associated with a lower prevalence of asthma among children with high-risk TT genotype, but there was no such protective effect in participants with the CC/CT genotypes.[66] Further analysis which used allergen levels in homes as markers of exposure mirrored these interactions for cat but not dog allergen.[66] Another analysis in a rural birth cohort showed that dog (but not cat) ownership was protective against wheeze at age 1 year, with no interaction between SNPs in *ORMDL3/GSDMB* with dog ownership.[67] Of note, in this study, the

protective effect of the exposure to animal sheds was restricted to genotypes 17q12-q21, which have previously been shown to increase the risk of asthma.[67]

The largest study to date of the gene–environment interaction between 17q21 locus and cat and dog ownership in infancy and wheezing illness from birth to adolescence[68] confirmed that rs2305480 risk allele (G) is associated with increased risk of asthma diagnosis, and with late-onset and persistent wheeze classes (which were derived using latent class analysis[69]). Consistent with the results of a large meta-analysis in European children,[14] this study of 5 UK birth cohorts reported no association between early-life dog and cat ownership and asthma or any wheeze class (phenotype) in the whole population.[68] However, when the interaction between genotype and pet ownership was investigated, among dog owners (but not cat owners), the most replicated asthma risk allele (rs2305480_G) was no longer associated with an increased risk of asthma diagnosis or persistent wheezing.[68] By contrast, among those children not exposed to pets, or exposed to cats only, the risk allele was consistently associated with an increased risk of asthma and persistent wheeze.[68]

3.3 | More complexity: Gene–environment–environment interactions

The impact of early-life mite allergen exposure on mite sensitization is modulated by endotoxin exposure in individuals with a specific genotype in *CD14* (CC homozygotes, but not T-allele homozygotes in rs2569190, *CD14/−159*).[70] High allergen exposure may protect against sensitization when combined with an environment rich in specific bacterial families such as *Firmicutes* and *Bacteriodetes*.[71] The inference we can make from these studies is that the effect of interventions to alter allergen exposure is likely to differ between children with different genetic predisposition[72] and concomitant environmental exposures (primarily bacterial), and that individuals with differing genetic susceptibility and exposome may benefit from different interventions (either avoidance or high-level exposure).

4 | ALLERGEN AVOIDANCE IN PRIMARY PREVENTION OF SENSITIZATION AND ASTHMA

The association between allergen exposures, sensitization, and asthma observed in epidemiological studies, and the findings that high allergen exposure early in life combined with the development of allergic sensitization increases the risk of subsequently developing asthma symptom,[13,73] prompted several primary prevention studies to ascertain whether allergen control during pregnancy and early life can modify the risk of the development of these clinical outcomes (reviewed in[74]). Due to the differences between the studies in design and characteristics of included populations, the results are not directly comparable.

Clinical outcomes from primary prevention studies published to date are inconsistent. For example, in the Isle of Wight prevention study, both mite sensitization and asthma were significantly reduced by age 18 years in the mite allergen avoidance group.[75] By contrast, the Manchester primary prevention study reported a decrease in early-life severe wheeze[76] but a significant increase in mite sensitization by early-school age in the intervention group[77] (which comprised a wide-ranging comprehensive avoidance of mite and pet allergens[78]). The Australian study reported no overall effect of mite allergen avoidance, but the effect of intervention differed at different ages.[79]

Given this heterogeneity, we cannot provide any evidence-based recommendations on environmental control for disease prevention, and more nuanced analyses are required before we can draw definitive conclusions and give any meaningful advice.

5 | ALLERGEN EXPOSURE AND ASTHMA SEVERITY

The evidence about the impact of allergen exposure in sensitized patients with asthma on disease control, severity, and exacerbations is more consistent compared with the above-discussed data on the role of allergen exposure in the development of sensitization and asthma. Among sensitized asthmatics in whom sensitization is relevant to clinical symptoms,[80,81] asthma severity is associated with high domestic exposure to sensitizing allergens (reviewed for dust mite in[2]), and the combination of specific sensitization and high exposure to sensitizing allergen increase airway inflammation,[82] triggers symptoms[83,84] and is associated with poorer lung function in preschool age.[85] Virus infections and high allergen exposure may interact to increase the risk of asthma attacks leading to hospital admissions in sensitized children.[86] Some studies have reported that mite exposure adversely impacts asthma control among nonatopic asthmatics.[87]

In the USA, asthma attacks were found to be more common if patients are exposed to high levels of pet allergens to which they are sensitized.[88] Extrapolation of these data suggest that 1.5 million asthma exacerbations per year (in adults and children) are attributable to pet ownership among pet-sensitized asthma sufferers. However, >80% of the pet-sensitized pet owners in this study did not report an asthma attack during the 1-year follow-up period. Thus, it is likely that ongoing exposure to the pet is more of a problem for some pet-sensitized pet owners with asthma, than for others. Further work is needed to identify sensitized patients with asthma in whom specific allergen exposure is relevant and contributing to disease severity, and initial results from a new basophil activation test are promising.[89]

A series of studies involved the relocation of atopic asthmatic children to the high-altitude sanatoria where allergens were not detectable; significant improvement in bronchial

hyper-responsiveness (BHR) was seen from 3 months.[90–92] Although neither randomized nor controlled, these studies indicate that non-pharmacological measures can improve some measures of asthma severity/control (particularly BHR), although improvements took several months to plateau, and lung function did not generally improve.

6 | ALLERGEN AVOIDANCE IN HOMES IN THE MANAGEMENT OF ASTHMA

6.1 | Measures to reduce allergens in home

6.1.1 | House-dust mites

Approaches to reduce mite allergens in home include:[93–95]

- Cover the mattress, duvet, and pillows with encasings that are allergen-impermeable.
- Wash bedding regularly (if possible, >55°C to kill the mites).
- Consider carpet removal and replacement with hard flooring.
- If carpets remain, expose to direct sunlight, steam clean, use acaricides, or tannic acid.
- Reduce humidity in the home to control of mite population.

Major reduction in mite allergen levels in homes can be achieved and maintained using a comprehensive allergen control regime combining several of the above measures.[78]

6.1.2 | Pet allergens

The only way to substantially reduce personal exposure is to find the alternative home for the pet.[93] This advice has not been the subject of randomized controlled trial; however, one nonrandomized study of pet removal ($n = 20$) showed some benefit.[96] Of note, even after permanent rehousing of the pet, it can take many months for allergen levels in the reservoirs within the home to fall.[97] Furthermore, due to their aerodynamic nature, pet allergens are not restricted to homes with pets and are found ubiquitously in the environment, including homes without pets,[98–100] schools, hospitals, and other public places[101–103] (reviewed in[104]) potentially at levels capable of worsening asthma symptoms.[105]

Air cleaning units with high-efficiency particulate air (HEPA) filters can reduce the airborne pet allergens, but their effectiveness under experimental conditions does not fully reflect the impact on personal inhaled exposure.[106] Other measures that have been investigated include pet washing, with some short-lived reduction in home allergen levels,[107,108] and regular cleaning with HEPA filter vacuum cleaners, with variable effects.[109,110] Restricting pets' presence in the home may also lead to some reduction in allergen levels (for example, homes with outdoor pets have been found to have lower allergen levels than those with indoor pets, albeit at still higher levels than homes with no pets[111]).

6.1.3 | Cockroach

Physical and chemical procedures to control cockroach populations in infested houses include sealing cracks and holes to restrict cockroach access, general cleaning to remove food sources, and use of insecticides (in a gel or bait form).

6.2 | Clinical effectiveness of allergen control measures in childhood asthma

The role of avoidance of dust mites and other inhalant allergens in the management of asthma remains a subject of controversy.[1] This is reflected in differing recommendations in various national/international asthma management guidelines. For example, the US NHLBI 2020 Focused update to the Asthma Management Guidelines recommends the use of a multicomponent intervention to try to control the relevant indoor allergen for sensitized patients with asthma who are exposed to sensitizing allergen within their home, as a conditional recommendation with low certainty of evidence.[112] The expert panel suggests that allergen mitigation can be used in patients of all ages and at all levels of asthma severity.[112] By contrast, the Global Initiative for Asthma (GINA) Global strategy for asthma management and prevention (2022) states that "allergen avoidance is not recommended as a general strategy for asthma," and that "for sensitized patients, there is limited evidence of clinical benefit for asthma in most circumstances with single-strategy indoor allergen avoidance".[113] However, GINA also recognizes that for children (but not adults) with asthma who are sensitized to mites and/or pets, there is limited evidence of clinical benefit for asthma with multifaceted avoidance strategies. It is notable that many national asthma guidelines (including the British National Institute of Clinical Excellence guideline on asthma, 2017[114]) focus mostly on pharmacological treatment, with little emphasis on potential benefits on nonpharmacological strategies.

The Cochrane Library has produced several meta-analyses of the efficacy of mite allergen avoidance in asthma,[115–117] combining study results for adults and children. Based on data from 54 trials with >3000 patients, the most recent meta-analysis concluded that single interventions using chemical and physical methods cannot be recommended.[117] For pet allergens, the Cochrane Group systematic review on the effect of avoidance with the pet *in situ* highlighted the paucity of good-quality studies.[118]

Another systematic review of 59 randomized and eight nonrandomized trials of allergen avoidance reported that the evidence base was inconclusive or showed no effect, and that no interventions demonstrated a consistent improvement in asthma control measures or lung function.[119] Platts-Mills[120] summarized the potential problems with meta-analyses and systematic reviews, and

this and several other review articles questioned over-reliance on meta-analyses/systematic reviews to inform clinical practice on allergen avoidance.[2,120,121] As a minimum, meta-analyses/systematic reviews should assess data in adults and children separately, and use only outcome measures for which an appropriate power calculation has been provided.[121] The choice of clinical outcomes can make interpretation of the results challenging, particularly as for most protocols, changes in medication during the intervention period were decided by the participants' physicians, rather than as part of the study protocol. This may be of relevance for BHR, where changes in controller medication can also change airway reactivity, and it is unlikely that an environmental intervention would lead to an improvement in BHR when controller medication had been reduced. High-altitude studies indicate that a period of several months is necessary to see a benefit, and as many of the included studies were of shorter duration, effects may have been missed.

6.3 | Studies of mite allergen avoidance in childhood asthma

Many studies of mite allergen avoidance in childhood asthma were small (10–20 subjects) and underpowered (summarized in Table 1). The first (open) study in children was published in 1974.[122] Following a 6-week observation period, parents were advised to clean the child's bedroom thoroughly, encase the mattress in plastic and remove feather duvets and carpets. The duration of the intervention was not specified, but mite numbers fell in all mattresses and symptom scores improved in all children. Although no formal comparisons were done and methodologies lacked the rigor of a modern clinical trial, this was a useful proof-of-concept study. This was followed in 1980s by a series of small, short, and unblinded studies of partial encasings, plus other physical measures,[123–125] one of which showed an improvement in the primary outcome of BHR, as well as lung function and medication use.[126] Three randomized controlled trials (RCTs) combined physical (encasings of mattress pillow and duvet) with chemical (tannic acid or benzyl benzoate to bedroom carpet) interventions. Ehnert et al reported a sustained improvement in BHR compared with a control group (although there were no placebo encasings, nor did the authors comment on medication usage at the start or end of the trial).[127] Carswell et al reported a significant improvement in BHR at 6 weeks in the active group, but this was not sustained to 24 weeks; however, this study did report improvements in symptoms and a reduction in medication usage at 24 weeks as secondary outcomes.[128] Shapiro et al reported that more children in the active group showed a significant improvement in BHR but no difference in secondary outcomes of symptoms or treatments.[129] A small open study of encasings in Singapore showed a reduction in symptom scores from baseline, but no between-group comparisons were made.[130] A study from Australia tested new feather pillows and duvets in the active group (both groups used mite-proof encasings for mattress) but was unable to demonstrate a difference in any outcome measures tested.[131]

Three early double-blind randomized placebo-controlled RCTs (DBRPCT) of mite-proof encasings have published findings.[132–134] One study reported no change in the primary outcome of peak expiratory flow (PEF),[132] but ~80% of children were not requiring inhaled corticosteroids (ICS) at recruitment, indicating very mild disease with little scope for improvement. A study of more severe patients (>80% on ICS) demonstrated a reduction in a secondary outcome of serum eosinophil peroxidase, but no effect on BHR, lung function, or symptoms.[133] A Danish study of children with a positive mite bronchial challenge and high exposure used reduction in ICS treatment as a primary outcome and was able to demonstrate that more children could reduce ICS in the active compared with the placebo group.[134] There was no significant difference in BHR, lung function, or symptoms between groups.[134]

Four studies used devices to clean the air. Three were crossover designs in which the active treatment period lasted <6 weeks, and each had <20 patients. The ionizer[135] and electrostatic precipitator[136] studies reported negative results. A very small study of HEPA filters showed a reduction in symptom scores from baseline, but no between-group comparisons were performed.[130] One small study (12 children completed) of an active laminar airflow system reported fewer symptoms whilst the active device was *in situ*.[137]

Chemical methods using acaricides (without encasings) have been tested in five studies; one study that tested a chemical that was ineffective (natamycin) unsurprisingly found no improvement in clinical outcomes.[138] Two studies from Israel used acaricide acardust. In one study, levels of allergen in the mattress fell and asthma symptoms reduced in parallel in the active group, as did medication requirements.[139] In the other study, no reduction in allergen was seen, and no change in lung function or symptoms was observed.[140] One very short study (2–3 weeks) investigated the additional effect of Acarosan in children returning from a stay at high altitude and saw no difference between groups.[141] A further study of Acarosan found that levels of mite allergen were reduced in the carpets but not mattresses, but no improvement was seen in BHR.[142]

6.4 | Selected double-blind, randomized, placebo-controlled trials (DBRPCT) of allergenavoidance

The largest DBRPCT of mite-impermeable bed covers as a single intervention in adults with asthma found no benefits on lung function, treatment use, symptom scores, and quality of life.[143] By contrast, a more recent large DBRPCT of mite-impermeable encasings in children aged 3–17 years who were recruited after attending a hospital with an asthma attack (Preventing asthma exacerbations by avoiding mite allergen—PAXAMA)[144] demonstrated a significant reduction in hospital attendance with asthma exacerbation over a 12-month period, with ~45% lower risk in the active compared with placebo group (Figure 2).[144] This simple and relatively

TABLE 1 Mite allergen avoidance studies in mite-sensitized children with asthma.

Author Country year	Study design; number; subjects characteristics; follow-up	Evidence level	Avoidance measures	Other allergens	Effectiveness of intervention on mite allergen levels
Ehnert Germany 1992[127]	RCT DBPC for B vs Pl, not A 3 groups; $N = 24$; Median age 10 years; 12 months	1−	**A:** M/P/D: Encasings—polyurethane coated, carpets sprayed (3% tannic acid) 4 monthly **B:** mattress and carpet treated with benzyl benzoate **PL:** placebo-treated mattress and carpet	No comment	Significant decrease in mattress Der p1 in group A ($p < .005$); no change in groups B and PL
Carswell UK 1996[128]	RCT DBPC; $n = 49$; Mean age 9.9 years; 6 months	1+	**A:** BC—benzyl benzoate; M/P/D- benzyl benzoate then polyurethane encasing, wash linen at 60°C **PI:** BC—chalk dust; M/P/D- water spray, cotton encasings, wash linen at 40°C	Cat-sensitized cat owners excluded	100% reduction in active vs. 53% reduction in placebo for encasings ($p < .001$); no difference in carpet
Shapiro USA 1999[129]	RCT DBPC; $n = 36$; age 6–15 years; 12 months	1+	Aggressive-M/P/: Encasings, clean linen delivered monthly, tannic acid to carpets Standard—placebo tannic acid spray to carpet, cleaning advice	Pet-sensitized pet owners were included.	Reduced mite allergen exposure in aggressive intervention compared with standard intervention ($p = .03$)
El-Ghitany 2012[151]	RCT unblinded, 3 intervention groups, $n- = 160$ aged 6–12 years FU at 8 and 16 weeks		**A:** M/P encasing, cleaning, carpet removal, no pets **B:** tannic acid to carpet and bedding 2× weeks **C:** A + B **PI:** control group	No pets	Small reduction in exposure in 3 intervention groups
Sheikh UK 2002[132]	RCT DBPC; $N = 43$; Mean age 11 years; 6 months	1+	**A:** M/P/D: Encasings **PI:** placebo covers supplied by the same manufacturer. Both groups given written instructions on how to minimize mite exposure	Pet owners excluded	Not measured
Halken Denmark 2003[134]	RCT DBPC; $N = 47$; Age 5–15 years; 12 months	1+	**A:** M/P: Zippered encasings semipermeable polyurethane **PI:** cotton covers	Excluded pollen allergy and cat-sensitized cat owners	Greater reduction in mattress Der p 1 in active compared with placebo at 12 months ($p = .03$)
Frederick UK 1997[133]	RCT SBPC Crossover; $n = 31$; Mean age 9 years; 3 months−1 month washout between	1−	**A:** M/P: Zippered encasings, wipe down weekly with damp cloth. **PI:** polycotton covers	Pet-sensitized pet owners included ($n = 7$)	Significant reduction in Der p 1 in M/P/D in active compared with placebo: ($p < .0001$)
Glasgow Australia 2011[131]	RCT; $N = 197$; 7–14 years; 12 months	1+	All given mite-proof encasing for mattress **A**: duck feather duvet and pillow **PI**: standard advice of encasings for pillow and duvet and hot washing		Assessed with nasal air samplers NS
Warner UK 1993[135]	DBPCT crossover; $n = 20$; 3–11 years; 6 weeks ×2	1−	**A**: active ionizers; **PL:** placebo ionizers		Active Vs control period Airborne Der p 1 reduced ($p < 0.0001$)

Primary outcome	Effect size	Other outcomes Active vs placebo	Source of funding	Has study answered original question	Limitations
BHR	Significant improvement in BHR (PC20) in group A compared to others ($p < .05$)	None reported	Deutsche Forschungsgemeinschaft	Encasings Tannic acid +ve 1^0 Tannic acid only −ve	No placebo encasings. no comment on medication received at start or end of trial
BHR	NS	PEF: NS; FEV1: $p < .05$; symptoms: $p < .05$; medication use $p < .01$	Wellcome Trust Intervent provided covers	Encasings Acaricide Cleaning +ve 2^0	Transient improvement in BHR at 6 weeks
Doubling in PD20	In 9 of the aggressive intervention group and 4 standard; $p = .05$	Symptom scores, QOL, FEV1, OCS usage NS	*National Institute of Allergy and Infectious Diseases.*	Encasings Tannic acid Cleaning +ve 1^0	
Asthma severity	Improved in Group A and C $p < .001$	FEV_1 and PEFB improved in A, B, and C	*Not reported*		No power calculation. Not clear who funded the intervention. Not clear what the encasings are made of. V small reduction in allergen
PEFR	NS (improved in both groups)	Symptom score, health care utilization: NS ICS reduction NS.	*National Respiratory Training centre, Warwick* Allerayde provided encasing. ALK supplied SPT solutions.	Encasings −ve	Only 21% of subjects were on ICS at recruitment. ICS reduction program from month 1
50% reduction in ICS dose	**A**: 73% reduced ICS **PI**: 24% reduced ICS $p = .007$	BHR, symptoms, PEF: NS (both groups improved)	Danish Asthma and allergy Ass; Danish research foundation	Encasings +ve 1^0	
Symptoms; PEFR	NS	FEV1, BHR (PC20 histamine): NS EPX: NS EPO: $p = .02$	NAC and BLFand Intervent. Pharmacia provided assay kits	Encasings +ve 2^0	
Four or more episodes of wheeze; speech limiting wheeze, sleep disturbance	NS in Intention to treat analysis	FEV1 BHR QoL Medication usage All NS	*National Health and Medical Research Council, Australia.*	New bedding −ve	Decreased risk of sleep disturbance in per-protocol analysis
PEFR Symptom scores Medication use	NS ($n = 14$) NS NS		*Not stated* Ionizers provided by London Ioniser Centre	Air cleaning −ve	Study too short

TABLE 1 (Continued)

Author Country year	Study design; number; subjects characteristics; follow-up	Evidence level	Avoidance measures	Other allergens	Effectiveness of intervention on mite allergen levels
Mitchell New Zealand 1980[136]	Randomized crossover trial; *n* = 10; Age 6–14 years; 4 weeks ×2	2–	**A:** Electrostatic precipitator in child's BR **C:** Nil Standard mite avoidance measures in both groups (cleaning, laundering, and plastic cover over mattress top and sides)		Not monitored
Villaveces USA 1977[152]	DB Randomized crossover; *N* = 13 Age 7–15 years	2–	**A:** laminar airflow HEPA unit close to pillow **PI:** placebo filter	Extrinsic asthma, not on ICS, house-dust control measures taught	Not measured (particle counts)
Thiam Singapore 1999[130]	Open; *N* = 24; 6–14 years; 4 months	2–	**A**: M/P/D encasings (*n* = 6) **B**: HEPA filter in bedroom (*n* = 12) **PL**: nothing (*n* = 6) All removed carpets and soft toys from bedroom	No pet owners	Significantly reduced in A over 2 months then back to baseline
Geller-Bernstein Israel 1995[139]	RCT DBPT; *N* = 32; 4–12 years; Asthma and/or rhinitis; 6 months	1–	**A:** Thorough cleaning, bedrooms sprayed Acardust day 0 and 90. **PI:** Thorough cleaning, bedrooms sprayed with placebo day 0 + 90	No mention	Reduced allergen in active group *p* = 0.02
Bahir Israel 1997[140]	DBPC 3 arm study *N* = 46; 6–18 years; 6 months	1–	**A**: laundering, cleaning, and vacuuming advice **B**: mattress and floor acaricide application 3 monthly **PL**: application of placebo to mattress and floor 3 monthly		Acarex test NS
Reiser UK 1990[138]	DBPCT *n* = 46; 5–16 years; 24 weeks	1–	**A:** M sprayed at 2 weekly intervals for 3 months with Natamycin **PL:** M sprayed at 2 weekly intervals for 3 months with placebo		Small, NS trend to fall in Der p 1 in both groups
Sette Italy 1994[141]	DBPCT *N* = 32 (3 groups); Mean age 12.8 years; 10–20 days	3	**A**: M sprayed with benzyl benzoate foam (Acarosan) **PI**:: M sprayed with placebo foam **C**: no spraying All homes: removal of carpets; synthetic materials in bedroom; daily vacuuming and mopping; no feather pillows	No pets in households	Assessed by Acarex test. No difference between 3 groups
Manjra South Africa 1994[142]	RCT *N* = 60; Mean age 9.6 years (Age range 5–12 years); 3 months		**A:** Detergent to M and Carpets **B:** Detergent plus BB to M and Carpets **PI:** no treatment	No comment on asthma severity or power	Baseline M Der p 1 > 20 mcg/g; significant reduction in C for A and B but not in M.
Burr UK 1980[124]	Crossover RCT; *n* = 21; Age 5–14 years; 1 month each arm	1–	**A:** New sleeping bags, pillows and blankets; M encased (plastic); carpets vacuumed		Colonization occurred on new bedding after the second study period
Burr UK 1980[123]	RCT *N* = 53; Age 5–14 years; 8 weeks	1–	**A:** vacuuming, washing, airing of bedding and bedroom; P encased **P:** Dusting and vacuuming of living room	Children with exacerbations from other exposures were excluded	Mite counts, mite allergen: NS

Primary outcome	Effect size	Other outcomes Active vs placebo	Source of funding	Has study answered original question	Limitations
PEFR	NS	Use of bronchodilator NS	Dome Labs provided an electrostatic precipitator	Air cleaning −ve	Study too short
PEF	NS	Improvement in symptom scores $p < .05$	Not stated	Aire cleaning +ve 2^0	Enviraciare filter
Daily symptom score	Reduced within groups A and B	A: reduced PEF variability and higher FEV_1 $p < .05$	Honeywell (Singapore, Allergy Management Systems, National University of Singapore	Encasings and air cleaning +ve 2^0	No between-group comparison
Asthma symptom score	Reduced $p = .03$	PEFR NS Medication taken reduced $p = .01$	*Not stated*	Acaricide Cleaning +ve 1^0	Acardust (esbiol 0.9% and, piperonyl butoxide 7.2%)
FEV1	NS	Morning & evening PEFR NS; symptom scores NS	Trupharm provided acaricide sprays (A and P)	Acaricide or cleaning −ve	Acardust (esbiol 0.9% and, piperonyl butoxide 7.2%)
Symptoms PEFR BHR (histamine) Lung function	NR NS NS NS		*Brocades Ltd funded JR and supplies sprays*	Acaricide −ve	Natamycin had no effect.
BHR Nasal secretory IgE	− NS between 3 groups		*Not stated*	Acaricide −ve	Subjects returned from high-altitude low-allergen environment to home. Study too short
BHR	NS		*Snowchem Ltd*	Acaricide −ve	Acarosan
PEFR variability	NS	Actual PEF higher during treatment ($p < .01$)	*Not stated*	Partial Encasings + new bedding +ve 2^0	Study too short
PEFR	NS	Pediatricians assessment of progress: NS	*Not stated*	Partial Encasings + cleaning -ve	Improvements seen in both groups Study too short

(Continues)

TABLE 1 (Continued)

Author Country year	Study design; number; subjects characteristics; follow-up	Evidence level	Avoidance measures	Other allergens	Effectiveness of intervention on mite allergen levels
Murray Canada 1983[126]	Unblinded, 2-arm study, alternate allocation; *N* = 20; Age 6+; 6 weeks	2+	**A**: M/P Vinyl zippered encasings, laundering and cleaning 2 weekly. Remove carpets from bedroom **PI:** no change	Pets kept outside if pet-sensitized	Not measured
Gillies UK 1987[125]	Unblinded RCT *N* = 26; Age 6–16 years; 12 weeks	2−	**A**: 12/52 M/P encased (plastic covers); soft toys and pets excluded from bedroom, weekly damp dusting, vacuuming. **B:** 6/ 52 observation followed by 6/52 of above avoidance measures		Mite counts: reduced in both groups
Zwemer 1973[137]	DB Crossover *N* = 12 Age range 6–16 years; 4 weeks	2−	**A:** active laminar airflow system **PI:** placebo filter in device	'extrinsic asthma'	Mite allergen not measured
Sarsfield UK 1974[122]	Open study *N* = 14; Age 3–13 years; 6-week run in followed by unspecified avoidance period.	3	**A:** Vacuuming, laundering advice, P & D replace feather with synthetic filling, and plastic cover over mattress top and sides. Remove BC	No mention	Mite counts fell from mean 80 to mean 2 (no stats performed)

Abbreviations: A, active; B, 2nd active group where included; BC, bedroom carpet; C, carpet; C, 3rd active group; D, duvet; DBPC, double-blind placebo-controlled; EPO, eosinophil peroxidase; ICS, inhaled corticosteroids; M, mattress; *N*, number; NS, no significant difference; O, other; OCS, oral corticosteroid courses; P, pillow; Pl, placebo; RCT, randomized controlled trial; SB, single-blind.

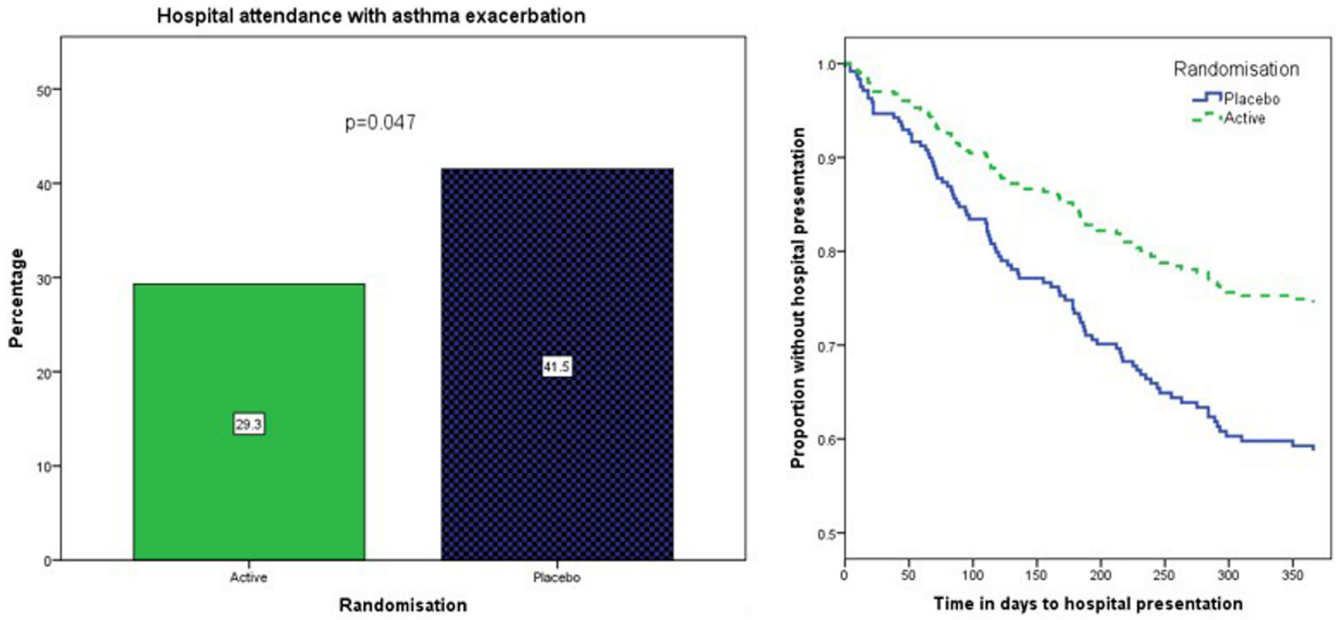

FIGURE 2 Proportion of children who suffered one or more severe exacerbation during the 12-month follow-up period in PAXAMA study (for all children who completed 12-month follow-up, *n* = 241; Results are shown for one or more hospitalizations or ED visits requiring systemic corticosteroids because of an asthma exacerbation), and time to first hospitalizations or ED visit because of severe exacerbation of asthma. Active covers (mite-impermeable) (green line) and Placebo covers (blue line). Adapted from reference,[144] with permission.

Primary outcome	Effect size	Other outcomes Active vs placebo	Source of funding	Has study answered original question	Limitations
BHR	A had increased PC20: $p = .007$	A had better PEFR $p = .035$; Symptoms $p = .003$ Medication $p = .03$	British Columbia Lung Foundation	Encasings Cleaning Carpet removal +ve 1^0	Study too short. Group allocation not stated
BHR	PC20: NS	Symptom scores NS PEFR NS: Total IgE reduced ($p < .005$)	*Not stated* Pharmacia did RASTs	Encasings Cleaning +ve 2^0	Study too short; mild Asthma-bronchodilators only
Symptom diary and medication usage	All reduced but no statistics performed	none	*Not stated*		Pure-zone system clean air headboard
Symptom score	All reduced but no statistics performed		*Not stated* Bencard Ltd provided allergen extracts		

inexpensive intervention costing a one-off investment of ~US$200 (and requiring no further adherence once the covers were *in situ*) halved emergency hospital attendance with asthma attacks. The effectiveness was greatest in younger children (<11 years) who were mono-sensitized to mite, living in nonsmoking households, and requiring more ICS.[144]

Studies of multifaceted environmental control in children with asthma are summarized in Table 2. The largest trial which tested the effectiveness of the comprehensive environmental intervention tailored to the patient's sensitization and exposure status, which included targeted allergen avoidance, but also parent/carer education and advice on the reduction of passive smoke exposure when appropriate, showed a significant reduction in asthma symptoms within 2 months of starting, which was sustained throughout the 2-year period.[145] The number of emergency room (ER) visits for uncontrolled asthma was also reduced.

Environmental control using temperature-controlled laminar airflow (TLA) device, which displaces aeroallergens from the breathing zone,[146] may improve quality of life and reduce airway inflammation in patients with atopic asthma (both adults and children).[147] A real-life observational study of the effects of night-time TLA device for 12 months in addition to the regular medication reported a reduction in asthma attacks, asthma-related ER visits, and hospitalisations.[148]

An open-label proof-of-concept study suggested that the addition of TLA device to pharmacological treatment may be an effective add-on to the management of severe atopic eczema in children.[149]

6.5 | Pragmatic approach to allergen avoidance in clinical practice

Based on the evidence to date, the pragmatic approach to mite and cockroach allergen avoidance in clinical practice is to use a multifaceted approach that requires more than simple advice on measures to reduce exposure (e.g., bed covers) but also includes patient education, regular removal of allergen by routine cleaning, frequent laundry, etc. Interventions should be tailored to the patient's sensitization and exposure status. However, as assessment of exposure is not feasible in most health care settings, a titer of allergen-specific IgE antibodies or the size of skin test wheal can be used as an indicator to help decide whether to recommend avoidance (the greater the specific IgE or skin test wheal, the more likely it is that sensitization is relevant to patient's asthma symptoms.[150])

TABLE 2 Multifaceted studies in children with asthma.

Author Country year	Study design; number; subjects characteristics; follow-up	Evidence level	Allergens targeted	Avoidance measures	Effect on mites/ allergen	Primary outcome	Effect size	Other outcomes Active vs placebo	Source of funding	Limitations
Morgan USA 2004[145]	Open RCT *n* = 937 (821 completed 2-year follow-up) Age 5–11 years sensitized to ≥1 of 11 indoor allergens, Asthma-DD 60% living in poverty 12 months intervention, further 12 months follow-up	1+	Mite, cockroach, cat, dog	**A**: education package. Encasings to mattress and pillow, HEPA vacuum cleaner and air filter, professional pest control. Interventions targeted to sensitizations and exposures **C**: no intervention	Der p 1 ($p < .01$) and Bla g 1 and Fel d 1 fell in active group	Maximal number of days with symptoms in 2 weeks, carried out 2 monthly	lower in each 2-week period throughout intervention and FU year in active vs control group ($p < .001$)	Unscheduled asthma visits $p = .04$, FEV1: NS, PEF: NS. Strong correlation between reduction in mite and cockroach exposure and asthma-related morbidity ($p < .001$)	NIH	Mould exposure and passive smoking targeted. Interviewer masked to study group. Poor households with smokers (50%) cockroaches (60%) and damp (45%). Intervention cost ~$1000 per annum
Carter USA 2001[153]	SB RCT *n* = 85 age 5–16 years Sensitization status not ascertained Asthma- (<50% on controller meds) 80% living in poverty 12 months	1−	Mite, cockroach	**A:** Encasings to mattress and pillow, cockroach bait and hot washing instructions. **PI:** Dummy covers and placebo cockroach baits, normal washing instructions **C**: No visits	No difference in decrease in allergen between active and placebo. Decrease in allergen levels only in 1/3 of homes.	Acute visits for asthma	NS for active vs. Placebo	Children sensitized and exposed to mite who had a reduction in mite exposure had a reduction in acute asthma visits ($p = .035$)	NIH	Sensitization revealed only at end of the study. Acute visits for asthma in active and control were reduced compared to no visit control ($p < .001$)
Williams USA 2006[154]	Unblended RCT *N* = 161 Age 5–12 years Sensitization not ascertained at start Asthma exacerbation 60% living in poverty 12 months	1−	Mite, cockroach	**A**: education; encasing M & P professional cleaning to remove allergens, cleaning and laundering advice, cockroach eradication, decrease ETS exposure, remove fungus, remove furry pets **C**: no intervention (provided at end of study)	Mite allergens stable in intervention group, increased in nonintervention group at 12 months, no difference for cockroach	Asthma severity score between groups	NS	Medication use and exacerbations not different between groups	Centres for disease control and prevention	Powered on PEF but PEF not reported. Only 60% were sensitized to mite, 40% to cockroach.

For pet-allergic pet owners who experience symptoms upon exposure, pet removal is the only appropriate advice,[93] but this can cause much distress and, anecdotally, is rarely complied with, emphasizing the need for better evidence in this area.

CONFLICT OF INTEREST STATEMENT

Dr. Custovic reports personal fees from Novartis, personal fees from Regeneron/Sanofi, personal fees from Thermo Fisher Scientific, personal fees from Boehringer Ingelheim, personal fees from Novartis, and personal fees from Philips, outside the submitted work. AS reports lecture fees from Thermo Fisher Scientific. Other authors have no competing interests to declare.

ORCID

Adnan Custovic https://orcid.org/0000-0001-5218-7071

REFERENCES

1. 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.
2. Zuiani C, Custovic A. Update on house dust mite allergen avoidance measures for asthma. *Curr Allergy Asthma Rep*. 2020;20(9):50.
3. Kuehr J, Frischer T, Meinert R, et al. Mite allergen exposure is a risk for the incidence of specific sensitization. *J Allergy Clin Immunol*. 1994;94(1):44-52.
4. Lau S, Illi S, Sommerfeld C, 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):1392-1397.
5. 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):502-507.
6. Wahn U, Lau S, Bergmann R, 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):763-769.
7. Scrivener S, Yemaneberhan H, Zebenigus M, et al. Independent effects of intestinal parasite infection and domestic allergen exposure on risk of wheeze in Ethiopia: a nested case-control study. *Lancet*. 2001;358(9292):1493-1499.
8. Thyssen JP, Ahluwalia TS, Paternoster L, et al. Interaction between filaggrin mutations and neonatal cat exposure in atopic dermatitis. *Allergy*. 2020;75(6):1481-1485.
9. 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):105-110.
10. Halken S. Early sensitisation and development of allergic airway disease – risk factors and predictors. *Paediatr Respir Rev*. 2003;4(2):128-134.
11. Lodrup Carlsen KC, Roll S, Carlsen KH, et al. Does pet ownership in infancy lead to asthma or allergy at school age? Pooled analysis of individual participant data from 11 European birth cohorts. *PLoS One*. 2012;7(8):e43214.
12. Collin SM, Granell R, Westgarth C, et al. Pet ownership is associated with increased risk of non-atopic asthma and reduced risk of atopy in childhood: findings from a UK birth cohort. *Clin Exp Allergy*. 2015;45(1):200-210.
13. Pinot de Moira A, Strandberg-Larsen K, Bishop T, et al. Associations of early-life pet ownership with asthma and allergic sensitization: a meta-analysis of more than 77,000 children from the EU Child Cohort Network. *J Allergy Clin Immunol*. 2022;150(1):82-92.
14. Almqvist C, Egmar AC, Hedlin G, et al. Direct and indirect exposure to pets – risk of sensitization and asthma at 4 years in a birth cohort. *Clin Exp Allergy*. 2003;33(9):1190-1197.
15. Lau S, Illi S, Sommerfeld C, 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):1392-1397.
16. Wahn U, Lau S, Bergmann R, et al. Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol*. 1997;99(6 Pt 1):763-769.
17. Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet*. 2001;357(9258):752-756.
18. Custovic A, Hallam CL, Simpson BM, Craven M, Simpson A, Woodcock A. Decreased prevalence of sensitization to cats with high exposure to cat allergen. *J Allergy Clin Immunol*. 2001;108(4):537-539.
19. Custovic A, Simpson BM, Simpson A, et al. Current mite, cat, and dog allergen exposure, pet ownership, and sensitization to inhalant allergens in adults. *J Allergy Clin Immunol*. 2003;111(2):402-407.
20. Woodfolk JA. High-dose allergen exposure leads to tolerance. *Clin Rev Allergy Immunol*. 2005;28(1):43-58.
21. Holt PG, Strickland D, Bosco A, et al. Distinguishing benign from pathologic TH2 immunity in atopic children. *J Allergy Clin Immunol*. 2016;137(2):379-387.
22. Shamji MH, Valenta R, Jardetzky T, et al. The role of allergen-specific IgE, IgG and IgA in allergic disease. *Allergy*. 2021;76(12):3627-3641.
23. Custovic A, Simpson BM, Simpson A, Kissen P, Woodcock A. 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):188-193.
24. Perzanowski MS, Ronmark E, Platts-Mills TA, Lundback B. Effect of cat and dog ownership on sensitization and development of asthma among preteenage children. *Am J Respir Crit Care Med*. 2002;166(5):696-702.
25. Erwin EA, Wickens K, Custis NJ, et al. Cat and dust mite sensitivity and tolerance in relation to wheezing among children raised with high exposure to both allergens. *J Allergy Clin Immunol*. 2005;115(1):74-79.
26. Wegienka G, Johnson CC, Havstad S, Ownby DR, Nicholas C, Zoratti EM. Lifetime dog and cat exposure and dog- and cat-specific sensitization at age 18 years. *Clin Exp Allergy*. 2011;41(7):979-986.
27. Hesselmar B, Aberg N, Aberg B, Eriksson B, Bjorksten B. Does early exposure to cat or dog protect against later allergy development? *Clin Exp Allergy*. 1999;29(5):611-617.
28. Lin S, Jones R, Munsie JP, Nayak SG, Fitzgerald EF, Hwang SA. Childhood asthma and indoor allergen exposure and sensitization in Buffalo, New York. *Int J Hyg Environ Health*. 2012;215(3):297-305.
29. Carlsten C, Dimich-Ward H, Becker AB, et al. Indoor allergen exposure, sensitization, and development of asthma in a high-risk birth cohort. *Pediatr Allergy Immunol*. 2010;21(4 Pt 2):e740-e746.
30. al Mousawi M, Behbehani N, Arifhodzic N, Lovel H, Woodcock A, Custovic A. Environmental allergens in Kuwait. *Allergy*. 2001;56(12):1237-1238.
31. Woodcock A, Addo-Yobo EO, Taggart SC, Craven M, Custovic A. Pet allergen levels in homes in Ghana and the United Kingdom. *J Allergy Clin Immunol*. 2001;108(3):463-465.
32. Addo-Yobo EO, Custovic A, Taggart SC, Craven M, Bonnie B, Woodcock A. Risk factors for asthma in urban Ghana. *J Allergy Clin Immunol*. 2001;108(3):363-368.
33. Al-Mousawi MS, Lovel H, Behbehani N, Arifhodzic N, Woodcock A, Custovic A. Asthma and sensitization in a community with low

indoor allergen levels and low pet-keeping frequency. *J Allergy Clin Immunol*. 2004;114(6):1389-1394.
34. Stevens W, Addo-Yobo E, Roper J, et al. Differences in both prevalence and titre of specific immunoglobulin E among children with asthma in affluent and poor communities within a large town in Ghana. *Clin Exp Allergy*. 2011;41(11):1587-1594.
35. Brunekreef B, Von Mutius E, Wong G, et al. Exposure to cats and dogs, and symptoms of asthma, rhinoconjunctivitis, and eczema. *Epidemiology*. 2012;23(5):742-750.
36. Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. *JAMA*. 2002;288(8):963-972.
37. Sitarik AR, Havstad S, Levin AM, et al. Dog introduction alters the home dust microbiota. *Indoor Air*. 2018;28(4):539-547.
38. von Mutius E. The "hygiene hypothesis" and the lessons learnt from farm studies. *Front Immunol*. 2021;12:635522.
39. Dunn RR, Fierer N, Henley JB, Leff JW, Menninger HL. Home life: factors structuring the bacterial diversity found within and between homes. *PLoS One*. 2013;8(5):e64133.
40. Fujimura KE, Johnson CC, Ownby DR, et al. Man's best friend? The effect of pet ownership on house dust microbial communities. *J Allergy Clin Immunol*. 2010;126(2):410-412. 412.e1-3.
41. Tun HM, Konya T, Takaro TK, et al. Exposure to household furry pets influences the gut microbiota of infant at 3-4 months following various birth scenarios. *Microbiome*. 2017;5(1):40.
42. Song SJ, Lauber C, Costello EK, et al. Cohabiting family members share microbiota with one another and with their dogs. *Elife*. 2013;2:e00458.
43. Du G, Huang H, Zhu Q, Ying L. Effects of cat ownership on the gut microbiota of owners. *PLoS One*. 2021;16(6):e0253133.
44. Older CE, Diesel AB, Lawhon SD, Queiroz CRR, Henker LC, Rodrigues Hoffmann A. The feline cutaneous and oral microbiota are influenced by breed and environment. *PLoS One*. 2019;14(7):e0220463.
45. Sandøe P, Nørspang AP, Forkman B, Bjørnvad CR, Kondrup SV, Lund TB. The burden of domestication: a representative study of welfare in privately owned cats in Denmark. *Animal Welfare*. 2017;26(1):1-10.
46. Foreman-Worsley R, Finka LR, Ward SJ, Farnworth MJ. Indoors or outdoors? An international exploration of owner demographics and decision making associated with lifestyle of pet cats. *Animals (Basel)*. 2021;11(2):253.
47. 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):820-822.e7.
48. Lazic N, Roberts G, Custovic A, et al. Multiple atopy phenotypes and their associations with asthma: similar findings from two birth cohorts. *Allergy*. 2013;68(6):764-770.
49. Schoos AM, Jelding-Dannemand E, Stokholm J, Bonnelykke K, Bisgaard H, Chawes BL. Single and multiple time-point allergic sensitization during childhood and risk of asthma by age 13. *Pediatr Allergy Immunol*. 2019;30(7):716-723.
50. Simpson A, Tan VY, Winn J, 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):1200-1206.
51. Smillie FI, Elderfield AJ, Patel F, et al. Lymphoproliferative responses in cord blood and at one year: no evidence for the effect of in utero exposure to dust mite allergens. *Clin Exp Allergy*. 2001;31(8):1194-1204.
52. Jones AC, Miles EA, Warner JO, Colwell BM, Bryant TN, Warner JA. Fetal peripheral blood mononuclear cell proliferative responses to mitogenic and allergenic stimuli during gestation. *Pediatr Allergy Immunol*. 1996;7(3):109-116.
53. Flicker S, Marth K, Kofler H, Valenta R. Placental transfer of allergen-specific IgG but not IgE from a specific immunotherapy-treated mother. *J Allergy Clin Immunol*. 2009;124(6):1358-1360.e1.
54. Jenmalm MC, Bjorksten B. Cord blood levels of immunoglobulin G subclass antibodies to food and inhalant allergens in relation to maternal atopy and the development of atopic disease during the first 8 years of life. *Clin Exp Allergy*. 2000;30(1):34-40.
55. Lupinek C, Hochwallner H, Johansson C, et al. Maternal allergen-specific IgG might protect the child against allergic sensitization. *J Allergy Clin Immunol*. 2019;144(2):536-548.
56. Oykhman P, Kim HL, Ellis AK. Allergen immunotherapy in pregnancy. *Allergy Asthma Clin Immunol*. 2015;11:31.
57. Bonnelykke K, Ober C. Leveraging gene-environment interactions and endotypes for asthma gene discovery. *J Allergy Clin Immunol*. 2016;137(3):667-679.
58. Custovic A, Marinho S, Simpson A. Gene-environment interactions in the development of asthma and atopy. *Expert Rev Respir Med*. 2012;6(3):301-308.
59. Liu X, Beaty TH, Deindl P, 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):489-495.
60. Henderson J, Northstone K, Lee SP, et al. The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study. *J Allergy Clin Immunol*. 2008;121(4):872-877.
61. Bisgaard H, Simpson A, Palmer CN, et al. Gene-environment interaction in the onset of eczema in infancy: filaggrin loss-of-function mutations enhanced by neonatal cat exposure. *PLoS Med*. 2008;5(6):e131.
62. Brough HA, Simpson A, Makinson K, et al. Peanut allergy: effect of environmental peanut exposure in children with filaggrin loss-of-function mutations. *J Allergy Clin Immunol*. 2014;134(4):867-875.e1.
63. 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*. 2020;145(3):993-1001.
64. Blekic M, Kljaic Bukvic B, Aberle N, et al. 17q12-21 and asthma: interactions with early-life environmental exposures. *Ann Allergy Asthma Immunol*. 2013;110(5):347-353.e2.
65. Brauner EV, Loft S, Raaschou-Nielsen O, Vogel U, Andersen PS, Sorensen M. Effects of a 17q21 chromosome gene variant, tobacco smoke and furred pets on infant wheeze. *Genes Immun*. 2012;13(1):94-97.
66. Stokholm J, Chawes BL, Vissing N, Bonnelykke K, Bisgaard H. Cat exposure in early life decreases asthma risk from the 17q21 high-risk variant. *J Allergy Clin Immunol*. 2018;141(5):1598-1606.
67. Loss GJ, Depner M, Hose AJ, et al. The early development of wheeze. Environmental determinants and genetic susceptibility at 17q21. *Am J Respir Crit Care Med*. 2016;193(8):889-897.
68. Tutino M, Granell R, Curtin JA, et al. Dog ownership in infancy is protective for persistent wheeze in 17q21 asthma-risk carriers. *J Allergy Clin Immunol*. 2022;S0091-6749(22):01413-0. doi:10.1016/j.jaci.2022.10.012. Online ahead of print.
69. Oksel C, Granell R, Haider S, et al. Distinguishing wheezing phenotypes from infancy to adolescence. A pooled analysis of five birth cohorts. *Ann Am Thorac Soc*. 2019;16(7):868-876.
70. Simpson A, John SL, Jury F, et al. Endotoxin exposure, CD14, and allergic disease: an interaction between genes and the environment. *Am J Respir Crit Care Med*. 2006;174(4):386-392.
71. Lynch SV, Wood RA, Boushey H, 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.
72. Kerkhof M, Daley D, Postma DS, et al. Opposite effects of allergy prevention depending on CD14 rs2569190 genotype in 3 intervention studies. *J Allergy Clin Immunol*. 2012;129(1):256-259.

73. Illi S, von Mutius E, Lau S, et al. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. *Lancet*. 2006;368(9537):763-770.
74. Simpson A, Custovic A. Prevention of allergic sensitization by environmental control. *Curr Allergy Asthma Rep*. 2009;9(5):363-369.
75. Scott M, Roberts G, Kurukulaaratchy RJ, Matthews S, Nove A, Arshad SH. Multifaceted allergen avoidance during infancy reduces asthma during childhood with the effect persisting until age 18 years. *Thorax*. 2012;67(12):1046-1051.
76. Custovic A, Simpson BM, Simpson A, Kissen P, Woodcock A, NAC Manchester Asthma and Allergy Study Group. 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):188-193.
77. Woodcock A, Lowe LA, Murray CS, et al. Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years. *Am J Respir Crit Care Med*. 2004;170(4):433-439.
78. Custovic A, Simpson BM, Simpson A, 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):252-258.
79. Toelle BG, Garden FL, Ng KK, et al. Outcomes of the childhood asthma prevention study at 11.5 years. *J Allergy Clin Immunol*. 2013;132(5):1220-1222.e3.
80. 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.
81. Roberts G, Fontanella S, Selby A, et al. Connectivity patterns between multiple allergen specific IgE antibodies and their association with severe asthma. *J Allergy Clin Immunol*. 2020;146(4):821-830.
82. Simpson A, Custovic A, Pipis S, Adisesh A, Faragher B, Woodcock A. Exhaled nitric oxide, sensitization, and exposure to allergens in patients with asthma who are not taking inhaled steroids. *Am J Respir Crit Care Med*. 1999;160(1):45-49.
83. Gore RB, Curbishley L, Truman N, et al. Intranasal air sampling in homes: relationships among reservoir allergen concentrations and asthma severity. *J Allergy Clin Immunol*. 2006;117(3):649-655.
84. 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):362-368.
85. Lowe LA, Woodcock A, Murray CS, Morris J, Simpson A, Custovic A. Lung function at age 3 years: effect of pet ownership and exposure to indoor allergens. *Arch Pediatr Adolesc Med*. 2004;158(10):996-1001.
86. Murray CS, Poletti G, Kebadze T, 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):376-382.
87. 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.
88. Gergen PJ, Mitchell HE, Calatroni A, et al. Sensitization and exposure to pets: the effect on asthma morbidity in the US population. *J Allergy Clin Immunol Pract*. 2018;6(1):101-107.e2.
89. Wu J, Bahri R, Tsoumani M, et al. Progenitor cell-derived basophils: a novel barcoded passive degranulation assay in allergic diseases. *Clin Exp Allergy*. 2022. doi:10.1111/cea.14251. Online ahead of print.
90. Boner AL, Niero E, Antolini I, Valletta EA, Gaburro D. Pulmonary function and bronchial hyperreactivity in asthmatic children with house dust mite allergy during prolonged stay in the Italian Alps (Misurina, 1756 m). *Ann Allergy*. 1985;54(1):42-45.
91. Peroni DG, Boner AL, Vallone G, Antolini I, Warner JO. Effective allergen avoidance at high altitude reduces allergen-induced bronchial hyperresponsiveness. *Am J Respir Crit Care Med*. 1994;149(6):1442-1446.
92. Valletta EA, Comis A, Del Col G, Spezia E, Boner AL. Peak expiratory flow variation and bronchial hyperresponsiveness in asthmatic children during periods of antigen avoidance and reexposure. *Allergy*. 1995;50(4):366-369.
93. Custovic A, Murray CS, Gore RB, Woodcock A. Controlling indoor allergens. *Ann Allergy Asthma Immunol*. 2002;88(5):432-441. quiz 42-43, 529.
94. Custovic A, Simpson A. The role of inhalant allergens in allergic airways disease. *J Investig Allergol Clin Immunol*. 2012;22(6):393-401. qiuz follow.
95. Tovey E, Ferro A. Time for new methods for avoidance of house dust mite and other allergens. *Curr Allergy Asthma Rep*. 2012;12(5):465-477.
96. Shirai T, Matsui T, Suzuki K, Chida K. Effect of pet removal on pet allergic asthma. *Chest*. 2005;127(5):1565-1571.
97. Wood RA, Chapman MD, Adkinson NF Jr, Eggleston PA. The effect of cat removal on allergen content in household-dust samples. *J Allergy Clin Immunol*. 1989;83(4):730-734.
98. Heinrich J, Bedada GB, Zock JP, et al. Cat allergen level: its determinants and relationship to specific IgE to cat across European centers. *J Allergy Clin Immunol*. 2006;118(3):674-681.
99. Custovic A, Green R, Fletcher A, et al. Aerodynamic properties of the major dog allergen Can f 1: distribution in homes, concentration, and particle size of allergen in the air. *Am J Respir Crit Care Med*. 1997;155(1):94-98.
100. 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):612-616.
101. Custovic A, Fletcher A, Pickering CA, et al. Domestic allergens in public places III: house dust mite, cat, dog and cockroach allergens in British hospitals. *Clin Exp Allergy*. 1998;28(1):53-59.
102. Custovic A, Green R, Taggart SC, et al. Domestic allergens in public places. II: dog (Can f1) and cockroach (Bla g 2) allergens in dust and mite, cat, dog and cockroach allergens in the air in public buildings. *Clin Exp Allergy*. 1996;26(11):1246-1252.
103. Custovic A, Taggart SC, Woodcock A. House dust mite and cat allergen in different indoor environments. *Clin Exp Allergy*. 1994;24(12):1164-1168.
104. Zahradnik E, Raulf M. Respiratory allergens from furred mammals: environmental and occupational exposure. *Vet Sci*. 2017;4(3):38.
105. Almqvist C, Wickman M, Perfetti L, et al. Worsening of asthma in children allergic to cats, after indirect exposure to cat at school. *Am J Respir Crit Care Med*. 2001;163(3 Pt 1):694-698.
106. Gore RB, Bishop S, Durrell B, Curbishley L, Woodcock A, Custovic A. Air filtration units in homes with cats: can they reduce personal exposure to cat allergen? *Clin Exp Allergy*. 2003;33(6):765-769.
107. Avner DB, Perzanowski MS, Platts-Mills TA, Woodfolk JA. Evaluation of different techniques for washing cats: quantitation of allergen removed from the cat and the effect on airborne Fel d 1. *J Allergy Clin Immunol*. 1997;100(3):307-312.
108. Hodson T, Custovic A, Simpson A, Chapman M, Woodcock A, Green R. Washing the dog reduces dog allergen levels, but the dog needs to be washed twice a week. *J Allergy Clin Immunol*. 1999;103(4):581-585.
109. Gore RB, Durrell B, Bishop S, Curbishley L, Woodcock A, Custovic A. High-efficiency particulate arrest-filter vacuum cleaners increase personal cat allergen exposure in homes with cats. *J Allergy Clin Immunol*. 2003;111(4):784-787.
110. Popplewell EJ, Innes VA, Lloyd-Hughes S, et al. The effect of high-efficiency and standard vacuum-cleaners on mite, cat and

dog allergen levels and clinical progress. *Pediatr Allergy Immunol*. 2000;11(3):142-148.
111. Nicholas C, Wegienka G, Havstad S, Zoratti E, Ownby D, Johnson CC. Dog characteristics and allergen levels in the home. *Ann Allergy Asthma Immunol*. 2010;105(3):228-233.
112. 2020 Focused updates to the Asthma Management Guidelines. 2020. https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma. Accessed December 13, 2022.
113. Global strategy for asthma management and prevention. 2022. https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf. Accessed December 13, 2022.
114. Asthma: diagnosis, monitoring and chronic asthma management. 2017. https://www.nice.org.uk/guidance/ng80/chapter/recommendations. Accessed December 13, 2022.
115. Gotzsche PC, Johansen HK, Burr ML, Hammarquist C. House dust mite control measures for asthma. *Nurs Times*. 2001;97(33):37.
116. Gotzsche PC, Johansen HK, Schmidt LM, Burr ML. House dust mite control measures for asthma. *Cochrane Database Syst Rev*. 2004;4:CD001187.
117. Gotzsche PC, Johansen HK. House dust mite control measures for asthma: systematic review. *Allergy*. 2008;63(6):646-659.
118. Kilburn S, Lasserson TJ, McKean M. Pet allergen control measures for allergic asthma in children and adults. *Cochrane Database Syst Rev*. 2003;1:CD002989.
119. Leas BF, D'Anci KE, Apter AJ, et al. Effectiveness of indoor allergen reduction in asthma management: a systematic review. *J Allergy Clin Immunol*. 2018;141(5):1854-1869.
120. Platts-Mills TAE. Allergen avoidance in the treatment of asthma: problems with the meta-analyses. *J Allergy Clin Immunol*. 2008;122(4):694-696.
121. Custovic A, Murray CS, Simpson A. Dust-mite inducing asthma: what advice can be given to patients? *Expert Rev Respir Med*. 2019;13(10):929-936.
122. Sarsfield JK, Gowland G, Toy R, Norman AL. Mite-sensitive asthma of childhood. Trial of avoidance measures. *Arch Dis Child*. 1974;49(9):716-721.
123. Burr ML, Neale E, Dean BV, Verrier-Jones ER. Effect of a change to mite-free bedding on children with mite-sensitive asthma: a controlled trial. *Thorax*. 1980;35(7):513-514.
124. Burr ML, Dean BV, Merrett TG, Neale E, St Leger AS, Verrier-Jones ER. Effects of anti-mite measures on children with mite-sensitive asthma: a controlled trial. *Thorax*. 1980;35(7):506-512.
125. Gillies DR, Littlewood JM, Sarsfield JK. Controlled trial of house dust mite avoidance in children with mild to moderate asthma. *Clin Allergy*. 1987;17(2):105-111.
126. Murray AB, Ferguson AC. Dust-free bedrooms in the treatment of asthmatic children with house dust or house dust mite allergy: a controlled trial. *Pediatrics*. 1983;71(3):418-422.
127. Ehnert B, Lau-Schadendorf S, Weber A, Buettner P, Schou C, Wahn U. Reducing domestic exposure to dust mite allergen reduces bronchial hyperreactivity in sensitive children with asthma. *J Allergy Clin Immunol*. 1992;90(1):135-138.
128. Carswell F, Birmingham K, Oliver J, Crewes A, Weeks J. The respiratory effects of reduction of mite allergen in the bedrooms of asthmatic children - a double-blind controlled trial. *Clin Exp Allergy*. 1996;26(4):386-396.
129. Shapiro GG, Wighton TG, Chinn T, et al. House dust mite avoidance for children with asthma in homes of low-income families. *J Allergy Clin Immunol*. 1999;103(6):1069-1074.
130. Thiam DG, Tim CF, Hoon LS, Lei Z, Bee-Wah L. An evaluation of mattress encasings and high efficiency particulate filters on asthma control in the tropics. *Asian Pac J Allergy Immunol*. 1999;17(3):169-174.
131. Glasgow NJ, Ponsonby AL, Kemp A, et al. Feather bedding and childhood asthma associated with house dust mite sensitisation: a randomised controlled trial. *Arch Dis Child*. 2011;96(6):541-547.
132. Sheikh A, Hurwitz B, Sibbald B, Barnes G, Howe M, Durham S. House dust mite barrier bedding for childhood asthma: randomised p trial in primary care [ISRCTN63308372]. *BMC Fam Pract*. 2002;3:12.
133. Frederick JM, Warner JO, Jessop WJ, Enander I, Warner JA. Effect of a bed covering system in children with asthma and house dust mite hypersensitivity. *Eur Respir J*. 1997;10(2):361-366.
134. Halken S, Host A, Niklassen U, et al. Effect of mattress and pillow encasings on children with asthma and house dust mite allergy. *J Allergy Clin Immunol*. 2003;111(1):169-176.
135. Warner JA, Marchant JL, Warner JO. Double blind trial of ionisers in children with asthma sensitive to the house dust mite. *Thorax*. 1993;48(4):330-333.
136. Mitchell EA, Elliott RB. Controlled trial of an electrostatic precipitator in childhood asthma. *Lancet*. 1980;2(8194):559-561.
137. Zwemer RJ, Karibo J. Use of laminar control device as adjunct to standard environmental control measures in symptomatic asthmatic children. *Ann Allergy*. 1973;31(6):284-290.
138. Reiser J, Ingram D, Mitchell EB, Warner JO. House dust mite allergen levels and an anti-mite mattress spray (natamycin) in the treatment of childhood asthma. *Clin Exp Allergy*. 1990;20(5):561-567.
139. Geller-Bernstein C, Pibourdin JM, Dornelas A, Fondarai J. Efficacy of the acaricide: acardust for the prevention of asthma and rhinitis due to dust mite allergy, in children. *Allerg Immunol*. 1995;27(5):147-154.
140. Bahir A, Goldberg A, Mekori YA, et al. Continuous avoidance measures with or without acaricide in dust mite-allergic asthmatic children. *Ann Allergy Asthma Immunol*. 1997;78(5):506-512.
141. Sette L, Comis A, Marcucci F, Sensi L, Piacentini GL, Boner AL. Benzyl-benzoate foam: effects on mite allergens in mattress, serum and nasal secretory IgE to Dermatophagoides pteronyssinus, and bronchial hyperreactivity in children with allergic asthma. *Pediatr Pulmonol*. 1994;18(4):218-227.
142. Manjra A, Berman D, Toerien A, Weinberg EG, Potter PC. The effects of a single treatment of an acaricide, Acarosan, and a detergent, Metsan, on Der p 1 allergen levels in the carpets and mattresses of asthmatic children. *S Afr Med J*. 1994;84(5):278-280.
143. Woodcock A, Forster L, Matthews E, et al. Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. *N Engl J Med*. 2003;349(3):225-236.
144. 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):150-158.
145. Morgan WJ, Crain EF, Gruchalla RS, et al. Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med*. 2004;351(11):1068-1080.
146. Gore RB, Boyle RJ, Gore C, et al. Effect of a novel temperature-controlled laminar airflow device on personal breathing zone aeroallergen exposure. *Indoor Air*. 2015;25(1):36-44.
147. Boyle RJ, Pedroletti C, Wickman M, et al. Nocturnal temperature controlled laminar airflow for treating atopic asthma: a randomised controlled trial. *Thorax*. 2012;67(3):215-221.
148. Schauer U, Bergmann KC, Gerstlauer M, 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. doi:10.3402/ecrj.v2.28531
149. 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.

150. Mohammad HR, Belgrave D, Kopec Harding K, Murray CS, Simpson A, Custovic A. Age, sex and the association between skin test responses and IgE titres with asthma. *Pediatr Allergy Immunol*. 2016;27(3):313-319.
151. El-Ghitany EM, Abd El-Salam MM. Environmental intervention for house dust mite control in childhood bronchial asthma. *Environ Health Prev Med*. 2012;17(5):377-384.
152. Villaveces JW, Rosengren H, Evans J. Use of laminar air flow portable filter in asthmatic children. *Ann Allergy*. 1977;38(6):400-404.
153. Carter MC, Perzanowski MS, Raymond A, Platts-Mills TA. Home intervention in the treatment of asthma among inner-city children. *J Allergy Clin Immunol*. 2001;108(5):732-737.
154. Williams SG, Brown CM, Falter KH, et al. Does a multifaceted environmental intervention alter the impact of asthma on inner-city children? *J Natl Med Assoc*. 2006;98(2):249-260.

How to cite this article: Custovic A, de Moira AP, Murray CS, Simpson A. Environmental influences on childhood asthma: Allergens. *Pediatr Allergy Immunol*. 2023;34:e13915. doi:10.1111/pai.13915