



# Environmental control for asthma: recent evidence

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## Purpose of review

To review and interpret recent literature related to the role of environmental control in prevention and treatment of asthma.

## Recent findings

Environmental control has a clearly established role in the management of asthma, but its role as a primary prevention tool is not supported by recent clinical trials. Although some of the interventions tested in these trials reduced the risk of asthma, the interventions often included dietary modification and those trials intervening only on environmental exposures were largely negative. Environmental interventions that target multiple asthma triggers, such as a laminar airflow device and relocation to high altitude, continue to demonstrate efficacy in asthma. Several studies highlight the efficacy of portable HEPA purifiers in reduction of indoor particulate matter and improving asthma outcomes. Several recently published practice parameters provide evidence-based recommendations for environmental control practices targeting furry pet, rodent, and cockroach allergens. Emerging work highlights the potential impact of spatial-temporal aspects of exposure and the shape of the dose–response relationships on the indoor allergen exposure–asthma relationship.

## Summary

Environmental interventions likely have no effect on the risk of developing atopic disease, but multifaceted interventions are generally of benefit in the management of asthma, particularly in children.

## Keywords

allergy, asthma, environmental control, indoor allergens, indoor pollutants

## INTRODUCTION

Indoor allergen exposure has been recognized as a cause of morbidity among sensitized asthmatics for several decades, yet progress on identifying affordable, highly feasible, and clinically efficacious environmental control methods and effectively implementing them as an integral component of routine asthma management has been frustratingly slow. In addition, although the renewed enthusiasm for the potential role of environmental control methods in the primary prevention of asthma in the last decade led to the conduct of several primary prevention trials, the results of these trials have been mixed, and have cast a shadow on the potential of allergen environmental control methods as a primary prevention tool. Nevertheless, the insight gained from these primary prevention trials into the role of environmental exposures in allergic pathogenesis has been significant, and emerging data and concepts suggest that there is promise for identifying more effective allergen environmental control and implementation approaches that can be integrated into standard asthma management for allergic patients.

## HISTORICAL CONTEXT AND BACKGROUND

In 1982, a study confirmed the long-held belief that relocation to a different, low allergen environment improves asthma. In this study [1], nine asthmatic patients allergic to dust mites lived in hospital rooms for at least 2 months and experienced marked improvements in their symptoms, peak flow, and bronchial hyper-responsiveness. Although this study lacked a control group and provided no direct evidence that it was the reduction in house dust mite exposure that resulted in the improvements in asthma, the results were striking and consistent with reports that asthma patients relocating to high altitude regions of the Alps, where there are few dust mites, experienced marked improvement [2]. Several years later, dust mite exposure

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## KEY POINTS

- Environmental control interventions for primary prevention of asthma have not reduced risk of allergic sensitization and have only been associated with a reduction of the risk of asthma when combined with dietary interventions.
- Studies of interventions aimed at reducing multiple environmental asthma triggers continue to demonstrate beneficial effects on asthma.
- Nonallergen exposures, such as pollutants, contribute to asthma morbidity and targeting indoor particulate matter with portable air purifiers both reduces PM concentrations and improves asthma.
- Innate immune stimulants, which coexist in indoor environments with allergens, may modify the effect that allergen exposure has on incident allergic sensitization and asthma.
- A deeper understanding of the many facets of allergen exposure, such as temporal and spatial distribution and dose–response relationships, will provide important insights into optimizing current approaches to allergen exposure reduction.

was implicated as a risk factor for development of mite sensitization and asthma in a prospective cohort study [3] in the United Kingdom, suggesting that perhaps dust mite avoidance could be effective in preventing the development of allergic sensitization and asthma. As these earlier observations, there have been many studies [4–9] evaluating the efficacy of various approaches to reduce home dust mite allergen exposure, as well as a large body of evidence linking exposure to other indoor allergens, including pets, pests, and molds, to asthma morbidity in sensitized patients. As a result, the most recent NAEPP EPR asthma guidelines in 2007 endorse evaluating asthmatics, particularly persistent asthmatics, for allergic sensitizations and implementing individually tailored, multifaceted environmental control practices as a part of asthma management [10].

In the past few years, new findings in some key conceptual areas have further refined our view of the role of environmental control in treatment and prevention of asthma. For example, several studies have helped provide insight into the effects of various characteristics of allergen exposure such as timing, location, variability of exposure. Dose–response studies have also lead to re-evaluation of the longstanding assumption that any reduction in allergen exposure would be expected to result in an improvement in allergic disease outcomes. In addition, several intervention studies have

provided insight into the efficacy of specific environmental control practices in reducing indoor exposures and improving asthma outcomes. Lastly, a growing body of work suggests that other environmental exposures that co-exist with allergens may confound, or even modify, the effects of allergen exposure on allergic sensitization and asthma.

## KNOWLEDGE NEEDED FOR SUCCESSFUL APPLICATION OF ENVIRONMENTAL CONTROL

In order to understand if, and how, environmental control could be applied to achieve the objectives of prevention and treatment of asthma, a few fundamental questions must be answered for each allergen in question. First, a causal relationship must be established between exposure and outcome; second, we must understand temporal and spatial aspects of exposure and the shape of the exposure–response relationship; and third, environmental control practices that result in a meaningful reduction in allergen exposure must be identified. Even when the answers to these questions are known, it is becoming clear that understanding which patients are most likely to benefit and what the effect of the intervention is on co-exposures will also be important for refining environmental control approaches for the treatment and prevention of asthma.

## ENVIRONMENTAL CONTROL AND PRIMARY PREVENTION OF ALLERGIC DISEASES

Several randomized, controlled trials of primary prevention of asthma were begun more than a decade ago so that we now have outcome data in older children in whom allergic sensitization and asthma should be established [11,12,13<sup>■</sup>,14,15<sup>■</sup>,16,17] (Table 1). All of these trials enrolled high-risk children prenatally or at birth and interventions focused on modifying allergen exposure in the first year(s) of life. A total of seven such trials have been completed with results reported for children ranging in age from 2 to 18 years. Of the seven trials, only three conducted isolated inhalant allergen reduction interventions [12,14,15<sup>■</sup>], which often emphasized dust mite exposure reduction, while the remaining four incorporated food allergen avoidance as well [11,13<sup>■</sup>,16,17], making it difficult to draw conclusions about the independent effect of inhalant allergen avoidance on incident asthma. Nevertheless, of the three trials focused on inhalant allergen exposure reduction, none reduced the risk of asthma-associated outcomes. One study [14]

**Table 1. Randomized, controlled primary prevention trials**

| Study population               | CAPPS                                                                                                                                                                       | CAPS                                                                                         | Isle of Wight                                                      | MAAS                                                                                                                                                          | PIAMA                                                                                                                        | PREVASC                                                                                                  | SPACE                                                                       |
|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|--------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
|                                | Canada                                                                                                                                                                      | Australia                                                                                    | UK                                                                 | UK                                                                                                                                                            | Europe                                                                                                                       | Europe                                                                                                   | Europe                                                                      |
|                                | High risk                                                                                                                                                                   | High risk                                                                                    | High risk                                                          | High Risk                                                                                                                                                     | High risk                                                                                                                    | High risk                                                                                                | High risk                                                                   |
|                                | N = 545                                                                                                                                                                     | N = 616                                                                                      | N = 120                                                            | N = 291                                                                                                                                                       | N = 1282                                                                                                                     | N = 476                                                                                                  | N = 696                                                                     |
| Intervention                   | RCT, Allergens and smoke exposure interventions and dietary avoidance                                                                                                       | RCT, Factorial design of omega-3 fatty acid supplementation and dust mite avoidance          | RCT, Dietary avoidance, dust mite exposure reduction               | RCT, stringent environmental control measures focused on dust mite                                                                                            | RCT, mattress/pillow encasements                                                                                             | RCT of reduction of exposure to inhalant and food allergens                                              | RCT of encasements and education about inhalant and food allergen avoidance |
| Last age of outcome assessment | 7 years                                                                                                                                                                     | 8 years                                                                                      | 18 years                                                           | 3 year                                                                                                                                                        | 8 years                                                                                                                      | 6 years                                                                                                  | 2 years                                                                     |
| Exposure outcomes              | Modest reduction in dust mite, transient, small reduction in cat allergen, delayed introduction of solids, longer duration of breast feeding, no effect on SHS <sup>a</sup> | At age 5, reduction in HDM. At age 8, no difference in HDM between active and control groups | Marked reduction in dust mite allergen levels                      | Marked reduction in mite allergen                                                                                                                             | Reduction in Der f 1, but not Der p 1, allergen levels among participants still using covers at age 8 (53–58% of population) | Reduced levels of inhalant allergens (mite, cat, and dog), delayed introduction of cow's milk and solids | Not measured                                                                |
| Clinical outcomes              | Asthma RR (95% CI): 0.44 (0.25–0.79), no effect on AR, AD, atopy, BHR                                                                                                       | No effect on asthma or other allergic outcomes overall                                       | Asthma RR: 0.23, 95% CI 0.08 to 0.70, P = 0.01, no effect on atopy | Increased risk of sensitization in intervention group. RR (95% CI): 1.61 (1.02–2.55); improvement in some lung function measures in active intervention group | Temporary reduction in asthma at age 2, no reduction in asthma or other outcomes                                             | No effect on asthma                                                                                      | No effect on wheeze, dust mite sensitization, or other atopic diseases      |

AD, atopic dermatitis; AR, allergic rhinitis; CAPPS, Canadian Childhood Asthma Primary Prevention Study [11]; CAPS, Childhood Asthma Prevention Study [12]; MAAS, Manchester Asthma and Allergy Study [13]; PIAMA, Prevention and Incidence of Asthma and Mite Allergy [15]; PREVASC, Prevention of Asthma in Susceptible Children [16]; SPACE, Study of Prevention of Allergy in Children in Europe [17].  
<sup>a</sup>second hand smoke.

reported improvement in some lung function measures in the active intervention group; however, these were not accompanied by a lower risk of asthma. Moreover, the active intervention group had an increased risk of allergic sensitization generally as well as an increased risk of dust mite sensitization specifically. Of the remaining four trials, two reduced the risk of asthma at school age, but did not reduce the risk of other allergic outcomes, including allergic sensitization [11,13<sup>¶</sup>].

Although the results across all seven trials are mixed, a recent meta-analysis estimated that the multifaceted interventions, which all included dietary avoidance, reduced the risk of current asthma by approximately 30–50% [children <5 years, OR (95% CI): 0.72 (0.54–0.96), and >5 years: 0.52 (0.32–0.85)] [18]. Despite this almost 50% reduction in risk of school-age asthma, multifaceted primary prevention interventions have not been embraced by professional organizations. Although the reasons for this are likely complex, these interventions in many cases are quite cumbersome, appear to vary in efficacy between populations, and do not reduce the risk of other atopic diseases or allergic sensitization itself. The lack of effect on other atopic outcomes, including allergic sensitization, suggests that the interventions, as hoped, do not redirect the developing immune system away from an allergic phenotype. Instead, the interventions appear to reduce the risk of the clinical manifestations of allergic sensitization by lowering allergen levels. Why these prevention trials uniformly had no effect on the allergic march is poorly understood, but a plausible hypothesis is that, in addition to reducing inhalant allergen exposure, the interventions also reduced exposure to innate immune stimulants, such as microbial products, that are thought to afford some protection against the development of an allergic immune phenotype [19–21,22<sup>¶</sup>]. It is also possible that high dose exposure to some allergens, particularly furred animal allergens, confers some protection against the development of allergic sensitization to the allergen [19,23,24], so that much greater reductions of these allergens are needed before a protective effect would be observed. Whether the protective effect of animal exposure is allergen-specific [24] or due to concomitant exposure to beneficial microbes that are associated with animals [25] is an area of active investigation. Lastly, allergens are found in many locations outside of the home, including daycares and schools [26–29], so that children may still be exposed to sufficient levels of allergens to induce allergic sensitization outside of the home.

## ENVIRONMENTAL CONTROL AND TREATMENT OF ALLERGIC DISEASES

Although many questions remain about the role of environmental control in the management of asthma, overall the evidence supports a role for individually tailored, multifaceted interventions in the management of asthma, particularly in children. A multifaceted approach, rather than targeting a single exposure, makes intuitive sense and reflects clinical practice, but much of the foundational research has focused on single allergens, so each allergen will be discussed individually below before concluding with a broader discussion of multifaceted interventions.

### Dust mites

The major dust mite allergens are Der f 1 and Der p 1 from the two most common house dust mite species, *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*. Several different approaches to dust mite allergen exposure reduction have been studied and generally focus on source removal (i.e. killing the dust mites) and/or removal of the allergen. As the major dust mite allergens are carried on larger particles (>10 microns), they quickly settle to dependent surfaces after disturbance of the reservoir [30]. For this reason, air filtration is not likely to have any meaningful effect on dust mite allergen exposure. The primary approaches include measures that target the bed, which are frequent washing of all bed linens in hot water and use of allergen impermeable mattress and pillow encasements; and measures that target other allergen reservoirs, which are vacuuming, pulling up carpet, and application of acaricides or allergen denaturing agents. Application of acaricides and allergen denaturing agents is cumbersome, but one Cochrane review suggests that acaricides may be beneficial [6,31]. Home or room dehumidification, with a goal of reducing relative humidity less than 45% can reduce dust mite populations [32]. Sustained reduction of indoor relative humidity is difficult to achieve, and carpet removal is expensive and of unclear benefit. First-line approaches to reduce dust mite allergen exposure include washing of bed linens and use of allergen-impermeable mattress and pillow encasements and these are highly effective in reducing mite allergen in the bed [12,15<sup>¶</sup>,18]. In studies [4,5,33,34] with carefully selected patients who are very likely to have dust mite-driven asthma, dust mite interventions that result in a substantial reduction in dust mite allergen levels have had a clinical effect. In contrast, in an unselected population of adults with asthma, allergen impermeable covers were not associated

with any improvements in asthma [9]. This experience with dust mite allergen interventions highlights the importance of patient selection in the efficacy of allergen exposure interventions. Pediatric patients, for example, have more atopy-driven asthma than adults, so may be more responsive to environmental interventions [10,35].

Despite some positive clinical trials, there have been many negative clinical trials, including a negative meta-analysis [36], resulting in heated debate about the efficacy of dust mite control measures in asthma [37]. However, there are several possible explanations for the negative trials and these should be scrutinized so that an opportunity to improve upon current intervention methods is not missed. Because dust mite exposure, like other indoor allergens, occurs outside of the home [28], some have suggested that the bed is not the site of greatest exposure so that interventions focused on the bed may have little effect on a patient's total exposure throughout the day [38<sup>¶</sup>]. The spatial and temporal aspects of dust mite allergen exposure may be more complex than previously thought and explain the limited efficacy of first-line dust mite environmental control practices. These issues related to complex spatial-temporal aspects of exposure are applicable to at least some, if not all of the other major indoor allergens [23,39<sup>¶</sup>], and could lend insight into how to most effectively reduce allergen exposure.

### Furry pets

The most common furry pets are cats and dogs, so this discussion will focus on these two major allergens. The major dog allergen is Can f 1 and the major cat allergen is Fel d 1. These allergens, in contrast to dust mite and cockroach allergens, are predominantly carried on smaller particles (<10–20 microns) so remain airborne for long periods and are readily detectable in air samples from homes. Because of this characteristic, and the reluctance of patients to give up their pets, there have been several studies [40–42] examining the efficacy of air filtration in reducing airborne pet allergen levels and improving asthma in sensitized patients. Overall, these studies have found that this approach is ineffective at improving asthma outcomes and at best, only modestly reduces airborne allergen levels. Only one study that evaluated this general approach reported a positive effect and in this study, children with well controlled, persistent asthma and pet sensitization with a pet in the home were enrolled. This study [41] was a double-blind placebo-controlled crossover study of two air purifiers – one in the living room and one in the

bedroom. Settled dust allergen levels were not changed, but active filters captured significantly more pet allergen than sham filters. Lung function did not improve, but airway hyper-responsiveness improved in the active air purifier group. Even if, in some circumstances, air filtration improves asthma in pet-allergic patients, there is no evidence to suggest that either the short-term or long-term effects on asthma are equivalent to pet removal. A recent study [43<sup>¶</sup>] addressed the question of whether certain dog breeds are 'hypoallergenic' by measuring dog allergen levels in dust and air samples collected from homes with a variety of dog breeds, including ones considered 'hypoallergenic'. The investigators found that homes with 'hypoallergenic' dogs had similar levels of dog allergen as homes with 'nonhypoallergenic' dogs.

Almost all studies support the notion that significant reductions in animal allergen levels require source removal, or relocating the pet. Even after removing the pet from the home, it can take several months before significant reductions in allergen levels are observed [44]. There is only one trial of pet removal, and it is not a randomized trial, likely because of the obvious feasibility issues related to patients being willing to be randomized to pet removal or pet keeping groups [45]. In this one study, airway hyper-responsiveness was significantly improved in the pet removal group, and none of the participants in this group required inhaled corticosteroids at the end of the study while almost all in the pet-keeping group did. Indirect exposure to cat allergen can also cause asthma symptoms in sensitized children. Cat allergen brought in by students with cats at home has been linked to asthma symptoms and worsening peak flow in cat-sensitized classmates with asthma, demonstrating that indirect exposure can trigger asthma [46].

Similarly to the concept that high-level allergen exposure can protect against the development of an allergen-specific IgE response, high-level exposure may also attenuate symptoms. This has been called the 'Thanksgiving effect' and is recognized in clinical practice when cat-allergic asthma patients living with, and apparently tolerating, a cat go away to college in the fall, and then return home for Thanksgiving and, upon re-exposure to the cat, develop significant asthma symptoms [47]. However, there are no data to support the idea that sustained animal allergen exposure is better than, or even equivalent to, pet removal in asthma management, so this cannot be a recommended approach for pet-allergic asthmatics. A recent practice parameter focusing on furred pet allergens and allergic disease provides more detail on this topic [48<sup>¶</sup>].

## Rodents

Rodent allergens have been recognized as a cause of occupational allergy and asthma for many decades, but have only recently been recognized as a potential cause, and exacerbator of, asthma in community populations. Mus m 1, the major mouse allergen, is found primarily on small particles, like other furred animal allergens, so is readily airborne [49,50]. It is found in virtually all inner-city homes, particularly in communities in the northeastern and Midwestern US [51–53]. Although 75–80% of US homes have detectable mouse allergen, concentrations in inner-city homes are as much as 1000-fold higher than those found in suburban homes [54,55]. Early-life IgE sensitization to mouse has been linked to an increased risk of recurrent wheeze and other atopic diseases in an inner-city birth cohort [56], and exposure has repeatedly been linked to increased risk of a range of markers of uncontrolled and more severe asthma among sensitized children [39<sup>■</sup>,52,53]. One pilot study [57] of 18 homes demonstrated an approximately 75% reduction in settled dust mouse allergen levels with a professionally delivered integrated pest management intervention that included both trap placement and application of rodenticide. Although reducing home mouse allergen levels in mouse-sensitized patients with asthma would be expected to be clinically efficacious, whether this is the case is unclear. Rat allergen sensitization and exposure has also been linked to asthma morbidity in inner-city children, but only one-third of inner-city homes have detectable rat allergen and 20% of inner-city children with asthma are sensitized to rat, so that overall, a small proportion of inner-city asthma patients is affected by rat allergen exposure [58]. A recent practice parameter focusing on rodent allergens and allergic disease provides more detail on this topic [59<sup>■</sup>].

## Cockroach

The most common cockroaches in US inner-cities are the German and American cockroaches, and the major German cockroach allergens, Bla g 1 and Bla g 2, are the best studied in terms of health effects. Cockroach allergen exposure among sensitized inner-city children with asthma was first linked to asthma morbidity in the NCICAS in a study [60] published in 1997. Since then, the link with asthma morbidity has been replicated [61], and highly effective methods based on integrated pest management principles to reduce cockroach allergen levels have been identified [62]. Moreover, in a successful multifaceted environmental intervention in inner-city children with asthma, the degree of reduction in

cockroach allergen was correlated with the degree of improvement in asthma symptoms, providing support for recommending cockroach allergen environmental control measures as an integral part of asthma management in cockroach-sensitized children with asthma [34]. There is also a recent practice parameter that provides more detail about the role of cockroach allergen in allergic diseases (under review at JACI).

## Other indoor exposures

Although allergens immediately come to mind when thinking about the effect of indoor environmental exposures on asthma, there are nonallergen indoor exposures that adversely affect nonatopic, as well as atopic, patients with asthma. Dampness has received much attention as a risk factor for asthma and asthma symptoms, and recent meta-analyses confirm previous work that a damp indoor environment is a risk factor for incident asthma [63,64]. Whether the effect of dampness is attributable to mold, dust mites, or other factors is not clear; however, one environmental trial of moisture remediation demonstrated beneficial effects on asthma [65]. Indoor pollution, particularly airborne fine and coarse particulate matter (PM<sub>2.5</sub> and PM<sub>2.5-10</sub>, respectively), has been repeatedly linked to asthma symptoms and other measures of asthma morbidity [66,67] as has indoor NO<sub>2</sub> [68]. Cigarette smoke is a major source of indoor particulate matter (PM), but cooking and sweeping are also important sources of PM [69]. NO<sub>2</sub> is produced by combustion; so homes with gas appliances and gas heat have higher NO<sub>2</sub> concentrations and one school-based trial found an improvement in asthma when unvented gas-heating systems were replaced with either flued gas or electric systems [70].

In the past few years there have been several studies [71<sup>■</sup>,72–75] supporting the efficacy of portable high efficiency particulate air (HEPA) purifiers in reducing indoor PM and, in some cases, also improving asthma outcomes. This approach has been effective even when used in homes of asthmatic children who live with a smoker [71<sup>■</sup>]. Although the air purifiers do not reduce indoor PM concentrations to levels found in homes without smokers, so they cannot be recommended over a home smoking ban, they are effective in lowering indoor PM concentrations by 50% or more, so are a reasonable alternative when a home smoking ban is not feasible or while a family is working towards a home smoking ban.

Not surprisingly, interventions explicitly aimed at multiple indoor exposures continue to demonstrate clinical efficacy. For example, legal assistance

to implement environmental control practices was effective at improving asthma in one retrospective chart review study [76]. Interestingly, a device that distributes filtered cooled laminar airflow over the bed was shown to be highly effective in a randomized, placebo-controlled crossover study [77]. Although the results of this clinical trial are encouraging, questions regarding the cost-effectiveness and acceptability of this type of intervention for the general asthma patient population remain. In addition, a recent trial of relocation to high altitude highlights the fact that the environmental interventions that have been tested can never specifically target only one environmental exposure [78<sup>■</sup>]. This trial, which was designed to determine whether the beneficial effects of high altitude observed in earlier studies were specific to allergic asthmatic patients, found that nonatopic asthmatics not only improved with relocation to a high altitude environment, but that their magnitude of improvement was the same as that observed in atopic patients. These findings suggest that there are other environmental features of high altitude aside from the lack of dust mites that have beneficial effects on asthma. From a practical standpoint, the fact that all environmental interventions by nature target more than one environmental contaminant is irrelevant when the overall objective is to identify interventions that are clinically effective; however, it makes understanding the nature of the relationships between any given environmental contaminant and allergic disease outcomes challenging.

## CONCLUSION

Environmental control has a clearly established role in the management of asthma, but its role as a primary prevention tool is not supported by recent clinical trials. Individually tailored, multifaceted interventions are recommended as a part of standard asthma management, as single allergen interventions appear to be less effective than multifaceted interventions. Emerging work highlights the potential impact of key concepts on our current view of environmental control. These concepts include individual susceptibility; co-exposures, such as pollutants and microbes; spatial-temporal aspects of exposure, and dose-response relationships. A better understanding of how these factors influence the relationship between environmental exposures and asthma should lead to more effective environmental control strategies.

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## Conflicts of interest

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## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 457–459).

1. Platts-Mills TA, Tovey ER, Mitchell EB, *et al.* Reduction of bronchial hyper-reactivity during prolonged allergen avoidance. *Lancet* 1982; 2:675–678.
  2. Boner AL, Niero E, Antolini I, *et al.* 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; 54:42–45.
  3. 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; 323:502–507.
  4. Dorward AJ, Colloff MJ, MacKay NS, *et al.* Effect of house dust mite avoidance measures on adult atopic asthma. *Thorax* 1988; 43:98–102.
  5. Ehner B, Lau-Schadendorf S, Weber A, *et al.* Reducing domestic exposure to dust mite allergen reduces bronchial hyperreactivity in sensitive children with asthma. *J Allergy Clin Immunol* 1992; 90:135–138.
  6. Hayden ML, Rose G, Diduch KB, *et al.* Benzyl benzoate moist powder: investigation of acaricidal [correction of acarical] activity in cultures and reduction of dust mite allergens in carpets. *J Allergy Clin Immunol* 1992; 89:536–545.
  7. Carswell F, Birmingham K, Oliver J, *et al.* The respiratory effects of reduction of mite allergen in the bedrooms of asthmatic children: a double-blind controlled trial. *Clin Exp Allergy* 1996; 26:386–396.
  8. Halcken 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; 111:169–176.
  9. 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; 349:225–236.
  10. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007 *J Allergy Clin Immunol* 2007; 120 (Suppl 5):S94–S138.
  11. Chan-Yeung M, Ferguson A, Watson W, *et al.* The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. *J Allergy Clin Immunol* 2005; 116:49–55.
  12. Toelle BG, Ng KK, Crisafulli D, *et al.* Eight-year outcomes of the Childhood Asthma Prevention Study. *J Allergy Clin Immunol* 2010; 126:388–389.
  13. Scott M, Roberts G, Kurukulaarachy RJ, *et al.* Multifaceted allergen avoidance during infancy reduces asthma during childhood with the effect persisting until age 18 years. *Thorax* 2012; 67:1046–1051.
- This study demonstrates that a stringent environmental control and dietary intervention reduces the risk of asthma into early adulthood, but had no effect on allergic sensitization.
14. 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; 170:433–439.
  15. Gehring U, de Jongste JC, Kerkhof M, *et al.* The 8-year follow-up of the PIAMA intervention study assessing the effect of mite-impermeable mattress covers. *Allergy* 2012; 67:248–256.
- This study of a simple dust mite intervention found no effect on asthma or other outcomes at age 8.

16. Maas T, Dompeling E, Muris JW, *et al.* Prevention of asthma in genetically susceptible children: a multifaceted intervention trial focussed on feasibility in general practice. *Pediatr Allergy Immunol* 2011; 22:794–802.
17. Horak F Jr, Matthews S, Ihorst G, *et al.* Effect of mite-impermeable mattress encasings and an educational package on the development of allergies in a multinational randomized, controlled birth-cohort study: 24 months results of the Study of Prevention of Allergy in Children in Europe. *Clin Exp Allergy* 2004; 34:1220–1225.
18. Maas T, Kaper J, Sheikh A, *et al.* Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma. *Cochrane Database Syst Rev* 2009; CD006480.
19. Schram-Bijkerk D, Doekes G, Boeve M, *et al.* Nonlinear relations between house dust mite allergen levels and mite sensitization in farm and nonfarm children. *Allergy* 2006; 61:640–647.
20. Nembrini C, Sichelstiel A, Kisielow J, *et al.* Bacterial-induced protection against allergic inflammation through a multicomponent immunoregulatory mechanism. *Thorax* 2011; 66:755–763.
21. Wlasiuk G, Vercelli D. The farm effect, or: when, what and how a farming environment protects from asthma and allergic disease. *Curr Opin Allergy Clin Immunol* 2012; 12:461–466.
22. Hansel TT, Johnston SL, Openshaw PJ. Microbes and mucosal immune responses in asthma. *Lancet* 2013.  
This review describes the current state of knowledge in the emerging field of microbial influences on asthma.
23. Peng RD, Paigen B, Eggleston PA, *et al.* Both the variability and level of mouse allergen exposure influence the phenotype of the immune response in workers at a mouse facility. *J Allergy Clin Immunol* 2011; 128:390e7–396e7.
24. Platts-Mills T, Vaughan J, Squillace S, *et al.* Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet* 2001; 357:752–756.
25. 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; 126:410–412.
26. Perry TT, Vargas PA, Bufford J, *et al.* Classroom aeroallergen exposure in Arkansas head start centers. *Ann Allergy Asthma Immunol* 2008; 100:358–363.
27. Chew GL, Correa JC, Perzanowski MS. Mouse and cockroach allergens in the dust and air in northeastern United States inner-city public high schools. *Indoor Air* 2005; 15:228–234.
28. 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; 26:1246–1252.
29. Permaul P, Hoffman E, Fu C, *et al.* Allergens in urban schools and homes of children with asthma. *Pediatr Allergy Immunol* 2012; 23:543–549.
30. Platts-Mills TA, Heymann PW, Longbottom JL, Wilkins SR. Airborne allergens associated with asthma: particle sizes carrying dust mite and rat allergens measured with a cascade impactor. *J Allergy Clin Immunol* 1986; 77:850–857.
31. 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; 67:158–165.
32. Hyndman SJ, Vickers LM, Htut T, *et al.* A randomized trial of dehumidification in the control of house dust mite. *Clin Exp Allergy* 2000; 30:1172–1180.
33. Walshaw MJ, Evans CC. Allergen avoidance in house dust mite sensitive adult asthma. *Q J Med* 1986; 58:199–215.
34. 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; 351:1068–1080.
35. Crocker DD, Kinyota S, Dumitru GG, *et al.* Effectiveness of home-based, multitarget, multicomponent interventions with an environmental focus for reducing asthma morbidity: a community guide systematic review. *Am J Prev Med* 2011; 41 (2 Suppl 1):S5–S32.
36. Gotzsche PC, Johansen HK. House dust mite control measures for asthma. *Cochrane Database Syst Rev* 2008; CD001187.
37. Platts-Mills TA. Allergen avoidance in the treatment of asthma: problems with the meta-analyses. *J Allergy Clin Immunol* 2008; 122:694–696.
38. Tovey E, Ferro A. Time for new methods for avoidance of house dust mite and other allergens. *Curr Allergy Asthma Rep* 2012; 12:465–477.  
In this review, Tovey *et al.* highlight the complexities of allergen exposure and the implications this has on development of new environmental control approaches.
39. Torjusen EN, Diette GB, Breyse PN, *et al.* Dose-response relationships between mouse allergen exposure and asthma morbidity among urban children and adolescents. *Indoor Air* 2012.  
In this study of mouse allergen exposure and asthma morbidity, both the shape of the dose–response relationship and the site of home exposure of greatest clinical relevance are examined.
40. Wood RA, Johnson EF, Van Natta ML, *et al.* A placebo-controlled trial of a HEPA air cleaner in the treatment of cat allergy. *Am J Respir Crit Care Med* 1998; 158:115–120.
41. van der Heide S, van Aalderen WM, Kauffman HF, *et al.* Clinical effects of air cleaners in homes of asthmatic children sensitized to pet allergens. *J Allergy Clin Immunol* 1999; 104 (2 Pt 1):447–451.
42. Sulser C, Schulz G, Wagner P, *et al.* Can the use of HEPA cleaners in homes of asthmatic children and adolescents sensitized to cat and dog allergens decrease bronchial hyperresponsiveness and allergen contents in solid dust? *Int Arch Allergy Immunol* 2009; 148:23–30.
43. Vredegoor DW, Willemse T, Chapman MD, *et al.* Can f 1 levels in hair and homes of different dog breeds: lack of evidence to describe any dog breed as hypoallergenic. *J Allergy Clin Immunol* 2012; 130:904e7–909e7.  
This study demonstrates that there are no differences in home dog allergen levels between homes with 'hypo-allergenic' and non-'hypo-allergenic' dog breeds.
44. 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; 83:730–734.
45. Shirai T, Matsui T, Suzuki K, Chida K. Effect of pet removal on pet allergic asthma. *Chest* 2005; 127:1565–1571.
46. Almquist 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.
47. Erwin EA, Woodfolk JA, Ronmark E, *et al.* The long-term protective effects of domestic animals in the home. *Clin Exp Allergy* 2011; 41:920–922.
48. Portnoy J, Kennedy K, Sublett J, *et al.* Environmental assessment and exposure control: a practice parameter–furry animals. *Ann Allergy Asthma Immunol* 2012; 108:223e1–223e15.  
This practice parameter provides a thorough review of furry animal allergens and asthma and evidenced-based recommendations for patient care.
49. Ohman JL Jr, Hagberg K, MacDonald MR, *et al.* Distribution of airborne mouse allergen in a major mouse breeding facility. *J Allergy Clin Immunol* 1994; 94:810–817.
50. Matsui EC, Simons E, Rand C, *et al.* Airborne mouse allergen in the homes of inner-city children with asthma. *J Allergy Clin Immunol* 2005; 115:358–363.
51. Phipatanakul W, Eggleston PA, Wright EC, Wood RA. Mouse allergen. I. The prevalence of mouse allergen in inner-city homes. The National Cooperative Inner-City Asthma Study. *J Allergy Clin Immunol* 2000; 106:1070–1074.
52. Pongracic JA, Visness CM, Gruchalla RS, *et al.* Effect of mouse allergen and rodent environmental intervention on asthma in inner-city children. *Ann Allergy Asthma Immunol* 2008; 101:35–41.
53. Matsui EC, Eggleston PA, Buckley TJ, *et al.* Household mouse allergen exposure and asthma morbidity in inner-city preschool children. *Ann Allergy Asthma Immunol* 2006; 97:514–520.
54. Matsui EC, Wood RA, Rand C, *et al.* Mouse allergen exposure and mouse skin test sensitivity in suburban, middle-class children with asthma. *J Allergy Clin Immunol* 2004; 113:910–915.
55. Cohn RD, Arbes SJ Jr, Yin M, *et al.* National prevalence and exposure risk for mouse allergen in US households. *J Allergy Clin Immunol* 2004; 113:1167–1171.
56. Donohue KM, Al-alem U, Perzanowski MS, *et al.* Anticockroach and antimouse IgE are associated with early wheeze and atopy in an inner-city birth cohort. *J Allergy Clin Immunol* 2008; 122:914–920.
57. Phipatanakul W, Cronin B, Wood RA, *et al.* Effect of environmental intervention on mouse allergen levels in homes of inner-city Boston children with asthma. *Ann Allergy Asthma Immunol* 2004; 92:420–425.
58. Perry T, Matsui E, Meriman B, *et al.* The prevalence of rat allergen in inner-city homes and its relationship to sensitization and asthma morbidity. *J Allergy Clin Immunol* 2003; 112:346–352.
59. Phipatanakul W, Matsui E, Portnoy J, *et al.* Environmental assessment and exposure reduction of rodents: a practice parameter. *Ann Allergy Asthma Immunol* 2012; 109:375–387.  
This practice parameter provides a thorough review of rodent allergens and asthma and evidenced-based recommendations for patient care.
60. Rosenstreich DL, Eggleston P, Kattan M, *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; 336:1356–1363.
61. Gruchalla RS, Pongracic J, Plaut M, *et al.* Inner City Asthma Study: relationships among sensitivity, allergen exposure, and asthma morbidity. *J Allergy Clin Immunol* 2005; 115:478–485.
62. Arbes SJ Jr, Sever M, Mehta J, *et al.* Abatement of cockroach allergens (Bla g 1 and Bla g 2) in low-income, urban housing: month 12 continuation results. *J Allergy Clin Immunol* 2004; 113:109–114.
63. Fischer CG, Hohmann C, Thiering E, *et al.* Meta-analysis of mould and dampness exposure on asthma and allergy in eight European birth cohorts: an ENRIECO initiative. *Allergy* 2011; 66:1570–1579.
64. Quansah R, Jaakkola MS, Hugg TT, *et al.* Residential dampness and molds and the risk of developing asthma: a systematic review and meta-analysis. *PLoS One* 2012; 7:e47526.
65. Kercsmar CM, Dearborn DG, Schluchter M, *et al.* Reduction in asthma morbidity in children as a result of home remediation aimed at moisture sources. *Environ Health Perspect* 2006; 114:1574–1580.
66. McCormack MC, Breyse PN, Matsui EC, *et al.* In-home particle concentrations and childhood asthma morbidity. *Environ Health Perspect* 2009; 117:294–298.
67. Trenga CA, Sullivan JH, Schildcrout JS, *et al.* Effect of particulate air pollution on lung function in adult and pediatric subjects in a Seattle panel study. *Chest* 2006; 129:1614–1622.

68. Hansel NN, Breyse PN, McCormack MC, *et al.* A longitudinal study of indoor nitrogen dioxide levels and respiratory symptoms in inner-city children with asthma. *Environ Health Perspect* 2008; 116:1428–1432.
  69. McCormack MC, Breyse PN, Hansel NN, *et al.* Common household activities are associated with elevated particulate matter concentrations in bedrooms of inner-city Baltimore preschool children. *Environ Res* 2008; 106:148–155.
  70. Pilotto LS, Nitschke M, Smith BJ, *et al.* Randomized controlled trial of unflued gas heater replacement on respiratory health of asthmatic schoolchildren. *Int J Epidemiol* 2004; 33:208–214.
  71. Butz AM, Matsui EC, Breyse P, *et al.* A randomized trial of air cleaners and a health coach to improve indoor air quality for inner-city children with asthma and secondhand smoke exposure. *Arch Pediatr Adolesc Med* 2011; 165:741–748.
- This study is one of several recent studies demonstrating a beneficial effect of portable HEPA purifiers on asthma in children.
72. Eggleston PA, Butz A, Rand C, *et al.* Home environmental intervention in inner-city asthma: a randomized controlled clinical trial. *Ann Allergy Asthma Immunol* 2005; 95:518–524.
  73. Du L, Batterman S, Parker E, *et al.* Particle concentrations and effectiveness of free-standing air filters in bedrooms of children with asthma in Detroit, Michigan. *Build Environ* 2011; 46:2303–2313.
  74. Batterman S, Du L, Mentz G, *et al.* Particulate matter concentrations in residences: an intervention study evaluating stand-alone filters and air conditioners. *Indoor Air* 2012; 22:235–252.
  75. Lanphear BP, Hornung RW, Khoury J, *et al.* Effects of HEPA air cleaners on unscheduled asthma visits and asthma symptoms for children exposed to secondhand tobacco smoke. *Pediatrics* 2011; 127: 93–101.
  76. O'Sullivan MM, Brandfield J, Hoskote SS, *et al.* Environmental improvements brought by the legal interventions in the homes of poorly controlled inner-city adult asthmatic patients: a proof-of-concept study. *J Asthma* 2012; 49:911–917.
  77. Boyle RJ, Pedroletti C, Wickman M, *et al.* Nocturnal temperature controlled laminar airflow for treating atopic asthma: a randomised controlled trial. *Thorax* 2012; 67:215–221.
  78. Rijssenbeek-Nouwens LH, Fieten KB, Bron AO, *et al.* High-altitude treatment in atopic and nonatopic patients with severe asthma. *Eur Respir J* 2012; 40:1374–1380.
- Findings from this study suggest that dust mite allergen exposure reduction may be responsible for only some, or even none, of the beneficial effects of relocation to high altitude environments.