

## EDITORIAL

# On allergens and asthma (again): does exposure to allergens in homes exacerbate asthma?

The severity of asthma symptoms has a major impact on patients' lives and the quantity of medical care that an individual patient requires. Amongst numerous other factors, exposure to allergens has been related to asthma severity [1–4]. However, showing the direct relationship between personal allergen exposure and symptoms has always been difficult, in part due to a number of possible confounding factors. Patients are often sensitized and exposed to more than one allergen, and viral infection and medication may obscure the relationship. Furthermore, it is often difficult to differentiate clearly between the effect of sensitization, and that of exposure. Sensitization to mites, cat and cockroach was found to be a significant risk factor for acute asthma in patients requiring treatment in Hospital emergency room in several American studies [4–8]. However, none of these studies unequivocally established a quantitative relationship between current allergen exposure and the exacerbation of asthma requiring admission to Hospital.

In an experimental situation, following a controlled challenge with either high- or low-dose allergen, sensitized subjects experience an increase in non-specific airway reactivity [9]. Low-dose allergen challenge of allergic asthmatic patients (which mimics 'real life' situation) can produce the characteristic eosinophilic infiltration of the airways and an increase in proinflammatory cytokines (e.g. IL-5) [10]. The evidence of a similar relationship between personal exposure in homes and severity of symptoms or markers of airway inflammation is less convincing. In this issue of the journal, Maestrelli *et al.* demonstrate in a 1-year prospective study of dust mite-sensitive patients with mild to moderate asthma receiving an optimal medication that exposure to lower levels of mite allergens in bedrooms was associated with an improvement in non-specific airway reactivity [11]. This adds to other evidence that exposure to high levels of allergens in homes is associated with more severe asthma in sensitized individuals.

### Does allergen exposure increase asthma severity in sensitized individuals?

Peat *et al.* investigated the relationship between mite allergen exposure and asthma by comparing two population

samples of Australian children aged 8–11 years living in a hot, humid, coastal region or a hot, dry inland region [12]. Mite allergen levels were much higher by the coast (83 vs. 11.2 µg/g), but the prevalence of mite sensitivity was similar in both regions (probably since levels in both places were high enough to cause sensitization). However, airway reactivity assessed by histamine challenge test in children sensitized to mites was more severe in coastal children. The authors concluded that very high mite levels in the coastal region significantly increased bronchial responsiveness in sensitized children. In a further population-based epidemiological study in six different regions, the same authors found that mite-allergic children with asthma had more reactive airways when living in the areas where mite allergen levels are high compared with areas where exposure to mites is low [13].

In the American National Co-operative Inner-City Asthma Study, 476 children from eight major inner city areas were assessed for atopy and environmental allergen exposure [14]. Those children who were both allergic to cockroaches and exposed to high levels of cockroach allergens in the dust had 3.6-fold higher hospitalization rates, more unscheduled medical visits for asthma per year, significantly more missed school days, more days of wheezing and nights with disturbed sleep compared with all other children. Neither increased exposure to cockroach allergen alone, nor allergy to cockroaches by itself, was associated with greater morbidity.

There is further indirect epidemiological evidence that high levels of exposure to allergens may be associated with asthma symptoms in the UK. Strachan & Carey showed that the most powerful risk factors for severe asthma in 11–16-year-old children were pet ownership (which indicates high exposure to pet allergens) and the use of non-feather bedding [15]. The authors estimated that if the association between non-feather pillows and severe asthma was causal, it could account for 53% of the severe asthma in the studied population. Several studies have recently found that polyester pillows contain five to eight times more mite, cat and dog allergen than feather pillows [16–18].

Exposure to allergens may be important in maintaining airway inflammation in asthma. Exposure to *Alternaria*

allergen has been shown to be a risk factor for sudden respiratory arrest in asthmatics [19]. However, the relationship between allergen exposure in homes and symptoms of asthma among sensitized patients is much more complex than in the case of exposure and sensitization, and simple threshold levels for provocation of asthmatic symptoms are almost certainly not appropriate. A significant correlation was observed between three measures of disease severity (non-specific bronchial reactivity, peak expiratory flow rate (PEFR) variability and pulmonary function) and mite allergen levels in beds in subjects with positive skin tests to mites, but no relationship was seen in those who were skin test-negative [20]. An uncontrolled study in the UK has shown that the majority of children admitted to Hospital with asthma exacerbation were both sensitized and exposed to mite allergen and suggested that continued exposure to higher concentrations of mite allergen might be associated with the risk of readmission [21]. These studies could suggest that a high level of allergen exposure is associated with increased airway reactivity in patients with stable asthma treated outside the Hospital setting, and also with a risk of exacerbation.

A recent case-control study in Birmingham, UK, has shown that patients with brittle asthma are significantly more often both sensitized and exposed to high levels of allergens (mite, cat and dog) to which they are allergic, compared with patients with mild disease [22]. Exhaled nitric oxide (NO), a marker of airway inflammation, is much higher in asthmatics who are both sensitized and exposed to the relevant allergen compared with those that are sensitized, but not exposed [23].

### Allergen exposure and response to treatment

There is some evidence that allergen exposure may confound the pharmacological management of the disease [24]. A significant reduction in glucocorticosteroid receptor (GCR) binding affinity was observed in ragweed-allergic patients with asthma during the pollen season compared with pre- and post-season measurements. Furthermore, peripheral blood mononuclear cells of ragweed-allergic asthmatics obtained outside the pollen season and of cat-allergic patients not exposed to cats, developed significantly lower GCR binding affinity after incubation with ragweed and cat allergen *in vitro*. The observed effect appeared to be allergen-specific, was restricted to atopic asthmatic patients, and made the lymphocytes from atopic asthmatics significantly less responsive to the inhibitory effect of hydrocortisone. These findings could suggest that high allergen exposure in sensitized individuals might contribute to poor asthma control by both maintaining the inflammatory process in the airways and reducing the effectiveness of steroid treatment. However, as yet there is

no evidence that personal exposure in homes can exert a similar effect.

### Allergen exposure and asthma severity—is there a threshold?

There is probably a considerable variability between individuals in the magnitude of response to the same levels of allergen exposure. In a group of individuals with similar high levels of specific IgE antibodies (or similar size of skin weal), some will develop respiratory symptoms only if they are exposed to high levels of allergens, while others apparently require very low exposure to be symptomatic. It is likely that the level of exposure necessary to induce and maintain airway inflammation, bronchial reactivity and symptoms varies between individuals over a wide range. Furthermore, using the linear assumption, it appears that a 'No Observed Adverse Effect Level' for the exposure to allergens in relation to symptoms can not be identified. Thus, it is unlikely that there is a threshold concentration that could be generally applicable to every individual and below which no adverse effect on airway responsiveness, symptoms or variability in pulmonary function would occur. However, a pattern emerges in which sensitized patients will have more severe disease if their exposure to offending allergen is high, than when it is low. Does this mean that these patients would benefit from effective environmental control?

### Implications for treatment

Although the primary aim of the study by Maestrelli *et al.* was not to examine the success of avoidance measures, the data could indirectly suggest that exposure to low levels of allergens is associated with the improvement in disease control. In agreement with this, Marks *et al.* used the data from a randomized controlled trial of mite allergen avoidance to show that in mite-sensitive patients with asthma changes in mite allergen levels were significantly positively correlated with changes in the severity of airway reactivity [25]. However, whilst the evidence is growing that allergen exposure in sensitized individuals can lead to the persistence of symptoms and cause exacerbation of asthma, we have to be careful in extrapolating these data into potential benefits of allergen avoidance for individual patients. If the level of exposure necessary to induce and/or maintain symptoms amongst sensitized asthmatics does vary over a wide range, it is likely that the case will be similar with respect to the potential benefits afforded by the reduction in exposure. For example, whilst in some patients effective environmental intervention may result in sizeable improvement in the

control of disease, others may not benefit at all. Furthermore, the timing of intervention may prove crucial (e.g. in occupational asthma the benefits of removal from exposure tend to decrease noticeably with the increasing duration of exposure prior to intervention) [26]. Thus, whilst the overall body of evidence would currently strongly favour specific allergen avoidance to be a part of an overall management package for sensitized patients, we still have no indicators which would help us determine who are the patients who would benefit, or the size of the potential benefit. Furthermore, there are no data on the relative importance of different interventions in multiple-sensitized and exposed patients (e.g. is it reasonable to use mite-proof bedding in subjects still sensitized and exposed to a pet).

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A. CUSTOVIC  
A. WOODCOCK

*North-west Lung Centre  
Wythenshawe Hospital  
Southmoor Road  
Manchester M23 9LT  
UK*

*E-mail: acostovic@fs1.with.man.ac.uk*