

EDITORIAL

Indoor environmental factors and respiratory illness

Outdoor air pollution has received much scientific interest as a possible cause of respiratory symptoms and a contributory factor in the increase of asthma. However, the majority of people in the developed world spend the overwhelming majority of their time inside one type of building or another, and the indoor environment has begun to attract deserved attention over the last several years. We are beginning to appreciate that living in a damp house may have more adverse effects on respiratory health than living next to a busy motorway.

A study by Andriessen *et al.* in this month's issue of the journal is the last in a series of papers investigating the association between home dampness and respiratory health [1]. This is one of the first studies which relies not only on questionnaires, but also on the objective measurement of both pulmonary function (PEF variability) and atopic status (skin prick testing). Performed as part of the PEACE study (Pollution Effects on Asthmatic Children in Europe), it examined the relationship between observed moisture stains and moulds in homes and PEF variability, symptoms and medication use in 1614 children in 14 centres across Europe. PEF variability in atopic children, but not in those who were non-atopic, was found to be associated with reported moulds in the home. The study also provides some fascinating insights into the differences between European countries in housing conditions (reported moisture stains varied from 2.9% in Norway to 38.8% in Poland; moulds from 2.9% in Norway to 36% in Italy), use of gas stoves (<3% in Scandinavia, >70% in The Netherlands, Poland and Italy), smoking habits (regular smoking inside the home ranged from 4% in Finland to >70% in Greece) and even pet ownership (ranging from <10% in some places in Scandinavia to over 30% for cats in Amsterdam).

Living in damp conditions has been identified as a risk factor for respiratory symptoms in children [2]. Is it because of a direct relationship with moulds, or are home dampness and moulds simply a surrogate for high house dust mite allergen levels? High indoor humidity is a prerequisite for house dust mite population growth and the presence of moisture stains and moulds may thus be an indicator of high mite allergen levels. Furthermore, certain fungi that are present in house dust may partially digest human skin scales making them more palatable for mites, and fungi may even be the food source for mites. The techniques for measuring mite allergen levels were

developed over a decade ago enabling quantification of allergen exposure in epidemiological studies and the investigation of the properties of allergen-carrying particles. Exposure and sensitization to dust mites has been suggested as a major cause of asthma in most parts of the world.

House dust mite allergens and asthma

Sensitization to mite allergens is the single strongest risk factor for asthma, especially among children in temperate climates [3]. Mites seem to be important throughout the world and not only in the USA and Europe. Leung *et al.* recently reported that atopic sensitization was a significant risk factor for asthma in ethnic Chinese populations living in three different areas of southeast Asia (Hong Kong, Kota Kinabalu and San Bu), with adjusted odds ratios for mite sensitization being 1.9, 5.8 and 5.6, respectively [4].

The level of exposure to mite allergens in early life may be the determinant of a subsequent sensitization. In a German Multicentre Atopy Study (MAS-90), more than 1300 newborn babies were followed to investigate the influence of exposure to indoor allergens on atopic sensitization [5]. The number of children who were sensitized to mites was small at the first birthday but increased gradually, with cumulative rates of sensitization being 0.5%, 1.9% and 3.8% at 1, 2 and 3 years of age. Those children who developed sensitization to dust mite by 3 years of age had significantly higher level of mite allergen in their homes than nonsensitized ones. Only one of 86 children with a strong family history of allergic disease, followed from birth until 5 years of age in Linköping, Sweden, developed sensitization to dust mites [6]. This is probably consequent to the very low exposure to mite allergens (the highest level recorded was only 3.5 µg/g). Even in the areas with relatively few mites in homes (e.g. Norway), sensitization to mites was shown to correlate strongly to levels of mite allergen in mattresses (corresponding to odds ratio [OR] of 16) [7].

In addition to sensitization, exposure to mite allergens may be a risk factor for the development of symptomatic asthma. Peat *et al.* have recently studied children from six regions of New South Wales, Australia, with a range of levels of mite allergens [8]. Mite-sensitive children in each of the areas were at significant risk of having asthma, with the magnitude of this risk doubling for every doubling of the current level of exposure to mite allergens.

Finally, there may be a dose-response relationship

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between mite allergen exposure and asthma severity but there are many potential confounders. Many asthmatic patients are sensitized and exposed to more than one allergen, and viruses, air pollution, exercise, emotion, may make asthma severity worse; the relative contribution of each of these factors to the airway inflammation is difficult to elucidate. Nevertheless, when Peat *et al.* compared children living in areas with different levels of exposure to mites, the greater bronchial reactivity was found in mite-sensitized children in the area with the highest mite levels [9]. We have found a modest but significant correlation between the concentration of Der p 1 and Der p 2 in the bed and objective indices of asthma severity (non-specific bronchial hyperreactivity, FEV₁, and PEF variability) in mite-sensitized adult asthmatics, but not for patients with negative skin prick tests to mites [10].

Cats, dogs and cockroaches

Over the last few years, several studies have presented evidence about communities with low mite exposure in which other allergens dominate sensitization. Warner *et al.* have studied the prevalence of sensitization to mite, cat and dog allergen in relation to current exposure at home in 124 asthmatic children living in three climatic zones in Sweden [11]. Dust mite allergen levels were higher in homes in the south whilst cat and dog allergens tended to be higher in the north. House dust mite sensitization was significantly higher in the south, while sensitivity to cat and dog allergens was more prevalent in children in central and northern parts of the country. In this MAS-90 study, there was a quantitative relationship between exposure to Fel d 1 in early life and sensitization to cats (median Fel d 1 concentrations 150 ng/g vs 64 ng/g in sensitized and nonsensitized children, respectively) [5]. Pet ownership in traditional Chinese living in Kota Kinabalu and San Bu is rare, and asthma is not associated with pet allergy. Contrary to this, in the westernized Hong Kong where pet ownership (and thus exposure) is much higher, being sensitized to animal dander represents a significant risk factor for asthma (OR 2.3) [4].

A recent study suggested that in the inner city areas with low mite allergen levels and high proportion of cockroach-infested houses, sensitization to cockroach allergens was common and the most important risk factor for asthma [12]. Cockroach sensitization is not confined to inner-city populations but occurs wherever substandard housing or apartment buildings sustain cockroach infestation.

Are indoor moulds important?

In a desert environment in Tucson, Arizona, the mould *Alternaria* is the major allergen associated with asthma in

11-year-old children and in a multiple regression analysis both persistent asthma (diagnosed by age 6 and present at age 11) and new asthma (diagnosed after age 6) were significantly associated with positive skin test to *Alternaria* at age 6 (OR 3.4 and 2.2, respectively) [13]. Although *Alternaria* found indoors is predominantly from outdoor sources, it is present in similar concentrations both indoors and outdoors. Exposure to *Alternaria* allergen has also been shown to be a risk factor for sudden respiratory arrest in asthmatics [14].

In a recent publication in this journal, Garrett *et al.* investigated factors associated with airborne fungal spore concentrations and health outcomes in children [15]. Respiratory symptoms were associated with an increase in indoor *Cladosporium* exposure, but not with mean total spore concentrations. Visible mould growth in houses was not associated with respiratory symptoms. Asthma in children was associated with exposure to *Penicillium* in winter and atopy with exposure to *Aspergillus* spores. Exposure to *Cladosporium* and *Penicillium* was a risk factor for sensitization to these genera but also for allergy to other fungal extracts and, in the case of *Penicillium* exposure, for allergy to house dust and dog. It is thus possible that fungal exposure may have an allergen-specific effect on sensitization but also a non-specific effect on immune system facilitating sensitization to other allergens (perhaps via mycotoxins and β -glucans).

A different approach to assess the relationship between home dampness, moulds and respiratory symptoms has been used in a recent study: in a case-control design the authors investigated whether asthmatic patients are more likely to live in damp housing than age- and sex-matched control subjects, and whether increasing severity of dampness is associated with the increasing severity of asthma [16]. The dampness survey assessing objective measurement of dampness including spot temperature and relative humidity measurement within each room, measurement of humidity of the walls and the presence and severity of visible mould growth was performed. Asthmatic patients were 2–3 times more likely to live in a damp house than controls (after controlling for employment status, household income, active and passive smoking, age, sex and pet ownership). Furthermore, the severity of asthma increased with increasing dampness (both self-reported and observed) and a significant correlation was found between the severity of dampness and both asthma severity score and airflow obstruction. The authors suggested exposure to house dust mites and/or moulds as a possible causal factor.

Whilst exposure to dust mite, cat, dog and cockroach allergens can be assessed using monoclonal antibody-based ELISAs, there is as yet no reliable objective method of measuring exposure to mould allergens. Most studies have

used either questionnaires to assess home dampness and fungal contamination, or air sampling for spore concentrations as an alternative way of measuring fungal exposure. This means that epidemiological evidence for the relationship between exposure to moulds and asthma development is approximate at best.

Indoor environment and respiratory disease: is it all due to mites?

The indoor environment of modern homes contains many antigens that can cause allergic disease in susceptible individuals. The major biological sources of allergens range from acarids (e.g. house dust mites), insects (e.g. cockroaches), domestic animals (cats and dogs) and fungi to such sources as rodents and pollens derived from outside. In addition, we must not forget the potential role of indoor air pollution (e.g. NO₂ and ozone) and endotoxins as the enhancers of allergic sensitization. The evidence for a causal relationship between factors in the indoor environment and asthma is most complete for exposure to house dust mites. This is due in part to mites being the most important source of allergens in temperate climates and partly because two site monoclonal antibody-based ELISA to Group 1 mite allergens was the first to be developed. It is tempting to try to explain any relationship between indoor environment and respiratory health, such as the presence of moisture stains and fungi, as being mediated by high exposure to mites (in damp homes) in house dust mite-sensitized individuals. Indeed, in a study by Verhoeff *et al.* the association between home dampness and respiratory symptoms appeared to be characteristic of mite allergic children [17].

However, there is much more in house dust than house dust mites. In the study by Andriessen *et al.* [1], the restriction of the analysis to subjects whose skin tested positive to mites did not make the association stronger, even though atopic children living in houses with moulds had higher PEF variability than non-atopic children. This may imply that it was not house dust mite allergy, but sensitization to some other allergen(s) that was important. When analysis was restricted to subjects sensitized to moulds, association with PEF variability was found to be stronger, suggesting that mould allergy may be important in Europe.

The isolation of house dust mite, cat, dog and cockroach allergens allowed the biochemical properties of these allergens to be defined. The usage of the purified allergens for skin testing and serum IgE antibody assays enabled their allergenic properties to be established. Furthermore, the production of monoclonal antibodies has provided reliable and consistent markers for specific allergens. This has led to improved purification procedures and the

development of allergen detection tests. It is essential that similar developments are achieved with mould allergens. We need reliable and effective ways of measuring individual exposure to mould allergens so that quantitative relationships between exposure, sensitization and symptoms can be investigated in epidemiological studies; aerodynamic characteristics of allergen-carrying particles can be determined; and the biochemical properties of these allergens defined.

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