

Time for New Methods for Avoidance of House Dust Mite and Other Allergens

Euan Tovey · Andrea Ferro

© Springer Science+Business Media, LLC 2012

Abstract Asthma is a common disease in which environmental exposures and lifestyle factors play critical roles in expression and symptoms. Recommended methods for reducing exposure to domestic allergens as a component of asthma and rhinitis management have changed little over the last 30 years. The data that implementation of these provides clinical benefit are inconsistent. We contend that current methods are ineffective at reducing chronic personal exposure. More effective strategies can be developed based on understanding when people are exposed, the sources of this exposure and the activities associated with this exposure. Developing new methods should be founded on understanding the aerodynamic behavior of particles, their aerosolization, removal from surfaces, and the complex relationships between exposures and clinical outcomes. It will also require developing better proxy measures of chronic exposure, identifying markers for the subset of people who benefit, and integrating this with strategies addressing other domestic exposures and lifestyle factors.

Keywords Allergen · Aeroallergen · Avoidance · Intervention · Asthma · Reaerosolization · Personal exposure · Methods · HDM · House dust mite

Introduction

There are many recent and comprehensive reviews of allergen avoidance, including [1–4], which share common features

about approaches and methods. This article instead attempts to bring together new directions that are emerging in the literature, including a recent Rostrum [5•], which calls for a re-think of strategies for mite allergen avoidance. The core of this strategy is to determine when and how personal airborne exposure to allergen occurs, and to develop methods that are evaluated on their ability to reduce personal inhaled exposure in houses or other times in the day, with the final arbiter being clinical benefit.

Why Are New Methods of House Dust Mite Avoidance Required?

Rising Prevalence

Asthma has a global prevalence of around 300 M and is the most common chronic disease among children. This prevalence is projected to reach 400 M by 2025 as countries become more urbanized [6]. There are no effective public health interventions for asthma based on causal pathways, unlike the situation with most other chronic diseases. Likewise there are no drugs, which permanently arrest asthma progression, supporting the need to address the environmental drivers. Developing such interventions has been identified by the WHO as an urgent research priority [7]. Developing new strategies for effective interventions, if based on reducing allergen exposure, will require a significant shift in thinking and original experimental approaches.

Management Guidelines Are Inconsistent

The advice of different National and International Asthma Management Guidelines on allergen avoidance differs widely, reflecting different disease models and the lack of high quality data. The National Heart, Lung, and Blood Institute (2007) [8] is generally supportive of existing avoidance

E. Tovey (✉)
Woolcock Institute of Medical Research, Sydney Medical School,
University of Sydney,
PO Box M77 Missenden Road,
Sydney, NSW 2050, Australia
e-mail: euan.tovey@sydney.edu.au

A. Ferro
206 Rowley Laboratories, Clarkson University,
PO Box 5710, Potsdam, NY 13699-5710, USA
e-mail: aferro@clarkson.edu

paradigms and advises on a multifaceted, comprehensive approach involving beds, carpets, furnishings, dampness and other measures. Both the Global Initiative for Asthma (2009) [9] and British Thoracic Society Guidelines (2009) [10] are more cautious and note that the evidence that avoidance can reduce morbidity is tenuous. The Finnish Allergy program 2008–2018 [11, 12] only advocates allergen avoidance in ‘mandatory situations’ and instead promotes a holistic concept of ‘allergy health,’ through diet, physical activity, and a close connection with nature.

Stasis in Recommendations

The methods generally advocated in guidelines, reviews and textbooks for avoidance of house dust mites (HDM) and other domestic allergens (cats, cockroaches, mice, fungi) have remained largely unchanged for over 30 years. This situation is exploited in many web-based resources and infomercials on asthma, which focus on ‘the most suitable vacuum cleaner/washing machine/bed encasing’, and imply their purchase will improve symptoms, without robust clinical evidence. Thus, the existing conceptual basis for performing allergen avoidance remains largely oriented towards products and sites (particularly beds) and is disengaged from the uncertainty of the medical evidence. The topic is in benign stasis and there has been little disruptive thinking driving new and innovative R&D, or different approaches articulated.

The Evidence from Clinical Trials Is Inconclusive

Birth-cohort studies aimed at preventing asthma and/or allergic sensitization by reducing allergen exposure (primary interventions) have had mixed and generally disappointing results, see reviews [13, 14]. This is despite several adequately powered and well-controlled trials, which achieved significant reductions of HDM allergen concentrations at the treated sites. While it is generally accepted that both mite allergen exposure and mite allergy are frequently associated with childhood asthma in epidemiologic studies, the relationships appear more complex than anticipated and other innate and non-allergen exposures, non-linear allergen dose-response effects, and other disease risk factors, determined by genes, diet, infections, and lifestyle, all play a role. Until the role of allergen exposure in an individual’s asthma aetiology is more clearly delineated, it will be difficult to advocate simply for reduction of HDM exposure in early life as a way to prevent later asthma.

Surprisingly, there is a lack of investigation into the role of HDM avoidance for preventing progression to established asthma in those already demonstrating risk factors such as HDM allergy, eczema, persistent rhinitis, and/or transitory wheeze (secondary interventions) [2]. Given the long-term health benefits, parental demand and observable

nature of these factors, this situation is disappointing. The same lack of observation of the role of allergens applies to studies of asthma progression, or remission (especially during the gender-switch in asthma prevalence in teenagers), and of the incidence in adult immigrants to countries with high asthma prevalence.

Deciphering the role of allergen avoidance in the management of existing allergic asthma (tertiary interventions) is much more complex. From a pragmatic perspective, it is difficult to ignore the oft-cited Cochrane meta-analysis of allergen avoidance [15]. This analysis selected 54 trials, including 36 trials using physical methods (including 26 with mattress covers), 10 using chemical methods, and 8 using a combination of chemical and physical methods; most trials only used 1 method. The meta-analysis found, on average, no clinical benefit. This finding has been deeply influential. While the analysis can be criticized in many ways, (requiring more space than is available here), what is frequently overlooked is that the review attributed this lack of benefit to a failure to reduce exposure by the methods used, and surmized that it was inherently implausible that removal from a major provoking agent would be ineffective. Thus, the challenge is to not repeat the failed approaches of past methods, but to develop effective interventions and test them clinically.

Emerging Approaches Are More Promising

There are 2 groups of emerging data, which support the use of allergen avoidance in established disease.

The first group are studies that have used multi-trigger, multi-component approaches tailored to individuals’ needs and frequently involve more education. The best known is the large study by Morgan et al. [16], which was excluded from the Cochrane meta-analysis. This study addressed mite, cat, fungal, and cockroach allergens based on individual allergies, supplied extensive education as well as encasings, vacuum cleaners, and where required, HEPA air filters (for smoking and fungi). The treatment group had significantly fewer asthma symptoms and fewer unscheduled visits for treatment. The Breathe-Easy Home project is another multifaceted intervention, involving moisture-reduction features, enhanced ventilation systems, and selection of building materials; this also showed improvements in several but not all clinical outcomes [17]. Another recent study used a combined heating/air cleaning/ventilation unit in children’s bedrooms and showed improvements in asthma markers and symptoms [18]. A recent review of 23 home-based, multi-trigger, multi-component interventions found data supporting improvements in children and adolescents, but insufficient data for determining improvements in adults [19].

The second group of studies of interest are those that have used clean air delivered directly to the bed occupant.

The most sophisticated used a descending laminar ‘shower’ of clean air delivered from above the occupant’s head; this displaces the aeroallergen generated by movement and thermals from the bed occupant’s breathing zone, despite the bed containing normal allergen concentrations [20]. This showed improvements in quality of life and FeNO, but not in lung function, and curiously an increase in cat sIgE in the placebo group. Another study delivered the clean air through the fabric of the pillow itself; here nasal and ocular symptoms were improved [21]. There have been several earlier and clinically successful studies delivering clean air to the sleeper, and the approach dates back to the 1920s [22]. See also later comments about nocturnal exposures, particle size and the time-geography of exposure.

While the Role of Domestic Allergens in Asthma Is Complex, They Remain Important

We previously noted that ‘the golden age of the dust mite’ of the 1980s and early 1990s was over [5•], and the major risk factors for asthma are now seen as a complex mixture of environmental and lifestyle factors operating on unclear genetic susceptibilities. We [5•] and many others [23•] have reviewed the increasing number of external and internal microbial factors, early infections, dietary factors, nurturing practices, non-allergen exposures, and lifestyle factors that confer either risk or protection for asthma.

However, despite all this complexity and new information, it remains likely that domestic allergen exposures frequently play a synergistic and critical role in the aetiology and outcomes of asthma, particularly among children. Sensitization to one or more of a few domestic allergens (HDM, cockroaches, cats, mice, depending on the population) is strongly associated with asthma in cross-sectional studies and is a key prognostic indicator for wheezing among children [24]. Furthermore, allergy and allergen exposure are strongly related to elevated levels of markers of airway inflammation, such as FeNO [25], and the effectiveness of anti-IgE (omalizumab) therapy for asthma [26] provides additional support for the on-going role of allergen-allergic pathways in chronic disease. Allergen exposure may function sub-clinically to increase exacerbation risk from viral infections [27] and probably from other triggers.

Features of a New Approach

Deconstruct Past Dogmas

The current strategies for avoidance of HDM and other allergen are inhibited by 2 dogmas, which are not well substantiated.

The first dogma is that the bed is the site of most HDM exposure and should be the main target of interventions.

This concept was founded on the ‘logic’ of high HDM allergen concentration in bed dust, proximity of the person to the source, and proportion of time spent in bed [28]. However there is an emerging view that most mite allergen exposure does not occur in bed at night, and similar questions are being asked about the time-geography of mouse, cat, and other exposures. Early measurements of domestic HDM aeroallergen supported the dominant role of bed exposure [29], but these do not form a cohesive model of personal exposure over time. Our own thinking on this matter was initially challenged when we first measured inhaled HDM exposure during the day at different locations [30] and with different types of clothing [31]. In a later study, we collected 6 samples, each of 30 minutes, during the day, and a seventh sample on first getting into bed [32]. Using a model that presumed exposure in the 30-minute samples represented average exposure at these sites over longer times, we suggested about 40 % of HDM exposure occurred in the day, rather than at night. However this conclusion was challenged when we later found that nocturnal exposure declined greatly after the first 30 minutes in bed [33]. See also Fig. 1 for the decline of $>10\ \mu\text{m}$ particles after getting into bed, with only brief peaks of exposure during the night. Our recent data, collecting continuous, sequential aeroallergen samples, over the full 24-hour period, [in preparation for publication] suggests that most of the HDM aeroallergen exposure occurring over 24 hours

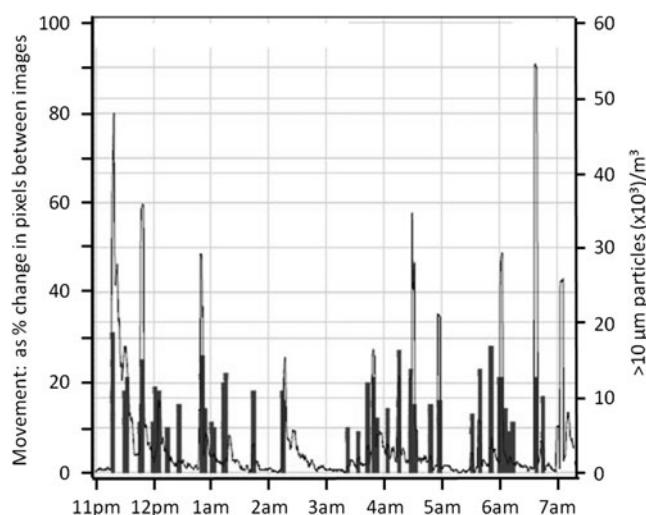


Fig. 1 A composite figure of $10\ \mu\text{m}$ particles/ m^3 throughout the night (black line) as collected in the breathing zone using a laser particle counter (AeroTrak, model 6880) and episodes of movement, (dark columns, denoting % change in pixels between consecutive images) made using an IR-enabled webcam and the software Yawcam. The larger peaks are typically associated with $\frac{1}{2}$ and $\frac{1}{4}$ body rolls, large movements of arms and adjustments to bed covers, whereas additional small peaks in exposures are mainly associated with hand and head movements. Note for most of the night, exposure to large particles is low, and a significant proportion of exposure occurs following initial bed entry [Tovey, unpublished data]

does not occur in bed [34]. This view is also indicated by another study using fixed-site and backpack personal air samplers, that showed that PM10 mite and other exposures in the school room were generally greater than the lounge room, and both sites were greater than in the bedroom [35•]. If it is consistently shown that HDM exposure mainly occurs outside the bedroom by larger studies in other populations then avoidance methods should be more focussed on these other sites.

The second and related dogma is the reliance on single reservoir measurements (mass-based concentrations of allergen per g of bed dust, or occasionally carpet, collected with a vacuum cleaner) to provide an adequate proxy for HDM exposure. The difficulty of assessing exposures within asthma studies that reflect the complex exposure variables have recently been discussed [23•, 36•, 37]. This convention is based on historical precedent and convenience and it continues to be used, largely unchallenged. Almost everything we understand from epidemiologic studies about the role of HDM exposure has been calculated using such ‘reservoir’ measurements. However, the relationship of this site becomes tenuous when a single sample (which varies locally with season, site, and repetition [38, 39] and low and variable proportion of aerosolizable particles by weight) is used as a proxy for an individual’s overall chronic inhaled exposure and even more tenuous when this is used to measure the success of an intervention, which depends on changing chronic aeroallergen exposure. Although some studies do find a weak relationship between reservoirs and airborne exposure in rooms (eg, [35•, 40] the large majority do not [41]), and exposure within a room is very different than exposure throughout the day. More reliable methods of estimating personal exposure are needed, preferably based on measurements the subject can perform repeatedly in order to assess their personal risk and, which do not require house visits by a technician (see section on assessing chronic exposure, below).

Base New Approaches on Personal Aeroallergen Exposure

The primary aim of domestic interventions is to reduce people’s personal (inhaled) chronic aeroallergen exposure. For the moment this ignores secondary issues such as the shape of the dose-response curve, whether the clinically most relevant exposure is to peaks, thresholds, time-weighted averages, particle sizes, and co-presentation, etc [37].

This approach of using personal aeroallergen was recent adopted in a cohort intervention study [42]. This study showed a roughly 2-fold reduction in both inhaled and static-sampled aeroallergen with feather bedding compared with synthetic bedding and no significant clinical improvement in an

intention-to-treat analysis, but a strong trend towards less sleep disturbed by wheeze and severe wheeze within the full-compliance group.

Personal aeroallergen exposure measurement applied in the context of real houses provides a novel and insightful perspective for evaluating avoidance methods. For example, there was no significant advantage in using a vacuum cleaner with a HEPA filter as opposed to one without [43, 44] as allergen is aerosolized by the common physical activity of cleaning; this finding is quite different than an evaluation in a test-laboratory rig. In another study, there was only a small and slow reduction in personal exposure to cat allergen using a HEPA air filter located in an occupied room [45]. This was not because air filters are inefficient as mechanical devices, but rather that dust was constantly and locally aerosolized by subjects or animals. In addition, we have shown that fitting encasings to beds provides a much shorter and small reduction in personal aeroallergen exposure than if measured by reservoir sampling [46] and that air-filters mounted over occupied beds provide a large reduction in exposure [47], also [48]. Sequential air sampling in an occupational setting provides insights into the process of sensitization (involving both amount and variability), which could not have been obtained in other ways [49•].

Measure Personal Exposure

Comprehensive technical reviews of measuring personal aeroallergen exposure are available [41, 50], and some of the issues of technique and interpretation of air sampling are covered elsewhere [36•]. Personal aeroallergen can be sampled using small, quiet, personally-worn pumps connected to sampling heads that collect either the entire inhalable (by WHO definition, the fraction ‘breathed into nose or mouth’) fraction [50–52] or the PM10 [35•] or smaller particle fractions. Such pump and filter units are around US\$1000. Several groups have also used our intranasal air samplers, see [43, 50, 53]; these generally correlate well with IOM filter samplers ($r^2 \sim 0.8$). These are inexpensive and collect inhaled particles $> \sim 3\text{--}4\text{ }\mu\text{m}$ in size. Another approach has been to use a silent, large-volume, electrostatic air filter sampler [54]; while this collects a large sample, there is some uncertainty about standardization of sampling efficiency and volumes. Current modified commercial ELISA assays [36•, 42], MARIA assays (Indoor Biotechnologies, Charlottesville, VA) [36•] and Halogen assays [55] are sufficiently sensitive to measure the low pg quantities of allergen encountered in less than an hour [30] during normal activity in locations with moderate HDM reservoirs. A recent novel approach to develop a robotic personal sampling surrogate that collects samples while imitating some movements and location of a child has been developed [56]. However, ‘exposure’ is complex biological phenomenon

varying in intensity, content, and particle size over intervals of time and we do not yet have an adequate suite of tools to monitor this complexity for allergens.

Determine the Individual Time-Geography of Exposure

The term ‘time geography of exposure’ describes the ‘summation of travel through hazard fields in space over time’ in order to better understand the effects of exposures on health outcomes [57•]. Such measurements are now occurring for small particulates and noxious gases due to rapid improvements in portable and personal digital sensors and data acquisition systems. They are feasible but have not been performed for aeroallergens.

The limited available evidence (see section on deconstructing dogmas) suggests that personal aeroallergen exposure to HDM over 24-hour time frames is more or less continuous, occurs both indoors (houses, schools, transport, etc) and even outside (from clothing), and fluctuates markedly with time, place, situation, ventilation, person, and activity. The precise determinants remain unexplored. It is probably in many ways similar to known aspects of exposure to other domestic biological and nonbiological particles, such as cat allergen, endotoxin, and PM_{10-2.5} particles. See also the section “integrate immune-biology with engineering.”

Differentiate Between Inhalable and Respirable Particles

The size of the particles carrying aeroallergens also needs to be considered when monitoring exposure, as this affects their deposition site in the airways and clinical consequences. The particle size also affects the infiltration, deposition, resuspension of particles, and particle-bound allergens in the indoor environment. In general, for particles greater than 0.5 μm in diameter, an increase in particle size is associated with a decrease in infiltration from outdoors [58], an increase in deposition rate on surfaces in a room [59], and an increase in the resuspension rate from human activity [60]. Large (>5 μm diameter) airborne particles found in residences tend to be from indoor resuspension activities (eg, walking, cleaning) that disturb the settled dust rather than from outdoor sources. Monitoring of allergen particle sizes are described elsewhere, including during stationary [51, 61–63] and personal [30, 64] sampling, see also review [41]. Particles carrying mite [30, 61], cat [62], cockroach [51], and fungal [63] allergens each occur over a wide range of sizes, not always on their recognized airborne sources (feces, skin flakes, spores, pollen grains, etc) and differ markedly in time and distribution depending on the situation, activity and clearance from the air.

Large particles (>5 μm diameter) can occur as short peaks (5–30 minutes) following disturbance due to their

relatively quick deposition rate. Smaller particles take longer to deposit after a disturbance and have other sources (eg, indoor combustion sources and infiltration of outdoor particles) and, therefore, appear as a more or less constant background. As allergen content is somewhat biased towards larger particles, and large particles make up the bulk of the airborne particle mass, it can be speculated that ‘large particle’ exposure provides much of the total aeroallergen dose for many domestic allergens and influences sensitization via upper airway deposition, whereas ‘small particle’ exposure largely involves the lower airways and provides subclinical stimulation affecting airway function [65]. This clinical effect is also demonstrated by pollen-sensitive asthmatics (and rhinitics), who, if highly exposed to small allergen-bearing starch granules from disrupted pollen, can have profound (‘thunderstorm’) asthma [66], with increased airway hyper-responsiveness, which can last for months. It can be further speculated that during the day, as people are active and in well ventilated spaces, exposure to HDM allergens is mainly ‘large particles’ whereas nocturnal exposure, with little disturbance and low air-exchange rates in rooms, is largely distributed towards ‘small particles’ and each has different impacts. In this context it can be questioned whether the supply of clean air at night (via filters, room ventilation etc) is more clinically important and effective than reducing exposure during the day. This question requires further investigation.

Develop and Validate Proxies for Chronic Aeroallergen Exposure

If most exposure to domestic allergens occurs from multiple and dispersed sources and if widespread air sampling is not feasible, alternative proxy methods will need to be developed, using some function of the ‘time-geography of exposure’ as a ‘gold standard.’ As only small samples of dust (5–20 mg) are typically obtained by vacuuming aeroallergen sources such as clothing and hard flat interior surfaces, and many of the particles are very small, it could be speculated that collecting multiple wipe samples [67, 68, 69•] would be more suitable as a simple, portable method. A sample of chronic ex-aeroallergen exposure can be collected using open Petri dishes [70] or dust-fall collectors [69•] to collect settling particles.

Emulate Strategies and Practices Used in Occupational Allergen Exposure

In the related field of occupational allergy, remediation would normally only be attempted after first understanding the sources, sites, and risks of exposure, and the same rationale should apply domestically. Studies of occupational exposure have long used air sampling as a way of defining

hazards [71], and the industrial hygiene departments of pharmaceutical industry animal labs routinely analyze samples for mouse and rat allergen exposure [personal communication Eva-Maria King, 2012]. Combined sampling of aeroallergen, settling aeroallergens, and wipes of surfaces provides a comprehensive view of exposure and sources within the workplace, leading to identification of possible hazards and ways of remediation [69•]. From an etiologic perspective, it is noteworthy that occupational sensitization and/or asthma occurs in ~30 % of adults occupationally exposed to rodents [72] and this does not require the ‘window of vulnerability’ which is thought to occur in infancy. It is also abundantly clear that in occupational situations, clinical benefits are most likely to occur with timely removal from exposure [73].

Recognize the Complex Relationship Between Multiple Exposures and Adaptive and Innate Responses

The term ‘exposome’ (another ‘...ome’!) is used to describe the totality of different exposures an individual may receive over a lifetime, which may interact with genomic/epigenomic susceptibilities to provide health outcomes. There are several complexities in the associations of exposure to any allergen and the clinical outcomes, which need to be recognized if reducing exposure is to be used in management. These include the possible non-linearity of dose-response to mite, mouse, rat, and cat allergens, at least in some studies, and the possible reversibility of tolerance to cat allergen exposure. This has been described by us elsewhere, see text and references E91-E102 [5••]. These responses are important in the context of allergen avoidance and primary prevention. Recent data suggests that the greatest risk of developing mouse allergy is from moderate mean aeroallergen exposure and low variability [49•]; an interplay occurs between IgE and IgG₄ with different exposure outcomes. For a useful discussion see [37]. Additionally, there is interest whether all exposure to normal “aeroallergens” occurs via inhalation, and some data suggests that dermal exposure [74, 75] and ingestion [76] might also modulate outcomes.

Another and different complexity is that exposure to allergens also involves co-exposure to many other molecules such as endotoxin, beta-glucans, and chitin, and indoor particulates, all of which may modulate effects. Higher endotoxin exposures appear to function paradoxically, such that exposure in infancy may provide protection against current and later asthma, whereas adult exposure may inflame asthma in established disease [77]. This is further complicated, as such responses are under genetic controls and therefore differ between people [78]. Indoor particulate exposures also increase asthma symptoms, in both atopic and non-atopic asthmatics [79].

Another example of the complexity of the relationship between environmental exposures and asthma symptoms are the recent studies of relocation to low-allergen environments. Even avoidance-sceptics probably accept that many subjects with allergic asthma relocated from urban cities to mountain sanatoria frequently have marked improvements in symptoms and multiple disease markers [5••]. Interestingly, this recent data shows many of the benefits also occur in patients with severe refractory asthma irrespective of their allergic sensitization, although the sensitized patients show a larger decrease in total IgE, eosinophils and FeNO [80•]. Such findings reinforce our understanding that complex environmental factors can contribute to all asthma, whether allergic or not.

The difficulty of identifying the basis of responses to environmental exposures raises the topic of ‘entropy;’ the observation of apparent allergy highly localized to respiratory sites in subjects classified as non-atopic on the basis of conventional skin or blood tests. This has been suggested to involve either localized antibody production or free light chain immunoglobulins [81]. While entropy is more commonly associated with idiopathic rhinitis, some subjects with asthma have worse disease markers on high exposure to allergens to which they have no sensitization [82–84] suggesting this phenomena may be more widespread. This also raises the additional issue of the limited capacity of conventional diagnostic tests to detect allergy to naturally occurring particles, such as basidiospores [85].

Other situations are recognized as providing protection from asthma and sensitization and it is unclear what exposures are involved. These situations include having earlier siblings, attending childcare, using feather bedding, and living indigenous and alternative ‘natural’ lifestyles. Most explanations are founded within the ‘hygiene hypothesis’ [86], or more recently the ‘biodiversity hypothesis’ [87]. The first author has contributed another hypothesis [88].

One general and hypothetical concern with avoidance protocols is that by concurrently creating more ‘sterile,’ dust-free, and allergen-free domestic environments, then ‘natural’ allergy/asthma protective mechanisms are not stimulated [89], particularly during infancy.

Integrate Immune-Biology with Engineering: Particle Resuspension, and CFD Modeling etc

A key to understanding the origins and control of aeroallergen exposure is to understand resuspension (or reaerosolization) of reservoir dust. Many allergens become ubiquitously distributed in the reservoir dust found throughout houses, with a distribution dependent on housing characteristics, sources, the patterns of domestic microclimates, and other features. Exposure occurs when this dust is resuspended into the air and inhaled. There are at least 15 papers that describe resuspension

of dust particles and/or allergens by activity from a range of surfaces; these include [35•, 60, 62, 90, 91]. At present, there is no comprehensive review of this critical entity which is fully accessible to the allergist/domestic aerobiologist. Such studies often describe the theory and physics involved, and use fixed-site air sampling in chambers and rooms, rather than human inhaled exposure, which differs. Figure 2 shows 1 example of disturbance during the day with a simultaneous recording of human activity, 10 μm particle number concentration, and location. Additionally, a person is exposed to detached dust drawn from the floor boundary layer via the rising body thermals, as shown by CFD modeling [92]. The occurrence of these thermals as visualized by Schlieren optics and modeled by CFD is used to understand virus aerosol transmission [93•]. Allergen exposure via thermals extends to other sources such as furnishings and bedding when the warmth of the body provides this delivery of detached particles. The role of activity in disturbing particles is shown in Fig. 1, which shows the disturbance of dust during the night, with high particle exposure on bed entry, and then intermittent exposure coinciding with largely involuntary movement through the night (Tovey, in preparation for publication). The contribution is also shown in

a recent study where airborne particles, protein, endotoxin and (1 $\rightarrow$ 3)- β -D-glucan were (2–4 $\times$) higher indoors during the day compared with night, with the coarser fractions strongly correlated with the strength of human activity [94]. The first study of the distribution of per-person emission rates of size-resolved particles and bacterial and fungal genomes was published recently [95•] and showed the differing dependency of exposure to these on occupancy and disturbance within the room, reinforcing the need to think of allergens in the same way. Two studies of personal exposure to endotoxin associated with PM_{2.5} [96•] and both PM_{2.5} and PM₁₀ [97] showed personal airborne exposure (sampled with back-pack samplers) was ~ 10 – $100\times$ greater than exposure measured with fixed site monitors indoors or outside. The authors proposed a ‘personal exposure cloud’ associated with local sources and personal activity. It is likely this occurs with domestic allergens.

As discussed above, particle size determines both the resuspension and deposition rate. For example, during a resuspension event with a human walking indoors, a 10 μm particle has a resuspension rate coefficient approximately 10 times higher and deposition loss rate coefficient approximately 100 higher

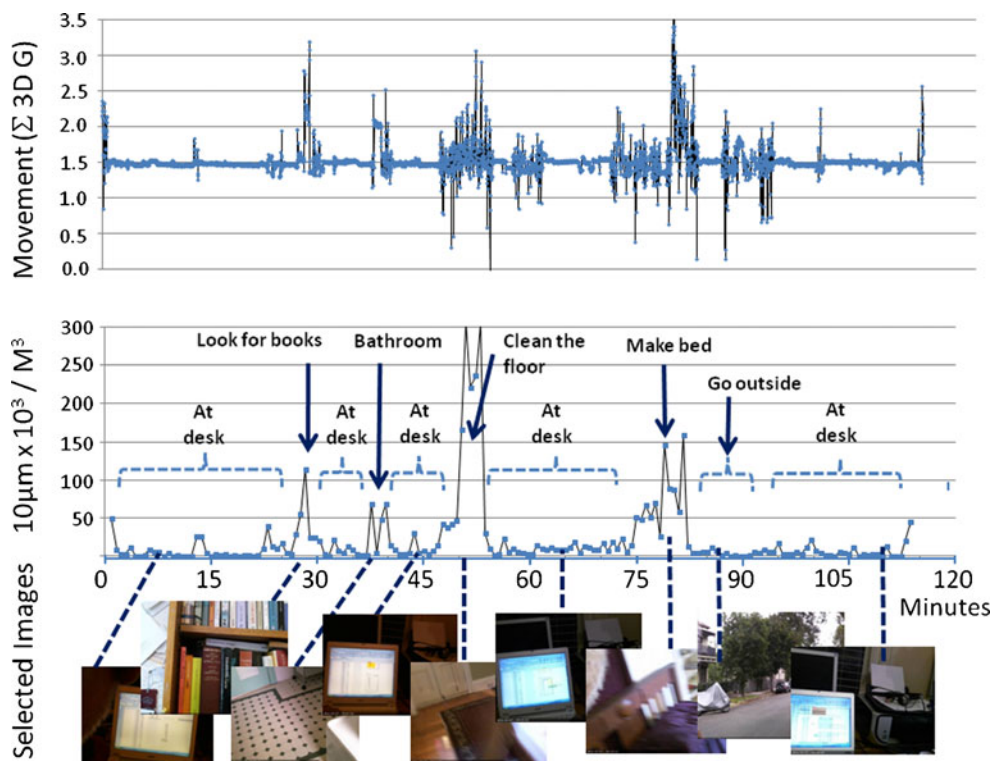


Fig. 2 An example of the simultaneous monitoring of human movement, particle exposure and location. Images and 3D acceleration were acquired using 2 iPods (Apple) running the apps ‘Accelerometer Pro’ and ‘Timelapse Pro’ respectively, located on shoulder straps of a backpack, which contained a laser particle counter (AeroTrak, model 6880) whose inlet tubing was located in the breathing zone. The majority of the 2 hours is spent in front of a computer providing low

exposure, with episodes of higher particle exposure while looking for books, going to the bathroom, cleaning a floor and making a bed. In different places during the day, particles may not correlate with allergen as the sources differ, but at night with a single source, they would. Techniques for real-time monitoring of allergen are feasible, but have not been developed [Tovey, unpublished data]

than a 1 μm particle [59, 98]. Therefore, the size distribution of the resuspended allergen in the air is not the same as the size distribution of the allergen in the settled dust. However, by characterizing the size distribution of allergen in the settled dust, and understanding the relationship of settled dust to airborne allergen concentration by particle size, we can better estimate human exposure and dose.

An additional consideration is the length of time an allergen remains in the indoor environment. Qian et al [60] has noted that particles undergo resuspension/deposition cycles corresponding with human activity, but that particles are not easily removed from the home. Small particles ($<2\ \mu\text{m}$) in particular, have enormously long residence times indoors (on the order of months or years) because they are difficult to detach from surfaces (eg, by vacuuming or human activity) and may require different approaches for remediation than large particles, (discussed for cockroach [36•]).

Develop Strategies Based on Materials, Design and Hygiene Protocols

Currently, developing new ways to practice HDM and other allergen avoidance lacks the critical and necessary framework describing how such personal exposure occurs over the course of the day and night, and what the main sources and determinant of this are. It is likely that current approaches are misdirected and new approaches could be developed.

On the basis of limited data and extrapolation, we anticipate that the main sources of both mite and cat personal allergen exposure are the clothing of the individual and of other proximal people, plus furnishings, flooring, and bedding, possibly in that order, with exposure driven by human activity/dust disturbance. Clearly different approaches to reducing this will apply in different situations with the arbiter being reduction in chronic personal exposure. Such approaches focus on choice and management of reservoirs/surfaces, which minimize resuspension and effective removal of allergens from these, as well as providing removal of airborne materials by air flow, exchange, and filtration.

In terms of managing allergen in clothing and bedding, there is adequate data that mite and cat allergen sources are highly soluble and the carrier-particles are largely removed by a complete laundry cycle with warm water and detergents [99]. While hot water [100] or additives are required to kill all mites, this approach is not supported without more data, as it is likely that washing needs to be performed so frequently (probably once every 2–3 weeks) [46] to maintain the priority of low allergen resuspension, that mite populations will decline. We would hypothesise that regular washing of upper and lower bedding and pillows would provide lower personal aeroallergen exposure (particularly if combined

with a simple supply of filtered air in the head of the bed) than occlusive encasings, although encasings may be complementary.

Although the traditional mechanical tools of domestic hygiene, such as vacuum cleaners or washing machines, will continue to have a place in an avoidance regimen, the emphasis would be less on how each of these varies in performance, but rather the establishing protocols for their effective use in the context of reducing aeroallergen. That is, how frequently does bedding need to be washed, or floors cleaned by different methods etc to achieve and maintain low aeroallergen resuspension in specific situations.

Overall, while resuspension has been explored from an engineering perspective, (see previous section) its application to domestic allergen avoidance is more complex. This topic could be a separate review in itself. For methods such as vacuuming many factors are involved; the intensity and nature of the disturbance that occurs at these sites, the surface loading of dust and allergen, the physical structure and electrostatic properties of the surface and particles themselves, and the differences in the particles that are released. In reality, it is not as simple as advocating that carpets be replaced by hard floors, as both need to be evaluated as aeroallergen sources, and as sites, which can be treated, and how these behave over time. While ‘adequate’ cleaning of carpets requires extensive effort [63] and hard floors would be more easily cleaned, the rate of personal exposure from a poorly cleaned hard floor may be greater than from a poorly cleaned carpet, as particles have been shown to be more easily resuspended from hard floors than from some carpets [101]. Floorings vary greatly in their properties.

Several studies have found a dependence on flooring type for particle resuspension from human activity. However, conflicting results make it difficult to recommend 1 flooring type over another. Price et al [102] reported that, for similar allergen concentrations in the settled dust, wool carpets resulted in higher mite exposures than hard floors and synthetic carpets, and hard floors and synthetic carpets had similar rates of mite aeroallergen exposure. Ferro et al [91, 103] estimated a higher emission rate of house dust from human activity on carpeted flooring vs hard flooring. This study was conducted in a residence, and the particle loading on the floor (mass of particles per area flooring) was not determined. Qian and Ferro [98], who conducted a study in a room-sized chamber in which participants walked across flooring pre-seeded with 20 g/m^2 of Arizona test dust, found that the resuspension rates from level-loop carpeting were approximately 10 times as high as those from vinyl tiles. Shaughnessy and Vu [104] however, reported that vinyl flooring resulted in resuspension rates 4 times higher than flow-through carpet and 10 times higher than tufted textile flooring. They conducted studies using a mobile chamber in a laboratory and at a school with a floor loading of $\sim 150\ \text{g}/\text{m}^2$ of

school dust. Using a mechanical foot to resuspend house dust at 2 different floor loadings (2 g/m² and 8 g/m²), Tian et al. [105] investigated the flooring effect from several flooring types. They found that resuspension rates were highest for low density cut pile carpet than for four other types of flooring, including hard wood, vinyl, high density cut pile carpet, and level loop carpet. The somewhat contradictory results from these studies are likely due to differences in materials, experimental methods and experimental conditions. In particular, the floor loading has varied greatly and methods for estimating floor loading are not consistent among resuspension studies. Also, vacuum methods used for floor loading estimation are more efficient on hard flooring than on carpets, resulting in inconsistent estimates of floor loading. In general, low floor loading results in a monolayer of particles on the surface, while high floor loading (eg, [104]) results in a multilayer of particles. For the high floor loading case, the particle adhesive properties are based on particle-to-particle interaction versus particle to flooring surface interaction. Better estimates of floor loading and experimentation under realistic conditions are needed to understanding the effect of flooring on particle resuspension.

Similar principles of reviewing changes in personal aeroallergen exposure and clinical effects apply to the assessment of air filtration. While the majority of studies using stand alone filters have not shown clinical benefit [106], probably as their impact on inhaled dust is small [44, 45], recent studies either directing the clean air close to the bed [20], or as room-based systems that also provide outside ventilation [18] have shown clinical benefit.

Most interest has been in avoidance strategies for house dust mite (HDM) allergens, but the principles of reducing exposure to other inhaled domestic allergens are generally similar as they involve aeroallergens and reservoirs, although each source requires different measures to control and allergens may be differently distributed. An excellent review of assessment and exposure control of furred pet allergens has recently been published [107•].

The Swedish experience of reducing cat aeroallergen exposure in schools is salient. Here, despite intensive and regular cleaning of class rooms, substantial reductions in aeroallergen exposure were not achieved until children changed to fresh clothing on arrival at school [108].

Efforts to develop low allergen houses, especially by retrofitting, are not trivial and require a different perspective of all aspects: design, surfaces, materials, hygiene, furnishings, climate control and ventilation underwritten by R&D and collaborations between different disciplines. While this may seem formidable, trends in houses change, driven by evidenced-based data that satisfies people's needs and addresses opportunities. One recent review estimated that for every dollar spent on interventions, the resulting benefits were from \$5.30 to \$14.00 (in 2007 US\$) in averted medical costs and productivity losses [109]. Given the rising global prevalence of asthma,

the stasis with current management approaches, and the recognition that more sophisticated approaches to avoidance are feasible, then it would seem worthwhile to continue to develop methods for better determining the role of allergen avoidance in the management of asthma.

Determining Individual Predictors of Response

In the past, subjects have been selected for interventions or recommended for avoidance based on criteria of symptoms and specific allergies and possibly a case history indicative of benefit. It likely that subjects with asthma differ in their response to reduced allergen exposure. Unfortunately, clinical trials in sanatoria, which do achieve very low allergen exposure where this could be tested, have not published data on markers of differences in individual responses. Only the classic UK study, conducted 30 years ago, in hospital rooms with 9 similarly mite-sensitive subjects reported this showing marked improvements in 5 and more modest improvements in the remainder [110]. While different predictive markers can be hypothesised (FeNO, eosinophils, comorbidities such as perennial rhinitis, intensity and/or number of allergies, sIgG₄ or sIgE etc) their usefulness needs to be established from the review of existing data and within new studies using subjects of different phenotypes, including those without skin sensitization.

Integrating Allergen Exposure with Other Factors

Given the complexity of environmental drivers in asthma, it would also seem prudent to suggest that allergen avoidance should be practiced in the overall context of creating a healthy living environment and lifestyle, although what is 'healthy' is not always clear. Studies of farming Steiner and Amish communities all suggest that exposure to rich and diverse animal, flowering plant, and microbial communities are associated with reduced asthma and allergic disease, but this is currently difficult to translate into an urban environment. Instead multi-component domestic interventions attempt address other urban risks such as exposure to indoor tobacco smoke, VOCs and off-gassing materials, carbon particulates from road transport, the use of NO_x-generating heating and cooking practices and the adverse effects of high exposure to indoor fungi. This reflects houses that are safe, warm, dry, with ample fresh air, and low pollutants. The additional effects of lifestyle factors, ranging from increased exercise, reduced maternal stress, not smoking and diet are all worthy of attention.

Require Interventions of Have a Clinical Evidence-Base

The final usefulness and practicality of allergen avoidance will not be known until it is possible to conduct studies,

which provide substantial, known and chronic reductions in domestic aeroallergen exposure and determine whether they translate into clinical benefit. The past contains many examples of methods, which were effective in test tubes, in culture, in laboratory rigs, over short time frames or at very limited sites. These properties were extrapolated to reductions in aeroallergen exposure in houses and to clinical benefits, without any proof of either. This has resulted, 30 years later, in the costly trialing and advocacy of interventions that have no clear benefit. It is fundamentally important that the clinical benefits of individual or collective methods are demonstrated.

Conclusions

Given that allergens from HDM, rodents, and cockroaches may be the most inflammatory component of the complex environmental exposure received by many people with asthma, and that this exposure functions synergistically with other risk factors, then developing allergen exposure reduction would seem a promising objective for future asthma management strategies. However, there is significant uncertainty about many aspects of currently advised strategies. We postulate that the framework for developing and improving interventions needs to be founded on the basis of reducing chronic personal exposure. This will require insight into when personal exposure occurs, what the sources are, and what is the efficacy of methods to prevent exposure. Such explorations will likely lead to new and different approaches to allergen avoidance. The role of allergen exposure in the inception, progression, and exacerbation of asthma will continue to be explored, and there needs to be parallel understanding of methods to modulate this domestic exposure in order to manage and reverse the effects.

Acknowledgment The authors wish to thank Julian Crane and Eva-Maria King, who contributed ideas and comments to this manuscript.

Disclosure Dr. Tovey has served on the board of the Asthma Foundation of NSW and on an advisory committee for Asthma Australia, and has applied for an NHMRC grant on allergen avoidance methods. Dr. Ferro reported no potential conflicts of interest relevant to this article.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Matsui EC. Role of environmental control in the management of asthma and allergy. *J Allergy Clin Immunol*. 2012;129:271–2. e1–3.
2. Arshad SH. Environmental control for secondary prevention of asthma. *Clin Exp Allergy*. 2010;40:2–4.
3. Rao D, Phipatanakul W. Impact of environmental controls on childhood asthma. *Curr Allergy Asthma Rep*. 2011;11:414–20.
4. Bush RK. Does allergen avoidance work? *Immunol Allergy Clin North Am*. 2011;31:493–507.
5. •• Tovey ER, Marks GB. It's time to rethink mite allergen avoidance. *J Allergy Clin Immunol*. 2011;128:723–7. e1–6. *Heralds the first significant divergence from traditional approaches to HDM allergen avoidance and provides more detailed review of the complexity of the environmental drivers of asthma and the potential of allergen avoidance to be clinically effective. The current article focuses on the practical framework of how to achieve this.*
6. To T, Stanojevic S, Moores G, Gershon A, Bateman E, Cruz A, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health*. 2012;204:12:204.
7. Bousquet J, Kiley J, Bateman ED, Viegi G, Cruz AA, Khaltayev N, et al. Prioritized research agenda for prevention and control of chronic respiratory diseases. *Eur Respir J*. 2010;36:995–1001.
8. National Heart, Lung and Blood Institute. Expert panel report 3: guidelines for the diagnosis and management of asthma: 2007. Available at www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed January 2012.
9. Global strategy for asthma management and prevention 2009. Available at <http://www.ginasthma.org/guidelines-gina-report-global-strategy-for-asthma.html>. Accessed January 2012.
10. British guideline on the management of asthma. 2009. Available from: www.sign.ac.uk/pdf/sign101.pdf. Accessed January 2012.
11. Haahtela T, von Hertzen L, Makela M, Hannuksela M. Finnish Allergy Programme 2008–2018 - time to act and change the course. *Allergy*. 2008;63:634–45.
12. von Hertzen LC, Savolainen J, Hannuksela M, Klaukka T, Lauerma A, Makela MJ, et al. Scientific rationale for the Finnish Allergy Programme 2008–2018: emphasis on prevention and endorsing tolerance. *Allergy*. 2009;64:678–701.
13. Simpson A, Custovic A. Prevention of allergic sensitization by environmental control. *Curr Allergy Asthma Rep*. 2009;9:363–9.
14. Martinez FD. New insights into the natural history of asthma: primary prevention on the horizon. *J Allergy Clin Immunol*. 2011;128:939–45.
15. Gotzsche PC, Johansen HK. House dust mite control measures for asthma: systematic review. *Allergy*. 2008;63:646–59.
16. Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, et al. Results of a home-based environmental intervention among urban children with asthma. *N Eng J Med*. 2004;351:1068–80.
17. Takaro TK, Krieger J, Song L, Sharify D, Beaudet N. The breathe-easy home: the impact of asthma-friendly home construction on clinical outcomes and trigger exposure. *Am J Public Health*. 2011;101:55–62.
18. Xu Y, Raja S, Ferro AR, Jaques PA, Hopke PK, Gressani C, et al. Effectiveness of heating, ventilation and air conditioning system with HEPA filter unit on indoor air quality and asthmatic children's health. *Build Environ*. 2010;45:330–7.
19. Crocker DD, Hopkins D, Kinyota S, Dumitru G, Herman E, Ligon C. A systematic review of home-based multi-trigger multi-component environmental interventions to reduce asthma morbidity. *J Allergy Clin Immunol*. 2009;123:63.
20. Boyle R, Pedroletti C, Wickman M, Bjerner L, Valovirta E, Dahl R, et al. Nocturnal temperature controlled laminar airflow for treating atopic asthma: a randomized controlled trial. *Thorax*. 2012;67:215–21.
21. Stillerman A, Nachtsheim C, Li W, Albrecht M, Waldman J. Efficacy of a novel air filtration pillow for avoidance of perennial allergens in symptomatic adults. *Ann Allergy Asthma Immunol*. 2010;104:440–9.
22. van Leeuwen WS, Eintoven Jr W, Kremer W. The allergen-proof chamber in the treatment of bronchial asthma and other respiratory diseases. *Lancet*. 1927;1:287–9.

23. •• Arrandale VH, Brauer M, Brook JR, Brunekreef B, Gold DR, London SJ, et al. Exposure assessment in cohort studies of childhood asthma. *Environ Health Perspect.* 2011;119:591–7. *Provides a comprehensive overview of the issues, which make the measurement of environmental exposures in asthma a challenge and suggests strategies for improving such measurements in longitudinal cohort studies.*
24. Holt PG, Rowe J, Kusel M, Parsons F, Hollams EM, Bosco A, et al. Toward improved prediction of risk for atopy and asthma among preschoolers: a prospective cohort study. *J Allergy Clin Immunol.* 2010;125:653–9.
25. de Jongste JC, Carraro S, Hop WC, Baraldi E, Grp CS. Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma. *Am J Respir Crit Care Med.* 2009;179:93–7.
26. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized trial of omalizumab (anti-ige) for asthma in inner-city children. *N Eng J Med.* 2011;364:1005–15.
27. Murray CS, Poletti G, Keadze T, Morris J, Woodcock A, Johnston SL, et al. Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax.* 2006;61:376–82.
28. Tovey E, Marks G. Methods and effectiveness of environmental control. *J Allergy Clin Immunol.* 1999;103:179–91.
29. Sakaguchi M, Inouye S, Yasueda H, Irie T, Yoshizawa S, Shida T. Measurement of allergens associated with dust mite allergy. II. concentrations of airborne mite allergens (Der i and Der ii) in the house. *Int Arch Allergy Appl Immunol.* 1989;90:190–3.
30. Poulos LM, O'Meara TJ, Sporik R, Tovey ER. Detection of inhaled Der p 1. *Clin Exp Allergy.* 1999;29:1232–8.
31. De Lucca SD, O'Meara T. J, Tovey ER. Exposure to mite and cat allergens on a range of clothing items at home and the transfer of cat allergen in the workplace. *J Allergy Clin Immunol.* 2000;106:874–9.
32. O'Rourke SD, Tovey ER, O'Meara T. J. personal exposure to mite and cat allergens. *J Allergy Clin Immunol.* 2002;109(Suppl):S47.
33. Marriott C, O'Meara T, Salome CM, Tovey ER. The impact of bed encasing on the nocturnal der p 1 exposure and asthma. *J Allergy Clin Immunol.* 2004;113:S22.
34. Mites, Asthma and Domestic Design 5. Mite allergens and myths. Available at: www.madd5.org/wp-content/uploads/2011/08/24.-Euan-Tovey.pdf. Accessed January 2012.
35. •• Raja S, Xu Y, Ferro AR, Jaques PA, Hopke PK. Resuspension of indoor aeroallergens and relationship to lung inflammation in asthmatic children. *Environ Int.* 2010;36:8–14. *This is perhaps the first paper (to be read in combination with reference 18, Xu), which comprehensively measures multiple aeroallergen and airborne endotoxin exposures in children throughout the day and night and includes addressing issues such as resuspension of dust from reservoirs. There is a wealth of information collected, which although underexplored, helps to establish new directions for such studies.*
36. • Esposito WA, Chew GL, Correa JC, Chillrud SN, Miller RL, Kinney PL. Quantitative measurement of airborne cockroach allergen in New York City apartments. *Indoor Air.* 2011;21:512–20. *This is also part of the 'new generation' of studies examining chronic airborne exposure to allergens, including consideration of the size of their particles and aerodynamic behavior.*
37. Mites, Asthma and Domestic Design 5. The dose response relationships between asthma and allergen exposure. Available at: www.madd5.org/wp-content/uploads/2011/08/32.Elizabeth-Matsui.pdf. Accessed April 2012.
38. Marks GB, Tovey ER, Peat JK, Salome CM, Woolcock AJ. Variability and repeatability of house dust mite allergen measurement: implications for study design and interpretation. *Clin Exp Allergy.* 1995;25:1190–7.
39. Mitakakis TZ, Mahmic A, Tovey ER. Comparison of vacuuming procedures for reservoir dust mite allergen on floors. *J Allergy Clin Immunol.* 2002;109:122–4.
40. Gore RB, Hadi EA, Craven M, Smillie FI, O'Meara TJ, Tovey ER, et al. Intra-nasal air sampling and reservoir house dust in the quantitation of *Dermatophagoides pteronyssinus* exposure. *J Allergy Clin Immunol.* 2001;107:S220.
41. O'Meara T, Tovey ER. Monitoring personal allergen exposure. *Clin Rev Allergy Immunol.* 2000;18:341–95.
42. Glasgow NJ, Ponsonby AL, Kemp A, Tovey E, van Asperen P, McKay K, et al. Feather bedding and childhood asthma associated with house dust mite sensitization: a randomized controlled trial. *Arch Dis Child.* 2011;96:541–7.
43. 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;111:784–7.
44. Gore RB, Durrell B, Bishop S, Curbishley L, Woodcock A, Custovic A. High-efficiency vacuum cleaners increase personal mite allergen exposure, but only slightly. *Allergy.* 2006;61:119–23.
45. 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;33:765–9.
46. Lau J, Sercombe J, Rimmer JS, Tovey ER. Bed encasings reduce reservoir allergens but not aeroallergens. *J Allergy Clin Immunol.* 2006;117.
47. Wrzeszcz K, Sercombe JK, Tovey ER. Localized air filtration can reduce airborne der p 1 allergen concentration and airborne particle count in both disturbed and undisturbed conditions. *J Allergy Clin Immunol.* 2008;121:S92.
48. Gore R, Boyle RJ, Hanna H, Custovic A, Gore C, Svensson P, et al. Personal allergen exposure is increased by turning over in bed and improved by temperature-controlled laminar airflow. *Clin Exp Allergy.* 2011;41:1848.
49. • Peng RD, Paigen B, Eggleston PA, Hagberg KA, Krevans M, Curtin-Brosnan J, 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;128:390–396. e1–7. *This study uses serial measurements of aeroallergen exposure to show that the types of antibody responses are functions of both the amount, and the variation of exposure. This extends our understanding of the clinical response to inhaled allergens.*
50. Renstrom A. Exposure to airborne allergens: a review of sampling methods. *J Environ Monit.* 2002;4:619–22.
51. De Lucca SD, Taylor DJM, O'Meara TJ, Jones AS, Tovey ER. Measurement and characterization of cockroach allergens detected during normal domestic activity. *J Allergy Clin Immunol.* 1999;104:672–80.
52. Green BJ, O'Meara T, Sercombe JK, Tovey ER. Measurement of personal exposure to outdoor *aeromycota* in northern New South Wales, Australia. *Ann Agric Environ Med.* 2006;13:225–34.
53. Renstrom A, Karlsson AS, Tovey E. Nasal air sampling used for the assessment of occupational allergen exposure and the efficacy of respiratory protection. *Clin Exp Allergy.* 2002;32:1769–75.
54. Custis NJ, Woodfolk JA, Vaughan JW, Platts-Mills TAE. Quantitative measurement of airborne allergens from dust mites, dogs, and cats using an ion-charging device. *Clin Exp Allergy.* 2003;33:986–91.
55. Tovey E, De Lucca S, Poulos L, O'Meara T. The halogen assay: a new technique for measuring airborne allergen. In: Jones MG, Lympny P, editors. *Methods in molecular medicine: allergy methods and protocols.* Totowa: Humana Press Inc; 2008. p. 227–46.

56. Wang Z, Shalat SL, Black K, Liroy PJ, Stambler AA, Emoekpere OH, et al. Use of a robotic sampling platform to assess young children's exposure to indoor bioaerosols. *Indoor Air*. 2012;22:159–69.
57. • National Academy of Sciences. Using Personal Monitors and Sensors to Characterize Individual Exposures. Available at: <http://www.nas-sites.org/emergingscience/files/2011/12/Michael-Jerrett.pdf>. Accessed January 2012. *This is one talk from a great website containing many recent conference presentations about the new science of exposure measurement.*
58. Liu DL, Nazaroff WW. Particle penetration through building cracks. *Aerosol Sci Technol*. 2003;37:565–73.
59. Thatcher TL, Lai ACK, Moreno-Jackson R, Sextro RG, Nazaroff WW. Effects of room furnishings and air speed on particle deposition rates indoors. *Atmos Environ*. 2002;36:1811–9.
60. Qian J, Ferro AR, Fowler KR. Estimating the resuspension rate and residence time of indoor particles. *J Air Waste Manag Assoc*. 2008;58:502–16.
61. Custovic A, Woodcock H, Craven M, Hassall R, Hadley E, Simpson A, et al. Dust mite allergens are carried on not only large particles. *Pediatr Allergy Immunol*. 1999;10:258–60.
62. Montoya LD, Hildemann LM. Size distributions and height variations of airborne particulate matter and cat allergen indoors immediately following dust-disturbing activities. *J Aerosol Sci*. 2005;36:735–49.
63. Salares VR, Hinde CA, Miller JD. Analysis of settled dust in homes and fungal glucan in air particulate collected during HEPA vacuuming. *Indoor Built Environ*. 2009;18:485–91.
64. Bogdanovic J, De Pater AJ, Doekes G, Wouters IM, Heederik DJJ. Application of porous foams for size selective measurements of airborne wheat allergen. *Ann Occup Hyg*. 2006;50:131–6.
65. Zeidler MR, Goldin JG, Kleerup EC, Kim HJ, Truong DA, Gjertson DW, et al. Small airways response to naturalistic cat allergen exposure in subjects with asthma. *J Allergy Clin Immunol*. 2006;118:1075–81.
66. Taylor PE, Jonsson H. Thunderstorm asthma. *Curr Allergy Asthma Rep*. 2004;4:409–13.
67. Wood RA, Mudd KE, Eggleston PA. The distribution of cat and dust mite allergens on wall surfaces. *J Allergy Clin Immunol*. 1992;89:126–30.
68. Sercombe J, Liu-Brennan D, Garcia M, Tovey ER. Evaluation of home allergen sampling devices. *Allergy*. 2005;60:515–20.
69. • Samadi S, Heederik DJJ, Krop EJM, Jamshidifard AR, Willemse T, Wouters IM. Allergen and endotoxin exposure in a companion animal hospital. *Occup Environ Med*. 2010;67:486–92. *This paper uses a range of sampling methods, including aeroallergen and wipe samples, to provide a comprehensive description of the sites and origins of exposure in an occupational setting.*
70. Karlsson AS, Hedren M, Almqvist C, Larsson K, Renstrom A. Evaluation of Petri dish sampling for assessment of cat allergen in airborne dust. *Allergy*. 2002;57:164–8.
71. Raulf-Heimsoth M. Allergen quantification at workplace. *Allergologie*. 2008;31:142–6.
72. Corradi M, Romano C, Mutti A. Laboratory animal allergy. *Med Lav*. 2011;102:428–44.
73. Baur X, Sigsgaard T, Aasen TB, Burge PS, Heederik D, Henneberger P, et al. Guidelines for the management of work-related asthma. *Eur Respir J*. 2012;39:529–45.
74. Fox AT, Sasieni P, du Toit G, Syed H, Lack G. Household peanut consumption as a risk factor for the development of peanut allergy. *J Allergy Clin Immunol*. 2009;123:417–23.
75. Brough H, Stephens A, Turcanu V, Lack G. Distribution of peanut in the home environment. *Allergy*. 2009;64:1428.
76. Matsumoto T, Miike T, Ono T. Mite-related allergy and oral tolerance. *Allergy*. 1996;51:276–7.
77. Doreswamy V, Peden DB. Modulation of asthma by endotoxin. *Clin Exp Allergy*. 2011;41:9–19.
78. Simpson A, John SL, Jury F, Niven R, Woodcock A, Ollier WER, et al. Endotoxin exposure, CD14, and allergic disease - An interaction between genes and the environment. *Am J Respir Crit Care Med*. 2006;174:386–92.
79. McCormack MC, Breyse PN, Matsui EC, Hansel NN, Peng RD, Curtin-Brosnan J, et al. Indoor particulate matter increases asthma morbidity in children with non-atopic and atopic asthma. *Ann Allergy Asthma Immunol*. 2011;106:308–15.
80. • Rijssenbeek-Nouwens L, Fieten K, Bron A, Hashimoto S, Bel E, Weersink E. High altitude treatment in atopic and non-atopic patients with severe asthma. *Eur Respir J*. 2012 [Epub ahead of print 22 March]. *While this paper confirms that severe asthma greatly improves when people are relocated from urban houses to mountain sanatoria, it shows that these improvements occur in both allergic and non-allergic subjects. This both confirms and questions the nature of environmental drivers of asthma.*
81. Powe DG, Kormelink TG, Sisson M, Blokhuis BJ, Kramer MF, Jones NS, et al. Evidence for the involvement of free light chain immunoglobulins in allergic and nonallergic rhinitis. *J Allergy Clin Immunol*. 2010;125:139–45.
82. Burney PGJ, Newson RB, Burrows MS, Wheeler DM. The effects of allergens in outdoor air on both atopic and nonatopic subjects with airway disease. *Allergy*. 2008;63:542–6.
83. Rabito FA, Carlson J, Holt EW, Iqbal S, James MA. Cockroach exposure independent of sensitization status and association with hospitalizations for asthma in inner-city children. *Ann Allergy Asthma Immunol*. 2011;106:103–9.
84. Langley SJ, Goldthorpe S, Craven M, Woodcock A, Custovic A. Relationship between exposure to domestic allergens and bronchial hyperresponsiveness in non-sensitized, atopic asthmatic subjects. *Thorax*. 2005;60:17–21.
85. Rivera-Mariani F, Bolaños-Rosero B. Allergenicity of airborne basidiospores and ascospores: need for further studies. *Aerobiologia*. 2012;28:83–97.
86. Liu AH. Endotoxin exposure in allergy and asthma: reconciling a paradox. *J Allergy Clin Immunol*. 2002;109:379–92.
87. von Hertzen L, Hanski I, Haahtela T. Natural immunity. *EMBO Rep*. 2011;12:1089–93.
88. Tovey ER, Kemp AS, Almqvist C, Sharland A, Marks GB. Do immune responses to inhaled skin flakes modulate the expression of allergic disease? *Clin Exp Allergy*. 2007;37:1199–203.
89. Woodcock A, Lowe LA, Murray CS, Simpson BM, Pipis SD, Kissen P, et al. Early life environmental control - effect on symptoms, sensitization, and lung function at age 3 years. *Am J Respir Crit Care Med*. 2004;170:433–9.
90. Gomes C, Frelhaut J, Bahnfleth W. Resuspension of allergen-containing particles under mechanical and aerodynamic disturbances from human walking. *Atmos Environ*. 2007;41:5257–70.
91. Ferro AR, Kopperud RJ, Hildemann LM. Source strengths for indoor human activities that resuspend particulate matter. *Environ Sci Technol*. 2004;38:1759–64.
92. Murakami S. Analysis and design of micro-climate around the human body with respiration by CFD. *Indoor Air*. 2004;14:144–56.
93. • Tang JW, Noakes CJ, Nielsen PV, Eames I, Nicolle A, Li Y, et al. Observing and quantifying airflows in the infection control of aerosol- and airborne-transmitted diseases: an overview of approaches. *J Hosp Infect*. 2011;77:213–22. *Although the paper concerns virus transmission it provides fascinating insight into the dynamics of particle movement associated with the human body.*
94. Chen Q, Hildemann LM. The effects of human activities on exposure to particulate matter and bioaerosols in residential homes. *Environ Sci Technol*. 2009;43:4641–6.

95. • Qian J, Hospodsky D, Yamamoto N, Nazaroff W, Peccia J. Size-resolved emission rates of airborne bacteria and fungi in an occupied classroom. *Indoor Air*. 2012; epub Jan 18. *This paper, uses a range of sophisticated gene-based detection methods, to examine the timing and size distribution of different and clinically-relevant biological particles under real exposure conditions.*
96. • Delfino RJ, Staimer N, Tjoa T. Personal endotoxin exposure in a panel study of school children with asthma. *Environ Health*. 2011;10:69. *The second paper (first is 98) to examine the 'personal cloud' of exposure to endotoxin, which is much higher than measurements made away from the person and is associated with activity.*
97. Rabinovitch N, Liu AH, Zhang LN, Rodes CE, Foarde K, Dutton SJ, et al. Importance of the personal endotoxin cloud in school-age children with asthma. *J Allergy Clin Immunol*. 2005;116:1053–7.
98. Qian J, Ferro AR. Resuspension of dust particles in a chamber and associated environmental factors. *Aerosol Sci Technol*. 2008;42:566–78.
99. Tovey ER, Taylor DJ, Mitakakis TZ, De Lucca SD. Effectiveness of laundry washing agents and conditions in the removal of cat and dust mite allergen from bedding dust. *J Allergy Clin Immunol*. 2001;108:369–74.
100. McDonald LG, Tovey ER, Woolcock A. The role of water temperature and laundry procedures in reducing house dust mite populations and allergen content of bedding. *J Allergy Clin Immunol*. 1992;90:599–608.
101. Mites Asthma and Domestic Design 5. Re-aerosolization of dust and fungal spores from flooring. Available at: <http://www.madd5.org/wp-content/uploads/2011/08/16.Caroline-Shorter-web.pdf>. Accessed April 2012.
102. Price JA, Pollock I, Little SA, Longbottom JL, Warner JO. Measurement of airborne mite antigen in the homes of asthmatic children. *Lancet*. 1990;336:895–7.
103. Ferro AR, Kopperud RJ, Hildemann LM. Elevated personal exposure to particulate matter from human activities in a residence. *J Expo Anal Environ Epidemiol*. 2004;14:S34–40.
104. Shaughnessy R, Vu V. Particle loadings and resuspension related to floor coverings in chamber and in occupied school environments. *Atmospheric Environment*. 2012;55:515–524.
105. Tian Y, Sul K, Howard-Reed C, Leber D, Ferro A. comparative study of estimating particle resuspension rate using a consistent test mechanism. Presented at the 12th International Conference on Indoor Air Quality and Climate (Indoor Air 2011), June 5–10, Austin, TX. 2011.
106. Sublett JL. Effectiveness of air filters and air cleaners in allergic respiratory diseases: a review of the recent literature. *Curr Allergy Asthma Rep*. 2011;11:395–402.
107. • Portnoy J, Kennedy K, Sublett J. Environmental assessment and exposure control: a practice parameter-furry animals. *Ann Allergy Asthma Immunol*. 2012;108:223.e1–15. *This is a recent and very comprehensive overview of the nature, components and evidence for exposure and removal from furry animals (mainly cats).*
108. Karlsson AS, Andersson B, Renstrom A, Svedmyr J, Larsson K, Borres MP. Airborne cat allergen reduction in classrooms that use special school clothing or ban pet ownership. *J Allergy Clin Immunol*. 2004;113:1172–7.
109. Nurmagambetov TA, Barnett SBL, Jacob V, Chattopadhyay SK, Hopkins DP, Crocker DD, et al. Economic value of home-based, multi-trigger, multicomponent interventions with an environmental focus for reducing asthma morbidity a community guide systematic review. *Am J Prev Med*. 2011;41: S33–47.
110. Platts-Mills TAE, Mitchell EB, Nock P, Tovey ER, Moszoro H, Wilkins SR. Reduction of bronchial hyper-reactivity during prolonged allergen avoidance. *Lancet*. 1982;2:675–8.