



Bedroom Allergen Exposure Beyond House Dust Mites

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Abstract

Purpose of Review The review provides insight into recent findings on bedroom allergen exposures, primarily focusing on pet, pest, and fungal exposures.

Recent Findings Large-scale studies and improved exposure assessment technologies, including measurement of airborne allergens and of multiple allergens simultaneously, have extended our understanding of indoor allergen exposures and their impact on allergic disease. Practical, streamlined methods for exposure reduction have shown promise in some settings, and potential protective effects of early-life exposures have been further elucidated through the investigation of specific bacterial taxa. Advances in molecular allergology have yielded novel data on sensitization profiles and cross-reactivity.

Summary The role of indoor allergen exposures in allergic disease is complex and remains incompletely understood. Advancing our knowledge of various co-exposures, including the environmental and host microbiome, that interact with allergens in early life will be crucial for the development of efficacious interventions to reduce the substantial economic and social burden of allergic diseases including asthma.

Keywords Asthma · Pet allergen · Rodent allergen · Cockroach allergen · Fungal allergen · Environmental intervention

Introduction

Indoor allergen exposures are important risk factors for asthma and allergies [1]. Sensitization to indoor allergens has been strongly associated with allergic respiratory disease [2, 3]. Although the role of indoor allergen exposures in the development of allergic sensitization and disease is complex and not fully understood [1], elevated indoor allergen levels in the home, particularly in the bedroom, can trigger and exacerbate symptoms in allergic and asthmatic individuals [4–8].

Residential exposure to multiple allergens is common and in many homes, allergens are found at elevated levels [9, 10•]. A large national study in the United States (U.S.) demonstrated that more than 90% of bedrooms had three

or more detectable allergens and over two thirds (73%) had at least one allergen at elevated levels [10•]. Bedrooms are considered a central site of exposure, although allergens can be found throughout the home. Not only the time spent in bed but also the close proximity of allergen reservoirs (e.g., bedding) to a person's breathing zone contribute to the site's importance. Studies have shown that a significant fraction of airborne particles, which are resuspended by human movements in bed, can be inhaled during sleep [11, 12]. Several studies have linked bedroom allergen exposures to allergic sensitization and disease morbidity [13, 14].

In this article, we review recent findings on indoor allergens, focusing on pet, pest, and fungal allergens. We describe allergen-specific exposure characteristics and discuss the role of these exposures in relation to allergic respiratory disease. Remediation measures, environmental interventions, and new trends in exposure assessment techniques are also briefly discussed. We summarize key findings and identify future research needs. We have intentionally excluded dust mite allergens from this article—while they represent a common exposure in bedrooms [10•, 15], their role in allergic disease has been reviewed extensively in numerous recently published articles [16–20].

This article is part of the Topical Collection on *Allergens*

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Bedroom Allergen Exposures

Cat and Dog Allergens

Exposure to cat and dog allergens is ubiquitous. Cats and dogs are the most commonly owned pets; ownership varies around the world, averaging 33% for dogs and 23% cats [21]. Over half of U.S. households have cats or dogs as pets, and their ownership has been increasing over the past decades [22, 23•]. Dogs are more commonly owned (38–48%) than cats (28–38%), and in many homes, both types of pets are present (14%). Although exposure and sensitization to cat and dog allergens are important risk factors for allergic sensitization and disease [8, 24], pet ownership has not been found to be less prevalent among atopic individuals than in non-atopics [23•, 25].

Exposure to cat and dog allergens has been predominantly assessed by measuring levels of two major allergens, Fel d 1 and Can f 1, in dust or air samples. Fel d 1 is a member of the secretoglobulin family of proteins, and the major Fel d 1 IgE epitopes have been mapped [26–29]. In contrast, Can f 1 is a member of the lipocalin family of proteins [27–29]. More than 90% of cat-allergic individuals react to Fel d 1, whereas reactivity to Can f 1 has been found to be lower and more variable among dog-sensitive patients [24, 26, 27, 29]. Besides these two allergens, other clinically relevant allergens have been identified. Recent advances in molecular allergology of cat and dog allergens have been reviewed in several articles [24, 27–29].

“Hypoallergenic” cat and dog breeds, which have become popular over the past years, are thought to shed less allergens, particularly Fel d 1 and Can f 1, and be “allergen-friendly” [30]. However, supporting scientific data are scarce [30–33]. In fact, one study showed that “hypoallergenic” dogs had higher Can f 1 levels in hair and coat than “non-hypoallergenic” dog breeds [33]. Truly “hypoallergenic” breeds will be difficult to develop because secretion of cat and dog allergens is not limited to the two major allergens, Fel d 1 and Can f 1 [21, 27, 30].

Cat and dog allergens are shed into the environment by pet hair, dander, saliva, and urine [8, 21]. Allergens accumulate on interior materials, including carpeting, upholstery, and bedding, which serve as continuous reservoirs for these allergens. Both allergens become aerosolized easily and remain airborne for long periods of time due to the aerodynamic characteristics of cat and dog allergen-carrying particles [34, 35]. Highest reservoir allergen concentrations are found in places where the pet(s) mostly reside (e.g., pets’ dens, and living room upholstered furniture) [36, 37], but pet allergens spread throughout the home, including bedrooms, even if the pet’s access has been restricted [38]. Allergen levels have been shown to vary notably by race/ethnicity, socioeconomic status, geographic location, and housing characteristics [10•, 36,

39]. While the presence of the pet(s) is the strongest predictor of elevated pet allergen levels [10•, 36], allergen levels are also influenced by the number of pets and pet-keeping habits [37, 38, 40]. However, exposure to cat and dog allergens is not limited to direct contact with pets [41, 42]. Both allergens attach easily to clothing and hair [43, 44], and are passively transported into other environments, including petless homes, schools, daycares, workplaces, hospitals, and private as well as public transportation vehicles [21, 37]. Although allergen levels in these environments are usually much lower than in homes with pets, exposure levels in homes without cats and dogs can exceed thresholds associated with allergic sensitization and asthma morbidity [23•, 36]. Higher community prevalence of pets, especially cats, is thought to be an important determinant of pet allergen levels in homes of non-pet owners [39, 45]. Several studies, on the other hand, have shown that pet allergen levels, airborne and in dust, can be higher in schools and daycares than in bedrooms [37, 46–48], highlighting the relevance of pet allergen exposures outside the home [49].

Exposure to cat and dog allergens can induce sensitization, i.e., development of allergen-specific IgE, in susceptible individuals. Upon continued exposure, sensitization may lead to the development and exacerbations of allergic disease, such as asthma and rhinoconjunctivitis [8, 23•, 24, 50].

Prevalence of sensitization to cat and dog allergens varies greatly worldwide, showing higher rates in urbanized and westernized regions [27]. In the general U.S. population, approximately 12% are sensitized to cats and dogs, while the sensitization rates (19–65%) and pet-specific IgE levels are notably higher among those with atopic disorders [51, 52, 53•]. Sensitization also differs by sociodemographic factors, including age, gender, race/ethnicity, and socioeconomic status [51]. Novel data on sensitization patterns have emerged from recent studies that have used component-resolved diagnostics to increase knowledge on sensitization profiles and cross-reactivity [28, 49, 54, 55]. Numerous studies have demonstrated that sensitization, especially high pet-specific IgE levels and co-sensitization, is strongly associated with the prevalence, severity, and persistence of asthma [5, 26, 49, 54, 56–58]. Among pet-sensitive individuals, increased exposure levels can have considerable public health effects. In the U.S., a nationally representative study estimated that among pet-sensitive asthmatics, more than 1,700,000 excess asthma attacks and over 700,000 excess emergency visits for asthma annually were associated with exposure to elevated levels of pet allergens in the bedroom [23•].

Increased exposure does not necessarily lead to increased sensitization and disease [59, 60]. Findings from several longitudinal studies suggest that prenatal and early-life exposures to cat(s) and dog(s) are not associated with increased risk of atopic disorders and may provide protection against allergic sensitization and disease [45, 61–64]. Studies have proposed

various hypotheses to explain the observed protective effects, but the underlying mechanisms are not yet fully understood [24, 59, 65, 66]. While high doses of inhaled pet allergens, especially Fel d 1, are thought to induce specific IgG4 production, helping to block IgE responses, inconsistent findings have been reported [66, 67]. Increasing numbers of studies have also shown that exposure to pets is not limited to allergens. Cats and dogs can alter the abundance, richness, and/or diversity of host and home microbiome, which in turn may influence the development of a child's immune system and responses to allergens, supporting the "hygiene hypothesis" [66, 68–74]. While interactions between bacterial endotoxin and pet allergens have been most extensively studied [30, 75], research interests have expanded into more diverse microbial taxa [68–72, 73•]. Induction of sensitization and subsequent allergic disease are also thought to be influenced by genetic and/or epigenetic mechanisms [76, 77]. It has been proposed that pet exposure may confer an increased or decreased risk, or show no effect, depending on the study design and population, the extent of non-residential exposures, and the timing and assessment of exposures and outcomes [55, 60].

Rodent Allergens

Rodents represent another important source of bedroom allergen exposures, particularly those associated with mice and rats. A nationally representative study found *Mus m 1*, the major mouse allergen, to be present in the bedrooms of over 80% of U.S. homes, exceeded only by cat and dog allergens [10•]. The same study found a prevalence of more than 30% for the major rat allergen, *Rat n 1*. Many studies have identified *Mus m 1* in particular as a critical exposure in inner-city bedrooms and other home environments [14, 53•, 78], and its presence in rural and suburban homes has been established as well [79, 80].

Mus m 1 has been isolated from mouse urine and is sometimes described as mouse urinary protein, although it has also been found on mouse hair follicles. Biochemically, both *Mus m 1* and *Rat n 1* are classified as lipocalins, and adhere to small and large particles that remain airborne, readily enabling transport of the allergen and migration throughout buildings [6, 29]. In particular, it has been shown that rat allergens can remain airborne for 60 min or longer after disturbance of the environment [81].

Various studies have identified predictors for detectable or elevated bedroom or household *Mus m 1* in settled dust samples. These include demographic factors such as living in high-rise apartments or mobile homes, other multi-family homes, rentals, older constructions, presence of children, and low-income households, and after adjusting for those factors, with household characteristics such as reportedly observed rodent or cockroach activity, absence of a cat, and absence of an impermeable mattress cover [10•, 82–88]. The subset

of those studies that also investigated *Rat n 1* found generally similar predictors.

While the issue of airborne transport was originally studied in animal testing laboratories and other industrial environments, substantial prevalence of airborne *Mus m 1* has been found in inner-city homes, at levels sufficiently high to be associated with respiratory symptoms among sensitized individuals [89]. In addition, detectable levels of airborne *Mus m 1* were associated with predictors such as having cracks or holes in walls or doors, evidence of mouse infestation, and exposed food in the kitchen. Studies have demonstrated an association between exposure to household rodent allergens and development of allergic sensitization specific to those allergens [90], and some have estimated the prevalence of sensitization to mouse as high as 26 to 52% among urban, low-income populations of children [53•, 78, 89]. Much lower prevalence has been observed in the U.S. as a whole and in some European cohorts [51, 91].

Mouse allergen sensitization coupled with exposure has been demonstrated through numerous studies to be associated with an increased risk of asthma morbidity, particularly (although not exclusively) among low-income, urban children [5, 14, 53•, 78, 80, 89, 92]. While cockroach allergen exposure represents another important risk factor among these populations, mouse allergen may have greater clinical importance, at least in certain urban populations [53•]. Additionally, similar to the discussion above in regard to pet allergens, recent research has helped to elucidate inner-city schools as another critical site for exposure to mouse allergens among children, and such school-based exposure has been associated with both clinical and nonclinical measures of asthma severity [93].

Given the complex relationship between exposure, sensitization, and disease, it is perhaps not surprising that a number of studies have demonstrated a direct association between mouse allergen sensitization and disease, without directly measuring or considering exposure [94, 95], as well as between exposure and disease, without directly measuring sensitization [96].

In addition to its persistent relationship with asthma morbidity, sensitization to mouse allergen has also been found to be independently associated with other adverse outcomes, such as rhinitis among urban children with asthma [97]. However, inverse associations between mouse exposure and rhinitis have also been found [98]. While mouse allergen has been the focus of many of these studies, it should be noted that rat exposure and sensitization has also been associated with increased asthma morbidity in inner-city children, exhibiting similar relationships to those observed for mouse [99].

Similarly to cats and dogs, recent research has also examined the potential for protective effects of rodents on allergy and asthma development, particularly early in life. A meta-analysis of longitudinal studies found a reduced risk of allergic sensitization to aeroallergens in general associated with rodent

ownership during the first 2 years of life [100]. In contrast, longitudinal studies investigating rodent ownership not limited to early life found associations with non-atopic asthma, wheezing, and sensitization to rodents [61, 62]. In inner-city environments, examination of early-life periods through multiple age windows showed that cumulative exposure to mouse allergen over first 3 years was associated with wheeze; however, first-year exposure to mouse allergen exhibited an inverse relationship with wheeze, as well as an additive reduction with co-exposure to cockroach and cat, regardless of sensitization status [101]. Furthermore, a reduced risk of asthma at age 7 was associated with cumulative exposure to mouse allergen, as well as cockroach and cat allergen, through age 3 years [102•]. These studies also investigated bacterial taxa related to these favorable clinical outcomes, and found them to be positively associated with mouse and cockroach allergen levels—thereby demonstrating that some of these bacteria-asthma risk associations may serve to mediate the inverse allergen exposure-asthma risk relationships, and raising the possibility that that household pests might be the source of some of the beneficial bacteria in the inner-city environment.

Cockroach Allergens

Cockroach allergen exposure, a long-recognized risk factor in respiratory health [103], has generally been demonstrated to be greatest in the kitchen within home environments [104, 105]; however, numerous studies have also investigated the bedroom as another important source of cockroach allergen exposure [106].

Of the more than 4000 known species of cockroaches, only about 25 have adapted to human habitats, and of these, two species—German (*Blattella germanica*) and American (*Periplaneta americana*) cockroaches—predominate in temperate and tropical areas, respectively, and have been identified as key sources of allergen exposure and studied extensively [53•, 107–109]. The primary allergens associated with these species, Bla g 1, Bla g 2, and Per a 1, are found in saliva, secretions, cast skins, egg casings, and fecal material. The molecular structures of Bla g 1 and Per a 1 consist of tandem repeats of approximately 100 amino acids, whereas Bla g 2 is a globular protein belonging to the family of aspartic proteases [28, 110, 111]. Bla g 1 and Bla g 2 in particular, once thought to be carried mainly on larger particles of greater than 10 µm [53•, 107–109] and thus primarily found in settled dust, have more recently been studied in air sampling with the conclusion that they also exist on smaller particles and are often airborne, so that kitchen and bedroom exposures are actually highly correlated [112]—a particularly important finding from an exposure assessment perspective [106].

Cockroach allergen exposures have been associated extensively with low-income, urban homes in a variety of regional settings [113–115]. While the allergen is pervasive—with

detectable levels found in 63% of US homes in one study of national scope that considered multiple sampling locations in the home and was not limited to urban areas [105]—levels are generally higher in high-rise apartments, older constructions, and homes that are rented rather than owned by the inhabitants. Higher levels of the allergen have also been associated with observed cockroach activity, food debris, and moisture, as well as presence of a smoker in the home [10•, 105]. In addition, while cockroach allergen exposure is generally higher in warmer, moister climates such as the southeast U.S. [10•], and the American cockroach in particular is known to prefer warmer, humid climates such as those in South America and Southeast Asia [109, 116], the German cockroach adapts well to cooler, drier climates, and its allergen has been well established even in cold weather areas of the U.S. and Europe, particularly in urban settings and among lower income households [117]. In particular, cockroach allergen may dominate over dust mites in inner-city apartments of the northern U.S., where buildings are heated but very dry so that cockroaches can thrive but mites do not [28].

Numerous studies throughout the 1990s and early 2000s consistently established an association between exposure to cockroach allergen in the home and allergic sensitization and asthma morbidity, particularly in children [53•, 86, 108, 114]. These and more recent studies have further identified cockroach allergens as one of the strongest risk factors for allergic sensitization and asthma morbidity in low-income, urban populations [86, 118–122]. Although some investigations have suggested that mouse allergen may be more clinically important in these populations [53•, 123], co-exposure to both allergens is common, and more than 50% of urban children with asthma are sensitized to one or the other [119]. Studies have also demonstrated that even prenatal exposure to cockroach allergen is associated with a greater risk of allergic sensitization in the young child [124].

Apart from the question of its relationship with mouse allergen, for inner-city children and young adults with asthma, the combination of exposure and sensitization to cockroach allergen likely impacts asthma morbidity and severity to a greater degree than most other highly prevalent allergens such as dust mites and pets [114]. However, the exposure-sensitization-disease risk is not limited to these young, inner-city populations. For example, an association between exposure and increased asthma severity has also been observed among cockroach allergic adult patients with asthma [125, 126]. In addition, associations between cockroach exposure and asthma have been found in non-urban areas where cockroach infestation may occur, including rural and suburban communities [127]. Furthermore, there is recent evidence to suggest that exposure to cockroach may increase the risk of asthma exacerbations even in non-sensitized children [5]. Conversely, sensitization to cockroach alone—independent of

exposure—may be predictive of asthma severity among young children [128].

The overall prevalence of allergic sensitization to German cockroach has been estimated to range from 4.3 to 26% in nationally representative studies of the U.S. including both children and adults [51, 129], but higher rates have been reported among those with atopic disease [125]. Thus, the health risks associated with cockroach allergen exposure can be regarded as somewhat universal—yet are clearly greatest in low-income, inner-city environments, where 60–80% of children with asthma have been found to be sensitized to cockroach [13, 86].

Early-life exposure to cockroach allergen has been found to exhibit similar protective characteristics to those discussed above for mouse, including inverse relationships between first-year exposure and recurrent wheeze, and between 3-year exposure and asthma risk at age 7—possibly owing in part to early-life exposure to beneficial bacteria [101]. Indeed, investigators conducted a mediation analysis that isolated two bacterial taxa in particular that appeared to explain part of the inverse association between higher cockroach allergen concentration and lower asthma risk [102••].

Fungal Allergens

Fungi are sources of numerous allergenic and biologically active molecules, including enzymes, cell wall components, and secondary metabolites such as toxins and volatile organic compounds [130, 131]. Allergens are dispersed by airborne spores and fungal fragments, which can be highly variable in size. However, most spores from allergenic genera are smaller than 10 µm and fragments are even smaller in size, allowing them to penetrate deeply into the airways [132, 133].

One of the major limitations in assessing exposure to fungal allergens has been the difficulty to quantify the exposure. Various indirect measures, including spore counts, have been used for the assessment; however, spore counts may not reflect allergen content accurately as allergen content in spores may vary and allergens are also present in fungal components other than intact spores, including hyphal fragments [134]. New assessment techniques, including DNA-based characterization methods, have been developed, but their use remains limited [135, 136••, 137].

Fungal exposures are encountered in both indoor and outdoor environments. Exposures show great variation by geographic and climatic region, while residential fungal exposures often reflect outdoor taxa, albeit at lower levels [138–140]. Despite the strong effects of outdoor characteristics (e.g., vegetation, urbanization), fungal exposure profiles in the home are also affected by housing characteristics and occupants' behavior [139, 141–143]. Residential exposure is common as fungal spores and fragments can enter the indoor environment multiple ways, including through open windows and doors, and on clothing and pets [53•, 141]. In a nationally

representative survey, fungal antigens were detected in almost all homes, including over 93% of the bedrooms [9]. Since excess moisture promotes fungal growth, lack of air conditioning or improperly maintained HVAC systems can support residential fungal growth [144, 145]. Elevated fungal levels have also been associated with older age of the home, the presence of mold and moisture problems, and the use of a dehumidifier [141, 146]. In homes with excess moisture and water damage, not only are the exposure levels higher but also differing patterns in fungal taxa, especially in *Aspergillus* and *Penicillium* species, have been detected [140, 142, 144].

Residential mold and moisture problems are common worldwide, with prevalence estimates ranging from 14 to 50%, or even higher [147–149]. Dampness and mold in buildings have been associated with increased risk of respiratory and asthma symptoms (30–50%), as well as respiratory infections and bronchitis (8–20%) [148, 150]. While the health effects of fungal exposures, especially due to residential exposures, remain widely debated and a topic of controversy [151], a recent study has estimated that in the U.S. annual costs attributable to dampness and mold range from \$1.9 billion to \$15.1 billion for various respiratory health outcomes, costs being highest for asthma [152].

Despite the well-recognized role of fungi in allergic respiratory disease, progress in the field of molecular allergology has been much slower for fungal allergens compared to other inhalant allergens [130]. The selection of commercially available fungal allergens remains limited, and fungal extracts are non-standardized [149, 153]. However, advances have been made in identifying species-specific and cross-reactive allergen components from different fungal sources, and in understanding immune responses to fungal antigens [4, 149, 154–158].

Sensitization to fungi has been associated with a number of hypersensitivity diseases, including allergic rhinitis, asthma, allergic bronchopulmonary mycoses, allergic fungal sinusitis, and hypersensitivity pneumonitis [153, 159]. In population-based studies, fungal sensitization rates have often been reported to be less than 10%, but the prevalence of sensitization has showed significant variation by fungal species and subject age, gender, and race/ethnicity, as well as regional factors (e.g., level of urbanization) [51, 130]. Similarly to other allergens, fungal sensitization rates are much higher among those with atopic disease [130]. For example, in a U.S. study, 76% of asthmatics were sensitized to fungal allergens [160]. Fungal sensitization often reflects phylogenetic relationships, suggesting extensive cross-reactivity among fungal allergens [131]. Thus, it is not surprising that the highest sensitization rates have been found among those who are polysensitized to fungi, as extensive cross-reactivity among fungal allergens exists [4, 130, 161]. A recent study has also reported that specific IgE levels to non-fungal allergens can be higher in asthmatics sensitized to fungi compared to asthmatics without fungal sensitization [162].

Asthma, especially persistence and severity, has often been linked with sensitization to outdoor fungal species, such as *Alternaria* and *Cladosporium* [159], but an increasing body of literature supports the link between indoor fungal exposures and asthma [142, 158, 163, 164•, 165]. In numerous studies, residential fungal exposures have been associated with asthma exacerbations and severity [142, 158, 163, 164•, 166, 167]. Although most of the asthma-related studies have been case-control studies or cross-sectional in nature, supporting data has also emerged from birth cohort studies [142, 158, 164•, 168–170]. In a recent study, asthma severity in atopic children was associated with fungal community composition, whereas in non-atopic children, asthma severity was related to levels of total fungi, suggesting that effects of fungal exposures may differ by asthma subtypes [167]. However, protective effects of early-life fungal exposures have also been reported. In a longitudinal birth cohort study, elevated levels of dustborne yeasts in the child's bedroom were associated with lower odds of early-onset and persistent wheeze, as well as asthma development and fungal sensitization by early adolescence [135].

Consistent associations between different forms of rhinitis and commonly used mold indicators, visible mold and mold odor, have been reported [171]. Similar findings have also been found in longitudinal studies [135, 170]. Results from systematic reviews and meta-analyses have been summarized in a recently published review article [164•].

Yet, linking residential fungal exposures to specific health outcomes is challenging, not only because of the lack of standardized, quantitative methods of measuring fungal allergens but also due to various concomitant co-exposures that are often associated with moldy and damp indoor environments (e.g., dust mites and cockroaches as well as other biologically active fungal and microbial components) [145, 172]. Another layer of complexity comes with spatial and temporal variation (e.g., seasonal variation) that is characteristic for fungal exposures [173]. Furthermore, it remains largely unknown whether genetic susceptibility plays a role in the development and exacerbations of associated outcomes [135, 174]. New, emerging exposure assessment technologies may help in facilitating a better understanding of various fungal and microbial components, including fungal allergens, that can influence human health [136, 175, 176].

Multiple Allergen Exposures

Household allergens are often studied individually, but residential exposure to multiple allergens is common [9, 10•, 38]. In many homes, several allergens can be found at elevated levels, while the levels may vary by room and location [9, 10•]. Although individual allergen levels are strongly influenced by sociodemographic and regional factors, residential allergen burden has shown less variation by socioeconomic

status and climatic conditions. High exposure burden to bedroom allergens has been most consistently found in homes with pets and pests, mobile homes and/or trailers, older and rental homes, and in nonmetropolitan areas [10•]. Reported differences and overlaps between exposure and sensitization patterns in the U.S. population highlight the complex nature of the relationships between allergen exposures, allergic sensitization, and disease [10•]. Indeed, while a recent study reported inverse associations between the presence of multiple allergens and asthma and eczema [177], another nationally representative survey has linked high residential allergen burden with increased asthma symptoms among allergic asthmatics [9].

To date, most indoor allergen studies have focused on a limited set of major allergens from cats, dogs, dust mites, cockroaches, mice, rats, and molds. New data, however, are emerging on additional allergens, including pollen and food, which have been found in bedrooms and other living spaces [38, 178, 179]. Although little data exist on less commonly owned pets such as rodents, recently published articles have discussed their role in allergic sensitization and disease [24, 61, 62, 180].

Remediation and Environmental Interventions

Pet removal remains the only effective way to reduce pet allergen levels in the home [8, 53•]. Because many people tend to be reluctant to give up their pets, numerous studies have investigated interventional measures to reduce pet allergen exposures. Single measures have generally been shown to be inefficient, but reductions in allergen concentrations have been reported when combinations of several control measures have been used. A recent practice parameter has evaluated various environmental control measures (e.g., regular use of high-efficiency particulate air (HEPA) vacuum cleaners and air purifiers, increased ventilation, pet washing, and limiting the pet's access to the bedroom) in detail. Achieved reductions in exposures, however, are often transient, and it remains unclear to what extent these strategies provide clinical benefits for pet-sensitive patients [8, 181].

With regard to interventions to lower risk of asthma morbidity associated with rodent allergen exposures, generally recommended steps include the setting of traps, sealing of holes and cracks in walls, and thorough cleaning designed to reduce access to food remains. When study participants receive education on these and other measures, exposure has been demonstrably reduced [6, 92, 182]. In addition, nonclinical measures such as missed school days and reduced sleep disruption are suggestive of a beneficial impact on asthma morbidity, although this has not been substantiated through clinical measures. Beyond these steps, any benefit to asthma morbidity associated with more intensive interventions, such as a professionally

delivered, integrated pest management program delivered in combination with this education, has not been proven [183].

Risks posed by cockroaches can be mitigated to some extent. As first demonstrated by the Inner-City Asthma Studies (ICAS), environmental interventions designed to reduce cockroach infestation and exposure—through a combination of professional cleaning, food removal, bait traps, insecticides, and HEPA filters—can be effective in also reducing asthma symptoms [184]. Other studies have subsequently shown 80–90% reductions in cockroach allergen levels through integrated pest management (IPM) techniques [7, 184–189], and some recent studies have even suggested that comparable reductions can be achieved through the strategic placement of bait traps alone, with associated improvements in asthma morbidity [190, 191].

Numerous guidelines and recommendations on residential mold remediation have been published over the past decades [147, 188, 192–194]. To prevent mold problems from occurring (or reoccurring) in the home, it is crucial to eliminate the source(s) of excess moisture (e.g., water damage, leaks, faulty designs and materials, and/or behaviors promoting increased humidity). Besides removing the underlying cause(s) that promote fungal growth, it is also important to clean contaminated surfaces and discard materials that cannot be completely cleaned. Regardless of whether the remediation is conducted by the occupant or professionals, the use of protective clothing (e.g., disposable coveralls, gloves, goggles) and respirators (e.g., N-95 mask) is often recommended to limit inhalation and skin and/or eye contact with molds. However, the level of protection depends on the extent of contamination, planned activities, and person's health status. Large and complex problems, including severe water damage caused by floods and storms, are often costly and require professional help. Despite the increasing evidence that remediation of residential mold and dampness problems can reduce adverse respiratory health outcomes, inconsistent findings have been reported regarding the development of allergic diseases such as asthma, especially among children [188, 192, 195].

Several outstanding articles have reviewed the most recently published interventional and remediation studies, providing new insights into the effectiveness of interventions, as well as identifying gaps in knowledge and further research needs [53•, 136, 181, 196, 197]. Interestingly, some studies suggest that interventions that target only a single allergen, or even a single location, for example the bedroom, can be efficacious [183, 190, 198]. Although studies have reported mixed findings [53•, 123, 181, 197], they highlight the need to revisit the widely debated issue of the efficacy of single- versus multifaceted interventions and to improve behavioral compliance in a sustainable way. Given the clinical and economic burden of allergic diseases

[199, 200], such as asthma, cost-effective interventions could have significant public health impacts.

Table 1 Summary of key findings

Pets:

- Exposure to pet allergens is ubiquitous but not limited to home exposures. The presence of the pet(s) in the home is not a good proxy for exposure.
- Pet exposures can have considerable public health effects among pet-sensitive individuals.
- Longitudinal studies suggest that prenatal and early-life exposures to cat and dogs may provide protection, or at least do not increase the risk of atopic disease.
- The underlying mechanisms of pet exposures are not completely understood, but several mechanisms have been proposed.
- New diagnostic methods have increased knowledge on sensitization profiles and improved understanding on cross-reactivity and clinical relevance of identified pet allergens.
- Longitudinal data on pet exposures among adults are scarce.
- Improved exposure assessment schemes are needed because studies have shown the importance of non-residential exposures.

Rodents:

- Mus m 1 is estimated to be present in the bedrooms of over 80% of U.S. homes.
- Especially critical exposure in inner-city homes, but also is present in rural and suburban homes.
- Substantial prevalence of airborne Mus m 1 has been found in inner-city homes, at levels sufficiently high to be associated with respiratory symptoms among sensitized individuals.
- Exposure to household rodent allergens is associated with development of allergic sensitization.
- Mouse allergen sensitization coupled with exposure is associated with an increased risk of asthma morbidity.
- Studies have identified the potential for protective effects of rodent exposures, particularly early in life.

Cockroaches:

- Cockroach allergen levels are generally greatest in the kitchen but the bedroom is another important source of this exposure.
- Cockroach allergen exposures are especially prevalent in low-income, urban homes, but are not limited to those areas.
- Cockroach allergen may dominate over dust mites in heated, but dry, inner-city apartments of the northern U.S.
- Household allergen exposure is associated with allergic sensitization and asthma morbidity, and the combination of exposure and sensitization to cockroach allergen likely impacts asthma morbidity and severity to a greater degree than most other highly prevalent allergens such as dust mites and pets.
- Early-life exposure to cockroach allergen may have protective effects against recurrent wheeze and asthma, potentially promoting presence of beneficial microbial taxa.

Fungi:

- Fungal sensitization reflects phylogenetic relationships, suggesting extensive cross-reactivity among fungal allergens.
- Increasing evidence suggests that fungal exposure, alone or combined with dampness, may promote the development and morbidity of asthma in children, although protective effects in early life have been reported.
- Residential exposure to mold and dampness may have significant economic impacts, especially among those with allergic rhinitis and asthma.
- Improved fungal exposure assessment methods are needed to enable more detailed characterization of fungal profiles.

Table 2 Future research directions**Allergology/immunology:**

- Studies to identify and investigate potential associations between specific inhalant allergen molecules and different clinical outcomes, including investigations of specific biochemical characteristics.
- Improved determination of subjects' sensitization, especially sensitization to fungal allergens.
- Mechanistic studies of natural adjuvants, microbial substances, and inhaled irritants, and how they work individually or together to impact immune and airway responses involved in allergy and asthma.
- Improved understanding of any predictive value for disease progression associated with IgE sensitization profiles.

Early-life exposure:

- Research to better define and understand interactive associations between early-life allergen and microbial exposures, especially those that account for observed protective effects. This would enable formulation of evidence-based interventions that appropriately balance the competing issues of microbial exposure enhancement and allergen abatement.
- Observational research of early-life environmental influences on asthma and allergy development, including patterns of the microbiome.

Interventions:

- Research that enhances our understanding of the sustainability of both the exposure and clinical effects of the interventions.
- Rigorously designed studies such as prospective intervention trials or nested case-control designs to confirm associations and investigate the causality and effectiveness of real-world environmental interventions, and sufficiently powered to detect clinically meaningful differences in measures of asthma morbidity and severity.
- Trials conducted at the community and population level in order to address pragmatic considerations and inform translation into practice, for example through single interventions.
- Trials to investigate building-level interventions such as free-standing air filtration systems, or modern construction approaches, with respect to their ability to reduce indoor allergens and other exposures.
- Investigation of methods that enhance compliance with indoor environmental interventions.
- Development of effective mold prevention and remediation strategies appropriate to differing geographic and climactic factors.

Exposure assessment:

- Technological improvements such as personal monitoring devices for allergen, pollutant, and microbial exposures to improve understanding on critical exposure sites, time windows, and thresholds.
- Development of methods for the collection and processing of environmental microbiome samples in air and dust.
- Further work to streamline and standardize exposure assessment methods for allergens and dampness-related microbial agents.
- Further development of methods for measuring multiple combined environmental agents, including indoor allergens, microbes, and other air pollutants.

Assessment of Allergen Exposures

In large epidemiological studies, residential allergen exposures have been traditionally assessed using allergen concentrations in household dust as surrogates of exposures [10•]. Concentrations in reservoir dust samples have been thought

to be less influenced by temporal and spatial variability, more reproducible, and represent long-term exposure better than short-term air sampling [10•, 201]. However, the relevance of reservoir dust sampling in estimating personal exposures has been recently challenged. While for many allergens, especially dust mites, bedrooms have been considered the central site of exposure, some studies have questioned the site's importance, suggesting that currently used methods might be over-simplifying and/or misleading [202•, 203]. Because inhalation of allergens is the most relevant exposure route, allergen exposure assessment should ideally be based on measurements of airborne allergen concentrations [201]. Although measuring personal exposure to airborne allergens in a longitudinal fashion is challenging for many technical and logistical reasons [201, 202•], progress has been reported, and recent studies have introduced new sampling equipment and approaches [38, 179, 202•, 203–206].

In most studies, allergen levels have been measured with enzyme-linked immunosorbent assay (ELISA), but increasing numbers of studies have switched to newer multiplex technology (MARIA) that enables simultaneous measurement of several allergens, currently up to 13 allergens, with increased sensitivity and reproducibility [207]. Several other newer technologies have emerged in the recent years and have been reviewed in detail elsewhere [136••].

Novel, more standardized exposure assessment methods would help in further characterizing allergen-specific thresholds and in examining dose-response relationships between allergen exposures, sensitization, and disease. Although clinically relevant thresholds have been proposed for some of the allergens, they all are based on allergen levels in reservoir dust and do not take host susceptibility or other environmental factors into account (e.g., age, gender, race, family history of atopy, or other modifying factors and/or exposures). Furthermore, inconsistent findings have been reported, especially for allergens that are easily transported from one environment to another. For example, results from a large European population-based study did not support the proposed morbidity thresholds for cat allergen levels [208].

Objective information on allergen exposures is not only needed for research purposes but can also be informative for clinicians and patients. A recent study, which used a patient-operated air sampling device to measure airborne bedroom allergen levels, demonstrated that each home had a unique allergen profile [38]. In addition to potential improvements in disease management, monitoring of indoor allergen levels might help in encouraging behavioral changes. In a randomized controlled pilot study, parental use of an in-home test kit, which assessed dust mite allergen levels on bed and floor surfaces, led to reductions in dust mite allergen levels in homes of dust mite allergic children [209].

Summary and Future Research Needs

In recent years, much progress has been made in advancing our understanding of the public health risk associated with bedroom and other household allergen exposures. Important advancements include further establishing and characterizing the widespread prevalence of these exposures across various regions and types of communities, disentangling the complex relationships between exposure, sensitization, and disease, and improving our understanding of potential environmental interventions to mitigate risk. Key findings for pet, pest, and fungal allergen exposures are summarized in Table 1:

Future research priorities span the areas of allergology and immunology, early-life exposures, exposure-reduction interventions, and exposure assessment [5, 28, 53, 101, 136, 181, 196, 197], as delineated in Table 2.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

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