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Exposure and Health Effects of Fungi on Humans

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Abstract

Fungi are ubiquitous microorganisms that are present in outdoor and indoor environments. Previous research has found relationships between environmental fungal exposures and human health effects. We reviewed recent articles focused on fungal exposure and dampness as risk factors for respiratory disease development, symptoms and hypersensitivity. In particular, we reviewed the evidence suggesting that early exposure to dampness or fungi is associated with development of asthma and increased asthma morbidity. While outdoor exposure to high concentrations of spores can cause health effects such as asthma attacks in association with thunderstorms, most people appear to be relatively unaffected unless they are sensitized to specific genera. Indoor exposure and dampness, on the other hand, appears to be associated with increased risk of developing asthma in young children and asthma morbidity in individuals who have asthma. These are important issues because they provide a rationale for interventions that might be considered for homes and buildings in which there is increased fungal exposure. In addition to rhinitis and asthma, fungus exposure is associated with a number of other illnesses including

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allergic bronchopulmonary mycoses, allergic fungal sinusitis and hypersensitivity pneumonitis. Additional research is necessary to establish causality and evaluate interventions for fungal and dampness-related health effects.

Keywords

Fungus; mold; health effects; asthma; hypersensitivity

Introduction

Fungi are ubiquitous microorganisms that can be found in all parts of the world. When airborne, fungi take the form of spores, mycelia and hyphael fragments. Such bioparticulates, when inhaled, are believed to contribute to adverse health effects in individuals who are predisposed to experience disease. Such individuals include those who produce specific IgE to fungal antigens, others with respiratory conditions that are susceptible to irritant effects of exposure, and immunocompromised patients who are susceptible to infections.

Common outdoor fungi include *Alternaria, Cladosporium, Epicoccum*, as well as ascospores and basidiospores. Though, these fungi are often found indoors as they enter through open doors and windows and can be carried indoors. Fungi more classically associated with indoor water damage or decay include Penicillium, Aspergillus, Stachybotrys, and Chaetomium. A review of these diverse fungi can be found in the accompanying article Taxonomy of allergenic fungi by Levetin et al.

In all epidemiologic studies, exposure to mold and dampness are considered together. Dampness is a generic term that is used to communicate a range of moisture conditions. While most people can recognize an environment that is damp, there is no consensus description or measurement that defines the term. In this article, dampness is defined as sufficient moisture on or in a substrate to support microbial growth. Dampness has often been associated with a combination of the following factors occurring simultaneously: visible water damage or stains, visible mold and odors from microbial growth.[1] However, dampness also supports dust mites and sometimes the growth of actinomycetes which can be associated with other health problems. Thus, it can be challenging to isolate the health effects of fungal exposure in damp environments.[2]

Another limitation of studies designed to identify health risks of fungal exposure is that total fungal exposure is difficult to measure. There is no gold standard method to identify and quantify fungus. Methods vary from direct microscopy or culture based volumetric air sampling to measurement of fungal metabolites such as beta-D-glucan or ergosterol. Fungal diversity can also be evaluated by immunoassays, polymerase chain reaction and genomic sequencing.[3] Further, many fungal allergens are broadly cross-reactive [45]. In sensitized individuals, exposure to related species can cause symptoms due to shared epitopes.

In this review, we will address the evidence linking dampness and fungal exposure and adverse health effects. In particular, we will review evidence suggesting that early exposure

to dampness or fungi is associated with development of asthma and that exposure to dampness or fungi in asthmatics increases morbidity. These are important issues because they provide a rationale for interventions that might be considered for homes and buildings in which there is an increase in occupant fungal exposure. In addition to rhinitis and asthma, exposure to fungi is associated with a number of other illnesses including allergic bronchopulmonary mycoses, allergic fungal sinusitis and hypersensitivity pneumonitis.

Outdoor fungal exposure

Starting in the 1930s, quantitative measurements of outdoor pollen and spore concentrations have been conducted in the United States [6]. Quantitation is performed using visual or culture-based air sampling methods which enumerate the bioaerosol composition of the atmosphere. Volumetric air sampling of fungal spores involves impaction, impingement, or filtration utilizing a variety of instruments. Newer techniques include immunoassays, molecular methods such as polymerase chain reaction and genomic sequencing are becoming more widely used. [3]

Mean spore concentrations outdoors usually range from 50 spores/M^3 during cold, snowy weather to 50,000 or more spores/M^3 of air during warm moist seasons. [78] Since spores can be transported long distances in dust clouds arising in warmer areas [9], they can be detected in even the most remote regions of the globe [10]. Temperature and dew point appear to be important factors that determine the types of spores found in outdoor air.[11] For example, ascospores typically are associated with precipitation while *Alternaria* and *Cladosporium* are associated with dry conditions.

In temperate regions, spores in outdoor air tend to peak in the mid to late-summer and decrease with the first hard frost in regions that experience cold winter seasons. Xerophilic spores (eg: *Alternaria*, *Cladosporium*, and *Epicoccum*) tend to peak in the afternoon during periods of low humidity, while hydrophilic spores tend to peak during pre-dawn hours when there is high humidity. These include ascospores and basidiospores (mushrooms, puffballs). *Alternaria* is the most prevalent fungus in dry, warm climates.[121314]

Cladosporium is the most commonly identified outdoor fungus.[15] It is found on dead plants or vegetable matter. *Aspergillus* is often isolated from house dust. It is also found in compost heaps and dead vegetation.[16] *Penicillium* is found in soil, food and grains, and house dust. It grows in water damaged buildings, wallpaper, and decaying fabrics, often giving a green “mildew” color.

Indoor fungal exposure

Indoor fungal taxa are likely to vary depending on building construction and climate. The most common taxa are a combination of fungi classically associated with dampness as well as outdoor fungi that enter through openings in the building such as doors and windows.

In a study of 23 buildings, water leakage through roofs, dampness, and defective plumbing were the main reasons for damage leading to fungal contamination. [17] In a study of damp buildings the genera most frequently encountered indoors included *Penicillium* (68%),

Aspergillus (56%), *Chaetomium* (an ascospore.) (22%), *Ulocladium* (which is related to *Alternaria*) (21%), *Stachybotrys* (19%) and *Cladosporium* (15%).[17] One study of 21 offices in four office buildings showed that concentrations of dustborne fungi positively related to carbon dioxide and were highest at temperatures between 20 and 22.5 °C. In addition, fungal concentrations were highest in September and lowest in March. [18]

In a survey of 190 homes in Paris, the most common indoor isolates were *Cladosporium* and *Penicillium* species. *Aspergillus* was recovered in 60% of homes and *Alternaria* in less than 20%. The best predictors for indoor fungal concentrations were their outdoor concentrations when windows were open and the overall dampness in the house when windows were closed.[19] In recent studies exploring the fungal species spectrum in 173 homes in the Midwest region of the United States, Cladosporium, Penicillium, Aspergillus, Basidiospores, Epicoccum and *Pithomyces* were more frequently present and in higher concentrations in homes with a child who has asthma than in homes without an asthmatic child even after adjusting outdoor spore concentration.[20]

Building products most vulnerable to mold attacks include organic materials containing cellulose, wood, jute, wallpaper, drywall, and cardboard.[17] *Penicillium*, can utilize a variety of nutrients such as decaying vegetation with relatively little dampness for short periods of time while *Stachybotrys* requires easily digestible cellulose such as drywall or paper, and sustained wetness. Despite these variations in growth requirements, there is a surprising overall consistency in the types of indoor spores.

One study demonstrated that rankings by prevalence and abundance of the types of airborne and dustborne fungi did not differ from winter to summer, nor did their indoor to outdoor ratios differ.[21] During the winter when infiltration of spores from outdoors was minimal, mean indoor levels of airborne spores in one study ranged from <10 spores/M^3 to >20,000 spores/M^3.[22]

Indoor fungal exposure and the risk of developing asthma

Studies of the possible association between early fungal exposure and subsequent development of asthma or rhinitis have been performed. Such studies are necessarily observational since it is not feasible to randomly assign children to live in environments with various amounts of fungal exposure and to then monitor their health over time. While observational studies provide information about associations, they cannot be used to infer causality because other factors that correlate with fungal exposure may also influence any observed health effects.

A systematic review by Mendell evaluated various types of fungal exposure and the risk of developing asthma.[1] The authors identified 17 studies of fungal exposure and subsequent asthma (8 that had been included in an earlier Institute of Medicine (IOM) report [23] and 9 new studies) that met their inclusion criteria. Of these studies, 6 were prospective, 8 were retrospective and 3 were cross-sectional. The odds ratios for development of asthma in these studies ranged from 0.63 to 7.08 both in retrospective and prospective studies, however, only the cross sectional studies included OR ranges that were consistently greater than 1. They

concluded that evidence showed indoor dampness or mold to be associated with asthma development. The limitation of this review is that the studies were not quantitatively evaluated or combined into a meta-analysis, so it is difficult to draw conclusions from the combined results of the various studies.

The authors did call attention to the Pekkanen study which was a case-control study of 121 children 12-84 months old with recent onset of wheezing and 241 controls.[24] Homes were inspected by engineers for evidence of moisture, visible mold, moldy odor and water damage. While dampness or mold in the main living area of houses was found to be associated with asthma onset, most of the correlations for other interior spaces were not significant. A methodological criticism of this study is that the home inspections were done after asthma was diagnosed thus it is difficult to differentiate between asthma development versus worsening. This demonstrates the limitations of observational studies of fungal exposure and asthma onset.

A number of prospective cohort studies of fungal exposure and subsequent development of asthma were recently evaluated by Quansah in a systematic review.[25] In this review, the authors identified 16 studies that evaluated the relationship between dampness or mold exposure and development of asthma. Of these, 8 evaluated water damage, 9 evaluated dampness, 12 evaluated visible mold and 8 looked at moldy odor. There were no studies meeting inclusion criteria that evaluated fungal exposure and development of rhinitis. Summary effects (a combination of odds ratios and incidence rate ratios) of these studies did not show a significant relationship between water damage and subsequent development of asthma. On the other hand, significant summary effects were found for dampness (1.33, CI 1.12-1.56), visible mold (1.29, CI 1.04-1.60) and moldy odor (1.73, CI 1.19-2.50). The authors suggested that each of these types of exposure can be placed into a sequence of occurrence with water damage leading to dampness leading to visible mold and then to moldy odor, though the clinical relevance of this postulated sequence is unclear unless it suggests a way to prevent progression to the next step.

Karvonen et al. recently reported the results of a prospective birth cohort study evaluating the association between moisture damage and visible mold exposure during infancy and the development of asthma up to the age of 6 years.[26] 442 children were followed. A trained civil engineer conducted a home inspection when the child was 5 months old. Moisture damage was classified as no damage, minor damage or major damage and the area was quantified, and presence of mold odor or visible mold noted. Questionnaires were used at 12, 18 and 24 months and then annually to obtain information about respiratory symptoms and physician-diagnosed asthma. During the 6 years follow up, 65 children developed asthma and 35 children had persistent asthma at 6 years. The strongest associations, with dose-related responses, were found between persistent asthma and moisture damage with visible mold in the child's bedroom (OR 4.82, CI 1.29-18.02) and in the living room (OR 7.51, CI 1.49-37.83). The association was stronger if asthma was diagnosed at ≤ 2 years old and in atopic children. The results indicate that exposure to moisture damage and mold at an early age is associated with asthma ever and persistent asthma.

The conclusion to take from these studies is that early exposure to environments with dampness, visible mold and moldy odor are associated with subsequent development of asthma. What is still not known is how much exposure is required (amount and duration), whether there is a dose-response, whether specific genera of fungi are responsible for the effect and whether interventions to reduce exposure would prevent development of asthma. We also do not know if certain populations are more sensitive to exposure. These are areas that require more study. In the meantime, it seems to the authors that it would be prudent for young children to avoid excessive moisture damage and fungal exposure as much as is feasible until further evidence becomes available.

Indoor fungal exposure and current asthma

A great deal of study has gone into the potential adverse health effects of indoor fungal exposure. Such studies are complicated by the fact that measurement of personal exposure in terms of amount and duration is difficult, many different fungal species contribute to the exposure, and sensitivity to the exposure is likely to vary depending on the person who is exposed. In addition, the only way to infer that exposure to fungi is a cause of observed health effects is to prospectively, in a randomized controlled manner, expose patients to fungi or to reduce fungal exposure in symptomatic patients to document improvement. Given the difficulty of performing such investigations, virtually all studies have been observational.

The systematic review by Mendell evaluated in detail various types of fungal exposure and the risk of developing specific asthma symptoms.[1] The authors identified 103 studies that included 16 health outcomes. Types of exposure reported in these studies included visible water damage, dampness, leaks, flooding, visible condensation, visible mold and moldy odor. Fewer studies evaluated more quantitative measures of fungal exposure such as culturable or microscopically identified fungi, ergosterol, extracellular polysaccharides, (1→3)-ß-d-glucans, endotoxin or lipopolysaccharides. They concluded that evidence from epidemiologic studies and meta-analyses showed indoor dampness or mold to be associated consistently with increased asthma exacerbations, dyspnea, wheeze and cough and evidence strongly suggested causation of asthma exacerbations in children.

An Institute of Medicine meta-analyses of the 33 studies evaluated health outcomes such as upper respiratory tract symptoms, wheeze, cough, asthma diagnosis in relation to visible mold, dampness and airborne spores [23]. These showed evidence of an association between the presence of fungal growth and dampness and upper respiratory symptoms, cough, wheeze, and asthma. Fisk et al. reported results of quantitative meta-analyses of these studies from the Institute of Medicine report plus other related studies and concluded that building dampness and fungal growth are associated with increases of 30–50% in cough, wheeze and asthma.[27]

A recent Cochrane meta-analysis by Suani et al. evaluated the evidence from controlled clinical studies and trials on the role of interventions geared towards reducing mold exposure and a reduction of asthma symptoms. They found that repairing mold-damaged houses, schools and offices decreased asthma-related symptoms and respiratory infections compared

to no intervention in adults, but not in children and suggested there is a need for better randomized controlled trials to provide more evidence. By inference, this meta-analysis provides evidence that interventions that reduce mold exposure can possibly improve asthma symptoms and suggests a linkage between health effects and exposure in adults but further studies in children are needed.[28] A detailed review of interventions is discussed elsewhere in this issue.

A study of 4600 children from the Harvard Six Cities Study that evaluated 10 year old children with a questionnaire found that wheeze and cough were significantly associated with the presence of fungi and dampness.[29] The Health Canada study included nearly 13,000 children and 15,000 adults from the interior of British Columbia to Nova Scotia [30] who lived in single family detached houses (81%), small apartment buildings (13%) or in one family attached homes (6%). Visible fungi were reported in 32% of homes, flooding in 24%, and moisture in 14%. For children, bronchitis, cough and increased wheeze were found to be more frequent in homes with reported fungi or dampness.[30] For adults, the presence of home dampness and visible fungi was associated with increased prevalence of lower respiratory symptoms regardless of other factors or the presence of allergies (OR 1.62, CI 1.48-1.78).[31]

A recent review by Kanchongkittiphon et al.[32] provided an update to the 2000 review of environmental exposures by the Institute of Medicine. The authors identified 6 studies that provided updated evidence on associations between fungal exposure and asthma morbidity. All the studies were done in children: 5 were prospective and 1 was cross-sectional. The two most recent studies in the review were prospective studies that found that in fungus sensitized children, indoor *Penicillium* was associated with increased asthma exacerbations.[33, 34] The study by Gent et al. found that children sensitized and exposed to low levels of *Penicillium* had increased morbidity. Pongracic et al. found that there was a significant increase in maximum symptom days per 2 weeks (MSD) in fungus sensitized inner city asthmatic children exposed to indoor *Penicillium* (1.19 MSD per 2 weeks, p .03). A prospective study by Bundy et al. found indoor *Penicillium* to be associated with increased peak expiratory flow variability greater than 18.5% (OR 2.4; CI 1.2-4.8).[35] The authors of the review concluded that there was limited evidence of an association between indoor culturable *Penicillium* exposure and exacerbations in asthmatic children.

Allergic Sensitization to Fungi and Health Effects

Some of the above studies found an association between exposure to fungi and the risk of respiratory symptoms regardless of sensitization (i.e.: the presence of fungus-specific IgE). However, sensitization to fungi may increase the risk of morbidity as noted in the studies by Gent et al. and Pongracic et al. as described above. Though, the majority of evidence is related to outdoor fungal sensitivities. In one study, patients admitted to an intensive care unit (ICU) for asthma were more likely to have a positive skin test to fungi but not to grass mix, cat dander, or house-dust mite.[36] In adults with asthma, skin prick test positivity to five fungi (*Aspergillus, Alternaria, Cladosporium, Penicillium* and *Candida*) and four other common allergens was explored in relation to asthma severity as measured by the number of hospital admissions. 76% of patients with multiple admissions had at least one positive

fungal skin test compared with 16%-19% of other asthma patients; and multiple fungal skin test positivity and larger skin test reactions to fungal allergen were also correlated to multiple hospital admissions.[37] Sensitivity to *Aspergillus fumigatus* has been associated with severe persistent asthma in adults.[38]

Alternaria sensitivity has been found to be a risk factor for severe asthma attacks and epidemic asthma. In one study, Chicago asthma deaths were more than 2 times higher on days when there were 1000 *Alternaria* spores/M^3 of air. [14] In another study, increased exposure to *Alternaria* was associated with sudden respiratory arrest in 11 *Alternaria*-sensitive patients with asthma at Mayo Clinic. [13] Another study found that outdoor increases in exposure to *Cladosporium* and *Epicoccum* also were correlated with reductions in peak flow and increased cough in children with asthma, independent of total particle counts and air pollution.[39]

Fungal spores and bioaerosols also are suspected to be associated with thunderstorm-induced asthma epidemics.[40-44] For example, in the United Kingdom, an epidemic of 26 asthma admissions was associated with a thunderstorm that contained increased levels of *Alternaria, Cladosporium*, and *Didymella* species. Most of the patients had *Alternaria*-specific IgE suggesting that allergy to *Alternaria* may have been the cause.[12]

Tables 1 and 2 highlight recent studies that summarize evidence of the relation of fungal exposure and asthma and allergic symptoms.

Other hypersensitivity disorders

Several other well-defined human diseases are known to be caused or triggered by exposure to fungi or their metabolites. These include Allergic Bronchopulmonary Mycosis (ABPM), Allergic Fungal Sinusitis (AFS) and Hypersensitivity Pneumonitis (HSP).[45] While exposure to fungi clearly can worsen each of these conditions, complete fungal avoidance has not been shown to result in clinical improvement. The goal of environmental control for these disorders therefore is to avoid making them worse.

ABPM is an inflammatory lung disease which is characterized by a constellation of criteria that include asthma, fleeting pulmonary opacities, proximal bronchiectasis, eosinophilia, and elevated total IgE in addition to elevated specific IgE and precipitating IgG to certain fungi. It often occurs in individuals with asthma or cystic fibrosis.[46] The most common fungus associated with this disorder is *Aspergillus*. More recently it has been described with other genera of fungi leading to the generic term bronchopulmonary mycosis.[47][48] This disorder is exacerbated by exposure to fungal allergens to which the patient is sensitive, making avoidance an important component of management. Conventional wisdom is that exposure to the offending fungus genus is associated with increased disease severity, however there have not been any controlled trials of fungal avoidance in this disorder. Extensive reviews of this condition have been published recently.[49][50]

Allergic fungal sinusitis (AFS) is a distinct non-invasive fungal sinusitis that is under-diagnosed with the incidence varying by region of the country.[51] The offending organisms typically include taxa as *Alternaria, Epicoccum, Ulocladium, Botrytis* and *Bipolaris*. The

presence of nasal polyps has been reported in conjunction with allergic fungal sinusitis and sensitivity to fungi as evidenced by elevated specific IgE levels.[51] This condition represents an intense allergic response against fungi giving rise to formation of allergic (eosinophilic) mucin, mucostasis, and sinus opacification.[52] Several potential deficits in the innate and acquired immunity of patients with fungal sinusitis appear to alter host ability to respond to fungi. It is also possible that fungi have a disease modifying role in the development of this condition.[53] Several reviews of AFS have been published recently.[54, 5556]

Hypersensitivity pneumonitis (HP) is an inflammatory lung disease that is caused by an exaggerated immune response to the inhalation of a large variety of organic particles. The most frequent causal antigens are bird proteins and bacteria such as *thermophilic actinomycetes*. Fungi also have been implicated both in occupational and nonoccupational outbreaks.[57] When fungi are involved, it is characterized by the presence of precipitating IgG antibodies directed at the fungus.[58] The clinical course of the disease is variable and its diagnosis is difficult since no specific test or biomarker provides a consistent diagnosis. The histopathology usually consists of a granulomatous interstitial bronchiolocentric pneumonitis characterized by the presence of poorly formed granulomas and a prominent interstitial infiltrate composed of lymphocytes, plasma cells, and macrophages.[59]

In a German study 23 children with confirmed HP were identified in 2005-2006 and fungal sensitivity was second only to bird sensitivity as the suspected sensitizing agent.[60] There is also is a well-documented pediatric case in which home exposure to *Aspergillus* was demonstrated.[61] Similar cases have been reported in adults for other fungi including taxa such as *Cladosporium.*[62] Morbidity clearly is increased if exposure to the offending substance persists. What is less clear is whether having the patient avoid exposure to the offending agent can reduce morbidity. Several reviews of HP have been published recently.[6364]

Summary

Fungi are ubiquitous microorganism that are present both in outdoor and indoor air. While outdoor exposure to high concentrations of spores can cause health effects such as asthma attacks in association with thunderstorms, most people appear to be relatively unaffected unless they are sensitized to specific genera. Indoor exposure and dampness, on the other hand, appears to be associated with an increased risk of developing asthma in young children, and with asthma morbidity in individuals who have asthma. Reduced indoor exposure using a variety of interventions primarily aimed at reducing moisture, killing fungi and removing contaminated materials, has been shown to decrease this risk of morbidity.

What is not known is how much exposure is necessary to cause a particular health effect and whether certain species are more likely to cause such effects. This review summarizes recent studies pointing towards health effects related to mold. Future studies determining the most accurate method to identify and quantify fungi may help answer the remaining questions.

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Abbreviations used

ABPM	Allergic Bronchopulmonary Mycosis
AFS	Allergic Fungal Sinusitis
HSP	Hypersensitivity Pneumonitis

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Table 1

Recent studies evaluating the association of culturable fungi with asthma exacerbations or severity

Source	Study Design	Measured Exposures	Findings
Children			
(Dannemiller et al. 2015)[65]	Birth cohort	Fungal taxa and diversity	They found that a lower fungal diversity demonstrated significant associations with development of childhood asthma. Though, they didn't report about fungal quantity.
(Gent et al. 2012)[33]	Prospective (over 1 month)	Culturable (1-minute samples) airborne fungi (*Penicillium, Cladosporium)* in living room	Among specifically sensitized asthmatic children, relative to unexposed or exposed non-sensitive, significant positive association of any *Penicillium* exposure with doubled levels of increased asthma severity score, wheeze, and persistent cough. No associations seen with *Cladosporium*.
(Pongracic et al. 2010)[34]	Prospective cohort	Indoor and outdoor culturable (1-minute samples) airborne fungi levels measured at baseline and throughout the 2-year study	Among asthmatic children with any fungal sensitization, total indoor fungi, the four most common fungi combined (*Alternaria, Aspergillus, Cladosporium, and Penicillium*), and indoor *Penicillium* were associated with increased severe exacerbations after controlling for outdoor exposure; *Penicillium* exposure was associated with increased symptoms among children who were fungus-sensitized but not to *Penicillium*. Among species, only *Penicillium* exposure demonstrated significant effects among non-specifically sensitized. The sum of 4 most common indoor fungi and indoor *Penicillium* were associated with increased symptom days. In conclusion, outdoor and indoor fungi, especially *Penicillium*, worsen asthma morbidity in inner city children. Indoor *Penicillium* uniquely affected both symptoms and UVs.
(Wu et al. 2010)[66]	Prospective cohort study (outcomes every 4 months over 4 years)	Total cultural fungi/in vacuumed dust from 5 home locations at initial visit, and genetic polymorphisms	For high values of total culturable fungi in house dust, although not directly related to outcomes of urgent care visits, lung function, IgE, or eosinophils, relationships with urgent care visits were significantly modified by three SNPs of chitinase, in unadjusted analyses. (As estimated from a figure, the association of high vs. low fungi with severe exacerbations (~30% vs. 0%) in those with no or one copy of SNP rs2486953 approximately doubled with two copies.). Thus, reduced enzymatic breakdown of fungal chitin may increase susceptibility to effects of chitin.
(Bundy et al. 2009)[35]	Prospective (over 2 wks)	Culturable (1-minute samples) airborne *Penicillium* and *Cladosporium* in main living area of home	Any measured culturable airborne *Penicillium* in the main living area was significantly associated in asthmatic children (unknown sensitization, but adjusted for maternal-reported atopy) with more than doubled peak expiratory flow variability (PEFV) over next 2 weeks; exposure to any *Alternaria* was associated nonsignificantly with twice the likelihood to have the highest PEFV. No associations were found with total mold, *Cladosporium*, or *Aspergillus*. Analyses atopy-adjusted.
(Inal et al. 2007)[67]	Prospective (monthly over 1 year)	Culturable (time unspecified) airborne fungi in living room and bed room	In children with asthma (17 of 19) and/or rhinitis, sensitized only to molds, in unadjusted analyses in 19 children, neither total indoor molds, *Cladosporium, Alternaria, Penicillium, or Aspergillus* had significant correlations with daily asthma symptom score, morning PEF, or evening PEF.
(Turyk et al. 2006)[68]	Cross-sectional	Culturable (time unspecified) airborne fungi in kitchen and bedroom	Bedroom *Penicillium*, in models adjusted for home dampness, had a significantly positive (dose-response) association with frequent asthma symptoms in asthmatic children (unknown atopic status), and a nearly significant positive association with number of asthma symptoms. No associations seen for kitchen *Penicillium*.

Abbreviations: PEFR, peak expiratory flow rate; FEV1, forced expiratory volume in 1 second; IgE, Immunoglobulin E; PEFV, peak expiratory flow variability; SNPs, single nucleotide polymorphisms; UVs, unscheduled medical visits.

Table 2

Recent studies evaluating dampness, visible mold, or dampness-related agents with asthma exacerbations

Source	Study Design	Measured Exposures	Findings
Children			
(Karvonen et al. 2015)	Birth Cohort	Moisture damage	They showed that moisture damage and mold exposure at an early age in the child's main living areas were associated with asthma development: Associations with asthma ever were strongest for visible mold in the child's bedroom (OR of 4.82 [CI 1.29–18.02]) and in the living room (OR of 7.51 [CI 1.49–37.83]).
(Tiesler et al. 2015)	Birth cohort	Visible mold	German based population study found that visible mold or dampness at home negatively influenced sleep in children. Results were significant for any sleep problem, problems sleeping through the night and short term sleep.
(Weinmayer et al. 2013)	Cross Sectional	Damp housing	ISAAC phase 2, cross sectional study of 8-12 yo in 20 countries evaluating the influence of damp housing conditions on upper and lower respiratory symptoms. Damp housing was associated with wheezing in the past year (OR 1.58 [CI 1.4-1.79], also significant for occurrence of severe wheeze, speech limiting wheeze and 4 or more attacks per week. Exposure to dampness, both at present and earlier in life was associated with wheeze occurrence.
(Hagmolen of Ten Have et al. 2007)[69]	Prospective	Parentally reported damp stains or mold growth, in living room or bedroom, in last 2 years	Damp stains or mold growth were associated with significant increases in severe airway hyperresponsiveness, more days with respiratory symptoms, and greater PEF variability
(Kercsmar et al. 2006)[70]	Randomized controlled intervention.	Remediation of root causes of home moisture and mold, removal of water damaged building materials, and cleaning	In the period after remediation, relative to the control group, visible mold scores were significantly more reduced (−2.6 vs.−1.4), and measured mold indices were nonsignificantly reduced (−0.41 vs. 0.33); in the remediation group compared to the control group, maximum symptom days were significantly reduced, and subjects having 1+ acute care visits were reduced by 64% in the as-randomized analysis, and by 86% in the as-treated analysis. About 1/3 of subjects were sensitive to fungi.
(Bernstein et al. 2006)[71]	Controlled intervention	Intervention – 2-week ultraviolet radiation to reduce microbial exposures	In children sensitized to fungi, ultraviolet radiation was associated with a significant reduction in PEFR variability, and non-significant reduction in FEV1; significant reductions in severity scores for shortness of breath and chest tightness, and in number of days of shortness of breath and chest tightness, as well as in amount of medication use; non-significant reductions in all other disease severity measures.
(Bonner et al. 2006)[72]	Cross-sectional	Presence of any moisture or mildew	Presence of moisture or mildew at home associated with 3.31 times more hospitalization visits for breathing-related problems, 3.25 times more frequent wheezing episodes, and expected 2.19 times greater frequency of night symptoms.
(Teach et al. 2006)[73]	Cross sectional	Mold or dampness in the home in the previous month	Visible dampness or mold in the home in the previous month, in asthmatic children of unknown sensitization status, was not associated with unscheduled visits above the median, persistent asthma symptoms, or quality of life scores below the median.
(Venn et al. 2003)[74]	Prospective	Observed mold, and measured wall moisture	In children with persistent wheezing across a 3-year interval, dose-related increase in wheezing with increasing measured wall dampness, significantly more in atopic cases. For nighttime symptoms and bedroom dampness, OR 2.51 (1.36-4.64) per

Source	Study Design	Measured Exposures	Findings
			increasing category, with OR=7.0 for the highest category; for daytime symptoms and living room dampness, OR 1.86 (1.02-3.42) per increasing category. Visible mold was not significantly associated with either symptoms, although significantly associated with wheezing illness
Adults			
(Jaakkola et al. 2013)	Meta-analysis	Mold odor or visible mold	Meta-analysis of 31 studies looking at the relationship of mold odor or visible mold and rhinitis. There was a significant odds ratio for mold odor and rhinitis (OR 2.18) and allergic rhinitis (OR 1.87). Also significant was presence of mold and rhinitis (1.82) and allergic rhinitis (1.51).
(Wen et al. 2009)[75]	Cross-sectional	Visible mold from interview	Prevalence of asthma attacks among those exposed to indoor mold was roughly twice that in those not exposed, in either obese or non-obese subjects.
(Williamson et al. 1997)[76]	Prospective	inspector-assessed visible mold, and measured wall moisture as total dampness or worst dampness	In diagnosed asthmatics, asthma severity had significant positively dose-related association with measured total dampness and with visible mold score; measured airflow obstruction was significantly greater with higher measured dampness.

Abbreviations: ENO, exhaled nitric oxide; FEV1,; PEFR, peak expiratory flow rate; SNP, single nucleotide polymorphism; UVs, unscheduled medical visits.