The effect of mold sensitization and humidity upon allergic asthma

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Abstract

Introduction: Humidity is commonly associated with increased airway hyperresponsiveness in asthma.

Objective: To examine mold sensitization in patients with allergic asthma or allergic rhinitis and self-reports of humidity as exacerbating factors of clinical symptoms.

Methods: A retrospective, cross-sectional study at a University hospital outpatient allergy and asthma clinic was performed. A total of 106 patients with either allergic asthma or allergic rhinitis completed standard prick-puncture skin testing with 17 allergens and controls and completed standardized forms addressing trigger factors for clinical symptoms.

Results: Allergic asthmatics sensitized to *Cladosporium* were more likely to have a more severe asthma severity class (odds ratio = 4.26, confidence interval = 1.30–16.93). Sensitization to *Alternaria*, *Cladosporium*, *Helminthosporium*, *Aspergillus* and *Dermatophagoides pteronyssinus* in asthma was associated with higher likelihood for previous hospitalization, while sensitization to *Cladosporium*, *Helminthosporium*, *Aspergillus*, *Dermatophagoides pteronyssinus* and cockroach in asthma was associated with higher likelihood of having reduced pulmonary function based on forced expiratory volume in 1 s. Furthermore, allergic asthmatics more commonly reported humidity as an exacerbating factor of symptoms than did patients only with allergic rhinitis (68.42% vs 42.86%, respectively; $P < 0.05$).

Conclusion: Mold sensitization is highly associated with more severe asthma, while humidity is more of an exacerbating factor in patients with allergic asthma as compared with allergic rhinitis alone. Further delineation between mold sensitization and humidity is needed to determine whether these are independent factors in asthma.

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Ethics
This study was approved by the Institutional Review Board in accordance with the ethical standards laid down by the appropriate version of the 2000 Declaration of Helsinki.

Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Declaration of interests
The authors disclose no financial, consulting or personal relationships with other people or organizations that could influence or bias this work. Furthermore, there was no financial support for completion of this study or development of this manuscript. Employment for each author is the listed affiliation as outlined on the title page.
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Introduction

Allergic sensitization has been associated with the risk of having asthma and worsened asthma severity. Studies have been inconsistent on which allergens confer the greatest risk, but molds, house-dust mite and cockroach have been implicated in multiple studies (1–6). Evaluating asthmatic patients for allergic sensitization to perennial allergens through skin testing or *in vitro* testing is currently recommended (7). Furthermore, reducing exposure to known allergens in order to improve asthma control is also recommended in the most recent National Asthma Education and Prevention Program guidelines (NAEPP) (7). Specifically, for patients sensitive to house-dust mite and/or mold, reduction of indoor humidity levels to at or below 60% (ideally 30%–50%) and outdoor avoidance when mold counts are highest is recommended. It has been shown, however, that damp housing conditions have been associated with increased airway hyperresponsiveness after adjusting for house-dust mite allergen levels (8). High levels of indoor humidity support the growth of mold and bacteria, with molds emitting bioaerosols and spores along with volatile organic compounds. Additionally, exposure to high cockroach allergen levels independent of sensitization has been associated with greater asthma morbidity in inner-city children (9). This suggests that factors independent of allergens associated with increased humidity or humid air itself may play a role with higher indoor humidity contributing to cough, wheeze, phlegm production and asthma, especially in children. Subsequently, the American College of Occupational and Environmental Medicine released a statement on the relationship of indoor environments and the adverse affect of molds and other fungi upon human health through three processes, including allergy, infection or toxicity (10).

Humidity has been studied extensively in asthma with conflicting results. A reduction in the bronchoprovocation response or development of asthma symptoms with exercise occurred with increasing relative humidity of inspired air (11–13). The use of a mask retaining heat and moisture effectively controlled exercise-induced bronchoconstriction in asthmatic subjects (14). In contrast, there have been numerous studies that associate an increase in humidity in the homes of asthmatics to increased asthma symptoms and wheezing in both adults and children (15–30). The majority of these studies have addressed the higher house-dust mite and mold content or both because homes with higher absolute or relative humidity and poor ventilation often contain higher levels of these allergens compared with homes with lower humidity and better ventilation.

The current study was performed to identify differences in self-reported triggering factors, such as humidity, for patients with allergic rhinitis and allergic asthma. Additionally, the frequency of allergic sensitization to specific allergens was determined in patients with allergic rhinitis and allergic asthma. The association between allergic sensitization and asthma morbidity was evaluated using various measures of asthma severity, such as NAEPP-defined severity, pulmonary function and history of severe exacerbations.

Materials and methods

This was a retrospective, cross-sectional study involving 106 subjects with either allergic rhinitis or allergic rhinitis and asthma seen between August 2005 and December 2007 in a university-based Allergy and Immunology Clinic. The study was approved by the University of Kentucky Institutional Review Board. Patients with allergic rhinitis were selected by International Classification of Diseases (ICD)-9 codes with the presence of at least one positive skin test that correlated with clinical symptoms. Patients with allergic asthma were also selected based on ICD-9 who had at least one positive allergy prick skin test and spirometry performed. The diagnosis of asthma was confirmed by an allergist/immunologist according to current NAEPP guidelines (7). Diagnosis was typically made by reversibility after a one-time bronchodilator of 12% and 200 mL or by methacholine challenge. The patients were selected by consecutive chart reviews with all subjects fulfilling criteria included in the analysis.

The study population included 49 subjects with allergic rhinitis and 57 subjects with allergic asthma. All study subjects underwent prick-puncture skin testing with a saline and histamine control and 17 allergens. Allergens tested included tree mix #1 (elm, maple, willow, cedar and mulberry), tree mix #2 (hickory, walnut, oak, ash and sweet gum), grass mix (Johnson, Kentucky Blue, Meadow Fescue, Orchard, Red Top and Timothy), Bermuda grass, ragweed mix (short and giant), indoor molds (*Aspergillus* and *Penicillium*), outdoor (seasonal) molds (*Alternaria alternate*, *Cladosporium*, *Epicoccum*, *Fusarium*, *Helminthosporium*), cat, dog, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus* and cockroach. A skin test was considered positive if the difference in mean wheal diameters between the allergen-specific test and negative control was at least 3 mm. In order to be included in this study, all subjects needed to have at least one positive skin test.

All information regarding triggering factors for symptoms were extracted from the chart in which standardized forms were used during the initial history and examination and subsequent clinic visits. For all patients seen in this clinic, the same forms were used by the provider(s). The forms inquired about certain factors that caused worsening of asthma and allergy symptoms, including season of the year (i.e. spring, summer, fall or winter), potential allergic exposures (house dust, cats, dogs, cockroaches and molds), humidity, being indoors or outdoors or being at work. Standardized forms were also used to assess the frequency of daytime and nighttime asthma symptoms, the frequency of rescue inhaler use and the history of hospitalizations for asthmatics. No actual scoring system was used. Asthma severity (intermittent, mild, moderate or severe) was assessed based on current NAEPP guidelines (daytime symptoms, nighttime symptoms, short-acting beta-agonist use for rescue and pulmonary function) (7) with this data collected on each clinic visit with the standardized forms. All subjects with asthma underwent pulmonary function testing to assess baseline forced expiratory volume in 1 s (FEV1).

Statistical analysis

Differences in skin test results and triggering factors between subjects with allergic rhinitis and allergic asthma were analyzed using χ^2 tests. Unadjusted odds ratios (ORs) were calculated to identify relationships between allergic sensitization in asthmatics and measures of asthma morbidity (NAEPP severity classification, history of asthma-related hospitalization and FEV1). Multivariate logistic regression analyses were conducted to identify adjusted ORs while controlling for age, sex and race (white and nonwhite). All statistical analyses were performed using SAS 9.2 (SAS Institute Inc, Cary, NC, USA). A significance level of $\alpha = 0.05$ was used.

Results

Allergic rhinitis and allergic asthma comparisons

Demographic characteristics for the study population are outlined in Table 1. Study subjects with allergic asthma more commonly reported humidity as an exacerbating factor for their asthma or rhinitis symptoms compared with subjects with allergic rhinitis only (68.42% vs 42.86%, respectively; $P < 0.05$). Other triggering factors such as season, outdoor environment and mold exposure were reported similarly for both groups (Fig. 1). Indoor environment, dog and cat exposure, house dust and work were more commonly reported by asthmatics as triggers, but these differences were not significant.

Table 1. Demographic characteristics of the study population

	N = 106 (%)
Mean age, years (standard deviation)	37.9 (13.63)
White	84 (79.2)
Female	72 (67.9)
Asthmatic	57 (53.8)
Intermittent	11 (19.3)
Mild persistent	14 (24.6)
Moderate-severe persistent	32 (56.1)
Skin test results, number positive (%)	
Tree mix #1*	38 (35.8)
Tree mix #2†	40 (37.7)
Grass mix	56 (52.8)
Bermuda	47 (44.3)
Ragweed mix	56 (52.8)
Alternaria	39 (36.8)
Cladosporium	28 (26.4)
Epicoccum	22 (20.8)
Fusarium	20 (18.9)
Helminthosporium	28 (26.4)
Aspergillus	25 (23.6)
Penicillium	21 (19.8)
Cat	49 (46.2)
Dog	26 (24.5)
Dermatophagoides pteronyssinus	56 (52.8)
Dermatophagoides farinae	57 (53.8)
Cockroach	32 (30.2)
Any positive skin test	106 (100%)
Any perennial positive skin test	84 (79.2)
Any positive house-dust mite	67 (63.2)
Any positive mold skin test	66 (62.2)
Mean number positive skin tests	6.04

*Tree mix #1 includes: elm, maple, willow, cedar and mulberry.
†Tree mix #2 includes: hickory, walnut, oak, ash and sweet gum.

Subjects with allergic rhinitis alone were more frequently sensitized to tree mix #2 (48.98% vs 29.82%, $P < 0.05$), while asthmatics were more commonly sensitized to *Helminthosporium* (36.84% vs 14.29%, $P < 0.05$), *Penicillium* (29.82% vs 8.16%, $P < 0.05$), *Dermatophagoides farinae* (64.91% vs 40.82%, $P < 0.05$) and any perennial allergen (89.47% vs 67.35%, $P < 0.05$) (Fig. 2).

Asthma severity and allergic sensitivity

The mean FEV1 for the asthmatic group was 93.1% predicted. A total of 20.75% of the asthmatics had an FEV1 <80% predicted with a distribution of asthma severity groups of 19.3% intermittent asthma, 24.6%

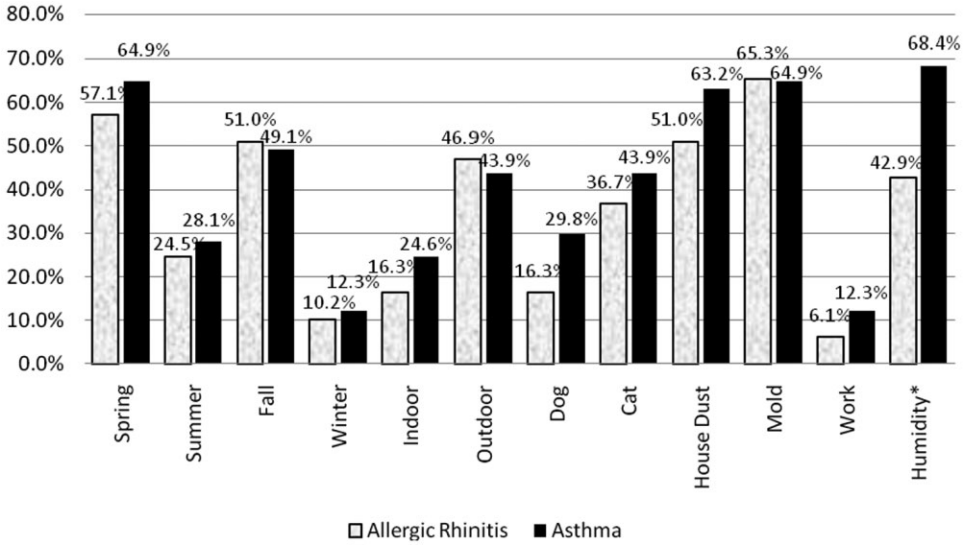

Figure 1. Triggering factors. *$P < 0.05$ between groups.

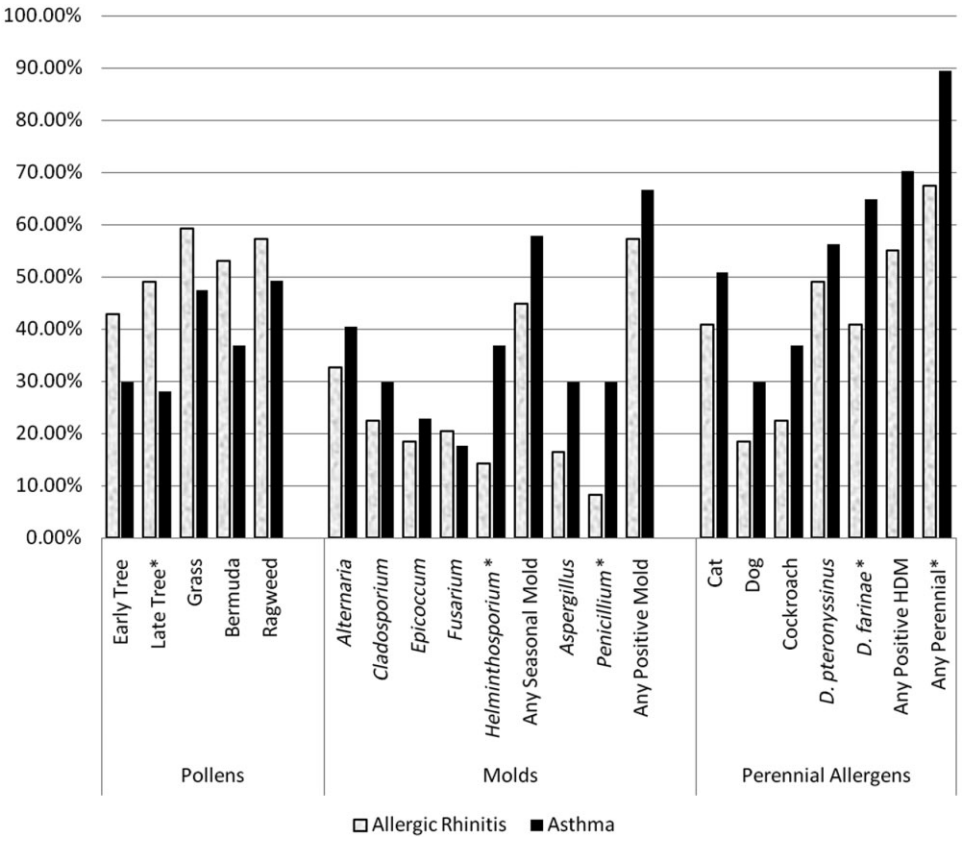

Figure 2. Skin test results in subjects with allergic rhinitis and allergic asthma. *$P < 0.05$ between groups. Any seasonal mold = outdoor mold. *D. farinae*, *Dermatophagoides farinae; D. pteronyssinus, Dermatophagoides pteronyssinus;* HDM, House dust mite.

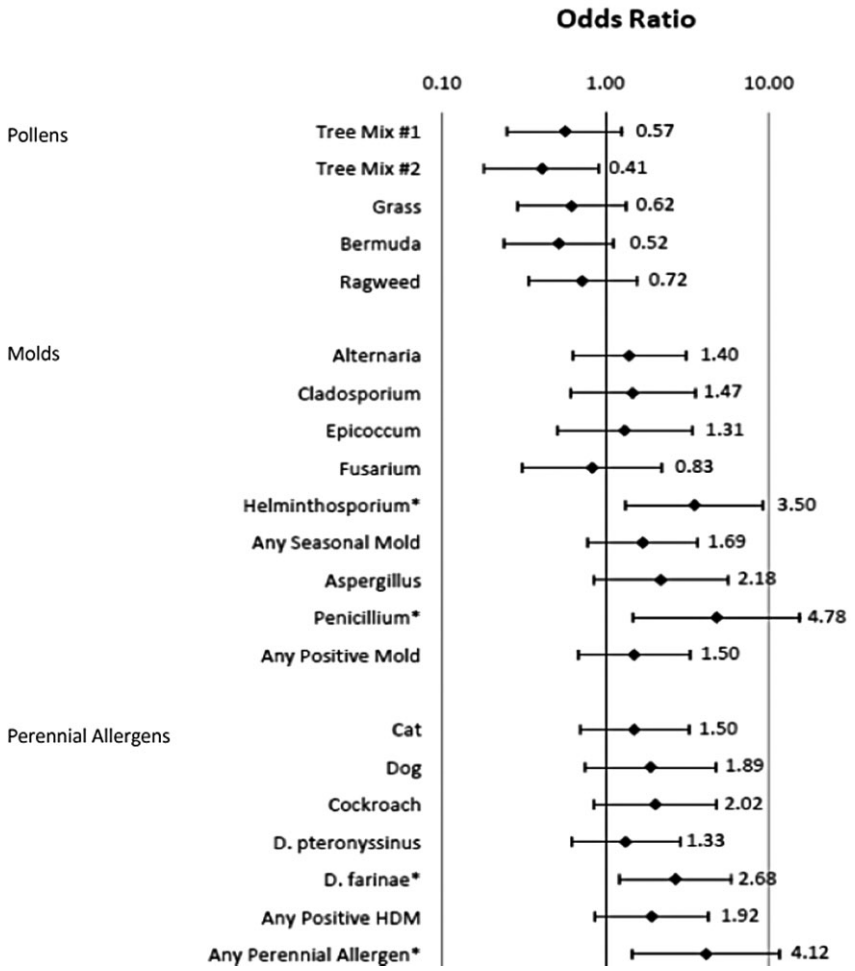

Figure 3. Odds ratios for asthma diagnosis by positive skin test. Patients with allergic rhinitis are the referent group. *D. farinae, Dermatophagoides farinae; D. pteronyssinus, Dermatophagoides pteronyssinus;* Significant value denoted by '*'. HDM, House dust mite.

mild persistent asthma and 56.1% moderate-severe persistent asthma (Table 1). ORs were calculated for measures of asthma severity (NAEPP severity class, history of hospitalizations for asthma, FEV1) and of allergic sensitivities. No significant associations were found between allergic sensitization to trees, grasses, weeds or cat and asthma severity (Fig. 3). Associations between other allergic sensitivities and asthma severity are reported in Table 2. Asthmatics sensitized to *Cladosporium* were more likely to have a more severe asthma severity class (OR = 4.26, confidence interval = 1.30–16.93). This finding persisted after controlling for age, sex and race (4.45, 1.29–18.5). Asthmatics sensitized to *Alternaria*, *Cladosporium*, *Helminthosporium*, *Aspergillus* and *Dermatophagoides pteronyssinus* were more likely to have had a history of hospitalization for asthma (Table 2). These findings also persisted after controlling for age, sex and race. Asthmatics with allergic sensitization to *Cladosporium*, *Helminthosporium*, *Aspergillus*, *Dermatophagoides pteronyssinus*,and cockroach were more likely to have reduced pulmonary function, as measured by FEV1. After controlling for age, sex and race, asthmatics sensitized to *Alternaria*, *Helminthosporium*, *Aspergillus*, dog, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* were more likely to have a lower FEV1.

Humidity, mold and house-dust mite sensitization, and asthma severity

Multiple logistic regression analysis was performed to assess the relationship between worsened symptoms with humidity exposure and allergic asthma. As shown in Table 3, the unadjusted OR for worsening symptoms with humidity exposure and having allergic asthma (compared with allergic rhinitis) was 2.89 (1.30–6.42). After controlling for several demographic characteristics, subjects with asthma more commonly reported worsened symptoms with increased humidity compared with patients with allergic rhinitis alone

Table 2. Allergic sensitization and asthma severity

Allergen	OR asthma severity class*	OR hospitalization†	OR FEV1	AOR asthma severity class*	AOR hospitalization†	AOR FEV1
Alternaria	1.70 (0.61–4.91)	**6.64 (1.70–33.5)**	2.44 (0.94–6.52)	1.76 (0.62–5.21)	**7.12 (1.76–37.72)**	**2.91 (1.08–7.81)**
Cladosporium	**4.26 (1.30–16.93)**	**4.90 (1.30–20.00)**	**3.48 (1.21–10.42)**	**4.45 (1.29–18.5)**	**6.08 (1.46–29.37)**	2.58 (0.86–7.68)
Epicoccum	1.57 (0.48–5.68)	3.30 (0.81–13.32)	1.46 (0.52–4.18)	2.26 (0.65–8.85)	4.16 (0.92–20.17)	1.53 (0.53–4.47)
Fusarium	0.91 (0.28–3.52)	3.25 (0.70–14.3)	1.54 (0.50–4.79)	1.39 (0.38–5.53)	4.65 (0.90–24.90)	2.75 (0.87–9.02)
Helminthosporium	1.35 (0.48–3.89)	**4.92 (1.32–21.23)**	**2.72 (1.00–7.43)**	1.95 (0.65–6.20)	**8.75 (1.86–59.27)**	**5.24 (1.73–15.91)**
Aspergillus	1.33 (0.45–4.17)	**4.90 (1.30–20.00)**	**2.95 (1.06–8.48)**	1.24 (0.40–4.06)	**4.93 (1.26–21.16)**	**3.01 (1.03–8.82)**
Penicillium	1.75 (0.58–5.77)	1.96 (0.50–7.40)	2.68 (0.95–7.76)	1.71 (0.53–5.98)	1.99 (0.49–7.77)	2.07 (0.73–5.90)
Cat	0.41 (0.14–1.15)	0.96 (0.26–3.49)	0.95 (0.37–2.44)	0.42 (0.14–1.19)	1.12 (0.29–4.41)	1.45 (0.56–3.84)
Dog	0.72 (0.25–2.11)	3.09 (0.82–11.93)	2.58 (0.90–7.70)	0.66 (0.22–2.03)	3.42 (0.87–14.07)	**4.19 (1.37–13.43)**
Dermatophagoides pteronyssinus	1.58 (0.57–4.39)	**5.23 (1.21–36.6)**	**6.43 (2.28–19.40)**	1.38 (0.47–4.04)	**6.12 (1.30–46.60)**	**5.34 (1.83–15.57)**
Dermatophagoides farinae	1.35 (0.47–3.81)	3.33 (0.76–23.4)	2.75 (0.99–7.92)	1.10 (0.37–3.23)	3.31 (0.74–23.55)	**2.87 (1.03–7.99)**
Cockroach	1.19 (0.43–3.46)	0.82 (0.20–3.05)	**2.96 (1.10–8.25)**	1.19 (0.41–3.57)	0.83 (0.19–3.17)	2.36 (0.87–6.61)

AOR adjusted for age, sex and race.
*Asthma severity class based on National Asthma Education and Prevention Program guidelines for frequency of daytime symptoms, night symptoms, rescue inhaler use, FEV1, medication use.
†Hospitalization indicates any history of hospitalizations for asthma.
Significant values in bold. OR, odds ratio; AOR, adjusted odds ratio; FEV1, forced expiratory volume in 1 s.

[OR = 2.56 (1.13–5.80)]. The finding continued to be present despite controlling for allergic sensitization to molds, house-dust mite or both allergens (Table 3). No significant associations were found between asthmatics that reported worsened symptoms with humidity exposure and asthma severity, as assessed by NAEPP guidelines (7), history of hospitalizations or FEV1 (Table 4).

Discussion

In this study, patients with coexistent asthma and allergic rhinitis frequently reported humidity as an exacerbating factor for their symptoms and were more commonly sensitized to molds than subjects with allergic rhinitis alone. Mold sensitization was also associated with more severe asthma as measured by NAEPP severity classification, history of hospitalizations for asthma and FEV1. Additionally, sensitization to *Dermatophagoides pteronyssinus* was associated with a history of asthma hospitalizations and reduced pulmonary function. Importantly, asthma symptom worsening with exposure to humidity was independent of allergic sensitization to mold or house-dust mites. Worsened symptoms with humidity exposure itself, however, was not associated with any measure of asthma morbidity. Moreover, the typical asthmatic requiring hospital admission includes children and older patients, which our cohort did not represent.

Allergic sensitization has been associated with asthma diagnosis in previous studies. In a study using data from the Third National Health and Nutrition Examination Survey, Arbes *et al.* (31) calculated the population attributable risk of atopy on asthma diagnosis in over 10 000 individuals ranging in age from 6–59 years. It was estimated that 56.3% of asthma cases were attributable to atopy. Specifically, sensitization to cat, *Alternaria* and white oak were found to be independently and positively associated with asthma. Importantly, the only mold that subjects were skin tested to was *Alternaria*. In our study, while *Alternaria* sensitization was more commonly found in asthmatics, the difference was not statistically significant when compared with subjects with allergic rhinitis only; however, sensitization to *Helminthosporium, Penicillium, Dermatophagoides farinae* and any perennial allergen was significantly associated with an asthma diagnosis.

Other studies have also investigated the association between allergic sensitization and various measures of asthma control and severity. The results of these studies have differed between children and adults. In a

Table 3. Humidity, allergic asthma and allergic sensitization to molds and house-dust mite

	OR humidity	AOR humidity
Unadjusted model		
Asthma	2.89 (1.30–6.42)	–
Adjusted model*	–	2.56 (1.13–5.80)
Any positive mold skin test	–	2.53 (1.11–5.75)
Any positive HDM skin test	–	2.39 (1.05–5.54)
Any positive mold/HDM skin test	–	2.38 (1.04–5.52)

*Adjusted for age, sex, race.
OR, odds ratio; AOR, adjusted odds ratio; HDM, House dust mite.

study by Akerman *et al.* (32), sensitization to *Cladosporium*, trees and grasses was positively correlated with asthma severity in adults but not in children. In fact, a negative association between *Cladosporium* sensitivity and asthma severity was found in children. Other studies in children, however, have found positive correlations between asthma severity and sensitization to molds, cat and cockroach (33–36). The association of allergic sensitization with lung function and bronchial responsiveness has also been assessed using data from the Childhood Asthma Management Program (37). Study subjects were children with mild to moderate asthma and were skin tested to multiple inhalant allergens which included *Alternaria*, *Aspergillus* and *Penicillium*. Although there was no significant correlations found between any allergen tested and pulmonary function, sensitivity to *Alternaria*, dog and cat were strongly associated with methacholine responsiveness.

In adults, multiple studies using data from the European Community Respiratory Health Survey have demonstrated an association between sensitization to mold, particularly *Cladosporium*, and to house-dust mite with worsened asthma severity (2, 38, 39). Measures of asthma severity in these studies included pulmonary function (FEV1), frequency of asthma attacks, asthma associated hospital/intensive care unit admissions and Global Initiative for Asthma classification. A study by Niedoszytko *et al.* (40) demonstrated significant associations between sensitization to *Aureobasidium pullulans* and asthma severity. This same study found *Helminthosporium* sensitization to be associated with asthma-related hospitalizations. A study by O'Driscoll *et al.* (4) also found a strong correlation between allergic sensitization to molds and hospital admissions in the United Kingdom. Sensitization to *Alternaria* has been associated with poor pulmonary function, and *Cladosporium* sensitization with more severe bronchial hyperresponsiveness in a Korean study (41). Sensitization to the same two molds, *Alternaria* and *Cladosporium*, has also been implicated in epidemic thunderstorm-related asthma (42). Our results also confirm a relationship between sensitivity to *Cladosporium* and more severe asthma, as assessed by NAEPP severity class, history of hospitalizations and FEV1. Sensitization to other molds, such as *Alternaria*, *Helminthosporium* and *Aspergillus*, as well as sensitization to *Dermatophagoides pteronyssinus,* was also associated with more severe asthma in our study.

The current research that evaluated the effects of humidity upon asthma has conflicting results. Exposure to low humidity along with cold air has long been demonstrated as a method of provocation of asthma symptoms and development of bronchoconstriction in the setting of hyperventilation or exercise (43–49). Although cold, dry air is well studied in asthma, we

Table 4. Humidity and asthma severity

Allergen	OR asthma severity class*	OR hospitalization†	OR FEV1	AOR asthma severity class*	AOR hospitalization†	AOR FEV1
Humidity	1.10 (0.36–3.23)	0.57 (0.15–2.22)	0.78 (0.28–2.16)	1.17 (0.36–3.66)	0.49 (0.12–2.02)	0.54 (0.18–1.57)

AOR adjusted for age, sex, race.
*Asthma severity class based on National Asthma Education and Prevention Program guidelines for frequency of daytime symptoms, night symptoms, rescue inhaler use, FEV1, medication use.
†Hospitalization indicates any history of hospitalizations for asthma.
OR, odds ratio; AOR, adjusted odds ratio; FEV1, forced expiratory volume in 1 s.

do not truly understand the underlying mechanism of why this occurs. Alternatively, a study published in 1982 demonstrated that peak expiratory flow rates were significantly decreased in 10 asthma patients during exercise in a climate chamber with 30°C and a relative humidity of 70% (50). Moreover, two separate studies published in the 1980s demonstrated marked bronchoconstriction in asthmatic subjects who inhaled humidified warm air (51, 52). More recently, a study demonstrated bronchoconstriction in an animal with hyperventilation of humidified warm air, suggesting that humidity has a physiological effect on pulmonary sensory nerves (53).

The current study has significant limitations including the small sample size and the retrospective nature of the design. Moreover, the group had more females and was skewed to more severe asthma than typically seen in a normal population. The patients provided information regarding triggers of symptoms, including humidity, as self-reports in a qualitative manner, which may be perceived differently by individual patients. There is potential for a patient not completely understanding the correct meaning of humidity. Additionally, multiple statistical comparisons were made and appropriate caution should be used when interpreting the results. Although allergens could have been grouped together by class (molds, house-dust mite, pet dander, etc . . .) to limit the number of statistical comparisons, we felt it was important to evaluate individual differences between allergens. It is possible that antigenic differences between molds could be associated with more severe forms of asthma. A recent study in children demonstrated that HLA-DQB1*03 was protective, and HLA-DR restriction was positively associated with moderate-severe asthma in *Alternaria* sensitive subjects (54).

Mold sensitization is highly associated with more severe asthma as determined by asthma severity classification, pulmonary function and need for hospitalization. Interestingly, allergic asthmatics frequently report humidity as an exacerbating factor and were commonly sensitized to molds than patients only with allergic rhinitis. Despite these findings, there was no increased association of asthma morbidity. We cannot delineate whether mold sensitization and humidity are independent factors because of the retrospective study design. Humidity may play a role from a physiological mechanism, but sensitization to molds could easily be contributing simultaneously. Further research is warranted both to delineate whether humidity and mold sensitization are independent factors in allergic asthma and to establish better defined pathophysiologic mechanisms of asthma.

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