

ORIGINAL ARTICLE

Association of Atopy to Asthma Severity and Medication Use in Children

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The importance of aeroallergens as triggers for asthma is well recognized, but the relationship between asthma severity and atopic profiles in childhood has not been elucidated. This study assessed the relationship of allergen sensitization to asthma severity in a study of 114 asthmatic children followed for 8 weeks in three Southern California areas. Increased controller medication and β -agonist use were positively associated with number of positive skin tests and allergy to mold and pollens. Mold was associated with increased asthma symptoms. Degree of atopy and reactivity to mold and pollens plays a significant role in asthma severity in asthmatic children.

Keywords allergens, panel study, epidemiology, severity of illness index, risk factors

INTRODUCTION

The importance of aeroallergens as triggers for asthma is well recognized, but the association between atopic profiles in childhood to severity of asthma symptoms has not been clearly elucidated. Recently, increased degree of atopy (the total number of positive skin tests) has been linked to the persistence of childhood asthma into adulthood (1). Further, children with indoor allergic sensitization and an increased degree of atopy have also been shown to have a higher probability of maintaining their asthma into puberty (2). Previous studies have shown that childhood atopy is important in the development of asthma, and sensitization to indoor allergens has been strongly associated with asthma (3) as opposed to pollens (4). In particular, house dust mite has been established as a risk factor for the incidence of asthma (3). Bronchial hyperreactivity has also been shown to be induced by aeroallergens through bronchial challenges (5). However, the association of specific aeroallergen sensitivity to asthma severity has not been clearly established.

We evaluated the atopic profiles of 114 children with asthma living in Southern California in relation to asthma outcomes using repeated measures of asthma outcomes. Atopic profiles included both degree of atopy and allergy to specific allergen types. Outcomes included clinical asthma severity, daily asthma symptoms interfering with daily activities, and medication use. We hypothesized that the degree of atopy is positively related to asthma outcomes in children, and that indoor allergens, such as house dust mite and cat, influence asthma outcomes to a greater degree than pollens or mold.

MATERIAL AND METHODS

Design and Population

The sources of data for this investigation were eight panel studies involving repeated measures of health outcomes over 8 weeks in 123 subjects. A panel study is a longitudinal study of repeated measures in a targeted group, in this case asthmatic children. Participants recorded health outcome data daily, including peak flow measurements and a symptom diary. The parent study aimed to evaluate the effect of air pollution on asthma in children living in regions of Southern California with high air pollution levels (6). Data collection included not only health outcomes, but also personal and microenvironmental exposure to airborne particulate matter for 10 to 14 days, nested within an 8-week study period. Daily home visits were conducted for data collection and instrument preparation during the personal exposure phases and weekly during the remaining period. Panel studies took place in San Diego, CA ($N = 57$) in autumn 1993, spring to summer 1994, autumn 1995, spring 1996, autumn 1999, and spring-summer 2000. Additional panel studies took place summer through autumn 2003 in Riverside, CA ($N = 34$) and summer through fall 2004 in Whittier, CA, near East Los Angeles ($N = 32$). The present analysis used baseline data, including allergy testing, and each subject's first panel data. Some subjects participated in more than one panel period in San Diego.

A total of 123 children between 8 and 18 years of age (male $n = 78$) with a history of physician-diagnosed asthma were recruited for eight panels each lasting around 2 months. The Institutional Review Boards of the University of California, Irvine, and San Diego State University approved the study protocol, and informed written consent was obtained from all subjects and one of their legal guardians. We analyzed the aeroallergen skin tests of 114 participants.

Health Outcomes and Daily Follow-Up Procedures

A background questionnaire was administered by interview to subjects and their parents at baseline. It included

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questions on asthma history, prescribed medications, socioeconomic status (parental education, parental income), race-ethnicity, parental asthma, and pet ownership.

Peak expiratory flow (PEF) was used in the definition of the asthma severity outcome as described below. Participants were trained by staff to perform expiratory maneuvers and were given a subject manual with instructions. Participants were instructed to perform PEF measurements before using their as-needed β -agonist inhalers in the morning and evening. The morning maneuver was to be performed after being awake and alert soon after rising, and the evening was to be performed around 2100 hours or near bed time. Nose clips were not used in the San Diego panels but were used in the Riverside and Whittier panels. Several methods were used to measure PEF.

For panels followed from 1993 through 1996, a non-electronic peak flow meter was used (Assess; Healthscan Products, Inc., Cedar Grove, New Jersey, USA). The highest of three PEF maneuvers per session was retained for the analysis. Peak flows were invalidated if the same value was recorded for the three successive maneuvers, or if they did less than three maneuvers. Data were checked for repeated entries from day-to-day for the same PEF level as an indication that maneuvers may not have been performed. For panels followed from 1999 through 2000, we used the Vitalograph 2110 handheld electronic peak flow meter (Vitalograph Inc., Lenexa, Kansas, USA), which obviated the need to assess falsification of paper records. The alarm prompts the participant at home to begin the maneuver (or the participant can self-initiate) and to repeat maneuvers up to five times when shown an icon of a face blowing air. The unit stops prompting if two peak expiratory flow (PEF) readings are within 10%. The percent reliability between the highest and second highest PEF is logged in memory and the highest flow is logged as "good" for time to peak flow between 40 msec and 290 msec.

For panels followed from 2003 through 2004, we used another handheld electronic spirometer, the NDD EasyOne Frontline Spirometer (NDD Technologies, Chelmsford, MA, USA). Although it measures full expiratory lung function, for comparability with the above measures we only retain PEF here. Prompting of maneuvers was similar to the Vitalograph with up to six repeat maneuvers, and acceptability for time to peak flow was between 40 msec and 160 msec.

Daily diary responses included asthma symptom severity (6 levels), daily controller medication use, as-needed β -agonist inhaler use, respiratory infections, and time-activity. Responses were entered by participants into asthma diaries at least once in the morning and evening. We used paper diaries from 1994 to 1996, then small personal digital assistants for the remaining panels. Asthma symptoms (cough, wheeze, sputum production, shortness of breath, and chest tightness) were rated by the participants according to their global severity on a scale from 0 to 5 as follows: 0 = no asthma symptoms present; 1 = Very Mild, asthma symptoms present, but caused no discomfort; 2 = Mild, asthma symptoms caused discomfort, but did not interfere with daily activities or sleep; 3 = Moderate, asthma symptoms interfered somewhat with daily activities or sleep; 4 = Severe, asthma symptoms interfered with most activities (may have stayed home in bed, returned home early from school, or called a doctor or nurse for

TABLE 1.—Participant characteristics.

Participant characteristics	More severe asthma N = 71	Less severe asthma N = 43
Age (mean, $\pm$ SD)	12.25 ($\pm$ 2.15)	12.98 ($\pm$ 2.70)
Gender male/female	44 (62.0%)/27 (38.0%)	28 (65.1%)/15 (34.9%)
Race/ethnicity		
White non-Hispanic	37 (52.1%)	20 (46.5%)
Hispanic	16 (22.5%)	18 (41.9%)
Other races [†]	18 (25.4%)	5 (11.6%)
Body mass index (kg/m ² $\pm$ SD)	21.09 ($\pm$ 4.53)	22.55 ($\pm$ 5.66)
Severity characteristic		
Anti-inflammatory medications	48 (67.6%)	0
High frequency of symptoms [‡]	6 (8.5%)	0
PEF <80% predicted	28 (39.4%)	0
PEF >20% variability	22 (31.0%)	0

*The severity characteristics are based on National Heart, Lung, and Blood Institute (NHLBI) guidelines.

[†]Other races: 13 African Americans and 5 Asians with more severe asthma; 4 African Americans and 1 Asian with less severe asthma.

[‡]A high frequency of symptoms was defined as asthma symptoms that interfered with daily activities or sleep more than 2 or more times a week.

advice); 5 = Very Severe, asthma symptoms required going to a hospital, emergency room, or outpatient clinic. Staff visited the participant's home daily to weekly to examine the quality of outcome data and to retrain subjects as necessary.

As asthma is a heterogeneous and variable disease (7, 8), asthma severity was determined by several measures based, in part, on National Heart, Lung, and Blood Institute (NHLBI) guidelines (9). We divided participants into two groups, those with more severe versus less severe asthma. Participant characteristics are shown in Table 1. More severe asthma was defined as follows: (1) regular daily use of inhaled corticosteroids; (2) having asthma symptoms (score >2) on two or more times per week; and (3) an average percent predicted evening PEF less than 80% or variance in PEF greater than 20%. More versus less severe asthma is comparable to the NHLBI definition of persistent versus intermittent asthma. All criteria were derived from 2 months of repeated measures.

Aeroallergen Skin Testing

Skin testing was performed using Multi-Test II to a panel of relevant aeroallergens including mold (*Alternaria alternata*, *Penicillium* Mix, *Aspergillus* Mix, *Hormodendrum cladosporioides*, and *Helminthosporium interseminatum*), pollens common to the study area (grass mix, two tree mixes, and two weed mixes), house dust mite (HDM [*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*]) and cat [*Felis catus* (domesticus) epithelia in San Diego panels and hair in the Riverside/Whittier panels]. A positive skin test was defined as a wheal 5 mm or greater with an area of erythema. All reactions were read against the negative and histamine controls. Five atopy variables were defined based on the number of positive skin test results within each atopy variable: mold, pollen, house dust mite, cat, and total allergens. The degree of atopy variables were ordinal and ranged from 0 to 5 for molds, 0–3 for pollen (grass, any tree, any weed), 0–1 for house dust mite, 0–1 for cat, and the sum of these variables (0 to 10) defined as total allergens. The total allergens variable ranged from 0 to 10 and was computed as the sum of positive tests to mold, pollens, house dust mite, and cat. These

five atopy variables were the predictor variables of interest in statistical models.

Statistical Methods

The hypothesized distribution of outcome variables defined the statistical modeling method. Asthma severity, a binary outcome, was modeled using logistic regression. The frequency of asthma symptoms was summarized as a daily rate and modeled with Poisson regression. Similarly, the frequency of β -agonist use was summarized as a daily rate and modeled with Poisson regression. Each subject's medication regimen was converted to an ordinal score with higher scores for more intensive regimens. This ordinal outcome was modeled using a generalized linear model with a cumulative logit link function. The predictive significance of each of the five atopy variables was subsequently tested.

Asthma severity was defined as a binary outcome (more severe versus less severe) and modeled using logistic regression. Each of the five atopy variables was tested separately for significance as a predictor of severity. Thus, five logistic regression models were used. Candidate covariates included age, gender, race-ethnicity, body mass index, parental education, parental income, parental asthma, and study location. We aimed to select the most parsimonious model that explained changes in the outcome. The Wald Test for maximum likelihood estimates was used to assess the statistical significance of model parameters. The Hosmer-Lemeshow Test for logistic regression was used to help assess the goodness-of-fit of final models. From Wald Tests of model coefficients, age and study location were consistently significant covariates. Each of the remaining covariates (gender, race-ethnicity, body mass index, parental education, parental income, and parental asthma) was not significant as measured by the Wald statistic. Additionally, inclusion of the remaining covariates did not alter the magnitude of the atopy coefficient by 10% or greater. In other words, none of the remaining covariates appeared to be confounders with respect to the effect of atopy variables. Our final models included age, study location, and an atopy variable. Thus, the tabulated odds ratios for atopy variables are adjusted for age and study location (10).

The relationship between atopy and the risk of moderate to severe asthma symptoms (i.e., symptom severity) was also explored. The occurrence of moderate or worse asthma symptoms during panel studies was quantified as a daily rate. This symptomatic rate was defined as the number of study days with moderate or worse asthma symptoms divided by the days of study participation. Symptomatic rate, as an outcome, was modeled using a generalized linear model with Poisson link function. Five models were used to test each of the atopy variables for predictive significance. The Wald Test for maximum likelihood estimates was used to assess the statistical significance of model parameters. Models were corrected for age and study location. Final estimates are tabulated as a rate ratio or estimated increase in the rate of symptomatic study days for one unit increase in an atopy variable.

Also of interest was the relationship between atopy variables and the daily use of metered dose inhalers (MDI). The rate of MDI use was calculated as the number of inhaler puffs taken by each participant divided by the days of study participation. MDI rate was modeled using a generalized linear

model with Poisson link function. Five Poisson regression models were used to test each of the atopy variables for predictive significance. The Wald Test for maximum likelihood estimates was used to assess the statistical significance of model parameters. Each of the final models was corrected for age and study location (11). Results were tabulated as a rate ratio or estimated increase in the rate of MDI use for one unit increase in atopy variable (12).

Poisson models for MDI rate and for symptomatic rate were fit with a scaling factor to adjust for overdispersion (11). Overdispersion occurs when the actual variance of a measured response exceeds its nominal variance under an assumed probability model.

Finally, the relationship between atopy and medication regimen was tested. Each subject's medication regimen was converted to an ordinal score with higher scores for more intensive regimens as follows: (1) as-needed inhaler only; (2) nonsteroidal anti-inflammatory medication; (3) steroidal anti-inflammatory medication; (4) nonsteroidal anti-inflammatory medication plus steroidal anti-inflammatory medication. All subjects had access to an as-needed β -agonist inhaler. Medication regimen, as an ordinal outcome, was modeled using a generalized linear model with a cumulative logit link function. These models estimate the risk of a categorical increase in medication regimen from an increase in an atopy variable. Five generalized linear models were used to test each of the atopy variables for predictive significance. The Wald Test for maximum likelihood estimates was used to assess the statistical significance of model parameters. Models were corrected for age and study location. Final estimates are tabulated as odds ratios.

RESULTS

Descriptive Statistics

Table 1 summarizes the characteristics of the 114 participants with available skin test results. Atopy was identified in 96 (84%) of the participants. The pattern of aeroallergen reactivity is as follows: pollens (88%), molds (72%), HDM (59%), and cat (46%).

The Association of Atopy to Asthma Outcome Variables

Table 2 shows results of the selected models for all outcomes. The degree of atopy for total allergens was positively associated with more severe asthma ($p = 0.03$). Subjects were 1.18 times more likely to have more severe asthma with each additional allergy (range 0–10). Although pollen and cat allergies likely contributed to this global allergen association, atopy to molds was most significantly associated with increasing asthma severity ($p = 0.01$). Subjects were 1.42 times more likely to have more severe asthma with each additional mold allergy (range 0–5). The relationship between cat allergy and asthma severity was not statistically significant ($p = 0.10$). Similarly, there was no statistically significant relationship found between HDM allergy and asthma severity ($p = 0.15$). However, when including both cat and HDM allergy as predictors of asthma severity in the same model, cat allergy was statistically significant ($p = 0.05$, OR = 2.87); whereas HDM was not ($p = 0.07$, OR = 0.39) (not shown). These opposite findings were influenced by participants who were not HDM-allergic but were cat-allergic. They had more

TABLE 2.—Relationship of the degree of atopy to asthma outcomes.

Aeroallergen	Odds ratio for asthma severity (95% CI) [†]	Rate ratio for symptom severity (95% CI) [‡]	Rate ratio for β -agonist use (95% CI) [§]	Cumulative odds ratio for medication score (95% CI) [#]
Total allergens	1.18 (1.02, 1.37)*	1.06 (0.99, 1.13)	1.10 (1.02, 1.20)*	1.14 (1.02, 1.27)*
Mold	1.42 (1.10, 1.87)*	1.12 (1.00, 1.25)*	1.19 (1.04, 1.35)*	1.23 (1.03, 1.48)*
Pollens	1.33 (0.92, 1.94)	1.12 (0.94, 1.33)	1.29 (1.04, 1.60)*	1.36 (1.02, 1.48)*
Cat	2.26 (0.87, 6.23)	1.12 (0.70, 1.81)	1.05 (0.06, 1.84)	1.66 (0.80, 3.47)
Dust mite	0.50 (0.19, 1.28)	0.76 (0.47, 1.23)	0.75 (0.43, 1.31)	0.87 (0.43, 1.80)

*0.01 < p < 0.05.[†]Asthma severity was defined as a binary outcome (more severe vs. less severe). Odds ratios were computed using Logistic regression.[‡]Symptomatic rate was defined as the number of study days with moderate or worse asthma symptoms divided by the days of study participation. Rate ratios were computed using generalized linear model with Poisson link function.[§]Daily rate of metered dose inhaler use was calculated as the number of inhaler puffs taken by each participant divided by the days of study participation. Rate ratios were computed using generalized linear model with Poisson link function.[#]Medication regimen was converted to an ordinal score (1, 2, 3, 4) with higher scores for more intensive regimens. Odds ratios were computed using generalized linear model with cumulative logit link function.

severe asthma than participants who were not HDM allergic or cat allergic ($p = 0.03$).

The degree of atopy to mold was positively associated with the percentage of days with moderate or worse asthma symptoms ($p = 0.05$). There was also a borderline significant association between the degree of atopy for total allergens and the percentage of days with moderate or worse asthma symptoms ($p = 0.11$). Although pollen and cat allergies likely contributed to this global allergen association, atopy to molds was most significantly associated with the frequency of asthma symptoms ($p = 0.05$). There was an estimated increase of 12% in the percentage of days with moderate or worse asthma symptoms for each additional positive skin test to mold. Allergy to pollens, cat, and HDM was not significantly associated with symptom frequency.

There was a positive association between increased β -agonist use and degree of atopy to total allergens ($p = 0.02$), mold ($p = 0.01$), and pollens ($p = 0.02$). There was an estimated increase of 10.3% in the rate of β -agonist use for each additional positive skin test. There was also a positive association between the degree of atopy and increased asthma medication score for total allergens ($p = 0.02$), mold ($p = 0.02$), and pollens ($p = 0.03$). Cat allergic participants had a higher medication score than non-cat allergic participants, but the relationship was nonsignificant ($p = 0.18$, OR 1.66). The association for HDM was not significant. There was no association with percent predicted PEF or morning to evening PEF variability and sensitization to any allergen (results not shown).

The Association of Asthma Severity to Cat Ownership

In a logistic regression model controlling for age and study location, cat ownership was not associated with asthma severity ($p = 0.08$, OR = 0.41). We also tested the interaction of cat allergy and cat ownership, as predictors, in a logistic regression model for asthma severity that controlled for age, HDM allergy, and study location. The dichotomous variables of cat allergy and cat ownership were recoded to one categorical variable with four group levels: 0 = non-allergic, not a cat owner; 1 = allergic, not a cat owner; 2 = non-allergic, cat owner; and 3 = allergic, cat owner. The reference level was defined as those who were non-allergic and were not cat owners (group 0). The ORs for groups 1 and 3 were nonsignificant ($p = 0.70$, OR = 1.27 and $p = 0.75$, OR = 1.32, respectively). However, there was a statistically significant

OR in group 2 (OR = 0.28, 95% CI: 0.08, 1.00, $p = 0.05$). This indicated that, after adjusting for age, HDM allergy, and study location, non-cat allergic participants who were cat owners ($N = 23$) were less likely to have more severe asthma than non-cat allergic participants who were not cat owners. Therefore, among the four groups, non-allergic cat owners ($N = 23$) appeared to have a reduced likelihood of having severe asthma. Low power and self-selection may explain the lack of difference for cat allergic subjects owning cats ($N = 12$).

DISCUSSION

This is the first study to our knowledge to demonstrate that a greater degree of atopy is associated with increased asthma severity and medication use of asthmatic children in Southern California. It further demonstrates that reactivity to mold and pollens plays a significant role in the frequency of asthma symptoms and in both controller and rescue medication use. Surprisingly, HDM did not significantly influence asthma severity or the use of medications. This study also found that cat ownership was not associated with a significant difference in asthma severity in sensitized children, but cat ownership was associated with a significant decrease in asthma severity in non-sensitized children. However, cat allergy did not influence symptom severity, β -agonist use or medication use. In an era when atopy is on the rise worldwide, an understanding of the impact of aeroallergens on asthma severity in children is essential. We found the burden of aeroallergen sensitivities is a positive driving force on asthma severity in children. Moreover, in this Southern Californian study population, outdoor allergens, not HDM, was associated with asthma severity.

Aeroallergens have long been recognized to induce asthma attacks (13). This has been shown through direct instillation of allergen to the lung (bronchoalveolar challenges) and through “real-life” allergen exposures in which sensitized asthmatics develop bronchoconstriction (13, 14). Skin testing by the percutaneous method is a commonly used method of identifying aeroallergen sensitivity that strongly corresponds to patient history (15). In this study of Southern California asthmatic children, we found 84.2% of participants to be allergic to at least one aeroallergen on the skin test panel as assessed by the percutaneous method. This is similar to findings of the Childhood Asthma Management Study (CAMP), in which 83.9% of participants were atopic. The atopic profiles

of children in the present study show pollen reactivity predominated (88%), followed by molds (72%), HDM (59%), and cat (46%). These atopic profiles were further analyzed for their relationship to asthma severity.

Indoor allergens such as HDM, cat, and certain molds are thought to be a major cause of incident asthma (16). HDM sensitivity, in particular, has been linked to asthma incidence (3). It was therefore surprising to find that HDM was not associated with asthma severity in this study. We found no association between HDM sensitivity and asthma severity, whereas atopy to molds was associated with a greater asthma severity as well as more days with moderate or worse asthma symptoms, increased β -agonist medication use, and higher medication score (Table 2). Other investigators have also failed to find an association between HDM sensitivity and increased asthma severity (17, 18). Interestingly, O'Driscoll et al. found that mold sensitivity was associated with asthma severity while HDM sensitivity was not. Other studies have similarly demonstrated that mold sensitization is associated with an increased risk for asthma severity (19, 20). Several theories have been proposed to explain this, including that molds act as adjuvants to induce T-helper type 2 (T_H2) profiles through stimulation of IL-13 (21). O'Driscoll et al. suggested that fungal proteases act directly to disrupt airway epithelium and cause bronchial hyperresponsiveness (18). Although possible, these theories do not take into account that HDM also contains proteases, which not only facilitate the passage of allergens across the bronchial epithelium (22–23) but have also been shown to induce pro-inflammatory cytokine release from human bronchial epithelium (24). Perhaps the simplest explanation may be that molds, such as *Alternaria*, have a stronger influence in driving asthma severity in Southern California because they have greater dispersion in drier climates (13). Increased mold exposure has been linked to increased sensitization (25), in particular as compared with HDM in drier climates (26). It is therefore possible that mold is more important than HDM in influencing asthma severity in Southern California because of the environmental condition where children are exposed to mold.

Sensitivity to environmental aeroallergens has long been thought to play a significant role in influencing asthma severity (27). Recently this role has been challenged (28, 29). Several investigators have suggested that non-allergic immunostimulatory factors from biological material, such as endotoxins, may be more important in inducing airway inflammation than allergic mechanisms (16). It has been suggested that HDM and fungi are simply markers of the level of inhalable biomass. Endotoxin, which is ubiquitous in the environment, is a potent immunostimulatory component of the cell wall of all gram-negative bacteria that has been shown to induce and sustain asthma (30). The mechanism of induction and sustained asthma is proposed to occur through pattern recognition receptors such as CD14 and toll-like receptors on structural and resident inflammatory cells in the airway. The toll-like receptors and CD14 detect antigenic molecules that may mediate an effect, whereby endotoxin exposure prolongs eosinophil survival and aggravates airway inflammation. However, while these theories offer plausible explanations for the important non-allergic role of mold in wheezing, they do not explain why a greater degree of sensitivity to molds is associated with asthma severity in our study population.

Delfino et al. have previously shown that increased fungal spore counts in the atmosphere were associated with increased asthma symptoms in asthmatic children in three of the panels in the present study (31–33). Interestingly, they found in one study that the association was stronger for non-skin testable fungal spore counts than to the mold to which the patients were skin test positive, suggesting that current mold extracts do not identify all mold sensitivity (31). This may explain why few studies have shown a link between mold exposure and the expression of asthma. Other studies have shown that on days when mold counts are high, asthma deaths (34) and hospitalizations (35, 36) are increased. Skin test reactivity to mold has been shown to have a greater association to current asthma and asthma symptoms than HDM (37) (26) (16). Our study adds to the mounting evidence demonstrating that mold has a greater impact on asthma symptoms and medication use than HDM.

Pollens have long been known to be important triggers of asthma (38–40), but the effect of pollen sensitivity on asthma severity is not clear. We found that the degree of atopy to pollens is positively associated with controller medication use and β -agonist use. It has previously been shown that increased pollen exposure in infancy has been correlated to the increased likelihood of developing atopy (41). Pollen levels are influenced by a number of climate factors including thunderstorms, ultraviolet light, and rainfall. Recently, evidence has emerged that elevated CO_2 levels (42, 43) and increases in temperature (44, 45) are associated with increased pollen production. There is also evidence that warmer weather is associated with longer pollen seasons (40). In addition, it has been shown that trees grown in warmer climates have greater allergenicity (46, 47). Thus, increased pollen exposure may explain our findings of increased controller medication and β -agonist use in children with a greater degree of atopy to pollens.

Some studies have failed to show a correlation of exposure to pollens and the development of atopy (48). In fact, it has been suggested as early as 1873, by Blackley, that high pollen levels may confer protection. Recent studies have further shown that pollen allergenicity is more important in urban than rural areas, suggesting that pollen allergenicity may be related to adjuvant effects of environmental agents, such as air pollution. It has been speculated that air pollution may modify the relationship between pollen levels and asthma (49, 50). Studies by Diaz-Sanchez et al. have supported this by demonstrating the development of enhanced expression of specific immunoglobulin E (IgE) to pollen in nasal mucosa when administered in the presence of diesel exhaust (51). In Southern California, pollen counts are highest in the afternoon, when children are likely to be outside engaged in physical activity, which is also when ozone and particulate air pollutants can be highest. We speculate that the importance of the pollens in Southern California may be the combination of long pollination seasons with high air pollution driving allergenicity and medication use.

The role of cat reactivity to asthma severity appears far more complex. Counter intuitively, we found that in children with asthma who were skin-test-negative for cat, that cat ownership was protective. Interestingly, a subsequent analysis suggested that non-cat-sensitive participants who were cat owners did not have a reduced risk if their cat resided outdoors

compared to indoors. The literature has reported conflicting results on cat ownership and cat sensitivity (52). Ownby, in a recent review of the literature, reported that most studies on this subject show that early exposure to cats or dogs reduces the prevalence of sensitization and atopic disease later in childhood (53). However, Brussee et al. demonstrated that early cat allergen exposure can lead to sensitization (54), and Lau found that sensitization to cat is a risk factor for childhood asthma (55). Still other studies suggest that the association between cat and dog exposure and a lower risk of allergy is due to differences either in other environmental exposures or to genetic differences between exposed and non-exposed children. Our study focused on the asthma severity in atopic participants. It is unclear why owning a cat was associated with reduced asthma severity in non-cat-sensitive participants.

Many factors, in addition to atopy, have been implicated in determining asthma severity including genetics, environment, and the duration of asthma (56). Limitations of this study include an inability to link our findings to the long-term course of the participant's disease, and lack of quantifiable levels and duration of indoor allergen exposure. Correlation of aeroallergen exposure to sensitivity would have helped to delineate the causative role of exposure versus other pathogenic mechanisms, such as the non-immunologic role proposed for mold in asthma severity. However, a particular strength of this study is the longitudinal use of repeated measures to assess asthma severity rather than through one measure or participant recall, which can be inaccurate or biased (57). We were able to evaluate several repeated measures of asthma severity, including medication use, both controller medication and rescue medication use, days with moderate or worse symptoms (occurrence of asthma symptoms), and peak flow measures. By doing so, we found that the total number of positive skin tests was associated with more severe asthma ($p < 0.03$, OR 1.18 [95% CI, 1.02, 1.37]). This was primarily driven by medication use of both asthma controller medication and β -agonist use. There was an estimated increase of 10.3% in the rate of β -agonist use for each additional positive skin test. There was also a trend towards days with moderate or worse symptoms, but no association with peak flow measurements. Null results for PEF may be because of biases resulting from the use of different peak flow measurement methods or the relatively narrow representation by PEF of expiratory lung function.

This is the first study to demonstrate that an increased degree of atopy drives asthma severity, as determined through longitudinal repeated measures. The Childhood Asthma Study (CAS) has previously found in a cohort of allergic asthmatic children that the degree of atopy was associated with both persistence of asthma into adulthood and asthma severity as determined by pulmonary functions tests, clinical symptoms, and medication use (1). They concluded that the overall atopic burden may be more critical to the persistence of asthma into adulthood than individual aeroallergens. Indeed, they observed that individual aeroallergen sensitivity may vary with the local environment, and it is the degree of overall atopy that predisposes certain individuals to chronic airway inflammation and remodeling that leads to persistent disease. Further, it has been shown that despite the wide spectrum of modification of sensitivities, there is a trend for an

increasing degree of atopy with age, which peaks in young adults (58). It is clear that a critical period exists during childhood for the development of multiple allergic sensitizations. The CAS study suggests that asthma severity is established during this period. Our study supports these findings and demonstrates that the increasing degree of atopy in childhood drives asthma severity.

We found that the degree of atopy and reactivity to mold and pollens plays a significant role in medication use and frequency of asthma symptoms in asthmatic children in Southern California. While it is unclear why outdoor allergens have a stronger influence on asthma severity than HDM, it is possible that an interaction between high air pollution and extended pollination seasons of Southern California play a role by increasing pollen allergenicity (51, 59). In addition, the drier climate promotes increased release of mold spores and exposure due to the decay of dead vegetation (e.g., chaparral) beginning in the fall when particulate air pollution is often highest. The dry climate also inhibits the growth of dust mites. Nevertheless, further work is needed to understand why atopy to house dust mite was not associated with asthma severity, although it is established as a risk factor for the incidence of asthma.

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