

The relationships among environmental allergen sensitization, allergen exposure, pulmonary function, and bronchial hyperresponsiveness in the Childhood Asthma Management Program

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Background: Sensitivity and exposure to indoor allergens constitutes a risk factor for the development and persistence of asthma in children.

Objective: Our purpose was to evaluate the relationship between sensitivity and exposure to inhalant allergens and lung function and bronchial responsiveness in a group of children ($n = 1041$) aged 8.9 ± 2.1 years with mild to moderate asthma enrolled in the Childhood Asthma Management Program (CAMP).

Methods: With use of the extensive CAMP baseline cross-sectional data on spirometry, bronchial responsiveness, allergen sensitivities, and household allergen levels, the relationship of sensitization and exposure to allergens to lung function and methacholine sensitivity was evaluated. Children who enrolled in CAMP stopped all antiasthma medication except rescue use of albuterol and prednisone for exacerbations during the 5- to 16-week screening period. During the last 2 of these weeks they underwent spirometry and methacholine challenge. Indoor allergen exposures were determined from questionnaires completed by the parent. Household levels of indoor allergens (mite, cat, dog, cockroach, mold) were determined on house dust samples. Allergen sensitivity was determined by percutaneous skin testing with a standard battery of allergens plus locally important pollen and fungal spores. Lung function and bronchial hyperresponsiveness were compared for children sensitive and not sensitive to both indoor and outdoor allergens on skin testing and, if sensitive, for exposed and not exposed to the allergens to which they were positive on skin testing.

Results: There was a strong direct correlation between increased sensitivity to inhaled methacholine and skin test sensitivity to tree, weed, *Alternaria*, cat, dog, and indoor molds. When the relationship was examined by stepwise regression, the skin test sensitivities showing the strongest associations

with the concentration of methacholine that caused a 20% fall in FEV₁ were dog ($P = .003$), *Alternaria* ($P = .01$), and cat ($P = .05$). Children sensitive to any one of the aeroallergens tested were compared for the presence or absence of exposure to that allergen at the time that the methacholine challenge was performed. Those who were sensitive and exposed to weed and cat had greater methacholine sensitivity than those similarly sensitive but not exposed ($P = .003$ and $P = .02$, respectively).

Conclusions: Sensitivity to dog or cat dander or *Alternaria* by skin testing was associated with increased bronchial responsiveness but not decreased lung function in children with mild to moderate asthma. These findings support the important role that sensitization to certain allergens plays in modulating bronchial responsiveness. (*J Allergy Clin Immunol* 1999;104:775-85.)

Key words: Childhood Asthma Management Program, environmental allergen sensitization, allergens, bronchial hyperresponsiveness, pulmonary function, skin tests

In epidemiologic studies allergy has consistently constituted a risk for bronchial hyperresponsiveness¹⁻⁴ and current asthma³⁻⁷ in children and adults. This risk is particularly related to allergy to indoor allergens. Sensitivity to outdoor allergens, with the conspicuous exception of the fungus *Alternaria*, has been associated with little or no increased risk for asthma.^{1,3-7}

In this report we examine the baseline data from the National Heart Lung and Blood Institute (NHLBI)-sponsored Childhood Asthma Management Program (CAMP). This is a continuing 5-year clinical trial conducted at 8 clinical centers in the United States and Canada, involving 1042 children aged 5 to 12 years at entry.⁸ Children are randomized to receive treatment with budesonide, nedocromil, or placebo. The primary outcome variable is the FEV₁. The participants are monitored for asthma morbidity, psychologic development, somatic and lung growth, and potential side effects of asthma and its pharmacologic treatment. Unlike the epidemiologic studies referred to above¹⁻⁷ in which random population samples were studied, the children participating in CAMP were selected for the presence of mild to moderate asthma.

The data that form the basis for the analyses in this article are the patients' allergen exposures based on information provided by their parents or caregivers and an analysis of dust from their homes for allergens, their

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A complete list of participants in the CAMP Research Group appears at the end of the article.

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TABLE I. Home environment questionnaire

1. Has there ever been water damage to your home or its contents from broken pipes, leaks, or flood?
2. Has there been water damage to your home or its contents during the past year?
3. Does water ever collect on the basement floor?
4. Has there been mold or mildew on any surface inside your home during the past year?
5. Do you ever see cockroaches in your home?
6. Do you have any pets?
7. Number of pets (cat, dog, rabbit, guinea pig, hamster, gerbil, mice, bird, other pets)?
8. Which pets are allowed in the home?

Adapted from CAMP Form ES.⁹ Only those questions used for the analyses in this article are listed here.

Abbreviations used

CAMP:	Childhood Asthma Management Program
FEV ₁ PC ₂₀ :	Concentration of methacholine that causes a 20% fall in FEV ₁
MC:	Methacholine
NHLBI:	National Heart, Lung, and Blood Institute
SPT:	Skin prick test

sensitivities by prick skin testing (SPT) to environmental allergens, and the results of their spirometry and bronchial challenge with methacholine (MC), which were performed after at least 4 weeks of withholding all long-term control medications.

MATERIAL AND METHODS

Subjects

Subjects were recruited primarily through referral from primary care providers and by advertising to the public. In keeping with NHLBI policy, special efforts were made to ensure adequate representation of minorities.

To be eligible for enrollment in CAMP, a child was required to meet the following requirements: (1) age 5 to 12 years at initial interview, (2) chronic asthma symptoms as evidenced by one or more of the following for at least 6 months in the previous year: asthma symptoms more than once per week, inhaled bronchodilator use twice or more per week, or asthma medication daily, (3) asthma symptoms or morning or afternoon peak flow <80% personal best on at least 8 days during the screening period of 4 weeks, and (4) sensitivity to MC: concentration of MC that causes a 20% fall in FEV₁ (FEV₁PC₂₀) no greater than 12.5 mg/mL.

The following were reasons for exclusion: (1) presence of significant pulmonary disease other than asthma, (2) severe chronic sinusitis or nasal polyposis, (3) treatment for gastroesophageal reflux, and (4) severe asthma evidenced by one or more of the following:

- more than 1 hospitalization for asthma within the previous year
- more than 5 courses of oral corticosteroids in the previous year
- demonstrated need for continuous use of glucocorticoids either oral or inhaled
- FEV₁ <65% predicted when inhaled β_2 -agonists had been withheld for >4 hours and theophylline for >24 hours
- any history of intubation for asthma

Screening period

Children meeting the initial screening requirements were seen in the study center 5 to 16 weeks before randomization. Questionnaires about demographic characteristics, asthma history, and home environment were completed. At the second screening visit all anti-asthma medication except rescue use of albuterol was stopped. Peak flows and symptoms were then monitored for 4 weeks to further establish eligibility. The child's asthma was considered to be too mild if there were fewer than 8 days during the 4 weeks with a symptom score of at least 1 (on the basis of the preceding 24 hours: 0 = no asthma episodes; 1 = 1-3 asthma episodes, each lasting 2 hours or less; 2 = 4 or more mild asthma episodes, or 1 or more asthma episodes that temporarily interfered with activity, play, school, or sleep; 3 = 1 or more asthma episodes lasting longer than 2 hours, or resulting in shortening normal activity, seeing a physician, or going to a hospital), morning peak flow less than 80% of the previously determined personal best, or afternoon peak flow less than 80% personal best. Asthma was considered too severe if the child used more than 8 puffs of albuterol on 3 consecutive days, if nighttime awakenings because of asthma averaged more than 1.5 per week, if the mean diary card symptom score was greater than 2, or if the child used medication other than albuterol to control asthma. Those who still qualified underwent 3 visits in which additional baseline data were collected. Included in these data were an MC bronchial challenge and spirometry before and after inhaled albuterol performed on a different day.

Environmental questionnaire

Relevant questions from the home environment questionnaire that were used in the analyses for this study are listed in Table I.

House dust specimen collection

Approximately 6 months (range 0-2.2 years) after randomization a house dust specimen was collected from each child's home by a certified technician from the local CAMP center. The delay in collection was designed to allow the specimen to reflect environmental counseling and provision of mattress and pillow encasements for children sensitive on skin testing to house dust mites. The intended window for dust collection was approximately 6 months after randomization. However, specimens outside this window were accepted. A mixed house dust specimen (0.5 g) was obtained with a vacuum cleaner (Douglas Redivac model 6735, Scott-Fetzer, Walnut Ridge, Ariz) fitted with a disposable filter. Areas vacuumed for 2 minutes each were 2 m² of the upper surface of the patient's mattress, 1 m² of bedroom floor or carpet, 1 m² of living room-family room floor or carpet, 1 m² of kitchen floor, and a major item of upholstered furniture to which the child was exposed. The specimen was sieved to obtain fine dust. The specimens were then shipped frozen to the Dermatology Allergy Clinical Immunology Laboratory at Johns Hopkins University, Baltimore, Md, where they were quantitatively analyzed for the presence of major allergens of *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, dog, and cockroach with use of mAbs.¹⁰ An agar plate was streaked for enumeration of fungus colonies, which were not further identified.¹¹

TABLE II. Criteria for significant allergen exposure*

Allergen	Environmental survey†	House dust analysis
Cat	Cat in home	Fel d 1 >8 µg/g ¹¹
Dog	Dog in home	Can f 1 >10 µg/g ¹¹
House dust mite	No criteria	Der p 1 + Der f 1 >2 µg/g ¹¹
Cockroach	Sighting in home	Bla g 1 >2 U/g ¹¹
Fungi	Mold, mildew, water damage, or water collection in home	Mold plate from house dust >25,000 colonies
<i>Alternaria</i>	Enrollment during local <i>Alternaria</i> spore season	Not applicable

*Significant exposure was considered to be present if either criterion was fulfilled.

†Self-report on home environment questionnaire (Table I).

Spirometry

Spirometry was performed with a Stead-Wells volume displacement spirometer (Survey III Dry-seal spirometer, W. E. Collins, Braintree, Mass) interfaced to a computer (Dell model 325N, Dell Computer, Austin, Tex). The spirometry software was developed for the CAMP study by S & M Instrument (Doylestown, Pa). Quality control included a daily 3-L calibration check and leak test and a weekly linearity, healthy subject, and thermometer check. Pulmonary function technicians were required to have undergone certification on the basis of a written examination and having the records of 20 test sessions reviewed and approved. The spirometry data used in this analysis were obtained at least 4 weeks after the discontinuation of any long-term control medication and after the use of inhaled albuterol rescue medication by at least 4 hours.

MC bronchial challenge

MC challenge was performed as the method of 2 minutes of tidal breathing from a Wright nebulizer (Bayview Medical Supply, Baltimore, Md).¹² Children inhaled incremental doubling doses of MC from 0.098 to 12.5 mg/mL or until there was a 20% fall from the post-saline solution FEV₁. The FEV₁PC₂₀ was calculated by interpolation from the last 2 concentrations. The MC challenge was rescheduled if the child had used a bronchodilator within the prescribed period of time, if there had been a respiratory infection within the previous 4 weeks, if prednisone had been given within the previous 4 weeks, if an asthma episode had occurred, or if the FEV₁ was less than 70% of predicted. MC in the appropriate dilutions was prepared by the University of Iowa College of Pharmacy for the CAMP trial.

Allergen skin testing

A battery of allergen skin tests was performed on the back to determine the child's sensitivity. Children were to refrain from antihistamines or antidepressants for at least 72 hours. Drugs with known prolonged suppressive action on skin test reactivity were held for a longer period of time. The method used was either pricking or puncturing with the Wythe bifurcated needle (Allergen Laboratories, Columbus, Ohio). Both positive (5 mg/mL histamine) and negative (50% glycerin) controls were performed. A standard battery of extracts were tested at all 8 CAMP clinical sites. These were *D pteronyssinus* (10,000 AU/mL, Greer Laboratories, LaNoir, NC), *D farinae* (10,000 AU/mL, Greer Laboratories), cat (5,000 BAU/mL, ALK USA, Milford, Conn), dog, mixed breeds (1:20 wt/vol, Greer Laboratories), American cockroach (1:10 wt/vol, Meridian BioMedical, Berkeley, Calif), German cockroach (1:20 wt/vol, Greer Laboratories), *Penicillium* mix (1:20 wt/vol, Greer Laboratories), *Aspergillus* mix (1:20 wt/vol, Greer Laboratories), timothy grass (1:20 wt/vol, Meridian BioMedical), and short ragweed (1:20 wt/vol, Meridian BioMedical). *Alternaria tenuis* (1:20 wt/vol Greer Laboratories) was tested at all centers except Albuquerque, NM. The appropriate tree extracts for the region and any

additional grass or weed extracts were selected by the local investigator.

Before performing skin testing, the technician was required to undergo certification. This included a written examination plus demonstration of consistent ability to obtain negative reactions with saline solution and positive reactions of consistent size with histamine solutions.

After 15 minutes the wheals and flares of all positive reactions were outlined with ink and transferred with transparent tape to the case report forms. The longest and orthogonal diameters of the wheal and flare were then measured and those with a mean wheal of at least 3 mm or a flare at least 10 mm were considered positive.

Allergen exposure

For outdoor allergens, a season of exposure was determined for each site with use of the American Academy of Allergy, Asthma, and Immunology Pollen and Mold Survey.¹³ For perennial allergens, the presence of exposure was based on the parent's response to the home environment questionnaire and the analysis of the house dust specimen (Table II). Children were considered exposed to tree, grass, weed, or *Alternaria* if they had their randomization visit pulmonary function testing during the period that those pollens or spores were prevalent in the air in their location.

Statistical methods

Children were classified into those who were sensitive and those who were not sensitive to each allergen as determined by SPT. Children sensitive to one or more tree, grass, or weed extracts were considered sensitive to that category of aeroallergen. Analyses including *Alternaria* are limited to children from the 7 centers that tested for *Alternaria*. A child was considered sensitive to mite if he or she tested positive to either *D farinae* or *D pteronyssinus*, positive to nonseasonal mold if skin test positive to either *Aspergillus* or *Penicillium*, and sensitive to cockroach if positive to either American cockroach or German cockroach. The number of positive allergen skin tests used in several analyses is defined as the total number of categories of allergens to which the child had a positive skin test (up to 9).

Associations of allergen sensitivity with prebronchodilator FEV₁ percent of predicted and MC sensitivity were investigated with use of multiple linear regression techniques.¹⁴ Separate regression models were fit for each allergen sensitivity, controlling for age, race/ethnicity, gender, and center. Because the distribution of FEV₁PC₂₀ in the CAMP population was log normal and skewed in the direction of increased sensitivity to MC, regression models were fit with use of the natural logarithm of FEV₁PC₂₀ (Ln FEV₁PC₂₀) MC; means were then transformed back to the original scale. Models fitting FEV₁PC₂₀ also included duration of asthma, total eosinophil count (categorized as more than or equal to the median value and less than the median value) and log₁₀ total IgE (categorized as more than or equal to the median value and less than the median value) as covariates because these factors are associated with FEV₁PC₂₀.¹⁵ The adjusted mean values and differences or

TABLE III. Characteristics of CAMP participants

Total participants	1041
Age at randomization (y) (mean $\pm$ SD [range])	8.9 $\pm$ 2.1 (5.2-13.2)
Minority participation (%)	32
African American	13
Hispanic	9
Other	9
Gender, male (%)	60
Duration of asthma since diagnosis (y) (median [range])	5 (0-12)
Total eosinophil count (cells/mm ³) (median [range])	400 (0-3171)
Total IgE (IU/mL) (median [range])	418 (1-40,560)
Prebronchodilator FEV ₁ (% predicted) (mean $\pm$ SD [range])	93.8 $\pm$ 14.4 (43.8-148.0) ^{19,20}
Postbronchodilator FEV ₁ (% predicted) (mean $\pm$ SD [range])*	102.8 $\pm$ 12.7 (61.8-154.7) ^{19,20}
MC FEV ₁ PC ₂₀ (mg/mL) (mean $\pm$ SD [range])*	1.11 $\pm$ 3.22 (0.02-13.27)
Mean daily as-needed albuterol use in 28-day screening period (puffs/d) (mean $\pm$ SD [range])	1.5 $\pm$ 1.4 (0-7.4)

*Error in software calculation of FEV₁PC₂₀ MC allowed enrollment of children with value somewhat higher than $\leq$ 12.5 mg/mL cutoff value.

ratios (sensitive vs not sensitive to the allergen) for each outcome measure were computed from the regression model.¹⁶ The adjusted means estimate the expected outcome measure in either the exposed (sensitive) or unexposed (not sensitive) groups with the other covariates equated to their average values. Separate models including interaction terms for allergen sensitivity with gender, race/ethnicity, and center were also fit; these models assess the consistency of the relationship between the outcome measure of pulmonary function and allergen sensitivity within subgroups determined by the covariates. Regression models including additional terms for exposure to the allergen and interaction between sensitivity and exposure to the allergen were fit to assess the separate effects of sensitivity and exposure to the allergen (by self-report, home dust sample analysis, or month of enrollment, Table II) and the net effect of both sensitivity and exposure. Backward stepwise regression¹⁷ was used to assess the net effect of the different allergen sensitivities when all are included in the model. Regression models including the number of positive skin tests were used to assess the effects of "quantity" of sensitivity on FEV₁PC₂₀. *P* values derived from the regression models were used for primary outcome comparisons, and adjustments were not made for multiple comparisons or multiple outcomes.¹⁸ A *P* value $<.05$ was chosen as the cutoff value for statistical significance.

RESULTS

Demographic and general characteristics

One thousand forty-one children were enrolled at the 8 clinical study centers between November 1993 and September 1995. The distribution of enrollment was 210 (20%) during December to February, 318 (31%) during March to May, 316 (30%) during June to August, and 197 (19%) during September to November of the calendar year. The demographic and general characteristics of the children are listed in Table III. The male predominance reflected asthma prevalence in the ages enrolled. There was a representative participation of children from minority groups (32% of enrollees). The mean baseline spirometry was consistent with a population with mild to moderate asthma who were able to tolerate 5 weeks to 4 months without long-term control medication yet still had pulmonary function good enough to qualify for MC testing (FEV₁ at least 70% of that predicted for age).

SPT sensitivity

Eighty-eight percent of all the children had at least one positive SPT (Table IV). Nearly half the children were sensitive to grass, weed, mite, and cat extract; more than 40% to tree extracts; more than 30% to *Alternaria*, cockroach, and indoor mold extracts; and nearly one fourth to dog. Sensitivity to pollen extracts was equally as common as sensitivity to the indoor allergens.

Allergen exposures

Exposure to perennial allergens was common in these children (Table V). Two thirds of the subjects had furred or feathered pets in the home, whereas significant exposure to indoor fungal, house dust mite, and cockroach allergens was considered to be present in 72%, 42%, and 24% of the children, respectively. Indoor fungal exposure was suggested much more commonly by parents on the questionnaire than it was confirmed by mold colony counts from house dust samples. Overall, 56% of children were exposed to at least one indoor allergen to which they were sensitive.

Allergen sensitivity and pulmonary function

There was no statistically significant difference in prebronchodilator FEV₁ percent of predicted between the children who tested positive and the children who tested negative to any of the allergens examined, although there was a trend toward a lower FEV₁ for children sensitive to dog (*P* = .13) and cat (*P* = .14) and the prebronchodilator FEV₁ was lower in the groups with a positive SPT to all allergens except tree pollen. Allergen sensitivity was associated with a lower FEV₁PC₂₀ for all sensitivities examined except for grass, mite, and cockroach; the differences for the most part were all statistically highly significant (Table VI). Regression analyses for interaction of sensitivity with gender, race/ethnicity, and center (each considered separately for interaction) indicate that the association of greater sensitivity to MC with allergen sensitivity is similar in and present across all centers, both genders, and all racial/ethnic groups. Regression analyses, including terms for sensitivity, exposure, and interaction

TABLE IV. SPT sensitivity by allergen

Allergen extract	No. tested	No. positive	% positive
Grass extracts*	1041	514	49
Timothy	1041	485	47
Bermuda	518	195	38
Cat extract	1040	509	49
Weed extracts†	1041	496	48
Ragweed	1041	390	37
Mite	1040	503	48
<i>D farinae</i>	1040	436	42
<i>D pteronyssinus</i>	1039	450	43
Tree‡	1036	457	44
<i>Alternaria</i>	915	338	37
Cockroach	1041	353	34
German	1040	302	29
American	1041	247	24
Mold (indoor)	1040	318	31
<i>Penicillium</i>	1040	253	24
<i>Aspergillus</i>	1039	230	22
Dog extract	1040	236	23
At least 1 positive skin test	1041	914	88

*Grasses tested included English planter, plantago, and/or yellowdock in addition to Bermuda grass and Timothy grass.

†Weeds tested included artemisia, eastern weeds, kochia, lambs' quarter, pigweed, Russian thistle, and/or sagebrush in addition to short ragweed.

‡Trees tested included alder, birch, cedar, cottonwood, elm, juniper, mulberry, oak, olive, walnut, and/or a 6-tree mix.

TABLE V. Exposure to allergens in the home

Allergen	Prevalence (%)
Furred or feathered pet in home (by interview or dust level)*	65
Cat (self-report or dust level)*	31
Dog (self-report or dust level)*	42
Rabbit, guinea pig, hamster, gerbil, or mouse (interview only)	12
Bird (interview only)	9
Mold (self-report or dust level)*	72
House dust fungal count >25,000 U/g	20
History of fungal growth or dampness in home (interview only)	66
Cockroaches (self-report or dust level)*	24
House dust mites (dust level)*	42
At least 1 indoor allergen to which child is sensitive†	56

n = 1041.

*See criteria in Table II.

†At least 1 indoor allergen (cockroach, cat, dog, indoor mold, and/or dust mite) and sensitive to it by SPT.

between sensitivity and exposure to the allergen, indicate the sensitivity accounts for the lower FEV₁PC₂₀.

Because allergen sensitivity was so strongly and consistently correlated with increased sensitivity to MC, the effects of specific sensitivities and the quantity of sensitivity (considered as the number of positive skin tests) were investigated. Results from the backward stepwise regression indicate that sensitivity to dog extract has the strongest effect on FEV₁PC₂₀, with sensitivity to *Alternaria* the next strongest, and sensitivity to cat third strongest (Table VII). The elimination of the other sensitivities from the model suggests that sensitivity to mite, cockroach, seasonal pollens, and nonseasonal mold (*Aspergillus* or *Penicillium*) has less effect on FEV₁PC₂₀ or that the sensitivities that were eliminated were correlated with one or more of the sensitivities that remained in the regression model.

Results of fitting a regression model for FEV₁PC₂₀ that included the number of positive tests as categorized in 4 sequential strata are shown in Table VIII. The steadily decreasing ratio (for sensitive to not sensitive) as the number of positive skin tests increases indicates that sensitivity to MC increases as the number of allergen sensitivities increases.

Effect of allergen exposure in sensitive children

The children who were sensitive to the allergens tested were separated into those exposed and those not exposed to that allergen at the time of randomization. These 2 groups were then compared for their prebronchodilator FEV₁ and FEV₁PC₂₀ (Table IX). Among those allergens that had been demonstrated by stepwise regression (Table VII) to have the greatest independent effect

TABLE VI. Allergen sensitivity and pulmonary function

Allergen	Prebronchodilator FEV ₁ % of predicted						FEV ₁ PC ₂₀ MC (mg/mL)					
	Adjusted means						Adjusted means					
	No.	% Sens	Sens	Not sens	Diff	Statistical significance	No.	% Sens	Sens	Not sens	Ratio	Statistical significance
Outdoor allergens												
Tree extracts	1034	44	94.2	93.4	0.80	<i>P</i> = .38	1033	44	0.99	1.21	0.82	<i>P</i> = .005
Weed extracts	1039	48	93.4	94.2	-0.75	<i>P</i> = .41	1038	48	1.02	1.20	0.85	<i>P</i> = .02
Grass extracts	1039	49	93.5	94.1	-0.62	<i>P</i> = .49	1038	50	1.04	1.18	0.88	<i>P</i> = .08
<i>Alternaria</i>	913	37	92.9	93.7	-0.86	<i>P</i> = .39	912	37	0.98	1.24	0.79	<i>P</i> = .002
Indoor allergens												
Cat	1038	49	93.1	94.5	-1.33	<i>P</i> = .14	1037	49	0.97	1.26	0.76	<i>P</i> = .0002
Dog	1038	23	92.6	94.2	-1.58	<i>P</i> = .13	1037	23	0.80	1.22	0.66	<i>P</i> = .0007 × 10 ⁻³
Mite	1038	48	93.6	94.0	-0.36	<i>P</i> = .69	1037	48	1.06	1.16	0.92	<i>P</i> = .23
Mold	1038	31	93.0	94.2	-1.16	<i>P</i> = .22	1037	31	0.96	1.18	0.81	<i>P</i> = .005
Cockroach	1039	34	93.0	94.2	-1.17	<i>P</i> = .21	1038	34	1.03	1.15	0.89	<i>P</i> = .12

Regression models were fitted with use of $\ln(\text{FEV}_1\text{PC}_{20})$; means were then transformed to original scale. *Adjusted means*, Population-adjusted means and differences were derived from multiple linear regression models for each allergen sensitivity. Covariates were age, race/ethnicity, gender, clinic (all models), and total eosinophil count (more than or equal to median total eosinophil count, less than median total eosinophil count), $\log_{10}(\text{total IgE})$ (more than or equal to median $\log_{10}(\text{total IgE})$, less than median $\log_{10}(\text{total IgE})$, and duration since asthma diagnosis (models fitting $\ln(\text{FEV}_1\text{PC}_{20})$). *Sens*, Sensitive by SPT; *Not sens*, not sensitive; *Diff*, difference between adjusted means; *Ratio*, ratio of geometric means: Sensitive/Not sensitive.

TABLE VII. Stepwise regression to identify sensitivities associated with lower FEV₁PC₂₀

Allergen	Removed at step	Ratio: sens vs not sens	95% CI for ratio	Statistical significance
Dog	—	0.75	0.63-0.91	<i>P</i> = .003
<i>Alternaria</i>	—	0.82	0.71-0.96	<i>P</i> = .01
Cat	—	0.86	0.73-1.00	<i>P</i> = .05
Tree	6	0.93	0.79-1.08	<i>P</i> = .32
Mold	5	0.94	0.79-1.11	<i>P</i> = .46
Grass	4	1.04	0.88-1.22	<i>P</i> = .64
Cockroach	3	1.02	0.86-1.20	<i>P</i> = .86
Mite	2	0.99	0.84-1.15	<i>P</i> = .86
Weed	1	0.99	0.83-1.18	<i>P</i> = .92

Regression models were fitted with use of $\ln(\text{FEV}_1\text{PC}_{20})$; means were then transformed to original scale. Regression model forced to include age, race/ethnicity, gender, clinic, total eosinophil count (more than or equal to median total eosinophil count, less than median total eosinophil count), $\log_{10}(\text{total IgE})$ (more than or equal to median $\log_{10}(\text{total IgE})$, less than median $\log_{10}(\text{total IgE})$, and duration since asthma diagnosis. *n* = 902. *Sens*, Sensitive by SPT; *not sens*, not sensitive; *CI*, confidence interval; *ratio*, ratio of geometric means: Sensitive/Not sensitive.

on FEV₁PC₂₀, there was no difference between the children exposed and not exposed to dog and *Alternaria*. Sensitive children exposed to cat allergen had greater reactivity to MC than did sensitive children not exposed to cat (*P* = .02). For weed exposure, there was a significant increase in MC sensitivity with exposure, whereas with grass exposure the opposite was true.

DISCUSSION

In this study we used the baseline data of the CAMP trial to examine the effect of sensitivity to aeroallergens as well as exposure to aeroallergens in sensitized asthmatic children, on pulmonary function and bronchial hyperresponsiveness. Sensitivity to tree, weed, *Alternaria*, cat, dog, and indoor mold aeroallergens on skin testing was associated with a significantly increased sensitivity to MC (Table VI). Because many of the children had multiple SPT reactions, stepwise regression analysis

was performed to determine which sensitivities were independently associated with lower airway hyperresponsiveness. This analysis indicated that only sensitivity to the indoor allergens dog and cat dander and the outdoor fungus *Alternaria* demonstrated independent significant relationships (Table VII). Although the other sensitivities could not be demonstrated to independently affect bronchial hyperresponsiveness, there was a highly significant relationship between the total number of positive skin tests in a child and the level of sensitivity to MC (Table VIII). When children who were sensitive to the individual aeroallergens were compared with the children not sensitive to that allergen, no differences could be detected in the prebronchodilator FEV₁ (Table VI).

With aeroallergens there was both the factor of sensitivity to the aeroallergen, as measured by SPT (Table IV), and significant exposure in the home as indicated by the home environment questionnaire and by analysis of house dust collected from the home (Table V). An analy-

TABLE VIII. Analysis of FEV₁PC₂₀ (in milligrams per milliliter) by number of positive skin tests

No. of positive tests	Adjusted mean	Ratio: sens vs not sens	95% CI for ratio	Statistical significance
Not sensitive (0)	1.71	1.00	—	—
1	1.26	0.74	0.56-0.98	P = .03
2-4	1.13	0.66	0.52-0.84	P = .0009
5-9	0.97	0.57	0.44-0.73	P = .00001

Regression models were fitted with use of 1n(FEV₁PC₂₀); means were then transformed to the original scale. Regression model forced to include age, race/ethnicity, gender, clinic, total eosinophil count (more than or equal to median total eosinophil count, less than median total eosinophil count), log₁₀(total IgE) (more than or equal to median log₁₀[total IgE], less than median log₁₀(total IgE), and duration since asthma diagnosis. n = 906. *Sens*, Sensitive by SPT; *not sens*, not sensitive; *ratio*: Ratio of geometric means: Sensitive/Not sensitive; *CI*, confidence interval.

TABLE IX. Pulmonary function and exposure to allergens among allergen-sensitive asthmatic patients

	Prebronchodilator FEV ₁ % of predicted						FEV ₁ PC ₂₀ MC (mg/mL)					
	Adjusted means						Adjusted means					
	No.	% Exposed	Exposed	Not exposed	Diff	Statistical significance	No.	% Exposed	Exposed	Not exposed	Ratio	Statistical significance
Outdoor allergens												
Tree extracts	456	20	92.1	94.3	-2.22	P = .19	456	20	1.04	0.90	1.16	P = .27
Weed extracts	496	13	93.8	93.2	0.57	P = .77	495	13	0.65	1.01	0.64	P = .003
Grass extracts	512	17	94.6	92.3	2.23	P = .18	514	17	1.21	0.89	1.36	P = .02
<i>Alternaria</i>	338	17	94.0	92.0	2.03	P = .35	337	17	0.94	1.00	0.94	P = .70
Indoor allergens												
Cat	508	29	92.1	93.5	-1.39	P = .33	506	29	0.77	0.98	0.78	P = .02
Dog	235	40	93.9	92.0	1.93	P = .35	236	39	0.79	0.65	1.21	P = .21
Mite	481	54	93.4	91.8	1.56	P = .26	479	54	0.92	0.98	0.94	P = .61
Mold	318	75	92.3	92.9	-0.56	P = .78	317	75	0.88	0.88	1.01	P = .96
Cockroach	352	30	94.0	92.0	1.99	P = .32	353	30	0.88	0.89	0.98	P = .90

Regression models were fitted with use of 1n(FEV₁PC₂₀); means were then transformed to original scale. Adjusted means, Population-adjusted means and differences were derived from multiple linear regression models for each allergen sensitivity. Covariates were age, race/ethnicity, gender, clinic (all models), and total eosinophil count (more than or equal to median total eosinophil count, less than median total eosinophil count), log₁₀(total IgE) (more than or equal to median log₁₀[total IgE], less than median median log₁₀(total IgE), and duration since asthma diagnosis (models fitting 1n(FEV₁PC₂₀)). *Exposed*, Exposed by criteria in Table II; *Diff*, difference between adjusted means, Exposed - Not exposed; *Ratio*, ratio of geometric means, Exposed/Not exposed.

sis was performed to examine whether, in children who were sensitive to an aeroallergen, the bronchial responsiveness to inhaled MC was increased if they were also exposed at the time of pulmonary function and MC testing to that allergen (Table IX). Among the indoor allergens, there was a marginal increase in MC sensitivity in those cat-sensitive children who were exposed in the home. There was no trend for exposure to any of the other indoor allergens to increase MC sensitivity, nor was there increased bronchial responsiveness for those sensitive to *Alternaria* who were enrolled during the months of *Alternaria* spore prevalence. There were associations between MC sensitivity and performance of the challenge during or out of the weed and grass seasons in children sensitive to those allergens. For weed exposure, there was a significant increase in MC sensitivity with exposure, whereas with grass exposure the opposite was true: those sensitive children randomized during the grass pollen season had less bronchial sensitivity to MC (Table IX).

Although sensitivity and exposure to environmental factors such as indoor allergens and *Alternaria* have been reported in epidemiologic studies to increase bronchial responsiveness and the risk for asthma, it would not have

been a surprise if correlations were not observed in this study. Epidemiologic studies examine subjects randomly selected from the general population, the majority of whom have neither bronchial hyperresponsiveness nor current asthma. Therefore the effect of allergens on the airways is easily discernible. In the CAMP trial, however, all children were required to have asthma within a defined range of the mild and moderate categories. Furthermore, all were required to demonstrate a degree of hyperresponsiveness to MC. Therefore the effect of allergen sensitivity in some children could have been offset by other factors, either genetic or environmental, contributing to asthma severity in the other children in the study, and the effect of specific sensitivities on bronchial hyperresponsiveness could have been obscured. It is apparent that this was not the case. In contrast, although MC reactivity was significantly greater in children sensitive to these particular allergens, the degree of difference between sensitive and nonsensitive children was always less than one doubling dilution of MC.

Most epidemiologic studies have been in agreement that pollen sensitivity conveys, at the most, minimal risk for development of asthma in the general population.^{1,4,6,7} This lack of relationship to asthma has been

attributed to the large size of pollen grains, making penetration into the lower airways unlikely. In certain circumstances of very heavy pollen exposure, such as grass²¹ and birch,²² however, clinical exacerbations of asthma, evidence of increased lower airway inflammation,²² and increased nonspecific bronchial hyperresponsiveness²³ have been reported. In this study we could not demonstrate any convincing independent effect of sensitivity to pollens on levels of pulmonary function or bronchial responsiveness in children enrolled in the study.

Sensitivity to the seasonal fungal spore *Alternaria* has been found to be associated with an increased risk for asthma⁷ and increased bronchial responsiveness.⁴ Otherwise, the strongest associations in epidemiologic studies are between sensitivity to indoor allergens and risk for asthma⁴⁻⁷ and bronchial hyperresponsiveness.^{1,4} Sensitivity to cat,^{1-3,6} dog,⁶ house dust mite,¹⁻⁴ and crude house dust⁷ extracts has each been reported to increase the risk for asthma or bronchial hyperresponsiveness. House dust mite sensitivity has also been reported to be associated with lower levels of lung function in Norwegian adults.²⁴ Recently, cockroach sensitivity has been recognized as an important factor in asthma in North American inner-city populations.^{25,26}

Our study revealed highly significant independent increases in bronchial responsiveness to MC in children sensitive to dogs, *Alternaria*, and cats. The finding of a relationship between sensitivity to these indoor allergens and *Alternaria* and bronchial hypersensitivity is consistent with the body of epidemiologic studies and indicates that even in a population selected for asthma the importance of sensitivity to these allergens can be demonstrated.

There are several surprising results in our findings. Foremost would be the failure of sensitivity to the house dust mites to increase bronchial hyperresponsiveness independent of dog, cat, *Alternaria*, and the other sensitivities shown in Table VII. House dust mite sensitivity has been demonstrated to be a major risk factor for asthma and bronchial hyperresponsiveness in areas of high mite prevalence.²⁻⁵ In contrast, sensitivity to animal danders, but not mite sensitivity, has been found to be the major risk factor in an arid climate.⁶ Although significant levels of mite allergens were detected in 48% of the homes, many of the sites for the CAMP study were in the colder or drier parts of North America; this may have reduced the impact of house dust mite sensitivity. The analysis in Table VII was repeated excluding data from Denver (which is known to have low mite exposure); results were similar. An overall low level of cockroach allergen may have accounted for the lack of an effect of sensitivity to cockroach on MC sensitivity. The second surprising finding was the lack of an additive effect of allergen exposure on bronchial responsiveness to MC among those children sensitive to the individually important allergens: dog and *Alternaria*. In the case of dog-sensitive, and to a degree for cat-sensitive children, this might suggest that the virtually ubiquitous presence of these allergens^{11,27,28} is sufficient to affect bronchial reactivity

to MC with or without exposure in the home. In contrast, it should be remembered that the assessment of allergen exposure was based on both the home environment questionnaire and house dust analysis for cat, dog, fungi, and cockroach allergens, but only on house dust analysis for house dust mite allergen. Although the home environment questionnaire was completed at the time of enrollment, the house dust specimen was not collected until, on an average, 6 months later. Thus house dust collection often followed skin testing and counseling regarding institution of environmental controls, including mattress and pillow encasing for all children sensitive to mites at the 6 centers where mite allergen exposure was anticipated. The difference in time between skin testing and MC challenge and collection of the house dust specimen, plus the impact of environmental control measures, may help explain the failure of house dust mite allergen exposure to correlate with MC responsiveness in mite-allergic children. The differing effects of enrollment during the weed and grass pollen seasons in sensitive children is also difficult to reconcile. There was a trend for sensitivity to weed pollen extracts to be associated with increased sensitivity to MC; hence an effect of weed pollen exposure on bronchial sensitivity could be accepted. There was no tendency for sensitivity to grass pollen extract to be associated with increased MC responsiveness. Therefore the lesser sensitivity to MC in children enrolled during the grass pollen season might reflect the absence of other factors in the summer time, such as viral infections.

Why the difference in effect of allergens on levels of pulmonary function and bronchial responsiveness? It is likely that the effect of exposure on pulmonary function is more transient than that on bronchial responsiveness and hence less likely to be detectable in the clinic. Certainly, bronchial hyperresponsiveness decreases very slowly even after the complete elimination of allergen exposure.^{29,30} Alternately, bronchial hyperresponsiveness in children may be an early indication of airway inflammation, and decreases in FEV₁ may be a late effect with increasing duration of the exposure.

In summary, examination of the effect of aeroallergen sensitivity and exposure on children from a broad range of socioeconomic and ethnic backgrounds with mild to moderate asthma has once again confirmed the important role of sensitivity and to a lesser degree exposure to certain indoor allergens and the seasonal fungus *Alternaria* as factors in increasing bronchial hyperresponsiveness. Allergen exposure may also adversely affect levels of pulmonary function during periods of exposure; however, a persistent effect was not demonstrable on pulmonary function testing performed in the clinic. Further studies will be required to determine to what extent these observations apply to children with more severe asthma or to adults with asthma.

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