

Original article

Mouse allergen-specific antibody responses in inner-city children with asthma

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Background: Although mouse allergen exposure is common in inner-city homes, little is known about the relationships between exposure and humoral immune responses to mouse allergen in this population.

Objective: To examine relationships between mouse allergen exposure and allergen-specific IgE and IgG responses in inner-city children with asthma.

Methods: Inner-city children with asthma underwent skin testing and venipuncture for determination of mouse allergen-specific IgE and IgG levels. Settled dust samples were collected from their homes for allergen analysis.

Results: The study population (n = 112) was predominantly African American (92%) with a mean age of 4.4 years. The prevalence rate of mouse sensitization was 25% and did not consistently increase with increasing Mus m 1 levels. Instead, the prevalence rate was lowest among those exposed to <2 µg/g, increased among those exposed to 2-7.9 µg/g and 8-29.9 µg/g, and then decreased among participants exposed to >29.9 µg/g (14%, 20%, 40%, and 28%, respectively). Similarly, the prevalence rates of mouse allergen-specific IgG and IgG₄ did not increase across increasing exposure categories. Mouse allergen-specific IgG and IgG₄ were strongly associated with IgE sensitization (odds ratios [95% CI], 82.8 [20.5-334.4] and 50.4 [14.0-181.7], respectively).

Conclusion: High-level exposure to mouse allergen in children may be associated with attenuated humoral responses of all isotypes rather than selective attenuation of IgE.

Clinical implications: Protection against allergic sensitization by high-dose allergen exposure may not be mediated by preferential production of IgG over IgE. (*J Allergy Clin Immunol* ■■■■;■■■;■■■-■■■.)

Key words: Mouse allergen, inner-city asthma, mouse sensitization, IgG, IgG₄

Although mouse allergy is a well known occupational disease,^{1,2} recent studies have demonstrated that mouse allergen is commonly found in U.S. homes.³⁻⁶ In addition, several studies have found a surprisingly high prevalence rate of allergic sensitization to mouse among children with asthma^{3,7} as well as an association between household mouse allergen exposure and skin test sensitivity to mouse.^{3,7}

Although exposure to mouse allergen in general appears to be a risk factor for skin test sensitivity to mouse,^{3,7} a better understanding of the full shape of this dose-response curve is needed to develop strategies to reduce the risk of skin test sensitivity to mouse. If, for example, there is an increasing monotonic relationship between exposure and IgE-sensitization (i.e., the prevalence rate of sensitization always increases as exposure increases), then any reduction in exposure should result in an incremental decrease in the risk of sensitization.

On the other hand, the relationship between risk of sensitization and exposure may not be linear, so that any given reduction in exposure may not result in a reduction in the risk of IgE sensitization. For example, recent studies have suggested that high-level exposure to some indoor allergens, such as Fel d 1, might protect against allergic sensitization, and that this protective effect is characterized by a pronounced allergen-specific IgG response.^{8,9} It remains unclear whether this "high dose" protective effect is seen in the setting of household exposure to mouse allergen and, if so, if it is characterized by high serum levels of mouse allergen-specific IgG. To determine the shape of the dose-response relationship between Mus m 1 exposure and mouse allergen-specific antibody responses, we assessed household Mus m 1 levels, mouse allergen-specific IgG and IgG₄ levels, and allergic sensitization to mouse in inner-city preschool children with asthma.

METHODS

Study population and recruitment procedures

Recruitment for this study, a part of the Center for Childhood Asthma in the Urban Environment, occurred between September 2001 and December 2003. Because preschool children with asthma have not been well studied, and exposures during early childhood may play an important role in the pathogenesis of skin test sensitivity,

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Abbreviation used

NCICAS: National Cooperative Inner-City Asthma Study

we targeted preschool children with asthma. Participants were recruited from the health systems that provide care to the majority of residents of East Baltimore. Inclusion criteria were: (1) age between 2 and 6 years; (2) residence within the catchment area; (3) doctor-diagnosed asthma; and (4) symptoms of asthma and/or medication use for asthma in the preceding 6 months.

A home visit was scheduled for obtaining informed consent and conducting the home environmental assessment, and an appointment was made for the clinical assessment within 2 weeks of the home visit. The study was approved by the Johns Hopkins School of Medicine Institutional Review Board.

Home environmental assessment

During the home environmental visit, settled dust was collected for mouse allergen analysis. A household dust sample was collected from the kitchen, the television/living room, and the child's bedroom (including the bed and bed linens) using a standardized vacuum method.¹⁰ Protein was extracted from the filters and dust samples using a standardized protocol, and Mus m 1 was quantified by sandwich ELISA using immunosorbent purified sheep anti-Mus m 1 (kindly supplied by Dr J. Ohman).¹¹ The limit of detection for the Mus m 1 ELISA was 2.2 ng/g.

Clinical assessment

During the clinic visit, each child underwent skin prick testing (Multi-Test II; Lincoln Diagnostics, Decatur, Ill) to 14 aeroallergens: American and German cockroach (1:10 wt/vol; Hollister-Stier Laboratories, Spokane, Wash), dust mite mix (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, 5000 allergy units (AU)/mL each; Greer Laboratories, Lenoir, NC), cat dander (10,000 bioequivalent allergy units [BAU]/mL; Hollister-Stier), dog hair/dander (1:10 wt/vol; Hollister-Stier), mouse epithelia (1:20 wt/vol; Greer), rat epithelia (1:20 wt/vol; Greer), 3 pollens (Eastern Oak mix, 1:20 w/v; K-O-R-T Grass mix, 100,000 BAU/mL; Greer; and ragweed mix, 1:20 wt/vol; Hollister-Stier), and 4 molds (*Helminthosporium*, *Alternaria*, *Penicillium*, *Aspergillus*, 1:10 wt/vol; Hollister-Stier). Atopy was defined as at least 1 positive skin test to the panel of allergens tested. Serum samples were analyzed for mouse allergen-specific IgE by CAP-RAST (Pharmacia Diagnostics, Uppsala, Sweden; lot #60408) and for mouse allergen-specific IgG and IgG₄ using a solid-phase antigen-binding assay as previously described, using purified Mus m 1 as the substrate.¹² A mouse urine CAP-RAST greater than 0.35 kU_A/L was considered to be positive. A positive skin test was defined as a weal size of at least 2 mm greater than the negative control, as in previous childhood asthma studies.^{7,13} Because both skin test and RAST results were available for mouse, mouse sensitization was defined as either a positive skin test to mouse epithelial extract or a positive mouse urine CAP-RAST. A questionnaire was administered to the primary caregiver to assess sociodemographic characteristics.

Statistical analysis

All analyses were performed using Stata SE 8.0 (College Station, Tex). One hundred twelve participants had adequate allergen exposure data for the analyses of relationships between settled dust Mus m 1 levels and the allergic sensitization and the mouse allergen-specific IgG and IgG₄ outcomes. The Mann-Whitney U test was used to compare continuous variables, such as mouse allergen-specific

TABLE I. Characteristics of children with asthma (n = 112)

Characteristic	%
Race/ethnicity	
African American	92
White	3
Other	5
Gender	
Male	59
Female	41
Health insurance type	
Public insurance	90
Private	9
Self-pay/other	1
Educational attainment of caregiver	
8th grade/some high school	37
High school graduate	43
Some college or more	20
Housing type	
Row house/apartment	93
Detached/semidetached home	7

antibody levels, between groups. Cuzick test for trend was used to test for trends across multiple groups.¹⁴ Results of analyses examining the relationships between Mus m 1 levels and mouse sensitization were expressed as odds ratio (OR) and 95% CIs. Multivariable logistic regression was used to adjust for potential confounders.

The settled dust Mus m 1 level was expressed as an ordinal variable that included 4 groups. Cut points for the 4 exposure groups were based on previously proposed cut points for other indoor allergens of 2 µg/g and 8 µg/g. A *P* value of <.05 was set as the threshold for statistical significance.

RESULTS

Study population characteristics and mouse allergen exposure

The participants ranged in age from 2 years to 6 years (mean 4.4 years), and were predominantly African American (92%; Table I). Ninety percent of the study population received public health insurance, and only 20% of participants' caregivers had progressed beyond a high school education. Ninety-three percent resided in a row home or apartment. Sixty-seven percent of the participants had at least 1 positive skin test aside from mouse, and 43% had a positive skin test to cockroach.

Most of the study participants had persistent asthma symptoms and many had recent asthma-related health care utilization. Thirty-three percent of the participants reported nocturnal waking due to asthma symptoms in the preceding 2 weeks. Participants also reported a median of 4 days of cough without a cold during the preceding 2 weeks (interquartile range [IQR] 2-7), and a median of 1 day of albuterol use in the preceding 2 weeks (IQR 0-5). Eight percent had taken oral corticosteroids in the preceding 2 weeks. In addition, 33% had visited the emergency department for asthma in the preceding 3 months.

Settled dust levels of Mus m 1 in the kitchen were similar to levels reported in previous inner-city studies (median [IQR]: 7.4 µg/g [0.9-25.3]), and 82 caregivers

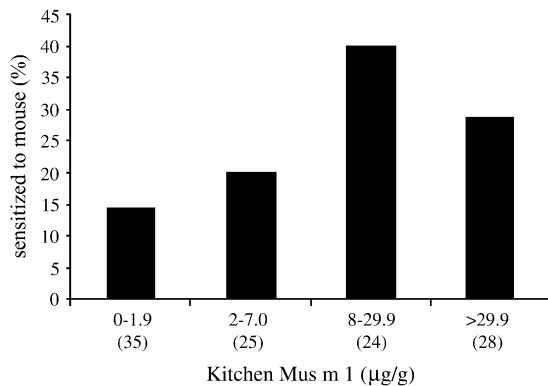


FIG 1. Prevalence rates of mouse sensitization by settled dust Mus m 1 levels. Settled dust Mus m 1 is expressed in µg/g, and the number of study participants in each group is indicated in parentheses below the x-axis.

(64.6%) reported current problems with mice. In addition, caregiver report of current problems with mice was associated with substantially higher Mus m 1 levels in settled dust (12.2 µg/g vs 2.1 µg/g; $P < .0001$). In fact, homes where the caregiver reported current problems with mice were more likely to have a Mus m 1 level of at least 2 µg/g than homes where the caregiver reported no problems with mice (80% vs 51%, respectively; $P = .002$).

Allergic sensitization to mouse and Mus m 1 exposure

Twenty-six percent of the study participants had evidence of IgE sensitization to mouse, by either SPT or quantification of serum levels of mouse allergen-specific IgE. Of the mouse-sensitized participants, 36% had both a positive skin test and a positive CAP-RAST, 36% had a positive CAP-RAST only, and 28% had a positive skin test only. When cut points of 2 µg/g and 8 µg/g were examined, children exposed to >2 µg/g tended to be more likely to be sensitized to mouse than those exposed to lower levels (29% vs 14%, respectively; $P = .08$), and children exposed to >8 µg/g were significantly more likely to be sensitized to mouse than those exposed to lower levels (34 vs 17%, respectively; $P = .03$).

However, when the relationship between sensitization and exposure was examined across the spectrum of Mus m 1 levels, the prevalence rate of mouse sensitization did not increase as Mus m 1 levels increased. Instead, the prevalence rate was lowest among those exposed to <2 µg/g Mus m 1, increased among those exposed to 2-7.9 µg/g and 8-29.9 µg/g Mus m 1, and then decreased among participants exposed to >29.9 µg/g Mus m 1 (14%, 20%, 40%, and 28%, respectively; Fig 1).

In a logistic regression model, the odds of IgE sensitization to mouse, relative to that for the lowest exposure group (<2.0 µg/g), was highest among those exposed to 8-29.9 µg/g Mus m 1 (OR [95% CI], 4.0 [1.1-13.8]). For participants exposed to either 2-7.9 µg/g or >29.9 µg/g, the odds of IgE sensitization to mouse were not statistically significantly different from that for participants

TABLE II. IgE sensitization to mouse by exposure category

Mus m 1 level	OR (95% CI)	OR* (95% CI)
2-7.9 µg/g	1.5 (0.4-5.8)	1.4 (0.3-5.7)
8-29.9 µg/g	4.0 (1.1-13.8)	4.5 (1.2-16.6)
>29.9 µg/g	2.4 (0.7-8.4)	2.1 (0.6-7.6)

*Adjusted for sex, atopy, and educational attainment.

exposed to <2.0 µg/g of Mus m 1 (Table II). After adjusting for gender, atopy, and educational attainment, the highest odds of sensitization were still observed among participants exposed to 8.0-29.9 µg/g Mus m 1 (OR [95% CI], 4.5 [1.2-16.6]). The relationship between IgE sensitization and bedroom settled dust Mus m 1 levels was similar to that observed between IgE sensitization and kitchen settled dust Mus m 1 levels (data not shown).

Because it is possible that the attenuated prevalence rate of mouse sensitization that was observed at the highest Mus m 1 levels was due to sensitized children moving from higher exposure to lower exposure homes, we also examined the relationship between sensitization and settled dust Mus m 1 levels among children who had lived in the same home throughout their lifetimes. When the analyses were restricted to the subgroup that had never moved, the relationship between allergic sensitization and Mus m 1 levels was similar to that observed in the study population as a whole (data not shown).

Mouse allergen-specific IgG and IgG₄ and Mus m 1 exposure

Twenty-seven percent of the study participants had detectable mouse allergen-specific IgG, and 25% had detectable mouse-allergen specific IgG₄. In addition, the IgG and IgG₄ responses were highly concordant: 93% of participants with mouse allergen-specific IgG also had mouse allergen-specific IgG₄.

The prevalence rates of detectable mouse allergen-specific IgG and IgG₄ did not increase with increasing settled dust Mus m 1 levels. In fact, the relationships between mouse allergen-specific IgG and IgG₄ and Mus m 1 levels were similar to the relationship observed between allergic sensitization and Mus m 1 levels (Fig 2). For example, prevalence rates of mouse allergen-specific IgG and IgG₄ increased with increasing levels of settled dust Mus m 1, except among those in the highest exposure category (>29.9 µg/g). For mouse allergen-specific IgG, the prevalence rates across exposure categories were 13%, 30%, 41%, and 28%, respectively. For mouse allergen-specific IgG₄, the prevalence rates across exposure categories were 13%, 30%, 36%, and 25%, respectively.

Mouse allergen-specific IgG/IgG₄ and IgE sensitization to mouse

A strong relationship was observed between mouse allergen-specific IgG and IgG₄ and allergic sensitization. Mouse-sensitized participants had substantially higher levels of both mouse allergen-specific IgG and IgG₄

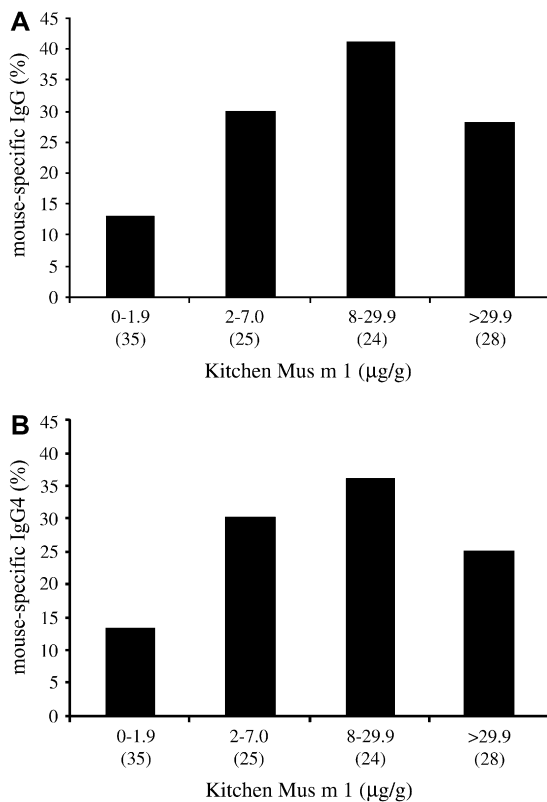


FIG 2. Prevalence rates of mouse-specific IgG (**A**) and IgG₄ (**B**) by settled dust Mus m 1 levels. Measures of mouse allergen exposure are displayed on the x-axes, and the prevalence rates of detectable mouse-specific IgG or IgG₄ are displayed on the y-axes. Settled dust Mus m 1 is expressed in µg/g, and the number of study participants in each group is indicated in parentheses below the x-axes.

than nonsensitized participants (IgG 18.6 AU/mL vs below detection [BD], respectively; $P < .0001$; IgG₄ 2.2 AU/mL vs BD, respectively; $P < .0001$; Fig 3). Furthermore, 82% of those with detectable mouse allergen-specific IgG were sensitized to mouse, compared with only 5% of those without detectable IgG ($P < .001$). For mouse allergen-specific IgG₄, 81% of those with detectable IgG₄ were sensitized to mouse, compared with only 8% of those without a detectable level of mouse allergen-specific IgG₄ ($P < .001$). Having detectable mouse allergen-specific IgG was associated with an 83-fold increase in the odds of allergic sensitization (OR [95% CI], 82.8 [20.5-334.4]), and detectable mouse allergen-specific IgG₄ was associated with a more than 50-fold increase in the odds of allergic sensitization (OR [95% CI], 50.4 [14.0-181.7]).

DISCUSSION

Findings from the present study suggest that there may not be an increasing monotonic relationship between exposure and allergic sensitization in inner-city populations where Mus m 1 levels are particularly high. Instead,

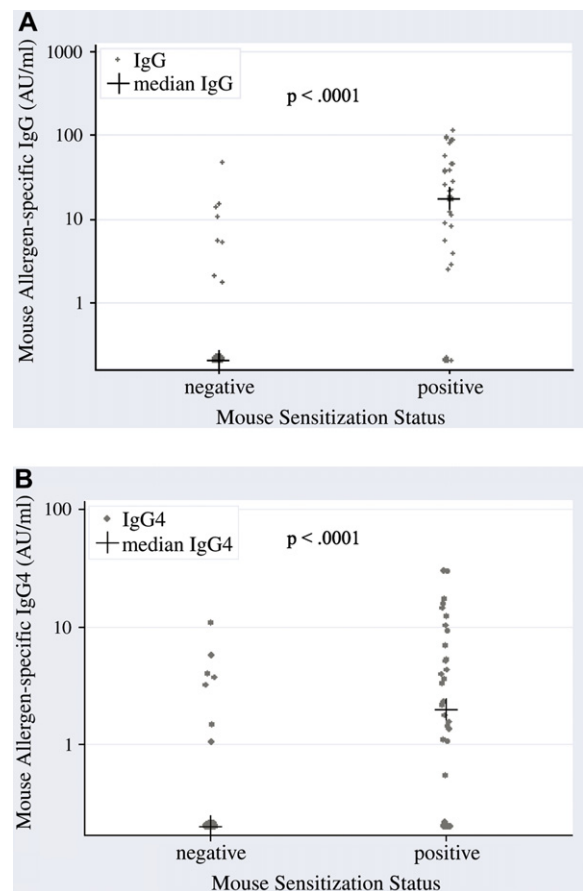


FIG 3. Dot-plots of mouse-specific IgG (**A**) and IgG₄ (**B**) levels by mouse sensitization status. IgE sensitization status is indicated on the x-axes, and the mouse-specific IgG and IgG₄ levels are indicated on the y-axes. The median IgG and IgG₄ levels are indicated by the plus signs. $P < .0001$ for both IgG and IgG₄, Mann-Whitney U test.

children who were exposed to Mus m 1 levels between 8.0 µg/g and 29.9 µg/g were most likely to have allergic sensitization, and no further increase in risk was observed among children exposed to >29.9 µg/g. In addition, mouse allergen-specific IgG and IgG₄ appear to be more strongly associated with allergic sensitization than with exposure, suggesting that the phenomenon of the “modified T_H2” response that has been observed with other indoor allergens in other age groups^{8,9} may not occur in preschool children with household mouse allergen exposure.

These findings have important implications for the development of immunomodulatory primary prevention strategies, suggesting that approaches aimed at increasing allergen-specific IgG levels may not afford protection against an allergen-specific IgE response in young children. The mechanisms involved in the interplay between allergen exposure and the IgE response deserve further study, particularly in young children who would be the primary candidates for immunomodulatory primary prevention.

Other studies have also examined relationships between Mus m 1 exposure and risk of allergic sensitization. In a previously published study of suburban school-age children with asthma, an increasing monotonic relationship was observed between household Mus m 1 levels and skin test sensitivity to mouse.³ It is important to note, however, that the Mus m 1 levels in those suburban homes were typically in ng/g concentrations (1000-fold lower than in the present study), suggesting that an increasing dose-response relationship occurs across a range of very low levels of exposure. However, the current study extends our understanding of the exposure range, and suggests that the shape of the dose-response relationship may differ at the markedly higher Mus m 1 levels seen in inner-city homes.

In the National Cooperative Inner-City Asthma Study (NCICAS) population, a study population in which Mus m 1 levels were similar to those observed in the present study population, children exposed to >1.6 µg/g Mus m 1 were at greater risk of having skin test sensitivity to mouse than children exposed to lower levels.⁷ However, the shape of the dose-response relationship was not reported, so that the findings in the NCICAS neither confirm nor refute the findings in the present study. In broad terms, the present findings are consistent with the NCICAS findings, because they suggest that the risk of allergic sensitization may be higher among inner-city children exposed to >2 µg/g than those exposed to lower levels, so that reducing exposure to the lowest levels may be required to reduce the risk of allergic sensitization.

Because allergen-specific IgG and IgG₄ have been associated with protection against allergic sensitization in some settings,⁸ we also examined serum levels of mouse allergen-specific IgG and IgG₄. Approximately 28% of the study participants had detectable specific IgG, and 25% had detectable specific IgG₄. These findings contrast with observations in a laboratory mouse worker population, where almost 84% of workers had detectable mouse allergen-specific IgG, but only 28% had detectable specific IgG₄.¹⁵ It may be that these differences in the pattern of IgG responses between these 2 study populations are due, at least in part, to differences in exposure as well as differences in the study population characteristics. For example, even though mouse allergen levels are high in inner-city homes, only about 25% of inner-city homes have levels of Mus m 1 that are similar to levels that can be found in occupational settings,⁴ indicating that the majority of homes have levels below those observed in occupational settings. In addition, the present study population may have a greater tendency to mount an allergen-specific IgG₄ response because they are very young and atopic, and both of these factors have been associated with a T_H2-skewed immunologic phenotype, which is associated with IgG₄ production.^{16,17}

It is also important to note that detectable mouse allergen-specific IgG or IgG₄ in the present study population is strongly associated with allergic sensitization to mouse. This observation is consistent with results from several occupational studies, where a rodent-specific

IgG₄ response has been a strong predictor of allergic sensitization.^{15,18,19} If children mount an IgG or IgG₄ response before allergic sensitization develops, then these non-IgE antibody responses may prove useful in identifying children at high risk of developing allergic sensitization to mouse. However, we cannot draw any conclusions about the temporal relationships between the IgG and IgE antibody responses in the context of the present cross-sectional study. Ultimately, prospective studies are needed to determine the potential utility of non-IgE antibody responses in predicting future allergic sensitization.

As discussed, we did not observe an increasing monotonic relationship between exposure and either specific IgG and IgG₄ levels or IgE sensitization to mouse. Although these findings do not support the “modified T_H2” hypothesis, they are consistent with observations made by other investigators with other indoor allergens. For example, exposure-skin test sensitivity response relationships for both cockroach²⁰ and dust mite allergens²¹ are not linear—similar to the findings in the current study. Specifically, the prevalence rate of cockroach sensitization increases with increasing exposure at low to moderate allergen levels, but then reaches a plateau, instead of continuing to increase.²⁰ In addition, investigators who conduct dose-finding studies for vaccines have observed that the highest doses can result in attenuated IgG responses.²² These observations are supported by evidence in cellular systems and animal models that higher antigen doses induce tolerance. For example, naïve T cells exposed to high doses of antigen elicit apoptosis in B cells, thereby inhibiting the production of antibody.²³ Several animal studies have also demonstrated that intranasal exposure to higher antigen doses induces tolerizing T cells, resulting in an immunologic phenotype characterized by absence of T cell cytokine responses, and reduction in IgE and IgG responses.^{24,25}

The results of the present study should be considered in the context of potential limitations of our study. For example, it is possible that families of children with allergic sensitization to mouse may have moved from a home with very high mouse allergen levels to one with lower levels to decrease their child's exposure because of apparent symptoms related to mouse infestation (similar to the healthy worker effect that can be observed in occupational studies). This source of bias could explain why allergic sensitization rates were attenuated at the highest Mus m 1 levels. However, this type of bias is unlikely for several reasons. First, when the analyses were restricted to children who had never moved, the relationships between Mus m 1 levels and IgE sensitization remained unchanged. Second, inner-city families have very little control over their environments. Waiting lists for subsidized housing are very long, and it can take a year or longer to find new housing. Third, available housing in the inner city is very likely to have mouse infestation, so that moving to another home is not likely to be associated with a significant reduction in mouse allergen exposure. The attenuated prevalence rate of allergic sensitization at the highest exposure levels are therefore not likely attributable to bias,

but the findings should be confirmed in prospective studies.

In the present population of inner-city preschool children with asthma, the risk of allergic sensitization to mouse does not appear to increase across all levels of *Mus m 1* exposure, and may be attenuated at the highest levels of exposure. In addition, neither mouse allergen-specific IgG nor mouse allergen-specific IgG₄ appears to be a marker for high-level exposure or protection against allergic sensitization. Instead, these non-IgE antibody responses are strong predictors of allergic sensitization in this population. These findings suggest that immunomodulatory strategies aimed at increasing allergen-specific IgG levels may not reduce the risk of IgE sensitization and instead may increase the risk of IgE sensitization. The mechanisms involved in the interplay between allergen exposure and humoral responses in young children may differ from those involved in older children and adults and deserve further study.

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