Published in final edited form as:

J Allergy Clin Immunol Pract. 2020 February ; 8(2): 596–602.e3. doi:10.1016/j.jaip.2019.08.044.

Do Baseline Asthma and Allergic Sensitization Characteristics Predict Responsiveness to Mouse Allergen Reduction?

Ammara Ahmed, DO¹, S. Christy Sadreameli, MD MHS⁷, Jean Curtin-Brosnan, MA¹, Torie Grant, MD MHS¹, Wanda Phipatanakul, MD MS², Matthew Perzanowski, PhD³, Susan Balcer-Whaley, MPH¹, Roger Peng, PhD⁴, Michelle Newman, BSN¹, Amparito Cunningham, MD MPH², Adnan Divjan, BA³, Mary E. Bollinger, DO⁵, Robert A. Wise, MD⁶, Rachel Miller, MD⁹, Ginger Chew, ScD³, Elizabeth C. Matsui, MD MHS⁸

¹Division of Pediatric Allergy/Immunology, Johns Hopkins University School of Medicine, Baltimore, MD

²Division of Pediatric Allergy/Immunology, Boston Children's Hospital, Harvard University Medical School, Boston, MA

³Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY

⁴Department of Biostatistics, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD

⁵Department of Pediatrics, University of Maryland School of Medicine, Baltimore, MD

⁶Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

⁷Division of Pediatric Pulmonology, Johns Hopkins University School of Medicine, Baltimore, MD

⁸Department of Population Health and Pediatrics, Dell Medical School at the University of Texas, Austin, TX

⁹Division of Pulmonary, Allergy and Critical Care Medicine, College of Physicians and Surgeons, Columbia University, New York, NY

Abstract

Corresponding Author: Elizabeth Matsui, MD MHS, The University of Texas at Austin, Department of Population Health, Dell Medical School, 1701 Trinity St., Stop Z0500, Austin, TX 78712, T: 512-495-5732, Elizabeth.matsui@austin.utexas.edu.

Conflict of interest statement: Dr. Phipatanakul has received consulting fees and honoraria from Genentech, Novartis, Teva, GlaxoSmithKline, and Sanofi/Regeneron, unrelated to the submitted work. Dr. Wise has received consulting fees and honoraria from GlaxoSmithKline, AstraZeneca, Novartis, Boehringer Ingelheim, Contrafect, Pulmonx, Roche, Regeneron, AbbVie, Spiration, Sunovion, Merck, Circassia, Pneuma, Verona, Bonti, Denali, Aradigm, Mylan, Theravance, Propeller Health, Kiniksa, and Syneos, unrelated to the submitted work. All other authors have nothing to disclose.

This study is registered under at clinicaltrials.gov

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Background: Mouse allergen reduction is associated with improvements in asthma among sensitized and exposed children, but whether clinical characteristics predict responsiveness to allergen reduction is unclear.

Objective: To examine the effects of clinical characteristics on relationships between mouse allergen reduction and asthma outcomes.

Methods: We performed a secondary analysis of data from a randomized, clinical trial of a mouse allergen intervention, examining the effects of atopy, demographics, lung function, asthma control, and asthma severity on relationships between mouse allergen reduction and asthma outcomes.

Results: Participants were predominantly low-income and minority (78% Black, 22% Hispanic), and had persistent asthma. Among less atopic participants (<6 +SPT), each 50% reduction in mouse allergen was associated with fewer symptoms (IRR [95% CI]: maximal symptoms: 0.94 [0.92–0.96]). There was little effect of mouse allergen reduction on symptoms among more atopic participants (p -values >0.05). The interactions between atopic status and mouse allergen reduction were statistically significant for all symptom outcomes; however, there was no evidence that atopic status influenced the effect of mouse allergen reduction on exacerbation-related outcomes. Older children (>9 years) tended to experience greater improvement in some asthma outcomes with reduction of mouse allergen exposure than younger children. There was no evidence that either mouse-specific IgE or lung function influenced the effect of mouse allergen reduction on any asthma outcomes.

Conclusion: Although there may be variability in the clinical response to mouse allergen reduction among low-income, minority children with asthma, there were no clinical characteristics that clearly identified a subgroup to whom the intervention should be targeted.

Keywords

Allergen exposure; allergen sensitization; allergen exposure reduction; mouse allergen exposure; allergen-sensitized and exposed asthmatic children; atopy; allergic asthma

Introduction

Exposure and sensitization to one or more of the major indoor allergens is strongly linked to asthma morbidity among children and adolescents (1–7). Also, there is an emerging body of evidence that reducing exposures, even to a single allergen in some populations, is associated with improvement in asthma outcomes (7–17). Children living in low-income, urban environments are particularly affected by indoor allergen exposure, often to pest allergens, which are major contributors to asthma morbidity in this population (1, 2, 5, 11, 13). Although interventions targeting pest allergens in this population can be efficacious, there is variability in clinical responses to allergen reduction, with some benefitting more than others. The predictors of response to allergen reduction are not well understood, and may be important for understanding how best to tailor home-based interventions targeting indoor allergen exposure.

We therefore sought to identify clinical characteristics that predict greater clinical response to allergen reduction. We used data from the Mouse Allergen and Asthma Intervention Trial (MAAIT), which was a randomized clinical trial that tested the effect of an intensive mouse allergen targeted integrated pest management (IPM) intervention plus pest management education, as compared to pest management education alone, among 5–17 year olds with persistent asthma and mouse sensitization and exposure. In this trial, there were no differences in mouse allergen exposure or clinical outcomes between groups, but across the whole population, substantial reductions in mouse allergen were observed, which were associated with improvements in measures of asthma control and exacerbation-related outcomes (12). To test our hypothesis that there are clinical characteristics that predict a greater clinical response to mouse allergen reduction, we examined the effects of baseline degree of atopy, demographic characteristics, and lung physiology on relationships between mouse allergen reduction and asthma outcomes in this population of urban, predominantly African-American and Latino/Hispanic, mouse-sensitized and exposed 5- to 17-year-olds with persistent asthma.

Methods

Study design

We performed a secondary analysis investigating relationships between study-participant associated characteristics, mouse allergen reduction, and symptom-related and exacerbation-related asthma outcomes. We analyzed data from an institutional review board–approved randomized clinical trial of 361 children and adolescents living in the Baltimore and Boston metropolitan areas, who were followed for 1 year. In MAAIT, participants were randomized to either receive an intensive mouse allergen targeted, professionally delivered integrated pest management (IPM) intervention plus pest management education or pest management education alone, and for the purposes of this analysis the groups were combined as there were no statistically significant differences in mouse allergen concentrations or asthma-related outcomes between the two groups. In this secondary analysis, the subset of participants who were not wheezing at the baseline visit, and therefore underwent skin testing to common environmental aeroallergens were included, resulting in a sample size of 297 children and adolescents.

Study Participants

Children and adolescents were recruited from emergency departments, outpatient primary care and subspecialty clinics, and databases of previous study participants who had given permission to be contacted. The major eligibility criteria were as follows: ages 5 to 17 years at enrollment, physician diagnosed asthma or asthma symptoms for at least 1 year, met National Asthma Education and Prevention Program criteria for persistent asthma or had been prescribed a controller medication, had an exacerbation in the previous 12 months, sensitized to mouse (either a positive skin prick test (net wheal ≥ 3 mm) or a positive mouse urine-specific IgE ≥ 0.10 kU/L), and highly exposed to mouse allergen (≥ 0.40 μ g/g of Mus m 1 in the bed settled dust or ≥ 0.50 μ g/g of Mus m 1 in bedroom settled dust). Written consent was obtained from the parent/guardian and assent was obtained from children and adolescents.

Pest Management Education and Professionally-delivered IPM

Pest Management Education—After randomization, pest management education regarding pest control measures was delivered to both the IPM intervention plus pest management education and pest management education alone groups at a home visit and included written information about and demonstration of setting mouse traps, sealing of holes and cracks, and general housekeeping practices.

Professionally-delivered IPM—The IPM group received targeted cleaning delivered to remove allergen reservoirs, placement of traps, extermination with rodenticide tracking powder, sealing of holes and cracks, installation of allergen-proof mattress and pillow encasements (CleanBrands LLC), and 2 portable air purifiers (Filtrete Room Air Purifier, 3M). Each primary treatment consisted of 2 to 2.5-hours followed by a 1-hour booster visit, approximately 4-weeks apart. Home visits occurred every 3 months to assess infestation. If infestation was persistent or recurred, an additional treatment was delivered. The pest management education alone group participants were offered an IPM intervention home visit after completing the study.

Clinic Visits

Outcome measures—Asthma-related outcomes were assessed by questionnaires administered by a trained research assistant at clinic visits at baseline, 6, and 12 months or by telephone calls at 3 and 9 months. Questionnaires captured controller medication treatment step (considered a measure of asthma severity), asthma control test (ACT), symptom-related asthma outcomes, asthma-related health care use and medication use. Symptom outcomes were the number of days with symptoms and number of days of rescue medication use in the 2 weeks before a visit or telephone call. The primary outcome, maximal symptom days, was defined as the largest value among the follow 3 symptom variables: days of slowed activity due to asthma; days of wheezing, coughing or chest tightness; and nights of waking with asthma symptoms in the previous 2 weeks. Exacerbation-related outcomes included asthma-related acute health care use (hospitalizations, emergency department visits, and unscheduled doctor's office visits) and oral steroid use in the previous 3 months. An acute care visit was defined as any hospitalization, emergency department visit, or unscheduled doctor's office visit.

Allergy skin testing—Allergy skin prick testing was performed to 14 common aeroallergens at the baseline visit by using a multitester device (Multitest II, Lincoln Diagnostics). The allergens tested were as follows: mouse epithelium, dog, cat, *Dermataphagoides pteronyssinus*, *Dermataphagoides farinae*, rat epithelia, German cockroach, American cockroach, tree mix, grass mix, *Alternaria* species, *Aspergillus* species, common ragweed, and *Cladosporium* species (Stallergenes Greer). A positive skin test response was defined as a net wheal diameter of ≥ 3 mm larger than the negative control, and a positive histamine control.

Pulmonary function testing—Pre- and post-bronchodilator spirometry was performed according to American Thoracic Society (ATS) guidelines using the Koko spirometer (18). Pulmonary function measurements of pre- and post-bronchodilator FEV1 and FVC were

collected at baseline, 6 months, and 12 months. Prebronchodilator lung function tests were defined by the National Asthma Education and Prevention Program (NAEPP) guidelines: FEV₁/FVC% less than 85%. Bronchodilator reversibility was defined as a ≥12% increase in FEV₁ (19). These measures were restricted to participants 8 years of age and older, as the Hankinson equations are valid down to the age of 8 years (20).

Home visits

Indoor allergen measures—Mouse allergen (Mus m 1) concentrations were measured by ELISA in dust samples collected from the bed, bedroom floor, and air from the participant's bedroom at baseline and every 3 months. Cockroach allergen (Bla g 2) concentrations were also measured at baseline and every 3 months, but only in bed dust samples. Other major indoor allergens (Fel d 1, Can f 1, Bla g 2, Der p 1, Der f 1, and Rat n 1) were measured in bed dust samples at baseline only.

Statistical analyses

We performed a secondary analysis of data from MAAIT to determine whether baseline clinical characteristics modified the effect of mouse allergen reduction on asthma outcomes. Mouse allergen levels were assessed every 3 months for a 1 year period and modeled as a time-varying, continuous log₂-transformed variable. Symptom-related outcomes were expressed as days/2 weeks and exacerbation-related outcomes were expressed as counts of the event over the previous 3 months, so both types of outcomes were considered to have a Poisson distribution. OCS use was expressed as a dichotomous variable indicating whether the participant reported OCS use in the previous 3 months or not and therefore binomial models were used. The baseline clinical characteristics that were pre-specified as potential effect modifiers were: degree of atopy (≥6 vs. <6 positive skin tests) and mouse-specific IgE. Post-hoc potential effect modifiers included: age, sex, lung function, bronchodilator reversibility, controller medication treatment step, and asthma control test (ACT) score. A high degree of atopy was defined as ≥6 positive skin tests as 6 was the median number of positive skin prick tests; mouse-specific IgE was divided into tertiles; age was dichotomized at the median age of 9 years; abnormal baseline lung function was defined as FEV₁/FVC of <85% based on the National Asthma Education and Prevention (NAEPP) 2007 guidelines(19), and bronchodilator reversibility was defined as ≥12% based on American Thoracic Society (ATS) criteria(18). Baseline controller medication treatment step was used as a measure of asthma severity: mild-moderate asthma was defined as being on treatment step 1–3 and moderate-severe asthma was defined as being on treatment step 4–5(19); uncontrolled asthma was defined as an ACT score ≤19 and well-controlled asthma was defined as an ACT score >19 using the child ACT/ACT tool(21).

Mixed effects general linear models were used to model relationships between mouse allergen reduction and asthma outcomes. We stratified these analyses by degree of atopy, mouse-specific IgE, age, baseline lung function, and bronchodilator reversibility to determine if there was evidence to suggest effect modification. To test for effect modification, we included an interaction term (i.e. baseline clinical characteristic*
log₂(mouse allergen level)) in the final models. Final models were adjusted for age, gender, race, insurance, and atopy. Other indoor allergens (cockroach, dust mite, dog, and cat),

treatment step, and site were not included in the final models as they did not influence the overall results. Analyses were performed with STATA/IC 15.0 software (StataCorp). A p value of less than .05 was considered statistically significant for both main effects and interactions.

Results

Study Population Characteristics

The mean age of our study population was 9.8 years (± 3.2 years), with a range from 5–17 years. The population was predominantly male, minority (78% African American, 22% Hispanic), and of low socioeconomic status (Table 1). Participants had a median [IQR] of 2 days [0–4 days] days of cough, wheeze, or chest tightness and 3 days [0–7 days] of rescue medication use in the past two weeks. Seventy-eight percent and 25% of participants reported an ED visit and hospitalization in the past year, respectively. The majority of participants had a pre-bronchodilator FEV1/FEV <85% (63%) and 63% of participants had bronchodilator reversibility. Of the 297 participants, 294, 282, 277, and 270 participants contributed data to the analysis at the 3, 6, 9, and 12 month follow-up visits, respectively. There were 297 observations for dust sample data at visit 0, 292 for visit 1, 277 for visit 2, 268 for visit 3, and 266 for visit 4.

The median number of positive skin tests was 6 (interquartile range (IQR): 4–8), and a majority were sensitized to grass (61%), cockroach (55%), and cat (54%) (Table 2); only 6% were mono-sensitized to mouse. Bedroom floor mouse allergen levels at baseline were generally high with a median concentration of 6.0 $\mu\text{g/g}$ (IQR: 1.6–21.0 $\mu\text{g/g}$), and over the course of the study, 60% of the participants had 75% allergen reduction at 1 follow-up visit. The median concentration [IQR] of other indoor allergens measured at baseline from bed dust were: cat 0.100 $\mu\text{g/g}$ [0.011–0.660 $\mu\text{g/g}$], dog 0.067 $\mu\text{g/g}$ [0.002–0.554 $\mu\text{g/g}$], cockroach 0.001 $\mu\text{g/g}$ [0.001–0.001 $\mu\text{g/g}$], and dust mite 0.001 $\mu\text{g/g}$ [0.001–0.001 $\mu\text{g/g}$] (Table 3).

Atopic Status Modifies the Effect of Mouse Allergen Reduction

Among less atopic participants, each 50% decrease in the bedroom floor dust mouse allergen level was associated with statistically significant reductions in the frequency of asthma symptoms and rescue medication use (IRR [95% CI]: maximal symptoms: 0.94 [0.92–0.96], cough, wheeze, or chest tightness: 0.95 [0.93–0.97], slowed activity: 0.92 [0.90–0.95], difficulty speaking: 0.81 [0.76–0.87], difficulty running: 0.88 [0.86–0.91], cough symptoms: 0.91 [0.89–0.96]) in the previous 2 weeks. In contrast, among highly atopic participants, there were no statistically significant associations between mouse allergen reduction and asthma symptoms (IRR [95% CI]: maximal symptoms: 1.00 [0.97–1.02], cough, wheeze, chest tightness: 1.01 [0.98–1.03], slowed symptoms: 0.99 [0.96–1.03], difficulty speaking: 1.02 [0.95–1.09], difficulty running: 0.97 [0.94–1.00], cough symptoms: 0.98 [0.95–1.02]). The interactions between atopic status and mouse allergen reduction were statistically significant for all symptom outcomes (Table 4), and the results remained similar after adjusting for age, sex, race, and insurance type. Sensitivity analyses adjusting for other potential confounders were performed and the results were not materially affected by

adjustment for treatment step, other indoor exposures, study group, or site. Additionally, results were similar using a continuous measure of atopy, defined as the total number of positive skin tests (Table 4).

Although overall mouse allergen reduction was associated with reductions in acute visits and ED visits for asthma as previously reported(12), there were no differences between highly atopic and less atopic participants for any of the exacerbation-related outcomes., including OCS use (interaction p value =0.69). The findings were similar for bed dust mouse allergen levels (Online Supplement Table E1).

Effects Modification by Other Clinical Characteristics

The effects of other baseline characteristics on the relationship between mouse allergen reduction and asthma outcomes were also examined. These characteristics included age, sex, baseline mouse-specific IgE, lung function, bronchodilator reversibility, controller medication treatment step, and ACT score. For baseline mouse-specific IgE, lung function, bronchodilator reversibility, controller medication treatment step, ACT score, there was no evidence that they influenced the effect of mouse allergen reduction on either asthma symptoms outcomes or exacerbation-related outcomes (data not shown). For age, there was some evidence that older children (≥ 9 years) experienced a greater reduction in some asthma symptom outcomes with reduction of bed mouse allergen levels than younger children (Online Supplement Table E2), but these findings were less prominent for reductions in bedroom floor mouse allergen levels (Online Supplement Table E3). There was no evidence that controller medication treatment step (as a marker of asthma severity) nor ACT score influenced the effect of mouse allergen reduction on asthma outcomes (Online Supplement Table E4 & Table E5).

Discussion

Our study's objective was to determine if there are clinical characteristics that predict a greater clinical response to mouse allergen reduction among a population of mouse-sensitized and exposed 5–17 year olds with persistent asthma. In this population, degree of atopy modified the effect of mouse allergen reduction on asthma symptom outcomes, but not exacerbation-related outcomes. Specifically, less atopic participants had a greater reduction in asthma symptoms and rescue medication use associated with reductions in mouse allergen levels than more atopic participants. The degree of atopy, however, did not modify the effect of mouse allergen reduction on exacerbation-related outcomes, such as asthma-related acute visits. There was also some evidence to suggest that older children might have benefited from mouse allergen reduction to a greater extent than younger children. There was no evidence that mouse-specific IgE, lung function, or bronchodilator reversibility predicted the clinical response to mouse allergen reduction.

Among the many environmental intervention trials over the past decade or so, only a few examined whether certain subgroups responded better to the environmental intervention. These included three studies of home environmental interventions in pediatric populations. One was a randomized, placebo-controlled trial of dust mite impermeable bedcoverings among children in the United Kingdom and two were multi-faceted home environmental

interventions among urban low-income children with asthma in the United States (8, 22, 23). Collectively, these studies evaluated the effects of asthma severity, allergic sensitization, and age as potential predictors of clinical responsiveness to the environmental intervention; however, similar to our study, none of these studies were powered for interaction analyses.

Although a greater burden of atopy tends to be associated with more severe asthma and greater pulmonary inflammation(24, 25), potentially identifying a subgroup that would have a greater response to allergen reduction, we found that less atopic participants, who had fewer sensitizations, tended to have greater reductions in asthma symptoms and rescue medication use in response to mouse allergen reduction. Why less atopic children would benefit to a greater extent in terms of asthma control-related outcomes, but not in terms of exacerbation-related outcomes is unclear. It is possible that mouse allergen exposure plays a larger role in asthma control among children who are less susceptible to other environmental exposures given that they have fewer sensitizations. In contrast, asthma exacerbations are largely mediated by upper respiratory viral infections, and allergen exposure may contribute to risk of virally-mediated exacerbations similarly between less and more atopic children. Although the mechanism underlying these observations is unclear, they suggest that allergen exposure reduction may affect asthma control and asthma risk domains differently, depending on degree of atopy. Notably, none of aforementioned environmental intervention trials studies examined a measure of the burden of atopy as a predictor of response to the intervention as done in our analysis (8, 22, 23).

The single allergen dust mite intervention trial examined the effect of some measure of allergic sensitization on the efficacy of the intervention, and subgroup analyses suggested that those who were mono-sensitized to dust mite experienced greater reduction in risk in time to first hospitalization from the intervention compared to those who were polysensitized (8). In our study, only 5.7% were mono-sensitized to mouse, suggesting that mono-sensitization to mouse in this population is uncommon, so that analyses stratified by mono-sensitization status are not likely to be meaningful. However, we did examine whether baseline mouse-specific IgE level predicted response to mouse allergen reduction, given that it may be a marker of clinical responsiveness to mouse allergen exposure. We found little evidence to suggest that mouse-specific IgE could serve as a predictor of responsiveness to allergen reduction, suggesting that mouse allergen reduction may be beneficial for sensitized patients regardless of the level of specific IgE.

In this study, there was some evidence that older children, defined as those were 9–17 years of age, may experience greater improvement with mouse allergen reduction than younger children. The single allergen dust mite intervention trial that enrolled children 3–17 years of age, found that younger children, aged 3–10 years, had a reduction in hospitalization risk associated with the intervention, while older children, ages 11–17 years, did not. However, only a modest number of children were 11–17 years of age (8). To our knowledge, no other studies have examined whether older children and adolescents respond differently to environmental interventions than younger ones, and few studies have enrolled adolescents. In contrast, we found no evidence that asthma severity, defined by either $FEV_1/FVC\% < 85\%$ or post-bronchodilator reversibility $\geq 12\%$, predicted response to mouse allergen reduction, which is consistent with findings from other studies (22, 23).

The major limitation of this study is that it is a secondary analysis from clinical trial data. However, two of the characteristics examined as potential modifiers of the effect of allergen reduction, degree of atopy and mouse-specific IgE, were prespecified. Although our findings might not be generalizable to all children and adolescents with asthma, they may be applicable to similar populations of urban minority children with allergic asthma where mouse allergen is a relevant allergen. In addition, this study examined modifiers of the effect of reducing a single allergen, mouse allergen, and other allergens or combinations of allergens may be affected differently. Because there were no differences in mouse allergen exposure or clinical outcomes between groups in this trial, we were unable to examine characteristics that may modify the effect of the intervention on asthma outcomes, so instead we focused on modifiers of the effect of allergen reduction. There are additional potential predictors of the effects of mouse allergen reduction, such as psychosocial factors and environmental exposures that were not the focus of this study, but should be examined.

Although these findings suggest that there may be variability in the clinical response to mouse allergen reduction among mouse-sensitized and exposed, low-income, urban minority children and adolescents with persistent asthma, there were no clinical characteristics that clearly identified a subgroup to whom the intervention should be targeted. Neither baseline lung function nor baseline mouse-specific IgE levels predicted response to mouse allergen reduction, and there was limited evidence that age affected responsiveness to mouse allergen reduction. We found that less atopic participants experienced a greater benefit for symptom-related outcomes than more atopic participants; however atopic status did not predict greater clinical benefit for exacerbation-related outcomes. Together these findings suggest that interventions aimed at reducing mouse allergen exposure should not be restricted to populations with certain clinical characteristics, especially given that mouse allergen reduction is a low-risk and modest cost intervention. The observation that degree of atopy influenced the effect of mouse allergen reduction on symptom-related outcomes, but not exacerbation-related outcomes may lend insight into how allergen sensitization and exposure might influence the complex relationship between allergen sensitization and exposure and virally-mediated exacerbations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by the following NIH grants: R01AI070630, R01AI0818451, P01ES018176, 1P50ES015903, M01-RR00052, U01 AI 083238, K24 AI 106822, K24 AI114769, R01 ES023447, R01 ES026170, P50ES015903, P01 ES018176 and 5T32AI007007

ABBREVIATIONS

IPM	Integrated Pest Management
MAAIT	Mouse Allergen and Asthma Intervention Trial
SPT	Skin Prick Test

FEV₁	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
ICS	Inhaled corticosteroids
NAEPP	National Asthma Education and Prevention Program
ATS	American Thoracic Society
SABA	Short Acting Beta Agonist
SD	Standard Deviation
BD	Below level of detection

REFERENCES

1. Ahluwalia SK, Peng RD, Breyse PN, Diette GB, Curtin-Brosnan J, Aloe C, et al. Mouse allergen is the major allergen of public health relevance in Baltimore City. *The Journal of allergy and clinical immunology*. 2013;132(4):830–5.e1–2. [PubMed: 23810154]
2. Ahluwalia SK, Matsui EC. Indoor Environmental Interventions for Furry Pet Allergens, Pest Allergens, and Mold: Looking to the Future. *The journal of allergy and clinical immunology In practice*. 2018;6(1):9–19. [PubMed: 29310769]
3. Gruchalla RS, Pongracic J, Plaut M, Evans R III, Visness CM, Walter M, et al. Inner City Asthma Study: Relationships among sensitivity, allergen exposure, and asthma morbidity. *Journal of Allergy and Clinical Immunology*. 2005;115(3):478–85. [PubMed: 15753892]
4. Matsui EC, Eggleston PA, Buckley TJ, Krishnan JA, Breyse PN, Rand CS, et al. Household mouse allergen exposure and asthma morbidity in inner-city preschool children. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology*. 2006;97(4):514–20.
5. Torjusen EN, Diette GB, Breyse PN, Curtin-Brosnan J, Aloe C, Matsui EC. Dose-response relationships between mouse allergen exposure and asthma morbidity among urban children and adolescents. *Indoor air*. 2013;23(4):268–74. [PubMed: 23067271]
6. Almqvist C, Wickman M, Perfetti L, Berglind N, Renstrom A, Hedren M, et al. Worsening of asthma in children allergic to cats, after indirect exposure to cat at school. *American journal of respiratory and critical care medicine*. 2001;163(3 Pt 1):694–8. [PubMed: 11254526]
7. Shirai T, Matsui T, Suzuki K, Chida K. Effect of pet removal on pet allergic asthma. *Chest*. 2005;127(5):1565–71. [PubMed: 15888829]
8. Murray CS, Foden P, Sumner H, Shepley E, Custovic A, Simpson A. Preventing Severe Asthma Exacerbations in Children. A Randomized Trial of Mite-Impermeable Bedcovers. *American journal of respiratory and critical care medicine*. 2017;196(2):150–8. [PubMed: 28282501]
9. Halken S, Host A, Niklassen U, Hansen LG, Nielsen F, Pedersen S, et al. Effect of mattress and pillow encasings on children with asthma and house dust mite allergy. *The Journal of allergy and clinical immunology*. 2003;111(1):169–76. [PubMed: 12532114]
10. Rabito FA, Carlson JC, He H, Werthmann D, Schal C. A single intervention for cockroach control reduces cockroach exposure and asthma morbidity in children. *The Journal of allergy and clinical immunology*. 2017;140(2):565–70. [PubMed: 28108117]
11. Pongracic JA, Visness CM, Gruchalla RS, Evans R, 3rd, Mitchell HE. Effect of mouse allergen and rodent environmental intervention on asthma in inner-city children. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology*. 2008;101(1):35–41.
12. Matsui EC, Perzanowski M, Peng RD, Wise RA, Balcer-Whaley S, Newman M, et al. Effect of an Integrated Pest Management Intervention on Asthma Symptoms Among Mouse-Sensitized

- Children and Adolescents With Asthma: A Randomized Clinical Trial. *Jama*. 2017;317(10):1027–36. [PubMed: 28264080]
13. DiMango E, Serebrisky D, Narula S, Shim C, Keating C, Sheares B, et al. Individualized Household Allergen Intervention Lowers Allergen Level But Not Asthma Medication Use: A Randomized Controlled Trial. *The journal of allergy and clinical immunology In practice*. 2016;4(4):671–9.e4. [PubMed: 27025297]
 14. Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R 3rd, et al. Results of a home-based environmental intervention among urban children with asthma. *The New England journal of medicine*. 2004;351(11):1068–80. [PubMed: 15356304]
 15. Burr ML, Matthews IP, Arthur RA, Watson HL, Gregory CJ, Dunstan FD, et al. Effects on patients with asthma of eradicating visible indoor mould: a randomised controlled trial. *Thorax*. 2007;62(9):767–72. [PubMed: 17389753]
 16. Kercksmar CM, Dearborn DG, Schluchter M, Xue L, Kirchner HL, Sobolewski J, et al. Reduction in asthma morbidity in children as a result of home remediation aimed at moisture sources. *Environmental health perspectives*. 2006;114(10):1574–80. [PubMed: 17035145]
 17. Mitchell H, Cohn RD, Wildfire J, Thornton E, Kennedy S, El-Dahr JM, et al. Implementation of evidence-based asthma interventions in post-Katrina New Orleans: the Head-off Environmental Asthma in Louisiana (HEAL) study. *Environmental health perspectives*. 2012;120(11):1607–12. [PubMed: 22894795]
 18. Standardization of Spirometry, 1994 Update. American Thoracic Society. *American journal of respiratory and critical care medicine*. 1995;152(3):1107–36. [PubMed: 7663792]
 19. National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma Bethesda (MD): National Heart, Lung, and Blood Institute (US); [updated 2007 Aug. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK7232/>.
 20. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *American journal of respiratory and critical care medicine*. 1999;159(1):179–87. [PubMed: 9872837]
 21. Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *The Journal of allergy and clinical immunology*. 2006;117(3):549–56. [PubMed: 16522452]
 22. Eggleston PA, Butz A, Rand C, Curtin-Brosnan J, Kanchanaraks S, Swartz L, et al. Home environmental intervention in inner-city asthma: a randomized controlled clinical trial. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology*. 2005;95(6):518–24.
 23. Williams SG, Brown CM, Falter KH, Alverson CJ, Gotway-Crawford C, Homa D, et al. Does a multifaceted environmental intervention alter the impact of asthma on inner-city children? *Journal of the National Medical Association*. 2006;98(2):249–60. [PubMed: 16708511]
 24. Langley SJ, Goldthorpe S, Craven M, Morris J, Woodcock A, Custovic A. Exposure and sensitization to indoor allergens: association with lung function, bronchial reactivity, and exhaled nitric oxide measures in asthma. *The Journal of allergy and clinical immunology*. 2003;112(2):362–8. [PubMed: 12897743]
 25. Grant T, Aloe C, Perzanowski M, Phipatanakul W, Bollinger ME, Miller R, et al. Mouse Sensitization and Exposure Are Associated with Asthma Severity in Urban Children. *The journal of allergy and clinical immunology In practice*. 2017;5(4):1008–14.e1. [PubMed: 27923647]
 26. Salo PM, Arbes SJ Jr., Crockett PW, Thorne PS, Cohn RD, Zeldin DC. Exposure to multiple indoor allergens in US homes and its relationship to asthma. *The Journal of allergy and clinical immunology*. 2008;121(3):678–84.e2. [PubMed: 18255132]

Highlights Box

What is already known about this topic?

- Mouse allergen reduction is associated with improvements in asthma among sensitized and exposed asthmatic children.

What does this article add to our knowledge?

- The effect of mouse allergen reduction among mouse-sensitized and exposed children on asthma outcomes may be modified by baseline clinical characteristics.

How does this study impact current management guidelines?

- Findings suggest interventions aimed at reducing mouse allergen exposure should not be restricted to populations with certain clinical characteristics, especially given that mouse allergen reduction is a low-risk and modest cost intervention.

Table 1.**Study Population Characteristics (n=297)**

Demographic Characteristics	n (%)
Age (y), mean (SD)	9.8 (3.2)
Male gender	189 (64)
Black race	231 (88)
Hispanic ethnicity	65 (22)
Socioeconomic Measures Public insurance	
Public insurance	259 (78)
Study Site	
Baltimore	201 (68)
Boston	96 (32)
Asthma Symptoms and Medication Use, d/2 weeks	median (IQR)
Maximum symptoms ^a	2 (0–6)
General symptoms	2 (0–4)
Slowed symptoms	1 (0–3)
Speech symptoms	0 (0–0)
Running symptoms	1 (0–3)
Nocturnal symptoms	0 (0–2)
Cough symptoms	0 (0–3)
SABA use	3 (0–7)
Asthma-related Health Care Use	n (%)
ED visits in prior year	232 (78)
Hospitalization in prior year	74 (25)
OCS use in prior 3 mo	137 (46)
Pre-bronchodilator Lung Physiology	
FEV ₁ [¥] , mean (SD), (%)	95.2 (18.3)
FVC [¥] , mean (SD), (%)	100.3 (15.2)
FEV ₁ /FVC [¥] (%)	80.9 (8.6)
Bronchodilator reversibility 12% [€] , n (%)	99 (37)

[¥]
n=279;

[€]
n=266, restricted to < 8y

^a Largest value across 3 types of symptom outcomes (slowed, nocturnal, and general)

Table 2.

Aeroallergen Sensitization Characteristics (n=297)

Highly atopic (6 +SPT), n (%)	162 (55)
Mouse-specific IgE, median (IQR), kU/L *	10.3 (1.7–38.5)
Skin test sensitivity, n (%)	
Rat	207 (77)
Grass	180 (61)
Cockroach	162 (55)
Cat	159 (54)
Dust mite	132 (44)
Tree	127 (43)
Mold [‡]	100 (34)
Ragweed	96 (32)
Dog	67 (23)

*
n=296[‡]
Included *Aspergillus* mix and *Alternaria tenuis*.

Table 3.

Aeroallergen Exposure Characteristics (n=297)

	median (IQR), µg/g
Mouse allergen exposure	
Bedroom floor dust	6.0 (1.6–21.0) [€]
Bed dust	1.0 (0.4–3.27) [€]
Other indoor allergens	
Cat	0.100 (0.011–0.660) [¥]
Dog	0.067 (BD–0.554) [¥]
Cockroach	BD (BD–BD) [¥]
Dust mite	BD (BD–BD) [¥]

BD= below lower limit of detection

[€] = these concentrations are generally considered high and associated with asthma morbidity(4, 26)[¥] = these concentrations are generally considered low(26)

Table 4.
Effect of bedroom floor mouse allergen reduction on asthma outcomes, by atopic status

	Crude		Interaction Term p-value	Adjusted*			Interaction Term p-value	Interaction Term p-value [‡]
	Less atopic <6 +SPT IRR [95% CI]	Highly atopic 6 +SPT IRR [95% CI]		Less atopic <6 +SPT IRR[95%CI]	Highly atopic 6 +SPT IRR [95% CI]			
Symptom outcomes:								
Maximum symptoms	0.94 (0.92–0.96)	1.00 (0.97–1.02)	<0.001	0.94 (0.92–0.96)	1.00 (0.98–1.02)	<0.001	<0.001	0.05
General symptoms	0.95 (0.93–0.97)	1.01 (0.98–1.03)	0.001	0.95 (0.93–0.97)	1.01 (0.99–1.04)	0.001	0.001	0.02
Slowed symptoms	0.92 (0.90–0.95)	0.99 (0.96–1.02)	0.001	0.92 (0.90–0.95)	1.00 (0.97–1.03)	<0.001	<0.001	0.13
Speech symptoms	0.81 (0.76–0.87)	1.02 (0.95–1.09)	<0.001	0.80 (0.74–0.85)	1.03 (0.96–1.10)	<0.001	<0.001	0.001
Running symptoms	0.88 (0.86–0.91)	0.97 (0.94–1.00)	<0.001	0.88 (0.86–0.91)	0.97 (0.94–1.01)	<0.001	<0.001	0.002
Nocturnal symptoms	0.91 (0.88–0.94)	0.99 (0.96–1.03)	<0.001	0.91 (0.88–0.94)	1.00 (0.96–1.04)	<0.001	<0.001	0.19
Cough symptoms	0.91 (0.89–0.94)	0.98 (0.95–1.02)	0.002	0.92 (0.89–0.95)	1.01 (0.97–1.05)	<0.001	<0.001	<0.001
SABA use	0.94 (0.92–0.96)	1.01 (0.99–1.03)	<0.001	0.94 (0.92–0.96)	1.02 (0.99–1.04)	<0.001	<0.001	<0.001
Exacerbation outcomes:								
Acute visit	0.92 (0.88–0.96)	0.93 (0.89–0.98)	0.71	0.92 (0.88–0.96)	0.94 (0.90–0.98)	0.67	0.67	0.71
Unscheduled doctor visit	0.91 (0.85–0.98)	0.93 (0.86–1.01)	0.65	0.91 (0.85–0.98)	0.94 (0.87–1.02)	0.60	0.60	0.61
ED visit	0.94 (0.88–1.00)	0.94 (0.89–1.00)	0.97	0.94 (0.89–1.00)	0.95 (0.89–1.01)	0.99	0.99	0.90
Hospitalization	0.91 (0.81–1.02)	0.93 (0.81–1.07)	0.50	0.91 (0.81–1.02)	0.97 (0.84–1.11)	0.48	0.48	0.84

Statistically significant IRR [95%CI] and interaction p-values indicated in bold;

* Adjusted for age, sex, race, and insurance type; 95% CI were generated from mixed effects generalized linear models with outcomes regressed on time-varying, continuous log2-transformed mouse allergen variable

‡ interaction p value from continuous measure of atopy*mouse allergen