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Reduction in mouse allergen exposure is associated with greater lung function growth

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Abstract

Background: Current childhood asthma therapies have little effect on lung function trajectory.

Objective: To determine if mouse allergen exposure reduction is associated with lung function growth in mouse-sensitized/exposed asthmatic children.

Methods: 350 mouse-sensitized/exposed asthmatic children (5–17y) were enrolled in a 1-year randomized trial of integrated pest management+education versus education alone. Pre-/post-bronchodilator (BD) spirometry was performed at baseline, 6 and 12 months, and bedroom floor mouse allergen was measured every 3 months. Mouse allergen reduction was defined as ≥75% decrease in mouse allergen from baseline. Treatment groups were combined for analyses, as there

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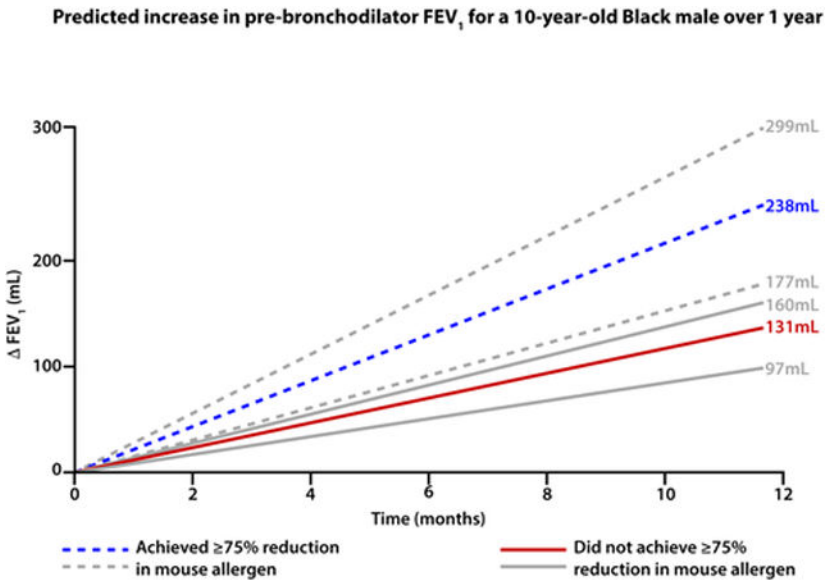
were no differences in outcomes between groups. Changes in lung function over time were modeled, adjusting for age, gender, race, atopy, group, BD reversibility and including an interaction term (allergen reduction*time).

Results: The study population was predominantly black (79.4%) and low-income (66.3% < $30,000). At baseline, median (IQR) mouse allergen level was 5.7ug/g (1.5–22.8); mean (SD) pre-BD FEV_1/FVC% was 80.2%(9.0). 92(26.3%) participants had ≥75% mouse allergen reduction. For a 10-year-old black male, ≥75% allergen reduction was associated with an increase in pre-BD FEV_1 of 238mL/yr (95% CI: (177–299mL/yr)); whereas <75% allergen reduction was associated with an increase in pre-BD FEV_1 of 131mL/yr (97–166mL/yr). The estimated differences in pre- and post-BD FEV_1 growth were: 107mL/yr (37–177mL/yr), p_{int}=0.003 and 48mL/yr (−17–113mL/yr), p_{int}=0.15, respectively. The estimated differences in pre- and post-BD $FEF_{25–75}$ growth were: 182mL/yr (61–304mL/yr), p_{int}=0.003 and 181mL/yr (48–314mL/yr), p_{int}=0.008, respectively.

Conclusion: Mouse allergen reduction is associated with greater increases in pre-BD FEV_1 and pre-/post-BD $FEF_{25–75}$ over 1 year among sensitized/exposed asthmatic children.

Graphical Abstract



Capsule summary:

Mouse allergen exposure reduction was associated with greater increases in pre-BD FEV_1 and pre-/post-BD $FEF_{25–75}$ over 1 year in sensitized/exposed asthmatic children, supporting a causal relationship between allergen exposure and impaired lung function growth.

Keywords

Allergen exposure; allergen exposure reduction; lung function growth; lung function trajectory; mouse allergen exposure; allergen-sensitized and exposed asthmatic children; allergic asthma

Introduction

Forced expiratory volume in 1 second (FEV_1) increases in childhood, then plateaus during late adolescence and early adulthood before starting a gradual decline[1]. Children with asthma are at risk for abnormal lung function growth, including reduced growth and early decline in lung function[2–4]. The lung function effects that occur in childhood have long-term implications as children with abnormal lung function are more likely to have lower lung function as adults[5], and low lung function in adulthood, including early adulthood, is a predictor of mortality[6–8] and chronic obstructive pulmonary disease (COPD)[9]. Repeated studies have shown that inhaled corticosteroids (ICS), the mainstay of guidelines-based asthma therapy, do not affect lung function trajectory among children[10–12]. Therefore, there is a great need to identify modifiable risk factors for abnormal childhood lung function growth.

Allergen exposure is one such modifiable risk factor that may influence the long-term lung function trajectory among children with asthma. Cross-sectional studies have shown an association between indoor allergen exposure and lower lung function (FEV_1, FEV_1/Forced vital capacity (FVC)) among children with asthma who are sensitized to the allergen[13,14]. However, to our knowledge, there are no studies that examine the effect of allergen exposure reduction on lung function growth in sensitized asthmatic children. An association between allergen reduction and improved lung function growth over time would suggest that existing interventions to reduce indoor allergen exposure could alter the lung function trajectory of sensitized children with asthma. We therefore tested the hypothesis that a reduction in indoor allergen exposure is associated with greater lung function growth by examining relationships between mouse allergen reduction and one year lung function growth among a population of mouse allergen sensitized children with persistent asthma enrolled in the Mouse Allergen and Asthma Intervention Trial (MAAIT). The primary findings of MAAIT are reported elsewhere[15]. Here we perform an ancillary analysis of MAAIT using pre-specified allergen reduction cutoffs[15] as our primary exposure variable.

Methods

Study Population and Recruitment Procedures

MAAIT is a multicenter, randomized clinical trial which randomized 361 children ages 5–17 years to intensive mouse allergen targeted integrated pest management (IPM) intervention plus education or to education alone. To be eligible for enrollment into the trial, children had to meet the following criteria: (1) be mouse sensitized (mouse-specific IgE ≥0.10 kU/L or a positive mouse skin test (wheal size ≥ 3mm)), (2) have uncontrolled asthma, which was defined as an exacerbation (an asthma-related emergency room or urgent care visit, overnight hospitalization, or oral steroid burst) in the last twelve months, (3) have persistent asthma, defined as use of a long-term controller medication or fulfillment of National Asthma Education and Prevention Program (NAEPP) guidelines for persistent disease, and (4) meet an exposure threshold for mouse allergen exposure, which was ≥0.4μg/g mouse allergen in bed dust or ≥0.5 μg/g mouse allergen in bedroom floor dust[15].

Recruitment occurred between December 2010 and August 2014, utilizing pediatric emergency rooms, primary care clinics, and specialty clinics. Participants were followed for 1 year at clinical sites in Baltimore and Boston. The study was approved by the Johns Hopkins Medicine and Boston Children's Hospital Institutional Review Boards and written, informed consent was obtained from parents or guardians of participants.

Clinic Visit Procedures

Questionnaires were used to capture socioeconomic, clinical, and environmental data and medication use was collected by questionnaire and by medications brought to the clinic visit by study participants. Participants underwent skin prick testing using the MultiTest II device (Lincoln Diagnostics, Decatur, Illinois) to 14 common aeroallergens and venipuncture was performed for mouse-specific IgE at baseline[15].

Pre- and post-bronchodilator (BD) spirometry was obtained at baseline, 6, and 12 months using a Koko spirometer (Longmont, Colorado). Post-bronchodilator spirometry was obtained approximately 15–20 minutes after administration of albuterol by nebulizer (2.5mg/3mLs). Bronchodilator reversibility was defined as an increase in FEV_1 by ≥12% following albuterol. Percent predicted values for participants 8 years and older were generated using Hankinson equations[16]. Percent predicted values for participants <8 years of age were not calculated. Spirometry data were reviewed for acceptability by the investigators in accordance with American Thoracic Society (ATS) guidelines[17].

Home Assessment Visit

Dust samples were collected from the bedroom floor at baseline, 3, 6, 9, and 12 months using a handheld vacuum cleaner using standard methods[18–20]. The samples were analyzed for Mus m 1 by enzyme-linked immunosorbent assay (ELISA)[21].

Study Design and Statistical Analysis

We performed a secondary analysis of 350 participants in MAAIT to determine if reduction in mouse allergen exposure is associated with improved lung function growth over time in mouse sensitized and exposed children with persistent asthma. Mouse allergen reduction was defined as at least a 75% decrease from baseline in the mean mouse allergen levels across all follow-up time points. The primary outcome was change in pre- and post-BD FEV_1 and FVC over 1 year.

MAAIT had high retention, as more than 88% of participants were followed to 12 months. Both treatment groups of the parent trial achieved significant reduction in mouse allergen levels which were not different from one another and there were also no differences in clinical outcomes between groups[15]; therefore we combined groups for our analyses.

All analyses were performed using Stata SE 13.1 (College Station, TX). As we set out to determine whether the average mouse allergen reduction over the follow-up period of the study affected the change in FEV_1 over 1 year, we evaluated the FEV_1 trajectory over 1 year between participants who achieved ≥75% decrease from baseline in the mean mouse allergen level and those who did not achieve ≥75% decrease from baseline in the mean

mouse allergen level. To accomplish this, linear regression models with generalized estimating equations (to account for repeated within person measures of the outcome) using an exchangeable correlation were used to model change in lung function over time. Independent generalized estimating equation models were fit with varying allergen reduction metrics (mean reduction ≥75&, ≥50%, and ≥95%) to examine the effect of different allergen reduction cutoffs. To determine if mouse allergen exposure reduction modified the relationship between time and lung function, we included an interaction term of allergen reduction*time. As lung function growth varies with age, we also included an interaction term of age*time. Final models were adjusted for age, gender, race, group assignment, BD reversibility, age*time and atopy (defined as number of +SPT). A two-tailed $p<0.05$ was considered statistically significant.

Results

Study Population

350 participants were included in the analysis of the effect of mouse allergen reduction on lung function growth over time and their characteristics are depicted in Table 1. Participants ranged in age from 5 to 17 years, with a mean age of 9.8 years. 63.2% were male, 79.4% were black or African American, and 21.4% were of Hispanic ethnicity. The large majority of participants were on public insurance (87.8%) with 66.3% of families reporting an annual household income of less than $30,000. 68.3% of participants were from Baltimore and the remaining 31.7% were from Boston. At baseline, 66.9% of participants had had an acute visit for asthma in the previous 3 months and 54.6% of participants were on step 4 or 5 asthma controller medication (equivalent to medium dose ICS with long-acting β-agonist or high dose ICS with or without long acting β-agonist). Baseline spirometry revealed 30.8% of participants 8 years and older had an FEV_1 of less than 80% predicted and 64.3% of participants had an FEV_1/FVC of less than 85%. All participants were sensitized and exposed to mouse. More than 50% of participants were also SPT positive to cockroach and cat. Median bedroom floor mouse allergen level was 5.7μg/g.

Associations between mouse allergen reduction and FEV_1 growth

Linear regression models with generalized estimating equations were used to model the relationship between FEV_1 and time and subsequently predict the estimated change in FEV_1 over time for the average participant, a 10-year-old black male. A 10-year-old black male who achieved ≥75% mean mouse allergen reduction is estimated to have an increase in pre-BD FEV_1 of 238mL (95% CI: (177 – 299mL)) over one year; a 10-year-old black male who did not achieve allergen reduction is estimated to have an increase in pre-BD FEV_1 of 131mL (97 – 166mL) over one year, with a difference in estimated FEV_1 growth of 107mL (37 – 177mL) (Table 2, Figures 1&2). The difference in predicted FEV_1 growth between those who did and did not achieve allergen reduction was statistically significant ($p=0.003$ for interaction term mouse allergen reduction*time) after adjusting for age, sex, race, group assignment, BD reversibility, and atopy (number of positive SPT). For post-BD FEV_1 growth, a 10-year-old black male who achieved allergen reduction is estimated to have an increase in post-BD FEV_1 of 216mL (95% CI: (159–273mL))over one year compared to 168mL (135 – 201mL) increase in a 10-year-old black male who did not achieve reduction.

This estimated difference in post-BD FEV_1 growth of 48mL (−17 – 113mL) was not statistically significant (p=0.15). Sensitivity analyses that additionally adjusted for site, oral steroid use in the previous 3 months, controller medication treatment step, body mass index, and cockroach exposure did not substantively change the results (Supplemental Table S1). In addition, adjusting for baseline urine cotinine does not affect the results (data not shown). When we control for bronchodilator reversibility as a continuous variable, instead of a dichotomous variable cut at ≥12%, the estimated difference in pre-BD FEV1 growth is attenuated. The estimated difference in pre-BD FEV1 growth is predicted to be 58mL ((95% CI: −9 – 127), p=0.09) greater for a 10-year-old black male who achieved ≥75% mean reduction in mouse allergen exposure as compared a 10-year-old black male who did not achieve ≥75% mean reduction in mouse allergen exposure. Estimated difference for post-BD FEV1 is 49mL (95% CI: (−21 −119), p=0.17).

We also examined other allergen reduction cutoffs, including sustained mean reductions of ≥50% and ≥90% in bedroom floor mouse allergen level from baseline (Table 2). A 10-year-old black male who achieved sustained mean reduction of ≥50% is estimated to have an increase in pre-BD FEV_1 of 205mL (95% CI: (160 – 250mL)) over one year compared to 120mL (79 – 161mL) increase in a 10-year-old black male who did not achieve reduction (estimated difference = 85mL (24 – 146mL), p=0.006). A 10-year-old black male who achieved sustained mean reduction of ≥90% is estimated to have an increase in pre-BD FEV_1 of 255mL (159 – 351mL) over one year compared to 147mL (115 – 180mL) increase in a 10-year-old black male who did not achieve reduction (estimated difference = 108mL (7 – 209mL), p=0.04). Estimated changes in post-BD FEV_1 growth were not statistically significant for either cutoff.

Associations between mouse allergen reduction and FVC growth

Linear regression models with generalized estimating equations stratified by allergen reduction were also used to predict the estimated change in FVC over time for the average participant, a 10-year-old black male. A 10-year-old black male who achieved ≥75% mean mouse allergen reduction is estimated to have an increase in pre-BD FVC of 270mL (95% CI:(191 – 348mL) over one year; a 10-year-old black male who did not achieve allergen reduction is estimated to have an increase in pre-BD FVC of 205mL (160 – 250mL) over one year, with a difference between these groups of people in estimated FVC growth of 65mL (−25 – 156mL) (Table 3). This difference in FVC growth did not reach statistical significance (p=0.16). For post-BD FVC growth, a 10-year-old black male who achieved allergen reduction is estimated to have an increase in post-BD FVC of 227mL (171 – 283mL) over one year compared to a 209mL (177 – 241mL) increase in a 10-year-old black male who did not achieve reduction, with an estimated difference in post-BD FVC growth of 18mL (−46 – 83mL) (p=0.58).

Additionally, we examined allergen reduction cutoffs of sustained mean reduction ≥ 50% and ≥ 90% reduction in bedroom floor mouse allergen level from baseline. There were no statistically significant differences in pre- or post-BD FVC growth for either allergen reduction metric (Table 3).

Associations between mouse allergen reduction and $FEF_{25–75}$ growth

Linear regression models with generalized estimating equations stratified by allergen reduction were again used to predict the estimated change in forced expiratory flow at 25–75% ($FEF_{25–75}$) over time for the average participant, a 10-year-old black male. A 10-year-old black male who achieved ≥75% mean mouse allergen reduction is estimated to have a 245mL (95% CI:(140 – 63mL) increase in pre-BD $FEF_{25–75}$ over one year, compared to a 63mL(2 – 123mL) increase in pre-BD $FEF_{25–75}$ over one year for a 10-year-old black male who did not achieve ≥75% mean mouse allergen reduction (estimated difference 182mL (61–304mL), p=0.003, Table 4). For post-BD $FEF_{25–75}$ growth, a 10-year-old black male who achieved allergen reduction is estimated to have an increase in post-BD $FEF_{25–75}$ of 310mL (195 – 425mL) over one year compared to a 129mL (63 – 194mL) increase in a 10-year-old black male who did not achieve reduction, with an estimated difference in post-BD FVC growth of 181mL (48 – 314mL) (p=0.008).

A similar trend for pre- and post-BD $FEF_{25–75}$ growth was seen for a 10-year-old black male who achieved ≥50% mean mouse allergen reduction compared to a 10-year-old black male who did not achieve ≥50% mean mouse allergen reduction (estimated difference in pre-BD $FEF_{25–75}$ growth 119mL (13 – 226mL), p=0.03; estimated difference in post-BD $FEF_{25–75}$ growth 138mL (23 – 254mL), p=0.02, Table 4). The estimated differences in pre- and post-BD $FEF_{25–75}$ growth were not statistically significant for a 10-year-old black male who achieved ≥90% mean mouse allergen reduction compared to a 10-year-old black male who did not achieve ≥90% mean mouse allergen reduction (Table 4).

Discussion

Our study's objective was to determine whether mouse allergen exposure reduction was associated with a difference in lung function growth over time among low-income, urban-dwelling, mouse-sensitized and exposed asthmatic children and adolescents. In this study population, we found that mean reduction in mouse allergen exposure by ≥75% from baseline was associated with a greater increase in pre-BD FEV_1 among participants who achieved this reduction metric compared with those who did not achieve this reduction metric. Those who achieved reduction had greater pre-BD FEV_1 growth over 1 year, which was independent of age, sex, race, group assignment, BD reversibility, and atopy. Additionally, we found that ≥75% mean reduction in mouse allergen exposure was associated with a greater increase in pre- and post-BD $FEF_{25–75}$. These findings suggest that mouse allergen exposure reduction may modify pre-BD FEV_1 and pre- and post-BD $FEF_{25–75}$ growth in sensitized and exposed asthmatic children.

Although the overall pattern of the associations between allergen reduction and lung function suggests that allergen reduction may be associated with improvements in lung function growth, the findings may instead be consistent with improvements in airway physiology. The uncertainty with respect to some of the post-BD lung function outcomes suggests that the overall findings may reflect improvements in airway obstruction or mid-flow volumes rather than lung growth. Studies designed specifically to examine the effects of allergen reduction on lung function growth will be needed to determine whether the effects seen here likely reflect improvements in physiology or lung growth. Additionally,

while there is controversy about the significance of $FEF_{25–75}$, particularly in pediatric populations, small airway disease has been associated with asthma, COPD,[22] and asthma severity and morbidity in adulthood[23], suggesting that the association between allergen reduction and greater pre- and post-BD $FEF_{25–75}$ growth observed here is worth noting.

Lower lung function in adulthood, as early as age 21[7,8], has been repeatedly associated with mortality[6–8]. Recent literature has described lung function trajectories from childhood into adulthood[4,24,25], which were predictable as early as preschool age in one study[25]. A number of risk factors for abnormal lung function trajectories have been identified. In children with mild-to-moderate asthma, male sex, baseline low FEV_1, baseline airway hyper-responsiveness, and smaller BD response[4] were associated with abnormal lung function growth. In population-based birth cohorts in the United Kingdom and Australia, childhood asthma, repeat wheezing, lung infections, allergic rhinitis, eczema, maternal smoking, and early allergic sensitization, including cat, dog, and dust mite, have been associated with abnormal childhood lung function trajectories[24,25]. Additionally, longitudinal studies in the United States, Europe, Mexico, and China have shown that air pollution and airborne particulate matter (PM) are associated with long-term abnormal lung function and lower lung function trajectories in children[26–29]. Each of these risk factors is important. While there have been no longitudinal studies in school-age children examining the long-term effects of allergen exposure on lung function growth, allergen sensitization and high exposure in the first 3 years of life has been associated with lower lung function at age 7[30]. Our study is the first, to our knowledge, to describe an association between allergen exposure reduction and improved lung function increase. By demonstrating that allergen reduction is associated with a greater increase in lung function, this study extends prior cross-sectional observations. This finding strengthens the hypothesis that allergen exposure is causally related to impaired lung development in children. In conjunction with increased air pollution regulation and smoking bans and cessation, indoor allergen exposure reduction may represent another important step toward reducing exposure to modifiable risk factors for abnormal lung function growth in children.

Our study found estimated differences in pre-BD FEV_1 growth from 85mL to 108mL over 1 year. These are large improvements in pre-BD FEV_1, as adults are estimated to lose approximately 20–30mL in FEV_1 per year[31–33], making the improved FEV_1 growth seen in our study equivalent to 3 to 4 years of expected FEV_1 decline in adulthood. This change in FEV_1 is also comparable to deficits and improvements seen with increased and decreased air pollution. Previous studies have shown an approximate 100mL difference in FEV_1 in children living in Southern California communities with the highest air pollution versus those living in communities with the lowest air pollution[34–36]. Furthermore, regional improvements in air quality in Southern California have been associated with approximately 65mL to 90mL mean increase in FEV_1 over 4 years per median community-specific decrease in PM (8.7μg/m^3 PM_{10}, 12.6μg/m^3 $PM_{2.5}$) and nitrogen dioxide (14.1 ppb), respectively[37]. Therefore, reduction of indoor allergen exposure could represent long-term lung function growth benefits in children similar to benefits seen from improvements in air quality and pollution.

There are notable strengths and limitations of our study. To our knowledge, our study is the first to suggest that there may be lung function growth benefits from reduction in indoor allergen exposure, and should this prove to be the case, indoor allergen exposure reduction could be a disease-modifying strategy for pediatric allergic asthma. In MAAIT, a significant proportion of participants achieved clinically meaningful allergen reduction, allowing us to examine the effect of indoor allergen exposure reduction on lung function growth in a population with high allergen exposure. MAAIT also had repeated, robust allergen measurement and pre-/post-BD spirometry over its 1 year duration. However, MAAIT's participants were only followed for 1 year. Further follow up is needed to make inferences about the effect of allergen exposure reduction on lung function growth given the uncertainty of the some of the post-BD lung function measures. Additionally, MAAIT's participants were primarily low-income, urban minorities who were all sensitized and exposed to mouse, potentially limiting the generalizability of our finding. However, this population has the highest asthma morbidity in the United States[38,39] and is at risk for increased COPD morbidity and mortality in adulthood[40–42] and would, therefore, greatly benefit from allergen exposure reduction interventions. While this study focused on mouse, mouse is a major contributor to asthma morbidity in low-income, minority populations[19], which are at greater risk for adult pulmonary morbidity. Future studies are needed to assess the applicability of the findings of this study to other indoor allergens in sensitized and exposed populations. Lastly, as there were no differences in allergen reduction or clinical asthma outcomes by treatment group in the parent trial, we were unable to examine the effect of randomization to integrated pest management on lung function growth. An important next step would be to study the effect on randomization to integrated pest management on lung function growth.

While our results suggest that a reduction in allergen exposure may improve lung function growth, they are observational, from a single study, and there is greater uncertainty with respect to some of the post-BD lung function outcomes. Therefore these findings alone should not be considered proof of a causal relationship between mouse allergen reduction lung function growth. It is also possible that changes in other exposures that were not measured, including microbes and their constituents, such as endotoxin, could explain our findings. Unmeasured confounding therefore cannot be excluded as an explanation for the findings. Additionally, we are limited by our lack of other markers of inflammation (blood eosinophils, fraction of exhaled nitric oxide, total IgE), which if reduced, could suggest that change in mouse allergen exposure is associated with greater lung function growth over time through reduction of inflammation.

In conclusion, among low-income, urban, minority children with persistent asthma who are mouse-sensitized and exposed, mouse allergen exposure reduction was associated with a greater increase in pre-BD FEV_1 and pre-and post-BD $FEF_{25–75}$ over 1 year. These findings suggest that mouse allergen reduction may improve lung function growth in sensitized and exposed asthmatics, potentially altering the lung function growth trajectory from childhood into adulthood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ATS	American Thoracic Society
BD	Bronchodilator
COPD	Chronic obstructive pulmonary disease
ELISA	Enzyme-linked immunosorbent assay
$FEF_{25–75}$	Forced expiratory flow at 25–75%
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IPM	Integrated pest management
MAAIT	Mouse Allergen and Asthma Intervention Trial
NAEPP	National Asthma Education and Prevention Program
SPT	Skin prick test

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Clinical Implications:

Mouse allergen exposure reduction was associated with greater increases in pre-BD FEV_1 and pre-/post-BD $FEF_{25–75}$ over 1 year in sensitized/exposed children, suggesting allergen exposure reduction may improve lung function growth..

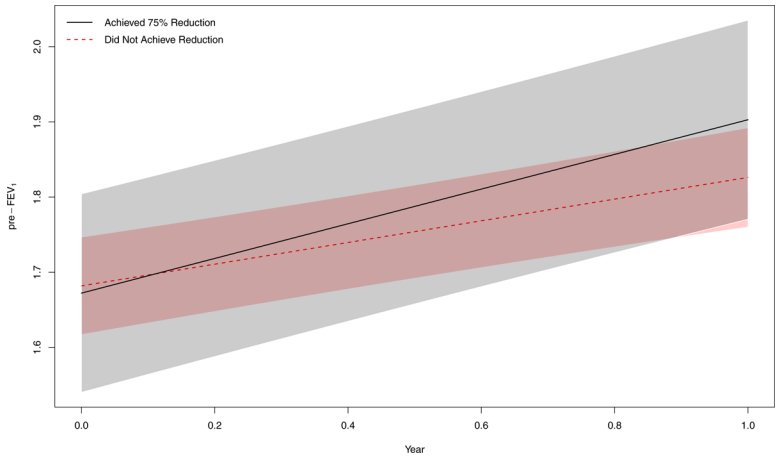

Figure 1:

Pre-BD FEV_1 growth over 1 year for a 10-year-old black male who achieved ≥75% mouse allergen reduction (solid black line, 95% CI gray shading) versus a 10-year-old black male who did not achieve ≥75% mouse allergen reduction (dashed red line, 95% CI red shading).

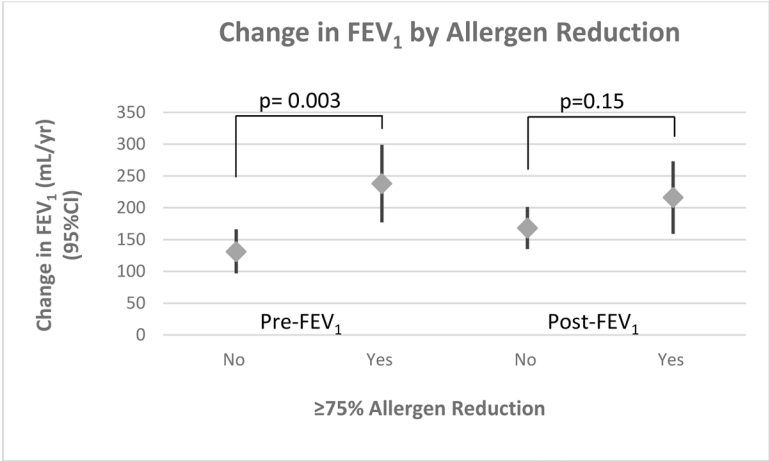

Figure 2:

Stock plot of predicted change in FEV_1 over 1 year for a 10-year-old black male who did not achieve ≥75% mouse allergen reduction versus a 10-year-old black male who did achieve ≥75% mouse allergen reduction. P-values derived from allergen reduction*time interaction term.

Table 1.

Study Population Characteristics (n=350)

	n (%)
Age (y), mean (SD)	9.8 (3.2)
Male gender	218 (63.2)
Race	
Black/African American	278 (79.4)
White	36 (10.3)
Other or Unknown	36 (10.3)
Hispanic ethnicity	75 (21.4)
Socioeconomic Measures	
Public insurance	303 (87.8)
Annual income < $30K	232 (66.3)
Study Site	
Baltimore	239 (68.3)
Boston	111 (31.7)
Asthma-related Acute Visits and Hospitalizations, last 3 months	
Acute (ED, urgent care, unscheduled PCP) visit	234 (66.9)
Hospitalization	44 (12.6)
Asthma Controller Medication (n=326)	
Step 1: Short acting β-agonist as needed	38 (11.7)
Step 2: Low-dose inhaled corticosteroids (ICS) or leukotriene modifier	61 (18.7)
Step 3: Low-dose ICS plus long acting β-agonist or medium-dose ICS	49 (15.0)
Step 4: Medium-dose ICS plus long acting β-agonist	16 (4.9)
Step 5: High dose ICS with or without long acting β-agonist	162 (49.7)
Lung Physiology (Pre-BD)	
FEV_1 % predicted, mean (SD) *	87.1 (17.3)
FEV_1 < 80% predicted *	65 (30.8)
FVC % predicted, mean (SD) *	96.8 (16.2)
FEV_1/FVC%^	80.2 (9.0)
FEV_1/FVC% < 85%^	211 (64.3)
Skin Prick Test (SPT) Sensitization (n=297)	
≥1 +SPT	291 (98.0)
No. +SPTs, mean (SD)	6.1 (3.2)
Cockroach	162 (54.6)
Cat	159 (53.5)
Dust mite	132 (44.4)
Dog	67 (22.6)
Allergen bedroom floor level	
Mouse (μg/g), median (25th-75th%ile)	5.7 (1.5–22.8)
≥75% mean reduction from baseline	92 (26.3)

* restricted to ≥8y, n=211; ^n=328

Table 2:

Associations between mouse allergen reduction and FEV_1 growth*

Lung function index	Achieved reduction ↑in mL(95%CI)	Did not achieve reduction ↑in mL(95%CI)	Difference in estimated FEV_1 growth (95%CI)**	p-value of interaction term*** (reduction*time)
Reduction metric: ≥50% mean reduction from baseline				
Pre-BD FEV_1	205mL (160 – 250) n=155	120mL (79 – 161) n=195	85mL (24 – 146)	p=0.006
Post-BD FEV_1	200mL (157 – 242) n=154	164mL (126 – 202) n=195	36mL (−21 – 93)	p=0.22
Reduction metric: ≥75% mean reduction from baseline				
Pre-BD FEV_1	238mL (177 – 299) n=92	131mL (97 – 166) n=258	107mL (37 – 177)	p=0.003
Post-BD FEV_1	216mL (159 – 273) n=92	168mL (135 – 201) n=257	48mL (−17 – 113)	p=0.15
Reduction metric: ≥90% mean reduction from baseline				
Pre-BD FEV_1	255mL (159 – 351) n=44	147mL (115 – 180) n=306	108mL (7 – 209)	p=0.04
Post-BD FEV_1	208mL (119 – 298) n=44	177mL (146 – 207) n=305	31mL (−63 – 126)	p=0.51

*Average change over 1 year the mean participant (10yo black male)

**Participants who achieved mean reduction minus participants who did not achieve mean reduction

***Adjusted for age, sex, race, group assignment, BD reversibility, and atopy (number of positive SPT), n=296

Table 3

Associations between mouse allergen reduction and FVC growth *

Lung function index	Achieved reduction ↑in mL(95%CI)	Did not achieve reduction ↑in mL(95%CI)	Difference in estimated FVC growth(95%CI) **	p-value of interaction term *** (reduction*time)
Reduction metric: ≥50% mean reduction from baseline				
Pre-BD FVC	250mL (191 – 308) n=155	197mL (145 – 250) n=194	53mL (−26 – 132)	p=0.19
Post-BD FVC	219mL (177 – 260) n=152	209mL (171 – 246) n=192	10mL (−46 – 66)	p=0.73
Reduction metric: ≥75% mean reduction from baseline				
Pre-BD FVC	270mL (191 – 348) n=92	205mL (160 – 250) n=258	65mL (−25 – 156)	p=0.16
Post-BD FVC	227mL (171 – 283) n=90	209mL (177 – 241) n=254	18mL (−46 – 83)	p=0.58
Reduction metric: ≥90% mean reduction from baseline				
Pre-BD FVC	248mL (124 – 371) n=44	218mL (176 – 259) n=305	30mL (−100 – 161)	p=0.65
Post-BD FVC	196mL (108 – 285) n=42	215mL (185 – 245) n=302	−19mL (−112 – 75)	p=0.69

* Average change over 1 year the mean participant (10yo black male)

** Participants who achieved mean reduction minus participants who did not achieve mean reduction

*** Adjusted for age, sex, race, group assignment, BD reversibility, and atopy (number of positive SPT), n=296

Table 4:

Associations between mouse allergen reduction and $FEF_{25–75}$ growth *

Lung function index	Achieved reduction ↑in mL(95%CI)	Did not achieve reduction ↑in mL(95%CI)	Difference in estimated FEF25–75% growth (95%CI)**	p-value of interaction term*** (reduction*time)
Reduction metric: ≥50% mean reduction from baseline				
Pre-BD $FEF_{25–75}$	174mL (95 – 253) n=153	55mL (−16 – 126) n=194	119mL (13 – 226)	p=0.03
Post-BD $FEF_{25–75}$	251mL (165 – 337) n=152	113mL (35 – 190) n=192	138mL (23 – 254)	p=0.02
Reduction metric: ≥75% mean reduction from baseline				
Pre-BD $FEF_{25–75}$	245mL (140 – 351) n=90	63mL (2 – 123) n=257	182mL (61 – 304)	p=0.003
Post-BD $FEF_{25–75}$	310mL (195 – 425) n=90	129mL (63 – 194) n=254	181mL (48 – 314)	p=0.008
Reduction metric: ≥90% mean reduction from baseline				
Pre-BD $FEF_{25–75}$	244mL (79 – 409) n=42	93mL (37 – 149) n=305	151mL (−23 – 325)	p=0.09
Post-BD $FEF_{25–75}$	275mL (96 – 456) n=42	163mL (102 – 224) n=302	112mL (−78 – 302)	p=0.25

* Average change over 1 year the mean participant (10yo black male)

** Participants who achieved mean reduction minus participants who did not achieve mean reduction

*** Adjusted for age, sex, race, group assignment, BD reversibility, and atopy (number of positive SPT), n=291