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Mouse allergen exposure, wheeze and atopy in the first seven years of life

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Abstract

Background—Little is known about mouse allergen exposure in home environments and the development of wheezing, asthma and atopy in childhood.

Objective—To examine the relation between mouse allergen exposure and wheezing, atopy, and asthma in the first 7 years of life.

Methods—Prospective study of 498 children with parental history of allergy or asthma followed from birth to age 7 years, with longitudinal questionnaire ascertainment of reported mouse exposure and dust sample mouse urinary protein allergen levels measured at age 2–3 months.

Results—Parental report of mouse exposure in the first year of life was associated with increased risk of transient wheeze and wheezing in early life. Current report of mouse exposure was also significantly associated with current wheeze throughout the first 7 years of life in the longitudinal analysis ($P = 0.03$ for overall relation of current mouse to current wheeze). However, early life mouse exposure did not predict asthma, eczema or allergic rhinitis at age 7 years. Exposure to detectable levels of mouse urinary protein in house dust samples collected at age 2–3 months was associated with a twofold increase in the odds of atopy (sensitization to ≥ 1 allergen) at school age (95% confidence interval for odds ratio = 1.1–3.7; $P = 0.03$ in a multivariate analysis).

Conclusions—Among children with parental history of asthma or allergies, current mouse exposure is associated with increased risk of wheeze during the first 7 years of life. Early mouse exposure was associated with early wheeze and atopy later in life.

Keywords

childhood asthma; indoor allergens; mouse allergen

The prevalence of childhood asthma has increased significantly in the US, making it a major public health problem (2). More than 80% of children with asthma are allergic to one or more inhaled allergens (3,4), and many studies have investigated the role of exposure to indoor allergens such as dust mites, pets, and cockroaches and the development of early childhood wheeze or asthma and atopy (5–8). There are few prospective studies of mouse allergen health effects in young children, while recent studies have shown that mouse allergen exposure in

homes of children with established asthma are highly prevalent and potentially important in both urban and suburban environments (9–17).

The Home Allergens and Asthma Study is a prospective birth cohort study of children with a parental history of asthma or allergies in the Boston metropolitan area. The primary purpose was to assess the relationship between exposure to indoor allergens in early childhood and the subsequent development of asthma and allergic disease. In this cohort, we have recently reported that mouse allergen exposure is highly prevalent (18), and that mouse exposure in these infants is also associated with wheeze in the first year of life (19). To date, there are no prospective studies evaluating the role of early mouse allergen exposure in home environments and the development of wheezing, asthma and atopy in later life. In this report, we examine the relationship between mouse allergen exposure in the first year of life and wheezing, atopy and asthma in childhood, as well as the longitudinal relation between mouse allergen exposure and wheezing over the first 7 years of life.

Methods

Study participants

Five hundred and five infants (including six sets of twins) and their 498 families with a history of allergy or asthma in at least one parent were recruited. The screening and recruitment of families have been described elsewhere (5).

After obtaining written informed consent from the child's parents, a home visit was made when the child was 2–3 months old, and a questionnaire regarding home characteristics and demographics was administered by trained research assistants. Every 2 months, beginning when the child was 2 months old, a telephone questionnaire was administered to the child's primary caregiver until the child's 2nd birthday. Afterwards, interviews were conducted every 6 months. Of the 505 children, seven were excluded from analysis because they were followed for ≤ 4 months during their first year of life, leaving us a total of 498 subjects for analysis. The study was approved by the Institutional Review Board of Brigham and Women's Hospital in Boston.

Analysis of house dust samples

Methods for the collection of dust samples from the bedroom, baby's bed, parent's bed, kitchen, and living rooms and the processing and assay of allergens have been detailed previously (5, 20–22). Allergen and endotoxin concentrations were assayed and grouped as previously reported in this cohort (5,20,23).

Dust samples collected at age 2–3 months in the living rooms were assayed for mouse and rat allergen by a competitive ELISA to determine the concentration of mouse urinary protein (MUP) and Rat n 1 in $\mu\text{g/g}$ of dust (Greer Laboratories, Lenoir, NC, USA) as described previously (18,19). The lower limit of detection for the MUP and Rat n 1 assay was $0.25 \mu\text{g/g}$ of dust. Mouse allergen concentrations were categorized as a binary variable (detectable vs nondetectable) and three categories (non detectable, detectable but $<$ median of detectable ($0.5 \mu\text{g/g}$) and detectable but $\geq$ median of detectable ($0.5 \mu\text{g/g}$). While threshold levels have not been well established, these categories have been consistently associated with allergic sensitization and allergic symptoms in our previous studies in this cohort and others (15,18, 19,24).

Definition of predictor variables by questionnaire

Reported exposure was treated primarily as a binary variable as previously reported (19) and was ascertained every 2 months in the first 2 years of life and every 6 months thereafter up

until the child was 7 years old. Every 2 months for the first 2 years of life, the primary caretaker was asked 'In the past 2 months, have you been troubled by any of the following pests? (mice)' Children whose primary caretaker answered yes to these questions during the first year of life were categorized as having mouse exposure in the first year of life. Starting at age 30 months, the primary caretaker was asked every 6 months, 'Since we last spoke, have you seen or noticed signs of mice?' up until age 7.

Children whose primary caretaker answered yes to the mouse exposure question that corresponded for ages 1–7 were categorized as those with current reported mouse exposure for each year from age 1–7.

Other variables considered for inclusion in the multivariate analysis are previously described (19,23) and included the child's sex; reported race or ethnicity; (25) annual household income; maternal education; residence within the city of Boston; birth-weight; season of birth; maternal age; maternal cigarette smoking during pregnancy; exclusive and supplemented breastfeeding; bottle-feeding before sleep time (26); maternal immunoglobulin E (IgE); and parental history of asthma, allergic rhinitis, atopic dermatitis and/or food allergy. Variables related to the home environment included type of dwelling; presence of any pets in the home when the child was 2–3 months old; cigarette smoking; number of older siblings; and day care attendance in the first year of life (27). Other binary variables examined in the first year of life included runny or stuffed nose, doctor-diagnosed croup, bronchitis, bronchiolitis, doctor-diagnosed ear infections and doctor-diagnosed sinus trouble (28).

Allergy skin testing

At a mean age of 7.4 years (range, 6.5–10.1 years), allergy skin testing was performed in 248 children and IgEs specific to common allergens were measured in an additional 23 children.

Allergy skin testing was performed on the volar aspect of the lower arms and is previously described (23). The allergens tested included common indoor [cat dander, dog dander, cockroach (*Blattella germanica*), dust mite (*Dermatophagoides pteronyssinus* and *D. farinae*) and mouse epithelial extract] and outdoor (*ragweed*, *mixed trees*, *Aspergillus*, *Alternaria*, *mixed grasses*, *Cladosporium* and *Penicillium*) allergens (Hollister Steir Labs, Spokane, WA, USA). Glycerinated saline and histamine were used as the negative and positive controls, respectively. Skin tests to specific allergens were considered positive if the mean diameter of the wheal was ≥ 3 mm after subtraction of the control wheal. Families were given results of skin testing and referred to their physicians for further treatment and recommendations.

Serum from 23 children who declined skin testing was assayed for IgE to the allergens listed above using the UniCAP 250 system (Pharmacia & Upjohn, Kalamazoo, MI, USA). IgEs to specific allergens were considered positive at a level ≥ 0.35 IU/ml.

Outcomes

Outcomes of wheeze, physician-diagnosed asthma, allergic rhinitis, and eczema were determined by parental report and have been previously described (29). We used two types of outcomes: endpoints at age 7 years (or school age) and repeated measures of wheeze over the course of follow-up. At age 7 years, asthma was defined as physician-diagnosed asthma (at any time since birth) and ≥ 1 episode of wheezing in the previous year, and allergic rhinitis as physician-diagnosed allergic rhinitis (at any time since birth) and a history of nasal discharge or sneezing apart from colds in the previous year. At age 7 years, transient wheeze was defined as ≥ 1 episode of wheezing before age 3 years but not thereafter, persistent wheeze as ≥ 1 episode of wheezing before age 3 years and ≥ 1 episodes of wheezing between ages 6 and 7 years, and late-onset wheeze as no episodes of wheezing before the age of 3 years and ≥ 1 episodes of

wheezing between ages 6 and 7 years (30). Sensitization to ≥ 1 allergen (atopy) was considered present at school age if there was at least one positive skin test or specific IgE to the allergens tested. For the longitudinal analysis of repeated measures of wheeze, wheeze was considered present at any time point between 12 and 84 months of age if an affirmative response was given to the question, 'Has your child had wheezing or whistling in the chest since we last spoke?'

Statistical methods

The analysis began with bivariate explorations between variables of interest. Statistical significance was assessed with chi-squared tests for categorical variables and two-tailed *t*-tests for continuous variables. Stepwise logistic regression was used to study the relation between mouse exposure in the first year of life and asthma, recurrent wheezing, allergic rhinitis, eczema and atopy at age 7 years, while adjusting for potential confounders and examining interactions. Variables were kept in the final models if they were significantly associated with the outcome ($P < 0.05$) or they satisfied a change in estimate criteria ($\geq 10\%$ change in the β coefficient estimate). These analyses employed the sas software package (SAS Institute Inc., Cary, NC, USA).

For the longitudinal analysis of the relationship between the repeated mouse exposures and wheezing in the first 7 years of life, we used generalized estimating equations (31,32). We analyzed the data using a generalized linear model implemented by PROC GENMOD in sas 9.1 with the binomial distribution and a logit link. We accounted for the repeated measures within a subject by using the repeated statement and an unstructured covariance matrix. We fit unadjusted and covariate-adjusted models for wheeze. All of the covariates in the models were dichotomous or categorical variables. To allow incidence rates to change over time, age was included in the model as a categorical variable. As we are using logistic regression, the parameter estimates from this model are 'log-odds' of risk of wheeze. The odds ratio approximates the risk ratio well when the outcome is rare as in our study and is appropriate for this analysis. Age-specific odds-ratios associated with the presence of mouse were computed by including an interaction between age and exposure, and adjustments were made for current report of mouse exposure in relation to any moves or changes in home environment.

Results

The characteristics of the 498 infants in the birth cohort have been described in detail elsewhere (18–20). Briefly, of the 498 participating infants, 375 (75.3%) were white, 439 (90.7%) lived in households with an annual income of at least \$30 000, and 357 (71.7%) resided outside of the city limits of Boston (in suburban areas). One hundred and three (20.7%) of the participating infants lived in homes with reported signs of mice during the first year of life. Signs of rats in the home were only reported for two infants, and only one parent reported rats or mice as pets in the home. MUP was detectable in 31.7% of kitchens and 33.3% of living rooms. Rat allergen was detectable in only one of the homes.

Of the 498 study participants, 440 (88.3%) were followed up to the age of 7 years. Table 1 compares the characteristics of those who were followed for 7 years vs those who were lost to follow-up. There was no statistically significant difference in reported exposure to mice in the first year of life or detectable MUP between those with and without 7-year follow-up or between those with and without an assessment of allergen sensitization at school age. Subjects who dropped out of the study before the age of 7 years were more likely to come from low-income families, to be of black or Hispanic (non-white) reported ethnicity, and to have increased levels of cockroach allergen. Subjects who had an assessment of allergen sensitization at school age had similar characteristics to the full cohort except that they were more likely to come from families with household incomes $> \$30\,000$ per year and to be of white race, as previously reported (28).

In bivariate analyses, there was no association between either reported mouse exposure in the first year of life or detectable MUP at age 2–3 months and asthma at the age of 7 years (Table 2). We found weak associations of borderline significance ($P > 0.05$) of report of mouse exposure in the first year of life with eczema and allergic rhinitis at age 7 (Table 2).

Reported mouse exposure was associated with transient wheeze but not with persistent wheeze and late-onset wheeze. This association persisted after adjustment for cockroach allergen exposure and other covariates (Table 3). Reported mouse exposure and detectable MUP in the first year of life had nearly twice the odds of wheeze in the first year of life (MUP OR = 1.82, 95% CI = 1.22–2.71, $P = 0.003$), but were not related to subsequent wheeze at age 2 through 7, in a repeated measures longitudinal analysis [P -value for relation of report of mouse in first year of life with wheeze in first 7 years of life = 0.5561 (Wald test)].

There was, however, a significant relationship between current report of mouse exposure and current wheeze throughout the 7 years of childhood. Overall, in the first 7 years of life children who had current report of mouse had 1.4 times the odds of having current wheeze (95% CI: 1.13–1.70; P -value = 0.002), with no significant effect modification by time. This association did not change when the analysis was repeated with the subset of 440 of 498 children who remained in follow-up at age 7 years.

Measurable MUP at age 1 predicted increased risk of atopy in the school-aged children (Table 4). After adjustment for potential confounders, including household income, infants who lived in homes with detectable MUP at age 2–3 months had nearly twice the odds of developing atopy at school age than those with no exposure ($P = 0.04$). The association remained after adjustment for croup and more than two ear infections in the first year of life (multivariate model 2). Inclusion of endotoxin and cockroaches in the models did not affect the relationship between mouse exposure and atopy (data not shown). Our results remained the same when atopy was defined as sensitization to allergens other than mouse. There was a dose–response relationship between level of mouse allergen and atopy [MUP > 0.5 µg/g OR = 2.2, 95% CI = 1.1–4.8, $P = 0.04$; MUP > LLOD and ≤ 0.5 µg/g, OR = 1.4 (95% CI = 0.7–2.9, $P = 0.3$, REF < LLOD)]. For MUP exposure in three categories and outcomes of wheeze, asthma, allergic rhinitis and eczema at age 7 we had limited power ($n < 10$) in some categories, and we were unable to observe a significant dose–response, but the direction of the association was consistent. Few children ($n = 10$) demonstrated sensitization to mouse allergen by either skin test or mouse-allergen-specific IgE at age 7, and we could not detect a relation of MUP at age 1 to specific sensitization to mouse at age 7. All of the 10 children with sensitization to mouse allergen were sensitized to at least one other allergen. Of the 10 children with mouse allergy, two had asthma at age 7 years and three had parental report of wheeze during the previous year at age 7 years.

Discussion

Extending our findings of a relation of current mouse exposure with current wheeze in the first year of life (19), in this longitudinal study, we found that current exposure to mouse was associated with current wheeze over the first 7 years of life. While our significant association was not robust, this may be due to the cumulative effect of exposure over time. However, while early exposure to mouse had an early life effect, as noted by early wheeze and transient wheeze, it was not related to subsequent persistent wheeze or asthma. This may be, in part, because a single measure of mouse exposure cannot be assumed to be a marker for chronic exposure to that allergen, unlike early life mite or cat allergen measurements, which tend to be more constant over time unless an intervention occurs (33). Furthermore, exposure to pet allergens such as cat may be much higher and more chronic than encountered by intermittent, lower pest allergen exposure from mice. Tolerance or protective immunologic mechanisms may be found

in these higher, chronic pet exposure levels and may explain why our study showed an association between mouse exposure and symptoms rather than a protective effect, which has been suggested for mammalian pets (34). It is also possible that mouse allergen is associated with current asthma symptoms of wheeze and exacerbations as opposed to asthma development. A recent Baltimore urban study demonstrated that within-home mouse exposure is variable over time (35). These findings are consistent with findings in our cohort, where the within-person correlation of report of mouse exposure over time was modest (correlation coefficient = 0.21).

A Baltimore study found a contemporaneous association with mouse exposure and asthma morbidity in preschool children (24). The relation of current mouse exposure to current wheeze could either be an irritant or an allergic effect, or both. Many laboratory workers report rhinitis and asthma symptoms without mouse allergen sensitization, suggesting that mouse exposure has an irritant effect on airways (36).

While not finding a relation of early life mouse exposure to subsequent asthma in later childhood, the direction of the association between report of mouse in the first year of life or measured early life MUP with eczema and allergic rhinitis at age 7 was positive but not statistically significant. Consistent with this suggestion of a relation of early mouse exposure to later allergic disease, we also found stronger associations between exposure to mice in early life as measured by MUP and the subsequent risk of allergic sensitization, with a dose response. It is possible that even short-term exposure to MUP influences overall risk of atopy if encountered at a vulnerable time in the life cycle (e.g. infancy). Although we found no significant association between measured MUP at age 2–3 months and specific sensitization to mouse allergen, we had limited statistical power for this analysis because of the very low prevalence of mouse allergy in our cohort.

Our ability to evaluate cumulative long-term exposure to mouse was limited by the lack of yearly repeated measures of MUP. However, we did have repeated measures of reported exposure, which have been previously shown to be fairly predictive of MUP levels, with a positive predictive value of nearly 70% in this cohort (18). Although reported mouse exposure may be subject to bias, there was a consistent positive association of either reported mouse exposure or measured MUP with wheeze in the first year of life. While the association between reported mouse exposure and transient wheeze was stronger than that between measured MUP and transient wheeze, this may be explained by the more remote MUP measurement at age 2–3 months vs the bimonthly reported mouse exposure measurement in the first year of life, which may more accurately represent current exposure. Furthermore, we had more children with reported mouse exposure measurements than measured MUP, and therefore had limited power in our analyses of the relation between measured MUP and the outcomes of interest.

It is possible that the association of MUP with atopy could be explained by an unmeasured confounder, but we found no evidence that our findings can be explained by poverty or class as measured in our cohort, or by loss to follow-up. We realize that we may have only partially controlled for complex confounders such as environmental tobacco smoke and socioeconomic status, and that there may be other unmeasured confounders. We also are limited in that we did not have measures of other potentially important modes of mouse allergen exposure such as the school. Despite the potential for misclassification in physician or parental report of wheeze (physicians may not be present when a child wheezes), parental report of wheeze is a standard outcome in ATS and ISAAC questionnaires, and in many US studies including our own, is highly predictive of asthma (37), slower lung function growth (38) and methacholine reactivity (38).

Finally, our findings are applicable to a group at high risk for the development of allergic diseases (a significant proportion of the general population), but may not be applicable to children at low risk for allergy or asthma.

In conclusion, our results suggest that current exposure to mouse allergen is associated with current wheeze over the first 7 years of life, and that early mouse exposure is associated with early and transient wheeze early in life and atopy later in life. From these findings, we conclude that exposure to mouse allergen may be important in exacerbating current asthma disease symptoms and general atopy later on in life.

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Abbreviations

MUP	mouse urinary protein
NCICAS	National Cooperative Inner-City Asthma Study
OR	odds ratio
RR	risk ratio

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Table 1
Comparison of children who remained in the study vs those who did not*

Variable	Remained in study	Lost to follow-up	P-value
Sex			
Male	240	28	
Female	200	30	0.4
Income			
≥\$50 000	327	24	Ref
\$30 000–\$49 999	76	12	0.04
<\$30 000	27	18	<0.0001
Race			
White	351	24	Ref
Black	36	24	<0.0001
Hispanic (non-white)	21	7	0.001
Asian/other	32	3	0.6
Report mice, year 1			
No	325	41	
Yes	115	17	0.6
MUP, living room			
Not detectable	254	27	
Detectable	119	21	0.1
In utero smoking			
No	416	49	
Yes	24	9	0.004
Bla g 1 living room/kitchen			
<0.05 µg/g	200	21	Ref
0.05–2 µg/g	203	17	0.51
≥2 µg/g	35	19	<0.0001
Der f+p, bedroom			
<0.05 µg/g	198	25	Ref
0.05–2 µg/g	135	24	0.26
2–10 µg/g	64	4	0.21
≥10 µg/g	42	5	0.91
Endotoxin quartiles, living room			
1st	83	17	Ref
2nd	90	10	0.15
3rd	92	9	0.09
4th	88	12	0.32

* There was missing information on household income (n = 14), mouse urinary protein (n = 77), Bla g 1 (n = 3) and endotoxin (n = 97).

Table 2
Mouse exposure in the first year of life and asthma, eczema and allergic rhinitis, at the age of 7 years

	Asthma (<i>n</i> = 43)		Eczema (<i>n</i> = 35)		Allergic rhinitis (<i>n</i> = 64)	
	No. (%)	OR, 95% CI	No. (%)	OR, 95% CI	No. (%)	OR, 95% CI
Report mice, year 1						
No	34 (79.1)	1.00	22 (62.9)	1.00	44 (68.8)	1.00
Yes	9 (20.9)	0.7 (0.3–1.6)	13 (37.1)	1.8 (0.9–3.6)	20 (31.3)	1.4 (0.8–2.4)
Detectable MUP (µg/g)						
No	30 (76.9)	1.00	18 (58.1)	1.00	34 (66.7)	1.00
Yes	9 (23.1)	0.6 (0.3–1.3)	13 (41.9)	1.6 (0.7–3.5)	17 (33.3)	1.1 (0.6–2.0)

Table 3
Mouse allergen exposure in the first year of life and transient, persistent, and late-onset wheeze at age of 7†§

Mouse allergen	Never (reference)	Transient wheeze		Persistent wheeze		Late-onset wheeze	
		<i>n</i>	Unadjusted [OR (95% CI)]	Adjusted3 [OR (95% CI)]	<i>n</i>	Unadjusted [OR (95% CI)]	Unadjusted [OR (95% CI)]
MUP (µg/g)							
Nondetectable	91	85	1.0		40	1.0	1.0
Detectable	34	47	1.5 (0.8–2.5)	1.4 (0.8–2.5)	15	1.0 (0.5–2.0)	1.6 (0.7–3.8)
Report of mouse							
No	119	105	1.0	1.0	50	1.0	1.0
Yes	32	52	1.8 (1.1–3.1)*	1.8 (1.02–3.0)*	14	1.0 (0.5–2.1)	1.0 (0.4–2.6)

* $P < 0.05$

† 36 children not included because of missing information ($n = 19$) or not fitting any wheeze category ($n = 17$). In addition, 65 homes did not have enough dust for mouse allergen analysis.

§ All models were adjusted for sex, household income, race, cockroach allergen and endotoxin.

Table 4 Association of mouse allergen exposure in the first year of life with atopy at age 7

Variable	Bivariate association		Multivariate model 1†		Multivariate model 2*	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Single detached home	0.62 (0.38–1.01)	0.052	0.57 (0.34–0.98)	0.04		
Cat in home	0.82 (0.48–1.41)	0.47				
Dog in home	0.75 (0.39–1.40)	0.36				
Mouse urinary protein	1.74 (0.99–3.07)	0.06	1.88 (1.03–3.43)	0.0397	2.00 (1.07–3.71)	0.03
Report of mouse Yr	0.9 (0.6–1.5)	0.9				
Bla g 1 (<0.05)						
0.05–2 µg/g	1.34 (0.81–2.20)	0.25				
≥2 µg/g	1.52 (0.55–4.18)	0.42				

* Also adjusted for croup and more than 2 ear infections in the first year of life.

† Also adjusted for income and sex.