

Predictors of Repeated Wheeze in the First Year of Life

The Relative Roles of Cockroach, Birth Weight, Acute Lower Respiratory Illness, and Maternal Smoking

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While more than 80% of childhood asthmatics are allergic to one or more inhaled allergens, the role of inhaled allergens in the induction of wheeze in the first year of life is unknown. In a prospective birth-cohort study of 499 children of asthmatic/allergic parents from metropolitan Boston, we examined home allergen concentrations measured within the first 3 mo of life as predictors of repeated wheeze episodes in the first year of life. In multivariate analyses adjusting for maternal asthma and dog in the home, predictors of two or more wheeze episodes in the first year of life included maternal smoking during pregnancy (relative risk [RR] = 1.83; 95% confidence limit [CL]: 1.12, 3.00), lower respiratory illness in the first year of life (croup, bronchitis, bronchiolitis, or pneumonia) (RR = 2.25; 95% CL: 1.58, 3.19), low birthweight (RR = 1.28, 95% confidence interval [CI]: 1.04, 1.58 for an inter-quartile difference), and *Blatella germanica* (cockroach) allergen level in the family room > 0.05 U/g dust (RR = 1.76; 95% CL: 1.20, 2.57). Cockroach allergen in the family room and repeated wheeze remained significant after adjustment for socioeconomic factors including race and income (RR = 1.63; 95% CL: 1.05, 2.55). It is unknown whether the association between cockroach and repeated wheeze in infancy represents a cockroach-related increased risk of bronchial inflammation through nonallergic or allergenic mechanisms. Gold DR, Burge HA, Carey V, Milton DK, Platts-Mills T, Weiss ST. Predictors of repeated wheeze in the first year of life: the relative roles of cockroach, birth weight, acute lower respiratory illness, and maternal smoking.

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the cockroach lives
in peace and plenty
while the human race
hustles to support him
all the social institutions
of all time have existed
for the purpose
of forming a pyramid
on the apex of which
perches the cockroach triumphant
it has taken us a long
time but we point
with pride to the achievement

archy the cockroach (from *Don Marquis, the lives and time of archy and mehitabel*. Doubleday & Company, Inc., New York, 1940).

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More than 80% of childhood asthmatics are allergic to one or more inhaled allergens. Recent studies suggest that two-thirds of childhood asthma cases in the United States are diagnosed by 5 yr of age (1). Repeated or persistent wheeze is the chief symptom leading to doctor-diagnosed asthma, yet not all children who wheeze are allergic, nor are they necessarily destined to become asthmatic. Particularly in the first year of life, children with relatively small airways may develop airway inflammation and symptoms of wheeze in response to viral illnesses, yet may not develop allergy or persistent wheeze that lasts beyond the first year of life (2).

A few prospective studies suggest an association between allergen exposure in the first year of life and subsequent development of specific allergic sensitization and asthma. In a cohort of 67 British children with a parental history of asthma or hay fever, the relative risk of asthma at age 11 was 4.8 for those children exposed in the first year of life to more than 10 μ g of *Der p 1* (dust mite allergen) per gram of dust (3). The age at which the first episode of wheezing occurred was inversely related to the level of allergen measured in the first year of life. Was the association between early infancy allergen exposure and subsequent expression of asthma significant by age 11 and not earlier because the study had insufficient power to detect earlier associations? Or is there a relatively long lag between exposure and subsequent disease expression?

Well documented predictors of wheeze in the first year of life include maternal smoking during pregnancy (4, 5), low birth weight, prematurity (6), and lower respiratory infections (7). Socioeconomic status and race/ethnicity are also strong predictors of early childhood wheeze (8, 9), but these factors may, in part, be indicators of as yet poorly defined environmental exposures, including allergen exposure.

In a birth cohort of children of parents with asthma or allergy, we tested the hypothesis that, even after the effects of these other predictors of early wheeze are taken into account, home allergen levels measured within the first 3 mo of an infant's life predict repeated wheeze episodes in the first year of life.

METHODS

Study Cohort

Participants were part of a metropolitan Boston prospective birth cohort study designed to examine relationships between exposure to indoor allergens and the development of allergic sensitization and asthma. The 505 infants (including six sets of twins) and their 499 families with a history of asthma or allergy in at least one parent were recruited between September 1994 and June 1996. Monday through Friday, all mothers who delivered at a large Boston hospital were approached for screening within 24 to 48 h after delivery if they lived within Route 128 (encircling the metropolitan area), were ≥ 18 yr old, and were able to speak English or Spanish. To reduce the chance of prematurity or respiratory distress syndrome as a potential confounder, families were not screened if the child was < 36 wk of gestation, had a major congenital anomaly, or was in the neonatal intensive care unit. Mothers were asked: (1) Have you ever had a doctor's diagnosis of asthma, hay fever, or allergies? (2) Has the biological father of your child ever had a doctor's diagnosis of asthma, hay fever, or allergies? Women who answered yes to any of these questions were asked to complete a screening questionnaire. One month after birth, a questionnaire regarding the child's health was administered by telephone to families who had initially expressed interest in participating in the study and who fit the inclusion criteria. At 1 mo, parents who expressed plans to move or lack of interest in the study were also excluded. Of the 1,405 families initially screened, 906 were excluded from the study before the first home visit. Reasons for exclusion were reluctance to participate in a longitudinal study (51% of those refusing), plans to move within 1 yr (39%), early loss to follow-up (9%), and other (1%). Mothers gave consent for screening; at the time of the first home visit, when the index child was 2 to 3 mo of age, they gave consent for participation in the longitudinal study. Every 2 mo the primary caregiver was asked a follow-up telephone questionnaire regarding respiratory symptoms and illnesses in the index child; changes in infant feeding and select home characteristics were also recorded.

Home Visit and Dust Collection

At the home visit, questionnaires regarding home characteristics, home environmental exposures (including smoking) and demographic and socioeconomic characteristics of the family were administered by trained research assistants. Methods used for the collection of dust samples and the processing and assay of allergens in this study have been detailed previously (10). In brief, four separate dust samples were collected in standardized fashion by vacuuming the following areas: (1) the baby's bedroom floor, (2) the baby's bed, (3) the parent's bed (if the child slept there $\geq 50\%$ of the time), (4) the family/living room chair or sofa most commonly used by the caregiver when holding or feeding the infant as well as the family room floor around the chair or sofa and in high-traffic areas, and (5) the kitchen floor. If a rug was present in any of the rooms, half of the time was devoted to sampling the rug.

Dust Extraction and Allergen Analysis

Dust extract was assayed for allergens including house dust mite (*Der p 1*, *Der f 1*), cat (*Fel d 1*), and cockroach (*Bla g 1*, *Bla g 2*). Two-site monoclonal antibody (MAB) immunoassays for *Der p 1*, *Der f 1*, and *Fel d 1*, and MAB/polyclonal immunoassays for *Bla g 1* and *Bla g 2*

were used (10–12). Allergen concentrations were reported as micrograms per gram ($\mu\text{g/g}$) of dust except for *Bla g 1* and *2* which were reported as units/gram (U/g) of dust. When limited dust was available from the bed, bedroom floor, or family room, *Der f 1* (more prevalent than *Der p 1* in Boston) was analyzed first, and the remaining extract was then analyzed for *Der p 1*, *Fel d 1*, and *Bla g 1*, in that order. A limited number of assays for *Bla g 2* were performed in locations other than the kitchen. In the kitchen *Bla g 1* was analyzed first and then (in order) *Bla g 2*, *Fel d 1*, *Der f 1*, and finally *Der p 1*.

Definition of Predictor Variables

The race/ethnicity of the child was defined according to parental self-reporting of race/ethnicity, which was considered as a socioeconomic factor. If either parent was black, the child was defined as being black; if no parent was black but a parent was Hispanic, the child was defined as being Hispanic; if no parent was black or Hispanic but a parent was Asian, the child was defined as being Asian; children with two white parents were defined as being white. Zip code boundaries were used to define the levels of poverty in areas within the greater Boston vicinity. The percent of the population below the poverty level was determined for each of the zip code areas (based on data from the 1990 U.S. Census). Zip code areas were then combined to form three poverty area categories: low (less than 5% of individuals below the poverty level, based on 1990 U.S. Census data), medium (5–20% of individuals below the poverty level), and high ($> 20\%$ of individuals below the poverty level). Parental asthma was considered active if the parent had a report of wheeze in the past year. Smoking variables considered included: maternal smoking during pregnancy; maternal smoking during pregnancy or the first year of the child's life; current maternal smoking reported at the home visit; and total number of cigarettes smoked in the home reported at the home visit. Season of birth was defined as winter (December–February), spring (March–May), summer (June–August), or fall (September–November). Birth weight and head circumference were considered both as continuous and as categorical variables. Any breast-feeding and number of months of breast-feeding (0 to < 2 , 2 to < 8 , 8 to ≤ 12) in the first 12 mo were considered as predictor variables. Lower respiratory illness was defined as doctor diagnosed croup, bronchitis, bronchiolitis, or pneumonia. Furry/feathered pets were defined as pet hamsters, pet mice, other furry pets other than cats and dogs, and birds.

As in previous analyses, allergen concentrations were grouped in categories with potential relevance to sensitization and development of allergy-related repeated wheeze (13–16). The maximal concentration in the home and the specific room concentrations (bed, bedroom floor, living room, and kitchen) were assessed as predictors of repeated wheeze to determine whether location influenced the magnitude or strength of association between the allergen and wheeze.

Dust mite exposure was categorized as *Der f 1* or *Der p 1* at the following levels: (1) ≥ 10 $\mu\text{g/g}$ (including concentrations exceeding detectable limits); (2) 2 to < 10 $\mu\text{g/g}$; (3) 0.05 to < 2 $\mu\text{g/g}$; and (4) < 0.05 $\mu\text{g/g}$ (including assays "below the limits of detection"). Those samples with "no dust" in the bed, bedroom floor, and living room were also assigned to category (4) because if any dust was available, the measure of dust mite concentration was first priority. The correlation between dust mite concentration per unit area and per unit mass in 484 living room samples was 0.98, also supporting the assumption that homes with no dust would have levels < 0.05 $\mu\text{g/g}$. We also checked whether exclusion of "no dust" from category 4 significantly altered the analytic results.

Cockroach exposure was categorized as *Bla g 1* or *Bla g 2* at the following levels: (1) ≥ 2 U/g (including concentrations exceeding detectable limits); (2) 0.05 to < 2 U/g; (3) < 0.05 U/g (including concentrations below the limits of detection). Samples with no dust available for *Bla g* assay were assigned to a separate category (4) given that if any dust was available, measurement of cockroach antigens was not first priority except in the kitchen. Cat exposure was categorized as *Fel d 1* at the following levels: (1) ≥ 8 $\mu\text{g/g}$ (including concentrations exceeding detectable limits); (2) ≥ 1 to < 8 $\mu\text{g/g}$; (3) < 1 $\mu\text{g/g}$ (including concentrations below the limits of detection), and (4) no dust available. A combined variable measuring *Fel d 1* concentrations in either the bedroom bed or bedroom floor was created to represent bedroom exposure because the result was fewer cases in which "no dust"

was available for the assay. Dog allergen exposure, measured only in the living room, was categorized as *Can f 1* at the following levels: (1) ≥ 200 $\mu\text{g/g}$; (2) 20 to < 200 $\mu\text{g/g}$; and (3) < 20 $\mu\text{g/g}$.

Definition of Outcome Variables

Every 2 mo the primary caregiver (usually the mother) was asked, "Since we last spoke with you on (date given), has your child had symptoms of wheeze?" The primary categorical outcome variable was two or more reports of wheeze in the first year of life compared with fewer than two. Any wheeze versus no wheeze report and two or more reports of wheeze versus no wheeze report were also examined for their relationship to exposure. Because the symptom questionnaire was scheduled to be administered when the index child was 1, 2, 3, 4, 6, 8, 10, and 12 mo of age, there were potentially seven questionnaires per child. Of the 505 children, 94.5% had a complete data set and 97% had their 12-mo questionnaire completed; these children were included in the analysis. Of the 14 children missing their 12-mo questionnaire, three had a 10-mo and a 14-mo questionnaire and two children had a 10-mo questionnaire; their data were included in the analyses. Because their repeated wheeze (outcome) classification was known, three children with two or more reports of wheeze were in-

cluded despite missing wheeze information from Months 10 through 14. Thus six children were excluded from the analysis.

Statistical Methods

SAS statistical software (SAS Institute, Inc., Cary, NC) was used to evaluate univariate and multivariate associations between predictor variables and wheeze. Univariate associations between categorical predictor variables and two or more episodes of wheeze were examined with 2×2 contingency tables; the logit method was used to calculate relative risk for a cohort. Log relative risk parameters were estimated directly (not approximated by the log odds ratio) with use of SAS PROC GENMOD (SAS Institute, 1997), with log link and binomial variance function.

Variables were chosen for the multivariate models because they entered into both forward and backward stepwise logistic regression at a level of $p \leq 0.1$, estimating odds ratios rather than relative risks, since these procedures were not practically applicable to relative risk estimation. Because odds ratio estimations uniformly resulted in a slight overestimation of the magnitude and precision of risk, somewhat more variables were included in final models estimating relative risk. Socioeconomic variables (race/ethnicity, income, area) were considered because they were potential confounders of the relationship between cockroach allergen level and repeated wheeze.

TABLE 1
UNIVARIATE PREDICTORS OF TWO OR MORE REPORTS OF WHEEZE IN THE FIRST YEAR OF LIFE: HEREDITARY, PRENATAL, AND PERINATAL FACTORS

Factors	Subjects		Relative Risk	95% CL
	n	Percent with 2 or More Reports of Wheeze		
Sex*				
Female = 0	233	18.9	1.00	—
Male	266	19.6	1.04	0.72, 1.49
Maternal asthma				
No asthma = 0	345	16.8	1.00	—
Active*	106	27.4	1.63	1.10, 2.40
Inactive	48	18.8	1.12	0.59, 2.10
Paternal asthma				
No asthma = 0	376	19.7	1.00	—
Active*	78	18.0	0.91	0.54, 1.53
Inactive	36	16.7	0.85	0.40, 1.81
Maternal age, yr				
18 to 30	124	25.8	1.00	—
30 to 33	125	14.4	0.56	0.33, 0.94
33 to 36	125	16.8	0.65	0.40, 1.06
36 to 46	125	20.0	0.78	0.49, 1.23
Birth weight, kg				
3.79 to < 4.91	125	12.8	1.00	—
3.46 to < 3.79	121	19.8	1.55	0.87, 2.77
3.18 to < 3.46	127	18.9	1.48	0.83, 2.64
1.84 to < 3.18	125	25.6	2.00	1.16, 3.45
			1.39 [†]	1.12, 1.72
Head circumference, cm				
36 to < 38.5	99	13.1	1.00	—
35 to < 36	108	14.8	1.13	0.57, 2.23
34 to < 35	54	16.7	1.27	0.58, 2.78
23 to < 34	112	27.7	2.11	1.17, 3.80
			1.25 [‡]	1.11, 1.41
Season of birth				
Winter (Dec–Feb) = 0	123	12.2	1.00	—
Spring (Mar–May)	144	18.8	1.54	0.86–2.76
Summer (Jun–Aug)	111	22.5	1.85	1.03–3.32
Fall (Sep–Nov)	121	24.0	1.97	1.11, 3.48
Maternal smoking in pregnancy				
No = 0	467	17.8	1.00	—
Yes	32	40.6	2.29	1.44, 3.63

* Unless otherwise stated, variables are categorical, with category of comparison labeled as 0.

[†] RR for birth weight as continuous variable, estimated for an interquartile difference (0.61 kg).

[‡] RR for head circumference as continuous variable, estimated for an interquartile difference (2 cm).

RESULTS

Wheeze Experience

Of the 499 children, 288 (58%) never wheezed, 115 (23%) had a report of wheeze in only one questionnaire, 55 (11%) had reports of wheeze in two questionnaires, 25 (5%) had reports of wheeze in three questionnaires, and 16 (3%) had reports of wheeze in more than three questionnaires in the first year of life. Of those who had two or more reports of wheeze in the first year of life, 43% had their first wheeze episode within the first 2 to 3 mo of life, but only one child had both episodes in that early period.

Cohort Characteristics as Wheeze Predictors: Univariate Analyses

Tables 1 and 2 show the cohort characteristics and their univariate relationship to two or more wheeze reports. Boys did not have a higher risk than girls of two or more reports of wheeze. Multiple wheeze reports were higher among children of black, Hispanic, and "other" backgrounds than among those whose parents were both white. Maternal history of asthma was a stronger predictor of multiple wheeze reports than paternal history of asthma. Children of asthmatic mothers with current wheeze had a higher risk of multiple wheeze reports than children of asthmatic mothers without current wheeze.

Children in the lowest quartile for birth weight had a significantly higher risk of multiple wheeze reports than children in the highest quartile, despite the narrow range of birth weight that resulted from the selection of children who were not pre-

mature and who did not require placement in the neonatal intensive care unit. Children in the lowest quartile for head circumference had a greater risk of multiple wheeze than those in the highest quartile. Analyses regarding head circumference were somewhat limited because of missing data. The relationship between maternal age and multiple wheeze reports was not linear; children whose mothers were in the highest and lowest quartiles were more likely to have multiple wheeze reports than children of mothers in the midrange for age.

Children born in the winter had a lower rate of multiple wheeze reports than those born in the spring, summer, or fall. Children born in the fall were at greatest risk for wheeze.

Maternal smoking during pregnancy, which was reported at low rates, was a strong predictor of multiple wheeze reports. Inclusion of paternal smoking or other sources of passive smoke exposure in the household did not add to the predictive power of maternal smoking during pregnancy.

Children of mothers who breast-fed (Table 2) had a somewhat lower risk of multiple wheeze episodes, though this association did not remain significant in multivariate analyses. Various socioeconomic factors were associated with a higher risk of multiple wheeze reports including residence in an area of Boston in which 20% or more of households were below the poverty level and an income of less than \$30,000. Minority participants were overrepresented among socioeconomically disadvantaged study participants.

The strongest predictor of multiple wheeze episodes was lower respiratory illness (Table 2), with or without bronchiolitis. However 51% of children with both lower respiratory illness and repeated wheeze had wheeze in months before their

TABLE 2
UNIVARIATE PREDICTORS OF TWO OR MORE REPORTS OF WHEEZE IN THE FIRST YEAR OF LIFE: NUTRITIONAL, INFECTIOUS, AND SOCIOECONOMIC FACTORS

Factors	Subjects			
	n	Percent with 2 or More Reports of Wheeze	Relative Risk	95% CL
Breast-feeding*				
No = 0	163	23.9	1.00	—
Yes	336	17.0	0.71	0.49, 1.02
Lower respiratory illness (croup, bronchitis, bronchiolitis, or pneumonia†)				
No = 0	366	13.9	1.00	—
Yes	133	33.8	2.43	1.71, 3.44
Lower respiratory illness (croup, bronchitis, or pneumonia†)				
No = 0	417	16.8	1.00	—
Yes	82	31.7	1.89	1.29, 2.77
Race/Ethnicity				
White = 0	375	16.8	1.00	—
Black	59	32.2	1.92	1.24, 2.96
Hispanic	30	23.3	1.39	0.70, 2.76
Asian	28	14.3	0.85	0.33, 2.17
Other	7	42.9	2.55	1.05, 6.18
Family income				
> \$50,000 = 0	352	16.2	1.00	—
\$30,000 to < \$50,000	88	22.7	1.40	0.89, 2.21
< \$30,000	43	30.2	1.87	1.12, 3.12
Unknown	16	37.5	2.32	1.18, 4.55
Area of Boston by percent households below poverty level				
< 5% = 0	197	17.8	1.00	—
5% to < 10%	145	19.3	1.09	0.69–1.70
10% to < 20%	115	16.5	0.93	0.56–1.55
≥ 20%	42	33.3	1.88	1.11, 3.16

* Unless otherwise stated, variables are categorical, with category of comparison labeled as 0.

† Questionnaire report of doctor-diagnosed disease.

TABLE 3
UNIVARIATE PREDICTORS OF TWO OR MORE REPORTS OF WHEEZE IN
THE FIRST YEAR OF LIFE: CAT ALLERGEN (*Fel d 1*), DOG ALLERGEN
(*Can f 1*), AND REPORTS OF ANIMAL EXPOSURE

	Subjects		Relative Risk	95% CL
	n	Percent with 2 or More Reports of Wheeze		
<i>Fel d 1</i> * (Cat) (μg/g)				
Bedroom bed/floor				
< 1 = 0	224	19.2	1.00	—
1 to < 8	133	18.8	0.98	0.63, 1.53
≥ 8 = 0	98	18.4	0.96	0.58, 1.57
Family room				
< 1 = 0	182	23.1	1.00	—
1 to < 8	182	16.5	0.71	0.47, 1.09
≥ 8	113	15.9	0.69	0.42, 1.14
Home Max				
< 1 = 0	160	21.9	1.00	—
1 to < 8	206	18.0	0.82	0.54, 1.24
≥ 8	132	17.4	0.80	0.50, 1.28
Cat in home				
No = 0	394	19.3	1.00	—
Yes	105	19.1	0.99	0.63, 1.54
<i>Can f 1</i> (Dog) (μg/g)				
Family room				
< 20 = 0	344	18.3	1.00	—
≥ 20 to < 200	27	14.8	0.81	0.32, 2.05
≥ 200	45	26.7	1.46	0.85, 2.48
Dog in home				
No = 0	420	17.9	1.00	—
Yes	79	26.6	1.49	0.98, 2.27
Other furry/feathered animals				
No = 0	484	18.6	1.00	—
Yes	15	40.0	2.15	1.13, 4.11
Signs of rats or mice				
No = 0	394	18.0	1.00	—
Yes	105	23.8	1.32	0.88, 1.98

* Unless otherwise stated, variables are categorical, with category of comparison labeled as 0.

first report of lower respiratory illness (croup, bronchitis, bronchiolitis, or pneumonia).

***Can f 1*, *Fel d 1*, and Reports of Animals as Predictors of Wheeze**

The presence of *Can f 1* concentrations of > 200 μg/g of dust in the living room and the reported presence of a dog in the household were both associated with increased risk of multiple reports of wheeze, with estimates of similar magnitude (Table 3). The relatively small number of living room samples assayed for *Can f 1* likely reduced the precision of the estimate for the actual allergen concentrations as compared with the precision of the estimate for the association between the presence of a dog in the household and wheeze. Neither *Fel d 1* concentrations nor the reported presence of a cat in the household predicted multiple wheeze episodes. Mouse or rat allergen levels were not measured, but households with other furry/feathered pet animals or households in which wild mice or rats had been seen tended to have a higher univariate risk of multiple wheeze reports in the children. Of the 15 homes with other furry/feathered pet animals, six had dogs, resulting in collinearity between the two variables; multivariate analyses focused on associations between dog and wheeze, because of the specificity of the exposure, the larger numbers, and the corroborative allergen data.

Cockroach Allergen (*Bla g 1* or 2) and Dust Mite Allergen (*Der f 1* or *Der p 1*) as Predictors of Wheeze

In each tested site in the home (child's bedroom bed and floor, family room, and kitchen), the presence of cockroach allergen levels predicted two or more episodes of wheeze in the children (Table 4). The magnitude of the relationship was highest for cockroach allergen measured in the bed. Compared with homes with no detectable cockroach allergen, the univariate data suggested a possible dose response, with a relative risk (RR) of 3.68 (95% confidence interval [CI]: 1.50, 9.02) for an exposure level of ≥ 2 U/g and RR of 2.59 (95% CI: 1.21, 5.56) for exposure level between 0.05 and 2 U/g. The estimated risk of wheeze when *Bla g* concentrations were ≥ 2 U/g on the bedroom floor was slightly lower than for comparable levels in the bed, with a similar suggestion of dose response. Whereas many more homes had cockroach allergen levels of ≥ 2 U/g in the kitchen than had such concentrations in the bedroom (bed or floor), the magnitude and strength of the univariate association with wheeze were smaller. In univariate analyses, compared with *Bla g* concentrations of < 0.05 U/g, the RR of two or more episodes of wheeze was 1.79 (95% confidence limit [CL]: 1.06, 3.00) if the maximal concentration in the home was > 2 U/g (n = 62). The estimate for the risk of two or more episodes of wheeze with exposure to family room *Bla g* concentrations of > 0.05 U/g (combining the categories ≥ 2 and ≥ 0.05 to < 2) was found to be the most precise and representative es-

TABLE 4
COCKROACH (*Bla g* 1 OR 2) AND DUST MITE (*Der f* 1 OR *Der p* 1) ALLERGENS AS
PREDICTORS OF TWO OR MORE REPORTS OF WHEEZE IN THE FIRST YEAR OF LIFE

	Subjects		Relative Risk	95% CL
	n	Percent with 2 or More Reports of Wheeze		
Bla g 1 or 2 (U/g)*				
Bedroom bed				
< 0.05 = 0	147	13.6	1.00	—
≥ 0.05 to < 2	17	35.3	2.59	1.21, 5.56
≥ 2	6	50.0	3.68	1.50, 9.02
Bedroom floor				
< 0.05 = 0	147	13.6	1.00	—
≥ 0.05	23	39.1	2.88	1.50, 5.52
Family room				
< 0.05 = 0	321	18.1	1.00	—
≥ 0.05 to < 2	99	17.2	0.95	0.58, 1.55
≥ 2	18	38.9	2.15	1.15, 4.02
Family room				
< 0.05 = 0	359	15.6	1.00	—
≥ 0.05 to < 2	97	28.9	1.85	1.25, 2.75
≥ 2	14	28.6	1.83	0.77, 4.34
Bedroom floor				
< 0.05 = 0	359	15.6	1.00	—
≥ 0.05	111	28.8	1.85	1.27, 2.70
Kitchen				
< 0.05 = 0	247	17.0	1.00	—
≥ 0.05 to < 2	185	18.9	1.11	0.74, 1.67
≥ 2	52	28.9	1.70	1.02, 2.82
Der f 1 or Der p 1 (μg/g)†				
Bedroom bed				
< 0.05 = 0	224	21.4	1.00	—
≥ 0.05 to < 2	160	21.2	0.99	0.67, 1.46
2 to < 10	68	13.2	0.62	0.32, 1.19
≥ 10	46	10.9	0.51	0.21, 1.20
Bedroom floor				
< 0.05 = 0	55	20.0	1.00	—
≥ 0.05 to < 2	205	18.1	0.90	0.49, 1.65
2 to < 10	109	16.5	0.83	0.42, 1.62
≥ 10	129	23.3	1.16	0.63, 2.15
Family room				
< 0.05 = 0	35	34.3	1.00	—
≥ 0.05 to < 2	218	18.4	0.54	0.31, 0.92
2 to < 10	113	17.7	0.52	0.28, 0.95
≥ 10	130	17.7	0.52	0.29, 0.93

* For *Bla g*, analyses consider no dust as a separate category. Unless otherwise stated, variables are categorical, with category of comparison labeled as 0.

† For *Der f* or *Der p*, analyses include no dust in category < 0.05.

timate of cockroach effect in multivariate analyses (Table 5), because of the small numbers of missing ("no dust available") data, because of the large numbers exposed, and because of the lack of strong collinearity between socioeconomic factors and exposure. The maximal *Bla g* concentrations in the family room were more modest than those in the kitchen, but were still at levels generally associated with overt cockroach infestation. For the family room category *Bla g* 0.05 to < 2 U/g, the median value was 0.32 U/g with a range of 0.05 to 1.6 U/g. For the category *Bla g* ≥ 2 U/g, the median family room value was 7.8 U/g (range 2.0 to 29 U/g), compared with a median bed value of 3.0 U/g (range 2.0 to 31 U/g), a median bedroom floor value of 8.7 U/g (range 3.0 to 140 U/g) and a median kitchen value of 10.5 U/g (range 2.0 to 412 U/g).

Dust mite allergen concentrations (*Der f* 1 or *Der p* 1) were not associated with an increased risk of multiple wheeze reports in the first year of life. Results were inconsistent across rooms, with univariate family room data actually suggesting an inverse relationship whereas bedroom floor data suggested an elevated (but not significant) estimate of risk of wheeze with exposure.

Persistence of the Association of Multiple Wheeze Reports with Cockroach Allergen in Multivariable Analyses

Compared with no detectable cockroach allergen, concentrations of living room *Bla g* 1 or 2 of ≥ 0.05 U/g were associated with 1.76 (95% CL: 1.20, 2.57) times the risk of two or more wheeze episodes in a model (Table 5, Model 1) including smoking while pregnant, lower respiratory illness, low birth weight, maternal asthma, and dog exposure. The magnitude of the risk was not significantly reduced from the univariate estimate. This result suggested that the effect of cockroach exposure was independent of the effects of these other variables. Multivariate analyses including family room *Der f* or *Der p* in addition to the variables in Model 1 confirmed the absence of an inverse or positive association between dust mite exposure and wheeze ($p = 0.95$ for *Der f* 1 or *Der p* 1 concentrations of ≥ 10 μg/g). When the socioeconomic variables (race/ethnicity and income) were included, cockroach allergen in the family room remained a significant predictor of repeated wheeze, but the magnitude of the estimate of effect was somewhat reduced

(Table 5). Area of residence did not further reduce the estimate of the estimate of the effect of cockroach. Area was a weak ($p > 0.1$) predictor of repeated wheeze in multivariate analyses and had no association with wheeze in models including race and income. The estimated risk of wheeze with cockroach exposure was of similar magnitude to the estimated risk with maternal smoking.

Compared with no detectable cockroach allergen, the risk of two or more wheeze episodes were 1.47 (95% CL: 1.01, 2.14) for maximum *Bla g* in the home ≥ 0.05 U/g ($n = 297$), 1.45 (95% CL: 0.87, 2.41) for maximum *Bla g* in the home ≥ 2 U/g ($n = 62$) and 1.66 (95% CL: 0.85, 3.23) for maximum *Bla g* in the bedroom ≥ 2 U/g ($n = 20$), considered separately in models including smoking while pregnant, lower respiratory illness, low birth weight, maternal asthma, and dog exposure. After further adjustment for race/ethnicity, the risk of two or more wheeze episodes were 1.37 (95% CL: 0.93, 2.01) for maximum *Bla g* in the home ≥ 0.05 U/g, 1.18 (95% CL: 0.69, 2.02) for maximum *Bla g* in the home ≥ 2 U/g and 1.22 (95% CL: 0.53, 2.84) for maximum *Bla g* in the bedroom ≥ 2 U/g. Nonwhite race/ethnicity and *Bla g* ≥ 2 U/g were highly collinear. Of the 14 families with *Bla g* in the family room ≥ 2 U/g, 11 (79%) were either black or Hispanic versus 3 (21%) who were white. In contrast, of the 947 families with *Bla g* in the family room ≥ 0.05 but < 2 U/g, 38% were nonwhite and 62% were white. Of the 20 families with bedroom *Bla g* ≥ 2 U/g, 18 (90%) were nonwhite.

Substituting the individual LRI diagnoses for any LRI in Model 1, Table 5, significant predictors of repeated wheeze included pneumonia (RR: 3.04; 95% CL: 1.70, 5.43) and bronchitis (RR: 1.79; 95% CL: 1.09, 2.93), as well as bronchiolitis (RR: 3.10; 95% CL: 2.03, 4.70). Croup had a positive association with repeated wheeze that did not reach $p \leq 0.05$ (RR: 1.22, 95% CL: 0.73, 2.02).

DISCUSSION

Cockroach Allergen Level as a Predictor of Repeated Wheeze in the First Year of Life

Cockroach exposure may increase the risk of repeated wheeze in the first year of life of children of allergic or asthmatic parents even when cockroach infestation is not obvious and the measured concentration is relatively low. Although cockroaches are most abundant in kitchens, their presence in the bedroom and the family room/living room may be more important for the induction of repeated wheeze in infancy.

Not all wheeze in the first year of life represents allergic sensitization and not all children who wheeze in the first year of life continue to wheeze thereafter (16). We did not perform skin prick testing or radioallergosorbent testing (RAST) at the end of the first year of life of the children in our cohort to evaluate whether the association between *Bla g* and repeated wheeze represented an early expression of allergy. However, previous studies suggest that IgE antibody to inhalant allergens (specifically *Der p*) is rarely detected in the first year of life (17); skin testing responses to inhalant allergens in that period are often negative (18). The appropriate serologic or cellular tests of the sensitization process during that early period have not yet been fully elucidated.

Many children wheeze in the first year of life if they are born with small airways and/or encounter a noninfectious or infectious proinflammatory exposure (2). It is possible that in infancy exposure to insect and other animal feces may increase the risk of bronchial inflammation through nonallergic as well as allergenic mechanisms. Like all insects (and acarids such as mites), cockroaches contain proteolytic digestive enzymes (16, 19). As well as being allergens, proteolytic enzymes may have direct proinflammatory effects on the lung (20). Cockroaches, which drink from sinks, bathtubs, and other

TABLE 5
COCKROACH ALLERGEN (*Bla g* 1 OR 2) IN THE FAMILY ROOM AS A PREDICTOR OF TWO OR MORE REPORTS OF WHEEZE IN THE FIRST YEAR OF LIFE, MULTIVARIATE MODELS

Predictor Variable	Model 1 RR (95% CL)	Model 2 RR (95% CL)	Model 3 RR (95% CL)	Model 4 RR (95% CL)
<i>Bla g</i> 1 or 2, family room, U/g				
< 0.05	1.00	1.00	1.00	1.00
≥ 0.05	1.76 (1.20, 2.57)	1.73 (1.15, 2.61)	1.62 (1.07, 2.46)	1.63 (1.05, 2.55)
Lower respiratory illness (croup, bronchitis, bronchiolitis, pneumonia)				
Yes*	2.25 (1.58, 3.19)	2.25 (1.58, 3.19)	2.18 (1.54, 3.06)	2.21 (1.55, 3.15)
Smoking during pregnancy				
Yes*	1.83 (1.12, 3.00)	1.48 (0.84, 2.59)	1.75 (1.03, 2.95)	1.61 (0.89, 2.90)
Low birth weight†	1.28 (1.04, 1.58)	1.31 (1.05, 1.63)	1.31 (1.06, 1.62)	1.31 (1.05, 1.64)
Maternal asthma‡				
Active	1.35 (0.91, 2.00)	1.20 (0.80, 1.78)	1.40 (0.94, 2.07)	1.31 (0.86, 1.99)
Inactive	1.15 (0.62, 2.15)	1.02 (0.53, 1.96)	1.19 (0.63, 2.24)	1.10 (0.56, 2.15)
Dog in home				
Yes*	1.32 (0.87, 2.01)	1.47 (0.94, 2.30)	1.42 (0.94, 2.16)	1.51 (0.97, 2.37)
Race/Ethnicity				
White	—	1.00	—	1.00
Black	—	1.50 (0.92, 2.44)	—	1.47 (0.83, 2.60)
Hispanic	—	1.13 (0.56, 2.25)	—	1.04 (0.49, 2.21)
Asian	—	0.93 (0.36, 2.36)	—	0.96 (0.37, 2.50)
Other	—	2.49 (0.93, 6.68)	—	2.50 (0.94, 6.68)
Income				
$\geq \$50,000$	—	—	1.00	1.00
\$30,000–< \$50,000	—	—	1.35 (0.86, 2.10)	1.22 (0.75, 1.97)
< \$30,000	—	—	1.28 (0.72, 2.28)	1.03 (0.50, 2.10)

* "No" is reference category.

† Estimated for an interquartile (0.61 kg) difference in birth weight.

‡ Active asthma is defined as doctor-diagnosed asthma with wheeze.

residual sources of moisture, are also known to be potential carriers of virus and enteric bacteria, though they have never been strongly implicated epidemiologically as sources of infectious disease (21, 22). Moreover, cockroach allergen levels in our study had no association with LRI. Toxic products of bacteria (e.g., endotoxin) in cockroach or dog feces may also have direct proinflammatory effects. In Belgium, home endotoxin concentrations have been implicated in the worsening of asthma symptoms (23), but data are not yet available on endotoxin and the onset of wheeze.

Few prospective studies are available on allergen exposure in infancy as a predictor of the development of sensitization, wheeze, and asthma. None are available in relation to cockroach allergen exposure. All suggest a lag of years between exposure to inhalant allergen in infancy and the development of allergen-associated specific sensitization and expression of allergic asthma. In a prospective English study, Rowntree and colleagues found that levels of *Der p* 1 > 5 µg/g of dust in infancy predicted positive skin test results and elevated IgG to *Der p* by the fifth year of life (17). In a prospective cohort study of 67 British children with a family history of asthma or hay fever, Sporik and colleagues found that the age at first onset of wheeze was inversely proportional to the level of *Der p* exposure in the first year of life, but the association between *Der p* and asthma was not observed until age 11. The RR of asthma at age 11 was 4.8 for those children exposed at age 1 to > 10 µg/g dust of *Der p* 1/g of dust (24). A cross-sectional analysis in a Dutch study of 104 infants suggested that, among children of allergic/asthmatic parents, mattress *Der p* 1 concentrations of > 2 µg/g of dust might be associated with wheeze and frequent cough in the first year of life (25). It is not clear whether the dust mite-associated symptoms in infancy represented allergy. It may be that more follow-up time in our study is required to detect an association between dust mite allergen and repeated wheeze, particularly because bed dust mite levels were relatively low in this cohort, in which most infants slept on plastic encased mattresses. In England and the Netherlands, crib mattresses tended to be covered with cotton.

Our study found no association between cat allergen concentrations and risk of repeated wheeze, again perhaps because more follow-up time must elapse for expression of allergic symptoms. Cats were less frequently kept in households where at least one of the parents was asthmatic, and this factor may have decreased the risk of sensitization in the children at highest risk because of family history. The concentration of cat allergen in individual houses may not define the risk of sensitization, because cat allergen exposure is widespread in the community. As suggested in the Report of the Third International Workshop on Indoor Allergens and Asthma, "the question is whether sensitization of children in a community relates to exposure in individual houses or to total exposure" (16).

How confident are we that cockroach exposure, and not the other exposures of poverty associated with the presence of cockroaches, is responsible for the increase risk of repeated wheeze? Detectable low levels of cockroach allergen were found throughout the Boston community, not just in the homes of socioeconomically disadvantaged families in our cohort. Family room *Bla g* 1 or 2 concentrations of > 0.05 U/g still predicted a higher risk of repeated wheeze after adjustment for various socioeconomic factors; these results suggested that cockroach allergen was not just a proxy for other exposures of poverty. It was more difficult to separate socioeconomic status from *Bla g* 1 or 2 concentrations of ≥ 2 U/g, where most exposure occurred in disadvantaged households and where the number of observations of *Bla g* was sparse.

While we have most confidence in the independent associa-

tion between detectable cockroach allergen in the living room and wheeze, we need to address issues regarding potential misclassification of exposure to low levels of cockroach allergen. Misclassification can occur either because of variability in sampling or because of assay interference owing to the presence of other substances in the dust. Chew has demonstrated that the presence of boric acid (used to kill cockroaches) can lead to an overestimation of *Bla g* levels and the presence of salt to an underestimation (26). However, cockroaches are usually present at some level where boric acid has recently been applied. Although misclassification of exposure is certainly possible, it is unlikely to be responsible for the association between detectable cockroach allergen and repeated wheeze.

When cockroach was detectable in the family room, it was also usually detectable elsewhere in the home, adding confidence that detectable cockroach in the family room represented the presence of cockroach in the home. Of the 111 homes with cockroach levels of > 0.05 in the family room, 30% had cockroach levels of 2 or more U/g in at least one other room and 86% had detectable levels of cockroach allergen in at least one other room.

The decision to examine cockroach allergen levels as a categorical rather than continuous variable was dictated by the skewness of the data and by the fact that a large proportion of the data was censored, with values "below detectable limits." Both the suggestion in the literature of concentrations above which sensitization to cockroach allergen might occur (15) and a sparsity of data dictated the categories for *Bla g* levels. Categorization did not allow a detailed evaluation of the dose-response relationship between allergen concentration and risk. The bedroom data on *Bla g* 1 concentrations did, however, suggest a dose response; the family room data suggested the possibility of risk for early-life repeated wheeze at levels of exposure below those demonstrated to increase risk for asthma morbidity in cockroach-sensitized children (27).

At family room cockroach allergen levels between 0.05 and 2 U/g, 79/97 (81%) of families reported no sign of cockroaches in the home, making reporting bias less of a potential issue than in the homes with ≥ 2 U/g *Bla g*, where 10/14 (71%) families had seen cockroaches. However, fewer people related cockroach levels to wheezing when this study began, prior to the Inner City Asthma Study article about asthma morbidity and cockroach allergen in cockroach sensitized asthmatic children (27).

Allergen concentration was measured at 2 to 3 mo of life; in all but one child, the second episode of wheeze occurred after that period, though the first episode may have occurred in the same period as measurement of the exposure. It is not known whether exposure measured at 2 to 3 mo of life also represented exposure during pregnancy, when T-cell function which can reflect the tendency to allergy begins to develop (28). The relative contributions of prenatal and early infancy allergen exposures to allergy/wheeze risk is an area of active investigation.

Other Predictors of Wheeze in the First Year of Life

As we anticipated, exposures known to be associated with infectious and noninfectious nonallergic bronchial inflammation were the strongest predictors of repeated wheeze in the first year of life. The most prevalent of these exposures was lower respiratory illness (LRI) as defined by a report of doctor-diagnosed croup, bronchiolitis, bronchitis, or pneumonia (7). Most of these illnesses were presumably viral in etiology, though misclassification is possible. The fact that specimens for viral analysis were not taken from these children limits our knowledge about whether illnesses diagnosed as bronchiolitis were caused by infections with respiratory syncytial virus or were

wheeze episodes without an associated viral infection. Because wheeze symptoms preceded LRI in 51% of cases (repeated wheeze preceded LRI in 18% of cases), it is possible that pathophysiologic factors predisposing children to wheeze also increased the risk that viral infections became lower respiratory rather than upper respiratory or asymptomatic illnesses. Viral infections may increase the risk of the persistence of wheeze or asthma in some infants, yet may protect against persistent wheeze, atopy, or asthma in others (29–33). Further follow-up is needed to evaluate in this cohort whether the various kinds of lower respiratory illness in the first year of life are protective or predictive of allergic asthma.

Despite the exclusion of premature children from the cohort, low birth weight and small head circumference predicted repeated wheeze. Prematurity, low birth weight, and respiratory distress syndrome are well-documented predictors of persistent wheeze and/or asthma (34). Further research is needed to investigate whether this association is due solely to abnormalities in airway size and architecture or whether prematurity is associated with T-cell immaturity at birth, which might lead to increased risk of atopy and asthma.

The association between maternal smoking in pregnancy and early wheeze has been well documented in other studies (4, 5) and was again seen in this study, despite the low number of smokers. Smoking increases the risk of developing small airways (35) and wheezing; whether or not it increases the risk of sensitization and allergic asthma is more controversial. Although the effect of maternal smoking during pregnancy ($n = 32$) was greater than the effect of maternal smoking either during pregnancy or during the first year of the child's life ($n = 41$), small numbers and study design limited further investigation into interactions with smoking or the relative effect of smoking before versus smoking after the birth of the child.

Season of birth has been a predictor of asthma in other studies (36, 37). A prospective birth cohort study of Swedish children found that asthma developed more often in children born in August through October (38). In our univariate analyses, a winter birth was associated with the lowest risk of wheeze and a fall birth was associated with the highest. The low risk in winter-born infants may relate to the fact that in Boston children born in the winter have their nadir in immune protection against viral illnesses in the spring, when fewer viral illnesses are circulating. They also tend to enter daycare in the spring rather than the winter, when there are fewer outbreaks of viral illnesses in the classrooms. Spring and summer are the seasons of highest-level exposure to pollen allergens, whereas outdoor fungal allergen exposure is generally greatest in the fall. Influences of these exposures on repeated wheeze in this cohort are unknown.

Even in multivariate analyses, maternal history (not paternal history) of asthma was marginally associated with repeated wheeze, suggesting either reporting bias or early manifestations of the influence of inherited traits on the risk of early expression of allergic asthma. In siblings of this cohort < 5 yr we found that maternal history of asthma predicted asthma (39). If allergen level in infancy ultimately predicts not only repeated wheeze but also asthma in our cohort, we hypothesize that a parental (particularly maternal) history of asthma will be found to influence the timing and strength of the associations between allergen exposure and allergy-related wheeze.

Areas for Future Investigation

Additional follow-up of this cohort will reveal whether early-life exposure to cockroach or other allergens in the home predicts sensitization and the development of childhood asthma. Further investigation is necessary to understand why low-level

exposure to cockroach allergen, which occurs in many households under diverse socioeconomic circumstances, is a risk factor for wheeze in infants. Research is needed to assess whether cockroach allergen is more potent than other allergens, whether it influences early wheeze through additional proinflammatory nonallergenic mechanisms, and whether there is an interaction between the other exposures of poverty and cockroach exposure on the risk of wheeze in children.

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