

A longitudinal analysis of wheezing in young children: The independent effects of early life exposure to house dust endotoxin, allergens, and pets

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Background: It has been postulated that exposure to bacterial endotoxins and animals early in life might confer protection against the development of asthma and allergies.

Objective: We investigated the longitudinal effects of exposure to house dust endotoxin (HDE), allergen levels, and the presence of a dog in the home on wheezing in young children over a 4-year period.

Methods: Two hundred twenty-six children younger than 5 years were followed for 4 years. Endotoxin and allergen levels were measured from house dust collected at baseline. Longitudinal associations were investigated by using a proportional hazards technique that allowed for multiple outcomes per subject.

Results: Exposure to high concentrations of HDE of greater than the median level was associated with an increased risk for wheezing over the period of observation (multivariate relative risk, 1.52; 95% CI, 1.07-2.14), but this risk rapidly decreased over time (*P* for trend = .005). Exposure to cockroach allergen was associated with increased risk for wheezing, whereas exposure to cat allergen and the presence of a dog in the home were both associated with decreased risk for wheezing. The risks associated with cockroach allergen, cat allergen, and dog did not change over the period of observation.

Conclusion: The negative associations between exposures to dogs and cat allergen and wheeze appear to be independent of the effects of endotoxin and suggest that separate mechanisms might mediate the effects of HDE exposure and pet exposure on the developing immune system. (*J Allergy Clin Immunol* 2002;110:736-42.)

Key words: Endotoxin, allergens, domestic animals, wheeze, asthma

Abbreviations used

HDE: House dust endotoxin

LRI: Lower respiratory tract illness

Endotoxin, a component of the cell wall of gram-negative bacteria, is a potent proinflammatory agent^{1,2} and causes reversible airway obstruction in subjects with established asthma.³ Endotoxin is present in house dust^{4,5} in varying concentrations, and levels have been shown to be associated with indices of severity in subjects with established asthma.⁵ The effects of endotoxin on reversible airway obstruction and airway inflammation can be seen in healthy nonasthmatic subjects, although higher doses are required.^{3,6}

In studies on human peripheral blood cells, endotoxin is a potent inducer of the T_H1 cytokines IFN- γ and IL-12.⁷⁻⁹ Because IFN- γ amplifies T_H1 development and inhibits proliferation of T_H2 cells,^{10,11} it has been postulated that exposure to endotoxin at a critical time might shift the developing immune system to a predominantly T_H1-type responsiveness, thus protecting against asthma and allergies.^{9,12} In fact, exposure to bacterial endotoxin is thought to mediate the effects of recent observations that the prevalence of asthma and allergies is decreased among those exposed to farm environments¹³⁻¹⁵ and household animals^{16,17} early in life.¹²

We have recently shown that exposure to house dust endotoxin (HDE) is associated with wheezing in the first year of life among infants with a familial predisposition to asthma and allergies.¹⁸ However, it remains to be seen whether those infants who wheeze in association with early life endotoxin exposure will be at greater or lesser risk of continued wheezing symptoms and development of asthma later in life. We performed an analysis on the older siblings of these infants to examine the longitudinal association of exposure to HDE, allergen levels, and the presence of a dog in the home and wheezing over a 4-year period.

METHODS

Population and study sample

The subjects for this analysis were the siblings of the index children participating in the Epidemiology of Home Allergens and Asthma study, an ongoing longitudinal family and birth cohort study with

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the primary aim of examining the role of indoor home allergen exposure in the development of asthma, wheezing, and allergic sensitization during early childhood in children whose parents have asthma or allergy. Recruitment and exclusion criteria have been published.¹⁹ In brief, 499 families were recruited between 1994 and 1996 within 48 hours of the birth of the index child at a tertiary hospital in Boston. If either parent had a history of doctor-diagnosed asthma, hay fever, or allergies, a screening questionnaire was administered, and if either parent was allergic to house dust or house dust mites, cockroaches, pollens, animals, or mold, then they were eligible for inclusion in the cohort. The study was approved by the Institutional Review Board of the Brigham and Women's Hospital.

At the home visit, questionnaires regarding home characteristics, home environmental exposures, demographic and socioeconomic characteristics of the family, and detailed respiratory symptoms of the siblings who were 5 years of age or younger were administered by trained research assistants. The sibling respiratory questionnaire was administered again by means of telephone 14 months after the first questionnaire. A revised sibling respiratory questionnaire was then administered on a yearly basis at 22, 34, and 46 months after the first questionnaire.

At the time of the first home visit, 246 siblings younger than 5 years were identified. Two hundred twenty-six children had information for 3 of the 5 questionnaires. Of these 226 children, 173 had information on HDE levels in the home.

Respondents to the sibling respiratory questionnaire administered at the home visit were asked about the child's wheezing; the child was labeled as having wheeze if this occurred within the last 12 months. *Repeated wheezing* was defined as wheezing in 2 of the 4 years of follow-up.

Predictor variables that were examined included maternal and paternal asthma, the child's race-ethnicity, maternal smoking during the perinatal period, current smoking in the home by any adult, and socioeconomic factors. Details of the ascertainment of these predictor variables have been reported previously.²⁰ *Lower respiratory tract illness* (LRI) was defined as doctor-diagnosed croup, bronchitis, bronchiolitis, or pneumonia in the past year and did not include asthma. *Ever LRI* was defined as an LRI in any of the years of follow-up.

Home visit, dust collection, endotoxin, and allergen analysis

Methods for the collection of dust samples and the processing and assay of allergens have been detailed previously.^{19,21} Briefly, 5 separate dust samples were collected in a standardized fashion by vacuuming the following areas: (1) the baby's bedroom floor, (2) the index baby's bed, (3) the parent's bed, (4) the family-living room, and (5) the kitchen floor. For this analysis, only allergens assayed from the family-living room and the kitchen floor dust samples were used because these were considered common locations in the home where siblings of the index children, who are the focus of this report, would likely be exposed. The higher measurement from either room was used for categorizing exposure. Allergen concentrations were grouped in categories with potential relevance to sensitization and development of allergy-related wheezing²²⁻²⁴ and consistent with previous reports on this cohort.^{19,21,25} Cockroach exposure was categorized as Bla g 1 or Bla g 2 at the following levels: (1) 2 U/g or greater (including concentrations exceeding detectable limits); (2) 0.05 to less than 2 U/g; and (3) less than 0.05 U/g (including concentrations below the limits of detection).^{22,23} Dust mite exposure was categorized as Der f 1 or Der p 1 at the following levels: (1) 10 µg/g or greater (including concentrations exceeding detectable limits); (2) 2 to less than 10 µg/g; and (3) less than 2 µg/g (including samples below the limits of detection).^{22,24} Cat exposure was categorized as Fel d 1 at the following levels: (1)

8 µg/g or greater (including concentrations exceeding detectable limits); (2) 1 µg/g or greater to less than 8 µg/g; and (3) less than 1 µg/g (including concentrations below the limits of detection).^{22,23} Among the 41 homes that reported a cat in the home, 38 (92.7%) had Fel d 1 measured in the highest category (≥ 8 µg/g), 2 had Fel d 1 in the middle category, and 1 had Fel d 1 in the lowest category (<1 µg/g). Can f 1 was not measured in all the homes, and thus we used the questionnaire response to the presence of a dog in the home as a measure of dog exposure. For all the allergens, if no dust was available or if the amount was too small to be assayed for a particular allergen, values were considered to be missing. Allergens were analyzed as 3-level categorical variables, as described above for the univariate models. The 3-level allergen variables were collapsed into 2-level categories for the time-interaction and multivariable models if effects of adjacent categories were not significantly different from each other.

Endotoxin was assayed from house dust samples only if there were sufficient dust after all other assays had been performed. We used data from the living room only because this was the one with the most complete data. Details of the methods have been published previously.¹⁸ Endotoxin exposure was defined in terms of the median endotoxin concentration (median, 81.3 EU/mg), in which high exposure meant a level equal to or above the median value and low exposure meant a level below the median value. An indicator variable for missing endotoxin values was included in multivariate analyses. We also examined the overall endotoxin amount in dust and endotoxin concentrations, controlling for total amount of dust, and both resulted in similar effects on wheezing as endotoxin concentration. Thus we report only results with endotoxin concentration as a predictor of wheezing.

Statistical analysis

The longitudinal relationships between the various predictors and the outcome (wheezing in the past year) were explored by using a proportional hazards model (Andersen-Gill multiplicative hazards model), allowing for repeated outcomes of the same kind.²⁶ Follow-up time in months was used for the time variable. The univariate and multivariate models were performed in the PHREG procedure in the SAS software package (SAS Institute Inc, Cary, NC). The multivariate model was selected by using the stepwise selection procedure in SAS. Because the Andersen-Gill model assumes mutual independence of observations within a subject,²⁶ the final multivariate models were run in S-Plus, accounting for correlations of repeated outcomes in the same subject, to obtain robust standard error estimates.

For the repeated wheezing outcome, univariate and multivariable relationships were investigated with logistic regression models by using the LOGISTIC procedure in SAS. The variables that were included in the multiple logistic regression models were the same as those in the Andersen-Gill models.

RESULTS

Baseline characteristics

Two hundred twenty-six children from 199 families were included in this analysis, and their characteristics on entry into the cohort are shown in Table I. Over the 46 months of follow-up, information was available from a cumulative frequency of 1089 children: 226 at baseline, 221 at 14 months, 215 at 22 months, 213 at 34 months, and 214 at 46 months. Of the 226 children, 190 (84.1%) had information at all 5 time points, 31 (13.7%) had information at 4 time points, and 5 (2.2%) had information at 3 time points. HDE concentrations ranged from

TABLE I. Baseline characteristics of the 226 children

Age, y (median [range])	2.87 (1.10-4.99)
Sex, n (%)	
Female	117 (51.8)
Male	109 (48.2)
Race, n (%)	
White	186 (82.3)
Black	18 (8.0)
Hispanic	13 (5.8)
Asian	9 (4.0)
Total family income, n (%)	
≥\$30,000	204 (93.2)
<\$30,000	15 (6.8)
Area of residence by percentage of households below poverty, n (%)	
<10%	167 (73.9)
10%-<20%	46 (20.4)
≥20%	13 (5.8)
Paternal asthma, n (%)	
No	170 (75.9)
Yes	54 (24.1)
Maternal asthma, n (%)	
No	160 (70.8)
Yes	66 (29.2)
Maternal age, n (%)	
>25 y	207 (91.6)
≤25 y	19 (8.4)
Birth weight, n (%)	
>6.8 lbs	168 (75.7)
<6.8 lbs	54 (24.3)
Prematurity, n (%)	
No	194 (85.8)
Yes	32 (14.2)
Maternal cigarette smoking during perinatal period, n (%)	
No	212 (93.8)
Yes	14 (6.2)
Current* cigarette smoking in the home by any adult, n (%)	
No	201 (88.9)
Yes	25 (11.1)
Endotoxin, n (%)	
<81.3 EU/mg	90 (39.8)
≥81.3 EU/mg	83 (36.7)
Missing	53 (23.5)
Fel d 1, n (%)	
<1 µg/g	108 (48.2)
1-8 µg/g	73 (32.6)
≥8 µg/g	43 (19.2)
Der p 1/Der f 1, n (%)	
<2 µg/g	103 (45.8)
2-10 µg/g	51 (22.7)
≥10 µg/g	71 (31.6)
Bla g 1 or 2, n (%)	
<0.05 U/g	118 (52.2)
0.05-2 U/g	94 (41.6)
≥2 U/g	14 (6.2)
Presence of dog in the home, n (%)	
No	204 (90.3)
Yes	22 (9.7)
LRI in the past year, n (%)	
No	192 (85.0)
Yes	34 (15.0)

*At the time of the first home visit.

9.4 to 486.0 EU/mg, and the median was 81.3 EU/mg. In a subset of 53 homes with 2 HDE measurements performed 8 months apart, HDE levels were found to be significantly correlated (Pearson correlation coefficient = 0.55, $P = .0001$, intraclass correlation coefficient = 0.45).

Homes with a dog had a higher geometric mean endotoxin levels than homes without a dog (95.80 vs 77.80 EU/mg, respectively), but this difference did not reach statistical significance ($P = .2$). There was no difference in endotoxin levels between homes with and without a cat (81.28 vs 79.00 EU/mg, respectively; $P = .8$).

Longitudinal univariate relationships

Longitudinal univariate relationships between independent variables with wheezing are shown in Table II (univariate models). Exposure to HDE above the median value was associated with increased risk for wheezing compared with exposure to levels of less than the median value over the 4-year period of follow-up. This effect remained whether the total HDE amount was used or control for the amount of total dust was performed. Among the allergens, exposure to higher levels of cockroach allergen was associated with greater relative risk for wheezing: 1.58 (95% CI, 1.12-2.22) for Bla g levels of 0.05 to less than 2 U/g and 2.37 (95% CI, 1.34-4.17) for Bla g 1 or 2 levels of 2 U/g or greater. Exposure to the middle and highest categories of dust mite and cat allergens were associated with less risk for wheezing compared with the lowest categories of the respective allergens. For Der p 1 or Der f 1, the relative risks for wheezing were 0.58 (95% CI, 0.37-0.92) and 0.80 (95% CI, 0.56-1.16) for exposure to 2 to less than 10 µg/g and 10 µg/g or greater, respectively. For Fel d 1, the relative risks for wheezing were 0.47 (95% CI, 0.31-0.71) and 0.76 (95% CI, 0.50-1.16) for exposure to 1 to less than 8 µg/g and 8 µg/g or greater, respectively. Because the effect estimates for the middle and highest categories of allergen exposures were in the same direction for all allergens (ie, increased risk for cockroach and decreased risks for both dust mite and cat), and these estimates were not significantly different from each other ($P > .08$ for all comparisons), the middle and highest categories were combined in subsequent analyses.

Having a dog in the household was associated with a decreased risk for wheezing over the period of observation compared with not having a dog in the household. LRI in the past year was very strongly associated with wheezing.

Time trends and interaction analyses

The proportions of children with wheezing episodes decreased over the 4 years of follow-up: 25.2% at baseline, 20.2% at 14 months, 19.3% at 22 months, 16.0% at 34 months, and 12.7% at 46 months. The proportions of children who reported wheezing in relation to the median level of HDE exposure at each time point of follow-up are shown in Fig 1. Over the period of follow-up, the proportion of children who had wheezing episodes remained relatively stable among those exposed to low levels of HDE. Among the children who were exposed to high lev-

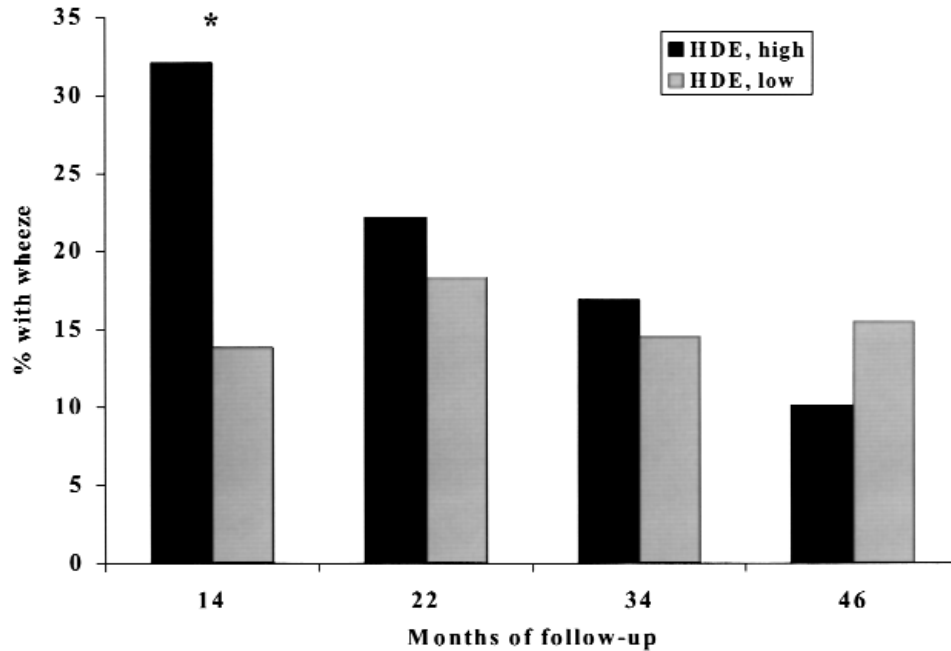


FIG 1. Proportions of children with wheezing at each of the follow-up time points with respect to HDE exposure. * $P = .006$ for the difference between 2 groups at 14 months of follow-up.

TABLE II. Risk ratios for wheezing from longitudinal models

Predictors (reference group)	Univariate models, RR (95% CI)*	Multivariate model 1, RR (95% CI)*	Multivariate model 2, RR (95% CI)†	Multivariate model 3, RR (95% CI)†
Endotoxin (<81.3 EU/mg), ≥81.3 EU/mg	1.37 (0.95-1.97)	1.45 (0.83-2.53)	1.52 (1.07-2.14)	—
Endotoxin (<81.3 EU/mg), ≥81.3 EU/mg				
14 mo	2.70 (1.36-5.36)	—	—	3.40 (1.70-6.80)
22 mo	1.30 (0.70-2.50)	—	—	1.90 (0.92-3.93)
34 mo	1.20 (0.60-2.60)	—	—	1.22 (0.55-2.70)
46 mo	0.58 (0.25-1.37)‡	—	—	0.91 (0.37-2.26)
Dog in the home (no), yes	0.43 (0.20-0.93)	0.40 (0.12-1.33)	0.38 (0.17-0.82)	0.34 (0.12-0.98)
Der p 1 or Der f 1 (<2 µg/g), ≥2 µg/g	0.71 (0.52-0.98)	—	—	—
Fel d 1 (<1 µg/g), ≥1 µg/g	0.57 (0.41-0.80)	—	0.62 (0.44-0.88)	0.61 (0.37-1.01)
Bl a g 1 or 2 (<0.05 U/g), ≥0.05 U/g	1.67 (1.20-2.32)	—	1.74 (1.22-2.49)	1.76 (1.02-3.04)
LRI in the past year (no), yes	4.70 (3.30-6.69)	—	3.62 (2.48-5.28)	3.65 (2.31-5.76)

RR, Relative risk.

*Models are adjusted for clustering of outcomes in the same child.

†Models are adjusted for maternal asthma, maternal age, sex, prematurity, area of residence, and clustering of outcomes.

‡ P for trend = .005; this model with time interaction also provided a better fit to the data compared with the model without time interaction ($P = .04$, see text).

els of HDE, the proportion of children who had wheezing episodes was significantly higher at 14 months but rapidly decreased over the period of follow-up. By 46 months, the proportion of children with wheezing episodes was lower among those exposed to high concentrations of HDE compared with the proportion among those exposed to low concentrations.

A model incorporating interactions between endotoxin level and the 4 follow-up time points provided a significantly better fit to the data than the model without the time interactions (likelihood ratio test: χ^2 , 3 $df = 8.27$, $P = .04$). Time interactions were explored for the allergen data and the presence of a dog in the home in the same manner as that for HDE. No significant time interactions

were found for the 3 allergens and dog in the home, meaning that the risk for wheezing associated with allergen and dog exposure did not vary over the follow-up period. Interactions between HDE and the individual allergens were also explored for their joint association with wheezing, but none of these interactions were statistically significant.

Multivariate model

The multivariate models are shown in Table II. Dust mite allergen (Der p 1/Der f 1) did not enter the model during the preliminary stepwise procedure. When both HDE and presence of a dog in the home were placed in a model (multivariate model 1), there was no significant

Asthma, rhinitis,
other respiratory
diseases

TABLE III. Logistic regression models for repeated wheezing

Predictors (reference group)	Univariate models, OR (95% CI)	Multivariable model, OR (95% CI)*
Endotoxin (<81.3 EU/mg), ≥81.3 EU/mg	1.81 (0.88-3.72)	2.57 (1.00-6.62)
Dog in the home (no), yes	0.34 (0.08-1.52)	0.12 (0.01-0.97)
Der p 1/Der f 1 (<2 µg/g), ≥2 µg/g	0.84 (0.44-1.60)	—
Fel d 1 (<1 µg/g), ≥1 µg/g	0.62 (0.32-1.18)	0.61 (0.27-1.35)
Bla g 1 or 2 (<0.05 U/g), ≥0.05 U/g	2.08 (1.07-4.02)	2.18 (0.94-5.08)
Ever LRI (no), yes	8.10 (3.88-16.96)	9.18 (3.89-21.67)

OR, Odds ratio.

*Models are adjusted for maternal asthma, maternal age, sex, prematurity, and area of residence.

change from the univariate case in either of the 2 risk ratios associated with these variables. Over the 46 months of observation, the overall risk for wheezing associated with exposure to high levels of HDE, controlling for other variables in the model, was found to be increased (multivariate model 2). Incorporation of the HDE-time interaction terms in the multivariate model confirmed that the risk for wheezing associated with HDE exposure was increased initially but rapidly decreased (multivariate model 3). Exposure to high levels of cockroach allergen was associated with a significantly increased risk for wheezing over the period of observation, during which exposure to high levels of cat allergen and having a dog in the home were associated with decreased risks for wheezing (multivariate models 2 and 3).

We considered whether these results, particularly our findings on cat allergen and the presence of a dog in the home, could be confounded by households that got rid of their pets during the period of follow-up. At the start of follow-up, 39 children lived in homes with cats, and 8 of those children were living in homes without a cat at 4 years. With regard to dog ownership, 22 children were living in homes with a dog at the start of follow-up, and 7 of those children were living in homes without a dog at 4 years. When the children living in homes that got rid of their pets were removed from the analysis, the associations between cat allergen and dog with wheezing were similar to those in the overall analysis.

Repeated wheezing: Logistic regression analyses

There were 47 (20.8%) children who had 2 or more reports of wheezing in the past year during the 4-year period of follow-up. Table III shows the results of analyses with repeated wheezing as the outcome. In general, the direction of the associations found with repeated wheezing were similar to those found in the longitudinal models for wheezing. Exposure to high HDE was associated with a greater number of repeated wheezing episodes. Exposure to a dog in the home was significant-

ly associated with a decreased risk for repeated wheezing episodes in both the univariate and multivariable models. Exposure to cockroach allergen was associated with increased risk for repeated wheezing, whereas exposure to dust mite and cat allergens were generally associated with decreased risk for repeated wheezing.

DISCUSSION

Endotoxin, a component of the outer membrane of gram-negative bacteria, is found in high concentrations in farm environments.²⁷ By virtue of its effects in enhancing T_H1-like immune responses,⁷⁻⁹ it is thought that endotoxin mediates the effects of animal exposure in protecting against allergic disease.¹² However, endotoxin is a known proinflammatory agent, especially in occupational settings.^{1,2} Our group had recently shown that exposure to high levels of HDE was associated with wheezing in the first year of life among infants of allergic or asthmatic parents.¹⁸ Similarly, a general birth cohort also showed that the risk for wheezing was increased in the first year of life in infants exposed to higher levels of HDE, despite a lower risk for atopic eczema.²⁸ Although we did not measure HDE levels in the children's first year of life, the current analysis extends the previous findings to older children. In these older children the risk associated with exposure to higher levels of HDE appears to decrease rapidly, such that after 4 years of follow-up, we found no significant difference in wheezing rates among children exposed to high compared with low levels of HDE. In fact, the analysis of time trends suggests decreasing rates of wheezing among those children exposed to higher levels of HDE compared with those exposed to lower levels of HDE by the end of the follow-up period (when the ages of the children ranged from 5 to 9 years).

Because we had no markers of atopy, we are unable to comment on the effects of HDE exposure on the developing immune system of these children. However, a recent report showed that homes of allergen-sensitized infants had significantly lower levels of HDE compared with homes of nonsensitized infants.²⁹ Additionally, HDE concentrations correlated with increased proportions of IFN- γ -producing CD4 T cells. Thus these effects of HDE exposure on allergen sensitization and on IFN- γ -producing T cells might partly explain our finding of a rapid decrease in risk for wheezing among children exposed to high HDE levels by causing a switch to T_H1-like responses. Although our analysis is limited by the fact that we only had one measurement of HDE for most of the homes, an analysis on a subset of homes with 2 measurements made 8 months apart shows that these levels are fairly³⁰ correlated within each home.

Our results also show that exposure to a dog in the home and to cat allergen in early life are negatively associated with wheezing episodes. This is consistent with previous findings that having a cat or a dog^{16,17} as a child is protective against asthma and allergies in adulthood. More recently, a prospective analysis in a general birth

cohort found that exposure to dogs in early life protected against the subsequent development of frequent wheezing in children without a parental history of asthma.³¹ Our results also suggest that the effects of exposure to a dog is independent of HDE exposure because when both are in the model together, the associated risk ratios do not change significantly from the univariate models (Table II). Furthermore, the patterns of risk associated with these variables differ over time. Thus our results do not support the hypothesis that bacterial endotoxin in animal products mediates the protective effect of exposure to pet dogs early in life¹² in this nonfarming situation. With regard to cat allergen, it was recently shown that exposure to high levels of cat allergen induced a modified T_H2 response in some children, which is indicative of immune tolerance,³² and suggests that the protective effect of exposure to animals early in life might not be explained simply by a shift in the balance of T_H1 and T_H2 immune responses, such as that proposed for exposure to endotoxin and infections.^{9,12} Our finding of independent effects of HDE and exposure to pets in relation to wheezing support the notion that these exposures might be working through different mechanisms.

We considered whether a bias could explain our results, particularly with respect to cat allergen exposure and the presence of a dog in the home. It is possible that families got rid of their pets during the course of the follow-up period to explain the inverse association with wheezing. However, repeating the analysis on the subset of children whose families did not get rid of pets showed similar results as the analysis on the whole cohort. The observation that the majority of the pet owners in our cohort continued to have pets throughout the period of follow-up also suggests that this type of bias is not the main explanation for our findings.

We recognize other limitations in our analysis. First, the outcome of interest in this analysis is wheezing, and it is known that wheezing early in life will not necessarily translate to asthma in later life.³³ However, our cohort is not a general population sample because the children have a familial predisposition to asthma, allergies, or both. Thus these wheezing children are at greater risk for asthmatic or allergic wheezing when compared with children without a familial predisposition. Second, we did not have more personal endotoxin and allergen measurements for the children, such as in dust obtained from mattresses. Exposure to endotoxin and allergens was defined in terms of concentrations in living room or kitchen dust. Despite this, we were able to find significant effects of exposure on wheezing in the children. We intend to confirm these findings in the index children, for whom more personal measurements of exposures are available.

In summary, we present a longitudinal analysis of childhood wheezing that has shown that in this cohort of children of allergic or asthmatic parents, exposure to high levels of HDE is associated with increased risk for wheezing early in life. This risk rapidly diminishes, and our analysis suggests that this exposure might protect against further episodes of wheezing as the children get

older. We have also shown that exposure to high levels of cat allergen and having a dog in the home are inversely associated with wheezing, independent of the effects of HDE exposure. These independent effects suggest that separate mechanisms might mediate the effects of HDE exposure and pet exposure on the developing immune system. Further follow-up of this cohort should clarify the effects of these exposures on the risk of asthma and allergic disorders.

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