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Influence of dog ownership and high endotoxin on wheezing and atopy during infancy

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Abstract

Background—Increased exposure to microbial products early in life may protect from development of atopic disorders in childhood. Few studies have examined the relationship of endotoxin exposure and pet ownership on atopy and wheezing during infancy.

Objective—Evaluate relationships among high endotoxin exposure, pet ownership, atopy, and wheezing in high-risk infants.

Methods—Infants (n = 532; mean age, 12.5 ± 0.8 months) with at least 1 parent with confirmed atopy were recruited. A complete medical history and skin prick testing to foods and aeroallergens were performed at age 1 year. House dust samples were analyzed for endotoxin.

Results—Prevalences of wheezing were not independently associated with dog or cat ownership or endotoxin levels. Percutaneous reactivity to at least 1 allergen was observed in 28.6% of infants. Univariate analyses showed significant associations of any wheezing, recurrent wheezing, and recurrent wheezing with an event with daycare attendance, number of siblings, respiratory infections, maternal smoking, and history of parental asthma. Logistic regression adjusting for the latter variables showed that recurrent wheezing (odds ratio, 0.4; 95% CI, 0.1–0.9) as well as 2 other wheeze outcomes were significantly reduced in homes with high endotoxin exposure in the presence of 2 or more dogs.

Conclusion—Pet ownership or endotoxin did not independently modify aeroallergen sensitization or wheezing during infancy. However, high endotoxin exposure in the presence of multiple dogs was associated with reduced wheezing in infants. Clinical implications: A home environment with many dogs and high levels of endotoxin may be conducive to reduced wheezing in infancy.

Keywords

Endotoxin; birth cohort; wheeze; house dust; pet ownership

The incidence of atopy and allergic respiratory diseases in childhood has increased dramatically in industrialized countries during the last 40 years.[1–6] Several theories have been proposed to

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explain this phenomenon, such as maternal diet during pregnancy,[7,8] increased use of antibiotics,[9,10] changes in dietary habits,[11] and possible adjuvant effects of air pollutants.[12] Among these, the hygiene hypothesis is the best investigated in epidemiologic studies.[13] It suggests that reduced microbial exposure early in childhood may be responsible for the rising incidences of allergic disorders.[13] Previous cross-sectional studies performed in farm children have shown that exposure to farm animals and high indoor endotoxin levels are inversely associated with incidences of aeroallergen sensitization, allergic rhinitis, and asthma.[14–18] In birth cohort studies, there is conflicting evidence that high endotoxin exposure is associated with either increased or decreased frequency of wheezing during infancy.[19,20] Furthermore, the exact role of endotoxin exposure during infancy and its possible influence on the development of childhood asthma remain uncertain.

The presence of dogs in homes has been directly associated with high levels of measured endotoxin in settled house dust.[21,22] Previous investigations suggest that the presence of pets and especially dogs is associated with reduced risk of asthma and aeroallergen sensitization in children.[20,23–25] However, many of these studies that assessed effects of pet ownership did not concomitantly assess indoor endotoxin levels in house dust. Therefore, it is not entirely clear whether it is endotoxin or other factors associated with dog ownership that contribute to these outcomes.[21] The Cincinnati Childhood Asthma and Air Pollution study is a long-term prospective birth cohort study of infants born to atopic parents. The study aim is to evaluate relationships of diesel exhaust exposure and development of atopy and allergic disease during early childhood. The objective of the present study was to determine relationships between early pet ownership and endotoxin exposure with atopy and wheezing during infancy.

METHODS

Study cohort

Infants were identified from birth records and enrolled in the study as previously described.[26] Parents were recruited approximately 6 months after the baby's birth and screened for seasonal or perennial allergic symptoms.[27] Parents reporting symptoms underwent skin prick testing. For infant inclusion, a parent was required to exhibit at least 1 positive skin prick test (SPT) to a panel of 15 aeroallergens.

At the screening visit, a baseline health questionnaire was administered that recorded demographic information, pet ownership, and maternal smoking status, as well as a medical and environmental history of both parents and infants. A home visit conducted at the subjects' primary place of residence included a detailed environmental assessment and house dust sample collection. All parents whose infants participated gave informed consent approved by the University of Cincinnati Institutional Review Board.

Clinical evaluation at year 1

The infants returned at age 1 year for a complete history and physical examination and for skin prick testing to a panel of 15 aeroallergens and 2 foods (ALK America, Round Rock, Tex). The skin test panel included fescue and timothy grass pollens, white oak, maple mix, American elm, red cedar, short ragweed, *Alternaria alternata*, *Aspergillus fumigatus*, *Penicillium* mix, *Cladosporium herbarum*, house dust mite mix (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), German cockroach, cat dander, and dog epithelium. Foods tested included egg white and whole milk. All SPTs were performed with a bifurcated device (Accusets; ALK America). A positive SPT was defined as a wheal ≥ 3 mm greater than the saline control with at least equivalent erythema.[28]

Medical and environmental history was collected by a questionnaire administered to all parents when the child was age 1 year. The questionnaire captured exposure characteristics as well as upper and lower respiratory symptoms observed within the previous 12 months. These data included number of siblings, parental asthma diagnosed by a physician, number of cigarettes smoked per day by mother, daycare attendance, presence of pets in the home, number of colds and wheezing episodes in the past 12 months, occurrence of wheezing at night, and required intervention or treatment for wheezing episodes. Questionnaire items are based on the validated International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire adapted for use in infants.[29,30]

Case definitions were used as dependent outcome variables as defined below:

1. Recurrent wheezing: ≥ 2 wheezing episodes in the past 12 months.[31,32]
2. Recurrent wheezing with an event: ≥ 2 wheezing episodes in the past 12 months that required any antiasthmatic medication (ie, inhaled/oral β_2 agonists, nebulized budesonide, and oral corticosteroids), a physician visit, or at least 1 sleep disturbance caused by wheezing. Infants who had 1 or no wheezing episodes in the last 12 months were used as the comparison group for both recurrent wheeze outcomes.
3. Any wheezing: ≥ 1 wheezing episode in the past 12 months. Infants with no wheezing episodes in the past year were used as the comparator group.
4. Allergic wheezing: ≥ 2 wheezing episodes in the past 12 months and a positive SPT response to at least 1 of 15 aeroallergens. Infants who had 1 or no wheezing episodes in the past 12 months and a negative SPT response to aeroallergens were used as the comparator group.
5. Atopy: a positive SPT response to at least 1 aeroallergen and/or food antigens.

Indoor dust sampling and house dust endotoxin analysis

During the home visit, the number and types of pets were recorded by the evaluation team. House dust samples were collected with a Filter Queen Majestic vacuum cleaner (Health-Mor; HMI Industries Inc, Seven Hills, Ohio) from the floor of the infant's primary activity room by vacuuming a 2-m^2 area at a rate of 2 min/m^2[33] (modified from Arlian et al[34]). After collection, samples were sieved with a pyrogen-free 355-μm mesh screen. Filtered dust was stored desiccated at −20°C until further analysis.

Endotoxin concentrations were determined by the limulus amebocyte lysate test (Associates of Cape Cod Inc, Falmouth, Mass) in all samples according to methods described by Milton et al.[35] All glassware and materials used were endotoxin and pyrogen-free. We evaluated assay reproducibility by calculating intraassay and interassay percent coefficient of variation (CV %). Intraassay mean CV % ranged from 2.1% to 4.6% (SD, 1.5–4.2), and the interassay mean CV % was 16.1% (SD, 9).

Statistical analysis

Histograms and quantile-quantile plots showed that endotoxin levels were approximately log-normally distributed. Endotoxin levels below the lower limit of detection (LOD) (37/532 [7%]) were analyzed as LOD/2 before log transformation.[36] Endotoxin levels ranged from 3 to 800 endotoxin units (EU)/mg of dust. Cut points for quartiles were 40.8, 78.7, and 161.0 EU/mg (25th, 50th, and 75th quartiles). After univariate analysis, recurrent wheezing, recurrent wheezing with an event, and any wheezing outcomes were analyzed separately by multiple logistic regression analyses, in which $\log_e$ endotoxin, number of cigarettes per day smoked by mother, number of dogs in the home, number of colds in the past 12 months, and number of siblings were modeled continuously. Dichotomously coded parental asthma (yes/no), daycare

attendance (yes/no), and sex were also modeled. Number of cigarettes per day smoked by mother was modeled with linear and quadratic effects to allow for a nonlinear effect of mother's cigarette smoking on infant wheezing. An interaction term was included to assess effects of endotoxin on wheezing outcomes with 2 or more dogs in the home. Covariates were chosen using a backward elimination technique, where all available variables believed a priori to be related to wheezing in infants initially were entered into a model. Covariates with significance levels > 0.15 were removed 1 at a time to assess the change in the regression coefficients and SEs of the primary exposure variables, endotoxin level, and number of dogs. Odds ratios (ORs) and CIs for continuous variables were obtained to estimate the odds of wheezing for an infant having a high (75th percentile) versus low (25th percentile) value of the variable. These percentiles represent endpoints of the interquartile range of the variable and are a reasonable choice for estimating the change in the covariate. Graphical interpretations of wheezing prevalence vs endotoxin level showed a nonlinear relationship, which was modeled by dividing the range of endotoxin into 4 nonoverlapping intervals, approximately equal to endotoxin quartiles. On each interval, a third degree function of endotoxin was fitted to wheezing prevalences. Fitted curves were smooth at the points of connection and were constrained to be linear in the tails. This transformation is known as a *restricted cubic spline function*. It allowed parameter estimates to be obtained for estimating the effect of endotoxin on wheezing outcomes over the interquartile range of endotoxin values. The analyses were performed using S-Plus software (Insightful Corp, Seattle, Wash).[37]

RESULTS

Subject and exposure characteristics

Clinical evaluations and home visits were completed for 532 infants as old as 15 months. The mean age at the first clinical evaluation was 12.5 ± 0.8 months, and 55% were male (81% white infants, 16% African American, and 3% other races). Pets (cats and/or dogs) were kept in 49.4% of homes (263/532 homes). Dogs only were kept in 159 homes, cats only were kept in 59 homes, and 45 (8%) had both. The geometric mean (GM) endotoxin level was higher ($P = .02$) in households with dogs alone (77.8 EU/mg dust; n = 159) versus households with no pets (58.7 EU/mg; n = 269). Homes with both cats and dogs had higher levels (GM = 108.7 EU/mg; n = 45) than homes with only dogs ($P = .10$), suggesting that cats contributed to endotoxin load. Endotoxin was higher in homes with only cats (GM = 76.2 EU/mg) but not significantly different from homes without pets ($P = .15$). As shown in Fig 1, GM endotoxin levels increased with the number of dogs (Spearman $P = .003$).

Infantile wheezing evaluation

Parents reported recurrent wheezing in 107 of 532 (20%) children at the first clinical evaluation. Similarly, 16% of infants (81/506) were identified with recurrent wheezing with an event. In Table I, the frequencies of subject characteristics are presented for both wheezing outcomes. Recurrent wheezing and recurrent wheezing with an event were more frequent among infants who attended daycare, who had 2 or more siblings, whose mothers smoked ≥ 20 cigarettes per day, who had ≥ 3 colds in the past year, and whose parent reported having asthma. Recurrent wheezing and recurrent wheezing with an event were more prevalent (although not significant) among infants sensitized to any allergen or to any aeroallergen (Table I). Any wheeze outcomes were reported in 137 of 532 (26%) of infants compared with nonwheezing infants (Table II).

Univariate analyses showed significant associations with all wheezing outcomes for daycare attendance, at least 2 siblings, more than 3 colds annually, mother having smoked at least 1 pack per day, and history of parental asthma from either parent (Tables I and II). The prevalences for all wheeze outcomes were not independently associated with dog or cat ownership or endotoxin level ($P > .05$), nor with race or presence of pets (data not shown).

However, an inverse relationship between prevalence of recurrent wheezing outcomes and endotoxin exposure was apparent in homes where endotoxin levels exceeded 100 EU/mg dust (Fig 2).

Because endotoxin directly correlated with number of dogs in the home (Fig 1), we evaluated whether wheezing outcomes were related to the interaction variate of high endotoxin analyzed continuously in combination with 2 or more dogs in the home in comparison with homes having no dogs (Table III). In this multivariate analysis, any wheeze (OR, 0.3; 95% CI, 0.1–0.8), recurrent wheezing (OR, 0.4; 95% CI, 0.1–0.9), and recurrent wheezing with an event (OR, 0.4; 95% CI, 0.1–1.0) were significantly less likely among infants with high endotoxin exposure and 2 or more dogs (Table III). The direct interaction between endotoxin and number of dogs was analyzed (ANOVA); the *P* values were .05 for recurrent wheeze, .03 for any wheeze, and .15 for recurrent wheezing with an event. However, when the endotoxin/number of dogs interaction term was eliminated from the model and the effect of endotoxin was tested adjusting for number of dogs, results were not significant ($P = .70$). When endotoxin was analyzed as a binomial variable (ie, <100 and ≥ 100 EU/mg) instead of continuously, results of the regression analysis were unchanged. Results were not significant when the interaction between endotoxin and number of cats was analyzed ($P = .60$; OR, 0.6; 95% CI, 0.3–1.6). The effect of a dog and cat in the same home was also investigated by adding number of cats to the regression model. As measured by ORs, the effect of endotoxin–multiple dog variate was essentially unchanged when number of cats was held fixed at 0 or ≥ 1.

Atopy evaluation

Atopy defined as percutaneous reactivity to at least 1 aeroallergen or food allergen (milk or egg) was observed in 152 of 532 (28.6%) subjects; 92 of 532 (17.3%) infants had a positive SPT result to at least 1 aeroallergen. As shown in Fig 3, therewas no significant difference in theprevalence of SPT positivity to aeroallergens among infants living in households with pets versus households without pets.

Atopy and allergic wheezing were also evaluated as outcome variables in the multiple logistic regression model. No significant relationship was found between endotoxin exposure and prevalence of atopy ($P = .22$). When atopy was incorporated into the multiple logistic regression model, the effect of endotoxin and multiple dog interaction variable on nonatopic wheezing outcomes was not modified (data not shown). The effect of the endotoxin–multiple dog variate was not significant when allergic wheeze was examined as the outcome variable ($P = .23$). Data for multivariate analysis of atopy and allergic wheezing are available in this article's Table E1 in the Online Repository at www.jacionline.org.

DISCUSSION

The aim of this study was to assess relationships of endotoxin exposure, pet ownership, atopy, and wheezing in high-risk infants. Epidemiologic findings that support the hygiene hypothesis[38] include evidence of a lower prevalence of atopic disorders among children raised with farm animals and exposed to high levels of indoor endotoxin.[39] Gereda et al[40] reported that mean indoor endotoxin levels were significantly lower among 61 wheezing babies (9–24 months) with positive SPTs compared with nonatopic babies and that house dust endotoxin concentrations were directly correlated with numbers of IFN-γ–producing $CD4^+$ T cells. In an infant study, endotoxin levels were inversely related to the presence of percutaneous sensitization in Swedish but not Estonian infants.[41] The latter investigations appear to support the hygiene hypothesis, although long-term atopic outcomes into childhood were not reported.

In our study, we found no direct relationship between atopy and endotoxin in house dust collected from the primary living areas of 532 high-risk infants. Our experience was similar

to that of Bolte et al,[42] who found no protective effect of high endotoxin measured in mothers' mattresses during infancy and aeroallergen specific IgE measured at age 2 years. Our data suggest that early endotoxin exposure may not be an important determinant of aeroallergen sensitization during infancy. Nevertheless, a significant relationship could become apparent as this cohort matures.

We also found no significant relationship between atopy and dog or cat ownership. Many studies addressing effects of pet ownership on development of atopy have been retrospective[43,44] or have been conducted in children older than 5 years.[14,15] There are a few prospective studies in infants.[42] In a population-based birth cohort study, Ownby et al[24] reported that exposure to 2 or more dogs or cats during infancy was associated with a lower risk of percutaneous reactivity to aeroallergens at age 7 years. In a population-based study of 4089 Swedish families, early dog ownership was inversely associated with aeroallergen sensitization at ages 2 and 4 years.[25] Recently, Gern et al[45] reported that atopic dermatitis and specific allergen sensitization (RAST) were less likely among high-risk infants who had been exposed to dogs or dogs and cats but not cats alone. In the Tucson birth cohort study of 1246 children, however, Remes et al[20] found no relationship between cat and dog exposure in early life and percutaneous reactivity to aeroallergens at ages 6 and 11 years. Indoor endotoxin was not measured in these studies, so it is uncertain whether modifying effects of pet ownership were attributable to endotoxin or other factors.

Our findings do not agree with some of the earlier reports that suggest a protective effect of pet ownership on development of atopy,[24,25] which could be attributable to intrinsic differences between study populations. We recruited high-risk infants of atopic parents with allergic symptoms, whereas other studies were population-based. We identified a 29% prevalence of atopy in our infants, and it is possible that strong genetic influences associated with parental atopy could obscure possible independent effects of pet or endotoxin exposure on wheezing outcomes that may be apparent in population-based cohorts.

We next examined whether pet ownership and endotoxin exposure influenced wheezing outcomes. As in previous studies, we found that any wheezing and recurrent wheezing outcomes were more likely among infants with colds, with parental asthma, whose mothers smoked, who attended daycare, and who had 2 or more siblings.[46–48] Wheezing outcomes were not independently associated with either dog or cat ownership or exposure to high levels of indoor endotoxin. We then examined the interaction variable of high endotoxin and multiple dogs in which the modifying effect of each of these variables on the other was taken into account. We confirmed direct interactions between endotoxin and dog exposure that were significant for 2 of 3 wheeze outcome variates. Multivariate analysis revealed that any wheezing, recurrent wheezing, and recurrent wheezing with an event were less likely among infants with high-level endotoxin exposure and multiple dogs in the home.

Investigators conducting similar studies report different outcomes that could be attributable to intrinsic differences in the cohorts, house dust collection, or approaches to data analysis. Bolte et al[42] reported that high endotoxin levels in mothers' mattresses increased the risk of repeated wheeze during the first 2 years in a birth cohort of 1942 children. In another birth cohort of 499 high-risk infants, Park et al[19] reported that repeated wheezing during infancy was significantly associated with high endotoxin in house dust collected from the family room after correcting for multiple variables, but this was not significant in a univariate model. In a subset of the same cohort evaluated at age 4 years, ownership of dog was associated with reduced wheezing, whereas high endotoxin exposure was associated with increased wheeze,[21] suggesting that pet ownership and endotoxin had divergent effects in early childhood. On the other hand, our data demonstrate an interactive effect of high endotoxin and multiple dog exposure that appears to be protective for wheezing in infancy.

It is likely that endotoxin reflects only partially the total indoor microbial exposure, and other undefined environmental exposures could explain differences between studies. For example, high concentrations of bacterial N-acetyl-muramic acid contained in mattress dust or high levels of fungal biomarkers (eg, β [1, 3]-glucans, extracellular polysaccharides) in house dust have been associated with reduced wheezing outcomes in farm children.[49,50]

In summary, we have found that high endotoxin exposure in the presence of multiple dogs modified the prevalences of multiple wheezing outcomes in infants. As we continue to follow this infant cohort into childhood and adolescence, it remains to be determined whether this exposure interaction continues to exert a protective influence.

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Abbreviations used

CV %
: Percent coefficient of variation

EU
: Endotoxin unit

GM
: Geometric mean

OR
: Odds ratio

SPT
: Skin prick test

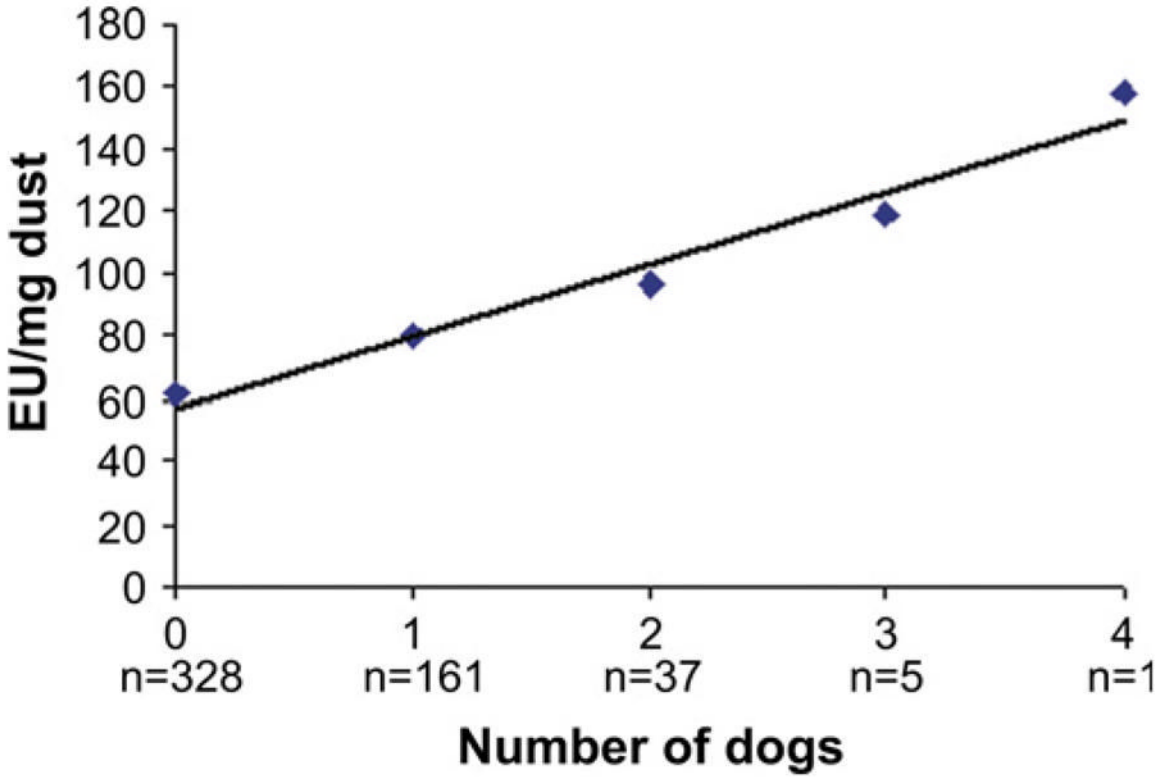

FIG 1.
GM of endotoxin levels (EU/mg) in settled dust according to number of dogs present in the home (n = 532; Spearman *P* = .003).

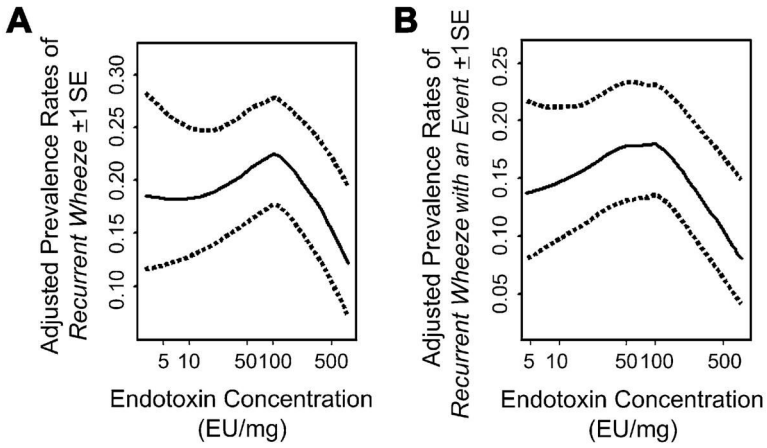

FIG 2.

Smoothed plots of the adjusted prevalence rates of recurrent wheeze **(A)** and recurrent wheeze with an event **(B)** in relation to endotoxin concentration plotted on a logarithmic scale *(solid lines). Dotted lines* represent ± 1 SE.

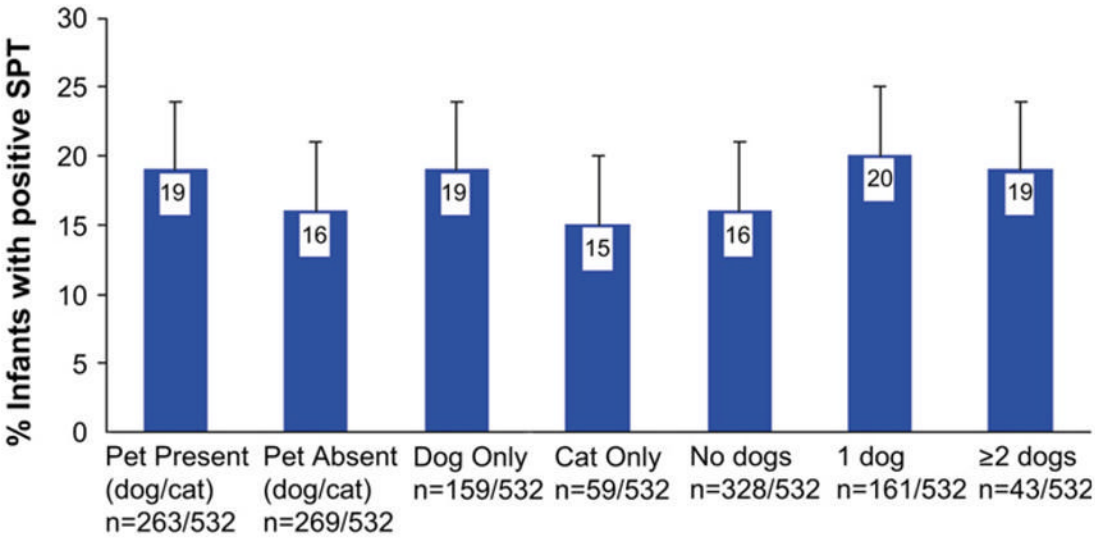

FIG 3.

Prevalence of positive SPTs to aeroallergens among infants (n = 532) in households with pets (dog/cat), no pets, dog only, cat only, and number of dogs at home. No significant differences were found between homes with pets and without pets.

TABLE I

Unadjusted ORs and 95% CIs of recurrent wheezing outcomes by subject characteristics and wheezing category

	Recurrent wheeze* N = 107/532 (20%)		Recurrent wheeze with an event† N = 81/506 (16%)		Control group‡ N = 425/532 (80%)
Characteristics	**N (%)**	**OR (95% CI)**	**N (%)**	**OR (95% CI)**	**N**
Endotoxin, family room dust (EU/mg)					
<100 EU/mg	63 (20)	1.0	49 (16)	1.0	253
≥ 100 EU/mg	44 (20)	1.0 (0.7–1.6)	32 (16)	1.0 (0.6–1.6)	172
Sex					
Female	41 (17)	1.0	30 (13)	1.0	198
Male	66 (23)	1.4 (0.9–2.2)	51 (18)	1.5 (0.9–2.4)	227
Day care					
No	92 (19)	1.0	68 (15)	1.0	395
Yes	15 (33)	2.1 (1.1–4.2)	13 (30)	2.5 (1.3–5.1)	30
No. of siblings					
0	28 (16)	1.0	19 (11)	1.0	148
1	39 (19)	1.2 (0.7–2.1)	30 (15)	1.4 (0.7–2.6)	169
≥ 2	40 (27)	2.0 (1.1–3.4)	32 (23)	2.3 (1.2–4.3)	108
No. of colds in the past year					
<3	20 (10)	1.0	15 (8)	1.0	180
≥ 3	87 (26)	3.2 (1.9–5.4)	66 (21)	3.2 (1.8–5.8)	245
Mother smoked (cigarettes/d)					
Not smoking	82 (188)	1.0	63 (14)	1.0	379
<20	15 (26)	1.7 (0.9–3.1)	11 (21)	1.6 (0.8–3.2)	42
≥ 20	10 (71)	11.6 (3.5–37.7)	7 (64)	10.5 (3–37)	4
Either parent had asthma					
No	59 (16)	1.0	43 (12)	1.0	304
Yes	48 (28)	2.0 (1.3–3.2)	38 (24)	2.2 (1.4–3.6)	121
No. of dogs in home					
None	67 (20)	1.0	49 (16)	1.0	261
1	31 (19)	0.9 (0.6–1.5)	25 (16)	1.0 (0.6–1.7)	130
≥ 2	9 (21)	1.0 (0.5–2.3)	7 (17)	1.1 (0.5–2.6)	34
No. of cats in home					
None	86 (20)	1.0	64 (16)	1.0	342
1	12 (23)	1.2 (0.6–2.4)	9 (18)	1.2 (0.6–2.6)	40
≥ 2	9 (17)	0.8 (0.4–1.8)	8 (16)	1.0 (0.5–2.2)	43
Positive SPT, any allergen					
No	70 (18)	1.0	53 (15)	1.0	310
Yes	37 (24)	1.4 (0.9–2.2)	28 (20)	1.4 (0.9–2.4)	115
Positive SPT, aeroallergen					
No	83 (19)	1.0	64 (15)	1.0	357
Yes	24 (26)	1.5 (0.9–2.6)	17 (20)	1.4 (0.8–2.6)	68

*Recurrent wheeze: ≥ 2 wheezing episodes in the past 12 months.

†Recurrent wheeze with an event: ≥ 2 wheezing episodes in the past 12 months that required a medical intervention or sleep disturbance caused by wheezing. Denominator does not include 26 infants who wheezed but did not require treatment.

‡Control group: ≤ 1 wheezing episodes in the past 12 months.

TABLE II

Unadjusted ORs and 95% CIs of any wheezing by subject characteristics

Characteristics	Any wheeze* N = 137/532 (25.7%)		No wheeze N = 395/532 (74.2%)
	N (%)	OR (95% CI)	N
Endotoxin, family room dust (EU/mg)			
<100 EU/mg	84 (27)	1.0	232
≥ 100 EU/mg	53 (25)	0.9 (0.6–1.3)	163
Sex			
Female	54 (23)	1.0	185
Male	83 (28)	2.1 (1.2–3.0)	210
Day care			
No	118 (24)	1.0	369
Yes	19 (42)	2.3 (1.2–4.3)	26
No. of siblings			
0	35 (20)	1.0	141
1	55 (26)	1.5 (0.9–2.3)	153
≥ 2	47 (32)	1.9 (1.1–3.1)	101
No. of colds in the past year			
<3	29 (15)	1.0	171
≥ 3	108 (33)	2.8 (1.8–4.5)	224
Mother smoked (cigarettes/d)			
Not smoking	110 (24)	1.0	351
<20	17 (30)	1.4 (0.7–2.5)	40
≥ 20	10 (71)	8.0 (2.5–25.9)	4
Either parent had asthma			
No	82 (23)	1.0	281
Yes	55 (33)	1.7 (1.1–2.5)	114
No. of dogs in home			
None	88 (27)	1.0	240
1	38 (24)	0.8 (0.5–1.3)	123
≥ 2	11 (26)	0.9 (0.5–1.9)	32
No. of cats in home			
None	111 (26)	1.0	317
1	14 (27)	1.1 (0.6–2.0)	38
≥ 2	12 (23)	0.9 (0.4–1.7)	40
Positive SPT, any allergen			
No	93 (25)	1.0	287
Yes	44 (29)	1.3 (0.8–1.9)	108
Positive SPT, aeroallergen			
No	109 (25)	1.0	331
Yes	28 (30)	1.3 (0.8–2.2)	64

* Any wheeze: ≥ 1 wheezing episode in the past 12 months.

TABLE III

Adjusted ORs and 95% CIs of recurrent wheezing, recurrent wheezing with an event, and any wheezing in relation to dust endotoxin (EU/mg) modified by the number of dogs in the home

Variable	Recurrent wheeze* OR (95% CI)	Recurrent wheeze with an event† OR (95% CI)	Any wheeze‡ OR (95% CI)
Endotoxin (EU/mg)§			
0 Dogs	1.3 (0.8–1.9)	1.1 (0.7–1.8)	1.1 (0.8–1.6)
1 Dog	0.7 (0.4–1.1)	0.6 (0.4–1.1)	0.6 (0.4–0.9)
≥ 2 Dogs	0.4 (0.1–0.9)	0.4 (0.1–1.0)	0.3 (0.1–0.8)
Sex (male vs female)	1.5 (0.9–2.3)	1.6 (1.0–2.8)	1.4 (0.9–2.1)
Day care	2.6 (1.3–5.5)	3.2 (1.5–6.9)	2.6 (1.3–5.1)
No. of siblings‖	2.0 (1.1–3.7)	2.4 (1.2–4.6)	2.0 (1.1–3.4)
No. of colds in the past year¶	1.3 (1.1–1.6)	1.3 (1.1–1.6)	1.4 (1.1–1.6)
Mother smoked (cigarettes/d)#	13.2 ($P < .001$; $df = 2$)	13.2 ($P < .001$; $df = 2$)	9.4 ($P < .001$; $df = 2$)
Either parent had asthma	2.3 (1.4–3.6)	2.7 (1.6–4.6)	1.8 (1.2–2.8)

*Recurrent wheeze: ≥ 2 wheezing episodes in the past 12 months.

†Recurrent wheeze with an event: ≥ 2 wheezing episodes in the past 12 months that required a medical intervention or sleep disturbance caused by wheezing.

‡Any wheeze: ≥ 1 wheezing episode in the past 12 months.

§95% CI endpoints correspond to the interquartile range of continuously measured endotoxin (EU/mg); high = 75th percentile, ~ 160; low = 25th percentile, ~ 40.

‖Two siblings vs no siblings.

¶Four colds vs 2 colds.

#Twenty vs 0 cigarettes/d. The *P* value corresponds to the additive effect of the linear and quadratic terms for cigarettes/d (2 *df*).