

Exposure to Dogs and Cats in the First Year of Life and Risk of Allergic Sensitization at 6 to 7 Years of Age

Dennis R. Ownby, MD

Christine Cole Johnson, PhD

Edward L. Peterson, PhD

THE INCREASING PREVALENCE OF asthma in the United States and other developed countries over the last few decades has been a cause for concern.^{1,2} While many factors appear to be involved in the development of childhood asthma, allergic sensitization to common allergens has consistently been shown to be related to the risk of developing asthma and to the risk of asthma persisting from childhood into adulthood.³⁻⁶ Many studies have attempted to elucidate relationships between environmental exposures, especially during infancy, and the risk of allergic sensitization in later life.^{7,8} These studies are based on the theory that an individual's genetic predisposition to allergic disease is activated or enhanced by early allergen exposure.^{4,7,9} The outcome of interactions between genetic influences and allergen exposures may be influenced by other environmental exposures, such as passive exposure to environmental tobacco smoke.^{7,9} If these relationships were better understood it might become possible to reduce the prevalence of allergic sensitization and perhaps asthma in children.

Exposure to dogs and cats during infancy has been thought to increase the

For editorial comment see p 1012.

Context Childhood asthma is strongly associated with allergic sensitization. Studies have suggested that animal exposure during infancy reduces subsequent allergic sensitization.

Objective To evaluate the relationship between dog and cat exposure in the first year of life and allergic sensitization at 6 to 7 years of age.

Design, Setting, and Subjects Prospective birth cohort study of healthy, full-term infants enrolled in a health maintenance organization in suburban Detroit, Mich, who were born between April 15, 1987, and August 31, 1989, and followed up yearly to a mean age of 6.7 years. Of 835 children initially in the study at birth, 474 (57%) completed follow-up evaluations at age 6 to 7 years.

Main Outcome Measures Atopy, defined as any skin prick test positivity to 6 common aeroallergens (dust mites [*Dermatophagoides farinae*, *D pteronyssinus*], dog, cat, short ragweed [*Ambrosia artemisiifolia*], and blue grass [*Poa pratensis*]); seroatopy, defined as any positive allergen-specific IgE test result for the same 6 allergens or for *Alternaria* species.

Results The prevalence of any skin prick test positivity (atopy) at age 6 to 7 years was 33.6% with no dog or cat exposure in the first year of life, 34.3% with exposure to 1 dog or cat, and 15.4% with exposure to 2 or more dogs or cats ($P=.005$). The prevalence of any positive allergen-specific IgE test result (seroatopy) was 38.5% with no dog or cat exposure, 41.2% with exposure to 1 dog or cat, and 17.9% with exposure to 2 or more dogs or cats ($P=.003$). After adjustment for cord serum IgE concentration, sex, older siblings, parental smoking, parental asthma, bedroom dust mite allergen levels at 2 years, and current dog and cat ownership, exposure to 2 or more dogs or cats in the first year of life was associated with a significantly lower risk of atopy (adjusted odds ratio, 0.23; 95% confidence interval, 0.09-0.60) and seroatopy (adjusted odds ratio, 0.33; 95% confidence interval, 0.13-0.83).

Conclusion Exposure to 2 or more dogs or cats in the first year of life may reduce subsequent risk of allergic sensitization to multiple allergens during childhood.

JAMA. 2002;288:963-972

www.jama.com

Author Affiliations: Section of Allergy and Immunology, Department of Pediatrics, Medical College of Georgia, Augusta (Dr Ownby); Department of Biostatistics and Research Epidemiology, Henry Ford Health System, Detroit, Mich (Drs Johnson and Peterson); National Institute of Environmental Health Sciences Center in Molecular and Cellular Toxicology with Human Applications, Wayne State University, Detroit (Drs Johnson and Peterson).

Financial Disclosure: Dr Ownby has received honoraria from AstraZeneca, Genentech, GlaxoSmithKline, Schering, Merck, and Aventis.

Corresponding Author and Reprints: Dennis R. Ownby, MD, Section of Allergy and Immunology, Department of Pediatrics, BG-1019, Medical College of Georgia, Augusta, GA 30912-3790 (e-mail: downby@mail.mcg.edu).

risk of subsequent allergy to these animals.^{8,10-12} This assumption is primarily based on a few retrospective studies reporting an increased likelihood of allergic sensitization following exposure during infancy.¹⁰⁻¹² Some studies, however, have suggested that exposure to dogs or cats during infancy is associated with reduced risk of allergic disease.¹³⁻¹⁸ Others have shown that children growing up on farms, especially farms with animals, were less likely to be allergic than were children growing up in urban environments.^{19,20}

This analysis is part of the Childhood Allergy Study, a prospective birth cohort study designed to simultaneously evaluate multiple relationships between early environmental exposures and subsequent allergic sensitization and asthma.²¹⁻³⁰ Among the variables considered were parental allergy histories, parental smoking, IgE levels in cord blood, month of birth, concentrations of dust mite and cat allergen in the child's bedroom at age 2 years, and pet exposure. In this analysis, we specifically examined exposure to dogs or cats in the first year of life and a child's risk of later allergic sensitization to common allergens after adjusting for potential confounding associations. We also examined relationships between early dog and cat exposure and allergen-specific serum IgE concentrations, lung function, methacholine airway responsiveness, and asthma.

METHODS

The selection of children for the Childhood Allergy Study has previously been described.²¹ Briefly, all pregnant women living in an area of northern, suburban Detroit, defined by contiguous ZIP codes, and belonging to a health maintenance organization, were eligible to participate if their infants were born between April 15, 1987, and August 31, 1989. Only infants born at term (36 or more weeks' gestational age) with valid measurements of cord serum IgE concentration were entered into the study. The study was approved by the institutional human rights committee, and

written informed consent was obtained when the mothers were enrolled, at the time of the first home visit, and prior to the clinical evaluations.

Study nurses interviewed mothers prior to delivery to obtain information concerning each parent's level of education; presence of allergies in general and of hay fever and asthma specifically; and parental smoking habits. The number of siblings was also noted along with other data about the home. Cord serum IgE concentrations were measured for all infants as previously described.²¹

We contacted parents by telephone when infants were aged 1 year to obtain information on prespecified variables of interest, including the presence and number of pets in the home during the first year. The number of dogs and cats reported at this time was used for this analysis. When children were aged 2 years, nurses visited each child's home to obtain information about the home environment and to collect dust samples from the child's bedroom, as well as urine samples from the child for measurement of urinary cotinine as a biomarker of passive cigarette smoke exposure. The dust samples were analyzed for concentrations of mite (Der p 1 and Der f 1) and cat (Fel d 1) allergens using a monoclonal antibody-based enzyme-linked immunosorbent assay as previously described.²⁸ We have documented the validity of parental smoking histories in this cohort with reference to children's urinary cotinine concentrations.²⁶ Questionnaire-based parental smoking histories from the first year of the child's life were used for these analyses because there were fewer missing values than for urinary cotinine concentrations. Follow-up telephone interviews also were conducted when the children were aged 3, 5, and 6 years, and a second home visit was conducted when the children were aged 4 years.

Evaluations for Allergic Sensitization and Asthma

Clinical evaluations for allergic sensitization and asthma were performed when the children were aged 6 to 7 years. In

addition to general medical histories and physical examinations, these evaluations included skin prick testing with commercial extracts of dust mites (*Dermatophagoides farinae*, *D pteronyssinus*), dog, cat, short ragweed (*Ambrosia artemisiifolia*), and blue grass (*Poa pratensis*), along with saline and histamine controls (all extracts and controls, Pharmaceutical Division, Bayer Inc, Spokane, Wash). Skin prick test results were considered positive if the product of perpendicular wheal diameters was 4 mm or more associated with a flare of at least 10 mm, and if there was no response to the negative control. Atopy was defined as a positive skin prick test result with any of the 6 allergens tested. Blood samples obtained during the evaluation were assayed for total serum IgE concentration and concentrations of allergen-specific IgE antibodies using a commercial assay (AlaSTAT, Diagnostic Products Corp, Los Angeles, Calif). Allergen-specific IgE testing included the same 6 allergens used for skin prick testing in addition to *Alternaria* species. Total and allergen-specific serum IgE levels were expressed in international units per milliliter (1 IU/mL corresponds to 2.4 ng/mL). Allergen-specific IgE levels of 0.35 IU/mL or higher were considered to be a positive test result in accordance with the manufacturer's recommendation. Seroatopy was defined as any positive test result for an allergen-specific IgE concentration. Numbers of children with seroatopy may have been slightly higher than those with atopy because one additional allergen, *Alternaria*, was also used to define seroatopy. Because a study published after the start of this study suggested that cockroach sensitization may be associated with asthma,³¹ a random sample of 100 sera were assayed for cockroach-specific IgE and only 2 sera were positive.²⁴ Given the low prevalence of detectable cockroach sensitization, no further testing for cockroach-specific IgE was performed.

At the time of skin prick testing, children were defined as having current asthma if a parent reported that they had been diagnosed by a physician as having asthma and that they had asthma

symptoms or used asthma medications in the preceding 12 months. Pulmonary function tests were performed as previously described, and the results are presented as the percentage of predicted using standard equations.²⁹ Methacholine airway responsiveness was determined as previously described.²⁹ After baseline spirometry and no response to a control saline challenge, 5 doses of methacholine (0.025-25 mg/mL) were administered through a dosimeter (Pulmonary Data Services, Louisville, Colo). Methacholine airway responsiveness was defined as a fall in forced expiratory volume in 1 second (FEV₁) of 20% or more from the postsaline challenge value at a concentration of administered methacholine of 10 mg/mL or less.²⁹

Statistical Analysis

The power of this study was originally based on the ability to detect a small to medium effect (0.2) for a χ^2 test as defined by Cohen.³² With this assumption, and assuming an α level of .05, the power to detect significant associations between outcomes in 3 exposure groups is greater than 90% with an overall sample size of 470. Given the same assumptions, it also is possible to stratify the data for a variable with approximately equal prevalences (ie, sex) and still have power greater than 70% with 235 in each group. If the prevalence of a variable is low in the cohort, such as current asthma, the power is much lower.

The collected data were first examined for potential imbalances between those children lost from the study and those who were retained. χ^2 Tests were used to compare the relative percentages.³³

Pet exposure in the first year of life was defined as an ordinal variable with 3 categories: no dog or cat exposure, exposure to 1 dog or cat, and exposure to 2 or more dogs or cats. The highest strata was truncated at 2 or more because of the small sample size above this level. Information about pet exposure at age 6 to 7 years was used to create the same 3 categories of pet exposure as was used for the first year of life. Binary variables

of interest (eg, atopy [yes or no], specific skin prick test positivity) were analyzed according to pet exposure category using a χ^2 test for 2 \times 3 contingency tables.³³ We did not have a preconceived hypothesis concerning a relationship between exposure to varying number of dogs and cats and the risk of allergic sensitization. Therefore, we tested the general hypothesis that outcomes differed across categories of dog and cat exposure rather than testing for trends with increasing exposure.

The relationships between pet exposure categories and continuous variables, such as percent predicted forced vital capacity (FVC) or total serum IgE, were evaluated with a 1-way analysis of variance technique.³⁴ Each continuous variable was transformed to natural logarithmic equivalents to reduce positive skewing prior to analysis. If the range of the variable to be logarithmically transformed included zero, 1 was added to the variable prior to transformation. When logarithmic data transformation did not result in a near normal distribution, such as for dust mite concentrations, a Kruskal-Wallis test was used. The number of children in each analysis varied slightly because of missing data.

Atopy and seroatopy were each used as a dependent binary variable in a linear logistic regression assessing 2 indicator variables for pet exposure: exposure to 1 dog or cat or exposure to 2 or more dogs or cats.³⁵ These models were fitted without other variables and with other potentially confounding variables, including cord serum IgE concentration, child's sex, having older siblings, parental smoking, mother or father with a history of asthma, and total bedroom dust mite allergen levels at child age 2 years. The logistic model is appropriate for modeling binary dependent variables. It makes minimal assumptions about the distributional properties of the independent variables and the exponentiation of the coefficient allows for estimation of the odds ratio (OR). We chose to include the number of dogs and cats as 2 binary indicator variables avoiding as-

sumptions concerning the direction of any associations. Using the Hosmer-Lemeshow test, we found no evidence to doubt the validity of the models.³⁵

We analyzed the entire data set and data sets defined by sex. In all analyses, an $\alpha = .05$ criteria was used to determine statistical significance. There was no attempt to impute data; all analyses were performed on all available data. SAS v8.0 (SAS Institute Inc, Cary, NC) was used for all analyses.³⁶

RESULTS

A total of 1194 pregnant women were potentially eligible for entry into this study, and consent for participation was obtained from 953 women. Infants of 106 of these women were not enrolled in the study because a cord blood sample was not obtained, leaving 847 eligible newborns. Six of the cord blood samples were thought to be contaminated by maternal blood,^{21,23} and an additional 6 children were found to be ineligible when each child's data were examined and verified prior to the 6- to 7-year evaluations, yielding 835 eligible children enrolled at birth. Of the 835 children initially enrolled, 235 had been lost to follow-up by age 6 years, and 126 of those contacted at age 6 years declined participation in the clinical evaluation. Thus, 474 (57%) of the 835 eligible children initially enrolled completed the clinical evaluation for allergic sensitization and asthma at an average age of 6.7 (SD, 0.17) years. Characteristics of children who were evaluated at 6 to 7 years did not differ significantly from those of children who did not undergo clinical evaluation at age 6 to 7 years, including whether the parent had a history of asthma or hay fever or whether there were dogs or cats in the household (TABLE 1). Also, interactions between each variable, any exposure to dogs and cats in the home in the first year of life, and whether the child participated in the clinical evaluation were not statistically significant (Table 1). When the relationship between maternal and paternal histories of asthma, allergies, and hay fever and presence of 2 or more dogs or cats in

the household was evaluated, no significant associations were found.

The parents of the children in this study were relatively well educated and almost all (804 [96.3%]) described themselves as white, non-Hispanic. Characteristics of the children completing the study are presented in TABLE 2. Boys and girls were approximately equally represented. The presence of a dog or cat in the home did not differ significantly between parents with a history of asthma, allergies, or hay fever and those who did not report these conditions.

To investigate the relationships between dog and cat exposure and aller-

gic sensitization, we initially compared the 184 children with any dog exposure in their first year of life to the 220 children without either dog or cat exposure. Children exposed to a dog were less likely to have a positive skin test result to dog allergen (3.3% vs 8.6%, $P=.03$) and detectable dog-specific IgE (3.7% vs 8.7%, $P=.06$) at follow-up. Any exposure to a dog was also associated with lower total serum IgE levels (geometric mean, 23.8 IU/mL vs 33.1 IU/mL for no dog or cat exposure; $P=.04$). The inverse association between dog exposure and allergic sensitization was further examined in relationship to number of dogs (TABLE 3).

The reference group remained the 220 children with neither dog nor cat exposure in the first year of life. An apparent dose-response effect for atopy and seroatopy was found across the 3 exposure categories. Atopy was present in 33.6% of the children without dog or cat exposure, in 29.7% with exposure to 1 dog, and in only 8.3% with exposure to 2 or more dogs ($P=.009$). The prevalence of seroatopy was 38.5% with no pet exposure, 36.7% with exposure to 1 dog, and 12.9% with exposure to 2 or more dogs ($P=.02$). The same analyses were performed with cat exposure during the first year. Using the same reference group of 220 unexposed children, the patterns toward less prevalent allergic sensitization with exposure to cats were similar to those observed with dog exposure, but none of the associations reached statistical significance. For example, the prevalence of atopy declined from 33.6% to 31.4% to 23.1% with exposure to no dogs or cats, 1 cat, or 2 or more cats, respectively ($P=.54$ for comparison across categories), while seroatopy declined from 38.5% to 34.5% to 26.1% ($P=.45$).

Based on finding similar relationships between dog and cat exposures in the first year of life and allergic sensitization at age 6 to 7 years, relationships were further analyzed by simultaneously considering combined dog and cat exposure. Combining dogs and cats increased the number of children in each category, allowing further exploration of the relationships through stratification of the data by sex. Atopy and seroatopy were each present in about one third of children. When all children were considered, the prevalence of skin prick test positivity to dog allergen, outdoor and indoor allergens, atopy, and seroatopy were significantly different across the 3 exposure categories and generally decreased with increasing pet exposure (TABLE 4). The pattern of decreasing skin prick test positivity to cat allergen with increasing exposure was similar but the relationship(s) failed to reach statistical significance.

Table 1. Comparison of Children in the Cohort Who Underwent Clinical Evaluation at Age 6 to 7 Years With Those Not Evaluated*

Variable	No./Total (%)		P Value	
	Not Evaluated	Evaluated	Evaluated vs Not Evaluated	For Cat and Dog Interaction†
Children				
Female	178/351 (50.7)	247/484 (51.0)	.93	.71
First-born	148/321 (46.1)	214/478 (44.8)	.71	.13
Exposure to dogs and cats in first year of life				
Dogs or cats				
0	139/285 (48.8)	223/474 (47.1)	.20	NA
1	88/285 (30.9)	173/474 (36.5)		
≥2	58/285 (20.4)	78/474 (16.5)		
Dogs only	113/252 (44.8)	184/407 (45.2)	.93	NA
Cats only	70/209 (33.5)	106/329 (32.2)	.76	NA
Parental Characteristics				
Smoking ≥1 cigarette per day				
Mother	66/351 (18.8)	78/484 (16.1)	.31	.46
Father	85/348 (24.4)	116/482 (24.1)	.90	.82
Asthma				
Mother	24/351 (6.8)	41/483 (8.5)	.38	.87
Father	28/333 (8.4)	25/463 (5.4)	.09	.46
Either parent	47/335 (14.0)	64/463 (13.8)	.93	.42
Allergy				
Mother	99/351 (28.2)	141/484 (29.1)	.77	.18
Father	86/321 (26.8)	113/429 (26.3)	.89	.69
Either parent	159/333 (47.8)	219/447 (49.0)	.73	.18
Hay fever				
Mother	62/350 (17.7)	76/483 (15.7)	.45	.09
Father	62/320 (19.4)	88/445 (19.8)	.89	.68
Either parent	108/329 (32.8)	142/453 (31.4)	.66	.83
Formal education beyond high school‡				
Mother	219/351 (62.4)	299/484 (61.8)	.86	.25
Father	239/349 (68.5)	331/483 (68.5)	.99	.40

*NA indicates not applicable.

†For interaction between any exposure to cats and dogs in the first year of life, the variable of interest, and being evaluated at age 6 to 7 years.

‡Includes some college or technical school training.

Table 2. Characteristics of 474 Children Evaluated for Allergic Sensitization and Asthma

Characteristic	All Subjects	Dog or Cat Exposure in First Year of Life		
		0 Dogs or Cats	1 Dog or Cat	≥2 Dogs or Cats
Age, mean (SD) [range], y	6.72 (0.17) [6.1-7.7]	6.71 (0.16)	6.74 (0.18)	6.69 (0.17)
Cord serum IgE, mean (SD) [range], IU/mL*	0.28 (0.27) [0.01-2.13]	0.28 (0.28)	0.27 (0.24)	0.32 (0.28)
Dust mite concentration (Der f 1 + Der p 1) in child's room at age 2 years, mean (SD) [range], µg/g dust†	0.82 (1.33) [-0.68 to 5.85]	0.93 (1.37)	0.72 (1.22)	0.67 (1.42)
Girls:boys (percentage)	242:232 (51:49)	113:110 (51:49)	90:83 (52:48)	39:39 (50:50)
No siblings, No./total (%)	210/469 (44.8)	92/221 (41.6)	78/173 (45.1)	40/75 (53.3)
Either parent smokes, No./total (%)	143/472 (30.3)	57/223 (25.6)	59/172 (34.3)	24/77 (35.1)
Dog and cat exposure in first year of life, No./total (%)				
Dog	184/474 (38.8)		125/173 (72.3)	59/78 (75.6)
Cat	106/474 (22.4)		49/173 (28.3)	57/78 (73.1)
Dog or cat	251/474 (53.0)			
Any dog or cat exposure by parental history, No./total (%)‡				
Parental asthma				
Present	56/100 (56.0)] P = .49		
Absent	195/374 (52.1)			
Parental allergy				
Present	116/216 (53.7)] P = .41		
Absent	110/221 (50.2)			
Parental hay fever				
Present	81/141 (57.4)] P = .17		
Absent	153/303 (50.5)			

*Values represent the natural logarithm of the IgE concentration plus 1.

†Values represent the natural logarithm of dust mite concentrations.

‡Dog or cat in the home in the first year of the child's life when either parent has or does not have a history of asthma, allergies, or hay fever.

When boys and girls were considered separately, different patterns emerged from the data (Table 4). Exposure to a single dog or cat in the first year of life was associated with an increased prevalence of atopy and seroatopy in girls while both outcomes declined in boys exposed to a single dog or cat. Lower prevalences of skin prick test positivity to dog, cat, and indoor and outdoor allergens, and of methacholine airway responsiveness were consistently found in association with exposure to a single dog or cat with boys but not with girls. Measurements of lung function were also related to dog and cat exposure for boys but not for girls. The prevalence of methacholine airway responsiveness in boys was 25.5% when there had been no dog or cat exposure, 20.3% with exposure to 1 dog or cat, and 5.1% with exposure to 2 or more dogs or cats ($P = .03$). In girls, the prevalence of methacholine responsiveness was unchanged across pet exposure categories. Similarly, the mean percent predicted FVC and FEV₁ increased significantly across pet expo-

Table 3. Relationship Between the Number of Dogs in the Home in the First Year of Life and the Prevalence of Allergic Sensitization at Age 6 to 7 Years*

Variable	No./Total (%)			P Value†
	No Dog or Cat Exposure	No. of Dogs		
		1	≥2	
Skin prick test positivity				
Dog	19/220 (8.6)	6/148 (4.1)	0/36 (0)	.06
Cat	34/220 (15.5)	16/148 (10.8)	1/36 (2.8)	.07
Outdoor allergens‡	62/206 (30.1)	28/137 (20.4)	2/27 (7.4)	.01
Indoor allergens§	60/220 (27.3)	37/148 (25.0)	2/36 (5.6)	.02
Atopy	74/220 (33.6)	44/148 (29.7)	3/36 (8.3)	.009
Seroatopy¶	74/192 (38.5)	47/128 (36.7)	4/31 (12.9)	.02
Methacholine airway responsiveness	53/220 (24.1)	34/144 (23.6)	4/34 (11.8)	.27
Current asthma	17/223 (7.6)	9/147 (6.1)	2/36 (5.6)	.81

*The group not exposed to dogs was further restricted to those children without any cat exposure in the first year of life since both dog and cat exposure appeared to be associated with the variables presented in this table.

†From χ^2 analysis comparing each of the 3 categories of dog exposure.‡Short ragweed (*Ambrosia artemisiifolia*), blue grass (*Poa pratensis*), and *Alternaria*.§*Dermatophagoides farinae*, *D pteronyssinus*, dog, and cat.||Positive skin test to 1 or more of *D farinae*, *D pteronyssinus*, dog, cat, short ragweed, or blue grass.¶Positive in vitro test for IgE specific to *D farinae*, *D pteronyssinus*, dog, cat, short ragweed, blue grass, or *Alternaria*.

sure categories among boys but not among girls, and were highest with exposure to 2 or more dogs or cats. Thirty-three (7%) of 473 children had current asthma. The prevalence of current asthma was lower in boys who had been

exposed to 2 or more dogs or cats in infancy compared with no exposure (5.1% vs 11.8%, respectively), but the difference across exposure categories was not statistically significant ($P = .43$) and no difference was seen for girls.

For all children, exposure to 2 or more dogs and cats in the first year of life was associated with a lower total serum IgE at age 6 to 7 years, but the analysis across exposure categories was not statistically significant ($P=.09$) (TABLE 5). In analyses stratified by sex, exposure to more dogs or cats was associated with significantly decreased geometric mean IgE among boys ($P=.02$) and among children with a parental history of asthma ($P=.03$), but not among girls ($P=.42$) or among children without a parental history of asthma ($P=.31$).

When mean total dust mite concentrations in the child's bedroom at age 2 years were compared for homes with no pet, 1 dog or cat, and 2 or more dogs or cats, the median (5th percentile, 95th percentile) dust mite concentrations were not significantly different (2.0 [0.5, 37.1] $\mu\text{g/g}$ dust; 1.8 [0.5, 16.6] $\mu\text{g/g}$ dust; 1.1 [0.5, 43.8] $\mu\text{g/g}$ dust; $P=.27$).

Logistic regression analysis was used to adjust for the effects of possible confounding variables (cord serum IgE concentration, levels of house dust mite allergen in the child's bedroom at age 2

years, child's sex, an older sibling, passive exposure to parental tobacco smoke, and parental history of asthma) on relationships between dog and cat exposure and risks of atopy and seroatopy. After adjusting for all of these variables, exposure to 2 or more dogs or cats was still associated with significantly lower risks of atopy (OR, 0.31; 95% confidence interval [CI], 0.14-0.72) and seroatopy (OR, 0.43; 95% CI, 0.19-0.96) in all children (TABLE 6, model 1).

When the analysis was further adjusted for current exposure to dogs or

Table 4. Relationship Between Number of Dogs and Cats in the Home in the First Year of Life, Prevalence of Allergic Sensitization, and Measures of Lung Function or Presence of Current Asthma at Age 6 to 7 Years*

Variable	Sex	No. of Dogs and Cats			P Value†
		0	1	≥2	
Skin prick test positivity Dog	All	19/220 (8.6)	6/172 (3.5)	2/78 (2.6)	.04
	Girls	6/112 (5.4)	4/90 (4.4)	1/39 (2.6)	.77
	Boys	13/108 (12.0)	2/82 (2.4)	1/39 (2.6)	.02
Cat	All	34/220 (15.5)	20/172 (11.6)	6/78 (7.7)	.18
	Girls	12/112 (10.7)	13/90 (14.4)	2/39 (5.1)	.30
	Boys	22/108 (20.4)	7/82 (8.5)	4/39 (10.3)	.05
Outdoor allergens‡	All	62/206 (30.1)	37/160 (23.1)	8/66 (12.1)	.01
	Girls	25/104 (24.0)	20/84 (23.8)	2/32 (6.3)	.08
	Boys	37/102 (36.3)	17/76 (22.4)	6/34 (17.7)	.04
Indoor allergens‡	All	60/220 (27.3)	49/172 (28.5)	8/78 (10.3)	.005
	Girls	23/112 (20.5)	28/90 (31.1)	2/39 (5.1)	.004
	Boys	37/108 (34.3)	21/82 (25.6)	6/39 (15.4)	.07
Atopy‡	All	74/220 (33.6)	59/172 (34.3)	12/78 (15.4)	.005
	Girls	30/112 (26.8)	34/90 (37.8)	3/39 (7.5)	.002
	Boys	44/108 (40.7)	25/82 (30.5)	9/39 (23.1)	.10
Seroatopy‡	All	74/192 (38.5)	61/148 (41.2)	12/67 (17.9)	.003
	Girls	28/93 (30.1)	32/76 (42.1)	6/37 (16.2)	.02
	Boys	46/99 (46.5)	29/72 (40.3)	6/30 (20.0)	.04
Methacholine airway responsiveness§	All	53/220 (24.1)	40/166 (24.1)	12/76 (15.8)	.29
	Girls	25/110 (22.7)	24/87 (27.6)	10/37 (27.0)	.71
	Boys	28/110 (25.5)	16/79 (20.3)	2/39 (5.1)	.03
FVC % predicted, mean (SD) [No. of children]¶	All	93.9 (11.7) [222]	96.5 (11.4) [169]	95.1 (12.4) [77]	.10
	Girls	94.4 (11.4) [112]	95.4 (10.7) [88]	91.0 (12.7) [38]	.14
	Boys	93.5 (12.1) [110]	97.7 (12.1) [81]	99.0 (10.9) [39]	.01
FEV ₁ % predicted, mean (SD) [No. of children]¶	All	93.1 (11.6) [222]	94.5 (12.2) [169]	94.7 (12.6) [77]	.41
	Girls	92.3 (11.0) [112]	91.8 (11.0) [88]	89.1 (12.0) [38]	.29
	Boys	93.8 (12.2) [110]	97.4 (12.8) [81]	100.1 (10.7) [39]	.01
Current asthma#	All	17/223 (7.6)	12/172 (7.0)	4/78 (5.1)	.76
	Girls	4/113 (3.5)	5/89 (5.6)	2/39 (5.1)	.77
	Boys	13/110 (11.8)	7/83 (8.4)	2/39 (5.1)	.43

*All data are No./Total (%) unless indicated otherwise. FVC indicates forced vital capacity; FEV₁, forced expiratory volume in 1 second.

†From χ^2 analysis except where noted.

‡See Table 3 footnote for definitions of outdoor and indoor allergens, atopy, and seroatopy.

§Defined as a provocative dose of ≤ 10 mg/mL for decreasing FEV₁ by 20%.

¶From analysis of variance.

||Results are presented as mean (SD) of the percent predicted from standard equations (see Ownby et al²⁹ for details).

#Defined as physician diagnosis of asthma and symptoms of asthma or use of asthma medications in the previous 12 months.

cats using the same exposure categories as in the first year of life (no exposure; exposure to 1 dog or cat; exposure to 2 or more dogs or cats at age 6-7 years), the risk of atopy and seroatopy associated with exposure in the first year of life remained significantly decreased (atopy: OR, 0.23; 95% CI, 0.09-0.60; seroatopy: OR, 0.33; 95% CI, 0.13-0.83) (Table 6, model 2). When the variable for dog or cat exposure at age 6 to 7 years replaced the variable for exposure in the first year of life, no statistically significant associations were

found. For example, with all children included in the analysis, risks of atopy and seroatopy among children with 2 or more dogs or cats at age 6 to 7 years were not significantly different than those among children with no current pet exposure (for atopy: OR, 0.79; 95% CI, 0.44-1.85; $P = .79$; for seroatopy: OR, 0.81; 95% CI, 0.43-1.94; $P = .81$).

COMMENT

In this prospective study we found that exposure to 2 or more dogs or cats in the first year of life was associated with

a lower prevalence of allergic sensitization at age 6 to 7 years regardless of exposure to dogs and cats at age 6 years. This inverse relationship was consistent whether skin prick tests for 6 common aeroallergens or tests for 7 allergen-specific IgE concentrations were considered as primary outcomes. The inverse relationship was present for both indoor (dust mites, dog, and cat) and outdoor (ragweed, grass, and *Alternaria*) allergens. The relationships remained significant after adjusting for a number of variables that may be risk

Table 5. Relationship Between Number of Dogs and Cats in the Home in the Child's First Year of Life and Total Serum IgE Concentration at Age 6 to 7 Years*

	No Dogs or Cats			1 Dog or Cat			≥2 Dogs or Cats			P Value§
	No.	Mean†	Ln Mean (SD)‡	No.	Mean†	Ln Mean (SD)‡	No.	Mean†	Ln Mean (SD)‡	
All children	204	32.8	3.49 (1.47)	155	26.8	3.29 (1.46)	72	21.8	3.08 (1.21)	.09
Girls	100	24.0	3.18 (1.24)	81	28.5	3.35 (1.43)	37	20.5	3.02 (1.18)	.42
Boys	104	43.8	3.78 (1.61)	74	25.0	3.22 (1.50)	35	23.1	3.14 (1.26)	.02
Child's parents free of asthma	163	29.4	3.38 (1.41)	126	23.6	3.16 (1.48)	50	22.7	3.12 (1.35)	.31
Child's parent has asthma	41	48.9	3.89 (1.63)	29	46.5	3.84 (1.22)	22	19.7	2.98 (0.083)	.03

*Ln indicates natural logarithm.
 †Geometric mean of the total serum IgE for each group, in IU/mL.
 ‡Natural logarithm of the mean serum IgE and SD of the Ln mean.
 §P value from analysis of variance comparing the 3 Ln means.

Table 6. Adjusted Relationships Between Dog and Cat Exposure, Atopy, and Seroatopy*

Variable	OR (95% CI)	P Value	Model 1†		Model 2‡	
			Adjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Exposure to 1 Dog or Cat in First Year of Life						
All children						
Atopy	1.03 (0.68-1.57)	.89	1.01 (0.61-1.67)	.97	0.85 (0.48-1.52)	.58
Seroatopy	1.12 (0.72-1.73)	.62	1.20 (0.71-2.02)	.50	0.93 (0.51-1.68)	.80
Girls						
Atopy	1.66 (0.91-3.02)	.10	1.99 (0.95-4.17)	.07	2.02 (0.84-4.84)	.11
Seroatopy	1.69 (0.89-3.19)	.11	2.21 (1.03-4.72)	.04	1.78 (0.73-4.34)	.20
Boys						
Atopy	0.64 (0.35-1.17)	.15	0.54 (0.25-1.15)	.11	0.36 (0.15-0.87)	.02
Seroatopy	0.78 (0.42-1.44)	.42	0.63 (0.29-1.37)	.25	0.46 (0.19-1.12)	.09
Exposure to ≥2 Dogs or Cats in First Year of Life						
All children						
Atopy	0.36 (0.18-0.71)	.003	0.31 (0.14-0.72)	.007	0.23 (0.09-0.60)	.003
Seroatopy	0.35 (0.18-0.69)	.003	0.43 (0.19-0.96)	.04	0.33 (0.13-0.83)	.02
Girls						
Atopy	0.23 (0.07-0.80)	.02	0.21 (0.04-1.00)	.05	0.15 (0.02-0.90)	.04
Seroatopy	0.45 (0.17-1.20)	.11	0.62 (0.20-1.96)	.42	0.54 (0.14-2.08)	.37
Boys						
Atopy	0.44 (0.19-1.01)	.05	0.37 (0.13-1.05)	.06	0.23 (0.07-0.79)	.02
Seroatopy	0.29 (0.11-0.77)	.01	0.30 (0.09-0.96)	.04	0.21 (0.06-0.79)	.02

*OR indicates odds ratio; CI, confidence interval.
 †Odds ratio and 95% CI with reference to no dog or cat exposure in the first year of life adjusted for cord serum IgE concentration, total dust mite allergen (Der f 1 + Der p 1) in child's bedroom at age 2 years, child's sex, older siblings, parental smoking, and parental history of asthma.
 ‡Odds ratio and 95% CI adjusted for variables in model 1 plus dog and cat exposure at age 6 to 7 years.

factors for allergic sensitization or that could have been associated with pet ownership, including cord serum IgE concentration, house dust mite exposure, older siblings, parental smoking, and parental history of asthma.^{4,37-42}

Other studies have also reported lower prevalences of allergic sensitization or symptoms related to allergic diseases in association with early exposure to dogs and cats,^{13,15,16,43,44} but a systematic review of the literature concerning this question concluded that previous exposure to dogs and cats increased the risk of asthma and wheezing in children older than 6 years.⁴⁵ The conclusions of this systematic review differ from the results of 2 large prospective birth cohort studies.^{43,44} Nafstad et al⁴³ found that after using logistic regression to adjust for potential confounders, being exposed to pets in early life reduced the risk of asthma (OR, 0.7; 95% CI, 0.5-1.1) and allergic rhinitis (OR, 0.6; 95% CI, 0.4-1.0) in a birth cohort of 2531 children followed to age 4 years. In a birth cohort of 1246 children in Arizona followed up to age 13 years, Remes et al⁴⁴ reported that children who had 1 or more dogs in the home at birth were significantly less likely to develop frequent wheeze than children without early dog exposure, but neither early exposure to dogs or to cats was associated with skin prick test positivity or total serum IgE concentrations. Remes et al did not find a difference between children exposed to 1 dog compared with those exposed to 2 or more dogs. They also found that the inverse relationship between dog exposure and frequent wheeze was predominantly among children without a parental history of asthma. Reasons for the differences in allergic sensitization outcomes between our study and the study by Remes et al are not clear, but may include differences in climate where the birth cohorts were located and differences in keeping pets inside the home.

In a recent cross-sectional study in children by Platts-Mills et al,¹⁸ and also in a subsequent study in adults,⁴⁶ a bell-shaped dose-response relationship be-

tween cat allergen exposure and cat-specific sensitization was observed. Decreased levels of cat-specific sensitization were associated with both the lowest and the highest cat allergen exposure groups. Platts-Mills and colleagues also found that cat-specific IgG antibody levels increased with increasing cat exposure, and were highest in the highest cat exposure group. They suggested that high levels of cat allergen exposure induced a modified T helper cell type 2 (T_H2) response with production of cat allergen-specific IgG and IgG4 antibodies without allergic sensitization. This interesting hypothesis is not entirely consistent with the data presented in our study because we found that allergen-specific IgE antibodies to dust mites, ragweed, and grass (allergens unrelated to dog and cat) were also less prevalent in children exposed to dogs and cats in the first year of life.

Other researchers have suggested that the protective effect of dogs and cats is not related to allergen exposure but rather to increased exposure to bacterial endotoxin associated with household pets.^{15,47} Endotoxin exposure is hypothesized to shift the developing immune system away from a T_H2-type pattern of response, which favors development of allergic sensitization, toward a T_H1-type response. Studies in animals have shown that concomitant exposure to endotoxin and allergen will prevent allergic sensitization normally induced by the allergen.⁴⁸ Recent studies have shown that endotoxin levels in homes are inversely related to T_H2-type cytokine production by lymphocytes of children residing in the homes and that the presence of household dogs is related to higher levels of indoor endotoxin.^{47,49} Our data are consistent with the hypothesis that exposure to 2 or more dogs or cats, and therefore exposure to higher levels of endotoxin, is associated with a T_H1 pattern of immune response and less allergic sensitization.

There were several associations with dog and cat exposure that were evident for boys but not for girls, including lower total serum IgE concentra-

tions, lower prevalence of methacholine airway responsiveness, and better lung function. These differences in associations between boys and girls are puzzling, but others have also observed differences between boys and girls in factors related to asthma.⁵⁰⁻⁵² Consistent with the pattern of the results of total serum IgE concentrations, methacholine airway responsiveness, and FEV₁ in boys, the prevalence of asthma was also lower in those boys exposed to 2 or more dogs or cats compared with those who were unexposed (5.1% vs 11.8%). This difference was not statistically significant across pet exposure categories; however, only 39 boys were exposed to 2 or more dogs or cats in the first year of life. Assuming prevalences that we found in our cohort, a study designed to detect a statistically significant difference in the prevalence of asthma among boys exposed to 2 or more dogs or cats would have required a final cohort of at least 1327 children followed up to age 6 to 7 years.

An important strength of this study is the prospective design using a population-based cohort of children followed yearly from birth. The prevalences of allergic sensitization, methacholine airway responsiveness, and asthma found in our cohort were similar to those reported by others studying children of similar ages.⁵³⁻⁵⁵ The mean values for total serum IgE were also similar to those reported by others.^{55,56} Animal exposure was ascertained when the child was 1 year old, not years later.^{10,14,15} Assessing animal exposure prior to assessing outcomes reduces concern of misclassification of exposure and recall bias. Information on other factors potentially related to risk of allergic sensitization, most importantly family history, was collected, allowing adjustment for the potential confounding effects of these other variables.⁵⁷ Another strength is the multiple objectively measured outcomes.^{10,14} The association between pet exposure and less allergic sensitization was found with both in vivo (skin prick test reactivity) and in vitro (allergen-specific IgE levels) tests. The per-

sons performing the skin prick tests, allergen-specific IgE tests, spirometry, and methacholine challenges were unaware of study hypotheses at the time the tests were performed, making systematic measurement bias unlikely.

Bronchial hyperresponsiveness is frequently stated to be a major component of asthma that can be objectively measured.⁵⁸⁻⁶⁰ Our findings of reduced methacholine airway responsiveness in boys with exposure to 2 or more dogs or cats suggest that exposure to dogs and cats may be associated with a reduced risk of asthma, at least in boys. While we did not find a statistically significant association for current asthma in this study, the prevalence of asthma in boys exposed to 2 or more dogs or cats was 57% lower than in unexposed boys, a difference that would likely be significant in a larger population.

There are limitations to our study. As with most prospective studies, some children did not complete the entire study. However, we found no important differences between children examined at age 6 to 7 years and those who were not examined. In addition, we could not detect differences in the relationship between dog and cat ownership and parental history of asthma, allergy, or hay fever among those examined and not examined. A second caveat is the limited racial, socioeconomic, and geographic diversity of our study population, suggesting that our conclusions can only be applied to similar populations of white children. Since our follow-up was limited to an average age of 6.7 years, we do not know if the associations we found will persist as the children grow older, but others have found that the association between dog and cat exposure and a lower risk of allergy-related symptoms persisted to age 12 to 13 years.^{15,44} Sample size is another limitation of the study. A larger sample would have allowed more reliable estimates and detailed examinations of the differences between boys and girls and between children with and without parental histories of asthma. A final caveat is that

we did not consider exposure to dogs and cats outside the child's home.

In this prospective study designed to examine multiple potential risk factors for allergic sensitization, we found that exposure to 2 or more dogs or cats in the first year of life was associated with a significantly lower probability of subsequent allergic sensitization to common aeroallergens. Exposure to 2 or more dogs or cats was also associated with significantly lower serum IgE concentration, less methacholine airway responsiveness, and better lung function in boys but not in girls. The association between pet exposure and decreased prevalence of allergic sensitization remained unchanged after adjustment for potentially confounding variables. These findings suggest that exposure to more than 1 dog or cat in the first year of life may reduce a child's risk of allergic disease.

Author Contributions: Study concept and design: Ownby, Johnson.

Acquisition of data: Ownby, Johnson.

Analysis and interpretation of data: Ownby, Johnson, Peterson.

Drafting of the manuscript: Ownby, Johnson, Peterson.

Critical revision of the manuscript for important intellectual content: Ownby, Johnson, Peterson.

Statistical expertise: Peterson.

Obtained funding: Ownby, Johnson.

Administrative, technical, or material support: Ownby, Johnson.

Study supervision: Ownby, Johnson.

Funding/Support: This work was supported by grant AI 24156 from the National Institute of Allergic and Infectious Diseases, by the Fund for Henry Ford Hospital, and by grant PO3ES06639 from the National Institute of Environmental Health Sciences.

REFERENCES

- Mannino DM, Homa DM, Akinbami LJ, Moorman JE, Gwynn C, Redd SC. Surveillance for asthma—United States, 1980-1999. *Mor Mortal Wkly Rep CDC Surveill Summ.* 2002;51:1-13.
- Yunginger JW, Reed CE, O'Connell EJ, Melton LJ III, O'Fallon WM, Silverstein MD. A community-based study of the epidemiology of asthma: incidence rates, 1964-1983. *Am Rev Respir Dis.* 1992;146:888-894.
- Sears MR, Burrows B, Flannery EM, Herbison GP, Holdaway MD. Atopy in childhood, I: gender and allergen related risks for development of hay fever and asthma. *Clin Exp Allergy.* 1993;23:941-948.
- Platts-Mills TA, Vervloet D, Thomas WR, Aalberse RC, Chapman MD. Indoor allergens and asthma: report of the third international workshop. *J Allergy Clin Immunol.* 1997;100:S1-S24.
- Litonjua AA, Sparrow D, Weiss ST, O'Connor GT, Long AA, Ohman JL Jr. Sensitization to cat allergen is associated with asthma in older men and predicts new-onset airway hyperresponsiveness. *Am J Respir Crit Care Med.* 1997;156:23-27.
- Sporik R, Ingram JM, Price W, Sussman JH, Honsinger RW, Platts-Mills TA. Association of asthma with serum IgE and skin test reactivity to allergens among children living at high altitude: tickling the dragon's breath. *Am J Respir Crit Care Med.* 1995;151:1388-1392.
- Von Mutius E. The environmental predictors of allergic disease. *J Allergy Clin Immunol.* 2000;105:9-19.
- Popp W, Rauscher H, Sertl K, Wanke T, Zwick H. Risk factors for sensitization to furred pets. *Allergy.* 1990;45:75-79.
- Steenberg PA, van Amsterdam JGC, Vanderbruel RJ, Vos JG, van Bree L, van Loveren H. Environmental and lifestyle factors may act in concert to increase the prevalence of respiratory allergy including asthma. *Clin Exp Allergy.* 1999;29:1304-1308.
- Suoniemi I, Björkstén F, Haahtela T. Dependence of immediate hypersensitivity in the adolescent period on factors encountered in infancy. *Allergy.* 1981;36:263-268.
- Vanto T, Koivikko A. Dog hypersensitivity in asthmatic children. *Acta Paediatr Scand.* 1983;72:571-575.
- Lindfors A, van Hage-Hamsten M, Rietz H, Wickman M, Nordvall SL. Influence of interaction of environmental risk factors and sensitization in young asthmatic children. *J Allergy Clin Immunol.* 1999;104:755-762.
- Burr ML, Merrett TG, Dunstan FDJ, Maguire MJ. The development of allergy in high-risk children. *Clin Exp Allergy.* 1997;27:1247-1253.
- Braback L, Breborowicz A, Julge K, et al. Risk factors for respiratory symptoms and atopic sensitization in the Baltic area. *Arch Dis Child.* 1995;72:487-493.
- Hesselmar B, Åberg N, Åberg B, Eriksson B, Björkstén B. Does early exposure to cat or dog protect against later allergy development? *Clin Exp Allergy.* 1999;29:611-617.
- Reijonen TM, Kotaniemi-Syrjänen A, Korhonen K, Korppi M. Predictors of asthma three years after hospital admission for wheezing in infancy. *Pediatrics.* 2000;106:1406-1412.
- Roost H-P, Kunzli N, Schindler C, et al. Role of current and childhood exposure to cat and atopic sensitization. *J Allergy Clin Immunol.* 1999;104:941-947.
- Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitization, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet.* 2001;357:752-756.
- Riedler J, Eder W, Oberfeld G, Schreuer M. Austrian children living on a farm have less hay fever, asthma and allergic sensitization. *Clin Exp Allergy.* 2000;30:194-200.
- Ernst P, Cormier Y. Relative scarcity of asthma and atopy among rural adolescents raised on a farm. *Am J Respir Crit Care Med.* 2000;161:1563-1566.
- Ownby DR, Johnson CC, Peterson EL. Maternal smoking does not influence cord serum IgE or IgD concentrations. *J Allergy Clin Immunol.* 1991;88:555-560.
- Johnson CC, Ownby DR, Peterson EL. Parental history of atopic disease and concentration of cord blood IgE. *Clin Exp Allergy.* 1996;26:624-629.
- Ownby DR, McCullough J, Johnson CC, Peterson EL. Evaluation of IgA measurements as a method for detecting maternal blood contamination of cord blood samples. *Pediatr Allergy Immunol.* 1996;7:125-129.
- Joseph CLM, Ownby DR, Peterson EL, Johnson CC. Racial differences in physiologic parameters related to asthma among middle-class children. *Chest.* 2000;117:1336-1344.
- Ownby DR, Johnson CC, Peterson EL. Incidence and prevalence of physician-diagnosed asthma in a suburban population of young adults. *Ann Allergy Asthma Immunol.* 1996;77:304-308.

26. Peterson EL, Johnson CC, Ownby DR. Use of urinary cotinine and questionnaires in the evaluation of infant exposure to tobacco smoke in epidemiologic studies. *J Clin Epidemiol*. 1997;50:917-923.
27. Johnson CC, Peterson EL, Ownby DR. Gender differences in total and allergen-specific immunoglobulin E (IgE) concentrations in a population-based cohort from birth to age four years. *Am J Epidemiol*. 1998;147:1145-1152.
28. Peterson EL, Ownby DR, Kallenbach L, Johnson CC. Evaluation of air and dust sampling schemes for Fel d 1, Der f 1, and Der p 1 allergens in home in the Detroit area. *J Allergy Clin Immunol*. 1999;104:348-355.
29. Ownby DR, Peterson EL, Johnson CC. Factors related to methacholine airway responsiveness in children. *Am J Respir Crit Care Med*. 2000;161:1578-1583.
30. Ownby DR, Johnson CC, Peterson EL. Passive cigarette smoke exposure of infants. *Arch Pediatr Adolesc Med*. 2000;154:1237-1241.
31. Rosenstreich DL, Eggleston PA, Kattan M, et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *N Engl J Med*. 1997;336:1356-1363.
32. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Revised ed. New York, NY: Academic Press; 1977.
33. Everitt BS. *The Analysis of Contingency Tables*. London, England: Chapman & Hall; 1977.
34. Neter J, Wasserman W, Kutner MH. *Applied Statistical Models: Regression, Analysis of Variance, and Experimental Design*. 3rd ed. Boston, Mass: Irwin; 1990.
35. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York, NY: Wiley & Sons; 1989.
36. SAS Institute Inc. *SAS/STAT Users Guide*. Version 8 ed. Cary, NC: SAS Institute Inc; 1999.
37. Bergmann RL, Edenharter G, Bergmann KC, et al. Predictability of early atopy by cord blood-IgE and parental history. *Clin Exp Allergy*. 1997;27:752-760.
38. Kjellman NIM, Croner S. Cord blood IgE determination for allergy prediction: a follow-up to seven years of age in 1,651 children. *Ann Allergy*. 1984;53:167-171.
39. Martinez FD, Antognoni G, Macri F, et al. Parental smoking enhances bronchial responsiveness in nine-year-old children. *Am Rev Respir Dis*. 1988;138:518-523.
40. Stoddard JJ, Miller T. Impact of parental smoking on the prevalence of wheezing respiratory illness in children. *Am J Epidemiol*. 1995;141:96-102.
41. Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (*Der p 1*) and the development of asthma in childhood. *N Engl J Med*. 1990;323:502-507.
42. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med*. 2000;343:538-543.
43. Nafstad P, Magnus P, Gaarder PI, Jaakkola JJK. Exposure to pets and atopy-related diseases in the first 4 years of life. *Allergy*. 2001;56:307-312.
44. Remes ST, Castro-Rodriguez JA, Holberg CJ, Martinez FD, Wright AL. Dog exposure in infancy decreases the subsequent risk of frequent wheeze but not atopy. *J Allergy Clin Immunol*. 2001;108:509-515.
45. Apelberg BJ, Aoki Y, Jaakkola JJK. Systematic review: exposure to pets and risk of asthma and asthma-like symptoms. *J Allergy Clin Immunol*. 2001;107:455-460.
46. Custovic A, Hallam CL, Simpson BM, Craven M, Simpson A, Woodcock A. Decreased prevalence of sensitization to cats with high exposure to cat allergen. *J Allergy Clin Immunol*. 2001;108:537-539.
47. Gereda JE, Leung DYM, Thatayatikom A, et al. Relation between house-dust endotoxin exposure, type 1 T-cell development, and allergen sensitisation in infants at high risk of asthma. *Lancet*. 2000;355:1680-1683.
48. Gold DR, Burge HA, Carey V, Milton DK, Platts-Mills T, Weiss S. Predictors of repeated wheeze in the first year of life: the relative roles of cockroach, birth weight, acute lower respiratory illness, and maternal smoking. *Am J Respir Crit Care Med*. 1999;160:227-236.
49. Park J-H, Gold DR, Spiegelman DL, Burge HA, Milton DK. House dust endotoxin and wheeze in the first year of life. *Am J Respir Crit Care Med*. 2001;163:322-328.
50. Horwood LJ, Fergusson DM, Hons BA, Shannon FT. Social and familial factors in the development of early childhood asthma. *Pediatrics*. 1985;75:859-868.
51. Skobeloff EM, Spivey WH, St Clair SS, Schoffstall JM. The influence of age and sex on asthma admissions. *JAMA*. 1992;268:3437-3440.
52. Osborne ML, Vollmer WM, Linton KLP, Buist AS. Characteristics of patients with asthma within a large HMO A comparison by age and gender. *Am J Respir Crit Care Med*. 1998;157:123-128.
53. Peat JK, Salome CM, Sedgwick CS, Kerrebijn J, Woolcock AJ. A prospective study of bronchial hyperresponsiveness and respiratory symptoms in a population of Australian school children. *Clin Exp Allergy*. 1989;19:299-306.
54. Peat JK, Britton WJ, Salome CM, Woolcock AJ. Bronchial hyperresponsiveness in two populations of Australian schoolchildren. III: effect of exposure to environmental allergens. *Clin Allergy*. 1987;17:291-300.
55. Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. *Pediatrics*. 1994;94:895-901.
56. Backer V, Ulrik CS, Wendelboe D, et al. Distribution of serum IgE in children and adolescents aged 7 to 16 years in Copenhagen, in relation to factors of importance. *Allergy*. 1992;47:484-489.
57. Withers NJ, Low L, Holgate ST, Clough JB. The natural history of respiratory symptoms in a cohort of adolescents. *Am J Respir Crit Care Med*. 1998;158:352-357.
58. Avital A, Noviski N, Bar-Yishay E, Springer C, Levy M, Godfrey S. Nonspecific bronchial reactivity in asthmatic children depends on severity but not on age. *Am Rev Respir Dis*. 1991;144:36-38.
59. Galdès-Sebaldt M, McLaughlin FJ, Levison H. Comparison of cold air, ultrasonic mist, and methacholine inhalations as tests of bronchial reactivity in normal and asthmatic children. *J Pediatr*. 1985;107:526-530.
60. Takeda K, Shibasaki M, Takita H. Relation between bronchial responsiveness to methacholine and levels of IgE antibody against *Dermatophagoides farinae* and serum IgE in asthmatic children. *Clin Exp Allergy*. 1993;23:450-454.