

A Prospective Study of Fel d1 and Der p1 Exposure in Infancy and Childhood Wheezing

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The impact of domestic exposure to cat allergen (Fel d1) and house dust mite (Der p1) on wheezing from birth to the age of 4 years was investigated in a multicenter prospective birth cohort; 1,611 mothers were recruited before delivery in Ashford, England, and Barcelona and Menorca, Spain. Exposures were gathered via dust sample collection at children's home in their first year of life. Families provided complete outcome data (wheezing status in all 4 years) for 1,289 children. Domestic allergen levels varied substantially between centers. Six hundred three (47%) children never wheezed during their first 4 years of life. Der p1 did not correlate with any type of wheezing outcome. Fel d1 significantly increased the risk of wheezing in 3- and 4-year-olds in comparison to 1-year-olds. Distinct risk profiles were found for wheezing at different ages. Multivariate analysis revealed an interaction between Fel d1 and maternal asthma among children who wheeze in Year 4 (relative risk = 2.77; 95% confidence interval = 1.19–6.46). Our data support the idea that several patterns of wheezing with different risk profiles exist among young children. The effect of Fel d1 exposure varied according to age and maternal asthma.

Keywords: allergens cohort; infants; wheezing

European researchers initiated the Asthma Multicenter Infants Cohort Study in response to the following three observations: First, atopy is said to affect up to one in four of all children in Europe. Second, the incidence of asthma in children is about one in seven, and a majority of these have a history of atopy. Third, these proportions are far higher than those recorded 30 years ago.

The link, if one exists, between allergen exposures, sensitization, respiratory symptoms, and asthma remains to be understood, although considerable literature exists regarding allergen exposure and sensitization (1, 2) as well as sensitization and asthma (3, 4). Several studies have demonstrated a correlation between allergen exposure and sensitization to that allergen (1, 5–8). Sensitization increases the risk of wheeze and asthma (6, 7, 9–11). However, allergen exposure early in life has not been linked consistently to a greater incidence of asthma (3, 6, 10–12). Investigations of this topic have been conducted within various age groups, and the appropriate time for the ascertainment of exposure is unknown.

The purpose of this study was to examine the exposure–response relationships between common domestic aeroallergens

(Der p1, Fel d1) and wheezing in early childhood in a population not chosen on the basis of allergic history and the modification of these relationships, if observed, by respiratory irritants (nitrogen dioxide [NO₂] and cigarette smoke) (1) and susceptibility (parental allergy or asthma) (13). Three-month postnatal exposure to cat and dust mite allergen and wheezing from birth to the age of 4 years are the relationships of primary interest. Analysis of exposures was limited to the first year, as this period has been hypothesized to be the most important in the development of allergic sensitization and asthma (14).

METHODS

The Asthma Multicenter Infants Cohort Study protocol has been reported in detail elsewhere (15); 1,785 pregnant women in Ashford, England, and Barcelona and Menorca, Spain, were invited to enroll their children in a prospective cohort study. All cohorts followed the same basic research protocol. Two of the cohorts (Ashford and Menorca) were population-based (including all women presenting for prenatal care in Ashford during 1995–1996 and in Menorca over 12 months starting in mid-1997). The third cohort was based in a hospital clinic in Barcelona. (Mothers were enrolled during last trimester of pregnancy in the obstetric department of Hospital del Mar during the years 1996–1997. Mothers were residents without plans to move, literate, and possessed telephones.) One thousand six hundred eleven children were subsequently enrolled (642, 487, and 482 in Ashford, Barcelona, and Menorca, respectively); 1,289 (613, 208, and 468, respectively) provided complete outcome data.

The outcome of interest was the presence or absence of wheeze each year described on annual interviewer-led questionnaires as “whistling or wheezing from the chest, but not noisy breathing from the nose.” One or more episodes of wheezing over 12 months constituted wheezing during a given year.

Exposure information was derived from questionnaires, by dust collection (16, 17), and by NO₂ measurement in the home (18). Collection of dust and NO₂ was done in the same standard way in the three centers, and analyses were performed in a single laboratory (Imperial College, London, UK). Parents were invited to undergo skin prick testing to determine their atopic status (13). A wheal of 3 mm or greater (mean of perpendicular measures) to at least one allergen (house dust mite, cat fur, or grass pollen) in the presence of a positive histamine control and a negative uncoated control constituted a positive atopy. As only 60% of fathers underwent skin prick testing, maternal atopy alone was used as a surrogate for the allergic susceptibility of the child.

The following variables came from the first year questionnaire: number of siblings, pet ownership, maternal smoking, self-reported parental asthma, antibiotic use, and lower respiratory tract infection. The UK Registrar General's 1990 classification was used to determine social class according to father's employment dichotomized as manual or nonmanual. Lower respiratory tract infection was defined as a positive response to this question: “Has a doctor ever said that your [child] has had a chest infection.” Mothers reported duration of exclusive breastfeeding. The children's birth weight and sex were obtained from information collected at birth.

Analyses of house dust mite (Der p1) and cat allergen (Fel d1) and NO₂ concentrations employed log-transformed data and geometric means because of their skewed distributions.

Analysis of the relationship between exposures and wheeze was

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conducted using two distinct types of regression models: generalized estimated equation (GEE) and random effects model (REM). In a first step, both models were used to calculate the significance of each exposure on the risk of wheezing in each year adjusting for wheezing status in all previous years, incorporating an interaction term between year and the exposure variable and adjusted for site. GEE models included only children with complete outcome data, wheezing status in all 4 years. REM models included subjects with missing outcome data (19). In a second step, adjustment for confounding variables and test for interactions were carried using both GEE and REM. GEE results were displayed in preference to those from REM models, as coefficients of REM models are difficult to interpret. All variables significantly related with wheezing in the first step ($p < 0.2$) were included in the second step and only retained if they had an association with (< 0.1) or modified the coefficient of Fel d1 by 5%. The use of GEE and REM models allowed an inspection of the variance of the effects of exposures on wheeze in each year controlling for prior wheezing history (20).

Analyses were conducted using Splus2000 (MathSoft, Seattle, WA). Statistical tests of hypotheses were two tailed with significance set at $p < 0.05$.

RESULTS

Figure 1 provides outcome data by center. In Ashford, the incidence of wheeze decreased with each additional year. Barcelona repeated this trend in the first 3 years and then reported almost as much wheeze in the fourth year (27%) as in the first (28%). In Menorca there was more wheeze in Year 2 (29%) than Year 1 (24%), but the incidence declined steadily thereafter.

Table 1 provides pertinent demographic, health, and environmental data on the children of this cohort and their families. Environmental exposures varied significantly by site. Ashford had a significantly higher median of Fel d1, Menorca of Der p1, and Barcelona of NO₂ than either of the other two centers, respectively. This table also provides information on children with missing outcome data. Barcelona, the site of the only hospital-

based cohort, accounted for 87% of children with missing outcome data. In Barcelona, the exposure profile of children with incomplete outcome data differed significantly from that of the children with complete outcome data in domestic Fel d1 level (0.47 [units] vs. 0.38 [units], respectively), percentage of households with cats (13% vs. 9%, respectively), percentage of mothers smoking during the first year (37% vs. 44%, respectively), and the percentage of children receiving antibiotics during the first year (57% vs. 63%, respectively).

Levels of Der p1 were higher in the homes of nonwheezers in comparison to wheezers, particularly at the age of 4 years (Figure 2A). In Figure 2B, there is a trend of higher levels of cat allergen in the homes of wheezers in comparison to nonwheezers, particularly at ages 3 and 4 years, which can be seen in all percentiles.

Table 2 presents the results of exposures and variables of interest with wheezing at each year. House dust mite did not significantly impact wheezing. The effect of Fel d1 varied according to age at time of wheeze. The relative risk of wheeze at age 1 was less than 1.0. In contrast, Fel d1 greater than the community median increased the risk of wheeze in Years 3 and 4 in both GEE models and REM models, and the difference in comparison to Year 1 was significant. Similar findings were obtained when Fel d1 was treated as a continuous log variable rather than dichotomous one. The presence of older siblings significantly augmented the risk of wheeze, except for having one sibling at ages 3 or 4 years. In contrast, maternal asthma increased the risk at older ages only. Maternal atopy was not related to wheezing outcome, except at the age of 4 years. Cat ownership during the first year of life did not significantly effect wheezing. Maternal smoking during the first year of life significantly increased the risk wheeze at all ages. Breastfeeding provided significant protection against wheeze at all ages. Lower respiratory tract infections and the use of antibiotics during the

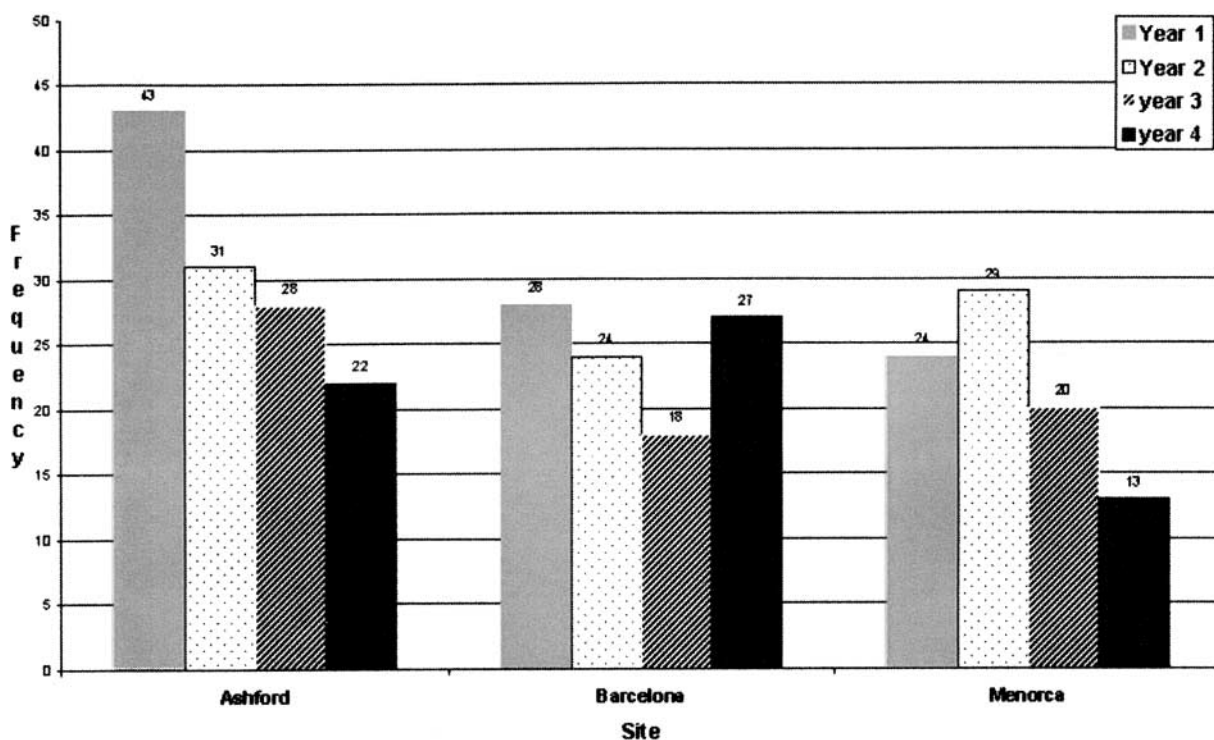


Figure 1. Annual incidence (per 100 infants) of wheeze (irrespective in prior years).

TABLE 1. FIRST-YEAR EXPOSURE PROFILE BY SITE

	Ashford (n = 642)	Barcelona (n = 487)	Menorca (n = 482)	Overall (n = 1,611)	Incomplete Outcome Data [‡] (n = 322)
Fel d1, $\mu\text{g/g}^*$	3.16	0.38	0.43	0.97	0.47
Der p1, $\mu\text{g/g}^*$	1.36	0.78	9.04	2.19	0.83
NO ₂ , ppb [*]	5.61	45.45	10.56	11.46	36.0
Family size at birth					
No siblings	42%	50%	49%	46%	51%
One older sibling	37%	37%	38%	37%	35%
Two older siblings	15%	9%	11%	12%	10%
Three or more older siblings	6%	4%	2%	4%	4%
Maternal Asthma	14%	8%	7%	10%	7%
Maternal Atopy	34%	20%	36%	30%	21%
Owned cat	34%	9%	2%	17%	13%
Maternal Smoking	22%	44%	35%	32%	37%
Breastfed	62%	79%	82%	73%	78%
Received antibiotics	78%	63%	45%	64%	57%
LRTI	39%	28%	45%	38%	31%
Birth weight $\geq 2,500$ g	93%	92%	93%	93%	89%
Male	53%	53%	51%	53%	54%
Father's work nonmanual [†]	43%	40%	36%	40%	40%

Definition of abbreviations: LRTI = lower respiratory tract infection; NO₂ = nitrogen dioxide.

* n (geometric mean).

[†] Manual = skilled (manual), partly skilled, unskilled; nonmanual = professional, managerial and technical, skilled (nonmanual).

[‡] By site: Ashford 29 (9%), Barcelona 279 (87%), and Menorca 14 (4%).

first year increased the risk wheezing, an effect which decreased by age. Male sex significantly augmented the risk of wheeze at all years, and the family's social class did not affect wheeze.

Household Fel d1 higher than the community mean significantly increased the risk of wheeze at the ages of 3 and 4 years, while adjusting for all significant exposures (Table 3). The risk of high levels of Fel d1 at the age of 4 years was seen among the children of mothers with asthma but not among the children of mothers without asthma. This interaction between cat allergen and maternal asthma was seen among 4-year-olds using GEE (p for interaction = 0.018). REM analysis confirmed the interaction at 4-year-olds (p for interaction = 0.018). This interaction also occurred in a model without adjustment for other exposures (p < 0.01). No interaction was seen between either Der p1 or Fel d1 and NO₂, maternal smoking, or maternal atopy.

We found no evidence of exposure avoidance. Neither maternal nor paternal atopy or asthma was associated with less cat ownership or lower levels of Fel d1 or Der p1 (data not shown). The association between Fel d1 and wheeze at the age of 4 years persisted whether or not the child's family owned a cat during their first year.

DISCUSSION

These findings inform the discussion of the impact of domestic aeroallergens on wheeze. In this cohort, the house dust mite was consistently unrelated to any wheezing phenotype, a finding that both supports and contradicts previous findings. The relationship between cat allergen and wheeze varied according to age. A high level of domestic cat allergen in early life appears to protect against early wheeze while increasing the risk of wheeze after the first 2 years, a risk magnified if the child's mother has asthma. Although domestic aeroallergen levels were measured only once in this cohort, there are data to suggest that levels remain consistent over time within households (21).

House dust mite did not impact incidence of wheeze at any age in this cohort, not even when previously proposed high exposure cut-offs were assessed (data not shown). Two similar, previous studies focused on the impact of domestic Der p1 on

the development of asthma up to age 7 years and neither detected a relationship between Der p1 level and the respiratory outcomes wheeze, bronchial hyper-responsiveness, or asthma (3, 11). In comparison to our cohort, one study reported lower median Der p1 levels, whereas the other reported levels consistent with ours. Both authors concluded that exposure to Der p1 increased the risk of sensitization, but not the diagnosis of asthma. In contrast, Sporik and colleagues reported that in a cohort of children with a family history of allergic disease domestic Der p1 greater than 10 $\mu\text{g/g}$ of dust in infancy was associated with active asthma and medicated asthma, but not wheeze, at age 11 years, but only weakly correlated with these outcomes at the age of 5 years (5).

High levels of domestic cat allergen increase the risk of wheeze in 3 and 4 year olds. Similarly, Gold and colleagues did not find Fel d1 to be a risk factor for wheeze during the first year of life (9). Lindfors and colleagues did not show that cat exposure led to an increased risk of developing asthma (22). Although Ingram and colleagues also found that greater cat allergen exposure increased the risk of sensitization and sensitization was associated with asthma, greater cat allergen exposure was not associated with asthma (6). In contrast, Perzanowski and colleagues found living with a cat to protect against sensitization and the development of asthma in Swedish children (23). Cat ownership did not affect our findings regarding cat allergen and wheeze. Whether cat allergen is a surrogate for another biologically relevant exposure or is in fact causally related to wheezing outcomes cannot be determined using our data. It may be that high levels of cat allergen induce tolerance, which protects against wheeze in very young children, but provoke symptoms in older children predisposed to wheeze for various reasons.

An interaction exists between cat allergen and maternal asthma in this cohort. The detrimental impact of cat allergen is significantly higher among children of mothers with asthma. This finding coincides with a study of 1- to 5-year-old American children of at least one atopic parent among whom it was noted that household exposure to greater than 8 $\mu\text{g/g}$ of cat allergen at 2–3 months was associated with a decreased risk of wheezing

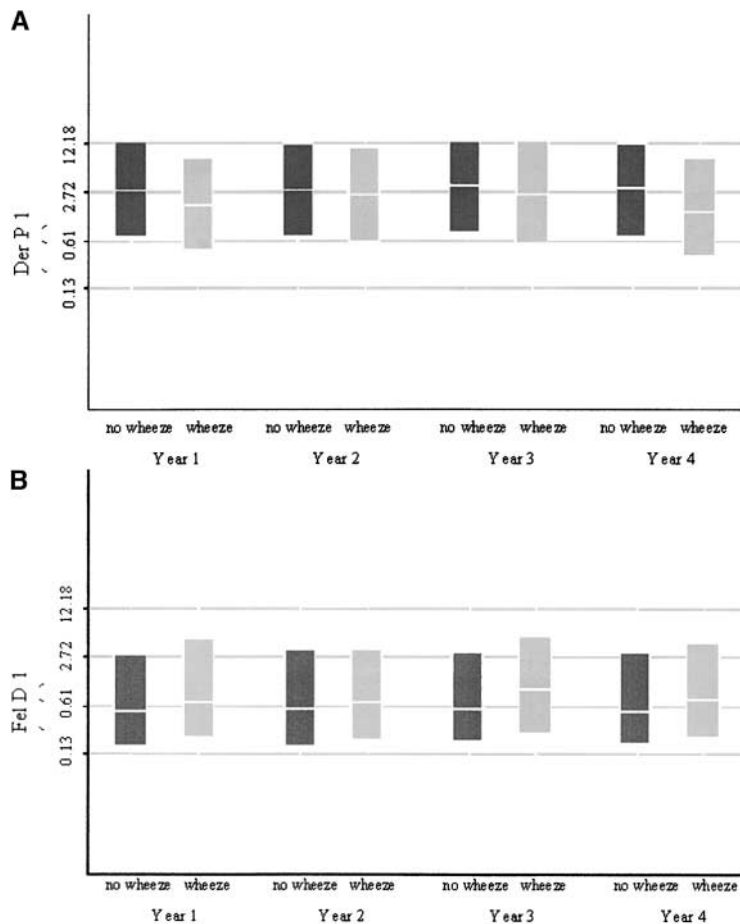


Figure 2. (A) Der p1, median and interquartile range, according to wheeze outcome and year. (B) Fel d1, median and inter-quartile range, according to wheeze outcome and year.

from the age of 1 to 5 years unless the child's mother had asthma, in which case the child had an increased risk of wheeze at or beyond the age of 3 years (13).

This modification of the effect of cat allergen on wheeze was seen with maternal, but not paternal, asthma as in the study by Celedon and coworkers (13). In a retrospective population-based study of children up to the age of 6–7 years, Rusconi and colleagues also found that the odds ratios for maternal asthma were greater than that for paternal asthma (24). Other studies report similar findings in cohorts of high-risk children (25, 26). Asthma is genetically heterogeneous with a polygenic inheritance that is reported to be end-organ specific, which would help explain why the influence of parental asthma on wheeze in our cohort is so strong, whereas no correlation is seen between parental atopy and wheeze (27).

Greater cat allergen increases the risk of wheeze at later ages compared with wheeze during Year 1. This may be due to the low threshold for wheeze as a response to lower respiratory tract infections in that year, a threshold that rises as the child grows. The effect of cat allergen on wheeze among older children did not vary by first year lower respiratory tract infection (data not shown). As skin prick testing had not been performed on these children at the time of analysis, the proposal that early allergen exposure leads to sensitization and that postsensitization exposure to allergens results in asthma was not addressed (28). It is possible that high domestic Fel d1 exposure was simply a surrogate of sensitization. If that were the case, it is interesting that elevated Der p1 and Fel d1 would not elicit a similar response. Particle size and behavior of the allergens might be an explanation. Both allergens likely represent exposure to a broad range of microbes, and perhaps Fel d1 is a more accurate marker

for an unrecognized social or environmental exposure (i.e., endotoxins, bacterial antigens, or feces of domestic pets).

Outcome definition in this cohort was a challenge. Physicians diagnose asthma with more certainty after children reach the age of 6 or 7 years (29). Because these children had been followed to the age of 4 years, respiratory symptoms seemed a more appropriate outcome than diagnosis of asthma. Wheezing was chosen as the outcome of interest after factor analysis showed that wheezing, cough, and chestiness grouped together at each age. Because childhood wheeze predicts future asthma better as the age at wheeze increases (30) and because their risk profile matches that of those with asthma best, wheezing at older ages in this cohort seem most likely to proceed to a diagnosis of asthma.

The primary limitation of this study was the measurement of the main exposure. Aeroallergens Fel d1 and Der p1 were measured only once and only in the home. We do not know whether this was an accurate approximation of the children's exposure. The importance of nondomestic exposure to aeroallergens has been documented. Among German school children, students from homes without cats had twice the risk of sensitization to cats if the proportion of schoolmates with cats was higher, demonstrating that important allergen exposure may occur outside the home (daycare, the homes of relatives or friends) (31). Reported maternal smoking might have been a suboptimal measure of these children's passive smoking exposure. There is likely variation in the smoking habits of other close contacts, in home ventilation, and in the location of parental smoking (indoors versus out as well as distance from the child) (32). However, urinary cotinine substudies in Ashford and Barcelona assuages

TABLE 2. ASSOCIATION OF ALLERGEN LEVELS AND VARIABLES OF INTEREST WITH WHEEZING AT EACH YEAR

Exposure	Wheezing by Age Adjusted for Autocorrelation			
	Wheezing at Age 1	Wheezing at Age 2	Wheezing at Age 3	Wheezing at Age 4
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Fel d1 > median [†]	0.82 (0.66–1.03)	0.94 (0.75–1.18)	1.24 (0.98–1.57)	1.09 (0.83–1.41)
Fel d1, per each log µg/g*	1.00 (0.95–1.05)	0.97 (0.92–1.02)	1.01 (0.96–1.06)	1.01 (0.96–1.07)
Der p1 > median [†]	0.85 (0.68–1.06)	0.80 (0.64–1.01)	1.01 (0.80–1.28)	0.90 (0.69–1.17)
Der p1, per each log µg/g	0.94 (0.89–1.00)	0.98 (0.92–1.05)	1.00 (0.94–1.06)	0.92 (0.86–0.98)
NO ₂ > median [†]	1.07 (0.85–1.33)	0.85 (0.68–1.07)	0.80 (0.63–1.02)	0.99 (0.76–1.29)
Older siblings*				
1	1.26 (1.12–1.42)	1.04 (0.92–1.17)	0.94 (0.83–1.07)	0.98 (0.85–1.12)
> 1	1.14 (1.04–1.25)	1.10 (1.00–1.21)	1.11 (1.01–1.23)	1.10 (0.99–1.22)
Mother with asthma*	1.20 (1.02–1.42)	1.36 (1.15–1.61)	1.60 (1.36–1.89)	1.59 (1.33–1.89)
Mother with atopy*	1.00 (0.89–1.12)	1.05 (0.93–1.19)	1.10 (0.98–1.25)	1.14 (1.00–1.30)
Owned cat	1.11 (0.96–1.29)	0.90 (0.77–1.05)	1.12 (0.97–1.31)	1.05 (0.89–1.25)
Maternal smoking	1.17 (1.04–1.32)	1.36 (1.21–1.54)	1.35 (1.19–1.53)	1.24 (1.08–1.42)
Breastfed	0.80 (0.71–0.90)	0.93 (0.82–1.05)	0.80 (0.70–0.90)	0.86 (0.75–0.99)
Received antibiotics*	1.77 (1.56–2.02)	1.13 (1.00–1.28)	1.26 (1.10–1.43)	1.17 (1.02–1.36)
Lower respiratory tract infection*	2.73 (2.42–3.08)	1.56 (1.39–1.76)	1.38 (1.22–1.56)	1.29 (1.13–1.47)
Birth weight ≥ 2,500 g	0.99 (0.80–1.22)	0.95 (0.76–1.19)	0.77 (0.62–0.95)	0.80 (0.64–1.00)
Male	1.22 (1.09–1.35)	1.15 (1.03–1.28)	1.19 (1.06–1.34)	1.22 (1.08–1.39)
Father's work nonmanual	0.94 (0.84–1.05)	1.00 (0.89–1.13)	0.94 (0.83–1.07)	0.93 (0.81–1.07)
Site				
Barcelona	0.72 (0.63–0.82)	0.85 (0.73–0.99)	0.80 (0.67–0.95)	1.11 (0.96–1.29)
Menorca	0.84 (0.78–0.91)	1.03 (0.95–1.11)	0.93 (0.86–1.02)	0.77 (0.70–0.85)

Definition of abbreviations: CI = confidence interval; RR = relative risk.

Each line derives from a model including the exposure variable, an interaction between exposure and year and site using generalized estimated equation.

* p for interaction between exposure and year < 0.05.

[†] Median according to center, not including site in the model.

concern regarding maternal reporting (18, 33). Because the vast majority of mothers in this cohort who smoked before and/or during pregnancy continued to do so afterward, we were not able to compare the effects of *in utero* versus postnatal exposure to maternal smoking. Although the number of children lost to follow-up in Barcelona is a limitation, excluding Barcelona from the analysis does not change any of the findings.

The design of this study is one of its greatest strengths. Much research on wheezing and asthma has been conducted in high-risk populations, whereas our participants constitute a general population sample, enhancing the generalizability of our findings. Prospective questioning of parents regarding the health and environments of their children should have diminished the

risk of recall bias. Standard symptom surveys, the source of our outcome data, have been reported to serve as a better surrogate measure of clinical asthma than bronchial hyperresponsiveness (28). Consideration of first-year exposures only should have diminished the previously observed risk of selective avoidance affecting the relationship between exposures (34).

In conclusion, our findings indicate that the aeroallergens Der p1 and Fel d1 play little role in the development of wheeze in the first 4 years of life. House dust mite allergen exposures did not show any association, and the small effect of Fel d1 varied according to age and maternal asthma. These relationships were not modified by maternal atopic status. The mechanism for the observed interactions between susceptibility factors and environ-

TABLE 3. ADJUSTED ASSOCIATION* (RELATIVE RISK AND 95% CONFIDENCE INTERVAL) BETWEEN CAT ALLERGEN AND WHEEZING

Exposure	Wheezing by Age Adjusted for Autocorrelation			
	Wheezing at Age 1	Wheezing at Age 2	Wheezing at Age 3	Wheezing at Age 4
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Fel d1 > median [†]	0.86 (0.69–1.08)	1.02 (0.79–1.31)	1.41 (1.08–1.83)	
If mother does not have asthma				1.16 (0.80–1.67)
If mother has asthma				2.77 (1.19–6.46) [‡]
Mother with asthma	1.29 (1.08–1.54)	1.36 (1.13–1.65)	1.78 (1.47–2.16)	1.70 (1.38–2.09)

For definition of abbreviations see Table 2.

* RRs for Fel d1 and maternal asthma were estimated in a multivariate model using generalized estimated equation, including interaction between Fel d1, maternal asthma, and year, in addition to the rest of significant exposures: older siblings, maternal smoking, breastfed, lower respiratory tract infections, and sex that were modeled constant for all of the years. RRs for the rest of exposures in the model were one older child = 0.97 (0.87–1.06), two or more older children = 1.11 (1.02–1.19), maternal smoking = 1.13 (1.03–1.25), breastfed = 0.85 (0.80–0.97), lower respiratory tract infection = 1.65 (1.51–1.80), and male sex = 1.22 (1.11–1.33).

[†] Median according to center.

[‡] p for interaction between Fel d1 and maternal asthma in year 4 = 0.018.

mental levels remains to be elucidated, and future data concerning these children's atopic status will be illuminating. It remains important to focus on readily modifiable risk factors of childhood wheeze, and in this respect, our findings highlight the harm posed to children's respiratory health by exposure to parental smoke. We emphasize the importance of a smoke-free environment for the benefit of all children.

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