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Specific Patterns of Allergic Sensitization in Early Childhood and Asthma & Rhinitis Risk

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Abstract

BACKGROUND—Specific patterns of allergic sensitization as well as quantification of the *in vitro* IgE response in early life may provide relevant clinical insight into future rhinitis and asthma risk.

OBJECTIVE—To define relationships among established sensitization to particular aeroallergens, quantitative analyses of allergen-specific IgE levels, pet exposure and sensitization, and asthma and rhinitis risk.

METHODS—Children at high-risk for the development of asthma and allergic diseases were enrolled at birth into the Childhood Origins of ASThma (COAST) study. Allergen-specific IgE was assessed at ages 1, 3, 6, and 9 years by fluoroenzyme immunoassay (Unicap® 100, Pharmacia Diagnostics). Current asthma and rhinitis were diagnosed at age 6 and 8 years.

RESULTS—Sensitization to dog was strongly associated with increased asthma risk ($p < 0.0001$). Sensitization to perennial compared to seasonal allergens was more strongly associated with asthma risk, while sensitization to seasonal allergens was more closely associated with rhinitis risk. Increased levels of specific IgE to perennial allergens were associated with an increased asthma risk ($p = 0.05$), while any detectable level of IgE to seasonal allergens was associated with increased rhinitis risk ($p = 0.0009$). While dog and cat sensitization were both independently associated with increased asthma and rhinitis risk, dog exposure at birth was associated with a reduced risk of asthma, regardless of dog sensitization status during the first 6 years of life ($p = 0.05$).

CONCLUSIONS & CLINICAL RELEVANCE—Analyzing specific patterns of an individual's allergic sensitization profile reveals additional relevant associations with asthma and rhinitis risk as opposed to the information gained from characterizing an individual as "atopic" by the presence of any demonstrable sensitization alone. Further, protective mechanisms of dog exposure with regards to asthma risk appear to be unrelated to the prevention of sensitization.

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Keywords

asthma; rhinitis; children; IgE; allergic sensitization; pet exposure

INTRODUCTION

Atopy, defined as the genetic predisposition to develop specific IgE to common allergens, is widely accepted as a major risk factor for developing asthma later in life [1]. Recently, it has been suggested that viewing allergic sensitization as a simple dichotomous variable may be an oversimplification that fails to entirely capture its underlying associations with disease [2]. This redefined view of atopy suggests that multiple atopic phenotypes may differ greatly with regards to their relationship with asthma. As such, it may not simply be the presence or absence of allergic sensitization, but rather the specific pattern of the response (age at onset and development, as well as the type and number of specific allergens involved) that plays a role in the development of asthma [3].

Multiple studies have reported significant associations between sensitization to inhalant aeroallergens and asthma development [4-8], and Custovic and colleagues have additionally shown a quantitative relationship between specific serum IgE levels to common inhalant allergens and the presence and persistence of childhood wheezing and reduced lung function [2]. This concept has also been extended to the development of rhinitis in a study conducted by the same group, which suggested that progressively increasing specific IgE to grass pollen was associated with a significantly greater risk of current rhinitis at 5 years of age [9]. Similarly, other studies have reported that sensitization to specific seasonal allergens such as grass and birch pollen significantly increases the association with rhinitis risk [4, 10, 11].

With specific patterns of allergic sensitization being shown to have important implications in asthma and rhinitis risk, it is also logical to examine the effects of exposure to these allergens on the subsequent risk of developing asthma and rhinitis. A controversial topic regarding exposure and allergy is the impact of domestic pet exposure, which has led to conflicting recommendations concerning pet avoidance [12]. We have previously reported that dog exposure at birth was associated with a reduced risk of wheezing in the third year of life [13]. Two other birth cohort studies have observed similar findings [14, 15], yet others have not [16-19]. Additionally, findings assessing the influence of exposure to dog on the development of allergic rhinitis have been inconsistent [18, 19]. Interestingly, multiple birth cohort studies have reported that dog ownership seems to have a protective effect on the development of sensitization to mixed aeroallergens, especially mixed outdoor aeroallergens [15, 16, 18, 20]. With regards to cat exposure, the effect on asthma and rhinitis development is even less clear, as a majority of birth cohort studies have found no association between cat exposure in early life and the development of wheezing symptoms [12].

Based on these findings, we assessed the relationships between the development of asthma and rhinitis and the following characteristics of atopy: (1) the presence or absence of sensitization to specific aeroallergens, (2) the degree of aeroallergen sensitization by quantitative analysis of specific serum IgE antibody levels, and (3) patterns of pet exposure and sensitization.

METHODS

Study Population

289 newborns at high-risk for the development of asthma and allergic disease were recruited from November 1998 through May 2000 into the Childhood Origins of ASThma (COAST)

study. Details of the study population and design have been described previously [21]. To qualify for the study, at least 1 parent was required to have respiratory allergies (defined as one or more positive aeroallergen skin tests) and/or a history of physician-diagnosed asthma. Of these children, 285 (98.6%) were followed prospectively for at least 1 year, 275 (95.2%) were followed through 3 years, 259 (90.9%) were followed through 6 years, and 238 were followed through 9 years (82.4%). Informed consent was obtained from the parents, and the Human Subjects Committee at the University of Wisconsin-Madison approved the study (IRB approval number H-2007-0044).

Measuring Allergen-Specific IgE

Peripheral blood samples were collected from the children annually. Allergen-specific IgE was measured in serum by fluoroenzyme immunoassay (FEIA) (UniCAP® 100, Pharmacia Diagnostics AB, Uppsala, Sweden) as previously described [22]. Serum concentrations of specific IgE antibodies for five common inhalant allergens (Dermatophagoides farinae, Dermatophagoides pteronyssinus, cat, dog, and *Alternaria alternata*) were determined at ages 1, 3, 6, and 9 years. Additionally, allergen-specific IgE to ragweed, silver birch, timothy grass and cockroach were measured at ages 6 and 9 years. The detection limit of the assay with regards to specific IgE was 0.35 kU_A/L, and a positive test was defined as ≥0.35 kU_A/L.

Clinical Definitions

Using a previously published clinical definition [23], current asthma was diagnosed at 6 and 8 years of age based on the documented presence of one or more of the following during the previous year: (1) physician diagnosis of asthma, (2) use of albuterol for coughing or wheezing episodes (prescribed by physician), (3) use of a daily controller medication, (4) use of a step-up plan including use of albuterol or short-term use of inhaled corticosteroids during illness, and (5) use of prednisone for asthma exacerbation. Rhinitis was defined as routinely or seasonally having frequent sneezes and/or itchy/runny nose, and was ascertained by parental report on historical questionnaires as reported previously [24]. The presence or absence of a dog or cat at home was determined by questionnaires on a yearly basis as previously described [13].

Statistical Analysis

Dichotomous outcomes of allergic sensitization were summarized using rates within the COAST cohort. Relationships between asthma, rhinitis, and allergic sensitization were evaluated using logistic regression models. These relationships were summarized using odds ratios (OR) with 95% confidence intervals (CI). To assess whether the level of specific IgE response beyond detectability was associated with asthma or rhinitis risk, generalized additive models (GAM) were fit with a covariate for detectability and a smooth term covariate for specific IgE quantity. Both asthma and rhinitis and their relationships with pet ownership and sensitization to pets were examined using multivariate logistic regression models with pet ownership and sensitization as covariates. For all statistical analyses, a two-sided p-value of < 0.05 was regarded as statistically significant.

RESULTS

Study Population

Of the 289 children originally enrolled in the COAST study, 259 were followed to at least 6 years of age and had aeroallergen specific IgE measured by FEIA at least once during this time period. At 6 years of age, 73 of 259 (28%) children had current asthma, 116 of 252 (46%) had current rhinitis, and 41 of 252 (16%) had both current asthma and rhinitis. There

was no participation bias for obtaining *in vitro* IgE measurements at 6 years of age with regards to gender, older siblings, parental asthma or allergies, or current asthma at 6 years of age. There was a slightly higher rate of *in vitro* IgE measurements at 6 years of age in children with current rhinitis ($p = 0.03$).

Timing and Rates of Sensitization

An analysis of the incidence of IgE sensitization was completed to track the longitudinal trends of allergic sensitization to specific aeroallergens throughout early childhood (Table 1). The prevalence of aeroallergen sensitization rose from 13.5% at 1 year of age to 53% at 9 years of age (Table 1). Mono-sensitization was more common than poly-sensitization at age 1 year; however, at ages 3 years and beyond, poly-sensitization was far more common than mono-sensitization (Table 1).

Pets (dog and cat) were the most common allergens infants were sensitized to by age 1 year. Rates of sensitization to dog and cat steadily increased to age 9 years (Table 1). Sensitization rates for both species of dust mite showed similar upward trends as age increased: *D. pteronyssinus* had a sensitization rate of 2.7% at 1 year and increased to 20.7% by 9 years of age, while *D. farinae* had a sensitization rate of 2.3% at year 1 that increased to 20.1% by 9 years of age.

Of all tested allergens, sensitization to *A. alternata* showed the largest increase between 1 and 9 years of age. At 1 year, only 2.3% of children were sensitized, but this number grew dramatically to a prevalence rate of 25.9% by 6 years of age and 32% by 9 years of age. In contrast, cockroach sensitization was less common in the COAST cohort. Prevalence rates remained rather low at both 6 years (5%) and 9 years (5.3%). Of seasonal allergens, sensitization to ragweed was the most common, with a prevalence of 17.9% at 6 years of age and 23.1% at 9 years of age. Silver birch and timothy grass showed similar increases in prevalence from age 6 years to age 9 years (Table 1).

Associations between allergen-specific sensitization and asthma

To investigate the relationships between allergen-specific sensitization and asthma development, we compared allergen-specific serum IgE concentrations at 1, 3, and 6 years with the presence of asthma at age 6 years (Fig. 1). Of all allergens tested, sensitization to dog consistently had the strongest association with asthma development. Allergen-specific IgE to dog and cat at 1 year were the only aeroallergens significantly associated with asthma risk [(dog: OR, 7.6; 95% CI, 2.3, 25.1), (cat: OR, 5.9; 95% CI, 1.9, 17.9)] (Fig. 1A). At 3 years of age, all perennial allergens tested were significantly associated with asthma at age 6 years, while dog sensitization (OR, 9.4; 95% CI, 3.7, 23.7) maintained the strongest association with future asthma risk, followed by cat (OR, 3.8; 95% CI, 1.8, 8.4), DM (OR, 2.9; 95% CI, 1.2, 7.0), and *A. alternata* (OR, 2.8; 95% CI, 1.2, 6.1) (Fig. 1B). Similarly, at 6 years of age, sensitization to any perennial allergen was significantly associated with concurrent asthma. The strongest association was sensitization to dog (OR, 9.2; 95% CI, 4.1, 20.7), followed by cat (OR, 4.4; 95% CI, 1.9, 10.1), cockroach (OR, 4.2; 95% CI, 1.1, 15.6), DM (OR, 2.9; 95% CI, 1.4, 6.1) and *A. alternata* (OR, 2.5; 95% CI, 1.3, 4.8) (Fig. 1C).

Relationships between pollen sensitization and asthma at age 6 were less consistent. Asthma was associated with sensitization to ragweed (OR, 2.2; 95% CI, 1.0, 4.6), but not silver birch or timothy grass (Fig. 1C). Poly-sensitization to aeroallergens was significantly associated with asthma when compared to absence of sensitization to allergens at age 1, 3, and 6 years [(OR, 5.7; 95% CI, 1.6, 20.4), (OR, 6.7; 95% CI, 3.1, 14.3), (OR, 3.4; 95% CI, 1.7, 6.7), respectively] (Fig. 1A-C). When poly-sensitization was compared directly with mono-sensitization with regards to asthma risk, the only statistically significant distinction between

the two was observed at 3 years (OR, 3.3; 95% CI, 1.2, 9.3) (Fig. 1B). Similar relationships were seen between aeroallergen sensitization in early life and asthma at age 8 years (Supplementary Figure 1A-C).

Associations between allergen-specific sensitization and rhinitis

We next evaluated relationships between allergen-specific sensitization and rhinitis at age 6 years (Fig. 2). At 1 year, sensitization to cat (OR, 5.0; 95% CI, 1.4, 18.3) was the only aeroallergen associated with an increased risk of rhinitis at age 6 years (Fig. 2A). By age 3 years, sensitization to both *A. alternata* (OR, 5.7; 95% CI, 2.2, 14.6) and cat (OR, 2.8; 95% CI, 1.3, 6.3) were associated with increased rhinitis risk (Fig. 2B). At age 6 years, sensitization to all allergens tested except cockroach was associated with concurrent rhinitis. Most notably, sensitization to *A. alternata* (OR, 7.9; 95% CI, 3.6, 17.5), ragweed (OR, 7.0; 95% CI, 2.7, 17.6), birch pollen (OR, 6.6; 95% CI, 2.2, 20.0), and timothy grass (OR, 5.1; 95% CI, 1.6, 15.7) had the strongest associations with rhinitis (Fig. 2C). These allergens were observed to have even stronger associations with rhinitis at 8 years of age, especially sensitization to birch pollen (OR, 26; 95% CI, 3.4, 197) (Supplementary Figure 2A-C)).

Poly-sensitization to aeroallergens was significantly associated with rhinitis when compared to absence of sensitization to allergens at age 3 and 6 years [(OR, 3.6; 95% CI, 1.7, 7.6 vs. OR, 11.3; 95% CI, 5.5, 23.3)] (Fig. 2B-C). However, no significant distinctions in associations with rhinitis were observed between children with poly-sensitization versus mono-sensitization at age 1, 3, or 6 years. (Fig. 2A-C).

Effect of degree of sensitization

We next sought to determine if the magnitude of allergen-specific IgE provides additional prognostic information beyond that provided by a positive response alone. In a generalized additive model for each allergen as a continuous variable, degree of sensitization at 1, 3, and 6 years was not associated with asthma or rhinitis prevalence at 6 years of age (data not shown).

Due to limited power to detect differences in the initial analysis, we next quantified the magnitude of an IgE response by grouping allergens into those with perennial (cat, dog, cockroach, *A. alternata, D. pteronyssinus, D. farinae*) and seasonal (ragweed, silver birch, timothy grass) patterns of exposure. The magnitude of a positive IgE response was separated into different levels of specific IgE concentration and compared with asthma and rhinitis at age 6. Greater levels of allergen specific IgE for perennial allergens at age 6 years were positively associated with concurrent asthma (Table 2). In contrast, greater levels of sensitization to seasonal allergens were not significantly associated with concurrent asthma (Table 2).

Any level of sensitization to seasonal allergens was associated with concurrent rhinitis, while higher levels of perennial allergen-specific IgE were needed before a significant positive association with concurrent rhinitis was observed (Table 2).

Pet sensitization/exposure and asthma/rhinitis outcome at 6 years

We have previously reported within the COAST cohort that dog exposure at birth was associated with a reduced risk of wheezing and a reduced cumulative prevalence of atopic dermatitis in the third year of life [13]. Due to this finding, as well as observing strong associations between dog and cat sensitization during early life and subsequent asthma risk, we next compared relationships between pet exposure at birth and pet sensitization at any point during the first 6 years of life with asthma and rhinitis prevalence at 6 years of age (Table 3).

Sensitization to dog during the first 6 years of life was independently associated with increased asthma risk, regardless of whether there was a dog in the home at birth or not [dog present: (46% vs. 15%), dog absent: (70% vs. 24%); ($p<0.0001$, Table 3)]. Interestingly, dog exposure at birth was associated with a reduced risk of asthma, regardless of dog sensitization during the first 6 years of life. Sensitization to dog at any point during the first 6 years of life was also independently associated with increased rhinitis risk, regardless of a dog being present or absent at birth ($p=0.0003$, Table 3). Dog exposure at birth was associated with a reduced risk of rhinitis in children who did not become sensitized to dog during the first 6 years of life, but was not associated with reduced rhinitis risk in children who did become sensitized to dog ($p=0.03$, Table 3).

Sensitization to cat during the first 6 years of life was also independently associated with increased asthma risk, regardless of whether a cat was present in the home at birth or not [cat present: (53% vs. 20%), cat absent: (57% vs. 23%); ($p<0.0001$, Table 3)]. In contrast to dog ownership, cat exposure at birth was not associated with a significantly reduced risk of asthma. Rhinitis risk was significantly increased with sensitization to cat, regardless of a cat being present or absent at birth [cat present: (69% vs. 39%), cat absent: (71% vs. 41%); ($p=0.0003$, Table 3)]. Cat exposure at birth did not alter asthma or rhinitis risk.

DISCUSSION

In this prospective birth cohort study, we have conducted three sets of analyses that examine the relationships among allergen sensitization and exposure and asthma and rhinitis outcomes at 6 and 8 years of age. These analyses include the presence or absence of sensitization to particular aeroallergens, the quantitative degree of allergic sensitization, and early life pet exposure. By analyzing patterns of allergen-specific sensitization, we have demonstrated that sensitization to specific aeroallergens differentially impacts subsequent asthma and rhinitis risk. Specifically, sensitization to perennial allergens, to dog in particular, was associated with the highest asthma risk. Furthermore, poly-sensitization at all ages was greatly associated with an increased asthma risk. For rhinitis, seasonal allergens were more closely associated with increased risk. These findings suggest that sensitization to perennial allergens is more closely linked to asthma development, while sensitization to seasonal allergens is more strongly associated with rhinitis development, potentially implicating differential mechanisms regarding both the process of sensitization and the pattern of disease expression in the upper and lower airways. A larger study population and inclusion of a wider panel of allergens may provide further insight into differential effects of specific allergens on asthma and rhinitis risk.

Our data analyzing the magnitude of allergen-specific IgE antibody formation demonstrate that increased levels of specific IgE to perennial allergens was associated with an increased asthma risk, while any detectable level of IgE to seasonal allergens was associated with increased rhinitis risk. These results confirm previous observations that absolute specific IgE antibody levels offer additional information in relation to asthma risk compared to the presence or absence of specific IgE alone [2, 3]. However, we have extended these findings by identifying two separate groups of aeroallergens (perennial and seasonal) that display different associations between the magnitude of their absolute specific IgE levels and the risk of asthma and rhinitis development. Previous results generated by Custovic and colleagues reported that when using specific IgE levels at 5 years of age as a continuous variable, the risk of current wheeze increased significantly with increasing specific IgE to mite, cat, and dog [2]. This risk was the greatest when the levels of specific IgE to mite, cat, and dog were summed. We have extended these associations by clearly showing that an increase in the magnitude of the IgE response to perennial aeroallergens is linked with not only current wheeze, but also asthma. Additionally, the same group reported that when using

specific IgE as a continuous variable, the risk of current rhinitis at 5 years of age increased significantly with increasing specific IgE to grass pollen [9]. Though our results are congruent with the fact that high levels of specific IgE to seasonal allergens are associated with an increased rhinitis risk, they contrast this finding by showing that rhinitis risk seems to increase significantly upon reaching the threshold of any detectable specific IgE to seasonal allergens.

Within the COAST cohort, dog and cat sensitization during the first 6 years of life were both independently associated with increased asthma and rhinitis risk, regardless of the respective exposure at birth. Additionally, dog exposure at birth was associated with a reduced risk of asthma, regardless of sensitization status to dog during the first 6 years of life. However, no such relationship was observed with cat exposure at birth. The association of dog exposure and reduced asthma risk, even in children who later become sensitized to dog, is intriguing and suggests that protective mechanisms of dog exposure are unrelated to the prevention of sensitization. Recent work has suggested that dogs may enrich the microbial communities of homes in ways that could influence the developmental pattern of innate immune responses [25]. Defining potential mechanisms underlying these observations is of interest for future study.

The strengths of this study include the prospective design, the high retention rate (90.9%) through age 6 years, and a diverse panel of specific aeroallergens tested at multiple time points in development. One limitation of the COAST study is that the study participants all have a parental history of atopy or asthma. It has been suggested that dog exposure is associated with stronger protective effects in children with atopic parents due to selective dog avoidance [26], though this is controversial [14]. Additionally, the COAST cohort is comprised of a relatively restricted population in regard to demographics such as ethnicity and socioeconomic status. It is possible that the results described may differ in other populations based upon effects of different allergen exposure frequencies and varying practices such as pet keeping that may impact patterns of sensitization [27-31].

In conclusion, our data suggest that increased levels of specific IgE to perennial allergens during early life are associated with an increased asthma risk at school age, while any detectable level of IgE to seasonal allergens is associated with increased rhinitis risk. These observational findings raise the question: why do increasing levels of allergen-specific IgE lead to greater asthma risk, and why is that outcome potentially different from rhinitis in terms of the target organ response? Additional studies are needed to resolve and understand the underlying immunological and physiological mechanisms behind these associations. Our findings, which expand the dichotomous phenotypic characteristic of “atopy” by examining specific patterns of an individual’s allergic sensitization response, could have potential ramifications in clinical practice by allowing clinicians to discern additional relevant associations with asthma and rhinitis risk as opposed to relying on the limited information gained from characterizing an individual as “atopic” by the presence or absence of demonstrable sensitization alone. Clinicians can obtain this additional information by quantifying allergic sensitization, as well as evaluating the type and number of specific allergens involved.

SUPPLEMENTARY FIGURE 1A-C. Relationships between allergen-specific sensitization at 1 (A), 3 (B), and 6 (C) years of age and asthma at 8 years of age. Dots represent the odds ratios (OR) and horizontal lines correspond to the 95% confidence intervals (CIs). (poly = poly-sensitization, mono = mono-sensitization, none = no sensitization, ANY = sensitization to any aeroallergen, DM = dust mite, A alternata = *Alternaria alternata*)

SUPPLEMENTARY FIGURE 2A-C. Relationships between allergen-specific sensitization at 1 (A), 3 (B), and 6 (C) years of age and rhinitis at 8 years of age. Dots represent the odds ratios (OR) and horizontal lines correspond to the 95% confidence intervals (CIs). (poly = poly-sensitization, mono = mono-sensitization, none = no sensitization, ANY = sensitization to any aeroallergen, DM = dust mite, A alternata = *Alternaria alternata*)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

COAST	Childhood Origins of ASThma, immunoglobulin E (IgE)
FEIA	fluoroenzyme immunoassay
DM	dust mite
D. farinae	Dermatophagoides farinae
D. pteronyssinus	Dermatophagoides pteronyssinus
A. alternata	Alternaria alternata
OR	odds ratio
95% CI	95% confidence interval

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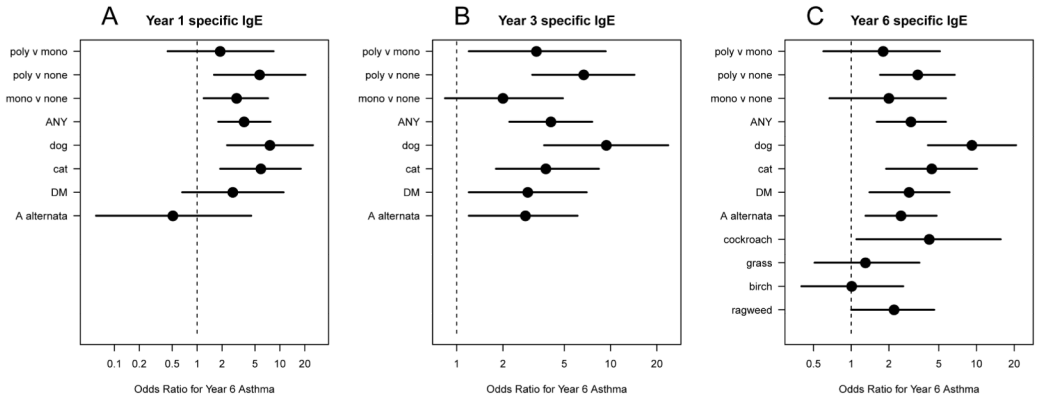

FIGURE 1A-C.

Relationships between allergen-specific sensitization at 1 (A), 3 (B), and 6 (C) years of age and asthma at 6 years of age. Dots represent the odds ratios (OR) and horizontal lines correspond to the 95% confidence intervals (CIs). (poly = poly-sensitization, mono = mono-sensitization, none = no sensitization, ANY = sensitization to any aeroallergen, DM = dust mite, A alternata = *Alternaria alternata*)

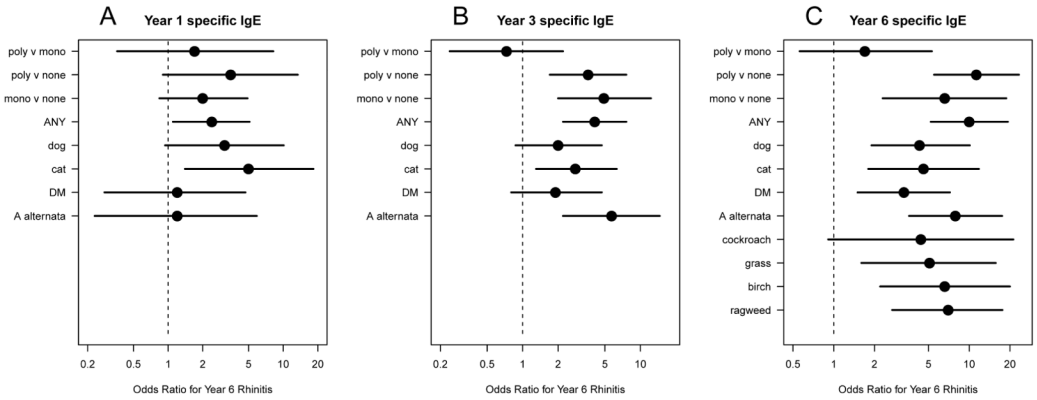

FIGURE 2A-C Relationships between allergen-specific sensitization at 1 (A), 3 (B), and 6 (C) years of age and rhinitis at 6 years of age. Dots represent the odds ratios (OR) and horizontal lines correspond to the 95% confidence intervals (CIs). (poly = poly-sensitization, mono = mono-sensitization, none = no sensitization, ANY = sensitization to any aeroallergen, DM = dust mite, A alternata = *Alternaria alternata*)

TABLE 1

Rates of allergic sensitization to specific aeroallergens throughout early childhood within the COAST cohort.

	Age 1	Age 3	Age 6	Age 9
Any Aeroallergen	34/252(13.5%)	64/231 (27.7%)	90/201 (44.8%)	89/168 (53 0%)
Only 1 Aeroallergen	23/252 (9.1%)	27/231 (11.7%)	20/201 (10.0%)	26/168 (15 5%)
2+ Aeroallergens	11/252 (4 4%)	37/231 (16 0%)	70/201 (34.8%)	63/168 (37 5%)
Cat	15/256(5 9%)	31/231 (13 4%)	28/201 (13.9%)	33/169(19 5%)
Dog	14/252 (5.6%)	26/231 (11.3%)	35/202 (17.3%)	40/169 (23 7%)
Dust Mite (DP)	7/256 (2.7%)	22/231 (9.5%)	33/201 (16.4%)	35/169 (20.7%)
Dust Mite (DF)	6/256 (2.3%)	16/231 (6.9%)	35/201 (17.4%)	34/169 (20 1%)
EITHER DM	8/256 (3.1%)	22/231 (9.5%)	36/201 (17.9%)	38/169 (22.5%)
A. Alternata	6/256 (2.3%)	29/231 (12.6%)	52/201 (25.9%)	54/169 (32.0%)
Cockroach	N/A	N/A	10/201 (5.0%)	9/169 (5.3%)
Ragweed	N/A	N/A	36/201 (17.9%)	39/169 (23.1%)
Silver Birch	N/A	N/A	25/201 (12.4%)	32/169 (18.9%)
Timothy Grass	N/A	N/A	21/201 (10.4%)	27/168 (16.1%)

(DM = dust mite, DP = *Dermatophagoides pteronyssinus*, DF = *Dermatophagoides farinae*, *A. alternata* = *Alternaria alternata*)

TABLE 2

Relationships between the degree of sensitization to perennial and seasonal allergens at 6 years of age and asthma and rhinitis at 6 years of age.

				P-value				
	Year 6 Perennial Allergens* (kU_A/L)	**n**	**asthma year 6**	**vs 0**	**vs 1**	**vs 2**	**vs 3**	**vs 4**
0	All IgE below detecdon	121	17%	--	--	--	--	--
1	All IgE < 1.7 but at least one IgE detectable	18	44%	0.01	--	--	--	--
2	All IgE < 10 but at least one IgE ≥ 1.7	22	27%	0.20	0.20	--	--	--
3	All IgE < 20 but at least one IgE ≥ 10	13	23%	0.61	0.23	0.78	--	--
4	All IgE < 50 but at least one IgE ≥ 20	10	50%	0.005	0.75	0.16	0.15	--
5	At least one IgE ≥ 50	11	91%	0.0003	0.03	0.004	0.005	0.05

				P-value				
	Year 6 Perennial Allergens * (kU_A/L)	n	rhinitis year 6	vs 0	vs1	vs 2	vs 3	vs 4
0	All IgE below detection	121	31%	--	--	--	--	--
1	All IgE < 1.7 but at least one IgE detectable	18	67%	0.006	--	--	--	--
2	All IgE < 1.7 but at least one IgE ≥ 1.7	22	68%	0.002	0.02	--	--	--
3	All IgE < 20 but at least one IgE ≥ 10	13	100%	<0.0001	0.03	0.03	--	--
4	All IgE < 50 but at least one IgE ≥ 20	16	81%	0.0003	0.34	0 .37	0.23	--
5	At least one IgE ≥ 50	11	73%	0.010	0.73	0.70	0.03	0.60

				P-value		
	Year 6 Seasonal Allergens ** (kU_A/L)	n	asthma year 6	vs 0	vs 1	vs 2
0	All IgE below detection	158	24%	--	--	--
1	All IgE < 1.7 but at least one IgE detectable	20	55%	0.006	--	--
2	All IgE < 10 but at least one IgE ≥ 1.7	14	29%	0.71	0.13	--
3	At least one IgE ≥ 10	9	33%	0.53	0.29	0.81

				P-value		
	Year 6 Seasonal Allergens ** (kU_A/L)	n	rhinitis year 6	vs 0	vs1	vs 2
0	All IgE below detection	158	40%	--	--	--

1	All IgE < 1.7 but at least one IgE detectable	20	85%		0.0009	--	--
2	All IgE < 10 but at least one IgE ≥ 1.7	14	79%		0.01	0.03	--
3	At least one IgE ≥ 10	9	89%		0.02	0.78	0.53

* cat, dog, cockroach, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Alternaria alternata*

** ragweed, silver birch, timothy grass)

TABLE 3

Relationships between pet exposure at birth and pet sensitization at any point during the first 6 years of life with asthma and rhinitis prevalence at 6 years of age.

				P-value	
dog in home at birth	**sensitized to dog, first 6 years of life**	**n**	**asthma year 6**	**dog in home**	**sensitization to dog**
No	No	134	24%		
Yes	No	78	15%	0.05 †	<0.0001 *
No	Yes	33	70%		
Yes	Yes	13	46%		
				P-value	
dog in home at birth	sensitized to dog, first 6 years of life	n	rhinitis year 6	dog in home	sensitization to dog
No	No	131	47%		
Yes	No	76	29%	0.03 ‡	0.0003 **
No	Yes	33	70%		
Yes	Yes	13	77%		
				P-value	
cat in home at birth	sensitized to cat, first 6 years of life	n	asthma year 6	cat in home	sensitization to cat
No	No	153	23%		
Yes	No	59	20%	0.64	<0.0001 *
No	Yes	30	57%		
Yes	Yes	17	53%		
				P-value	
cat in home at birth	sensitized to cat, first 6 years of life	n	rhinitis year 6	cat in home	sensitization to cat
No	No	149	41%		
Yes	No	57	39%	0.73	0.0003 **
No	Yes	31	71%		
Yes	Yes	16	69%		

* Associated with increased asthma

† associated with decreased asthma

** associated with increased rhinitis

‡ associated with decreased rhinitis