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Breastfeeding, aeroallergen sensitization and environmental exposures during infancy are determinants of childhood allergic rhinitis

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Abstract

Background—Infant predictors of early childhood allergic rhinitis (AR) are poorly understood.

Objective—Identify environmental exposures and host factors during infancy that predicts AR at age three.

Methods—High risk children from Greater Cincinnati were followed annually from ages one to three. Allergic rhinitis (AR) was defined as sneezing, runny or blocked nose in the prior 12 months and positive skin prick test (SPT) to one or more aeroallergens. Environmental and standardized medical questionnaires determined exposures and clinical outcomes. Primary activity area dust samples were analyzed for house dust endotoxin (HDE) and (1-3)- β -D-glucan. Fine particulate matter (PM_{2.5}) sampled at 27 monitoring stations was used to estimate personal elemental carbon attributable to traffic (ECAT) exposure by land use regression model.

Results—Of 361 children in this analysis, 116 had AR and 245 were non-atopic, non-symptomatic. Prolonged breastfeeding in African-American children (aOR 0.8; 95% CI 0.6–0.9) and multiple children in the home during infancy was protective of AR (aOR 0.4; 95% CI 0.2–0.8). Food SPT positivity and tree SPT positivity in infancy increased the risk of AR at age three (aOR 4.4; 95% CI 2.1–9.2) and (aOR 6.8; 95% CI 2.5–18.7), respectively. HDE exposure was associated with AR; the effect was dependent on exposure level. ECAT and ETS exposure showed no effect on AR.

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Clinical Implications:

Skin prick testing identifies infants at risk for AR. Encouraging prolonged breastfeeding could reduce the risk of childhood allergy in African-Americans.

Conclusion—Prolonged breastfeeding in African-Americans and multiple children in the home during infancy reduced the risk of AR at age three. SPT positivity to food and tree allergens enhanced risk. The HDE effect on AR was related to exposure.

Keywords

tobacco; atopy; rhinitis; endotoxin; breastfeeding; allergy; diesel; siblings; infants; African-American

INTRODUCTION

Upwards of 40% of children are afflicted with allergic rhinitis (AR) with direct costs estimated at \$ 11 billion in 2005.^{1, 2} Children with AR symptoms are at risk for developing asthma.³ The environmental factors associated with the development of AR are not well defined. Adolescents living near high truck traffic experience a higher frequency of AR symptoms.⁴ Human experimental studies demonstrated that diesel exhaust particles (DEP) can induce or enhance nasal specific IgE and Th2 cytokine responses to allergens.^{5–7} However, no prospective studies have investigated the combined effects of outdoor pollutants, including DEP, and multiple indoor exposure variables on childhood allergic rhinitis.

The Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS) is a prospective “high risk” birth cohort study of children born to atopic parents designed to determine the effects of infant and early childhood environmental exposures, including diesel pollution, on allergic disorders.⁸ The present study’s objective is to determine the interrelationship of host factors, outdoor and indoor environmental exposures in early life on the development of AR at age three.

METHODS

Subject Recruitment and Study Design

The CCAAPS cohort has been previously detailed.⁹ Infants born in the Greater Cincinnati and Northern Kentucky area were identified from birth records and recruited between 2001 and 2003. Parents living either within 400 meters or greater than 1500 meter of a major road were invited to a screening visit at one of three clinical study sites. At that visit, parents gave informed consent then were administered an allergy symptom questionnaire and received skin prick testing to a panel of aeroallergens. If one or both parents reported rhinitis, eczema or asthma and exhibited a positive skin prick test (SPT) to at least one regional aeroallergen, their infant was included in the study. The study protocol and informed consent statement were approved by the University of Cincinnati Institutional Review Board.

Parents and infant returned to the clinical study site at age one (mean age 13.7±2.6 months) for their first annual comprehensive study visit. Parents completed a medical history and home environmental questionnaire pertaining to their infants. The infant received a physical examination and underwent skin prick testing to a panel of 15 aeroallergens including: white oak, elm, maple mix, eastern red cedar, fescue and timothy grasses, short ragweed, four mold allergens (*Alternaria alternata*, *Aspergillus fumigatus*, *Penicillium* mix,

Cladosporium), cat, dog, house dust mite mix (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), and German cockroach [ALK-abelló, Round Rock, TX]. Two food allergens, milk and egg white, were also tested. A wheal diameter at least 3 mm greater than the negative saline control was considered positive.

At the age three follow-up comprehensive clinic visit, children were re-evaluated (by questionnaires administered to parents), examined and skin tested. Child respiratory symptoms were captured using items adapted from the validated ISAAC questionnaire.¹⁰ The primary study outcome of AR at age three was defined as a positive parental response to the question, “In the past 12 months, has your child ever had a problem with sneezing, or a runny or a blocked nose when he/she did not have a cold or flu” and a positive SPT to one or more aeroallergens. Subjects with AR cases were compared to children without symptoms and negative skin prick tests to all 15 aeroallergens at age three. The secondary outcome of atopy at age three was defined as SPT positive to at least one aeroallergen and compared to children SPT negative to all aeroallergens. The secondary outcome of rhinitis at age three was defined by parental report of symptoms to the aforementioned rhinitis questionnaire item, and the comparator group included children without symptoms.

Home evaluations

When the infant was eight months old, the home was inspected and house dust samples were collected from the primary living area.¹¹ A 2 m² area of floor surface in the infant’s primary activity room was vacuumed using a Filter Queen Majestic vacuum cleaner (Health-Mor; HMI Industries Inc, Seven Hills Ohio) at a rate of 2 min/m². Samples were filtered through a 355-µm pyrogen-free screen, desiccated and stored at –20 °C. Filtered house dust endotoxin (HDE) and (1–3)-β-D-glucan concentrations were determined by limulus amoebocyte lysate assay (Associates of Cape Cod Inc, Falmouth, MA).^{11, 12} HDE was expressed as endotoxin units/mg (EU/mg) while (1–3)-β-D-glucan was expressed as µg/g. Filtered house dust were tested for Fel d 1 (mU/ml) using a monoclonal sandwich ELISA assay (Indoor Biotechnologies Inc., Charlottesville VA).¹³ Indoor exposure variables were treated as continuous predictors.

Outdoor Exposure Estimation

Outdoor tree and grass pollens, ragweed pollen and fungal spore were sampled with a Rotorod Sampler (Sampling Technologies, Inc., Minnetonka, MN). Method of quantification and identification of pollens and fungal spores was previously reported.^{14, 15} Outdoor exposure variables were treated as continuous predictors.

Traffic Exposure Estimation

Ambient air sampling was performed from 2001 through to 2005 at 27 sites in Southwest Ohio and Northern Kentucky.¹⁶ Particulate matter 2.5 µm in diameter (PM_{2.5}) was collected on 37-mm membrane Teflon filters (nominal pore size, 1 µm; Paul Gellman, Ann Arbor, MI) and 37-mm Quartz filters using Harvard-type Impactors (Air Diagnostics and Engineering, Harrison, ME). Quartz filters and/or Teflon filters were used to determine PM_{2.5} elemental composition.¹⁷ Teflon filters were also used to determine particulate mass, and the elemental carbon component of PM_{2.5}. A marker of traffic-related air pollution,

Elemental Carbon Attributable to Traffic (ECAT) was determined at each sampling location by the multivariate UNMIX model and chemical mass balance model.¹⁷ Using the surrounding land use and traffic characteristics, a land use regression (LUR) model was developed to predict average daily ECAT levels ($\mu\text{g}/\text{m}^3$) at each of the 27 monitoring stations.¹⁸ The LUR model was then applied to each child's residence, and other locations where the child spent greater than eight hours/week, to derive a time-weighted average daily exposure to ECAT.¹⁸ ECAT exposure was treated as a continuous variable.

Predictor Variables

The CCAAPS cohort consists of 16% African-American children, 81% Caucasian children, and 3% other (ex. biracial, Pacific Islander). We *a priori* grouped Caucasian children with the 3% "other" children in the non-African-American category. Risk factors and exposures evaluated include: race (African-American; non-African-American); gender; household income at age one (< \$20,000; \$20,000); breastfeeding duration (number of months); number of other children living in the home at age one (less than two; two or more); report of parental rhinitis symptoms at initial visit (no; yes); child's season of birth; presence of one or more dogs in home at age one (no; yes); environmental tobacco smoke (ETS) estimated from parental report of the number of cigarettes smoked by all household members at age one (0; 1–19; 20); ECAT exposure; airborne pollen and fungal spores; SPT positivity to trees at age one; SPT positivity to milk and/or egg at age one. Exposure to ETS was analyzed as a categorical variable due to potential recall and reporting bias.

Data Analysis

Categories of predictor variables were evaluated for association with allergic rhinitis by Pearson χ^2 test (Table I), or by Fisher's exact test (Supplementary Table 1: analysis of parental positive SPT reactions). Categorical and continuous predictor variables were evaluated by univariate logistic regression. Collinearity was assessed by correlation coefficients. The scale for modeling each continuous predictor variable was determined by fitting a smooth function to the data.

Linear splines were modeled on separate intervals where the slopes changed as determined by significance testing and visual assessment using S-Plus 2000 (TIBCO Software Inc, Palo Alto CA).¹⁹ A final logistic regression model was developed using predictor variables identified with AR by univariate analysis. A $P < 0.15$ was chosen for inclusion in a multiple logistic regression model. Variables maintained in the final multiple regression model were chosen by the 'all subsets' method of stepwise regression, and removed if $P > 0.1$ except if a) model improved by log likelihood ratio and b) if likelihood coefficients of remaining variables changed by 20%. Logistic regression models, using a) the same original predictors in the primary AR outcome, and b) predictors irrespective of significance to AR, were developed for the secondary outcomes of atopy and rhinitis. All analyses were performed using SAS 9.1.3 (SAS Institute Inc., Cary NC).

RESULTS

Demographics and Exposure Characteristics

At age three, 606 children completed medical evaluations and skin prick testing. The outcome definition of AR was found in 116 children (19%) while 245 (40%) non-atopic, asymptomatic children were included in the comparator group. No further primary outcome analysis was conducted on the 151 (25%) atopic, asymptomatic children and 94 (16%) non-atopic, symptomatic children. The mean age of the AR group and the comparison group was 36.9 months $\pm$ 1.7 months and 36.7 months $\pm$ 1.6 months, respectively. Among the 361 in the AR and comparator groups, 80 infants (22.2 %) were African-American and 281 (77.8 %) which were non-African-American (278 of these were Caucasian). Of these 361 children there were 191 males (52.9%) and 170 females (47.1%). The allergic rhinitis case and comparator children that we have information on regarding to those who were breastfed and when solids were introduced, 95 infants (29.5%) were exclusively breastfed while 227 infants (70.5%) were breastfed with solids. Of all 606 three year old children, 130 were African-American (21.5%) and 476 were non-African American (78.6%). Supplementary Table I shows that regardless of whether one or both parents were skin tested, or if one or two of both parents tested had positive skin tests, the frequencies of allergic rhinitis, atopy and rhinitis outcomes did not significantly differ.

Univariate Evaluation of Predictors of Primary Clinical Outcome: Allergic Rhinitis at age three

Subject characteristics are presented in Table I. Characteristics significantly associated with AR and evaluated further in multivariate analysis included: season of birth [being born during the spring (OR, 2.4; 95% CI, 1.2–4.6), or the summer (OR, 2.0; 95% CI, 0.99–4.0)]; two or more children in the home during infancy (OR, 0.5; 95% CI, 0.3–0.9); a positive SPT to milk and/or egg in infancy (OR, 3.6; 95% CI, 1.9–6.7); and a positive SPT to any tree pollen in infancy (OR, 4.7; 95% CI, 2.0–11.4). Breastfeeding duration was protective in African-Americans (OR, 0.8; 95% CI 0.7–0.97). Low annual family income (<\$20,000) was significantly correlated with having at least one African-American biological parent ($r=0.5$; $P<0.0001$) and therefore not included.

Smoothed plots were used to determine the univariate associations of environmental exposures with AR. HDE concentrations ranged from 6 EU/mg (the limit of detection) to an 800 EU/mg, with a geometric mean of 212 EU/mg dust. HDE concentrations were log transformed to approximate normal distribution. As shown in Figure 1, the HDE smooth plot was significantly associated with AR ($\chi^2=6.4$; $P=0.01$). House dust endotoxin concentrations were protective of AR below 36.6 EU/mg and above 244.7 EU/mg, while predisposing to AR between 36.6–244.7 EU/mg. Therefore, HDE was included in the multivariate model as low HDE, medium HDE, or high HDE.

ECAT exposure was log transformed to approximate a normal distribution. A smooth plot of ECAT was associated with AR ($\chi^2=3.7$; $P=0.05$) and suggested levels $< 0.31 \mu\text{g}/\text{m}^3$ were protective while those $> 0.31 \mu\text{g}/\text{m}^3$ predisposed to AR. No significant associations with AR were found for: Fel d 1 cat allergen ($\chi^2=0.3$; $P=0.6$); number of dogs in the home ($\chi^2=2.0$;

$P=0.16$); (1-3)- β -D-glucan ($\chi^2=1.2$; $P=0.3$); fungal spore counts ($\chi^2=2.0$; $P=0.15$); ragweed pollen counts ($\chi^2=1.2$; $P=0.2$); tree and grass pollen counts ($\chi^2=1.2$; $P=0.3$); ETS ($\chi^2=0.8$; $P=0.4$).

Multivariate Evaluation of Predictors of Primary Clinical Outcome: Allergic Rhinitis at age three

Multivariate regression results are shown in Table II. Covariates included in the final multivariate regression model include: race, breastfeeding duration, race*breastfeeding duration interaction, season of birth, tree SPT positivity, milk and/or egg SPT positivity, two or more children in the home during infancy, low endotoxin level, and high endotoxin level. Prolonged breastfeeding in African-American was protective of AR (aOR, 0.8; 95% CI, 0.6–0.9). Skin prick test positivity to any tree pollen in infancy (aOR, 8.7; 95% CI, 3.0–24.8), SPT positivity to milk and/or egg allergen in infancy (aOR, 4.5; 95% CI, 2.1–9.8), being born in the autumn (aOR, 2.2; 95% CI, 1.1–4.9) and being born in the spring months (aOR, 2.9; 95% CI, 1.3–6.6) were each significantly associated with AR at age three. Infants with two or more other children in the home were significantly less likely to have AR (aOR, 0.5; 95% CI, 0.3–0.9). Low HDE and high HDE exposure in infancy was protective of AR (aOR, 0.5; 95% CI, 0.3–0.8) and (aOR, 0.002; 95% CI, <0.001–0.1), respectively. Medium HDE exposure during infancy was associated with a significantly increased risk of AR (aOR, 6.3; 95% CI, 2.3–17.2).

Multivariate Evaluations of Allergic Rhinitis Risk Factors on Secondary Outcomes of Atopy and Rhinitis

We aimed to determine if the effect of a predictor on AR was determined by the skin positivity component (i.e., atopy) or the symptom component (i.e., rhinitis). Multivariate models for atopy and rhinitis were built using only those predictors found significant for AR. Of these AR predictors, those found associated with atopy at age three (Table II) included: SPT positivity to any tree pollen at age one (aOR, 3.1; 95% CI, 1.4–6.9); and SPT positivity to milk and/or egg at age one (aOR, 2.9; 95% CI, 1.7–4.8). Multiple children in the home significantly reduced the risk for atopy at age three (aOR, 0.6; 95% CI, 0.4–0.9). Medium and high HDE concentrations were associated with atopy at age three, (aOR, 2.1; 95% CI, 1.1–4.0) and (aOR, 0.1; 95% CI, 0.03–0.5), respectively. There was no association with low HDE exposure.

Of AR risk factors, those found associated with rhinitis at age three (Table II) included: spring season of birth (aOR, 2.0; 95% CI, 1.2–3.4); summer season of birth (aOR, 1.8; 95% CI, 1.0–3.1); and SPT positivity to any tree pollen at age one (aOR, 2.5; 95% CI, 1.2–5.2). Prolonged breastfeeding in African American infants significantly reduced risk of rhinitis symptoms at age three (aOR, 0.8; 95% CI, 0.7–0.9). Low, medium or high HDE concentrations were not associated with rhinitis at age three.

Independent Multivariate Evaluations of Secondary Outcomes Atopy and Rhinitis

Independent of AR, multivariate models of atopy and rhinitis were developed. Significant predictors associated with atopy include: SPT positivity to any tree pollen in infancy (aOR, 3.3; 95% CI, 1.5–7.2); SPT positivity to milk and/or egg in infancy (aOR, 2.8; 95% CI, 1.7–

4.7); multiple children in the home in infancy (aOR, 0.6; 95% CI 0.4–0.9); medium HDE exposure (aOR, 2.1; 95% CI 1.1–3.8); high HDE exposure (aOR, 0.1; 95% CI 0.03–0.5). Non-significant independent variables remaining in the atopy model include: low HDE exposure; prolonged breastfeeding in African-American infants; prolonged breastfeeding in non-African-American infants. Significant predictors found associated with rhinitis include: spring season of birth (aOR, 2.6; 95% CI, 1.4–4.7); summer season of birth (aOR, 2.1; 95% CI, 1.1–4.0); SPT positivity to any tree pollen at age one (aOR, 2.4; 95% CI, 1.1–5.1); prolonged breastfeeding in African-American infants (aOR, 0.8; 95% CI, 0.7–0.96). Non-significant independent variables remaining in the rhinitis model include: low HDE exposure; medium HDE exposure; high HDE exposure; SPT positivity to milk and/or egg in infancy; prolonged breastfeeding in non-African-American infants.

DISCUSSION

In this CCAAPS birth cohort study of three year old children, the prevalence of AR was 19%. This is greater than the 5% prevalence of seasonal allergic rhinitis (SAR) at age three previously reported in another high-risk birth cohort study.²⁰ Differences in prevalence estimates may be due to the use of serum timothy and birch allergen specific IgE to define sensitization (and SAR) in the latter study, in sharp contrast to our study which employed skin prick testing to 15 aeroallergens.²¹

Another high-risk birth cohort study previously showed that African-Americans were at significantly greater risk than Caucasians for physician-diagnosed AR at age five.²² We showed that African-American infants receiving prolonged breastfeeding significantly decreased the risk of developing AR at age three (aOR, 0.8; 95% CI, 0.6–0.9). This breast feeding effect was not seen in non-African-American children (aOR, 1.0; 95% CI, 0.96–1.1). The effect was independent of income because when we substituted income for race in the multivariate model no significant association was observed.

This protective effect of prolonged breastfeeding in African-Americans has not been investigated or reported in other high-risk cohort studies. The NHANES III and the 2004 National Immunization Survey reported that breastfeeding rates are lower in African-American infants and particularly in lower socioeconomic subgroups.^{23, 24} The Breastfeeding Promotion Consortium, which includes the African-American Breastfeeding Alliance, promotes breastfeeding in women and African-Americans.^{25–27} If confirmed this finding could guide future recommendations for primary prevention of allergic disorders in African American children which could be disseminated through the aforementioned advocacy groups.

Indoor HDE exposure in the first year of life was associated with AR at age three. The bimodal effect of HDE in the univariate analysis persisted in the multivariate model. The risk of AR at age three was decreased with low HDE exposure in infancy (6–36.6 EU/mg), but the risk increased with medium HDE exposure (36.6–244.7 EU/mg). The risk of AR at age three was decreased with levels > 244.7 EU/mg; however, only 11 AR children were exposed to HDE levels in this range and therefore should be interpreted with caution. Although we have previously shown that HDE concentrations correlate with the presence of

multiple dogs, the effect of HDE concentrations on AR at age three was independent of pet keeping; i.e. the presence of multiple dogs was not significantly associated with AR, nor did it modify the HDE effect on AR in this multivariate model (data not shown).¹¹ The atopy and rhinitis secondary outcomes, while not significant, both trended to an increased risk with higher HDE exposure, which agreed with the primary AR outcome. It can be hypothesized that endotoxin could play an adjuvant role in enhancing early respiratory sensitization to aeroallergens. Experimental murine models showing that lipopolysaccharide is essential for ovalbumin (OVA) induced respiratory sensitization lend support to this hypothesis.^{28, 29}

We found that infants with SPT positivity to milk and/or eggs in infancy were four times more likely to develop AR at age three. Other childhood studies have indicated that egg sensitization in infancy is a predictor of allergic respiratory disorders later in life.³⁰ Rhodes et al. demonstrated that SPT positivity to hen's egg at age one predicted subsequent development of asthma in adults; however, rhinitis outcomes were not evaluated.³¹ Zeiger et al. demonstrated in a dietary intervention trial that SPT positivity to egg by 12 months of age was associated with asthma, allergic rhinitis and any atopic disorder at age seven.³² Kulig et al. showed that elevated serum specific IgE to egg in the first two years increased the likelihood of allergic rhinitis in five year old children from atopic families.³³ Thus, our findings are consistent with previous studies of atopic children.

Spring season of birth significantly increased the risk of AR at age three when compared to winter season of birth, which is consistent with another study showing that seasonal AR was associated with being-born during tree and grass season.³⁴ We also found that infants SPT positive to tree pollen during first year of life were at a five-fold significant increased risk for AR at age three. The effect of early SPT positivity to aeroallergens on AR has not been assessed in other high-risk birth cohort studies.

Living with multiple siblings in infancy significantly reduced the risk of AR as well as atopy, but not for the secondary "rhinitis" outcome, suggesting that this effect was due to atopy. Though living with multiple siblings was protective for rhinitis in population based epidemiological studies it has not been reported in other high risk birth cohort studies at age three.^{35, 36}

The central hypothesis of the CCAAPS birth cohort is that early exposure to diesel exhaust pollution, as estimated by ECAT, increases risk for allergic disorders in childhood. We found no associations of ECAT exposure in infancy to AR, atopy or rhinitis at age three. Recently, Morgenstern et al reported that physician-diagnosed hay fever at ages two and six was significantly associated with high PM_{2.5} exposure.³⁷ The conflicting results could be explained by the differences in the study populations and design. The Morgenstern study was population based, skin testing was not used to define AR, and PM_{2.5} was used to estimate traffic exposure instead of ECAT, a more precise measure of diesel pollutant exposure.

In summary, this study identified multiple risk factors for early childhood allergic rhinitis in a high-risk cohort. However, these findings may not be generalizable to a population-based sample. For the first time, we demonstrated a protective effect of prolonged breastfeeding in

African-American children on AR. Infants raised with multiple children in the home were less likely to develop AR. The effect of HDE was dependent on exposure level. Infants born in the spring, SPT positive to trees, and SPT positive to milk and/or eggs were more likely to develop AR at age three. These findings indicate that routine skin prick testing of high risk infants is useful in assessing subsequent risk of childhood allergy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AR	Allergic rhinitis
CCAAPS	Cincinnati Childhood Allergy and Air Pollution Study
DEP	Diesel exhaust particle
ECAT	Elemental carbon attributable to traffic
ETS	Environmental tobacco smoke
HDE	House dust endotoxin
LUR	Land use regression
PM_{2.5}	Particulate matter with diameter equal to or less than 2.5 μ m
SPT	Skin prick test

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Figure 1.
Smooth plot of allergic rhinitis prevalence in relation to house dust endotoxin concentration.

Table 1

Subject characteristics and risk factors for Allergic Rhinitis, Atopy, and Rhinitis at age three.

Variable in infancy	Allergic Rhinitis ¹ n=116/361 (32%)		Atopy ² n=267/606 (44%)		Rhinitis ³ n=210/606 (35%)	
	N (%)	p-value	N (%)	p-value	N (%)	p-value
Gender						
Female	52 (31)		117 (42)		95 (34)	
Male	64 (34)	0.6	150 (46)	0.4	115 (35)	0.8
Race						
Non-African American	83 (30)		200 (42)		161 (34)	
African-American	33 (41)	0.05	67 (52)	0.05	49 (38)	0.4
Season of Birth						
Winter	21 (22)		77 (42)		51 (28)	
Spring	33 (40)	0.01	58 (45)	0.6	55 (43)	0.01
Summer	24 (36)	0.05	43 (43)	1.0	39 (39)	0.07
Autumn	38 (33)	0.08	89 (46)	0.5	65 (34)	0.3
Family Income						
\$20,000	84 (29)		199 (42)		160 (33)	
< \$20,000	18 (40)	0.1	40 (49)	0.2	32 (40)	0.3
Children in home						
0-1	91 (36)		199 (47)		153 (36)	
2	25 (23)	0.01	68 (37)	0.02	57 (31)	0.2
Daycare						
No	67 (32)		160 (45)		117 (33)	
Yes	34 (30)	0.7	79 (40)	0.2	73 (37)	0.4
SPT+ milk and/or egg						
Negative	88 (28)		214 (41)		173 (33)	
Positive	28 (58)	<0.001	53 (65)	<0.001	37 (45)	0.03
SPT+ trees[§]						
Negative	100 (30)		244 (43)		190 (33)	
Positive	16 (67)	<0.001	23 (66)	0.01	20 (57)	<0.01

Variable in infancy	Allergic Rhinitis ¹ n=116/361 (32%)			Atopy ² n=267/606 (44%)			Rhinitis ³ n=210/606 (35%)		
	N (%)	p-value	N (%)	p-value	N (%)	p-value	N (%)	p-value	
Environmental Tobacco Smoke (cig/day)									
ECAT (µg/m ³)	0	75 (30)			194 (44)		141 (32)		
	1–19	13 (38)			25 (42)		26 (44)		
	20	13 (33)	0.6		19 (35)	0.4	23 (41)	0.1	
	<0.343	53 (29)			127 (41)		106 (34)		
Dogs in home	0.343	63 (35)	0.2		140 (47)	0.2	104 (35)	0.9	
	>1	81 (34)			181 (46)		135 (35)		
	0	35 (29)	0.4		86 (41)	0.2	75 (35)	0.8	
	<0.69749	62 (31)			140 (43)		110 (34)		
Mold (spores/m ³)	0.69749	54 (34)	0.6		127 (45)	0.6	100 (36)	0.6	
	<490,408	52 (29)			135 (44)		98 (32)		
	490,408	64 (35)	0.2		132 (44)	1.0	112 (37)	0.2	
	<37,583	56 (32)			138 (45)		108 (35)		
Tree and grass Pollen (pollens/m ³)	37,583	60 (32)	1.0		129 (43)	0.8	102 (34)	0.9	
	<3,243	116 (32)			267 (44)		210 (35)		
	3,243	0	NA		0	NA	0	NA	
	<55.5	76 (36)			166 (47)		130 (37)		
(1–3)-β-D-glucan (µg/g)	55.5	40 (26)	0.04		101 (40)	0.08	80 (32)	0.2	
	<4 months	71 (36)			148 (45)		122 (37)		
	4 months	45 (28)	0.1		119 (43)	0.6	88 (32)	0.2	
	<4 months	71 (36)			148 (45)		122 (37)		
House Dust Endotoxin (EU/mg)	4 months	45 (28)	0.1		119 (43)	0.6	88 (32)	0.2	

Variable in infancy	Allergic Rhinitis ¹ n=116/361 (32%)		Atopy ² n=267/606 (44%)		Rhinitis ³ n=210/606 (35%)	
	N (%)	p-value	N (%)	p-value	N (%)	p-value
6 – 36.6 [†]	47 (35)		95 (45)		76 (36)	
36.6 – 244.7 ^{††}	58 (31)		150 (45)		114 (34)	
244.7 ^{†††}	11 (27)	0.6	22 (36)	0.4	20 (33)	0.9

¹ Allergic Rhinitis: “In the past 12 months, has your child ever had a problem with sneezing, or a runny or a blocked nose when he/she DID NOT have a cold or flu” AND positive skin prick test to the 15 aeroallergens tested.

² Atopy: Positive skin prick test to 1 of the 15 aeroallergens tested.

³ Rhinitis: “In the past 12 months, has your child ever had a problem with sneezing, or a runny or a blocked nose when he/she DID NOT have a cold or flu”.

[§] Trees tested include: white oak (Quercus alba), American elm (Ulmus Americana), maple mix, Eastern red cedar (Juniperus virginiana).

[†] Low endotoxin level range 6–36.6 EU/mg dust.

^{††} Medium endotoxin level range 36.6–244.7 EU/mg dust.

^{†††} High endotoxin level range >244.7 EU/mg dust.

Note: p-value obtained by Pearson χ^2 test of independence. NA= not able to be tested due to zero count.

Table IIAdjusted Odds Ratios for Predictors of Allergic Rhinitis¹, Atopy², and Rhinitis³ at age three.

Variable at age one.	Allergic Rhinitis ¹ N= 100/322 (31%) Adjusted Odds Ratio (95% CI)	Atopy ² N=238/549 (43%) Adjusted Odds Ratio (95% CI)	Rhinitis ³ N= 189/549 (34%) Adjusted Odds Ratio (95% CI)
Breastfeeding duration (months) in African-Americans.	0.8 ^{**} (0.6, 0.9)	0.9 (0.9, 1.0)	0.8 [*] (0.7, 0.9)
Breastfeeding duration (months) in non-African Americans.	1.0 (0.96, 1.1)	1.01 (0.97, 1.1)	1.0 (0.96, 1.1)
Season of Birth:			
Winter	1.0	1.0	1.0
Autumn	2.2 [*] (1.0, 4.7)	1.2 (0.8, 1.9)	1.4 (0.9, 2.2)
Spring	2.9 [*] (1.3, 6.6)	1.1 (0.6, 1.8)	2.0 [*] (1.2, 3.4)
Summer	2.1 (0.9, 4.9)	0.8 (0.5, 1.4)	1.7 (1.0, 3.0)
SPT+ trees in infancy	8.7 ^{***} (3.0, 24.8)	3.3 ^{**} (1.5, 7.4)	2.6 [*] (1.2, 5.4)
SPT+ milk and/or egg in infancy	4.5 ^{***} (2.1, 9.8)	2.8 ^{***} (1.7, 4.7)	1.6 (0.98, 2.7)
2 Children in home in infancy	0.5 [*] (0.3, 0.9)	0.6 [*] (0.4, 0.9)	0.8 (0.5, 1.2)
Low HDE (EU/mg)[†] in infancy	0.5 [*] (0.3, 0.8)	0.8 (0.5, 1.1)	0.8 (0.5, 1.1)
Medium HDE (EU/mg)^{††} in infancy	6.3 ^{***} (2.3, 17.2)	2.1 [*] (1.1, 4.0)	1.8 (1.0, 3.5)
High HDE (EU/mg)^{†††} in infancy	0.002 ^{**} (<0.001, 0.1)	0.1 ^{**} (0.03, 0.5)	0.4 (0.1, 1.5)

Covariates include: race, breastfeeding duration, race*breastfeeding duration, season of birth, tree SPT positivity, milk and/or egg SPT positivity, number of children in the home during infancy, low endotoxin in infancy, high endotoxin in infancy.

The main effects of race and breastfeeding duration were included in the model. The odds ratios of the main effects of Race and Breastfeeding variables were determined by modeling without interaction term, but these were not significant.

* P<0.05,

** P<0.01,

*** P<0.001

[†] Low endotoxin level range 6–36.6 EU/mg dust.

^{††} Medium endotoxin level range 36.6–244.7 EU/mg dust.

^{†††} High endotoxin level range >244.7 EU/mg dust.

¹ Allergic Rhinitis: “In the past 12 months, has your child ever had a problem with sneezing, or a runny or a blocked nose when he/she DID NOT have a cold or flu” AND positive skin prick test to 1 of the 15 aeroallergens tested.

² Atopy: Positive skin prick test to 1 of the 15 aeroallergens tested.

³ Rhinitis: “In the past 12 months, has your child ever had a problem with sneezing, or a runny or a blocked nose when he/she DID NOT have a cold or flu”.