Endotoxin Exposure and Eczema in the First Year of Life

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ABSTRACT. *Objective.* **Exposure to endotoxin in early life has been proposed as a factor that may protect against the development of allergic diseases such as eczema. The objective of this study was to examine the relation between endotoxin exposure in early life and eczema in the first year of life in children with parental history of asthma or allergies.**

Methods. **This study used a prospective birth cohort study of 498 children who had a history of allergy or asthma in at least 1 parent and lived in metropolitan Boston. A subset of 401 living rooms had house dust samples adequate for analysis of endotoxin.**

Results. **In multivariate analyses adjusting for gender, income, and season of birth, endotoxin levels in the living room at 2 to 3 months of age was inversely associated with physician- or nurse-diagnosed eczema in the first year of life (odds ratio [OR] for each quartile increment: 0.76; 95% confidence interval [CI]: 0.61-0.96). Exposure to a dog in the home at age 2 to 3 months was also inversely associated with eczema in the first year of life, but the CI widened when endotoxin was included in the multivariate model (OR: 0.54; 95% CI: 0.27-1.09). Other variables associated with eczema in the first year of life included paternal history of eczema (OR: 1.91; 95% CI: 1.03-3.55) and maternal specific immunoglobulin E positivity to ≥1 allergen (OR: 1.61; 95% CI: 1.01-2.56).**

Conclusions. **Among children with parental history of asthma or allergies, exposure to high levels of endotoxin in early life may be protective against eczema in the first year of life. In these children, paternal history of eczema and maternal sensitization to at least 1 allergen are associated with an increased risk of eczema in the first year of life.** ***Pediatrics*** **2004;114:13–18;** ***endotoxin, eczema, dog, maternal sensitization.***

ABBREVIATIONS. Ig, immunoglobulin; OR, odds ratio; CI, confidence interval; T_h2, T-helper cell type 2.

Eczema is the most common atopic disease in infancy, and 60% of affected individuals manifest characteristic lesions during the first year of life.[1] The prevalence of eczema has increased by 2 to 3-fold during the past 3 decades in industrialized countries.[2] A number of studies have identified potential risk factors for eczema, including small family size and high socioeconomic status.[3]

Early childhood exposure to endotoxin has been hypothesized to be protective against the development of asthma,[4] allergy,[5–7] and eczema.[7] The Home Allergens and Asthma Study is a prospective birth cohort study of children with a parental history of asthma or allergies in the Boston metropolitan area. The primary purpose of this study is to assess the relationship between exposure to indoor allergens in early childhood and the subsequent development of asthma and allergic diseases. As part of this study, exposure to endotoxin in the household was measured at 2 to 3 months of age. In this report, we describe the relation between endotoxin exposure and eczema in the first year of life among children with parental history of asthma or allergies.

METHODS

Study Participants

The 505 infants (including 6 sets of twins) and their 499 families with a history of allergy or asthma in at least 1 parent were recruited between September 1994 and August 1996. The screening and recruitment of families have been described elsewhere.[8] In brief, eligibility criteria included residence inside route 128 (a highway encircling the Boston metropolitan area); maternal age ≥18 years; history of hay fever, bronchial asthma, or allergies in either parent; and maternal ability to speak English or Spanish. Families were not screened when the newborn was hospitalized in the intensive care unit, when his or her gestational age was <36 weeks, or when he or she had a congenital anomaly. A serum sample was drawn from the mothers at screening and was analyzed for total serum immunoglobulin E (IgE) and for allergen-specific IgE. After obtaining written informed consent from the child's parents, a home visit was made when the child was 2 to 3 months of age, and a questionnaire regarding home characteristics, environmental exposures, smoking, and demographics was administered by trained research assistants. Every 2 months, beginning when the child was 2 months of age, a follow-up telephone questionnaire was administered to the child's primary caregiver. Of the 505 children, 7 were excluded from analysis because they were followed for ≤4 months during their first year of life. The study was approved by the Institutional Review Board of the Brigham and Women's Hospital in Boston.

Analysis of Endotoxin and House Dust Samples

At the home visit, house dust samples were collected. Methods for the collection of dust samples and analysis of the dust for allergens and endotoxin have been detailed previously.[9,10] Briefly, 5 separate dust samples were collected in a standard manner by vacuuming the following areas: 1) the infant's bedroom floor, 2) the infant's bed, 3) the parents' bed, 4) the family-living room, and 5) the kitchen floor. Within 24 hours after collection, dust was weighed and sifted through a 425-μm mesh sieve, and the fine

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dust was reweighed and divided into aliquots for various analyses: allergens (dust mite, cat, dog, cockroach, and fungi) and endotoxin. Allergen concentrations were grouped in categories with potential relevance to sensitization and in consistency with previous reports in this cohort.[9,11] Endotoxin was assayed only when there was sufficient dust after all of the other assays had been performed. The endotoxin activity of dust samples was determined by the kinetic Limulus assay with the resistant-parallel-line estimation method.[12–14] We used data from the living room only because this room was the one with the most complete data. Endotoxin exposure was categorized into quartiles by concentration of endotoxin units per milligram of house dust (EU/mg) in the living room. Because there was an inverse linear relationship between increases in endotoxin levels by quartiles and eczema ($P < .01$), we recoded endotoxin as an ordinal variable with the reference as the lowest quartile for the multivariate analysis. An indicator variable for missing endotoxin values was included in multivariate analysis to allow us to control for the missing values in our models.

Definition of Predictor Variables

Potential predictors of eczema in the first year of life and potential confounders of the relation between predictor variables and eczema were considered for inclusion in the multivariate analysis. Sociodemographic variables included the child's race or ethnicity (according to parental report)[8] and annual household income, classified as <$30 000 versus ≥$30 000. Perinatal factors included birth weight (classified into quartiles from 1.84 to 4.91 kg), head circumference (classified into quartiles from 23 to 38.5 cm), maternal age, and season of birth (winter, spring, summer, and fall).[19] Infant diet factors that were considered included breastfeeding (yes or no), number of months of breastfeeding (never, <4 months, or ≥4 months), potentially allergenic foods (milk, eggs, peanuts, and fish) introduced to the child orally within the past year (yes or no), and maternal ingestion of potentially allergenic foods during breastfeeding (yes or no). Breastfeeding variables included supplemented breastfeeding and exclusive breastfeeding. Variables related to family history of allergies included parental history of eczema, asthma, hay fever, and food allergies (mother, father, or both). Variables related to the home environment included presence of rugs or carpets in the area where the child slept and presence of a cat or a dog in the home when the child was 2 to 3 months of age. Child care attendance in the first year of life was also assessed (yes or no).

Measurement of Maternal Sensitization to Allergens

The mother's serum sample was analyzed for specific IgE antibodies, as measured with the UNICAP System (Pharmacia, Uppsala, Sweden). For ~20 samples of low volume, IgE antibodies were measured with the CAP RAST FEIA System (Pharmacia), which requires less serum per assay. Specific IgE antibodies were assayed for dust mite, cat, cockroach, dog, ryegrass, ragweed, *Alternaria* species, and *Aspergillus* species allergens, with each allergen attached to a cellulose sponge (ImmunoCAP).[15] The results were given as international units (IU) of IgE. We defined sensitivity to a specific allergen as CAP class level 1 or above (>0.35 IU/mL). Mothers were stratified into those who had sensitivity to 1 or more allergens versus no sensitivity.

Definition of Outcome Variable

Every 2 months during the first year of life, the primary caregiver was asked, "Has a doctor or nurse ever said that your child has eczema?" Those who answered yes to this question in the first year of life were categorized as those who developed eczema in the first year of life.

Statistical Analyses

Univariate relationships between categorical predictor variables and eczema in the first year of life were examined with 2 × 2 contingency tables. Logistic regression was used to study the relationship between predictor variables and eczema in the first year of life while controlling for potential confounders and examining interactions. Stepwise logistic regression was used to develop the multivariate models. In the final models, we included those variables that satisfied a change-in-estimate criterion (≥10% in the odds ratio [OR] estimate) or that were significant at the $P <$ .05 level. SAS statistical software (SAS Institute, Cary, NC) was used for all analyses.

RESULTS

Table 1 summarizes the primary characteristics of the 498 infants who were followed throughout the first year of life. Most of the children were white and came from households with an annual income of at least $30 000. Most of the children had been breastfed (74.7%) in the first year of life, and 54% of the mothers had specific IgE positivity to at least 1 allergen. Of the 498 children, 140 (28%) had a diagnosis of eczema in the first year of life. Because 97 children had missing values for endotoxin, we also compared these children with the 401 children who had endotoxin levels and found no significant differences between the groups (Table 1).

Table 2 summarizes the results of the univariate analyses between predictor variables and diagnosis of eczema in the first year of life. Because the estimates of the association between the variables of interest and eczema were similar whether the child had parental report of eczema in the first or second 6 months of life, we combined eczema in the first and second 6 months of life. High levels of endotoxin at 2 to 3 months of age were inversely associated with eczema in the first year of life. Although paternal history of eczema was associated with eczema in the child, we found no significant association between maternal history of eczema and eczema in the child. Neither paternal nor maternal history of atopic diseases other than eczema (asthma, hay fever, and food allergy) was associated with eczema in the infant. Infants who were born in the fall had higher odds of eczema than children who were born in other seasons. There was no significant association between any of the allergen levels measured in house dust and eczema. Birth weight; head circumference; maternal age; maternal diet during breastfeeding; and infant diet of potentially allergenic foods such as milk, eggs, peanuts, and fish during the first year of life were not significantly associated with eczema. Neither child care attendance in the first year of life nor the number of older siblings in the home was significantly associated with eczema.

Table 3 shows the multivariate analysis of the relationship between the variables of interest and eczema in the first year of life. In this analysis, children who were exposed to a pet dog in the home at age 2 to 3 months had half the odds of having eczema in the first year of life than those who were unexposed (model 1). This association remained significant, even after restricting the analysis to the 401 infants who had complete endotoxin data (model 2). For every quartile increase of endotoxin house dust level in the infant's living room at age 2 to 3 months, there were decreased odds of developing eczema in the first year of life (models 3 and 4). After adjustment for endotoxin exposure, the association between exposure to a dog in the household and eczema became nonstatistically significant (model 4), but the point estimate was unchanged. Having a dog in the home was only moderately correlated with endotoxin levels in the homes of children in the study. Of the 65

TABLE 1. Characteristics of Children in the Cohort

Variable	Subjects With Endotoxin Values*	Subjects With Missing Endotoxin*	Total (n [%] (N = 498)
Dog in home at age 2–3 mo	N = 401	N = 97	
Yes	65 (16.21)	14 (14.43)	79 (15.86)
No	336 (83.79)	83 (85.57)	419 (84.14)
Cat in home at age 2–3 mo	N = 401	N = 97	
Yes	84 (20.95)	20 (20.62)	104 (20.88)
No	317 (79.05)	77 (79.38)	394 (79.12)
Gender (n [%])	N = 401	N = 97	
Male	223 (55.61)	45 (46.39)	268 (53.82)
Female	178 (44.39)	52 (53.61)	230 (46.18)
Household income (n [%])*	N = 401	N = 97	
<$30 000	33 (8.23)	12 (12.37)	45 (9.04)
≥$30 000	356 (88.78)	83 (85.57)	439 (88.15)
Unknown	12 (2.99)	2 (2.06)	14 (2.81)
Race (n [%])	N = 401	N = 97	
White	303 (75.86)	72 (74.23)	375 (75.30)
Black	50 (12.47)	10 (10.31)	60 (12.05)
Hispanic	22 (5.49)	6 (6.19)	28 (5.62)
Asian/other	26 (6.48)	9 (9.28)	35 (7.03)
Ever breastfed (n [%])	N = 401	N = 97	
Yes	297 (74.06)	75 (77.32)	372 (74.70)
No	104 (25.94)	22 (22.68)	126 (25.30)
Maternal history of eczema (n [%])*	N = 397	N = 94	
Yes	86 (21.66)	23 (24.47)	109 (22.20)
No	311 (78.34)	71 (75.53)	382 (77.80)
Paternal history of eczema (n [%])*	N = 390	N = 93	
Yes	48 (12.31)	14 (15.05)	62 (12.84)
No	342 (87.69)	79 (84.95)	421 (87.16)
Maternal specific IgE positivity to ≥1 allergen*†	N = 367	N = 89	
Yes	221 (60.22)	48 (53.93)	269 (58.99)
No	146 (39.78)	41 (46.07)	187 (41.01)
Child care attendance in the first year of life	N = 401	N = 97	
Yes	196 (48.8)	42 (43.30)	238 (47.79)
No	205 (51.12)	55 (56.70)	260 (52.21)
Season of birth	N = 401	N = 97	
Winter (Dec–Feb)	98 (24.44)	26 (26.80)	124 (24.90)
Spring (Mar–May)	119 (29.68)	25 (25.77)	144 (28.92)
Summer (Jun–Aug)	85 (21.20)	25 (25.77)	110 (22.09)
Fall (Sep–Nov)	99 (24.69)	21 (21.65)	120 (24.10)

* There was missing information on maternal history of eczema (n = 7), paternal history of eczema (n = 15), and maternal IgE positivity to at least 1 allergen (n = 42). Sample sizes for the variables are noted in the table.
† Maternal specific IgE was assayed to dust mite, cat, cockroach, dog, ryegrass, ragweed, *Alternaria* mold, and *Aspergillus* mold.

children who had a dog in their homes, 25 (38.5%) were exposed to endotoxin levels below the median level for our study, while 40 (61.5%) were exposed to endotoxin levels above the median level for our study. Of the 336 children who had no dog in their home, 161 (47.9%) were exposed to an endotoxin level above the median level for our study.

In these multivariate models, paternal history of eczema was associated with increased odds of eczema in the first year of life. In addition, infants who were born to mothers who were sensitized to at least 1 allergen had higher odds of eczema in the first year of life than infants who were born to nonsensitized mothers. Our results remained similar when we used more restricted outcome criteria for eczema (combination of physician-diagnosed eczema and medication use for eczema; data not shown).

DISCUSSION

Among children with parental history of asthma or allergies, we found that increased levels of endotoxin in the home at 2 to 3 months of age were inversely associated with eczema in the first year of life. To our knowledge, this is the first report of a potentially important protective effect of exposure to endotoxin in early life against the development of eczema in the first year of life.

The role of endotoxin has been a recent topic of interest in asthma development[14,16,17] and allergen sensitization.[4,6,11,18] Previous studies have suggested that endotoxin may shift the developing immune system away from an allergic T-helper cell type 2 (T_h2) response toward a nonallergic T_h1-type response.[5,7,19,20] Early exposure to high levels of endotoxin may cause early transient wheezing, whereas lack of exposure to high endotoxin levels may actually predispose to persistent wheezing and the development of allergy.[21] Less is known about the role of endotoxin and eczema. Gehring et al[7] found in a birth cohort of German children that infants who slept in beds of mothers who had higher levels of endotoxin (fifth quintile) in their mattress dust samples had half the odds of developing doctor-diagnosed eczema by 6 months of age. This association was not significant at age 1.

Several studies have evaluated pet ownership on the development of eczema.[22–26] Nafstad et al[22] found in their Norwegian cohort of 25 321 children that pet exposure in early life decreased the risk of atopic eczema at 0 to 6 months of life. Stratified

TABLE 2. Univariate Analyses of Predictors of Eczema in the First Year of Life

Covariate	Eczema (N = 140)	No Eczema (N = 358)	Univariate Analysis (OR [95% CI])
Dog in home at age 2–3 mo	16 (11.43%)	63 (17.60%)	0.60 (0.34–1.09)
Cat in home at age 2–3 mo	30 (21.43%)	74 (20.67%)	1.05 (0.65–1.69)
Dog allergen levels in house dust*			
<20 μg/g	100 (86.20%)	242 (81.21%)	1.00
≥20 to <200 μg/g	8 (6.90%)	19 (6.38%)	1.02 (0.43–2.40)
≥200 μg/g	8 (6.90%)	37 (12.41%)	0.52 (0.24–1.16)
Cat allergen levels in house dust*			
<1 μg/g	51 (36.69%)	108 (30.17%)	1.00
≥1 to <8 μg/g	53 (38.13%)	153 (42.74%)	0.73 (0.47–1.16)
≥8 μg/g	35 (25.18%)	97 (27.09%)	0.76 (0.46–1.27)
Maternal history of eczema*	29 (21.01%)	80 (22.66%)	0.91 (0.56–1.47)
Paternal history of eczema*	24 (17.91%)	38 (10.89%)	1.79 (1.03–3.11)‡
Endotoxin levels in the home at age 2–3 mo (EU/mg)			
First quartile (range: 2.14–52.48)	39 (35.14%)	61 (21.03%)	1.00
Second quartile (range: 52.50–80.00)	29 (26.13%)	71 (24.48%)	0.64 (0.35–1.15)
Third quartile (range: 80.48–123.19)	26 (23.42%)	75 (25.86%)	0.54 (0.30–0.99)‡
Fourth quartile (range: 125.61–713.20)	17 (15.31%)	83 (28.62%)	0.32 (0.17–0.62)‡
Maternal specific IgE positivity to ≥1 allergen*†	80 (66.11%)	189 (56.42%)	1.51 (0.98–2.32)
Season of birth			
Winter (Dec–Feb)	33 (23.57%)	91 (25.42%)	1.00
Spring (Mar–May)	31 (22.14%)	113 (31.56%)	0.76 (0.43–1.33)
Summer (Jun–Aug)	30 (21.43%)	80 (22.35%)	1.03 (0.58–1.84)
Fall (Sep–Nov)	46 (32.86%)	74 (20.67%)	1.71 (1.00–2.95)§

* There was missing information on cat allergen levels (n = 1), dog allergen levels (n = 84), maternal history of eczema (n = 7), paternal history of eczema (n = 15), maternal IgE positivity to at least 1 allergen (n = 42), and endotoxin levels (n = 97).
† Maternal specific IgE was assayed to dust mite, cat, cockroach, dog, ryegrass, ragweed, *Alternaria* mold, and *Aspergillus* mold.
‡ $P < .05$.
§ $P = .05$.

TABLE 3. Multivariate Analyses of the Association Between Predictors and Eczema in the First Year of Life*

Covariate (Reference)	Model 1 (OR [95% CI]; N = 498)	Model 2 (OR [95% CI]; N = 401)†	Model 3 (OR [95% CI]; N = 401)†	Model 4 (OR [95% CI]; N = 401)†
Dog in home at age 2–3 mo (no)				
Yes	0.48 (0.24–0.97)	0.41 (0.18–0.93)	—	0.54 (0.27–1.09)
Endotoxin levels (lowest quartile)				
Each 1-quartile increment	—	—	0.74 (0.60–0.93)	0.76 (0.61–0.96)
Paternal history of eczema (no)				
Yes	1.85 (1.00–3.41)	1.64 (0.81–3.34)	2.01 (1.09–3.70)	1.91 (1.03–3.54)
Maternal specific IgE positivity to ≥1 allergen (no)‡				
Yes	1.66 (1.04–2.62)	1.98 (1.16–3.37)	1.58 (1.00–2.51)	1.61 (1.01–2.56)
Fall season of birth (no)				
Yes	1.68 (1.03–2.75)	1.93 (1.12–3.31)	1.54 (0.94–2.52)	1.58 (0.96–2.59)

* Models also adjust for gender and household income.
† N = 401 in these models because there were missing values for endotoxin on 97 subjects. Model 2 is a comparison with model 1 using only those children with values for endotoxin.
‡ Maternal specific IgE was assayed to dust mite, cat, cockroach, dog, ryegrass, ragweed, *Alternaria* mold, and *Aspergillus* mold.

analysis showed that the associations were strongest in children of atopic parents. Conversely, Ring et al[23] found in a cohort of 30 000 preschool children that those with animal contact and animal furs in the bed room had a higher odds of developing atopic eczema. The results in our cohort were generally similar to Nafstad's study in showing a potential protective effect of exposure to a dog in early life. However, we did not find an association between exposure to a cat in early life and eczema.

The mechanism of a potential protective effect of exposure to a dog in early life on eczema in early childhood is unclear. Some researchers have suggested that high allergen exposure may increase IgG antibodies, which induces a modified T_h2 response with allergic sensitization.[27] The relationship between endotoxin levels and having a dog in the home is of interest because of the proposed mechanism that endotoxin shifts the developing immune system to a T_h1 response rather than a T_h2 response. In our cohort, we previously found that presence of dog in the home in early life was an important contributor to increased endotoxin levels in the home.[11,14,28] Other groups have found similar relationships between endotoxin levels and animals in the home.[29,30] Although exposure to a dog in early life was inversely associated with eczema in the first year of life, this association was no longer statistically significant after adjustment for exposure to endotoxin in early life. The inverse association between exposure to a dog in early life and eczema could be attributable to the residual confounding effect of endotoxin; however, the absence of a shift in the point estimate when endotoxin was added to the model suggests an independent protective effect of dog on the risk of eczema. However, we had limited statis-

tical power to test this hypothesis because fewer than a quarter of the infants lived with a dog, and we had missing information on dog allergen levels in a number of homes. The precision of the estimate for dog was decreased not by decreasing sample size but by adding endotoxin to the model. However, this does not exclude the possibility that dog has a biological protective effect, independent of endotoxin (see Table 3).

In our study, paternal history of eczema was associated with eczema in the first year of life, but maternal history was not. This is opposite of what has been observed in asthma.[8] In an earlier birth cohort study in England,[31] parental history of eczema was the most significant risk factor for a child's developing atopic dermatitis with a greater risk in paternal over maternal history of eczema. In addition, we found that infants who were born to mothers who were sensitized to at least 1 allergen had higher odds of developing eczema. In a study of 39 infants, Ruiz et al[32] found that children whose mother was sensitized to at least 1 allergen had an earlier onset of atopic dermatitis and that maternal sensitization was a stronger predictor than paternal sensitization.

We recognize several limitations to our study. Our outcome measure was doctor- or nurse-diagnosed eczema in the first year of life. We realize that this diagnosis may not be standard and that using more stringent criteria may affect these results. However, a doctor's diagnosis of other conditions such as asthma and allergic rhinitis have correlated well with indices of disease in our study.[11] Furthermore, maternal report of physician diagnosis of eczema has been previously validated versus clinic examination in the United States[33] and versus chart-recorded diagnosis in Britain.[34] Our study design also used frequent questionnaire administration over the first year of life, which would decrease the likelihood of significant recall and reporting bias between predictor variables and outcome. In addition, we realize that questionnaire report of doctor diagnosis of eczema is not definitive for atopic dermatitis, which is a more clinical diagnosis with features such as chronic dry rash, onset usually under age 2, and history of allergy or other atopic diseases.[35] However, children in our study were selected on the basis of a parental history of asthma or allergies; thus, eczema is more likely to represent atopic dermatitis in our cohort. Furthermore, in another Boston birth cohort, the report of eczema was highly correlated with clinical records of doctor-diagnosed atopic dermatitis.[36]

In conclusion, we found that exposure to high levels of endotoxin in house dust in the first 2 to 3 months of life is associated with a decreased risk of eczema in the first year of life among children with parental history of asthma or allergies. Paternal history of eczema and maternal sensitization to at least 1 allergen were associated with increased odds of eczema in the first year of life.

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HYPERLEXIA

"Children with hyperlexia often have great difficulty fitting in. But their precocious reading skills provide an avenue for interaction with the world. Often, parents and therapists say, such children respond to written directions—'Stop jumping on the couch.' 'Please use a yellow crayon.'—after apparently failing to comprehend spoken instructions. Their memory for the written word can be astonishing. Phyllis Kupperman, a speech pathologist and director of the Center for Speech and Language Disorders, in Elmhurst, IL, recalls the 3-year-old who came to her clinic and assembled crayons on the floor to spell 'Ponderosa Steakhouse.' She says parents can direct their children using written to-do lists: a mother who wants the child to eat dinner before a cookie might write, '1. Vegetable 2. Milk 3. Cookie'."

McGough R. *Wall Street Journal*. January 8, 2004

Submitted by Student

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