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The relationship of blood lead with immunoglobulin E, eosinophils, and asthma among children: NHANES 2005–2006

Ellen M. Wells^{a,b,*}, Tracey L. Bonfield^c, Dorr G. Dearborn^a, Leila W. Jackson^{a,b,d}

^a Department of Environmental Health Sciences, Case Western Reserve University School of Medicine, Cleveland, OH, USA

^b Department of Epidemiology and Biostatistics, Case Western Reserve University School of Medicine, Cleveland, OH, USA

^c Department of Pediatrics, Case Western Reserve University School of Medicine, Cleveland, OH, USA

^d Applied Public Health Research and Evaluation, Cleveland, OH, USA

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ABSTRACT

Early life lead exposure may alter immune function and predispose a child to develop asthma. In an initial exploration of this hypothesis, we examined the association between blood lead, and serum immunoglobulin E (IgE), eosinophils, and asthma prevalence in a cross-sectional study of 1788 children from the National Health and Nutrition Examination Survey 2005–2006. Geometric mean blood lead, serum IgE, and percent eosinophils were 1.13 $\mu\text{g/dL}$ (95% confidence interval (CI): 1.04, 1.22), 46.3 kU/L (95% CI: 40.3, 53.1), and 2.82 percent (95% CI 2.67, 2.98), respectively. Prevalence of asthma, atopic asthma, and atopy were 11.8% (95% CI: 9.5, 14.2), 8.1% (6.2, 9.9), and 44.4% (40.1, 48.7), respectively. Regression models controlled for season, age, sex, race/ethnicity, education, passive smoke exposure, and body mass index. Based on these models, there was an 11.1% (95% CI: 5.6, 16.9) increase in IgE and a 4.9% (95% CI: 2.3, 7.6) increase in eosinophils per 1 $\mu\text{g/dL}$ increase in blood lead. In independent stratified analyses, lead was found to increase IgE and eosinophils among non-Hispanic whites, but not other children; and stronger associations were observed among children who lived with a smoker vs. not. Lead was not associated with asthma, atopic asthma, or general atopy. This study provides additional evidence of a cross-sectional association between lead with IgE and new evidence for eosinophils. This may be a mechanism for development of downstream allergic disease. The mechanisms that determine ultimate development of allergic disease are currently unknown, but are the focus of ongoing studies.

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Introduction

Both childhood lead exposure and asthma are important children's environmental health concerns (Landrigan et al., 2002). There are remarkable similarities in the epidemiology of elevated blood lead levels and childhood asthma: those of lower socioeconomic status, living in poor quality housing, and African-Americans are at elevated risk for elevated blood lead levels as well as asthma (Joseph et al., 2005; Pugh Smith and Nriagu, 2011). Even though lead exposures have been decreasing in recent years, exposures of concern still occur, particularly among lower socioeconomic status children (Levin et al., 2008). This, combined with the fact that lead's immunotoxic responses occur at low exposure levels (Dietert and Piepenbrink, 2006), gave rise to a hypothesis that lead exposure may lead to asthma development (Rabinowitz et al., 1990).

One of the features of lead immunotoxicity is a shift of immune responses away from Th1-associated responses toward Th2-dependent responses (Gao et al., 2007; Heo et al., 1998; McCabe and Lawrence, 1991). This shift can result in reduced delayed hypersensitivity responses and reduced interferon- γ production, with elevated total serum immunoglobulin E (IgE) and production of interleukin-4 (Dietert et al., 2004). Studies have shown that serum IgE is associated with hyperresponsiveness, atopy and asthma (Burrows et al., 1989; Sears et al., 1991). Further, the bronchoalveolar Th2 response has been associated with atopic asthma (Robinson et al., 1992). It has also been established that lead is associated with enhanced airway epithelial cell sensitivity to allergen exposure (Bellanger et al., 2012).

Significant associations between lead and elevated serum IgE were reported in cross-sectional studies of children in Missouri (Lutz et al., 1999) and Germany (Karmaus et al., 2005) and a case-control study in China (Sun et al., 2003). This association was also seen at birth in a French study comparing maternal hair lead concentrations with cord umbilical cord serum IgE (Annesi-Maesano et al., 2003). The relationship of lead with other immune parameters, such as eosinophils, is less clear, in part due to

* Corresponding author at: Department of Environmental Health Sciences, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, OH 44106-4940, USA. Tel.: +1 216 368 5967; fax: +1 216 368 3194.

E-mail address: ellen.wells@case.edu (E.M. Wells).

limited evidence. Among German children there was an unadjusted, nonsignificant positive correlation of lead with eosinophils (Karmaus et al., 2005); however, among Nigerian occupationally exposed workers a significant negative correlation has been reported (Ukaejiofo et al., 2009).

There is also limited evidence regarding a relationship between lead and asthma. Although a recent cross-sectional study in Michigan found a significant association between elevated blood lead and asthma (Pugh Smith and Nriagu, 2011), other case-control (Myers et al., 2002) and cohort studies (Joseph et al., 2005; Rabinowitz et al., 1990) have not observed significant associations. Therefore, the relationship between lead exposure and immune activation and allergic disease has not been thoroughly defined.

The goal for the present study was to better understand the relationship between lead and asthma with emphasis on immunological biomarkers using data from the National Health and Nutrition Examination Survey (NHANES) 2005–2006.

Materials and methods

Study population

This cross-sectional analysis used data from the United States Centers for Disease Control and Prevention's (CDC) NHANES 2005–2006 dataset, which included special components on allergies and housing ((CDC) Centers for Disease Control and Prevention, 2010). The NHANES study population was a stratified, multistage probability sample of the civilian, non-institutionalized United States population. During 2005–2006, the study was oversampled for low-income persons, adolescents, persons >60 years of age, African Americans, and Mexican Americans. Detailed information regarding the NHANES survey can be found from the study website, <http://www.cdc.gov/nchs/nhanes.htm>. NHANES operates with approval from the National Center for Health Statistics Research Ethics Review Board.

Inclusion criteria

Inclusion criteria were being aged 2–12 years, having laboratory data on blood lead concentrations as well as having data on key confounders. Among the 10,348 individuals in NHANES 2005–2006, 1925 children were 2–12 years and had blood lead measurements. The IgE and eosinophil analysis were further limited to 1788 children due to missing data for IgE ($n=41$), eosinophils ($n=9$), cockroaches in the home ($n=12$), current or prenatal smoke exposure ($n=22$), adult educational status ($n=34$), and body mass index ($n=19$). Given asthma is difficult to diagnose in very young children, the asthma analysis was limited to the subset of children aged 4–12 years having asthma and allergy data, resulting in 1430 children.

Data collection and management

Blood samples were collected at the NHANES Mobile Examination Center by trained staff. Samples were analyzed for lead, IgE, and percent eosinophils. Details on collection and processing procedures are available elsewhere ((CDC) Centers for Disease Control and Prevention, 2010). All analytical procedures were conducted in accordance with the Clinical Laboratory Improvement Act.

Lead

Whole blood lead concentrations were determined using inductively coupled plasma mass spectrometry. The detection limit for lead was either 0.25 or 0.30 $\mu\text{g/dL}$, depending on the assay using quality control values for the lower and upper quartile of the standards curves. Only two measurements were below the detection

limit; these were replaced with the detection limit divided by square root of two for analyses. Lead was coded as quartiles for some descriptive and bivariate analyses.

Immunoglobulin E and eosinophils

Serum total IgE concentrations were analyzed using the Pharmacia Diagnostics ImmunoCAP 1000 System (Kalamazoo, Michigan). The lower limit of detection was 2.00 kU/L; samples below the limit of detection were replaced with the detection limit divided by square root of 2 for analyses. No upper limit of detection was reported for total serum IgE. Specific IgE concentrations (*D. farinae*, *D. pteronyssinus*, cat, dog, cockroach, *Alternaria*, peanut, egg, milk, ragweed, rye, Bermuda grass, oak, birch, shrimp, *Aspergillus*, thistle, mouse and rat) were determined with similar methods.

Complete blood counts and white blood cell differentiations were determined at the mobile examination center using a Beckman Coulter MAXM instrument. Complete blood counts were assessed on the Beckman Coulter method and the white blood cell differential uses the Beckman Coulter VCS technology.

Asthma and atopy

Current asthma was self-reported by a responsible adult. Categorization of current asthma required affirmative responses to the following questions: “has a doctor or other health professional ever told you that [the participant] has asthma?” and “does [the participant] still have asthma?” ((CDC) Centers for Disease Control and Prevention, 2010). Atopy was characterized as atopic if the child had at least one specific IgE concentration >0.35 kU/L, as used by Gergen and colleagues previously (Gergen et al., 2009). Allergies were also self-reported, in response to “has a doctor or other health professional ever told you that [the participant] has allergies?”

Demographic characteristics

Age, gender, six-month period of data collection, race/ethnicity and educational status were determined from the demographics questionnaire. Age was coded into tertiles for descriptive analyses. The only seasonal data available were six-month intervals: March through October vs. November through April. Race/ethnicity was reclassified as non-Hispanic white, non-Hispanic Black, and other. Educational status represented adult educational status and was defined as either the educational status of the household reference person or their spouse, whichever was higher. This was classified as less than high school, high school or equivalent, some college or associates' degree, and college graduate or higher. The household reference person is the first individual on the screener module who is over the age of 18 and owns or rents the family residence. Two smoking-related variables were used: the presence of smokers within the home at the time of participation and prenatal exposure to smoke; both were assessed via the participant interview.

The housing characteristics questionnaire was used to determine the presence of small furry animals, cockroaches, or mildew in the home as well as the year the home was built and whether water was treated. Two questions from the allergy questionnaire asked about whether families removed a pet from the home in the past twelve months or avoided bringing pets into the home because the participant had allergies or asthma. For statistical analyses, these were combined into one variable indicating whether the family avoided getting pets or removed pets due to the child's asthma.

Body measurements, including weight and height, were measured at the mobile examination center. These were used to calculate age-specific height, weight and body mass index (BMI) percentiles based on the CDC's 2000 Growth Charts and recommended

Table 1

Population characteristics, lead, IgE, and eosinophils among 2–12 year olds, NHANES 2005–2006.

Characteristic	N ^a (%) ^b	Geometric mean (95% confidence interval)		
		Lead (μg/dL) ^b	IgE (kU/L) ^b	Percent eosinophils ^b
Entire cohort	1788 (100)	1.13 (1.04, 1.22)	46.3 (40.3, 53.1)	2.82 (2.67, 2.98)
Age ^{c,d,e}				
2–5 years	671 (32.2)	1.43 (1.31, 1.55)	36.1 (29.0, 44.9)	2.59 (2.38, 2.82)
6–9 years	568 (36.1)	1.07 (0.97, 1.19)	49.1 (41.6, 58.0)	2.85 (2.61, 3.11)
10–12 years	549 (31.8)	0.94 (0.88, 1.00)	55.6 (47.0, 65.6)	3.02 (2.86, 3.19)
Gender ^{d,e}				
Male	894 (50.0)	1.15 (1.05, 1.26)	56.6 (50.3, 63.7)	3.17 (2.98, 3.37)
Female	894 (50.0)	1.10 (1.01, 1.20)	37.0 (30.9, 44.5)	2.47 (2.31, 2.65)
Race/ethnicity ^{c,d}				
Non-Hispanic white	479 (58.4)	1.04 (0.95, 1.14)	37.3 (29.8, 46.6)	2.83 (2.61, 3.07)
Non-Hispanic black	482 (13.4)	1.51 (1.33, 1.73)	83.0 (70.7, 97.5)	3.12 (2.80, 3.47)
Other race/ethnicity	827 (28.1)	1.16 (1.04, 1.28)	54.9 (44.7, 67.4)	2.65 (2.49, 2.82)
Educational status ^{c,d}				
< High school	532 (17.5)	1.57 (1.38, 1.78)	57.6 (48.8, 67.9)	2.78 (2.44, 3.17)
High school	359 (18.7)	1.16 (0.99, 1.35)	49.7 (35.3, 70.0)	3.05 (2.58, 3.61)
Some college	522 (32.2)	1.09 (0.98, 1.22)	44.8 (35.8, 55.9)	2.83 (2.59, 3.11)
College degree	375 (31.6)	0.95 (0.87, 1.03)	40.6 (30.3, 54.6)	2.68 (2.47, 2.92)
Body mass index ^d				
Normal weight	1218 (72.2)	1.15 (1.04, 1.26)	40.7 (34.7, 47.7)	2.80 (2.64, 2.96)
Overweight	254 (13.0)	1.11 (0.97, 1.28)	61.0 (43.7, 85.3)	2.93 (2.56, 3.36)
Obese	316 (14.8)	1.03 (0.93, 1.15)	67.8 (53.2, 86.6)	2.81 (2.57, 3.07)
Prenatal smoke exposure ^c				
Yes	260 (17.4)	1.31 (1.10, 1.56)	46.6 (34.2, 63.5)	3.00 (2.52, 3.57)
No	1528 (82.6)	1.09 (1.01, 1.18)	46.2 (39.6, 53.8)	2.78 (2.65, 2.91)
Smoker(s) in the home ^c				
Yes	265 (14.2)	1.53 (1.27, 1.83)	48.9 (36.6, 65.2)	2.82 (2.46, 3.23)
No	1523 (85.8)	1.07 (0.99, 1.15)	45.8 (39.0, 53.8)	2.82 (2.65, 2.99)
Season of interview ^c				
November–April	901 (44.5)	1.02 (0.94, 1.12)	47.6 (38.5, 59.0)	2.74 (2.58, 2.90)
May–October	887 (55.5)	1.21 (1.07, 1.37)	45.2 (37.7, 54.2)	2.88 (2.69, 3.09)

NHANES, National Health and Nutrition Examination Survey; IgE, immunoglobulin E.

^a Unweighted sample N.^b Corrected for survey design and weights.^c Statistically significant bivariate association with blood lead between at least two categories, based on linear regression with ln(lead) as the dependent variable, corrected for survey design and weights.^d Statistically significant bivariate association with blood lead between at least two categories, based on linear regression with ln(IgE) as the dependent variable, corrected for survey design and weights.^e Statistically significant bivariate association with blood lead between at least two categories, based on linear regression with ln(eosinophils) as the dependent variable, corrected for survey design and weights.

methods ((CDC) Centers for Disease Control and Prevention, 2011). Participants were then reclassified as normal weight (BMI percentile <85), overweight (BMI percentile 85–95), and obese (BMI percentile >95), according to published recommendations (Barlow and Expert Committee, 2007).

Statistical analysis

Data were analyzed using Stata 12.1 (College Station, TX), and SAS 9.3 (Cary, NC). Stata's survey command was used to accommodate the complex survey design and non-response of NHANES. The two-year examination weight variable was used and sampling error was estimated using the Taylor series linearized method. Geometric means, proportions, percent differences and odds ratios are population-based estimates; however, reported sample sizes are those of the study.

Distributions of blood lead, percent eosinophils, and serum IgE were highly right-skewed, therefore these variables are summarized as geometric means or in quartiles, and the natural logarithm of serum IgE and eosinophils was used in linear regression models. IgE, eosinophils and asthma were also described with respect to quartiles of blood lead concentrations.

Three linear (IgE, eosinophils) or logistic (asthma, atopy) regression models were constructed to examine the association between continuous blood lead concentrations: (1) an unadjusted model, (2) a model controlling for population characteristics (age,

gender, race/ethnicity, educational status, prenatal or current smoke exposure, and BMI), and (3) a model additionally controlling for housing-related characteristics (cockroaches in the home, and removing/avoiding pets). Covariates were considered for inclusion in models based on a priori hypotheses and the strength of their relationship with lead and outcomes in bivariate comparisons. Log transformed serum IgE or percent eosinophils were used in regression models and results were interpreted as the percent difference in IgE per unit increase in blood lead. Adjusted multivariable linear models for lead with IgE or eosinophils, stratified over smoking in the home, age, race/ethnicity, and parent's education were conducted post hoc, as recent work suggests environmental tobacco smoke is an effect modifier (Lutz et al., 2012).

Results

The mean age of children in the IgE/eosinophil analysis was 7.3 years (95% confidence interval (CI): 7.1, 7.5). Other population characteristics for this group are presented in Table 1. Half of the population was male and the majority were non-Hispanic white (72.2%, 95% CI: 67.6, 76.7). Roughly one-quarter of children were overweight or obese. For 63.8% of households, an adult had at least some college education or a college degree. Less than 20% of children were reported to have been exposed to smoke prenatally or have a smoker in the home. These characteristics were similarly distributed for children aged 4–12 years in the asthma analysis.

Table 2

Housing-related characteristics, lead, IgE, and eosinophils among 2–12 year olds, NHANES 2005–2006.

Characteristic	N ^a (%) ^b	Geometric mean (95% confidence interval)		
		Lead (μg/dL) ^b	IgE (kU/L) ^b	Percent eosinophils ^b
Entire cohort	1788 (100)	1.13 (1.04, 1.22)	46.3 (40.3, 53.1)	2.82 (2.67, 2.98)
Small furry pets				
Yes	674 (50.4)	1.09 (1.00, 1.19)	42.9 (36.6, 50.2)	2.83 (2.64, 3.02)
No	1114 (49.6)	1.16 (1.06, 1.28)	50.0 (42.3, 59.1)	2.80 (2.65, 2.97)
Removed pets/avoided getting pets ^{d,e}				
Yes	98 (5.2)	1.07 (0.90, 1.27)	109.6 (63.2, 190.0)	4.43 (3.62, 5.41)
No	1690 (94.8)	1.13 (1.04, 1.23)	44.1 (38.5, 50.7)	2.75 (2.59, 2.91)
Cockroaches ^{c,d}				
Yes	434 (16.5)	1.41 (1.26, 1.59)	68.9 (53.8, 88.2)	3.13 (2.79, 3.51)
No	1354 (83.5)	1.08 (0.99, 1.17)	42.8 (36.9, 49.6)	2.76 (2.60, 2.92)
Mold or mildew smell ^f				
Yes	393 (21.3)	1.23 (1.09, 1.39)	55.9 (45.0, 69.4)	3.02 (2.83, 3.23)
No	1391 (78.7)	1.10 (1.01, 1.20)	44.3 (37.8, 52.1)	2.77 (2.59, 2.97)
Year home was built ^{c,d}				
Before 1950	186 (11.0)	1.48 (1.32, 1.66)	37.9 (28.6, 50.3)	2.71 (2.35, 3.13)
1950 to 1977	390 (23.6)	1.10 (1.01, 1.20)	40.4 (31.5, 51.7)	2.81 (2.53, 3.13)
1978 to present	660 (47.8)	0.94 (0.84, 1.05)	45.9 (36.2, 58.1)	2.82 (2.61, 3.05)
Refused or do not know	552 (17.7)	1.60 (1.37, 1.87)	64.3 (54.5, 75.9)	2.87 (2.62, 3.14)
Water treatment device used ^f				
Yes	469 (66.2)	1.03 (0.94, 1.13)	44.7 (35.3, 56.5)	2.73 (2.55, 2.92)
No	1305 (33.8)	1.17 (1.05, 1.31)	47.1 (39.8, 55.7)	2.86 (2.68, 3.05)

NHANES, National Health and Nutrition Examination Survey; IgE, immunoglobulin E.

^a Unweighted sample N.^b Corrected for survey design and weights.^c Statistically significant bivariate association with blood lead between at least two categories, based on linear regression with ln(lead) as the dependent variable, corrected for survey design and weights.^d Statistically significant bivariate association with blood lead between at least two categories, based on linear regression with ln(IgE) as the dependent variable, corrected for survey design and weights.^e Statistically significant bivariate association with blood lead between at least two categories, based on linear regression with ln(eosinophils) as the dependent variable, corrected for survey design and weights.^f Missing data: mildew (*n* = 4); water (*n* = 14).

Housing characteristics are summarized in Table 2. Nearly half of homes were built after 1977. A slightly higher percentage reported a mold or mildew smell in their home (21.2%, 95% CI: 15.8, 26.8), compared to having cockroaches (16.5%, 95% CI: 12.1, 20.9). Roughly half of the children included in the IgE/eosinophil analysis had small furry pets in the home, and just over five percent reported removing a pet from the home or avoiding getting pets due to asthma. These characteristics were similarly distributed for children aged 4–12 years in the asthma analysis.

The geometric mean blood lead level was 1.13 μg/dL (95% CI: 1.04, 1.22) among the IgE/eosinophil group, and 1.07 μg/dL (95% CI: 0.99, 1.17) among the asthma group. Lead was significantly associated with age (either continuous or in tertiles), race/ethnicity, adult educational status, season of interview, prenatal smoke exposure, presence of smokers in the home, presence of cockroaches in the home, and year the home was built (Tables 1 and 2).

Immunoglobulin E and eosinophils

Geometric mean serum total IgE was 46.3 kU/L (95% CI: 40.3, 53.1) among 2 to 12 year olds. In bivariate analyses, higher total serum IgE was found among children who were older, non-Hispanic black, had parents with less education, had a higher body mass index, removed or avoided pets, had cockroaches in the home, and lived in older housing (Tables 1 and 2). Additionally, higher IgE was found among children with higher lead concentrations (Table 3).

In a model controlling for population characteristics (Model 1) there was an 11.1% (95% CI: 5.6, 16.9) increase in IgE per 1 μg/dL increase in blood lead (Table 4). The association decreased slightly, but remained statistically significant when housing-related variables were included (Model 2: 10.3, 95% CI: 3.5, 17.5). Results were attenuated but still statistically significant if Model 1 was further

adjusted for eosinophils (6.28%, 95% CI: 0.37, 12.53); if Model 2 was further adjusted for eosinophils results were of borderline statistical significance. Other characteristics significantly associated with increasing IgE concentrations included increasing age, male (vs. female), non-Hispanic black and other race/ethnicity (vs. non-Hispanic white), overweight and obese (vs. normal weight), and having removed or avoided obtaining a pet due to allergies or asthma (vs. not), in adjusted analyses (Model 1).

Geometric mean percent eosinophils was 2.82% (95% CI: 2.67, 2.98) among 2–12 year olds. In general, associations observed for eosinophils were similar those observed for IgE; there was a significant bivariate association between lead and eosinophils (Table 3). There was a 4.90% (95% CI: 2.28, 7.57) and 4.61% (95% CI: 2.44, 6.83) increase in percent eosinophils for each 1 μg/dL increase in blood lead in models adjusting for demographics (Model 1) and demographics and housing characteristics (Model 2), respectively (Table 4). When Model 1 was additionally adjusted for IgE, the lead and eosinophil association was attenuated but remained statistically significant (2.78%, 95% CI: 0.08, 5.54); results were also statistically significant when Model 2 was additionally adjusted for IgE.

Multivariable models were stratified by population characteristics and adjusted for the same covariates as Model 1 (Fig. 1). An association between lead and IgE was seen among children living with a smoker, but not among children living in smoke-free homes; for lead and eosinophil models, a significant association was observed within both strata. Both a lead–IgE and lead–eosinophil association was seen among non-Hispanic white children but not children of other race/ethnicity. A non-significant trend by age category and an association among children of low socioeconomic status, assessed by adult educational level, were also observed. Confidence intervals for the stratified analyses were notably larger than in the main analysis, due to reduced sample sizes.

Table 3

Immune outcomes and lead, IgE, and eosinophils, NHANES 2005–2006.

Characteristic	N ^a (%) ^b	Geometric mean (95% confidence interval)		
		Lead (μg/dL) ^b	IgE (kU/L) ^b	Percent eosinophils ^b
All 2–12 year olds	1788 (100)	1.13 (1.04, 1.22)	46.3 (40.3, 53.1)	2.82 (2.67, 2.98)
Immunoglobulin E, quartiles ^{c,d,e}				
1.41–17.8 kU/L	448 (28.5)	1.05 (0.93, 1.19)	7.8 (7.1, 8.6)	2.08 (1.96, 2.20)
17.9–50.4 kU/L	446 (24.6)	1.12 (1.00, 1.26)	30.0 (29.1, 30.9)	2.40 (2.23, 2.58)
50.5–146.0 kU/L	447 (25.4)	1.13 (1.02, 1.26)	81.3 (77.0, 85.9)	3.00 (2.76, 3.26)
147.0–535.0 kU/L	447 (21.5)	1.23 (1.06, 1.40)	412.1 (356.2, 476.8)	4.70 (4.07, 5.44)
%Eosinophils, quartiles ^{c,d,e}				
0.2–1.7%	511 (26.3)	1.07 (0.98, 1.17)	22.5 (18.3, 27.6)	1.21 (1.16, 1.27)
1.8–2.7%	418 (23.2)	1.09 (0.96, 1.24)	31.6 (25.5, 39.2)	2.22 (2.19, 2.26)
2.8–4.4%	426 (26.3)	1.16 (1.04, 1.29)	50.9 (41.2, 62.7)	3.41 (3.35, 3.47)
4.5–22.1%	433 (24.2)	1.20 (1.08, 1.33)	131.7 (96.5, 179.6)	7.15 (6.75, 7.59)
All 4–12 year olds	1430 (100)	1.07 (0.99, 1.17)	50.8 (44.9, 57.5)	2.89 (2.72, 3.08)
Asthma ^{d,e}				
Yes	162 (11.8)	1.00 (0.92, 1.09)	110.6 (60.1, 203.2)	4.17 (3.42, 5.09)
No	1268 (88.2)	1.08 (0.99, 1.18)	45.9 (39.7, 53.2)	2.75 (2.57, 2.94)
Atopy ^{d,e}				
Yes	691 (44.4)	1.07 (0.97, 1.18)	129.1 (107.8, 154.8)	3.70 (3.44, 3.98)
No	739 (55.6)	1.07 (0.99, 1.16)	24.2 (20.4, 28.8)	2.37 (2.21, 2.55)
Allergies ^{d,e}				
Yes	308 (23.4)	1.02 (0.92, 1.12)	76.1 (62.4, 92.7)	3.63 (3.25, 4.05)
No	1122 (76.6)	1.09 (1.00, 1.20)	45.1 (39.0, 52.1)	2.70 (2.52, 2.89)
Asthma and atopy ^{d,e}				
Yes	107 (8.1)	0.97 (0.83, 1.14)	213.5 (135.8, 335.9)	5.43 (4.27, 6.90)
No	1323 (91.9)	1.08 (1.00, 1.18)	44.9 (39.4, 51.3)	2.74 (2.56, 2.92)
Asthma, no atopy ^d				
Yes	55 (3.8)	1.07 (0.88, 1.31)	27.0 (15.0, 48.5)	2.37 (1.85, 3.04)
No	1375 (96.2)	1.07 (0.99, 1.17)	52.2 (45.8, 59.6)	2.91 (2.74, 3.10)
Atopy, no asthma ^{d,e}				
Yes	584 (36.3)	1.10 (0.98, 1.22)	115.5 (98.4, 135.6)	3.40 (3.13, 3.68)
No	846 (63.7)	1.06 (0.98, 1.15)	31.9 (27.2, 37.5)	2.64 (2.47, 2.82)
Allergies, no asthma, no atopy ^{d,e}				
Yes	82 (7.4)	1.13 (1.00, 1.28)	17.2 (11.0, 26.8)	2.44 (2.17, 2.75)
No	1348 (92.6)	1.07 (0.98, 1.16)	55.6 (48.3, 63.9)	2.93 (2.75, 3.12)

NHANES, National Health and Nutrition Examination Survey; IgE, immunoglobulin E.

^a Unweighted sample N.^b Corrected for survey design and weights.^c Statistically significant bivariate association with blood lead between at least two categories, based on linear regression with ln(lead) as the dependent variable, corrected for survey design and weights.^d Statistically significant bivariate association with blood lead between at least two categories, based on linear regression with ln(IgE) as the dependent variable, corrected for survey design and weights.^e Statistically significant bivariate association with blood lead between at least two categories, based on linear regression with ln(eosinophils) as the dependent variable, corrected for survey design and weights.

Asthma and atopy

Among 4–12 year olds, 11.8% (95% CI: 9.5, 14.2) reported currently having asthma. Prevalence was 10.1%, 11.1% and 13.9% among 4–6 year olds, 7–9 year olds, and 10–12 year olds, respectively. Fewer children, 8.1% (95% CI: 6.2, 9.9), had atopic asthma; these similarly increased by age category. In bivariate analysis (Table 3), asthma and atopic asthma were associated with IgE and eosinophils. Neither asthma nor atopic asthma was associated with higher lead concentrations. Results did not change after adjusting for covariates (Table 4). In the model controlling for population characteristics (Model 1), the adjusted odds ratio for asthma per 1 μg/dL increase in blood lead was 0.92 (95% CI: 0.73, 1.17). This was similar after adjusting for both population and housing-related characteristics (Model 2). In Model 2, having removed or avoided having pets due to asthma or allergies (vs. not) was related to a significantly increased odds of asthma prevalence. Results were similar for children who had atopic as well as nonatopic asthma (Table 4).

Less than half of the 4–12 year olds (44.4%, 95% CI: 40.1, 48.7) were atopic; somewhat fewer were atopic but did not have current asthma (36.3%, 95% CI: 32.5, 40.1). Bivariate associations were similar to those with asthma. In contrast to the asthma results, the point estimates from multivariable models suggest increasing

lead relates to increasing atopy or atopy without asthma; however, these results were not statistically significant.

Roughly one-quarter of the population reported having allergies; we observed a significant, negative association between lead exposure and self-reported allergies.

Discussion

In this study, we present a cross-sectional association between lead and the first line development of potential allergic responses, systemic levels of IgE and eosinophils. This suggests an important role in the mechanisms of potential down-stream development of allergic disease. The mechanisms that determine the ultimate development of allergic disease are unknown, but are the focus of on-going studies. We did not observe, however, an association of lead with asthma or atopy.

Our finding of a significant association between blood lead levels and serum IgE is similar to those from prior studies among children. A study in urban Missouri among 279 children aged 9 months to 6 years found a statistically significant increase in IgE with increasing lead exposure; analyses were adjusted for age (Lutz et al., 1999). In a case-control study, IgE concentrations were compared among 73 Chinese preschool children aged 3–6 years with blood lead levels ≥10 μg/dL vs. <10 μg/dL; a statistically significant relationship of

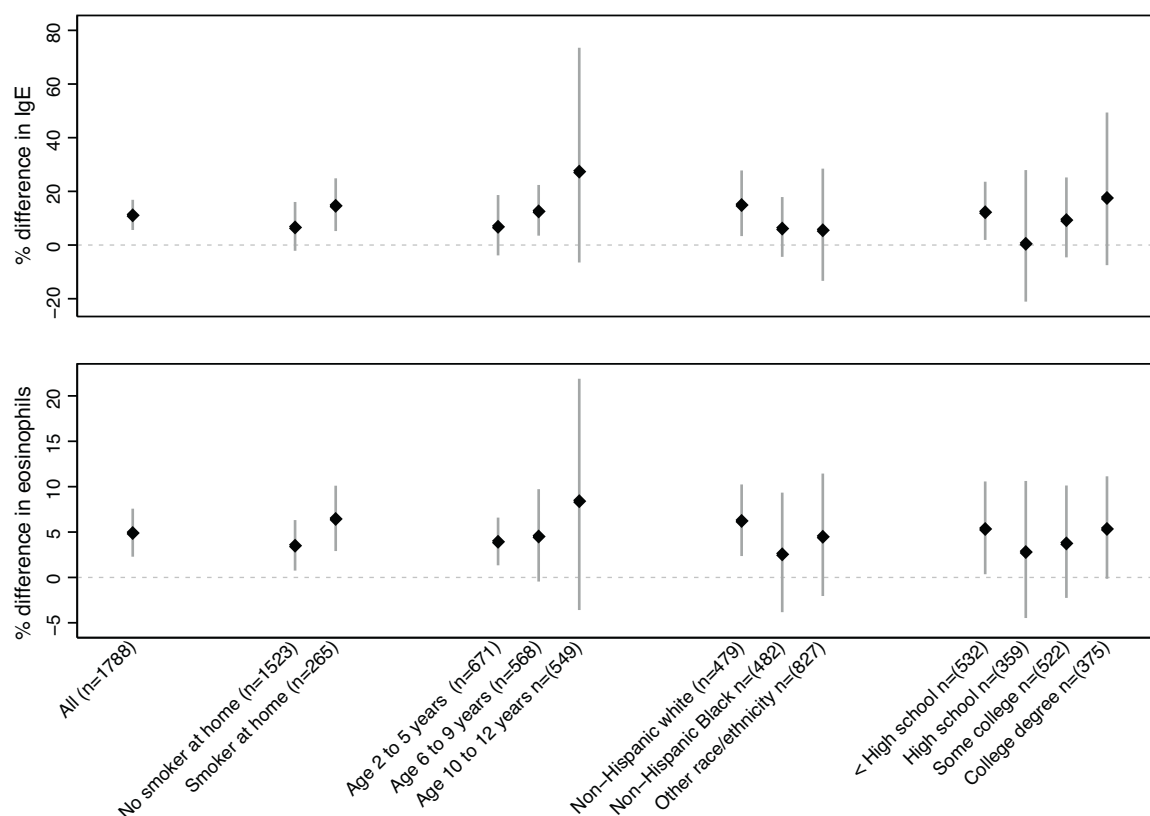


Fig. 1. The adjusted percent difference and 95% confidence interval in IgE or eosinophils per 1 µg/dL increase in blood lead among 2–12 year olds from NHANES 2005–2006. Results are shown for the entire study population (as reported in Model 1, Table 4) as well as stratified by self-reported smoker at the home, age group, race/ethnicity, and parental education. Percent difference is adjusted for age, sex, race/ethnicity, parental education, season (May–October/November–April), smoker in the home, and body mass index category. IgE = immunoglobulin E; NHANES = National Health and Nutrition Examination Survey.

lead and IgE was only found in a subanalysis limited to girls (Sun et al., 2003). More recently, a cross-sectional study among 331 German children 7–10 years old reported higher IgE concentrations among those with higher lead concentrations, adjusting for age, gender, infections, and passive smoke exposure (Karmaus et al., 2005). A cross-sectional study among 374 French mother-newborn pairs noted that the relationship between blood lead and IgE was stronger among children born to mothers without an IgE-mediated disease vs. children born to mothers with a condition potentially mediated by IgE, suggesting that the relationship with lead may be more important among those without a family history of allergic disease (Annesi-Maesano et al., 2003).

We also observed a significant association of lead with increased eosinophils. There is very little prior work on this association. A toxicology study by Hogan and colleagues found no association between lead and eosinophils (Hogan and Lee, 1987). Epidemiology studies among highly exposed populations have noted positive (Karmaus et al., 2005) and negative (Ukaejiofo et al., 2009) correlations between lead and eosinophils; however, these analyses were not adjusted for covariates.

Recent work has suggested that environmental tobacco smoke may be an effect modifier of the relationship between lead and IgE (Lutz et al., 2012). This relationship was also observed in the present study in stratified analyses. Similarly, we observed that low socioeconomic status, as identified through parental education, may also be an effect modifier. This is consistent with emerging evidence that the combination of multiple stressors, or exposures, may be involved with the development of disease (Schwartz et al., 2011). However, these results should be interpreted with some caution, due to the smaller sample sizes resulting from stratification within this complex dataset.

We did not observe any association of lead with asthma, atopic asthma, atopy, or atopy without asthma in this study. At the same time, we found a significant negative association between lead and allergies; however, as allergies was self-reported and is a very heterogeneous category, this is difficult to interpret further. Our results are not consistent with another cross-sectional study of lead exposure and asthma in Michigan (Pugh Smith and Nriagu, 2011). The former study consisted of inner city, low-income children (Pugh Smith and Nriagu, 2011), compared with our study population: a representative sample of the United States. Another possible explanation for differences between these studies could be higher lead exposures among the Michigan population, 19% ≥ 10 µg/dL, compared with the current study, <1% ≥ 10 µg/dL (Pugh Smith and Nriagu, 2011). Our results for asthma are consistent, however, with other prior studies on lead exposure and asthma among children (Joseph et al., 2005; Myers et al., 2002; Rabinowitz et al., 1990); notably, these studies also evaluated children with substantially higher average blood lead concentrations than the present analysis.

The hypothesis that immunotoxic effects of lead may result in development of asthma is not only dependent on exposure to lead occurring before asthma development, but potentially on lead exposure prenatally or in early childhood. Peden suggests that fetuses develop Th2 capacity early during development, and then develop Th1-mediated mechanisms later in life (Peden, 2000). In animal studies, pups exposed to lead *in-utero* exhibited an imbalance in Th1/Th2 (favoring Th2); whereas there was no effect seen in the exposed mothers (Miller et al., 1998). Based on this evidence, Dietert and colleagues argued that there were critical windows of exposure related to lead and immunotoxic outcomes which may affect the strength of the relationship between lead and these

Table 4

Association of blood lead with immune outcomes, NHANES 2005–2006.

Model	Outcome
IgE (kU/L) (N = 1788, 2–12 years)	Percent difference (95% CI)
Unadjusted model	10.17 (3.83, 16.89)
Model 1	11.09 (5.61, 16.85)
Model 2	10.27 (3.52, 17.47)
Percent eosinophils (N = 1788, 2–12 years)	Percent difference (95% CI)
Unadjusted model	4.30 (1.21, 7.48)
Model 1	4.90 (2.28, 7.57)
Model 2	4.61 (2.44, 6.83)
Asthma (N = 1430, 4–12 years)	Odds ratio (95% CI)
Unadjusted model	0.87 (0.71, 1.08)
Model 1	0.92 (0.73, 1.17)
Model 2	1.01 (0.76, 1.35)
Atopy (N = 1430, 4–12 years)	Odds ratio (95% CI)
Unadjusted model	1.03 (0.95, 1.11)
Model 1	1.04 (0.93, 1.16)
Model 2	1.05 (0.93, 1.18)
Allergies (N = 1430, 4–12 years)	Odds ratio (95% CI)
Unadjusted model	0.82 (0.70, 0.96)
Model 1	0.84 (0.75, 0.96)
Model 2	0.89 (0.79, 1.01)
Asthma and atopy (N = 1430, 4–12 years)	Odds ratio (95% CI)
Unadjusted model	0.84 (0.58, 1.21)
Model 1	0.87 (0.58, 1.33)
Model 2	0.97 (0.61, 1.55)
Asthma, no atopy (N = 1430, 4–12 years)	Odds ratio (95% CI)
Unadjusted model	0.04 (0.02, 0.06)
Model 1	1.02 (0.84, 1.23)
Model 2	1.07 (0.86, 1.33)
Atopy, no asthma (N = 1430, 4–12 years)	Odds ratio (95% CI)
Unadjusted model	1.08 (0.98, 1.19)
Model 1	1.08 (0.91, 1.27)
Model 2	1.06 (0.89, 1.25)
Allergies, no asthma, no atopy (N = 1430, 4–12 years)	Odds ratio (95% CI)
Unadjusted model	0.99 (0.82, 1.20)
Model 1	1.03 (0.82, 1.28)
Model 2	1.04 (0.83, 1.32)

NHANES, National Health and Nutrition Examination Survey; CI, confidence interval; IgE, immunoglobulin E. All models account for complex survey sampling and weights. Difference or odds is based on a 1 µg/dL increase of blood lead. Model 1 adjusts for 6-month season, age, sex, race/ethnicity (non-Hispanic white/non-Hispanic black/other), parental educational status (<high school, high school, some college, 4-year college degree), presence of smokers in the home (IgE only) or prenatal smoke exposure (asthma only) and body mass index category. Model 2 additionally adjusts for presence of cockroaches in the home and avoidance/removal of pets.

outcomes (Dietert et al., 2004). Our cross-sectional data of blood lead at age four (asthma) may be beyond this critical window.

The concept of critical windows in the prenatal period leading to atopy later in life is supported by recent work from a longitudinal birth cohort study in Poland (Jedrychowski et al., 2011). Jedrychowski and colleagues found a significant association between cord blood lead concentrations and a positive skin prick test to a common aeroallergen at age 5 (Jedrychowski et al., 2011). Early exposure to lead may set the stage for altering the overall predisposition of markers traditionally associated with the development of atopy, and how this translates into asthma or other types of atopic diseases is then ultimately defined by other genetic or environmental factors.

Literature suggests traces of toxic metals like lead have the capacity to participate as adjuvants when associated with allergens. This, in turn, can be involved in promoting IL-5 production, eosinophil migration and proliferation, as well as, activate Th2 cytokines (Bellanger et al., 2012). Some authors have shown lead

can stimulate the production of cytokines and IgE antibodies (Skoczynska et al., 2002). The theory is that since lead has the capacity to increase the ratio of Th2/Th1 cytokines, it has the potential to shift the cytokine environment in the direction of specifically promoting antibody switch to IgE antibody mediated B-cell maturation (Heo et al., 1996). Lead also has the capacity to define the direction of immune maturity and response through its impact on antigen presenting cells such as alveolar macrophages (Geertz et al., 1994; Shabani and Rabbani, 2000) and dendritic cells (Gao et al., 2007). Further, data has linked lead haptenization with antigen in defining MHC class II presentation and adaptive T-cell responses (Fang et al., 2012), suggesting lead can intervene in the adaptive communication process.

Alteration of antigen presentation and the enhanced capacity to augment the potency of the antigen sensitivity response suggest a viable mechanism associating lead with the immunopathology of atopic immune responses. The metal may initiate a response that stimulates a T-cell clonotype that takes on a lower threshold for activation, even in the absence of lead. Alveolar macrophages in healthy lung are thought to exist in the alternative state, quiescent to immediate exacerbations to antigenic exposure (Bonfield et al., 2008). Lead can alter the macrophage state shifting it to a different form of macrophage activation with the preferential antigen presentation pushing adaptive responses to the Th2 phenotype (Mantovani and Locati, 2009). Lead has the capacity of inhibiting antigen presentation, which in itself has the capacity to redefine the direction of the adaptive response (Lawrence and McCabe, 2002). Further, lead significantly inhibited bone marrow derived dendritic cell generation based upon CD11c expression, but the dendritic cells generated with lead exposure had greater MHC class II expression (Gao et al., 2007). These studies further showed that lead exposure altered response to LPS (a gram negative bacteria analog), resulting in less CD80 expression (T-cell co-stimulator) and altered IL-6, IL-10, IL-12(p70) and TNFα levels. The lead modification of dendritic cell function appears to be the main cause of the lead induced Th2-immunity which may be related to the ability of lead exposure to enhance the activation of the Erk/MAP kinase pathway (Gao et al., 2007).

It may be that in our study, phenotypic changes defined by alveolar macrophages, T-cells and macrophage exposure skewed IgE production with the potential of atopy or asthma to be a more downstream endpoint defined by other genetic modifiers. Future studies would involve teasing out the impact of lead on alveolar macrophage, T-cell or B-cell differentiation and maturity and how that might define events leading to IgE production. Whether the relative levels of IgE, have the ultimate capacity to define downstream allergic events, autoimmunity, or atopy beyond the age groups identified in this study remain to be determined.

The most interesting correlation in this manuscript is the impact of lead on the production of IgE and recruitment of eosinophils. The impact of lead on IL-5 production suggests an indirect role on the recruitment of eosinophils. In our study, there is a cross-sectional correlation of lead with percent eosinophils (Table 3). Eosinophils set the stage for the release of histamine and the forward development of atopic responses to allergy. Eosinophil activation is induced by many factors but the best described is the cross-linking on the receptor-ε, which implicates lead in not only the recruitment of eosinophils but also the availability of IgE to enhance activation. Eosinophils are generated in the context of IL-5, which can be induced by lead exposure. Lead also has the ability to induce B-cell activation and push the genetic rearrangement of the cells to secrete IgE. The combined effects of IgE and eosinophilic recruitment suggests that lead primes the immune system toward a scenario contributing to immune-pathology similar to asthma or other allergic diseases. Although our study does not show a direct correlation between lead and atopy or asthma, it does suggest that

there is an underlying modulation of the immune system post-lead exposure that results in a shift toward allergic diseases.

There are several strengths to the present study. The NHANES database provided a large, nationally representative sample of children. These data also provided information on a large number of potential confounders. In particular, the 2005–2006 survey included data relevant to both respiratory disease and housing-related exposures. Another strength of this study was its capacity to explore the relationships of interest among those with lower blood lead concentrations. Previous studies have examined associations in populations with higher blood lead levels often using 10 µg/dL or greater concentrations to categorize lead (Lutz et al., 1999; Myers et al., 2002; Sun et al., 2003); however, adverse health effects occur below this level. Blood lead concentrations in the current study are representative of current United States population levels; and the current study demonstrates the association between lead and IgE persists at these lower lead concentrations.

A limitation of this study is its cross-sectional design. Therefore, we are not able to establish that lead exposure occurred prior to asthma development or were causally associated with increased IgE levels, much less that lead exposures occurred prenatally. The lack of an association observed in the current study between concurrent blood lead levels and asthma status does not exclude the possibility that prenatal lead exposure may be related to the development of asthma in later childhood. Similarly, the prospective cohort study by Joseph and colleagues relied on blood lead levels taken at ages 1–3 years, which also does not necessarily reflect prenatal exposures (Joseph et al., 2005).

Another potential limitation is that asthma was self-reported by a responsible adult, instead of being verified using medical records, a standardized symptom questionnaire, or spirometry, none of which were available. The child's family and medical history and specific data on seasons were also not available. Our method for defining asthma could result in underreporting of asthma cases, as children may not yet be diagnosed with asthma or the responsible adult may not be aware of the child's asthma status. If underreporting of asthma was independent of lead exposure, the underreporting would bias the odds ratio toward the null, if an association between lead and asthma truly exists. It is not likely, however, that this has affected our results. Geometric mean lead levels were very similar between children with asthma and those who reported wheezing in the past 12 months (data not shown), which has been used as a proxy for undiagnosed asthma in other studies (Akinbami et al., 2005). Additionally, racial or ethnic disparities, which are frequently associated with lead exposures, do not seem to differ between those with undiagnosed vs. diagnosed asthma (Akinbami et al., 2005; Quinn et al., 2006).

In conclusion, this study confirms and adds to the growing body of work identifying a significant cross-sectional association between lead and IgE or eosinophils, but not between lead and asthma. Future longitudinal studies examining the association between lead and IgE, eosinophils, and asthma are recommended in order to establish temporality of exposure and disease, and to investigate potential critical windows of prenatal lead exposure.

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