

Lead exposure and increased food allergic sensitization in U.S. children and adults

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Background: Whether blood lead levels are associated with sensitization to food allergens in adults and children is unclear. Prior studies have shown that exposure to lead is associated with atopic sensitization and modulation of several cytokines (eg, interleukin [IL]-12, IL-10, interferon [IFN]- γ , and IL-4 production) and with T-cell dysregulation and bias toward T helper 2 (Th2) activity. The objective of this work was to assess whether exposure to lead is independently associated with allergic symptoms and sensitizations in a large nationally representative sample of children and adults.

Methods: We studied 2712 children and 4333 adults enrolled in the 2005-2006 cycle of the National Health and Nutritional Examination Surveys (NHANES). Participants were tested for serum-specific immunoglobulin E (IgE) levels to food allergens as well as blood lead levels. Food allergens tested included shrimp, egg, peanut, and milk. Logistic regression models adjusted for demographic factors, body mass index, history of asthma, smoking, housing characteristics, and current exposure to animals in the home, to assess the association of blood lead levels with sensitization to food allergens.

Results: Median (interquartile range [IQR]) for serum blood was 0.87 $\mu\text{g/L}$ (0.61 to 1.31) in children and 1.48 $\mu\text{g/L}$

(0.92 to 2.34) in adults. At baseline, 672 (24.7%) of children participants and 719 (16.6%) of adult participants tested positive for increased sensitization to food allergens. A 2-fold increase in blood lead levels in adult participants was associated with increased sensitization to food allergens (odds ratio [OR], 1.11; 95% confidence interval [CI], 1.02 to 1.22). Blood lead was not associated with sensitization to food allergens among pediatric participants (OR, 0.95; 95% CI, 0.82 to 1.10).

Conclusion: Exposure to lead was associated with increased odds of sensitization to food allergens in adult but not children participants. © 2014 ARS-AAOA, LLC.

Key Words:

lead; food allergy; sensitization; allergens; type I allergy

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Lead (Pb) exposure is a public health concern in the United States, especially in children and persons of low socioeconomic status who are disproportionately exposed to Pb.¹ The current screening threshold established by the Centers for Disease Control and Prevention (CDC) is 5 $\mu\text{g/dL}$; however, deleterious effects may occur at lower doses.² Pb is considered a xenobiotic and continued exposure may have deleterious immunotoxic effects.³

In small studies in children conducted in 1990s in the Midwest United States, Pb exposure was associated in a dose-dependent manner with increased levels of immunoglobulin E (IgE).^{1,4-7} These findings are potentially important as increased IgE is hypothesized to increase

allergic predisposition in adulthood. Epidemiologic cross-sectional studies observations in Europe suggest that exposure to heavy metal pollutants may in fact partly account for regional differences in the prevalence of allergic sensitization.⁸

Evidence of the link between environmental toxicants and allergy food sensitization is limited; however, recent studies have shown immunotoxic effects of Pb in adults, children, and animal models.⁹ The immune system specifically is very sensitive to Pb toxicity even at low subclinical levels.⁹ In mouse models, moderate Pb exposure may produce a mitogenic effect on lymphocytes, and toxic effect with cellular death at the highest levels of Pb exposure.¹ A recent study in adults from the National Health and Nutrition Examination Survey (NAHNES) 2005-2006 cycle evaluating urine Pb levels, showed an association between urine Pb levels and elevated allergen-specific IgE levels to egg, milk, and shrimp. However, blood Pb levels, a better biomarker of Pb exposure and the standard guideline measure used for evaluating Pb toxicity, was not evaluated.¹⁰

Exposure to Pb has shown to decrease host resistance to disease even at levels originally assumed to not be cytotoxic to immune cells.¹¹ Furthermore, although low levels of Pb exposure may not necessarily lead to immune cell death, a significant shift from T helper 1 (Th1)-dependent to Th2-dependent responses has been observed, perhaps contributing to increased incidence of allergic sensitization through increased production of interleukins, cytokines, and IgE.¹² Interestingly, exposure to Pb during different developmental periods of gestation in rats may lead to differing immunologic changes after birth through adulthood. Early gestation exposure to Pb may lead to predominately altered macrophage function, and late gestation exposure may lead to a shift in Th1/Th2 balance that may continue into adulthood.³

In this study, we investigated whether blood Pb levels are associated with food allergy sensitization as measured by food-specific serum immunoglobulin levels in a nationally representative sample of adult and pediatric participants in the NHANES 2005-2006 cycle.

Patients and methods

Study population

NHANES is a national, population-based, multiyear, cross-sectional epidemiological study designed to assess the health, functional, environmental, and nutritional status of the civilian, noninstitutionalized U.S. population. We analyzed data from the 2005-2006 cycle because food allergy sensitization was tested during that cycle. A total of 12,862 adults and children participated in NHANES 2005-2006 interviews and examinations. The response rate was 77%. This study was restricted to participants who were not missing food allergy sensitization test or whole blood Pb levels ($n = 2863$ children, $n = 4418$ adults). We fur-

ther excluded participants missing data on other covariates of interest ($n = 151$ children, $n = 85$ adults), leaving a total of 2712 children and 4333 adults for this study. The NHANES protocol was reviewed and approved by the National Center for Health Statistics institutional review board and informed consent was provided by the participants and their guardians for those younger than 18 years of age.

Food allergy sensitization testing

Participants were tested for serum-specific IgE levels to food allergens. Food allergens tested for included shrimp, egg, peanut, and milk.

Serum IgE concentrations were measured in children and adults using the ImmunoCAP 1000 system (Pharmacia Diagnostics, Kalamazoo, MI) at the NHANES medical examination center. For food sensitization identification, a clinical cutoff of 0.35 kU/L was used.^{13,14}

Blood lead

The National Center for Environmental Health measured blood levels following standardized protocols, including confirmation that collection and storage materials were not contaminated with Pb. Pb in whole blood was measured by means of coupled plasma mass spectrometry. The limit of detection was 0.3 $\mu\text{g/dL}$. For those participants ($<1\%$) whose blood Pb levels were below the limit of detection, blood Pb levels were replaced by limit of detection divided by the square root of 2 (Hornung and Reed¹⁵). Whole blood lead (Pb) concentrations were reported in micrograms per deciliter ($\mu\text{g/dL}$).

Other covariates

Questionnaire information included age, gender, race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American, Other), educational level of the household reference person (less than high school, high school or equivalent, more than high school), the year the family house was built (by self-report), presence of cockroaches, animals, or musty smell at home (by self-report). NHANES measured height and weight during the physical examination. Body mass index (BMI) percentiles in children were calculated based on the CDC's BMI for age- and gender-specific growth charts, and categorized as normal, overweight, or obese if BMI percentiles were ≤ 84 , 85 to 94, and ≥ 95 , respectively. For adults, BMI was defined as measured weight in kilograms divided by the square of the height in meters (kg/m^2).

Asthma was defined using self-report information from the participant questionnaire. Active smoking and secondhand tobacco smoke exposure was assessed using self-reported data from the participant questionnaire, the house questionnaire, and serum cotinine concentrations. Participants who self-reported having smoked during the last month as well as those who had serum cotinine

TABLE 1. Demographic characteristics of adult and children participants, National Health and Nutritional Examination Surveys, 2005–2006*

	Allergy sensitization to food in children (n = 2712)		Allergy sensitization to food in adults (n = 4333)	
	(+) Present (≥ 0.35 kU/L) (n = 672)	(–) Absent (< 0.35 kU/L) (n = 2040)	(+) Present (≥ 0.35 kU/L) (n = 719)	(–) Absent (< 0.35 kU/L) (n = 3614)
Gender				
Male	370 (58.0)	976 (49.7)	424 (60.2)	1650 (45.9)
Female	302 (42.0)	1064 (50.3)	295 (39.8)	1964 (54.1)
Ethnicity				
White	134 (53.3)	581 (63.8)	283 (61.2)	1903 (52.7)
Black	290 (22.2)	586 (12.2)	229 (18.0)	727 (20.1)
Mexican	189 (12.1)	703 (12.5)	151 (9.7)	738 (20.4)
Other	59 (12.4)	170 (11.4)	56 (11.1)	246 (6.8)
Education				
Less than high school	224 (20.6)	645 (18.2)	218 (20.0)	973 (17.0)
High school	142 (23.0)	510 (26.8)	179 (24.3)	850 (24.8)
Greater than high school	306 (56.4)	885 (55.0)	322 (55.7)	1791 (58.2)
BMI				
Normal	399 (59.4)	1270 (62.3)	197 (29.4)	1116 (30.9)
Overweight	103 (15.3)	334 (16.4)	245 (34.5)	1249 (34.6)
Obese	170 (25.3)	436 (21.4)	277 (36.1)	1249 (34.6)
Source of allergens				
Cockroaches at home	290 (35.3)	130 (3.8)	348 (43.6)	203 (4.3)
Cats at home	216 (36.4)	166 (7.5)	210 (32.8)	262 (8.1)
Dogs at home	290 (44.0)	172 (7.7)	260 (38.6)	193 (6.1)
Musty smell at home	126 (18.9)	383 (18.6)	104 (15.1)	568 (16.1)
Medical history				
Asthma	174 (28.8)	282 (14.3)	144 (23.2)	420 (12.7)
Secondhand smoke exposure	476 (67.9)	(1421)69.3	214 (28.0)	980 (25.2)
Active smoking	81(11.6)	(249)12.2	223 (32.2)	975 (29.4)
Serum lead level ($\mu\text{g/dL}$)	0.90 (0.62–1.38)	0.86 (0.61–1.29)	1.54 (0.94–2.35)	1.47 (0.91–2.34)
Year home built				
Before 1950	78 (11.2)	263 (12.3)	114 (16.9)	639 (18.2)
1950–1978	144 (20.9)	469 (24.8)	173 (23.6)	877 (24.7)
After 1978	256 (49.7)	731 (47.4)	233 (41.2)	1325 (44.1)
Unknown	194 (18.2)	577 (15.5)	199 (18.3)	773 (13.0)

*Data in are n (weighted percentages) for categorical variables and median (interquartile range) for continuous variables.
 BMI = body mass index.

concentrations ≥ 10 ng/mL were classified as active smokers. Secondhand smoke exposure was defined as nonactive smokers who self-reported living with at least one person who smoked or who had cotinine levels be-

tween 0.05 ng/mL and 10 ng/mL. Participants with serum cotinine levels below 0.05 ng/mL, those not living with an active smoker, and those who did not smoke within the last month were classified as unexposed to tobacco.

TABLE 2. Multiple logistic regression examining the association of serum lead level and food allergic sensitization in children and adults from the National Health and Nutrition Examination Survey, 2005–2006 cohort

		Odds ratio (95% CI)		
	n	Model 1 ^a	Model 2 ^b	Model 3 ^c
Children				
Lead quartiles				
≤0.60 μg/dL ^d	647	1.00	1.00	1.00
0.61–0.82 μg/dL	613	1.10 (0.87–1.38)	1.09 (0.87–1.37)	1.12 (0.89–1.40)
0.83–1.22 μg/dL	677	1.11(0.90–1.38)	1.07 (0.88–1.29)	1.11 (0.94–1.32)
≥1.23 μg/dL	775	0.93 (0.69–1.27)	0.86 (0.63–1.17)	0.89 (0.65–1.22)
<i>p</i> trend		0.64	0.28	0.42
per 2-fold increase	2712	0.97 (0.85–1.11)	0.94 (0.82–1.07)	0.95 (0.82–1.10)
Adults				
Lead quartiles				
≤0.89 μg/dL ^d	1039	1.00	1.00	1.00
0.90–1.41 μg/dL	1011	1.01 (0.74–1.37)	1.00 (0.74–1.32)	1.00 (0.77–1.33)
1.42–2.17 μg/dL	1053	1.26 (1.03–1.55)	1.22 (1.00–1.48)	1.22 (1.02–1.47)*
≥2.18 μg/dL	1230	1.21 (0.94–1.58)	1.15 (0.88–1.49)	1.18 (0.91–1.53)
<i>p</i> trend		0.03	0.10	0.08
per 2-fold increase	4333	1.12 (1.03–1.22)	1.10 (1.00–1.20)	1.11 (1.02–1.22)

^aModel 1 adjusted for age and sex.^bModel 2 adjusted for age, sex, ethnicity, education, body mass index, exposure to tobacco smoke.^cModel 3 further adjusted for asthma, musty smell at home, presence of cockroaches, domestic animals living in the home, and year house was built.^dReference serum lead quartile.**p* < 0.05.

CI = confidence interval.

Statistical analysis

NHANES uses a complex sampling design and constructs sample weights in order to produce nationally representative data. A complex and multistage probability sampling design is used to select participants who represent the non-institutionalized civilian U.S. population. Survey weights are constructed for each 2-year cycle, which takes into account nonresponse, oversampling, poststratification, and sampling error.

The association between blood Pb levels and food allergy sensitization was evaluated using multiple logistic regression. Three different models were formulated: model 1 was adjusted for age and sex; model 2 was adjusted for age, sex, ethnicity, education level, BMI categories, and tobacco exposure (unexposed, exposed to secondhand smoke, and active smokers); and model 3 was adjusted for age, sex, ethnicity, education level, BMI categories, tobacco exposure, self-reported diagnosis of asthma, housing characteristics (year the house was built), and potential environmental allergen exposure factors (musty smell at home, presence of cockroaches at home, presence of domestic animals at home). All regression models were stratified by age into 2 groups: children (ages 6 to 19 years) and adults (greater

than 19 years of age). Pb was modeled as quartiles, with the lowest quartile being the exposure reference. We also modeled ln-transformed Pb as a continuous variable, with results expressed per 2-fold increase. In addition, we modeled Pb as restricted cubic spline models with knots at the 10th, 50th, and 90th percentiles.

All significance tests were 2-sided with a type I error rate of 0.05. All analyses were performed using STATA version 13 (Stata Corps 2013, College Station, Texas).

Results

Our study population consisted of 2712 children and 4333 adult participants. Baseline characteristics are listed in Table 1. Median (interquartile range [IQR]) for serum Pb was 0.87 µg/L (0.61 to 1.31) in children and 1.48 µg/L (0.92 to 2.34) in adults. At baseline, 672 (24.7%) of children and 719 (16.6%) of adult participants tested positive for increased sensitization to food allergens. Children and adult participants with sensitization to food allergens were more likely to report the presence of cockroaches, cats, and dogs in the home in addition to higher self-reported rates of asthma (Table 1).

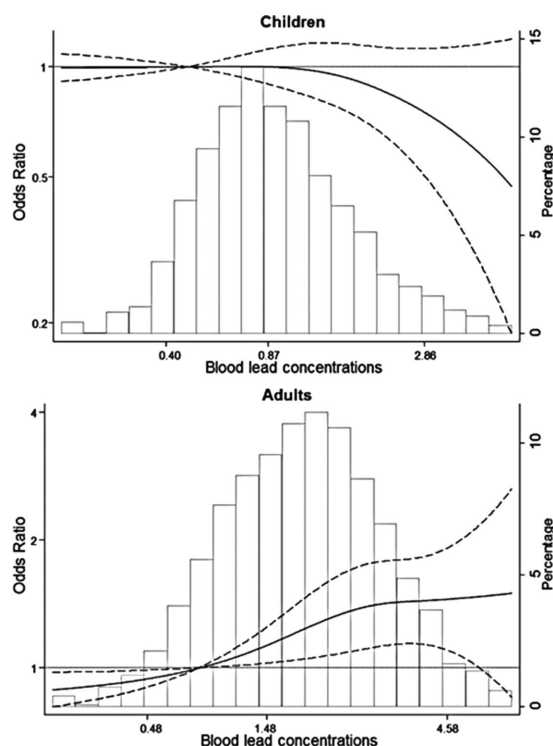


FIGURE 1. Odds ratios (95% CI) for food allergic sensitization in children and adults from the U.S. general population based on restricted cubic splines for ln-transformed blood Pb concentrations with knots at the 10th, 50th, and 90th percentiles. The reference value is set at the 10th percentile of Pb distribution. Odds ratios are adjusted for age, sex, ethnicity, education level, body mass index, exposure to tobacco smoke, asthma, musty smell at home, presence of cockroaches, domestic animals living in the home, and year house was built. Lines represent the odds ratios (thick line) and 95% CIs (dotted lines), and vertical bars represent the histogram of blood Pb distribution. CI = confidence interval.

Compared to the lowest quartile, the multivariable adjusted odds ratios (ORs) (95% confidence interval [CI]) for the second, third, and fourth quartiles of blood Pb in children were, respectively: 1.12 (95% CI, 0.89 to 1.40), 1.11 (95% CI, 0.94 to 1.32), and 0.89 (95% CI, 0.65 to 1.22); *p* value for linear trend 0.42. The corresponding results for adults were, respectively: 1.00 (95% CI, 0.77 to 1.13), 1.22 (95% CI, 1.02 to 1.47), and 1.18 (95% CI, 0.91 to 1.53), *p* for linear trend 0.08. Models per 2-fold increase in blood Pb levels showed an increased risk of food allergens sensitization among adult participants (OR = 1.11; 95% CI, 1.02 to 1.22), but not among children (OR = 0.93; 95% CI, 0.82 to 1.10) in the fully adjusted model (Table 2).

In spline models (Fig. 1), we confirmed the lack of association between blood Pb levels and food allergen sensitization in children with a dose-response that was mostly flat throughout the range of Pb (*p* value for the nonlinear component = 0.43.) In adults, the increase in food allergen sensitization with increasing blood Pb levels was positive and statistically significant throughout most of the range in Pb levels.

Discussion

Pb exposure, as determined in blood, was independently associated with increased serum-specific IgE levels to common food allergens in a representative sample of adults from the United States. However, among children, there appeared to be no association with increased serum Pb levels and elevation in serum-specific IgE levels.

Earlier studies have investigated the complex role and effects of heavy metal toxicity, including Pb, on the human and animal immune systems. A prior study evaluating the same cohort of adults in the NHANES showed similar findings showing that participants with elevated urinary Pb levels were more likely to have food allergies to egg, milk, and shrimp based on IgE levels. However, blood Pb levels of participants were not studied, which is the standard guideline measure used for evaluating Pb toxicity.¹⁰ In contrast to our findings, several studies have shown increased IgE production and atopic sensitization in children following exposure to Pb.^{7,16} These findings held true even after controlling for maternal allergic status as a surrogate measure of genetic predisposition. The lack of association between Pb and food allergen sensitization in our study in children could be related to the markedly lower serum Pb levels found in children in NHANES 2005-2006; however, in adults we observed a positive association with no evidence of a threshold.

Increased serum Pb levels may also be associated with a range of autoimmune-related illnesses. Exposure to Pb is independently associated with vasculitis, including Wegner's granulomatosis,¹⁷ bronchial hyperresponsiveness,⁹ and asthma^{18,19} secondary to elevation in serum IgE level, eczema disease severity,²⁰ and gout.²¹ Interestingly, patients diagnosed with Wegener's granulomatosis frequently report allergy symptoms prior to developing vasculitis.¹⁷ Furthermore, in children diagnosed with atopic dermatitis, higher serum Pb levels, despite being within the acceptable normal limits, have been shown to have more severe skin atopy, higher eosinophil account, and IgE levels.²⁰

There are several proposed mechanisms to explain Pb effects on the immune system to better elucidate our results. Pb may preferentially affect the T-cell-dependent immune response,^{1,6,11} thereby increasing alloantigenic-specific T-cell proliferation through altering the expression of the major histocompatibility complex (MHC) Class II antigen processing and presentation.^{11,22} Even mildly elevated Pb levels (11 $\mu\text{g}/\text{dL}$) have been showed to inhibit production of interferon γ (INF- γ) and tumor necrosis factor α (TNF- α), thereby inhibiting Th1 response, and instead enhancing Th2 allergic responses by upregulating interleukin (IL)-4, IL-5, IL-10, IL-13, and IgE.^{7,12,23-25} Sustained Th2-mediated immune response may then contribute to increase propensity toward allergic hypersensitivity. This skewed response is reversed at lower serum blood levels, where a Th1-mediated immune response is predominately observed.²⁵ Alternatively, Pb may preferentially lead to direct and indirect stimulation of B cells through binding

and alteration of allergens, resulting in the elevation of levels of IgA and IgE.²⁶ This thereby promotes the allergic immune response^{1,7} and increases the likelihood of food sensitization and allergies. However, the exact mechanism still remains poorly understood. Finally, in rodent studies, Pb has been reported to alter gut microbiota composition resulting in gut dysbiosis.²⁷ The Pb-gut microbe interaction is relevant since similar environmental disruptions of gut microbiota and loss of mucosal immune regulation appear to result in allergic sensitization to food allergens.²⁸

Pb exposure may occur through environmental sources such as Pb-contaminated house dust, soil, paint, floors, tobacco smoke exposure, filters in cigarette butts, recreational hobbies, and in the workplace, without the patient necessarily knowing.^{29,30} Pb-induced subclinical toxicity may occur in all persons exposed, rather than any specific susceptible group, though Caucasians and women may be more susceptible.^{3,19} Furthermore, while Pb toxicity has been demonstrated to occur at levels greater than 10 µg/dL with federal guidelines recommending intervention as low as 5 µg/dL, in reality, there is no safe lower limit since Pb may have subclinical effects on immune system function and regulation. Treatment for Pb toxicity is empiric and consists of chelation therapy; however, it is expensive, carries side effects, and is typically only recommended for severely elevated serum Pb levels. Resources should thus foremost be targeted to eliminating the sources of the exposure. However, despite known environmental exposures, susceptibility to increased Pb absorption may in fact be more closely tied to genetic alteration in enzymes critical to heme synthesis, such as delta-aminolevulinic acid dehydratase and C282Y mutation in the HFE gene than previously recognized.^{31,32}

The strengths of our study include the availability of serum Pb and IgE levels in a large, nationally representative

sample of children and adults with the ability to account for multiple potential confounders, including current environmental exposure to allergens, housing characteristics, and socioeconomic factors. However, the direction of the observed association between serum Pb levels and allergic sensitization profiles cannot be determined in the present study. Interestingly, in the present analysis, elevated serum Pb levels were not associated with increased allergic sensitization in children. Duration of exposure to Pb may be a factor in potentially developing allergic sensitization and immune profile changes in children. Longitudinal exposure to Pb in this cohort is unfortunately unable to be assessed. Last, Pb may be a confounder or surrogate for other unknown variables that may be associated with allergic sensitization, but is unable to be easily assessed or accounted for in our analytic models.

Conclusion

In summary, our results suggest that increased blood Pb levels may be associated with increased food allergic sensitization in adults. Additional investigations in cohort studies with longitudinal data are needed to further a better understanding of Pb exposure duration necessary to lead to the development of allergic sensitization over the lifetime of patients. 

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References

- Lutz PM, Wilson TJ, Ireland J, et al. Elevated immunoglobulin E levels in children with exposure to environmental lead. *Toxicology*. 1999;134:63–78.
- Bellinger DC. Lead. *Pediatrics*. 2004;113:1016–1022.
- Bunn TL, Parsons PJ, Kao E, Dietert RR. Exposure to lead during critical windows of embryonic development: differential immunotoxic outcome based on stage of exposure and gender. *Toxicol Sci*. 2001;64:57–66.
- Heo Y, Lee WT, Lawrence DA. In vivo the environmental pollutants lead and mercury induce oligoclonal T cell responses skewed toward type-2 reactivities. *Cell Immunol*. 1997;179:185–195.
- Sarasua SM, Vogt RF, Henderson LO, Jones PA, Lybarger JA. Serum immunoglobulins and lymphocyte subset distributions in children and adults living in communities assessed for lead and cadmium exposure. *J Toxicol Environ Health*. 2000;60:1–15.
- Sun L, Hu J, Zhao Z, Li L, Cheng H. Influence of exposure to environmental lead on serum immunoglobulin in preschool children. *Environ Res*. 2003;92:124–128.
- Annesi-Maesano I, Pollitt R, King G, et al. In utero exposure to lead and cord blood total IgG. Is there a connection? *Allergy*. 2003;58:589–594.
- Heinrich J, Hoelscher B, Wjst M, Ritz B, Cyrys J, Wichmann HE. Respiratory disease and allergies in two polluted areas in East Germany. *Environ Health Perspect*. 1999;107:53–62.
- Min J, Min K, Kim R, Cho S, Paek D. Blood levels and increased bronchial responsiveness. *Biol Trace Elem Res*. 2008;123:41–46.
- Shiue I. Association of urinary arsenic, heavy metal, and phthalate concentrations with food allergy in adults: National Health and Nutrition Examination Survey, 2005–2006. *Ann Allergy Asthma Immunol*. 2013;111:420–430.
- McCabe MJ Jr, Lawrence DA. Lead, a major environmental pollutant is immunomodulatory by its differential effects on CD4+ T cells subsets. *Toxicol Appl Pharmacol*. 1991;111:13–23.
- Dietert RR, Lee JE, Hussain I, Piepenbrink M. Developmental immunotoxicology of lead. *Toxicol Appl Pharmacol*. 2004;198:86–94.
- Savage JH, Matsui EC, Wood RA, Keet CA. Urinary levels of triclosan and parabens are associated with aeroallergen and food sensitization. *J Allergy Clin Immunol*. 2012;130:453–460.
- Crinnion WJ. Toxic effects of the easily avoidable phthalates and parabens. *Altern Med Rev*. 2010;15:190–196.
- Hornung W, Reed D. Estimation of average concentration in the presence of nondetectable values. *Appl Occup Environ Hyg*. 1990;5:46–51.
- Jedrychowski W, Perera F, Maugeri U, et al. Intrauterine exposure to lead may enhance sensitization to common inhalant allergens in early childhood: a prospective prebirth cohort study. *Environ Res*. 2011;111:119–124.
- Albert D, Clarkin C, Komoroski J, Brensinger CM, Berlin JA. Wegener's granulomatosis: possible role of environmental agents in its pathogenesis. *Arthritis Rheum*. 2004;51:656–664.
- Bener A, Almhedi AM, Alwash R, Al-Neamy FR. A pilot survey of blood lead levels in various types of workers in the United Arab Emirates. *Environ Int*. 2001;27:311–314.
- Joseph CLM, Havstad S, Ownby DR, et al. Blood lead level and risk of asthma. *Environ Health Perspect*. 2005;113:900–904.
- Hon K-Le, Wang SS, Hung ECW, et al. Serum levels of heavy metals in childhood eczema and skin diseases. Friends or foes. *Pediatr Allergy Immunol*. 2010;21:831–836.
- Reynolds PP, Knapp MJ, Baraf HS, Holmes EW. Moonshine and lead: relationship to the pathogenesis of hyperuricemia in gout. *Arthritis Rheum*. 1983;26:1057–1064.
- Heo Y, Parsons PJ, Lawrence DA. Lead differentially modifies cytokine production in vitro and in vivo. *Toxicol Appl Pharmacol*. 1996;138:149–157.
- Hsiao C, Wu K, Wan K. Effects of environmental lead exposure on T-helper cell specific cytokines in children. *J Immunotoxicol*. 2011;8:284–287.
- Boscolo P, Gioacchino M, Sabbioni E, et al. Expression of lymphocyte subpopulations, cytokine serum levels, and blood and urinary trace elements in asymptomatic atopic men exposed to an urban environment. *Int Arch Occup Environ Health*. 1999;72:26–32.

25. Iavicoli I, Carelli G, Stanek E 3rd, Castellino N, Calabrese EJ. Below background levels of blood lead impact cytokine levels in male and female mice. *Toxicol Appl Pharmacol.* 2006;210:94–99.
26. Ewers U, Stiler-Winker R, Idel H. Serum immunoglobulin, complement C3, and salivary IgA levels in lead workers. *Environ Res.* 1982;29:351–357.
27. Breton J, Massart S, Vandamme P, De Brandt E, Pot B, Foligne B. Ecotoxicology inside the gut: impact of heavy metals on the mouse microbiome. *BMC Pharmacol Toxicol.* 2013;14:1–11.
28. Cao S, Feehley TJ, Nagler CR. The role of commensal bacteria in the regulation of sensitization to food allergens. *FEBS Lett.* (in press) [Epub 2014 May 1. doi: 10.1016/j.febslet.2014.04.026].
29. Apostolou A, Garcia-Esquinas E, Fadrowski JJ, McLain P, Weaver VM, Navas-Acien A. Second-hand tobacco smoke: a source of lead exposure in US children and adolescents. *Am J Public Health.* 2012;102:714–722.
30. Novotny TE, Slaughter E. Tobacco product waste: an environmental approach to reduce tobacco consumption. *Curr Environ Health Rep.* 2014;1:208–216.
31. Onalaja AO, Claudio L. Genetic susceptibility to lead poisoning. *Environ Health Perspect.* 2000;108(Suppl 1):23–28.
32. Wright RO, Silverman EK, Schwartz J, et al. Association between hemochromatosis genotype and lead exposure among elderly men: the normative aging study. *Environ Health Perspect.* 2004;112:746–750.