associated with the substantially altered or defective T-cell immunity necessary for oral tolerance. This deficient immune regulation can lead to a skewed response, resulting in atopic disease. The high prevalence of FA in patients with primary hypogammaglobulinemia might suggest a concomitant T-cell dysfunction in these cases.

Importantly, the number of patients with FA, AD, or both registered in the USIDNET at the time of the query was small, and this might underrepresent PIDDs associated with atopy. The overall lower prevalence of FA in patients with PIDDs might also be underestimated because 55% of patients had severe combined immunodeficiency, X-linked agammaglobulinemia, or CVID. A follow-up study should be undertaken in the future. Another limitation of the study is that it is based on a physician report questionnaire form; hence FA and AD rates could be overestimated. Moreover, there was a limitation in the core registry form for further description of reactions to food and AD/eczema.

Manifestations of atopy, such as FA and AD, occurring early in life might be a presenting feature before diagnosis of a PIDD[4,5] and, if associated with recurrent infections, should warrant clinicians to pursue an immunologic evaluation. Early diagnosis of PIDDs might have a potential benefit of better outcome. Although the prevalence of both FA and AD in patients with PIDDs is lower than in the general population, there should be a lower threshold for suspecting FA in patients with certain PIDDs.

We thank the staff of the USIDNET and contributing sites for enabling this query. Per USIDNET policy, any site contributing more than 10% of the patients included in this analysis was to be offered authorship; however, no single site contributing to the registry contributed more than 10% of patients with PIDDs and FA or AD.

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REFERENCES

1. Notarangelo LD. Primary immunodeficiencies. J Allergy Clin Immunol 2010; 125(suppl):S182-94.
2. Janzi M, Kull I, Sjoberg R, Wan J, Melen E, Bayat N, et al. Selective IgA deficiency in early life: Association to infections and allergic diseases during childhood. Clin Immunol 2009;133:78-85.
3. Jacob CMA, Pastorino AC, Fahl K, Carneiro-Sampaio M, Monteiro RC. Autoimmunity in IgA deficiency: revisiting the role of IgA as a silent housekeeper. J Clin Immunol 2008;28(suppl 1):S56-61.
4. Sillevis Smitt JH, Kuijpers TW. Cutaneous manifestations of primary immunodeficiency. Curr Opin Pediatr 2013;25:492-7.
5. Al-Herz W, Nanda A. Skin manifestations in primary immunodeficient children. Pediatr Dermatol 2011;28:494-501.
6. USIDNET.org. Available at: http://www.usidnet.org/. Accessed January 14, 2014.
7. Liu AH, Jaramillo R, Sicherer SH, Wood RA, Bock SA, Burks AW, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005-2006. J Allergy Clin Immunol 2010;126:798-806.
8. Hanifin JM, Reed ML. Eczema Prevalence and Impact Working Group. A population-based survey of eczema prevalence in the United States. Dermatitis 2007;18:82-91.
9. Aghamohammadi A, Cheraghi T, Gharagozlou M, Movahedi M, Rezaei N, Yeganeh M, et al. IgA deficiency: correlation between clinical and immunological phenotypes. J Clin Immunol 2009;29:130-6.

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Environmental lead exposure and increased risk for total and allergen-specific IgE in US adults

To the Editor:

Allergic disease is a major public health concern because of increases in prevalence and significant burdens on the economy and quality of life. There is a growing interest in the role of environmental exposures (ie, air pollution, tobacco smoking, and metals) in the development of allergies.[1]

Lead is a ubiquitous environmental pollutant with potential immunotoxicity.[2] Although environmental lead exposures, as a result of the phase out of leaded gasoline, have been significantly decreased, lead is still found in paint, food, and lead-containing consumer products and detected in the general population. Concern, especially among some minorities and socioeconomically disadvantaged groups, has grown over the possible adverse effects of exposure to low levels of environmental lead.[3]

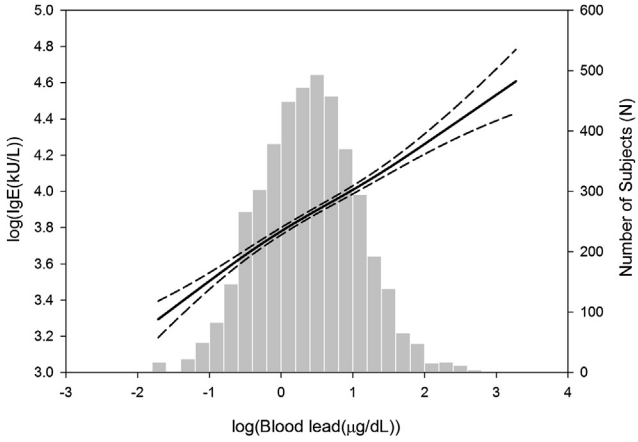

FIG 1. Adjusted association (spline function) plots of total IgE levels with blood lead levels. *Bars* indicate the frequency distribution of blood lead in the study participants. The spline function *(solid line)* is adjusted for age, sex, race/ethnicity, family income, cigarette smoking, a history of allergy, and BMI. *Dotted lines* indicate the 95% CI.

TABLE I. β-Coefficients (95% CI)* for total IgE levels and ORs (95% CIs)* for allergic sensitization by blood lead quartiles

	Quartile 1 (approximately 0.18-1.09 μg/dL)	Quartile 2 (approximately 1.1-1.69 μg/dL)	Quartile 3 (approximately 1.7-2.6 μg/dL)	Quartile 4 (approximately 2.61-26.4 μg/dL)
β-Coefficient (95% CI) for total IgE levels				
Total IgE levels	0 (Reference)	0.20 (0.05-0.34)	0.26 (0.10-0.42)	0.35 (0.20-0.51)
OR (95% CI) for sensitization to 7 allergen groups†				
Molds	1 (Reference)	1.01 (0.74-1.40)	0.88 (0.58-1.34)	0.86 (0.52-1.43)
Dust mites	1 (Reference)	1.32 (1.00-1.75)	1.30 (0.93-1.81)	1.35 (1.01-1.80)
Plants	1 (Reference)	0.94 (0.73-1.21)	1.03 (0.82-1.29)	0.79 (0.57-1.10)
Pets	1 (Reference)	1.32 (1.01-1.73)	1.09 (0.71-1.68)	0.94 (0.63-1.40)
Arthropods	1 (Reference)	1.10 (0.86-1.41)	1.16 (0.85-1.58)	1.80 (1.43-2.25)
Rodents	1 (Reference)	0.75 (0.28-2.00)	0.82 (0.34-1.95)	1.01 (0.26-3.90)
Food	1 (Reference)	1.11 (0.71-1.72)	1.14 (0.83-1.59)	1.14 (0.64-2.00)

*Statistical models were adjusted for age, sex, race/ethnicity, family income, cigarette smoking, a history of allergy, and BMI.
†Specific IgE against 19 allergens was divided into the following 7 categories: (1) molds (*Alternaria* and *Aspergillus*); (2) dust mites (*D farinae* and *D pteronyssinus*); (3) plants (rye grass, Bermuda grass, oak, birch, ragweed, thistle, and peanut); (4) pets (dog and cat); (5) arthropods (cockroach and shrimp); (6) rodents (mouse and rat); and (7) food (egg white and cow's milk).

Experimental and epidemiologic studies have shown that lead exposure is implicated in alterations in humoral and cell-mediated immunity and the development of allergic conditions, including the production of serum IgE and eosinophils and bronchial responsiveness.[2,4-6] However, it remains unclear whether exposure to environmental lead affects IgE-mediated allergic responses.

We hypothesized that environmental lead exposure could be a risk factor for increased allergic sensitization and examined the association between blood lead levels and total and allergen-specific IgE levels in serum among adults.

This study analyzed data from the 2005-2006 National Health and Nutrition Examination Survey (NHANES). Of the 4979 total participants aged 20 years and older, we included 4287 adults who underwent a complete panel of allergen-specific IgE tests, had blood lead measurements, and had no missing data on all variables of interest (see the Methods section in this article's Online Repository at www.jacionline.org). Blood lead levels were measured by using atomic absorption spectrometry. Total and allergen-specific IgE levels against 19 allergens were measured by using the ImmunoCAP System (Pharmacia Diagnostics, Kalamazoo, Mich). Nineteen specific allergens were divided into 7 categories to avoid the problem of similarities in their biological and statistical properties: (1) molds (*Alternaria* and *Aspergillus* species); (2) dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*); (3) plants (rye grass, Bermuda grass, oak, birch, ragweed, thistle, and peanut); (4) pets (dog and cat); (5) arthropods (cockroach and shrimp); (6) rodents (mouse and rat); and (7) food (egg white and cow's milk).[7] A specific IgE level of 0.35 kU_A/L or greater indicated sensitization. Age, sex, race/ethnicity, household income, cigarette smoking, a history of allergy, and body mass index (BMI) were considered confounding variables and entered as covariates in all models.

Blood lead levels were log transformed, during which they were either categorized into quartiles or treated as a continuous variable. The total IgE level was log transformed to normalize the distribution and analyzed as a continuous variable. Weighted estimates (2-year subsample weights: WTMEC2YR) of the population parameters were computed by using the NHANES Analytic and Reporting Guidelines to account for the complex sampling scheme. All analyses were performed with SAS 9.2 software (SAS Institute, Cary, NC) and R software (R Foundation for Statistical Computing, Vienna, Austria).

The geometric mean of blood lead in the entire population was 1.46 μg/dL (95% CI, 1.44-1.50 μg/dL). Overall, 2369 (55.3%) participants were sensitive to at least 1 specific allergen, and the mean total IgE level was 48.2 kU/L (95% CI, 46.1-50.5 kU/L; see Table E1 in this article's Online Repository at www.jacionline.org).

We explored the adjusted associations between total IgE and blood lead levels by using a spline function to fit the generalized additive model. The result was a significant linear association in which total IgE levels increased with increases in blood lead levels (β = 0.18; 95% CI, 0.08-0.28; $P = .0029$; Fig 1). With regard to the association between blood lead quartiles, total IgE levels, and allergen sensitizations, blood lead levels were significantly associated with total IgE levels (β value in quartile 4, 0.35; 95% CI, 0.20-0.51) and increased risk for specific IgE sensitizations to dust mites (odds ratio [OR] in quartile 4, 1.35; 95% CI, 1.01-1.80) and arthropods (OR in quartile 4, 1.80; 95% CI, 1.43-2.25) (Table I). Specifically, subjects with the highest blood lead levels had significantly increased risk for allergies to *D farinae* (OR, 1.46; 95% CI, 1.07-2.01), *D pteronyssinus* (OR, 1.47; 95% CI, 1.08-2.00), peanut (OR, 1.84; 95% CI, 1.20-2.81), cockroach (OR, 1.99; 95% CI, 1.55-2.54), and shrimp (OR, 1.51; 95% CI, 1.00-2.28) than those in the lowest quartile (see Fig E1 in this article's Online Repository at www.jacionline.org).

Few epidemiologic studies have suggested lead-induced overproduction of total IgE,[4,5] and most of these were conducted in children. A previous study by Heo et al[8] reported that adults with increased occupational exposure to lead were significantly more likely to have increased IgE levels. Our finding of a potential connection between lead exposure and total IgE levels extends the current limited evidence from particularly vulnerable subjects, such as children and highly exposed workers, to a general population of adults.

In addition, we estimated the associations between blood lead levels and sensitization to specific allergens among adults. Here, we provide the first evidence that higher blood lead levels increased the risk of having IgE to specific allergens, namely dust mites and arthropods, among adults. A recent study by Jedrychowski et al[9] reported the effect of lead on allergen

sensitization in childhood. After adjustment for potential covariates, children's atopic status was significantly associated with their cord blood lead levels (risk ratio, 2.28, 95% CI, 1.12-4.62), suggesting that allergic sensitization in early childhood might be enhanced by means of intrauterine exposure to lead. To our knowledge, there are no data on the association between lead exposure and hypersensitivity to specific allergens. The mechanism for the association between lead and increased total IgE levels and specific allergen sensitization are not fully understood. However, type I hypersensitivity has implications for lead exposure.[2,6,8] IgE is a major mediator of type I hypersensitivities. Lead has the capacity to modify the immune reaction by activating type 2 helper T cells and inhibiting type 1 T-cell activation[10]; this effect is dependent on the enhanced production of cytokines and interleukins, thereby promoting isotype switching to IgE.[11] Given that susceptibility to allergic responses is directly associated with IgE production,[11] exposure to lead might be responsible for the increases in allergen-specific IgE or allergic responses.

Our study has several limitations. First, the cross-sectional design of this study does not allow one to make a causal inference with the observed association. Second, the blood lead level is an adequate biomarker of recent exposure; however, it is not an accurate reflection of the lifetime toxicant burden. Lastly, it is possible that errors arising from self-reported data or unmeasured factors might have contributed to the bias.

In conclusion, the present study provides evidence of a positive dose-response relationship between blood lead levels and total IgE levels in US adults. Moreover, participants with high blood lead levels were at significantly increased risk for specific IgE sensitization to dust mites and arthropods. Although our findings require confirmation, they suggest that background exposures to lead might play an important role in development of allergic conditions among adults. These findings have potential implications for the prevention and control of allergies.

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REFERENCES

1. von Mutius E. The environmental predictors of allergic disease. J Allergy Clin Immunol 2000;105:9-19.
2. Mishra KP. Lead exposure and its impact on immune system: a review. Toxicol In Vitro 2009;23:969-72.
3. Tong S, von Schirnding YE. Prapamontol T.Environmental lead exposure: a public health problem of global dimensions. Bull World Health Organ 2000; 78:1068-77.
4. 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;92:124-8.
5. Wells EM, Bonfield TL, Dearborn DG, Jackson LW. The relationship of blood lead with immunoglobulin E, eosinophils, and asthma among children: NHANES 2005-2006. Int J Hyg Environ Health 2014;217:196-204.
6. Min JY, Min KB, Kim R, Cho SI, Paek D. Blood lead levels and increased bronchial responsiveness. Biol Trace Elem Res 2008;123:41-6.
7. Salo PM, Arbes SJ Jr, Jaramillo R, Calatroni A, Weir CH, Sever ML, et al. Prevalence of allergic sensitization in the United States: results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. J Allergy Clin Immunol 2014;134:350-9.
8. Heo Y, Lee BK, Ahn KD, Lawrence DA. Serum IgE elevation correlates with blood lead levels in battery manufacturing workers. Hum Exp Toxicol 2004;23: 209-13.
9. Jedrychowski W, Perera F, Maugeri U, Miller RL, Rembiasz M, Flak E, et al. Intrauterine exposure to lead may enhance sensitization to common inhalant allergens in early childhood: a prospective prebirth cohort study. Environ Res 2011;111:119-24.
10. Heo Y, Lee WT, Lawrence DA. Differential effects of lead and cAMP on development and activities of Th1- and Th2-lymphocytes. Toxicol Sci 1998;43:172-85.
11. Oettgen HC, Geha RS. IgE in asthma and atopy: cellular and molecular connections. J Clin Invest 1999;104:829-35.

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Metagenomic heterogeneity explains dual immune effects of endotoxins

To the Editor:

The classical role of endotoxin-driven inflammation has become enigmatic in view of recent clinical observations. Genomic analyses of the lung microbiome in healthy children and adults demonstrated that the lungs are not sterile but colonized with a broad spectrum of bacteria, including many endotoxin-producing gram-negative bacteria, which would be expected to cause airway inflammation.[1-3] Furthermore, bacterial endotoxin has been suggested to play a role in the origins of asthma and allergy based on observations of an inverse correlation between endotoxin exposure and the risk of childhood asthma and allergic sensitization.[4] Early on, this was explained by T_H1-driven inflammation caused by environmental endotoxin and a T_H2-based inflammation typical of asthma and allergies in the lack thereof. However, stimulation of T_H1-biased inflammation would be expected to promote excessive tissue damage as seen for example in patients with Crohn disease. Moreover, reduced risk of asthma and allergies would be anticipated after infection with T_H1-promoting gram-negative bacteria and viruses. Still, neither of these scenarios has been confirmed. Later, alleviation of T_H2-based inflammation through tolerogenic immunologic means was proposed as an endotoxin-mediated regulator of disease, but how this immune reaction is transmitted by endotoxin stimulation is yet unknown. These data allowed us to raise the question of whether heterogeneity within endotoxins, with some exhibiting proinflammatory effects and others with low-level or anti-inflammatory effects, could explain the relationship of endotoxins to asthma and allergic diseases.

In fact, gram-negative bacteria have several forms of endotoxins. The lipid A moiety is responsible for the molecule's endotoxic activity and is made up of a 1,4′-bis-phosphorylated diglucosamine backbone attached mainly with 5 or 6 acyl chains. Two different acyltransferases encoded by the genes *LpxL* and *LpxM* add the fifth and sixth acyl chains to the tetra-acylated endotoxin. Bacteria expressing *LpxL* produce penta-acylated endotoxin, whereas bacteria that express both *LpxL* and *LpxM* produce hexa-acylated endotoxin. Penta-acylated endotoxin exhibits around 100-fold less immune-stimulatory activity than its hexa-acylated counterpart and acts as a functional antagonist through competitive binding to the common coreceptor MD-2 and human Toll-like receptor 4 (TLR4).[5]

It is well established that the hexa-acylated endotoxin structure activates TLR4, resulting in activation of T_H1 cells promoting inflammation, but it has also been demonstrated recently that

METHODS

Study population

The 2005-2006 NHANES, which was conducted by the US Centers for Disease Control and Prevention, is a nationally representative survey of the noninstitutionalized civilian population in the United States. The study protocols and all NHANES testing procedures were approved by the Institutional Review Board of the National Center for Health Statistics. Both oral and written consent were obtained from all participants.

The present study used data regarding allergen-specific IgE tests and blood lead levels. Of the 4979 total participants aged 20 years and older, we initially selected 4485 adults who underwent a complete panel of allergen-specific IgE tests and had blood lead measurements. We excluded an additional 196 subjects who were missing at least 1 variable of interest (n = 189) or for whom the allergy questionnaire was not available (n = 7). Therefore a final study population of 4289 participants was included in the analyses.

The levels of total and allergen-specific IgE against 19 allergens were measured for all participants aged 6 years and older. Serum samples were analyzed for total and allergen-specific IgE by using the Pharmacia Diagnostics ImmunoCAP 1000 System (Pharmacia Diagnostics).

The lower limits of detection were 2.00 kU/L for total IgE and 0.35 kU/L for each allergen-specific IgE. A specific IgE level of 0.35 kU_A/L or greater indicated sensitization. Details of the laboratory methods and quality control procedures have been previously described.[E1]

REFERENCE

E1. National Center for Health Statistics. Laboratory procedure manual for NHANES 2005-2006 data: specific IgE/total IgE allergens in serum; 2008. Available at: http://www.cdc.gov/nchs/data/nhanes/nhanes_05_06/al_ige_d_met_specific_ige_total_ige.pdf. Accessed July 28, 2014.

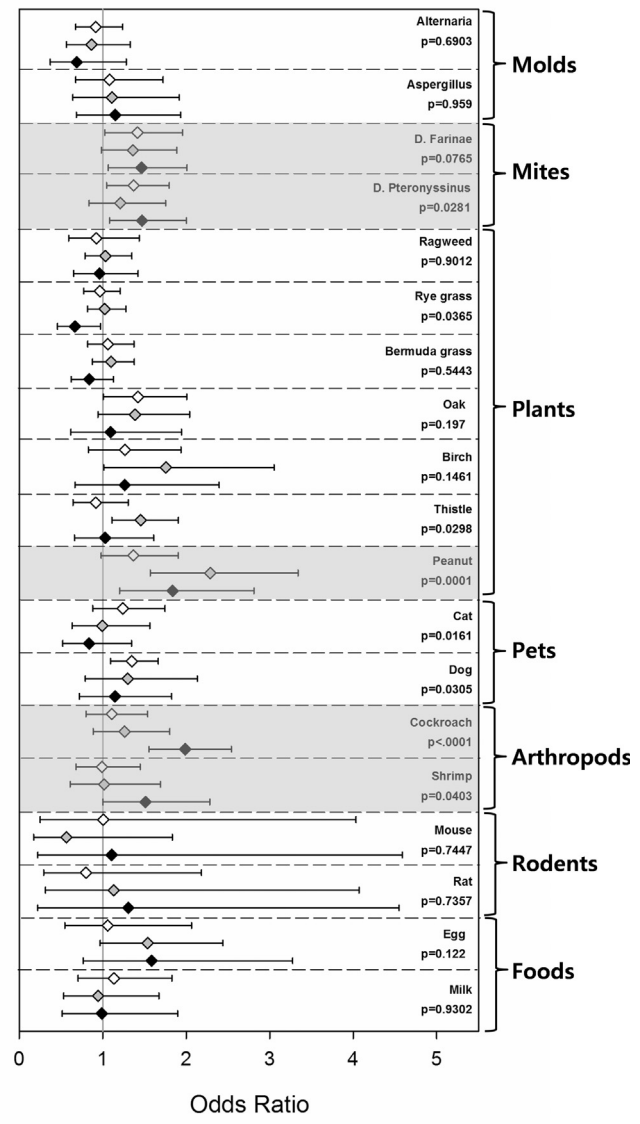

FIG E1. Adjusted ORs (95% CIs) for associations for IgE levels among 19 specific aeroallergens and blood lead quartiles. *Diamonds* represent the ORs for allergic sensitization in quartiles 2 *(white diamonds)*, 3 *(gray diamonds)*, and 4 *(black diamonds)*, respectively, compared with the reference levels of blood lead in quartile 1. All ORs are adjusted for age, sex, race/ethnicity, household income, cigarette smoking, a history of allergy, and BMI. *Error bars* represent 95% CIs.

TABLE E1. Geometric means (95% CIs) of blood lead levels by participants' characteristics

	Participants, no. (%)	Blood lead levels (μg/dL), mean (95% CI)	*P* value
Age (y)			
20-29	897 (20.9)	0.91 (0.87-0.95)	<.0001
30-39	749 (17.5)	1.11 (1.06-1.16)	
40-49	756 (17.6)	1.47 (1.41-1.53)	
50-59	573 (13.4)	1.85 (1.77-1.94)	
60-69	599 (14.0)	2.04 (1.95-2.14)	
70-79	423 (9.9)	2.17 (2.05-2.29)	
≥80	290 (6.8)	2.41 (2.26-2.57)	
Sex			
Male	2053 (47.9)	1.89 (1.83-1.94)	<.0001
Female	2234 (52.1)	1.17 (1.13-1.20)	
Race/ethnicity			
Non-Hispanic white	2189 (51.1)	1.45 (1.41-1.50)	.0083
Non-Hispanic black	950 (22.2)	1.57 (1.50-1.64)	
Hispanic	978 (22.8)	1.42 (1.35-1.48)	
Other	170 (4.0)	1.41 (1.29-1.54)	
Family income			
<$20,000	1060 (24.7)	1.68 (1.61-1.76)	<.0001
≥$20,000	3227 (75.3)	1.40 (1.37-1.44)	
Cigarette smoking			
Current smoker	945 (22.0)	1.85 (1.78-1.93)	<.0001
Former smoker	1089 (25.4)	1.66 (1.60-1.73)	
Never smoker	2253 (52.6)	1.25 (1.22-1.29)	
History of allergy			
Yes	1351 (31.5)	1.28 (1.24-1.33)	<.0001
No	2936 (68.5)	1.56 (1.52-1.60)	

The geometric mean of blood lead level in the entire population was 1.46 μg/dL (95% CI, 1.44-1.50 μg/dL). Overall, 2369 (55.3%) participants were sensitive to at least 1 specific allergen, and the mean total IgE level was 48.2 kU/L (95% CI, 46.1-50.5 kU/L). Blood lead levels significantly differed by age, sex, race/ethnicity, family income, cigarette smoking, and the presence of allergic disease. Blood lead levels were higher in participants who were older, were male, were non-Hispanic black, were current smokers, had an annual household income less than $20,000, and had no allergic disease.