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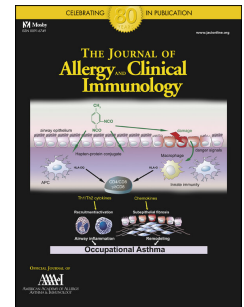
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The association of asthma, total IgE and blood lead and cadmium levels

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Abbreviations: BCL, blood cadmium levels; BHMLs, blood heavy metal levels; BLL, blood lead levels; BML, blood mercury levels; CI, confidence interval; KNHANES, the Korean National Health and Nutrition Examination Survey; OR, odds ratio.

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To the editor:

Asthma is a major cause of disability worldwide and is related to poor quality of life. It is considered an important public health issue, with a global prevalence of 4.3%.¹ More than 50% of adult asthma was potentially mediated by IgE,² and thus the increase in asthma cases could be closely associated with increases in IgE sensitization.

Adverse effects of exposure to heavy metals, including lead, mercury, and cadmium, have been a cause of concern over recent decades. Several lines of evidence associate exposure to lead and mercury with risk of asthma and increased total IgE.³ Epidemiologic evidence has not been sufficient to support any association of blood cadmium levels (BCL) with asthma and/or IgE sensitization. Moreover, no previous studies investigated the role of total or allergen-specific IgE in association with exposure to heavy metals and asthma.

This study investigated the relationships of blood lead levels (BLL), blood mercury levels (BML), and BCL with risk of asthma, high total IgE and allergen (*Dermatophagoides farinae*, cockroach, and dog)-specific sensitization in a representative Korean population. We hypothesized that blood heavy metal levels (BHMLs) are associated with asthma in Korean adults, in whom total or allergen-specific IgE would be involved in the association between BHMLs and asthma.

Data for this study were obtained from the fifth Korean National Health and Nutrition Examination Survey conducted from 2010 to 2012 (see the Methods section in this article's Online Repository at www.jacionline.org). This study analyzed 5,912 subjects (≥ 19 years old) to investigate associations between BHMLs and asthma, including 1,979 subjects in which associations of BHMLs with IgE levels were assessed (see Fig E1 in the Online Repository). BLL and BCL were measured by graphite furnace atomic absorption spectrometry with the Zeeman background correction (PerkinElmer Analyst 600; Perkin Elmer, Turku, Finland). BML was measured by a Direct Mercury Analyzer-80 (DMA-80; Milestone, Bergamo, Italy) using the gold-amalgam collection method. The following question was used to assess asthma for each subject: "Have you been diagnosed with asthma by a physician?" Total and allergen-specific IgE levels for *D. farinae*, cockroach, and dog allergens were measured using a 1450 Wizard Gamma Counter (Perkin Elmer, Turku, Finland). Subjects with total IgE levels >150 U/ml were defined as having high total IgE. Subjects with allergen-specific IgE levels >0.35 kU/L were defined as being sensitized.

The relationships of BHMLs with asthma, high total IgE, and allergen-specific sensitization were analyzed using the quintile cut-points of heavy metal levels. Firth multivariable logistic regression analyses were used with a penalized likelihood to address rare asthma events. Each analysis was performed with adjustments for age, sex, occupation, education, family income, serum vitamin D [25(OH)D], smoking, region of residence, and parental history of allergic diseases.

Mediation analyses were conducted to determine whether all or part of the relationship between BHMLs and asthma was explained by total or allergen-specific IgE. These analyses were conducted using the structural equation model with the Karlson-Holm-Breen decomposition method. Specific BHMLs and total or allergen-specific IgE levels that met the Baron and Kenny's criteria⁴ in the mediation analyses were investigated as predictors and mediators, respectively. In the statistical analyses, BHMLs and total and allergen-specific IgE levels were naturally log-transformed. The mediation proportion was calculated as follows: $100 \times \text{indirect effect} / (\text{indirect effect} + \text{direct effect})$. STATA 13.0 (Stata Corp., College Station, TX, USA) was used for mediation analyses. The other statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). A P value <0.05 was considered to indicate statistical significance.

The overall prevalence of asthma was 1.23% (see Table E1 in the Online Repository). Odds ratios (ORs) for asthma in subjects with the highest quintiles of BLL and BCL were 1.67 [95% confidence intervals (CI), 1.10–2.55] and 1.55 (95% CI, 1.03–2.33), respectively, compared to the lowest quintiles (Table I). Significant linear trends across quintiles were also observed. ORs for the highest vs. the lowest quintile for high total IgE levels was significant in the quintiles of BLL (OR, 1.29; 95% CI, 1.05–1.60) and BML (OR, 1.37; 95% CI, 1.12–1.68), with significant linear trends across quintiles. ORs for dog- and *D. farinae*-specific sensitization in the highest quintile of BLL and BML, respectively, were significantly higher than in the lowest quintile, with significant linear trends across quintiles. In sensitivity analysis on participants with complete data ($n=1,960$), the associations of BHMLs with asthma and high total IgE were in line with the results from the whole study population ($n=5,912$) (see Table E2 in the Online Repository). BLL and total IgE levels met the Baron and Kenny's criteria as predictors and mediators, respectively, and therefore, mediation analysis was performed using only these variables (see Table E3 in the Online Repository). In Fig 1, mediation analysis showed that total IgE levels significantly involves the association between BLL and asthma (indirect effect OR, 1.29; 95% CI,

1.06–1.57) and that the effect of BLL on total IgE levels (coefficient, 0.72; 95% CI, 0.57-0.87) and the effect of total IgE levels on asthma (OR, 1.42; 95% CI, 1.09-1.86) were simultaneously significant after controlling for the direct effect of BLL on asthma. However, the direct effect was not statistically significant. The estimated mediation effect explained 27.4% $\{=100 \times \ln(1.29) / [\ln(1.29) + \ln(1.96)]\}$ of the association, suggesting an indirect effect of BLL on asthma through total IgE.

In line with our results, previous studies found an increase in IgE levels with BLL (see the Discussion section in this article's Online Repository at www.jacionline.org).⁵ The mechanism of the association between lead exposure and high IgE levels is not clearly understood. However, it has been proposed that lead exposure results in type I hypersensitivity mediated by IgE.⁶ It has been proposed that BLL enhances Th₂ immune responses and inhibits Th₁ responses, and therefore increases the Th₂/Th₁ cytokine ratio.⁷ This reaction specifically promotes the production of IgE via B cell stimulation. Similar to BLL, the association between BML and total IgE revealed in this study may be explained by the fact that various forms of mercury can trigger autoimmune reactions. For example, HgCl₂ directly activates T cells and mast cells to produce mediators that induce the development of Th₂-lymphocytes and thereby the production of IgE.⁸ Among allergens, dog- and *D. farinae*-specific sensitization were most closely associated with BLL and BML, respectively. These sensitizations might enhance the associations between total IgE and those BHMLs. Despite the BML-total IgE association, however, BML was not significantly related to asthma. Considering the immune effects of total IgE, it is difficult to explain these non-significant results. Because no studies have described the potential biological mechanisms, future studies are warranted to elucidate the mechanism by which BML increases total IgE levels without affecting the incidence of asthma.

Exposure to lead (see the Discussion section in this article's Online Repository at www.jacionline.org) may be related to the increased risk of asthma and other allergic diseases, because susceptibility to allergic disease is closely related to IgE.⁹ Well *et al.* reported a non-significant association between BLL and asthma or atopy, but suggested the possibility of an underlying modulation in the immune system which may induce allergic diseases.⁵ Our results are in line with this speculation. This variation of study results might be attributed to genetic and environmental differences. However, it is interesting to note that BCL was significantly associated with asthma, but not with high total IgE. Some *in vitro* studies reported that low concentrations of cadmium markedly decreased IgE production in a concentration-

dependent manner.¹⁰ Therefore, we speculated that the mechanism of action of cadmium on asthma was not involved in increased total IgE levels. The significant association between BCL and asthma without involvement of total IgE levels may be explained by the fact that subjects with asthma have narrow airways, which may induce the pulmonary uptake of cadmium. In turn, cadmium exposure may alter the integrity of respiratory epithelia or mast cells, in turn elevating asthma severity.¹¹

Previous studies have theorized that serum IgE levels mediate the association between some BHMLs and asthma, but none have clearly demonstrated this association. To our knowledge, this is the first study to use mediation analysis to address this issue. One limitation of this study was the inability to confirm any causal associations of BHMLs with asthma, high total IgE and allergen-specific sensitization due to its cross-sectional design. Another limitation was the inability to analyze data on lead levels in bones, because data on BHMLs are relatively indicative only of recent exposure. An additional limitation was non-adjustments for some confounders (e.g., particulate matter exposure or specific job activities) in statistical analyses.

Our findings provide important evidence that BLL, BML and BCL represent important risk factors for asthma and high total IgE. Moreover, our study demonstrates that total IgE is a significant factor in the association of BLL with asthma. Future longitudinal studies should clarify the roles of BHMLs in asthma, high total IgE and allergen-specific sensitization in other populations and ethnicities.

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122 Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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References

1. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, Boulet L-P. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health* 2012;12:204.
2. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TA, Ring J, Thien F, Van Cauwenberge P, Williams HC. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;113:832-6.
3. Weidinger S, Kramer U, Dunemann L, Mohrenschlager M, Ring J, Behrendt H. Body burden of mercury is associated with acute atopic eczema and total IgE in children from southern Germany. *J Allergy Clin Immunol* 2004;114:457-9.
4. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986;51:1173-82.
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. Yang SN, Hsieh CC, Kuo HF, Lee MS, Huang MY, Kuo CH, Hung CH. The effects of environmental toxins on allergic inflammation. *Allergy Asthma Immunol Res* 2014;6:478-84.
7. 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.
8. Bagenstose LM, Salgame P, Monestier M. Murine mercury-induced autoimmunity: a model of chemically related autoimmunity in humans. *Immunol Res* 1999;20:67-78.
9. Oettgen HC, Geha RS. IgE in asthma and atopy: cellular and molecular connections. *J Clin Invest* 1999;104:829-35.
10. Jelovcan S, Gutschi A, Kleinhapfl B, Sedlmayr P, Barth S, Marth E. Effects of low concentrations of cadmium on immunoglobulin E production by human B lymphocytes in vitro. *Toxicology* 2003;188:35-48.
11. Hossny E, Mokhtar G, El-Awady M, Ali I, Morsy M, Dawood A. Environmental exposure of the pediatric age groups in Cairo City and its suburbs to cadmium pollution. *Sci Total Environ* 2001;273:135-46.

Fig. 1. Total, direct, and indirect effect of blood lead levels on asthma through total IgE levels based on structural equation models, KNHANES, 2010-2012. Adjusted for age, sex, occupation, education, family income, serum vitamin D [25(OH)D], smoking amount, the region of residence, and parental history of allergic diseases. Blood lead and total IgE levels were naturally log-transformed. Numbers represent odds ratios for a binary outcome (asthma) or a β coefficient for a continuous outcome (total IgE), 95% confidence intervals, and *P* values. Indirect and total effects were 1.29 (95% CI, 1.06-1.57; *P* value, 0.013) and 2.52 (95% CI, 0.96-6.62; *P* value, 0.060), respectively. Percent mediated, the total effect explained by the mediation of total IgE level, was 27.4%.

Fig E1. Venn diagram showing the number of study subjects (n=5,931), KNHANES, 2010-2012. Each numbers is the number of the subjects in each area. A total of 1,979, 5,912, and 1,960 subjects were analyzed for the associations between heavy metal levels and IgE, between heavy metal levels and asthma, and between IgE and asthma.

Table I. Odds ratio (95% confidence interval)* of asthma and allergic sensitization according to blood lead, mercury, and cadmium levels, KNHANES, 2010-2012.

	Quintiles of blood heavy metal level					P for trend
	Q1	Q2	Q3	Q4	Q5	
Lead (µg/dL)						
Asthma	0.33-1.48 [†] (n=1,182)	1.48-1.92 (n=1,183)	1.92-2.38 (n=1,182)	2.38-3.01 (n=1,181)	3.01-17.71 (n=1,182)	
	Reference	1.02 (0.63, 1.63)	0.90 (0.56, 1.45)	0.99 (0.62, 1.57)	1.67 (1.10, 2.55)	0.021
Allergic sensitization	0.42-1.56 (n=375)	1.56-2.04 (n=394)	2.04-2.47 (n=397)	2.48-3.11 (n=396)	3.11-17.71 (n=395)	
Total IgE (>150U/mL)	Reference	0.82 (0.67, 1.01)	0.96 (0.79, 1.17)	1.11 (0.91, 1.35)	1.29 (1.05, 1.60)	0.009
<i>D. farinae</i> -specific IgE (>0.35kU/L)	Reference	0.84 (0.69, 1.03)	0.94 (0.78, 1.14)	1.04 (0.86, 1.27)	1.18 (0.96, 1.46)	0.160
Cockroaches-specific IgE (>0.35kU/L)	Reference	1.11 (0.87, 1.41)	0.94 (0.74, 1.19)	0.92 (0.73, 1.16)	0.96 (0.76, 1.23)	0.521
Dog-specific IgE (>0.35kU/L)	Reference	1.17 (0.79, 1.73)	0.57 (0.35, 0.93)	1.18 (0.79, 1.75)	1.68 (1.11, 2.53)	0.029
Mercury (µg/L)						
Asthma	0.36-2.16 (n=1,181)	2.17-2.98 (n=1,185)	2.98-4.10 (n=1,181)	4.10-5.93 (n=1,181)	5.94-43.10 (n=1,183)	
	Reference	0.78 (0.47, 1.27)	0.79 (0.49, 1.30)	1.08 (0.70, 1.69)	1.49 (0.98, 2.26)	0.067
Allergic sensitization	0.68-2.41 (n=395)	2.42-3.33 (n=396)	3.34-4.56 (n=396)	4.57-6.46 (n=396)	6.46-40.9 (n=396)	
Total IgE (>150U/mL)	Reference	1.12 (0.92, 1.37)	1.01 (0.82, 1.23)	0.85 (0.70, 1.04)	1.37 (1.12, 1.68)	0.006
<i>D. farinae</i> -specific IgE (>0.35kU/L)	Reference	1.01 (0.83, 1.22)	1.05 (0.87, 1.27)	0.93 (0.77, 1.13)	1.24 (1.01, 1.51)	0.037
Cockroaches-specific IgE (>0.35kU/L)	Reference	1.06 (0.83, 1.34)	0.97 (0.77, 1.23)	0.96 (0.77, 1.21)	1.09 (0.87, 1.37)	0.508
Dog-specific IgE (>0.35kU/L)	Reference	0.97 (0.65, 1.45)	1.21 (0.83, 1.76)	1.15 (0.79, 1.68)	1.09 (0.72, 1.64)	0.370
Cadmium (µg/L)						
Asthma	0.07-0.62 (n=1,186)	0.62-0.88 (n=1,180)	0.88-1.17 (n=1,180)	1.17-1.60 (n=1,182)	1.60-6.42 (n=1,184)	
	Reference	0.84 (0.50, 1.42)	1.12 (0.71, 1.75)	1.19 (0.76, 1.85)	1.55 (1.03, 2.33)	0.019
Allergic sensitization	0.10-0.65 (n=394)	0.65-0.90 (n=397)	0.91-1.22 (n=396)	1.22-1.61 (n=396)	1.61-5.09 (n=396)	
Total IgE (>150U/mL)	Reference	1.07 (0.88, 1.31)	0.98 (0.81, 1.20)	0.93 (0.76, 1.14)	1.05 (0.85, 1.29)	0.911
<i>D. farinae</i> -specific IgE (>0.35kU/L)	Reference	1.01 (0.83, 1.22)	0.96 (0.79, 1.16)	0.99 (0.82, 1.21)	1.08 (0.88, 1.32)	0.543
Cockroaches-specific IgE (>0.35kU/L)	Reference	1.17 (0.94, 1.47)	1.14 (0.91, 1.43)	0.95 (0.74, 1.21)	0.97 (0.75, 1.24)	0.980
Dog-specific IgE (>0.35kU/L)	Reference	0.88 (0.59, 1.32)	1.22 (0.84, 1.77)	0.90 (0.59, 1.39)	1.24 (0.82, 1.87)	0.266

*Adjusted for age (unit, years), sex, occupation (white color/professional; blue color; unemployed/household/student), education (elementary school; middle school; high school; ≥college), family income (<\$4,000; ≥\$4,000/month), serum vitamin D [25(OH)D] (unit, ng/mL), smoking amount (unit, pack-year), the region of residence (urban; rural), and parental history of allergic diseases (asthma, allergy, or atopic dermatitis). [†]Ranges of blood heavy metal levels. Bold indicates *P* value < 0.05.

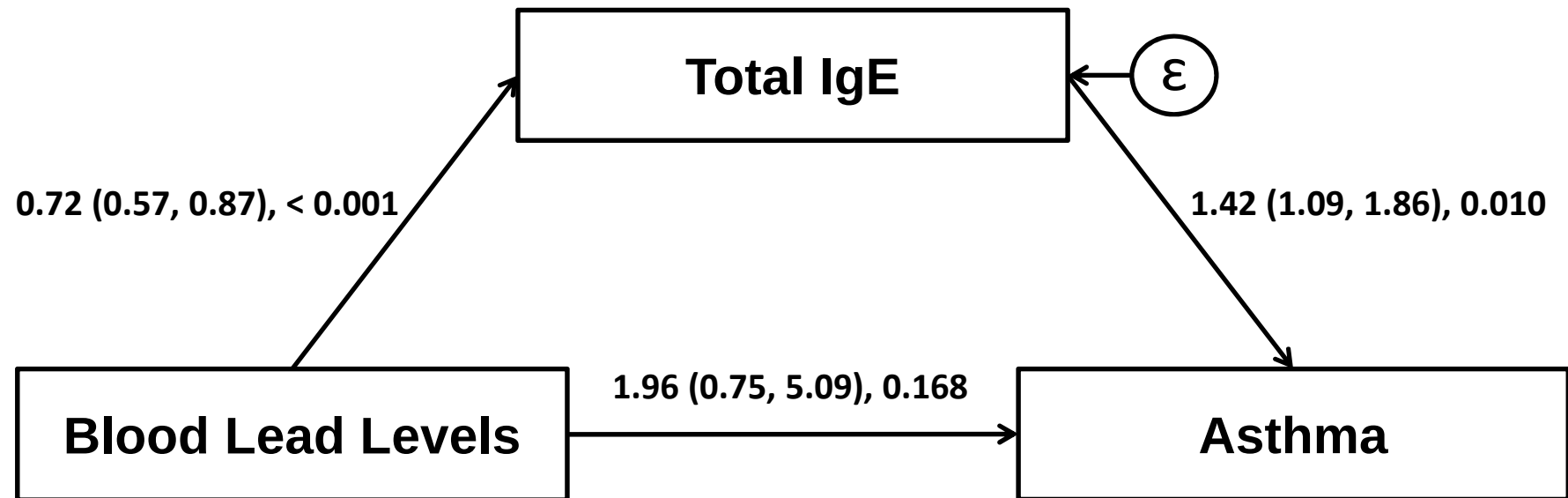


TABLE E1. Characteristics of study participants, KNHANES, 2010-2012*.

	Non-asthma		Asthma		P value
	Mean $\pm$ SD or %	Median (range)	Mean $\pm$ SD or %	Median (range)	
N (%)	5,839 (98.8)		73 (1.2)		
Women, %	50.9		52.1		0.847
Age, yr	44.8 $\pm$ 0.2	44 (19-87)	51.3 $\pm$ 1.7	51 (20-76)	<.001
Smoking, pack-years	7.6 $\pm$ 0.2	0 (0-180)	11.8 $\pm$ 2.1	0 (0-81.7)	0.056
Social economic status					
Education, %					
Elementary school	16.3		32.9		<.001
Middle school	10.2		20.6		
High school	38.1		19.2		
$\geq$ College/university	35.3		27.4		
Household income $\geq$ \$ 4,000/month, %	39.3		21.9		0.003
Occupation, %					
White collar/professional	24.9		16.4		0.220
Blue collar	40.4		42.5		
Unemployed/household/student	34.7		41.1		
Serum 25(OH)D, ng/mL	17.3 $\pm$ 0.1	16.4 (3.8-52.8)	17.3 $\pm$ 0.6	17.5 (5.8-32.3)	0.539
Urban resident, %	81.6		83.0		0.061
Parental history of allergic diseases [†] , %	25.5		66.7		0.218
Heavy metal					
Lead, μ g/dL	2.32 $\pm$ 0.01	2.14 (0.33-17.7)	2.72 $\pm$ 0.14	2.54 (0.78-7.84)	<.001
Mercury, μ g/L	4.43 $\pm$ 0.04	3.49 (0.36-43.1)	5.31 $\pm$ 0.6	4.00 (0.85-38.4)	0.196
Cadmium, μ g/L	1.15 $\pm$ 0.01	1.02 (0.07-6.42)	1.40 $\pm$ 0.08	1.27 (0.21-3.86)	<.001
Serum IgE measurments					
N (%)	1,932 (98.6)		28 (1.4)		
Total IgE, U/mL	271 $\pm$ 13	82.0 (2-5,000)	354 $\pm$ 83	193 (12- 1,897)	0.003
Total IgE >150U/mL, %	46.9		23.1		0.013
<i>D. farinae</i> -specific IgE, kU/L	4.8 $\pm$ 0.4	0.20 (0.01-100)	11.4 $\pm$ 5.1	0.50 (0.01-100)	0.025
<i>D.farinae</i> -specific IgE > 0.35kU/L, %	47.0		29.8		0.093
Cockroaches-specific IgE, kU/L	0.51 $\pm$ 0.05	0.06 (0.01-41.3)	1.11 $\pm$ 0.90	0.07 (0.02-25.3)	0.473
Cockroaches-specific IgE > 0.35kU/L, %	26.7		11.0		0.862
Dog-specific IgE, kU/L	0.22 $\pm$ 0.05	0.02 (0.01-68.7)	0.87 $\pm$ 0.56	0.03 (0.01-14.8)	0.066
Dog-specific IgE > 0.35kU/L, %	7.1		3.8		0.191

*Only participants with asthma variable were analyzed for the comparison between asthma and non-asthma groups, and thus 19 participants only with heavy metal and IgE variables (but without asthma variable) were not analyzed for the comparison (see Fig E1 in the Online Repository). [†]Allergic diseases include asthma, allergy, and atopic dermatitis. Continuous and categorical variables were analyzed by using the Wilcoxon rank sum test and the Chi-square test (or Fisher's exact test), respectively.

TABLE E2. Sensitivity analysis for odds ratio (95% confidence interval)* of asthma and allergic sensitization according to blood lead, mercury, and cadmium levels, KNHANES, 2010-2012.

	Quintiles of blood heavy metal level					P for trend
	Q1	Q2	Q3	Q4	Q5	
Lead (µg/dL)						
	0.42-1.56 [†] (n=391)	1.56-2.04 (n=390)	2.04-2.47 (n=394)	2.48-3.10 (n=391)	3.11-17.7 (n=392)	
Asthma	Reference	1.15 (0.58, 2.25)	0.64 (0.28, 1.47)	1.18 (0.60, 2.34)	2.08 (1.07, 4.06)	0.034
Allergic sensitization						
Total IgE (>150U/mL)	Reference	0.81 (0.66, 1.00)	0.96 (0.79, 1.17)	1.11 (0.91, 1.35)	1.29 (1.05, 1.59)	0.010
<i>D. farinae</i> -specific IgE (>0.35kU/L)	Reference	0.85 (0.69, 1.03)	0.94 (0.78, 1.14)	1.03 (0.85, 1.26)	1.20 (0.97, 1.48)	0.139
Cockroaches-specific IgE (>0.35kU/L)	Reference	1.11 (0.87, 1.42)	0.94 (0.74, 1.19)	0.92 (0.73, 1.16)	0.96 (0.75, 1.22)	0.502
Dog-specific IgE (>0.35kU/L)	Reference	1.17 (0.79, 1.74)	0.57 (0.35, 0.93)	1.19 (0.80, 1.77)	1.66 (1.10, 2.51)	0.030
Mercury (µg/L)						
	0.68-2.42 [†] (n=391)	2.42-3.33 (n=392)	3.33-4.56 (n=393)	4.57-6.45 (n=393)	6.46-40.9 (n=391)	
Asthma	Reference	0.58 (0.25, 1.34)	0.66 (0.29, 1.50)	1.44 (0.76, 2.72)	1.68 (0.89, 3.19)	0.091
Allergic sensitization						
Total IgE (>150U/mL)	Reference	1.12 (0.92, 1.37)	1.01 (0.83, 1.23)	0.86 (0.70, 1.05)	1.36 (1.12, 1.67)	0.007
<i>D. farinae</i> -specific IgE (>0.35kU/L)	Reference	1.02 (0.84, 1.24)	1.04 (0.86, 1.26)	0.93 (0.76, 1.12)	1.25 (1.02, 1.52)	0.033
Cockroaches-specific IgE (>0.35kU/L)	Reference	1.07 (0.84, 1.36)	0.96 (0.76, 1.22)	0.96 (0.76, 1.20)	1.10 (0.88, 1.38)	0.476
Dog-specific IgE (>0.35kU/L)	Reference	0.99 (0.66, 1.47)	1.20 (0.82, 1.75)	1.16 (0.79, 1.68)	1.09 (0.72, 1.64)	0.375
Cadmium (µg/L)						
	0.10-0.65 [†] (n=393)	0.65-0.90 (n=391)	0.91-1.21 (n=392)	1.22-1.60 (n=392)	1.61-5.09 (n=392)	
Asthma	Reference	0.83 (0.32, 2.17)	1.98 (0.92, 4.27)	2.54 (1.18, 5.45)	2.09 (0.95, 4.62)	0.017
Allergic sensitization						
Total IgE (>150U/mL)	Reference	1.07 (0.88, 1.31)	0.99 (0.81, 1.20)	0.93 (0.75, 1.14)	1.05 (0.85, 1.29)	0.918
<i>D. farinae</i> -specific IgE (>0.35kU/L)	Reference	1.00 (0.82, 1.21)	0.96 (0.79, 1.17)	0.99 (0.81, 1.20)	1.08 (0.88, 1.32)	0.564
Cockroaches-specific IgE (>0.35kU/L)	Reference	1.20 (0.95, 1.50)	1.14 (0.91, 1.43)	0.94 (0.73, 1.20)	0.98 (0.76, 1.25)	0.962
Dog-specific IgE (>0.35kU/L)	Reference	0.90 (0.60, 1.34)	1.22 (0.84, 1.77)	0.91 (0.59, 1.40)	1.23 (0.82, 1.86)	0.268

*Adjusted for age, sex, occupation, education, family income, serum vitamin D [25(OH)D], smoking amount, the region of residence, and parental history of allergic diseases. [†]Ranges of blood heavy metal levels. Bold indicates *P* value < 0.05.

TABLE E3. Associations among blood heavy metal levels, serum IgE levels, and asthma (multivariable logistic and linear regression analyses).

Independent variable	Dependent variable	Coefficient (95% CI)	Standardized coefficient	Odds ratio (95% CI)	P value
Heavy metal	Asthma				
Lead, µg/dL		0.66 (0.09, 1.24)	0.16	1.94 (1.09, 3.44)	0.023
Mercury, µg/L		0.30 (-0.07, 0.67)	0.10	1.35 (0.93, 1.95)	0.116
Cadmium, µg/L		0.47 (0.00, 0.93)	0.15	1.59 (1.00, 2.53)	0.049
IgE	Asthma				
Total IgE, U/mL		0.36 (0.12, 0.60)	0.30	1.43 (1.12, 1.83)	0.004
<i>D. farinae</i>-specific IgE, kU/L		0.21 (0.07, 0.35)	0.28	1.23 (1.07, 1.41)	0.003
Cockroaches-specific IgE, kU/L		0.08 (-0.14, 0.29)	0.07	1.08 (0.87, 1.34)	0.486
Dog-specific IgE, kU/L		0.31 (0.10, 0.52)	0.22	1.36 (1.11, 1.68)	0.004
Heavy metal	IgE				
Lead, µg/dL	Total IgE, U/mL	0.19 (0.01, 0.36)	0.047	-	0.040
	<i>D. farinae</i> -specific IgE, kU/L	0.10 (-0.21, 0.41)	0.014	-	0.528
	Cockroaches-specific IgE, kU/L	0.08 (-0.11, 0.27)	0.019	-	0.414
	Dog-specific IgE, kU/L	0.16 (0.00, 0.32)	0.044	-	0.056
Mercury, µg/L	Total IgE, U/mL	0.16 (0.05, 0.27)	0.063	-	0.005
	<i>D. farinae</i> -specific IgE, kU/L	0.14 (-0.06, 0.33)	0.031	-	0.174
	Cockroaches-specific IgE, kU/L	0.07 (-0.05, 0.19)	0.026	-	0.249
	Dog-specific IgE, kU/L	0.12 (0.02, 0.22)	0.051	-	0.024
Cadmium, µg/L	Total IgE, U/mL	0.07 (-0.06, 0.19)	0.024	-	0.297
	<i>D. farinae</i> -specific IgE, kU/L	-0.01 (-0.23, 0.21)	-0.002	-	0.913
	Cockroaches-specific IgE, kU/L	0.14 (0.01, 0.28)	0.048	-	0.035
	Dog-specific IgE, kU/L	0.09 (-0.02, 0.21)	0.036	-	0.120

*Adjusted for age, sex, occupation, education, family income, serum vitamin D [25(OH)D], smoking amount, the region of residence, and parental history of allergic diseases. The dash line means that odds ratios were not applicable measure of the association magnitude. All continuous variables were naturally log-transformed. Standardized coefficients were calculated as logistic or linear regression coefficients divided by standard deviation. Bold indicates *P* value < 0.05. 95% CI, 95% confidence interval.

