Serum heavy metal levels are associated with asthma, allergic rhinitis, atopic dermatitis, allergic multimorbidity, and airflow obstruction

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Clinical Implications

- Serum levels of heavy metals were significantly associated with asthma, atopic dermatitis, allergic rhinitis, allergic multimorbidity, and airflow obstruction. This suggests that implementation of strategies that reduce the environmental levels of these heavy metals may help to prevent allergic diseases.

TO THE EDITOR:

Heavy metal exposure is a major public health issue that has increased during industrial development because air pollution, heavy automobile traffic, use of agricultural chemicals, contaminated irrigation water, and smoking have increased exposures *via* inhalation, ingestion, and skin contact.[1] Heavy metal exposure is also associated with preferential biased activation of the T_H2 pathway, which functions in the pathogenesis of allergic disease.[2] Although nonclinical studies have identified a relationship between heavy metal exposure and allergic disease,[2] there is controversial epidemiologic evidence regarding the relationship between serum levels of heavy metals and asthma (positive association[3,4] and no association[5,6]), atopic dermatitis (positive association[7] and no association[8]), and airflow obstruction,[9] and only a few studies have investigated the effect of serum levels of heavy metals on the development of allergic rhinitis and/or allergic multimorbidity.

We examined the associations of the serum levels of 3 heavy metals (lead, mercury, and cadmium) with the prevalence of asthma, atopic dermatitis, allergic rhinitis, allergic multimorbidity, and pulmonary function in the general population of Korean adults (≥19 year old). Data were from the Korean National Health and Nutrition Examination Survey, a nationally representative health information survey of the Korean population, conducted by the Korea Center for Disease Control and Prevention. The study protocol was approved by the Institutional Review Board of the Korea Center for Disease Control and Prevention (2007-02CON-04-P, 2008-04EXP-01-C, 2009-01CON-03-2C, 2010-02CON-21-C, 2011-02CON-06-C, 2012-01EXP-01-2C, 2013-07CON-03-4C, and 2013-12EXP-03-5C), and written informed consent was provided by all participants.

The presence of asthma, atopic dermatitis, and allergic rhinitis was defined by affirmative answers to the following 2 questions[3]: "Have you been diagnosed with asthma/atopic dermatitis/allergic rhinitis by a doctor?" and "Do you still have asthma/atopic dermatitis/allergic rhinitis?" The severity of allergic rhinitis (mild or moderate-severe) was categorized using the Allergic Rhinitis and its Impact on Asthma guidelines.[10] Allergic multimorbidity was defined as the coexistence of at least 2 allergic diseases (asthma, allergic rhinitis, and/or atopic dermatitis).

Data were analyzed using weighted complex sampling analysis with the Wilcoxon rank sum test, chi-square test, and binary or multinomial logistic regression, and presented as odds ratios (ORs) with 95% CIs; the results of general linear models are presented as β coefficients with 95% CIs. These analyses were performed using SPSS version 24.0 (IBM, Armonk, NY) and R software version 3.1.1 (R Project for Statistical Computing, Vienna, Austria). Potential confounding factors were region of residence (rural vs urban), household income, occupation, education, body mass index category, and smoking. Disease outcomes were adjusted for confounding by sex and age (based on the *a priori* assumption that they were potential confounders) and by each potential confounding factor whose P value was less than .10. There was no interaction of Korean National Health and Nutrition Examination Survey year with any of the outcomes ($P > .10$). A P value below .05 was considered statistically significant.

We initially analyzed 18,686 participants whose concentrations of serum heavy metals were available in all Korean National Health and Nutrition Examination Surveys from 2005 to 2016. We then investigated the associations of serum heavy metal levels with asthma and/or atopic dermatitis (n = 16,089), with allergic rhinitis and/or allergic multimorbidity (n = 9,547), and with pulmonary function (n = 8,092) in subjects who were at least 19 years old and had these different diseases (Figure 1).

Among the participants, 1.9% (298 of 16,089) had asthma, 1.8% (285 of 16,089) had atopic dermatitis, 25.4% (2,428 of 9,547) had allergic rhinitis, and 0.9% (86 of 9,547) had allergic multimorbidity. Our results indicate that serum lead level (continuous variable) was associated with self-reported asthma (adjusted OR [aOR], 1.10; 95% CI, 1.02-1.17) and atopic dermatitis (aOR, 1.12; 95% CI, 1.02-1.23); cadmium level was associated with self-reported asthma (aOR, 1.36; 95% CI, 1.19-1.55) and allergic rhinitis (aOR, 1.11; 95% CI, 1.03-1.19); and mercury level was not associated with any of the 3 allergic conditions (Table I; see Table E3 in this article's Online Repository at www.jaci-inpractice.org). More specifically, all 3 heavy metals were associated with lower FEV_1/forced vital capacity z scores when measured as continuous variables (lead adjusted β [aβ], −0.004; 95% CI, −0.006 to −0.003; mercury aβ, −0.001; 95% CI, −0.001 to 0.000; cadmium aβ, −0.007; 95% CI, −0.010 to −0.005). We obtained similar results when serum heavy metal concentrations were examined as categorical variables divided into quartiles (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). In addition, lead exposure was associated with allergic multimorbidity (aOR, 1.16; 95% CI, 1.04-1.30) and cadmium exposure was associated with

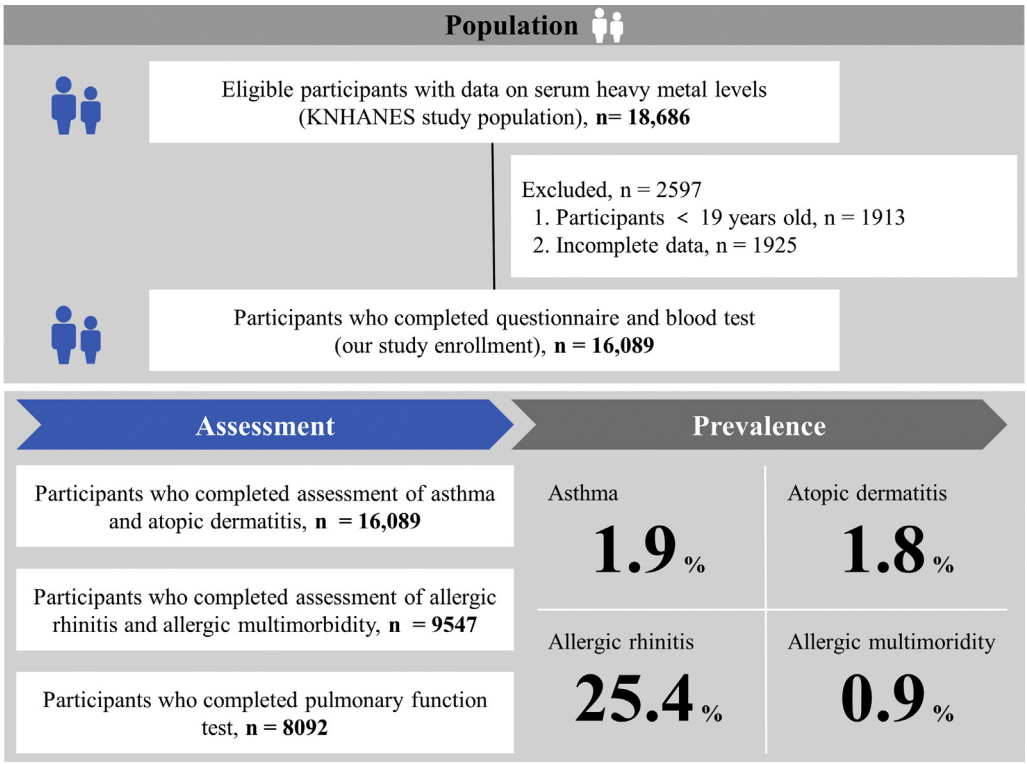

FIGURE 1. Disposition and classification of the 18,686 individuals from the KNHANES study population who had data on serum levels of heavy metals. A total of 16,809 adults (>19 year old) were assessed for asthma and atopic dermatitis, 9,547 were assessed for allergic rhinitis and allergic multimorbidity, and 8,092 completed pulmonary function testing. *KNHANES*, Korean National Health and Nutrition Examination Survey.

severity of allergic rhinitis (mild allergic rhinitis: aOR, 1.09; 95% CI, 1.00-1.18; moderate/severe allergic rhinitis: aOR, 1.14; 95% CI, 1.02-1.28) (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

This is one of the few comprehensive studies of a general population to measure serum levels of heavy metals and to assess allergic diseases, multimorbidities, and airflow obstruction. Compared with 2 previous studies, the present study assessed more allergic disease entities (atopic dermatitis, allergic rhinitis, and multimorbidity), examined more subjects (18,686 *vs* 5,912 or 4,509), and used more restrictive definitions of allergic diseases (current allergic disease *vs* ever allergic disease).[3,8] Although only a few studies have reported associations of serum levels of heavy metals with allergic rhinitis and/or allergic multimorbidity, the present study identifies significant associations of serum levels of heavy metals with allergic rhinitis, severity of allergic rhinitis, and allergic multimorbidity.

Heavy metals could contribute to the development of other allergic phenotypes that derive from asthma with allergen sensitization. Heavy metals directly activate T_H2 cells, as an adjuvant effect, and increase sensitization to unrelated antigens, such as coinjected trinitrophenyl-ovalbumin in the *in vivo* popliteal lymph node assay.[2] A T_H2-biased pathway, driven by elevated levels of heavy metals, can dysregulate the immune system,[2] leading to other atopic conditions,[11] *via* induction of thymic stromal lymphopoietin.[3] Previous studies may have failed to find a significant effect of heavy metals on the progression of allergic multimorbidity due to their insufficient sample sizes and study designs.[3,8] The different effects of lead and cadmium on atopic dermatitis and allergic rhinitis are probably because different organs have different specificity or susceptibility to each metal,[3] a topic that should be addressed in further molecular and mechanistic studies.

The main strengths of our study were the large sample size, the use of precise definitions of allergic diseases (assessment of current status), and comprehensive investigation of the relationship of serum levels of heavy metals with all allergic diseases. However, because our study was not longitudinal, we cannot infer casual relationships. Thus, future longitudinal studies are warranted to confirm the casual relationships between serum levels of heavy metals and development of allergic diseases. An additional limitation was that the analysis did not include other potential confounders (individual food intake, particulate matter exposure, heavy automobile traffic exposure, and/or specific occupations exposed to heavy metals) that may affect the relation between heavy metal levels and allergic diseases.

In conclusion, we found that the serum lead level was associated with asthma, atopic dermatitis, and allergic multimorbidity, the serum cadmium level was associated with asthma and allergic rhinitis, and the serum levels of all 3 tested heavy metals (lead, mercury, and cadmium) were associated with airflow obstruction in Korean adults. These results provide an

TABLE I. Multivariable analysis of the relationship of serum levels of 3 heavy metals (continuous variables) with atopic dermatitis, allergic rhinitis, asthma, and pulmonary function among KNHANES participants who completed the questionnaire and blood test (n = 16,089)

	Independent variable					
	Lead (μg/dL)		Mercury (μg/L)		Cadmium (μg/L)	
Dependent variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Binary logistic regression analysis						
Asthma*	**1.10 (1.02 to 1.17)**	**.008**	1.01 (0.99 to 1.03)	.214	**1.36 (1.19 to 1.55)**	**4.0×10^{-6}**
Allergic rhinitis†,‡	1.02 (0.98 to 1.06)	.276	0.99 (0.98 to 1.01)	.282	**1.11 (1.03 to 1.19)**	**.004**
Atopic dermatitis§	**1.12 (1.02 to 1.23)**	**.022**	1.02 (0.98 to 1.05)	.359	1.04 (0.81 to 1.33)	.776
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
General linear model analysis‖						
FEV_1/FVC¶,#	**−0.004 (−0.006 to −0.003)**	**7.9×10^{-11}**	**−0.001 (−0.001 to 0.000)**	**7.0×10^{-6}**	**−0.007 (−0.010 to −0.005)**	**1.2×10^{-9}**

BMI, Body mass index; *FVC*, forced vital capacity; *KNHNES*, Korean National Health and Nutrition Examination Survey.

Numbers in bold indicate a significant difference ($P < .05$).

*Risk factors were adjusted for age, sex, region of residence (urban and rural), household income (quartiles), occupation (white collar/professional, blue collar, and household/student/unemployed), education (elementary school or less, middle school, high school, college or above), and BMI category (normal weight, overweight, and obese).

†Study subjects who completed assessment of allergic rhinitis and allergic multimorbidity (n = 9547).

‡Risk factors were adjusted for age, sex, occupation, and education.

§Risk factors were adjusted for age, sex, and education.

‖A general linear model was used to calculate the β coefficient.

¶Study subjects who completed pulmonary function test (n = 8092).

#Risk factors were adjusted for age, sex, region of residence, smoking, household income, occupation, and education.

improved understanding of the immune responses to environmental exposures to these heavy metals, and the impact of exposures on allergic and respiratory diseases.

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REFERENCES

1. Jaishankar M, Tseten T, Anbalagan N, Mathew BB, Beeregowda KN. Toxicity, mechanism and health effects of some heavy metals. Interdiscip Toxicol 2014;7:60-72.
2. Carey JB, Allshire A, van Pelt FN. Immune modulation by cadmium and lead in the acute reporter antigen-popliteal lymph node assay. Toxicol Sci 2006;91:113-22.
3. Park S, Lee EH, Kho Y. The association of asthma, total IgE, and blood lead and cadmium levels. J Allergy Clin Immunol 2016;138:1701-1703.e6.
4. Kim KN, Bae S, Park HY, Kwon HJ, Hong YC. Low-level mercury exposure and risk of asthma in school-age children. Epidemiology 2015;26:733-9.
5. Heinrich J, Guo F, Trepka MJ. Brief report: low-level mercury exposure and risk of asthma in school-age children. Epidemiology 2017;28:116-8.
6. 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.
7. Kim JH, Jeong KS, Ha EH, Park H, Ha M, Hong YC, et al. Association between prenatal exposure to cadmium and atopic dermatitis in infancy. J Korean Med Sci 2013;28:516-21.
8. Wei J, Zhang J, Ji JS. Association of environmental exposure to heavy metals and eczema in US population: analysis of blood cadmium, lead, and mercury. Arch Environm Occup Health 2018:1-13.
9. Leem AY, Kim SK, Chang J, Kang YA, Kim YS, Park MS, et al. Relationship between blood levels of heavy metals and lung function based on the Korean National Health and Nutrition Examination Survey IV−V. Int J Chron Obstruct Pulmon Dis 2015;10:1559-70.
10. Yon DK, Lee SW, Ha EK, Lee KS, Jung YH, Jee HM, et al. Serum lipid levels are associated with allergic rhinitis, nasal symptoms, peripheral olfactory function, and nasal airway patency in children. Allergy 2018;73:1905-8.
11. Georas SN, Guo J, De Fanis U, Casolaro V. T-helper cell type-2 regulation in allergic disease. Eur Respir J 2005;26:1119-37.

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TABLE E1. Multivariable analysis of the relationship of serum levels of 3 heavy metals with asthma, atopic dermatitis, and allergic rhinitis among KNHANES participants who received assessments of asthma and/or atopic dermatitis (n = 16,089) and allergic rhinitis (n = 9,547)

	Independent variable, Lead (μg/dL)			
Dependent variable	**Q1**	**Q2**	**Q3**	**Q4**
Asthma				
Mean ± SD*	1.21 ± 0.27 (n = 4019)	1.85 ± 0.17 (n = 4025)	2.48 ± 0.21 (n = 4021)	3.93 ± 1.45 (n = 4024)
Adjusted OR† (95% CI)	1 (Reference)	1.76 (0.92-3.36)	1.83 (0.98-3.44)	**1.89 (1.01-3.56)**
Atopic dermatitis				
Mean ± SD*	1.21 ± 0.27 (n = 4019)	1.85 ± 0.17 (n = 4025)	2.48 ± 0.21 (n = 4021)	3.93 ± 1.45 (n = 4024)
Adjusted OR‡ (95% CI)	1 (Reference)	1.07 (0.66-1.72)	1.05 (0.64-1.74)	**1.64 (1.01-2.67)**
Allergic rhinitis				
Mean ± SD*	1.26 ± 0.25 (n = 2386)	1.90 ± 0.17 (n = 2387)	2.52 ± 0.20 (n = 2386)	3.89 ± 1.43 (n = 2388)
Adjusted OR§ (95% CI)	1 (Reference)	1.04 (0.91-1.18)	1.11 (0.97-1.26)	1.04 (0.90-1.19)
Independent variable, Mercury (μg/L)				
Asthma				
Mean ± SD*	1.78 ± 0.46 (n = 4021)	3.06 ± 0.36 (n = 4022)	4.58 ± 0.56 (n = 4024)	9.15 ± 5.11 (n = 4022)
Adjusted OR† (95% CI)	1 (Reference)	0.86 (0.61-1.22)	0.99 (0.712-1.39)	1.25 (0.90-1.72)
Atopic dermatitis				
Mean ± SD*	1.78 ± 0.46 (n = 4021)	3.06 ± 0.36 (n = 4022)	4.58 ± 0.56 (n = 4024)	9.15 ± 5.11 (n = 4022)
Adjusted OR‡ (95% CI)	1 (Reference)	0.76 (0.46-1.24)	1.09 (0.69-1.72)	1.22 (0.77-1.95)
Allergic rhinitis				
Mean ± SD*	1.89 ± 0.45 (n = 2384)	3.14 ± 0.36 (n = 2389)	4.65 ± 0.54 (n = 2387)	9.42 ± 5.80 (n = 2387)
Adjusted OR§ (95% CI)	1 (Reference)	1.03 (0.91-1.18)	0.91 (0.80-1.04)	1.04 (0.91-1.18)
Independent variable, Cadmium (μg/L)				
Asthma				
Mean ± SD*	0.47 ± 0.15 (n = 4015)	0.86 ± 0.10 (n = 4027)	1.26 ± 0.14 (n = 4025)	2.13 ± 0.64 (n = 4022)
Adjusted OR† (95% CI)	1 (Reference)	**1.64 (1.07-2.53)**	1.52 (0.99-2.33)	**2.18 (1.44-3.29)**
Atopic dermatitis				
Mean ± SD*	0.47 ± 0.15 (n = 4015)	0.86 ± 0.10 (n = 4027)	1.26 ± 0.14 (n = 4025)	2.13 ± 0.64 (n = 4022)
Adjusted OR‡ (95% CI)	1 (Reference)	0.92 (0.57-1.51)	1.38 (0.86-2.20)	1.18 (0.72-1.94)
Allergic rhinitis				
Mean ± SD*	0.44 ± 0.14 (n = 2382)	0.81 ± 0.10 (n = 2389)	1.20 ± 0.13 (n = 2388)	2.04 ± 0.63 (n = 2388)
Adjusted OR§ (95% CI)	1 (Reference)	1.02 (0.89-1.16)	1.06 (0.92-1.21)	**1.23 (1.08-1.42)**

BMI, body mass index; *KNHNES*, Korean National Health and Nutrition Examination Survey.
Values for each quartile are given as mean ± SD or OR (95% CI).
Numbers in bold indicate a significant difference ($P < .05$).
*Mean ± SD of serum heavy metal levels (μg/dL).
†Risk factors were adjusted for age, sex, region of residence (urban and rural), household income (quartiles), occupation (white collar/professional, blue collar, and household/student/unemployed), education (elementary school or less, middle school, high school, college or above), and BMI category (normal weight, overweight, and obese).
‡Risk factors were adjusted for age, sex, and education.
§Risk factors were adjusted for age, sex, occupation, and education.

TABLE E2. Multinomial regression analysis of the relationships of serum levels of 3 heavy metals with severity of allergic rhinitis and allergic multimorbidity among KNHANES participants who received assessments of allergic rhinitis and multimorbidity (n = 9547)

	Severity of allergic rhinitis				
		Mild allergic rhinitis (n = 1706)		Moderate/severe allergic rhinitis (n = 722)	
Heavy metal (μg/dL)	Control (n = 7119)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Lead	1 (Reference)	1.00 (0.96-1.05)	.868*	1.06 (0.99-1.12)	.080*
Mercury	1 (Reference)	0.99 (0.97-1.00)	.113*	1.00 (0.99-1.02)	.720*
Cadmium	1 (Reference)	**1.09 (1.00-1.18)**	**.039***	**1.14 (1.02-1.28)**	**.022***
	Allergic multimorbidity†				
		Single allergic disease (n = 2593)		Multiple allergic diseases (n = 86)	
Heavy metal (μg/dL)	None (n = 6868)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Lead	1 (Reference)	1.02 (0.98-1.06)	.357‡	**1.16 (1.04-1.30)**	**.011‡**
Mercury	1 (Reference)	1.00 (0.98-1.01)	.373‡	0.96 (0.88-1.04)	.338‡
Cadmium	1 (Reference)	**1.10 (1.03-1.18)**	**.007‡**	1.26 (0.89-1.79)	.190‡

BMI, Body mass index; *KNHNES*, Korean National Health and Nutrition Examination Survey.
Numbers in bold indicate a significant difference ($P < .05$).
*Risk factors were adjusted for age, sex, occupation (white collar/professional, blue collar, and household/student/unemployed), and education (elementary school or less, middle school, high school, college or above).
†Allergic multimorbidity was defined as a coexistence of at least 2 allergic diseases (asthma, allergic rhinitis, and/or atopic dermatitis).
‡Risk factors were adjusted for age, sex, region of residence (urban and rural), household income (quartiles), education, and BMI category (normal weight, overweight, and obese).

TABLE E3. Multivariable analysis of the relationship of serum levels of 3 heavy metals (continuous variables) with atopic dermatitis, allergic rhinitis, asthma, and pulmonary function among KNHANES participants who completed the questionnaire and blood test (including all 3 metals in the same statistical model) (n = 16,089)

	Independent variable					
	Lead (μg/dL)		Mercury (μg/L)		Cadmium (μg/L)	
Dependent variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Binary logistic regression analysis						
Asthma*	**1.09 (1.01 to 1.17)**	**.021**	1.01 (0.98 to 1.03)	.541	**1.36 (1.19 to 1.55)**	**2.2×10^{-5}**
Allergic rhinitis†,‡	1.02 (0.98 to 1.00)	.142	0.99 (0.98 to 1.00)	.142	**1.10 (1.03 to 1.19)**	**.007**
Atopic dermatitis§	**1.11 (1.01 to 1.23)**	**.029**	1.01 (0.98 to 1.05)	.511	0.99 (0.77 to 1.27)	.913
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
General linear model analysis‖						
FEV_1/FVC¶,#	**−0.004 (−0.005 to −0.002)**	**1.8×10^{-8}**	**−0.001 (−0.001 to 0.000)**	**.017**	**−0.006 (−0.009 to −0.004)**	**3.0×10^{-7}**

BMI, Body mass index; *FVC*, forced vital capacity; *KNHNES*, Korean National Health and Nutrition Examination Survey.
Numbers in bold indicate a significant difference ($P < .05$).
*Risk factors were adjusted for age, sex, region of residence (urban and rural), household income (quartiles), occupation (white collar/professional, blue collar, and household/student/unemployed), education (elementary school or less, middle school, high school, college or above), BMI category (normal weight, overweight, and obese), and serum levels of each of the 3 heavy metals (lead, mercury, and cadmium).
†Study subjects who completed assessment of allergic rhinitis and allergic multimorbidity (n = 9547).
‡Risk factors were adjusted for age, sex, occupation, education, and serum levels of each of the 3 heavy metals (lead, mercury, and cadmium).
§Risk factors were adjusted for age, sex, education, and serum levels of each of the 3 heavy metals (lead, mercury, and cadmium).
‖A general linear model was used to calculate the β coefficient.
¶Study subjects who completed pulmonary function test (n = 8092).
#Risk factors were adjusted for age, sex, region of residence, smoking, household income, occupation, education, and serum levels of each of the 3 heavy metals (lead, mercury, and cadmium).