

Serum Cadmium and Lead, Current Wheeze, and Lung Function in a Nationwide Study of Adults in the United States



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What is already known about this topic? Cadmium and lead are hazardous heavy metals that are linked to negative effects on respiratory health.

What does this article add to our knowledge? This study shows that serum cadmium is associated with current wheeze and current asthma in current smokers, as well as with lower lung function measures in never or former smokers. Serum lead was associated with lower forced expiratory volume in 1 second/forced vital capacity, regardless of smoking status.

How does this study impact current management guidelines? Exposure to relatively low levels of heavy metals (particularly cadmium) may negatively affect lung function in nonsmoking US adults.

BACKGROUND: Cadmium and lead are hazardous pollutants. **OBJECTIVE:** We examined the relation between serum levels of cadmium and lead and current wheeze, current asthma, and lung function in US adults.

METHODS: A cross-sectional study of 13,888 adults aged 20 to 79 years in 2007-2012 National Health and Nutrition Examination Survey (NHANES) was considered. Multivariable logistic or linear regression was used for the analyses of current wheeze, current asthma, and lung function measures (forced expiratory volume in 1 second [FEV₁]/% predicted, forced vital capacity [FVC]/% predicted, FEV₁/FVC% predicted, and fractional

exhaled nitric oxide [FeNO]), which were conducted first in all participants, and then separately in never/former smokers and current smokers.

RESULTS: High levels of serum cadmium were significantly associated with current wheeze in all participants and in current smokers (odds ratio for fourth vs first quartile = 2.84, 95% confidence interval = 2.07-3.90, $P_{\text{for linear trend}} < .01$), as well as with current asthma in current smokers. Serum lead was not significantly associated with current wheeze or current asthma, regardless of smoking status. Serum cadmium was significantly associated with lower FEV₁% predicted, FEV₁/FVC% predicted, and FeNO in all participants and in never/former smokers, and serum lead was significantly associated with lower FEV₁/FVC% predicted in all participants, with similar findings in never/former smokers and in current smokers.

CONCLUSIONS: Our findings suggest that exposure to cadmium is associated with an increased risk of wheeze and asthma in US adults who currently smoke. Moreover, our results suggest that exposure to cadmium or lead has negative effects on lung function in nonsmoking US adults. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2653-60)

Key words: Serum cadmium; Serum lead; Asthma; Lung functions

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Conflicts of interest: J. C. Celedón has received research materials from Merck and GSK (inhaled steroids), and Pharmavite (vitamin D and placebo capsules), to provide medications free of cost to participants in National Institutes of Health funded studies, unrelated to the current work. The rest of the authors declare that they have no relevant conflicts of interest.

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Asthma is a major public health issue in the United States, with 8.3% of population affected by current asthma.¹ Environmental risk factors, including pollutants, have been implicated in the pathogenesis of abnormal immune responses, asthma,²⁻⁴ and atopy.^{3,5,6} Such pollutants can be present both outdoors (eg, particulate matter,⁷ NO₂ and SO₂,⁸ and heavy metals^{6,9}) and indoors (eg, dust mite and mold allergens,¹⁰ and secondhand smoke^{8,11}).

Cadmium and lead are among the most common environmental and occupational pollutants. In 2017, the Agency for Toxic Substances and Disease Registry reported that lead and

Abbreviation used

BMI- Body mass index
 CI- Confidence interval
 COPD- Chronic obstructive pulmonary disease
 FEV₁- Forced expiratory volume in 1 second
 FeNO- Fractional exhaled nitric oxide
 FVC- Forced vital capacity
 NHANES- National Health and Nutrition Examination Survey
 OLD- Obstructive lung disease
 OR- Odds ratio

cadmium ranked second and seventh among the top 10 environmental hazardous substances.¹² Cadmium and lead are highly toxic metals that can be derived from natural resources or as a byproduct from industries such as mining. Cadmium is also a major toxicant in tobacco smoke and thus significantly higher in current smokers than in nonsmokers.¹³ The general population can be exposed through active or passive tobacco smoking exposure, contaminated water, soil, or food, whereas workers are mostly exposed by inhalation and ingestion of fumes or dusts.¹⁴

Experimental studies have shown the toxic effects of cadmium and lead on the immune system. In an *in vitro* study, low concentrations of cadmium led to diminished activation and proliferation of human B cells, likely through interruption of cell activation and induction of cytotoxic signals.¹⁵ Moreover, higher cadmium concentration in bronchoalveolar lavage was associated with higher expression of proinflammatory cytokines, such as tumor necrosis factor- α , interleukin-6, and interleukin-8.¹⁶ In a murine model, lead exposure inhibited Th1 cells and stimulated Th2 cells, thus skewing immune responses toward Th2 predominance.¹⁷

In this study, we hypothesized that serum cadmium and lead levels would be associated with current wheeze, current asthma, and worse lung function in US adults. We further hypothesized that the estimated negative effects of serum cadmium or lead on lung function would be more pronounced among nonsmokers. We examined these hypotheses in a large cross-sectional study of the US adults.

METHODS

Study population

The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional nationwide survey of the noninstitutionalized US civilian population. Study participants are selected using a stratified multistage probability design and are thus representative of the US population. Because of study design, NHANES oversamples persons 60 years and older and ethnic minorities (African Americans and Hispanics), to increase statistical power for data analysis in those subgroups. Figure 1 shows the flow chart for the selection of study participants. Adults aged 20 to 79 years who participated in the 2007-2012 NHANES surveys and had complete data on serum cadmium, serum lead, and smoking status were included in the current analysis.

NHANES was approved by the Institutional Review Board of the National Center for Health Statistics of the US Centers for Disease Control and Prevention. Informed consent was obtained from all participants. Details of the methods, protocols, and definitions used

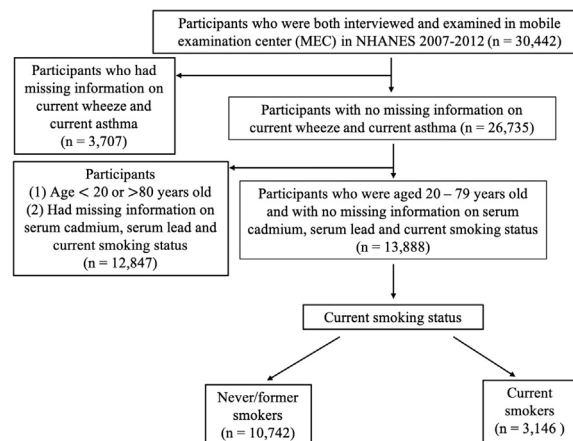


FIGURE 1. Flowchart for selection of study participants included in the current analysis. NHANES, National Health and Nutrition Examination Survey.

in NHANES can be found at <https://www.cdc.gov/nchs/nhanes/index.htm>.

Study procedures

Levels of serum cadmium and lead were measured using inductively coupled plasma mass spectrometry (PerkinElmer, Norwalk, Conn). Spirometry was performed according to American Thoracic Society recommendations.¹⁸ Participants excluded from testing include those who had been on supplemental oxygen or who had current chest pain or a physical problem with forceful expiration, recent surgery (eye, chest, or the abdomen), or a recent heart attack or stroke, tuberculosis exposure or recent coughed with blood, a personal history of detached retina, or a collapsed lung. The best forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) values were selected for data analysis. Our analyses of lung function measures were performed using percent predicted values calculated based on the Global Lung Function Initiative.¹⁹ Fractional exhaled nitric oxide (FeNO) was measured using the Aerocrine NIOX MINO (Aerocrine AB, Solna, Sweden). The NHANES protocol required 2 valid FeNO measurements that were reproducible. Participants excluded from FeNO testing include those who had current chest pain or a physical problem with forceful expiration, or those who were using supplemental oxygen. Detailed examination procedures can be found online at: <https://www.cdc.gov/nchs/nhanes/search/datapage.aspx?Component=Examination&CycleBeginYear=2007>.

Current wheeze was defined by a positive answer to the question: “In the past 12 months, have you had wheeze or whistling in your chest?” Current asthma was defined by positive answers to the questions: (1) “Has a doctor or other health professional ever told you that you have asthma?” and (2) “Do you still have asthma?” Subjects who had neither been diagnosed with asthma nor had current wheeze were selected as control subjects for the analysis of current wheeze and current asthma.

Statistical analysis

Primary sampling units and strata for the complex NHANES survey design were considered in data analysis. The R package “survey” was used to account for sampling weights, stratification,

TABLE I. Main characteristics of study participants, by current wheeze[‡]

Characteristics	Control subjects§ (n = 11,767)	Current wheeze (n = 2,121)
Age, y	45.7 ± 0.4	46.6 ± 0.4*
Female gender	5,912 (50.4)	1,135 (54.3)†
Race		
Non-Hispanic white	4,833 (66.9)	1,056 (70.8)†
Mexican American	2,106 (9.4)	213 (5.1)
Other Hispanic	1,312 (5.8)	195 (4.7)
Non-Hispanic black	2,414 (10.6)	519 (13.1)
Other	1,102 (7.3)	138 (6.2)
Had health insurance coverage	8,662 (79.1)	1,600 (79.0)
Annual household income ≥ \$20,000	8,920 (86.5)	1,380 (77.8)†
Smoking status		
Never/former smoker	9,481 (81.5)	1,261 (59.0)†
Current smoker	2,286 (18.5)	860 (41.0)
Body mass index	28.4 ± 0.1	30.5 ± 0.2†
Serum cotinine level, ng/mL	50.9 ± 2.6	112.4 ± 5.1†
Family history of asthma	1,796 (15.6)	738 (34.3)†
Vitamin D insufficiency (<30 ng/mL)	7,887 (62.2)	1,468 (67.6)†
Use oral or inhaled steroid in past 2 d	121 (1.3)	339 (19.9)†
Occupation exposure to mineral dusts or exhaust fumes	4,233 (36.7)	1,081 (50.0)†
Serum level of heavy metals, µg/L		
Cadmium	0.47 ± 0.01	0.82 ± 0.04†
Lead	1.54 ± 0.04	1.65 ± 0.05*
Lung function		
Percent predicted FEV ₁	98.8 ± 0.3	88.5 ± 0.6†
Percent predicted FVC	102.1 ± 0.2	96.7 ± 0.5†
Percent predicted FEV ₁ /FVC	96.5 ± 0.1	90.8 ± 0.4†
Fractional exhaled nitric oxide, ppb	16.7 ± 0.3	21.1 ± 0.8†

FEV₁, Forced expiratory volume in 1 s; FVC, forced vital capacity.

**P* < .05.

†*P* < .01.

‡Values are presented as number (%) or mean (mean ± standard deviation).

§Control subjects had neither current wheeze nor an asthma diagnosis.

||Wheeze or whistling in the chest in the previous 12 mo.

and clusters, in order to obtain proper effect estimates and their standard errors.

χ^2 tests and *t* tests were used for bivariate analyses of binary and continuous variables, respectively. Logistic or linear regression models were used for the multivariable analysis of serum cadmium or lead and current wheeze, current asthma, and lung function measures. All multivariable models were adjusted for age, gender, race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, other Hispanic, and others), annual household income (≥\$20,000/year vs <\$20,000/year), body mass index (BMI), family history of asthma, serum cotinine level, smoking status (never/former vs current), and occupational exposure to mineral dust or exhaust fumes. Models for lung function measures were adjusted for annual household income, BMI, serum cotinine, smoking status, occupational exposure to mineral dust or exhaust fumes (defined as the participant ever having been exposed to mineral dust or exhaust fumes at the kind of work he/she had done the longest), and use of oral or inhaled steroids in the previous 2 days. All analyses were first conducted in all participants, and then separately in current smokers and never/former smokers.

Our primary analysis was conducted by using quartiles of serum cadmium or lead level. Because of consistently significant linear trends, serum cadmium or lead level was also considered as

continuous in the analysis of lung function measures. A 2-tailed *P* value of less than .05 was considered statistically significant. R program (version 3.4.2) was used for all analyses.

RESULTS

The main characteristics of the 13,888 study participants are shown in Table I. Compared with the 11,767 control subjects, the 2,121 subjects with current wheeze were more likely to be older, female, non-Hispanic white, current smokers, and users of oral or inhaled steroids in the previous 2 days; and to have a household income less than \$20,000, a family history of asthma, vitamin D insufficiency, occupational exposure to mineral dusts or exhaust fumes, a higher BMI, a higher serum cotinine level, higher levels of serum cadmium and lead, a higher FeNO, and lower FEV₁, FVC, and FEV₁/FVC. Table E1 (available in this article's Online Repository at www.jaci-inpractice.org) shows a comparison of the characteristics of the adults with current asthma (n = 1,217) with those of the control subjects (n = 11,767), which yielded similar results to those of adults with current wheeze and control subjects, except that there were no significant differences in age, vitamin D insufficiency, or occupational exposure to mineral dusts or exhaust fumes and there

TABLE II. Serum cadmium and current wheeze in study participants, NHANES 2007-2012[†]

Exposure	Serum cadmium (µg/L)
	Odds ratio (95% confidence interval)
All participants (N = 13,888)	
Quartile 1 (<0.22 µg/L)	1.00
Quartile 2 (0.22-0.34 µg/L)	0.92 (0.75, 1.13)
Quartile 3 (0.34-0.62 µg/L)	1.01 (0.82, 1.25)
Quartile 4 (≥0.62 µg/L)	1.50 (1.20, 1.86)*
	<i>P</i> _{for linear trend} < .01
Never/former smokers (n = 10,742)	
Quartile 1 (<0.19 µg/L)	1.0
Quartile 2 (0.19-0.28 µg/L)	0.83 (0.63, 1.08)
Quartile 3 (0.28-0.43 µg/L)	1.10 (0.88, 1.37)
Quartile 4 (≥0.43 µg/L)	1.19 (0.92, 1.54)
	<i>P</i> _{for linear trend} = .08
Current smokers (n = 3,146)	
Quartile 1 (<0.61 µg/L)	1.0
Quartile 2 (0.61-0.99 µg/L)	1.91 (1.39, 2.63)*
Quartile 3 (0.99-1.50 µg/L)	2.40 (1.70, 3.39)*
Quartile 4 (≥1.50 µg/L)	2.84 (2.07, 3.90)*
	<i>P</i> _{for linear trend} < .01

BMI, Body mass index; NHANES, National Health and Nutrition Examination Survey.

**P* < .01.

[†]All models were adjusted for age, gender, race/ethnicity, annual household income, BMI, family history of asthma, serum cotinine, and occupational exposure to mineral dusts or exhaust fumes. The model for all participants was additionally adjusted for smoking status.

was a significant difference in health insurance coverage between adults with current asthma and control subjects.

Serum cotinine was significantly but weakly correlated with serum cadmium among never or former smokers (weighted Pearson correlation coefficient = 0.11, *P* < .01). Among current smokers, serum cotinine was more strongly correlated with serum cadmium, but the correlation was below 0.50 (weighted Pearson coefficient = 0.35, *P* < .01). Table II shows the results of multivariable analyses of serum cadmium and current wheeze. In the analysis of all participants, subjects whose serum cadmium was in the highest (fourth) quartile had 1.5 times higher odds of current wheeze than those whose serum cadmium level was in the lowest (first) quartile (95% confidence interval [CI] for the odds ratio [OR] = 1.20-1.86, *P*_{for linear trend} < .01). After stratification by smoking status, there was no significant association between serum cadmium and current wheeze among never or former smokers. Among current smokers, subjects whose serum cadmium level was above the first quartile had 1.91 to 2.84 times significantly higher odds of current wheeze than those whose serum cadmium level was in the first (lowest) quartile (*P*_{for linear trend} < .01).

Serum cotinine was significantly but weakly correlated with serum lead in either never/former smokers (weighted Pearson correlation coefficient = 0.07, *P* < .01) or current smokers (weighted Pearson correlation coefficient = 0.10, *P* < .01). Table III shows the results of the multivariable analysis of serum lead and current wheeze. In this analysis, serum lead was not

TABLE III. Serum lead and current wheeze in study participants*

Exposure	Serum lead (µg/L)
	Odds ratio (95% confidence interval)
All participants (N = 13,888)	
Quartile 1 (<0.83 µg/L)	1.00
Quartile 2 (0.83-1.27 µg/L)	0.98 (0.81, 1.19)
Quartile 3 (1.27-2.00 µg/L)	0.96 (0.78, 1.18)
Quartile 4 (≥2.00 µg/L)	1.15 (0.91, 1.45)
	<i>P</i> _{for linear trend} = .34
Never/former smokers (n = 10,742)	
Quartile 1 (<0.78 µg/L)	1.0
Quartile 2 (0.78-1.20 µg/L)	1.00 (0.81, 1.24)
Quartile 3 (1.20-1.83 µg/L)	0.95 (0.76, 1.19)
Quartile 4 (≥1.83 µg/L)	1.10 (0.82, 1.46)
	<i>P</i> _{for linear trend} = .63
Current smokers (n = 3,146)	
Quartile 1 (<1.04 µg/L)	1.0
Quartile 2 (1.04-1.60 µg/L)	0.94 (0.67, 1.31)
Quartile 3 (1.60-2.48 µg/L)	0.91 (0.59, 1.41)
Quartile 4 (≥2.48 µg/L)	1.24 (0.78, 1.96)
	<i>P</i> _{for linear trend} = .43

BMI, Body mass index.

*All models were adjusted for age, gender, race/ethnicity, annual household income, BMI, family history of asthma, serum cotinine, and occupational exposure to mineral dust or exhaust fumes. The model for all participants was additionally adjusted for smoking status.

significantly associated with current wheeze, either in all participants or in current smokers. We found no significant modification of the estimated effect of serum cadmium or serum lead on current wheeze by FeNO.

Tables E2 and E3 (available in this article's Online Repository at www.jaci-inpractice.org) show the results of the multivariable analysis of serum cadmium or serum lead and current asthma. In this analysis, serum cadmium was not significantly associated in all participants or in never/former smokers. Among current smokers, subjects whose serum cadmium was above the second quartile had 1.86 to 3.09 significantly higher odds of current asthma than those whose serum cadmium was in the first quartile (*P*_{for linear trend} < .01, Table E2). Serum lead was not significantly associated with current asthma, either in all participants or in current smokers (Table E3). We found no significant modification of the estimated effect of serum cadmium on current asthma by FeNO among all participants.

Figure 2 shows the results of the multivariable analysis of serum cadmium or serum lead (as quartiles) and percent predicted FEV₁ or percent predicted FEV₁/FVC. In this analysis, percent predicted FEV₁ and percent predicted FEV₁/FVC were significantly lower in subjects whose serum cadmium or serum lead was above the first (lowest) quartile than in subjects whose serum cadmium or serum lead level was in the first quartile (*P*_{for linear trend} < .01 in all instances).

Table IV shows the results of the multivariable analysis of serum cadmium or serum lead and lung function measures, before and after stratification by smoking status. Among all

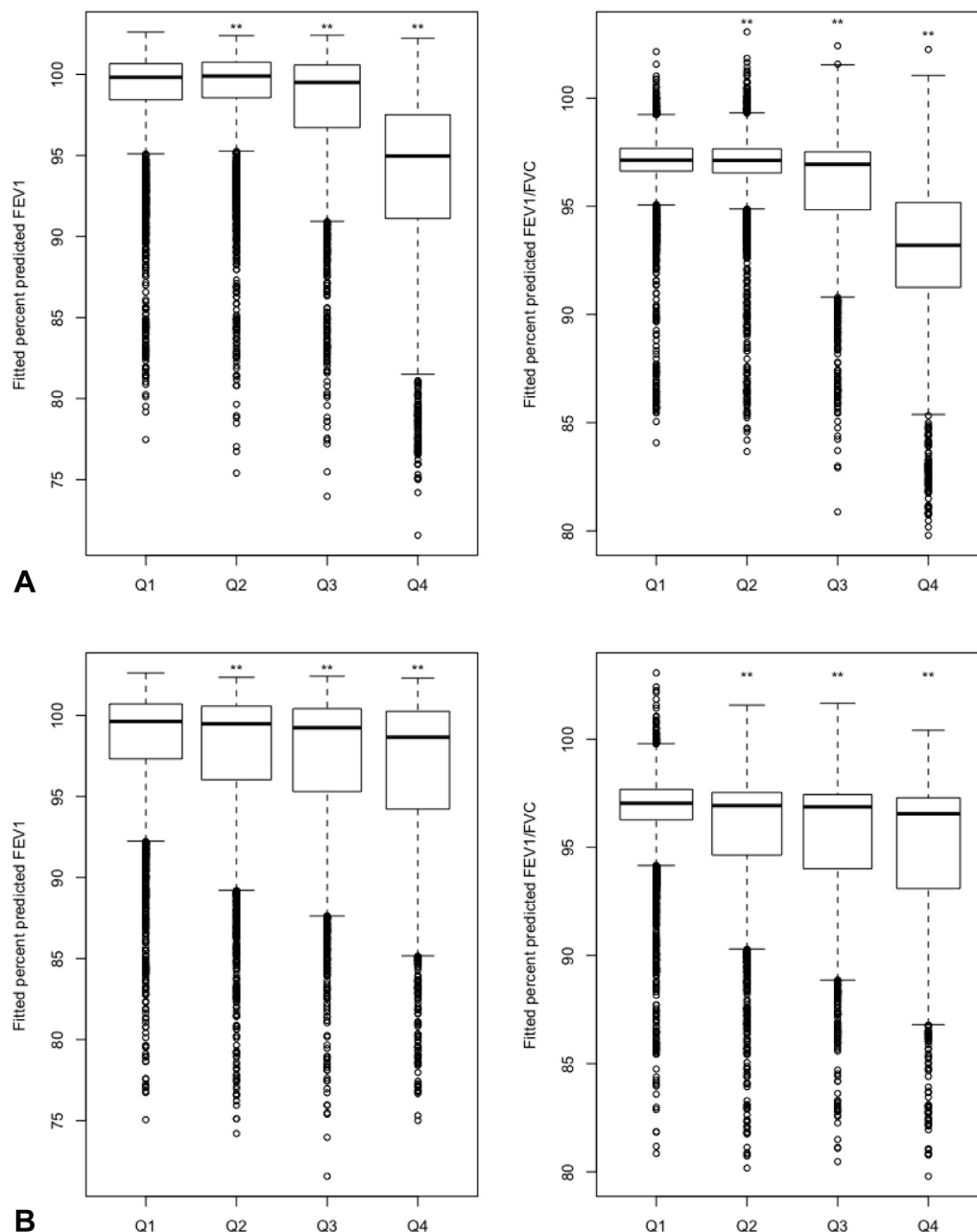


FIGURE 2. Boxplots of lung function measures for quartiles of serum cadmium and quartiles of serum lead in all adult participants. **A**, Fitted lung function measures for quartiles of serum cadmium. **B**, Fitted lung function measures for quartiles of serum lead. All models were adjusted for annual household income, body mass index, current wheeze status, serum cotinine, occupational exposure to mineral dust or exhaust fumes, use of oral or inhaled steroid in the past 2 days, and smoking status. Q1, the first quartile (lowest); Q2, the second quartile; Q3, the third quartile; Q4, the fourth quartile (highest). The widths of the boxes are proportional to the sample size in every quartile. * $P < .05$ and ** $P < .01$ for comparison with the first quartile (Q1). FEV_1 , Forced expiratory volume in 1 second; FVC , forced vital capacity.

participants, each $\mu\text{g/L}$ increment in serum cadmium was significantly associated with decrements in percent predicted FEV_1 , percent predicted FEV_1/FVC , and FeNO. After stratification by smoking status, serum cadmium was significantly associated with decrements in percent predicted in FEV_1 and FEV_1/FVC in both never/former smokers and current smokers, but the magnitude of the observed associations was greater in

never/former smokers than in current smokers. Moreover, serum cadmium was significantly associated with decreased FeNO in never/former smokers but not in current smokers. Serum lead was significantly associated with decrements in percent predicted FEV_1/FVC in all participants, with similar results in never/former smokers and current smokers. Moreover, serum lead was significantly associated with increments in

TABLE IV. Serum cadmium or lead and lung function measures in study participants‡

	Serum cadmium (µg/L)	Serum lead (µg/L)
Measures	β (95% confidence interval)	
All participants (N = 13,888)		
Percent predicted FEV ₁	−2.20 (−3.51, −0.88)†	−0.21 (−0.45, 0.03)
Percent predicted FVC	−0.67 (−1.54, 0.20)	0.19 (0.02, 0.35)*
Percent predicted FEV ₁ /FVC	−1.68 (−2.36, −1.00)†	0.37 (−0.59, −0.14)†
FeNO, [§] ppb	−0.95 (−1.46, −0.44)†	−0.07 (−0.21, 0.07)
Never/former smokers (n = 10,742)		
Percent predicted FEV ₁	−4.51 (−6.78, −2.25)†	−0.26 (−0.55, 0.03)
Percent predicted FVC	−0.82 (−2.53, 0.89)	0.13 (−0.09, 0.36)
Percent predicted FEV ₁ /FVC	−4.04 (−5.16, −2.91)†	−0.35 (−0.61, −0.10)†
FeNO, [§] ppb	−2.66 (−4.21, −1.11)†	−0.07 (−0.25, 0.12)
Current smokers (n = 3146)		
Percent predicted FEV ₁	−1.47 (−2.81, −0.13)*	−0.10 (−0.43, 0.22)
Percent predicted FVC	−0.49 (−1.45, 0.47)	0.29 (0.06, 0.51)*
Percent predicted FEV ₁ /FVC	−1.12 (−1.81, −0.42)†	−0.38 (−0.63, −0.12)†
FeNO, [§] ppb	−0.24 (−0.62, 0.14)	−0.07 (−0.21, 0.06)

FEV₁, Forced expiratory volume in 1 s; FeNO, fractional exhaled nitric oxide; FVC, forced vital capacity.

**P* < .05.

†*P* < .01.

‡All models adjusted for annual household income, BMI, serum cotinine, occupational exposure to mineral dust or exhaust fumes, use of oral or inhaled steroid in the past 2 d, current wheeze status. The model for all participants was additionally adjusted for smoking status.

§In addition adjusted for age, gender, and race/ethnicity.

percent predicted FVC in all participants and in current smokers. We found no significant association between serum lead and FEV₁ or FeNO, before or after stratification by smoking status.

We conducted a secondary analysis to examine the potential joint effects of elevated serum levels of cadmium and lead on current wheeze or lung function measures (see Figures E1 and E2 in this article's Online Repository at www.jaci-inpractice.org). Compared with subjects with low serum cadmium and low serum lead levels, those who had both a high serum cadmium level and a high serum lead level had 1.8 times significantly higher odds of current wheeze, and those who had a high serum cadmium level but a low lead level had 1.5 times significantly higher odds of current wheeze. In contrast, subjects who had a high lead level but a low cadmium level had no significantly higher odds of current wheeze than those who had low levels of both serum cadmium and serum lead (Figure E1). Similar results were obtained for the analysis of serum cadmium and serum lead and percent predicted FEV₁ or percent predicted FEV₁/FVC (Figure E2).

DISCUSSION

In a representative sample of 13,888 adults in the United States, a high level of serum cadmium was significantly associated with current wheeze and current asthma in current smokers. Serum cadmium was also significantly associated with decreased FEV₁% predicted, FEV₁/FVC% predicted, and FeNO in all participants, and this inverse association was more pronounced in never or former smokers than in current smokers. Moreover, serum lead was significantly associated with decreased FEV₁/FVC% predicted in all participants, with similar findings in never/former smokers and in current smokers.

Two studies of children in Egypt²⁰ and the United States,²¹ limited by small sample size²⁰ or lead exposure assessment,²¹ reported no association²⁰ or a borderline significant association²¹ between serum lead²⁰ or self-reported exposure²¹ and asthma. A case-control study of 1,102 adults 18 to 78 years old who attended outpatient clinics in a hospital in Wuhan (China) reported that urinary cadmium was significantly associated with increased odds of asthma and lower FEV₁ and FEV₁/FVC, but that urinary lead was significantly associated with reduced odds of asthma and increased FEV₁/FVC.⁴ In a population-based study of 5,912 Korean adults, subjects who had a serum cadmium level in the highest quintile (range = 1.60–6.42 µg/L, similar to the range of the highest quartile for current smokers but higher than that in all participants in our study) had 1.55 times significantly higher odds of lifetime physician-diagnosed asthma than those whose serum cadmium was in the lowest quintile (95% CI for OR = 1.03–2.33, *P*_{for linear trend} = .02), with similar findings for serum lead and lifetime asthma (OR for highest quintile [range = 3.01–17.71 µg/L, higher than the range of the fourth quartile in our study participants] vs lowest quintile = 1.67, 95% CI = 1.10–2.55, *P*_{for linear trend} = .02).⁵ In that study, a high serum lead level (but not a high serum cadmium level) was significantly associated with total serum IgE, suggesting that serum cadmium may affect asthma pathogenesis through nonallergic mechanisms. Limitations of prior studies in East Asian adults include selection bias,⁴ residual confounding by tobacco use,^{4,5} and misclassification of chronic obstructive pulmonary disease (COPD) as asthma.^{4,5}

A previous study of 9,575 adults in NHANES 2007–2010 reported that increasing concentrations of serum cadmium and serum lead were each associated with significantly increased odds of obstructive lung disease (OLD, defined as an FEV₁/FVC < 0.70) and worsening severity of OLD in current smokers, but

not in former or never smokers.²² In that study, serum cadmium and serum lead were significantly associated with reduced FEV₁% predicted in current smokers, but only serum lead was significantly associated with reduced FEV₁% predicted in never or former smokers. In contrast to those results in US adults, a study of 1,974 Korean men (40 years and older) showed that serum cadmium was significantly associated with OLD (defined as an FEV₁/FVC < 0.70), in both never/former smokers and current smokers.²³ However, those findings were not confirmed in a subsequent larger study of 5,972 Korean men and women (20 years and older), which showed that serum cadmium was significantly associated with OLD in current smokers but not in never or former smokers.²⁴ In that study, serum lead was not significantly associated with OLD, regardless of smoking status. Moreover, serum cadmium was significantly associated with lower FEV₁/FVC in current smokers but not in never smokers, whereas serum lead was significantly associated with lower FEV₁/FVC in never smokers but not in current smokers.²⁴

Although serum cadmium is correlated with recent exposure, urine cadmium level generally reflects longer duration of exposure. However, serum cadmium has been shown to have overlap²⁵ and significant correlation ($r_s = 0.5$, $P < .01$)²⁶ with urinary cadmium. In a study of 96 men followed for up to 8 years, a single 24-hour urinary cadmium level at baseline was associated with lower FEV₁ and FEV₁/FVC, with stronger estimated negative effects of urinary cadmium on FEV₁/FVC in current smokers than in never smokers.²⁷ Similar findings were obtained in a study of 16,024 adults, which found a significant association between urinary cadmium and lower FEV₁ and FEV₁/FVC in current and former smokers but not in never smokers.²⁸ In another study of US adults, urinary cadmium was correlated with smoking status and pack-years of smoking.²⁹ In that study, the estimated effects of former and current smoking on OLD were reduced by approximately 23% to 43% after adjustment for urinary cadmium, suggesting that cadmium exposure has independent effects on OLD or that urinary cadmium is a better marker of cumulative smoking exposure than self-reported smoking status.

Our results in 13,888 US adults expand or differ from previous studies of OLD or lung function^{22-24,26-28}; in that we demonstrate that serum cadmium is significantly associated with lower FEV₁% predicted, lower FEV₁/FVC% predicted, and lower FeNO in never or former smokers, and that serum lead is significantly associated with lower FEV₁/FVC% predicted in never or former smokers. Our findings thus suggest that exposure to lower levels of heavy metals (particularly cadmium) may have detrimental (subclinical) effects on lung function in nonsmokers. The observed association between serum cadmium and current wheeze or current asthma among current smokers in our study may be explained by residual confounding by long-term effects of smoking (not captured by serum cotinine), synergistic effects of serum cadmium and current smoking, or misclassification of COPD (or other respiratory disorders causing dyspnea, including asthma/COPD overlap syndrome) as current wheeze or current asthma in current smokers.

Our finding of an inverse association between serum cadmium and FeNO in never or former smokers is partially consistent with the results of a previous analysis in 7,813 adult participants in NHANES 2007-2010,³⁰ which showed that serum cadmium was significantly associated with lower FeNO, regardless of smoking status. Because FeNO is a marker of eosinophilic airway inflammation,³¹ our results

suggest that cadmium exposure may affect lung function, current wheeze, and current asthma through noneosinophilic inflammatory mechanisms, including downregulation of nitric oxide synthase and increased oxidative stress.³²⁻³⁵

Although we found no independent association between serum lead and current wheeze or current asthma, subjects with high serum levels of both cadmium and lead had slightly higher odds of current wheeze and slightly stronger estimated negative effects on lung function than those with high serum cadmium but a low serum lead. Experimental and observational human studies have shown that coexposure to cadmium and lead is linked to metabolic syndrome³⁶ and kidney disease,³⁷ but this is the first report of potential joint effects of cadmium and lead on current wheeze and lung function.

We acknowledge additional study limitations. We cannot determine temporal relationships between levels of serum cadmium or lead and wheeze, asthma, or lung function in this cross-sectional study. Moreover, we lack data on potential confounders or modifiers of the relation between cadmium or lead exposure and the outcomes of interest, such as air pollutants such as particulate matter and diesel exhaust.

In summary, our results suggest that US adults who are current smokers have a higher risk of wheeze and asthma after exposure to high levels of cadmium. Our findings also suggest that exposure to cadmium or lead has negative effects on lung function in nonsmoking adults in the United States.

Acknowledgments

G. Yang, T. Sun, W. Chen, and J. C. Celedón participated in study design, data analysis, manuscript writing, and interpretation of the study results. Y.-Y. Han, F. Rosser, and E. Forno participated in data analysis. All authors reviewed and approved the final version of the submitted manuscript. J. C. Celedón is the guarantor of this work and takes responsibility for the integrity of the manuscript.

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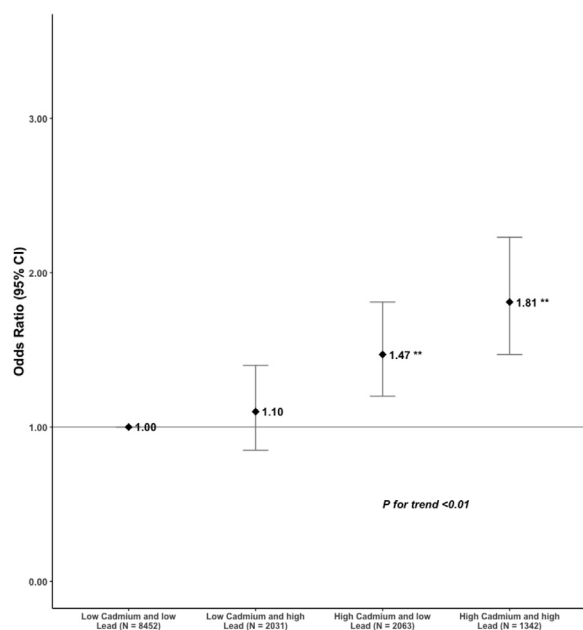


FIGURE E1. Multivariate analysis of serum levels of cadmium and lead level and current wheeze in study participants. All models were adjusted for age, gender, race/ethnicity, annual household income, body mass index, family history of asthma, serum cotinine, occupational exposure to mineral dusts or exhaust fumes, and smoking status. A level of serum cadmium or serum lead in the fourth (highest quartile) was considered high, and a level in the first to third quartiles was considered low. * $P < .05$; ** $P < .01$. CI, Confidence interval.

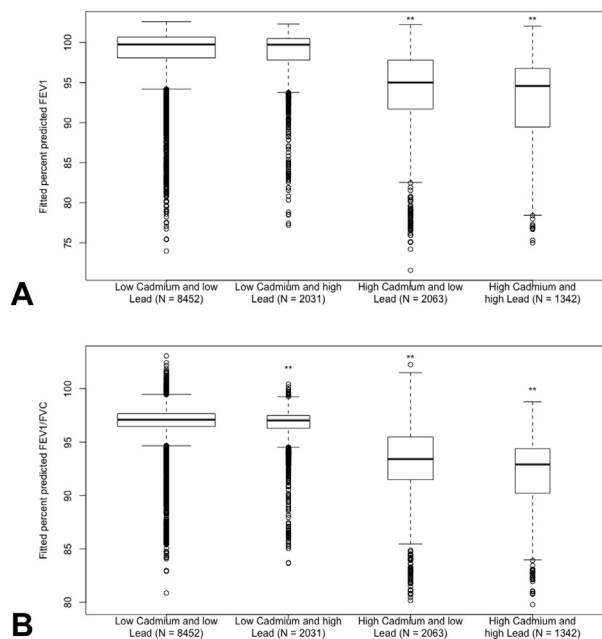


FIGURE E2. Boxplot of cadmium and lead level and lung function in adults ($20 \leq \text{age} \leq 79$ years). **A**, Fitted percent predicted forced expiratory volume in 1 second (FEV_1). **B**, Fitted percent predicted FEV_1 /forced vital capacity (FVC). All models were adjusted for annual household income, body mass index, current wheeze, serum cotinine, occupational exposure to mineral dusts or exhaust fumes, smoking status, and use of oral or inhaled steroids in the past 2 days. A level of serum cadmium or serum lead in the fourth (highest quartile) was considered high, and a level in the first to third quartiles was considered low. The widths of the boxes are proportional to the sample size in every group. * $P < .05$; ** $P < .01$.

TABLE E1. Characteristics of study participants, by current asthma^{‡¶}

Characteristics	Control subjects§ (n = 11,767)	Current asthma (n = 1,217)
Age, y	45.7 ± 0.4	46.2 ± 0.6
Female gender	5,912 (50.4)	781 (63.9) [†]
Race		
Non-Hispanic white	4,833 (66.9)	585 (70.6) [†]
Mexican American	2,106 (9.4)	89 (3.9)
Other Hispanic	1,312 (5.8)	137 (5.6)
Non-Hispanic black	2,414 (10.6)	317 (14.1)
Other	1,102 (7.3)	89 (5.8)
Had health insurance coverage	8,662 (79.1)	986 (83.5) [*]
Annual household income ≥\$20,000	8,920 (86.5)	770 (75.9) [†]
Smoking status		
Never/former smoker	9,481 (81.5)	873 (74.1) [†]
Current smoker	2,286 (18.5)	344 (25.9)
Body mass index	28.4 ± 0.1	30.9 ± 0.3 [†]
Serum cotinine level, ng/mL	50.9 ± 2.6	72.3 ± 5.9 [†]
Family history of asthma	1,796 (15.6)	524 (43.0) [†]
Vitamin D insufficiency (<30 ng/mL)	7,887 (62.2)	836 (65.7)
Use oral or inhaled steroid in past 2 d	121 (1.3)	358 (37.1) [†]
Occupation exposure to mineral dusts or exhaust fumes	4,233 (36.7)	477 (37.6)
Blood heavy metal, µg/L		
Cadmium	0.47 ± 0.01	0.66 ± 0.04 [†]
Lead	1.54 ± 0.04	1.40 ± 0.05 [†]
Lung function		
Percent predicted FEV ₁	98.8 ± 0.3	88.8 ± 0.9 [†]
Percent predicted FVC	102.1 ± 0.2	97.3 ± 0.8 [†]
Percent predicted FEV ₁ /FVC	96.5 ± 0.1	90.6 ± 0.6 [†]
Fractional exhaled nitric oxide, ppb	16.7 ± 0.3	22.8 ± 0.9 [†]

FEV₁, Forced expiratory volume in 1 s; FVC, forced vital capacity.^{*}P < .05.[†]P < .01.[‡]Values are presented as number (%) or mean (mean ± standard deviation).

§Control subjects had neither an asthma diagnosis nor current wheeze.

||Current asthma was defined by positive answers to the following 2 questions: (1) "Has a doctor or other health professional ever told you that you have asthma?" and (2) "Do you still have asthma?"

¶Participants who could not be classified as either control subjects or having current asthma (n = 904) were excluded from the analysis of current asthma.

TABLE E2. Serum cadmium and current asthma in study participants[‡]

Exposure	Serum cadmium (µg/L)
	Odds ratio (95% confidence interval)
All participants (N = 12,984)	
Quartile 1 (<0.21 µg/L)	1.00
Quartile 2 (0.21-0.33 µg/L)	0.80 (0.57, 1.11)
Quartile 3 (0.33-0.58 µg/L)	0.85 (0.63, 1.14)
Quartile 4 (≥0.58 µg/L)	1.04 (0.72, 1.49)
	<i>P</i> _{for linear trend} = .95
Never/former smokers (n = 10,354)	
Quartile 1 (<0.19 µg/L)	1.00
Quartile 2 (0.19-0.28 µg/L)	0.73 (0.54, 1.00)
Quartile 3 (0.28-0.42 µg/L)	0.90 (0.63, 1.29)
Quartile 4 (≥0.42 µg/L)	0.95 (0.65, 1.39)
	<i>P</i> _{for linear trend} = .96
Current smokers (n = 2,630)	
Quartile 1 (<0.57 µg/L)	1.00
Quartile 2 (0.57-0.94 µg/L)	1.35 (0.88, 2.09)
Quartile 3 (0.94-1.50 µg/L)	1.86 (1.03, 3.36)*
Quartile 4 (≥1.50 µg/L)	3.09 (1.90, 5.02) [‡]
	<i>P</i> _{for linear trend} < .01

**P* < .05.

[‡]*P* < .01.

[‡]All models were adjusted for age, gender, race/ethnicity, annual household income, body mass index, family history of asthma, serum cotinine, and occupational exposure to mineral dusts or exhaust fumes. The model for all participants was additionally adjusted for smoking status.

TABLE E3. Serum lead and current asthma in study participants*

Exposure	Serum lead (µg/L)
	Odds ratio (95% confidence interval)
All participants (N = 12,984)	
Quartile 1 (<0.82 µg/L)	1.00
Quartile 2 (0.82-1.25 µg/L)	0.99 (0.77, 1.27)
Quartile 3 (1.25-1.96 µg/L)	0.83 (0.63, 1.09)
Quartile 4 (≥1.96 µg/L)	0.98 (0.68, 1.42)
	<i>P</i> _{for linear trend} = .67
Never/former smokers (n = 10,354)	
Quartile 1 (<0.78 µg/L)	1.00
Quartile 2 (0.78-1.19 µg/L)	1.03 (0.78, 1.35)
Quartile 3 (1.19-1.82 µg/L)	0.89 (0.64, 1.25)
Quartile 4 (≥1.82 µg/L)	0.93 (0.62, 1.40)
	<i>P</i> _{for linear trend} = .59
Current smokers (n = 2,630)	
Quartile 1 (<1.02 µg/L)	1.00
Quartile 2 (1.02-1.56 µg/L)	1.03 (0.68, 1.58)
Quartile 3 (1.56-2.45 µg/L)	0.89 (0.48, 1.66)
Quartile 4 (≥2.45 µg/L)	1.85 (0.95, 3.61)
	<i>P</i> _{for linear trend} = .17

*All models adjusted for age, gender, race/ethnicity, annual household income, body mass index, family history of asthma, serum cotinine, and occupational exposure to mineral dusts or exhaust fumes. The model for all participants was additionally adjusted for smoking status.