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## Clinical Investigation and Reports

# Lead, Cadmium, Smoking, and Increased Risk of Peripheral Arterial Disease

Ana Navas-Acien, MD, MPH; Elizabeth Selvin, MPH; A. Richey Sharrett, MD, DrPH; Emma Calderon-Aranda, PhD, MD; Ellen Silbergeld, PhD; Eliseo Guallar, MD, DrPH

From the Departments of Epidemiology (A.N.-A., E. Selvin, A.R.S., E.G.) and Environmental Health Sciences (E.C.-A., E. Silbergeld), Johns Hopkins University Bloomberg School of Public Health, Baltimore, Md, and the Sección de Toxicología, Cinvestav, México (E.C.-A.).

Correspondence to Eliseo Guallar, MD, DrPH, Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Medical Institutions, 2024 E Monument St, Suite 2-639, Baltimore, MD 21205-2223. E-mail [eguallar@jhsph.edu](mailto:eguallar@jhsph.edu)

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## Abstract

**Background**— Lead and cadmium exposure may promote atherosclerosis, although the cardiovascular effects of chronic low-dose exposure are largely unknown. The objective of the present study was to evaluate the association between blood levels of lead and cadmium and peripheral arterial disease.

**Methods and Results**— We analyzed data from 2125 participants who were  $\geq 40$  years of age in the 1999 to 2000 National Health and Nutrition Examination Survey (NHANES). Peripheral arterial disease was defined as an ankle brachial index  $< 0.9$  in at least 1 leg. Lead and cadmium levels were measured by atomic absorption spectrometry. After adjustment for demographic and cardiovascular risk factors, the ORs of peripheral arterial disease comparing quartiles 2 to 4 of lead with the lowest quartile were 1.63 (95% CI, 0.51 to 5.15), 1.92 (95% CI, 0.62 to 9.47), and 2.88 (95% CI, 0.87 to 9.47), respectively ( $P$  for trend=0.02). The corresponding ORs for cadmium were 1.07 (95% CI, 0.44 to 2.60), 1.30 (95% CI, 0.69 to 2.44), and 2.82 (95% CI, 1.36 to 5.85), respectively ( $P$  for trend=0.01). The OR of peripheral arterial disease for current smokers compared with never smokers was 4.13. Adjustment for lead reduced this OR to 3.38, and adjustment for cadmium reduced it to 1.84.

**Conclusions**— Blood lead and cadmium, at levels well below current safety standards, were associated with an increased prevalence of peripheral arterial disease in the general US population. Cadmium may partially mediate the effect of smoking on peripheral arterial disease.



## Introduction

Lead and cadmium are established toxic and carcinogenic metals.<sup>1,2</sup> Most studies of the cardiovascular effects of these elements in humans have focused on their association with increased blood pressure.<sup>3,4</sup> Other cardiovascular end points remain largely unexplored, although increased exposure to lead and cadmium has been associated with cardiovascular events in some<sup>5-9</sup> but not all<sup>10,11</sup> studies. Lead and cadmium increase oxidative stress,<sup>12</sup> affect endothelial function,<sup>13</sup> promote inflammation,<sup>14</sup> downregulate nitric oxide production,<sup>15,16</sup> and induce renal dysfunction,<sup>17</sup> mechanisms that could implicate these metals in the development of atherosclerosis.

Peripheral arterial disease (PAD) is characterized by flow-limiting atherosclerosis in the muscular arteries of the lower extremities. Relative to other risk factors, smoking is more strongly associated with PAD than atherosclerosis in carotid or coronary arteries,<sup>18,19</sup> although the reasons are unknown. Smoking, however, is an important source of exposure to lead and especially to cadmium.<sup>20</sup> Cadmium in cigarettes has been proposed as a causative agent for cigarette smoke-induced cardiovascular disease.<sup>20,21</sup> We thus hypothesized that cadmium and lead exposure increases the risk of PAD and that they mediate the effect of smoking on PAD.

To investigate the association of lead and cadmium exposure with PAD, we evaluated the relation between blood lead and cadmium levels and the ankle-brachial blood pressure index (ABI), a highly specific marker of subclinical PAD,<sup>22</sup> in a representative sample of US adults  $\geq 40$  years of age.



## Methods

### Study Population

This study used data from the 1999 to 2000 National Health and Nutrition Examination Survey (NHANES), which was selected to represent the civilian, noninstitutionalized US population.<sup>23</sup> Detailed in-person interviews, physical examinations, and serum samples were obtained from 9965 persons. ABI was measured in subjects  $\geq 40$  years of age (3185 subjects). Among them, 2381 (75% of those eligible) had a valid ABI measurement. We excluded 6 participants with ABI values  $> 1.5$  (values usually related to noncompressible vessels in the legs)<sup>24</sup> and 250 participants (10.5%) with missing values in at least 1 of the variables of interest, leaving 2125 individuals in the sample.

### **Peripheral Arterial Disease**

A specific protocol was used to measure ABI in NHANES 1999 to 2000.<sup>23</sup> The measurements of blood pressure used for ABI were different from other measurements of blood pressure used to evaluate hypertension in NHANES 1999 to 2000. For ABI determination, systolic blood pressure was measured on the right arm (brachial artery) and both ankles (posterior tibial arteries) with a Doppler device, the Parks Mini-Laboratory IV, model 3100 (Parks Medical Electronics). If the participant had a condition that would interfere with blood pressure reading in the right arm, the left arm was used. Systolic blood pressure was measured twice at each site for participants 40 to 59 years of age and once at each site for participants  $\geq 60$  years of age. The left and right ABI measurements were obtained by dividing the ankle mean systolic blood pressure in each side by the mean systolic brachial blood pressure. PAD was defined as an ABI value  $< 0.90$  in at least 1 leg.<sup>24</sup>

### **Blood Lead and Cadmium**

Blood for lead and cadmium measurements was collected in ordinary tubes after confirmation of no background contamination in all collection and storage materials.<sup>23</sup> The cadmium and lead levels in whole blood were measured at the Centers for Disease Control and Prevention/National Center for Environmental Health (NCEH) Environmental Health Laboratory Sciences Laboratory on a Perkin-Elmer model SIMAA 6000 simultaneous multielement atomic absorption spectrometer with Zeeman background correction.<sup>23</sup> The detection limits were  $0.01 \mu\text{mol/L}$  for lead and  $2.5 \text{ nmol/L}$  for cadmium. Two subjects in the study sample had levels below the detection limit for lead, and 230 (9.7%) had levels below the detection limit for cadmium. For these subjects, we imputed a level equal to the limit of detection divided by  $\sqrt{2}$ .<sup>25</sup> The analytical laboratory followed extensive quality control procedures.<sup>23</sup> National Institute of Standards and Technology Standard Reference Materials whole-blood materials were used for external calibration. The interassay coefficients of variation ranged from 3.1% to 4.0% for lead and from 4.1% to 7.3% for cadmium.

### **Other Variables of Interest**

Information on age, sex, race-ethnicity, smoking, and alcohol consumption was based on self-report, and body mass index was calculated by dividing weight in kilograms by height in meters squared. Hypertension was defined as a mean systolic blood pressure  $\geq 140 \text{ mm Hg}$ , a mean diastolic blood pressure  $\geq 90 \text{ mm Hg}$ , a self-reported physician diagnosis, or medication use. Hypercholesterolemia was defined as a total cholesterol level  $\geq 6.2 \text{ mmol/L}$ , a self-reported physician diagnosis, or medication use. Diabetes was defined as a fasting glucose  $\geq 7.0 \text{ mmol/L}$ , a nonfasting glucose  $\geq 11.1 \text{ mmol/L}$ , a self-reported physician diagnosis, or medication use.

High-sensitivity C-reactive protein was measured with a Behring Nephelometer II Analyzer. Glomerular filtration rate was estimated by use of the Modification of Diet in Renal Disease Study formula with calibrated serum creatinine levels to account for laboratory differences between NHANES III and NHANES 1999 to 2000.<sup>26</sup> Serum cotinine was measured by an isotope-dilution high-performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometric method.<sup>23</sup>

### **Statistical Analysis**

All statistical analyses were performed with SUDAAN software (Research Triangle Institute) to account for the complex sampling design and weights in NHANES 1999 to 2000. The jackknife "leave-one-out" method was used to obtain appropriate SEs of all estimates.

Blood lead and cadmium levels were log transformed to improve normality. Adjusted ORs and their 95% CIs were used to compare each quartile of lead or cadmium distribution with their lowest quartile. Quartile cutoffs were based on the weighted distribution of lead and cadmium. Probability values for linear trend were obtained by including log-transformed metal levels as continuous variables in the regression models. Smoking was adjusted for by use of self-reported smoking status (never, former, current) and cotinine levels in serum. Similar results were obtained when smoking was modeled as number of cigarettes currently smoked or as cumulative pack-years of smoking (data not shown). The final models included adjustment for demographic variables, cardiovascular risk factors, glomerular filtration rate, and C-reactive protein. We also assessed possible interactions between lead and cadmium and between each metal with sex, race-ethnicity, smoking status, renal function, or C-reactive protein. Because no clear interactions were observed and no interactions were statistically significant, they were not included in the final models.

## **Results**

The geometric means of blood lead and cadmium levels were 0.10  $\mu\text{mol/L}$  and 4.5  $\text{nmol/L}$ , respectively ([Table 1](#)). Lead and cadmium levels were higher in older subjects, in those with lower educational levels, and in smokers. Both metals were highest in current smokers, although smoking was more strongly associated with cadmium. Lead levels were higher in men, in blacks, in Mexican Americans, and in alcohol drinkers. Cadmium levels were higher in women, with no substantial differences by race-ethnicity or by drinking status. The correlation between lead and cadmium was 0.32 ( $P < 0.001$ ).

**TABLE 1. Lead and Cadmium Blood Levels by Participant Characteristics**

	n	Lead, $\mu\text{mol/L}^*$			Cadmium, $\text{nmol/L}^\dagger$		
		Geometric Mean	Percentile		Geometric Mean	Percentile	
			25th	75th		25th	75th
Overall	2125	0.10	0.07	0.14	4.5	3.6	6.2
Sex							
Men	1070	0.13	0.09	0.17	4.4	2.7	6.2
Women	1055	0.08	0.06	0.12	4.7	3.6	7.1
Age, y							
40–49	556	0.09	0.06	0.13	4.2	2.7	6.2
50–59	447	0.10	0.07	0.14	4.6	2.7	7.1
60–69	583	0.11	0.08	0.15	4.6	3.6	6.2
$\geq 70$	539	0.12	0.08	0.16	4.9	3.6	6.2
Education							
Greater than high school	787	0.09	0.06	0.13	3.9	2.7	5.3
High school graduate or equivalent	453	0.10	0.06	0.14	4.9	3.6	7.1
Less than high school	885	0.12	0.08	0.18	5.5	3.6	8.9
Race							
White	1036	0.10	0.07	0.14	4.5	3.6	6.2
Black	356	0.12	0.08	0.17	4.7	2.7	7.1
Mexican American	581	0.11	0.07	0.16	4.9	3.6	6.2
Other	152	0.10	0.06	0.15	4.6	3.6	6.2
Smoking							
Never	985	0.08	0.06	0.12	3.4	2.7	4.5
Former	723	0.11	0.07	0.15	4.2	3.6	5.3
Current	417	0.14	0.10	0.19	9.2	6.2	12.4
Cotinine, $\text{nmol/L}$							
<0.6 (0.1 $\text{ng/mL}$ )	1164	0.09	0.06	0.12	3.7	2.7	4.5
0.6–57 (0.1–10 $\text{ng/mL}$ )	462	0.10	0.07	0.14	3.7	2.7	4.5
57–852 (10–150 $\text{ng/mL}$ )	181	0.12	0.09	0.19	6.6	4.5	9.8
852–1704 (150–300 $\text{ng/mL}$ )	215	0.14	0.09	0.19	9.4	7.1	12.5
$\geq 1704$ (300 $\text{ng/mL}$ )	103	0.15	0.11	0.21	8.5	6.2	12.5
Alcohol							
Never	721	0.08	0.06	0.12	4.3	3.6	5.3
Former	259	0.11	0.08	0.14	5.4	3.6	8.9
Current	1145	0.11	0.07	0.15	4.5	2.7	6.2
PAD							
Yes	139	0.14	0.10	0.21	6.7	4.5	10.7
No	1986	0.10	0.07	0.14	4.4	2.7	6.2

\*To convert to  $\mu\text{g/dL}$ , divide by 0.0483

†To convert to  $\mu\text{g/L}$ , divide by 8.896.

After adjustment for demographic and cardiovascular risk factors, subjects with PAD had 13.8% (95% CI, 5.9 to 12.9) higher mean levels of lead and 16.1% (95% CI, 4.7 to 28.7) higher mean levels of cadmium than subjects without PAD. The association of lead and cadmium with PAD was strong and progressive ([Table 2](#)), even after multivariable adjustment. Simultaneously adjusting for the other metal did not appreciably alter the association for either cadmium or lead.

**TABLE 2. ORs (95% CIs) of PAD by Quartile of Lead and Cadmium Blood Levels**

	Cases, n	Noncases, n	Model 1	Model 2	Model 3	Model 4
<b>Lead, <math>\mu\text{mol/L}</math></b>						
Quartile 1 (<0.07)	18	454	1.00 (Reference)	1.00 (Reference.)	1.00 (Reference)	1.00 (Reference)
Quartile 2 (0.07–0.10)	23	444	1.93 (0.60–6.21)	1.94 (0.63–6.03)	1.63 (0.51–5.15)	1.63 (0.50–5.27)
Quartile 3 (0.10–0.14)	37	510	2.29 (0.72–7.27)	2.41 (0.79–7.38)	1.92 (0.62–9.47)	1.77 (0.55–5.63)
Quartile 4 (>0.14)	61	578	3.78 (1.08–13.19)	4.07 (1.21–13.73)	2.88 (0.87–9.47)	2.52 (0.75–8.51)
<i>P</i> trend			0.002	0.003	0.02	0.05
<b>Cadmium, nmol/L</b>						
Quartile 1 ( $\leq 3.56$ )	27	829	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 2 (4.45)	20	334	1.16 (0.46–2.93)	1.13 (0.47–2.76)	1.07 (0.44–2.60)	0.96 (0.41–2.25)
Quartile 3 (5.34–6.23)	32	371	1.68 (0.90–3.15)	1.55 (0.81–2.97)	1.30 (0.69–2.44)	1.17 (0.61–2.25)
Quartile 4 (>6.23)	60	452	4.25 (2.27–7.97)	4.14 (2.12–8.06)	2.82 (1.36–5.85)	2.42 (1.13–5.15)
<i>P</i> trend			<0.001	<0.001	0.01	0.02
<p>Model 1 was adjusted for age, sex, race, and education; model 2, further adjusted for body mass index, alcohol intake, hypertension, diabetes, hypercholesterolemia, glomerular filtration rate, and C-reactive protein; model 3, further adjusted for self-reported smoking status (never/former/current) and serum cotinine; and model 4, further adjusted for lead or cadmium.</p>						

Compared with never smokers, current smoking was associated with an OR of 4.13 for PAD (Table 3). Adjusting for lead reduced the OR for smoking and PAD to 3.38, whereas adjusting for cadmium reduced this OR to 1.84.

**TABLE 3. ORs (95% CIs) of PAD by Smoking Status**

	Cases, n	Noncases, n	Not Adjusted for Lead or Cadmium	Adjusted for Lead	Adjusted for Cadmium	Adjusted for Lead and Cadmium
<b>Smoking status</b>						
Never	43	942	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Former	56	667	1.31 (0.82–2.10)	1.22 (0.75– 1.99)	1.04 (0.65–1.68)	1.02 (0.63–1.65)
Current	40	377	4.13 (1.87–9.12)	3.38 (1.56– 7.35)	1.84 (0.78–4.39)	1.75 (0.74–4.10)
<b>Cotinine levels, nmol/L</b>						
<0.7 (0.1 ng/mL)	68	1096	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
0.7–57 (0.1–10 ng/mL)	23	439	0.83 (0.43–1.63)	0.78 (0.39– 1.55)	0.80 (0.42–1.53)	0.76 (0.39–1.48)
57–852 (10–150 ng/mL)	11	170	1.50 (0.48–4.70)	1.35 (0.45– 4.01)	0.87 (0.31–2.46)	0.86 (0.31–2.40)
852–1704 (150–300 ng/mL)	25	190	3.87 (1.83–8.20)	3.22 (1.53– 6.75)	1.95 (0.87–4.37)	1.83 (0.80–4.17)
≥1704 (300 ng/mL)	12	91	4.33 (1.67–11.23)	3.44 (1.33– 8.89)	2.30 (0.81–6.57)	2.10 (0.74–5.97)
All models were adjusted for sex, age, race, education, body mass index, alcohol intake, hypertension, diabetes, hypercholesterolemia, and glomerular filtration rate.						



## Discussion

Blood lead and cadmium levels were strongly associated with an increased prevalence of PAD in a representative sample of US adults. The decrease in the association of cigarette smoking with PAD after adjustment for cadmium suggests that the effect of smoking on PAD is partly mediated by the cadmium content of cigarettes. The observed increase in PAD prevalence occurred at lead and cadmium levels much lower than current safety levels used by environmental and occupational regulatory agencies. For instance, only 1 study participant had lead levels  $>1.93 \mu\text{mol/L}$  ( $40 \mu\text{g/dL}$ ), the Occupational Safety and Health Administration (OSHA) Safety Standard for lead in whole blood,<sup>27</sup> and only 35 (1.6%) had lead levels  $>0.48 \mu\text{mol/L}$  ( $10 \mu\text{g/dL}$ ), the Centers for Disease Control and Prevention criterion for elevated blood levels in children and pregnant women.<sup>28</sup> Similarly, all participants had cadmium levels  $<44.5 \text{ nmol/L}$  ( $5 \mu\text{g/L}$ ), the OSHA Safety Standard for cadmium.<sup>29</sup>

The general population can be exposed to lead and cadmium in ambient air near industrial and combustion sources, in certain foods, through smoking, and sometimes in drinking water.<sup>1,2</sup> Lead exposure has declined substantially in the last 2 decades after the ban on leaded gasoline.<sup>30</sup> Lead exposure still occurs in urban environments, particularly in areas near emission sources, and through contact with lead dusts and soils. Exposure to cadmium in the general population results from exposure to cigarette smoke, inhalation of ambient air near coal-fired power plants and municipal waste incinerators, and from consumption of some foods (highest levels in shellfish, liver, and kidney meats). Compared with workers in smelting, refining, and manufacturing industries, the prevalence of elevated exposures to lead or cadmium in the general population is low,<sup>1,2</sup> and the levels in this study were much lower than those reported in retired workers.<sup>31,32</sup>

Several mechanisms may explain an increased risk of atherosclerosis with lead or cadmium. Experimental studies show that both metals contribute to oxidative stress by catalyzing the formation of reactive oxygen species,<sup>12,15</sup> increasing lipid peroxidation,<sup>33,34</sup> and depleting glutathione and protein-bound sulfhydryl groups.<sup>12</sup> Lead and cadmium may also stimulate the production of inflammatory cytokines<sup>14</sup> and may induce endothelial damage by downregulating nitric oxide production.<sup>15,16</sup> Both metals have also induced atherosclerosis in some models in vivo.<sup>35</sup> The relevance of these mechanisms to human atherogenesis and to PAD, however, is uncertain because mechanistic studies are typically conducted at higher doses than the concentrations observed in the present study. Furthermore, the effects of lead and cadmium in our study persisted after adjustment for glomerular filtration rate and for C-reactive protein, suggesting that mechanisms other than impaired renal function and inflammation were involved. Additional studies, at very low levels, are needed to elucidate the mechanisms of action of these metals at current levels of exposure in the general population.

An important finding of our study was the decrease in the association of smoking with PAD after adjustment for cadmium. This pattern suggests that the effect of smoking on PAD is mediated partly by cadmium. In addition to cadmium, several agents in tobacco are considered to contribute to cardiovascular disease, including carbon monoxide, nitrogen oxides, hydrogen cyanide, tar, zinc, and carbon disulfide.<sup>20</sup> Although we could not evaluate the relative contribution of cadmium compared with other tobacco components, it is important to note that the effect of cadmium persisted after adjustment for cotinine levels or for reported intensity of smoking, indicating that the effect of cadmium is not likely to be confounded by smoking or by compounds in cigarette smoke. Because ABI was the only marker of atherosclerosis available in NHANES 1999 to 2000, we could not evaluate whether cadmium is specifically associated with PAD or whether a similar association is present for other vascular territories. However, it is well established that smoking is more strongly associated with PAD than with atherosclerosis in other arteries<sup>18,19</sup>; therefore, the effect of cadmium on other cardiovascular outcomes is of great interest.

Our findings are consistent with previous cohort studies showing a positive association of blood lead with cardiovascular mortality in NHANES II<sup>5</sup> and with coronary heart disease incidence in Denmark.<sup>6</sup> Another cohort study in British men, however, did not show an association between blood lead and cardiovascular disease incidence.<sup>10</sup> Few studies have evaluated the association between cadmium and cardiovascular outcomes. Ecological studies have found associations of cardiovascular mortality rates with cadmium levels in air<sup>7</sup> and in soil and water.<sup>36</sup> Two small case-control studies found higher blood cadmium in subjects with myocardial infarction compared with control subjects,<sup>8,9</sup> but a cross-sectional study in Belgium found no association between blood cadmium and the prevalence of cardiovascular disease.<sup>11</sup> Finally, several autopsy

studies have found associations between tissue lead or cadmium levels and atherosclerotic lesions.<sup>37,38</sup>

Several limitations of this study should be considered. The cross-sectional design and the use of prevalent cases of PAD limit conclusions regarding the direction or causality of the observed associations. Because ABI is a subclinical marker and PAD is often asymptomatic,<sup>39</sup> our design may be somewhat resistant to biases introduced when symptomatic subjects modify their levels of exposures. Indeed, the associations between PAD and traditional risk factors in NHANES 1999 to 2000 were of the expected direction and magnitude (data not shown). Prospective studies with incident cases of PAD, however, are needed to confirm our findings. Another possible limitation of our study is confounding by socioeconomic status, by differences in urbanization, or by other pollutants that may occur in the same environmental settings. We note, however, that although no data are currently available in NHANES 1999 to 2000 on income or urban/rural residence, our results persisted after adjustment for educational level and for race-ethnicity. Finally, our analyses were based on single blood measurements of lead and cadmium, imperfect biomarkers of chronic exposure. Environmental exposures, however, are likely to be less changeable than occupational exposures, and single blood levels are frequently used biomarkers in population studies.<sup>5,11,25</sup> It is also likely that, because of the limitations of blood lead and cadmium as biomarkers, our results underestimate the associations of both metals with PAD.

The strengths of the study come from the rigorous sampling design and the quality of the study measurements used in NHANES. These results are representative of the US noninstitutionalized civilian population. Other strengths include the use of ABI, a noninvasive measure of atherosclerosis particularly useful for epidemiological studies, and the large sample size. Furthermore, lead and cadmium in blood are biomarkers of internal dose that integrate all routes of exposure.<sup>25</sup>

Although our findings need confirmation in prospective studies and support from mechanistic studies at low levels of exposure, we conclude that blood lead and cadmium, at levels well below current safety standards, were associated with an increased prevalence of PAD in a representative sample of US adults. In addition, cadmium exposure explained a substantial part of the effect of smoking on PAD.



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