Lead and Cadmium as Cardiovascular Risk Factors: The Burden of Proof Has Been Met

Gervasio A. Lamas, MD; Francisco Ujueta, MD, MS; Ana Navas-Acien, MD, PhD

Globally, cardiovascular disease (CVD) is the leading cause of mortality, taking an estimated 17.9 million lives annually. Myocardial infarction and stroke account for 80% of these deaths.\(^1\) Over decades, through epidemiologic, basic, and clinical studies, physician-scientists have recognized that increasing age, male sex, heredity, tobacco smoke, high blood cholesterol, high blood pressure, physical inactivity, obesity, diabetes mellitus, stress, excessive alcohol use, and diet/nutrition promote the development of atherosclerotic heart disease. We contend that 2 environmental contaminants, lead and cadmium, have met the burden of proof to be considered coronary risk factors. To support our viewpoint, we follow a framework that bases causality assessments on the integration of clinical, toxicological, and experimental evidence.\(^2\)

ENVIRONMENTAL CONTAMINANTS AND CVD

Inhaled Pollutants

Inhaled pollutants, including tobacco smoke, constitute a rich source of vasculotoxic compounds, including metals.\(^3\) Air pollution has long been associated with increased short-term cardiopulmonary mortality.\(^4\) The first World Health Organization report dealing with air pollution and health, published in 1958, identified a possible association between air pollution and adverse health effects.\(^5\)

Classification and Sources of Particulate Matter and Other Air Pollutants

Airborne particulate matter (PM), including tobacco smoke, consists of a mixture of solid and liquid particles varying in chemical composition and size. Particles with an aerodynamic diameter of \(\leq 10 \mu m\) are generally indicated by the shorthand PM\(_{10}\). Particles of \(\leq 2.5 \mu m\) (PM\(_{2.5}\)) are considered the most toxic, as they travel deep into the lungs, where they activate neural receptors, initiate local and systemic inflammatory response, and translocate directly to the bloodstream.\(^6\)

The chemical composition of airborne pollutants includes metals (eg, cadmium, lead, iron, nickel, zinc, and others).\(^7,9\) Tobacco smoking constitutes a special case of inhaled pollutants. Although cigarette smoke contains literally thousands of toxic and reactive compounds, it is a rich source of metal contaminants, including cadmium and lead.\(^3,10\) Multiple mechanisms have been reported by which PM\(_{10}\) and PM\(_{2.5}\) may, in fact, activate platelets, damage endothelium, and lead to myocardial infarction and death.\(^11-13\)

Epidemiologic Evidence of PM Pollutants and CVD

Several studies have demonstrated that airborne particulates containing increased amounts of heavy metals are potentially more harmful, especially to the cardiovascular system. PM\(_{2.5}\), for example, has been shown to be a source of inhaled metals in rural and urban areas.\(^14\)

In recognition of its relevance as a cardiovascular risk factor, the National Heart, Blood, and Lung Institute and the National Institute of Environmental Health Sciences have recently established a trans–National Institutes of Health partnership to foster clinical trial/intervention research examining the efficacy of personal interventions to reduce PM\(_{2.5}\) exposures and the associated benefits in cardiopulmonary outcomes.\(^15\) And relevant to this commentary, as referenced above, contaminant metals,
including lead and cadmium, constitute important components of particulate air pollution.16

**Toxic Metals**

We propose that, for lead and cadmium, there exists enough evidence to elevate them to the level of “official” cardiovascular risk factors (Figure).

**Lead**

The bone of a 20th century human has 1000-fold more lead than that of a preindustrial human.17 The modern history of lead exposure starts with leaded gasoline and increasing individual automobile ownership following World War II. Ultimately, leaded gasoline alone accounted for about 200 000 tons of lead released into the atmosphere annually, resulting in continuous lead exposure affecting practically all residents of the United States. Manufacturers decreased the lead content of gasoline by 1980, as they complied with regulations and standards established by the US Environmental Protection Agency.18

In addition to leaded gasoline, lead-based paint was used in US homes from the 1920s until 1978, when it was banned. Current sources of lead exposure to humans now result from soil, food, water, tobacco smoke and electronic cigarettes, lead-based paints in and around older construction, and water pipes, to name a few.

**Why Does Lead Cause Multisystem Toxicity?**

Following ingestion or inhalation, lead enters red blood cells, with high affinity for δ-aminolevulinic acid dehydratase, remaining there for the balance of the red cell’s lifespan. A large proportion of the absorbed lead binds hydroxyapatite, or bone mineral, and osteocalcin, a protein involved in bone mineralization.19 The half life of lead in cortical bone is approximately 30 years.20,21

Health effects of lead result from its ability to form strong bonds with proteins, and its interference with zinc and calcium (both divalent cations) dependent functions, particularly antioxidant functions and cellular signaling.22-25 The interference with antioxidant function is of particular relevance. Lead directly and indirectly inhibits glutathione synthesis and function, and depresses superoxide dismutase activity, a zinc metalloprotein in humans.23,24 Excess free radicals are atherogenic. Proatherosclerotic changes from lead exposure have also been associated with inactivation of paraoxonase activity, which decreases the antioxidant effects of high-density lipoprotein.25

Lead replaces calcium in various intracellular signaling reactions, including inhibiting the effect of calmodulin in the synthesis of NO, possibly explaining lead-induced hypertension.26 Furthermore, lead exposure results in oxidative stress by upregulation of superoxide-generating enzymes, nicotinamide adenine dinucleotide phosphate [NAD(P)H] and hydroxyl radical production.27 In rats, exposure to low lead levels compared with controls increased activation of nuclear factor-κB.28 Exposure to lead also results in epigenetic changes by inducing histone modifications.29 Lead-exposed humans demonstrate p16 promoter methylation proportional to blood lead concentration.30 Oxidative damage from long-term lead exposure at levels attainable by modern industrial workers has been associated with inhibition of protein binding to methyl-CpG (promoter regions are usually increased with CpG dinucleotides, known as CpG islands) and alteration of DNA methyltransferases.31 Finally, accumulation in bone remains as a continuous internal source of lead to the vascular endothelium and other tissues as it leaches out over decades of life.32

**Epidemiologic Studies Support the Role of Lead as a Cardiovascular Risk Factor**

The National Health and Nutrition Examination Survey (NHANES) is a national survey to assess the health and nutritional status of adults and children in the United States. Participants are selected to represent the overall US population. The first survey was conducted in 1971, and others have followed. In NHANES II (1976–1980), despite the decrease in blood lead levels during 1976 to 1980,33 lead exposure remained associated with increased mortality.34 The study found individuals with blood lead levels of 20 to 29 µg/dL experienced a 46% increase in all-cause mortality (relative risk [RR], 1.46; 95% CI, 1.14–1.86) and a 39% increase in circulatory mortality (RR,
1.93; 95% CI, 1.01–1.91) compared with those with blood lead levels of <10 μg/dL.34

In NHANES III (1988–1994), patients with the highest tertile of blood lead (≥3.62 μg/dL) compared with the lowest tertile (<1.94 μg/dL) experienced a significantly higher risk of death during follow-up. The increased risk was 25% for total mortality, 55% for cardiovascular mortality, 89% for myocardial infarction, and 151% for stroke.35 Nawrot concluded that blood lead levels as low as 0.10 μmol/L (2 μg/dL) likely represented a cardiovascular hazard.36

A subsequent analysis of NHANES III blood lead data from 1988 to 1994, and published in *Lancet Public Health* in 2018, extended follow-up through 2011 in a cohort of 14 289 subjects. The investigators compared participants with blood lead in the 10th versus 90th percentile (from 1.0 to 6.7 μg/dL). This increase in blood lead was associated with a higher all-cause mortality (hazard ratio [HR], 1.37; 95% CI, 1.17–1.60), CVD mortality (HR, 1.70; 95% CI, 1.30–2.22), and ischemic heart disease mortality (HR, 2.08; 95% CI, 1.52–2.85).37 The annualized lead-attributable excess deaths for the 90th versus 10th percentile of blood lead at baseline were 412 000 total deaths, 256 000 of which were cardiovascular, with 185 000 attributable to ischemic heart disease. The authors concluded that low-level environmental lead exposure, almost universally ignored by clinicians, constitutes an important cardiovascular risk factor.36 Another study compared NHANES 1999 to 2004 (continuous NHANES) with NHANES III (1988–1994) and estimated 230.7 CVD deaths/100 000 person-years avoided in the United States for multifactorial reasons. Of these, 22.5% (52 deaths per 100 000 person-years) could be statistically attributed to the changes in the distribution of blood lead levels observed between 1988 and 1994 and 1999 to 2004.38

In the most recent NHANES analyses, using blood lead measures in 1999 to 2012 and follow-up for cardiovascular mortality through 2015, blood lead levels together with data on cadmium and mercury increased the accuracy of prediction compared with traditional risk factors, with a change in C statistics from 0.845 to 0.854. This 9% increase in the C statistic is remarkable. It suggests that patient-level knowledge of contaminant metals can improve CVD risk prediction and be potentially useful for CVD risk assessment, prevention, and precision health.39 The study used the Environmental Risk Score,40 a measure that summarized the estimated health risk attributable to various metal contaminants (lead, cadmium, and mercury). The Environmental Risk Score is a predictive risk score, which estimated the joint effect of the 3 metals with CVD outcomes, allowing for linear effects, squared effects, and interactions of the 3 metals. The multivariable-adjusted HR of CVD comparing the 75th with 25th percentile of Environmental Risk Score was 1.84 (95% CI, 1.48–2.27).39

Recently, a systematic review and meta-analysis summarized the epidemiologic evidence on contaminant metals, including lead, as a CVD risk factor. A total of 37 studies comprising 348 259 participants reported risk estimates for total CVD, coronary heart disease, and stroke for metal contaminants, including lead, cadmium, mercury, copper, and arsenic. Comparing high versus low tertiles of baseline blood lead levels, the pooled RRs (95% CIs) for lead were 1.43 (1.16–1.76) for CVD, 1.85 (1.27–2.69) for coronary heart disease, and 1.63 (1.14–2.34) for stroke.41

In addition to an increased risk of cardiovascular mortality, long-term exposure to low levels of lead has been associated with persistent hypertension in animal and human studies.39,42 In a prospective population study of 179 participants, higher blood lead concentration at baseline predicted impaired systolic left ventricular function a decade later.43 Cross-sectional analyses from the NHANES 1999 to 2002 cohort additionally identified an association between blood lead and the prevalence of peripheral artery disease (PAD).44 Finally, a powerful Integrated Science Assessment from the Environmental Protection Agency recognized lead as a cardiovascular risk factor in 2013 after a thorough review of basic, epidemiologic, and clinical evidence.2

**Cadmium**

Cadmium is another divalent cation with a strong body of experimental and epidemiologic evidence supporting its role in CVD.45,46 The extraction of cadmium, often as a by-product of zinc ores, and its widespread industrial uses in batteries, pigments, solar panels, as a plastic stabilizer, and many other products, has resulted in widespread contamination of soil and fertilizers. Humans are exposed to cadmium through contaminated leafy green vegetables, grains, shellfish and organ meats, tobacco smoke, and airborne emissions from incinerators. Cadmium is long lived, with a half-life of 10 to 30 years.

**Why Does Cadmium Cause Multisystem Toxicity?**

Cadmium binds primarily to albumin and other proteins and is transported in the blood to soft tissues, particularly the liver and kidneys.47,48 Free cadmium as well as protein-bound cadmium is released into the circulation or delivered to target tissues, resulting in deleterious effects, including mitochondrial damage, cell death, inflammation, and fibrosis.49

Cadmium impairs NO functioning and signaling, via a reduction of phosphorylation of endothelial NO synthase,50 causing abnormalities in normal arterial
Cadmium modulates calcium concentration, and as a result, interferes with multiple intracellular signaling pathways.\(^5^2,5^3\) Cadmium-induced endothelial‐plasmic reticulum stress leads to cell death through activation of the apoptotic pathway.\(^5^4\) Cadmium has also been related to increased oxidative stress through glutathione depletion.\(^5^5-5^7\) Cadmium and zinc have many chemical similarities including a +2 valence. Due to their similarities cadmium may replace zinc in antioxidant enzymes, such as paraoxonase 1, catalase, superoxide dismutase, and glutathione peroxidase, leading to decreased free radical scavenging.\(^5^8,5^9\) Studies suggest that low levels of paraoxonase 1 activity may be associated with an increased prevalence of CVD.\(^5^0,6^1\)

Cadmium contamination may cause genetic and epigenetic changes. An epigenome-wide association study by Domingo-Relloso et al reported differential methylated positions in current and former smokers, which, in view of high cadmium concentration in cigarette smoke, could further link cadmium exposure to adverse health outcomes through epigenetic mechanisms.\(^6^2\)

### Epidemiologic Studies Support the Role of Cadmium as a Cardiovascular Risk Factor

The role of cadmium in CVD has been well documented in both epidemiologic and experimental studies. The first epidemiologic evidence, reported by Carroll in 1966, found the average concentration of cadmium in the air of 28 cities was positively correlated with death rates from hypertension and atherosclerotic heart disease (coefficient of correlation \(r=0.76\)).\(^5^3\)

Epidemiologic studies with individual patient-level data have prospectively associated urine and blood cadmium with cardiovascular risk. In residents with low compared with high cadmium exposure in Belgium, high blood cadmium and 24-hour urine cadmium were associated with an increased risk of cardiovascular and noncardiovascular mortality.\(^6^4\) In the SHS (Strong Heart Study), a cohort study of 3348 American Indian adults between the ages of 45 and 74 years, urine cadmium, a biomarker of cadmium body burden, was associated with increased CVD and mortality.\(^4^5,6^5\) The HR comparing the 80th with the 20th percentile (1.62 and 0.55 \(\mu\)g cadmium/g creatinine) was 1.43 (95% CI, 1.21–1.70; \(P<0.001\)) for cardiovascular mortality and 1.34 (95% CI, 1.10–1.63; \(P<0.001\)) for coronary heart disease mortality.\(^4^5\) In the same population (\(n=2864\)), urine cadmium levels were independently associated with incident PAD.\(^5^6\)

A systematic review published in 2013 reported "mounting evidence" that cadmium was significantly associated with CVD, and individually with coronary disease and peripheral arterial disease: CVD, 1.36 (95% CI, 1.11–1.66); CAD, 1.30 (95% CI, 1.12–1.52); and PAD, 1.49 (95% CI, 1.15–1.92), after controlling for smoking history.\(^6^6\) This systematic review did not include the Korean NHANES study reported in 2020.\(^6^7\)

In 2019, in a small group of patients with coronary disease, we found that higher urinary cadmium levels were linked to an increase in PAD severity\(^6^8\) and proposed urine cadmium as a potential biomarker for PAD outcomes.

Thus, following the causative framework established for lead, we conclude that a strong case can be made supporting cadmium as a cardiovascular risk factor.

### CONCLUSIONS

The totality of evidence reviewed above supports the recognition of both lead and cadmium as environmentally acquired contaminants that increase atherosclerotic cardiovascular risk in a dose-dependent manner. In fact, a 2020 American Heart Association statement in American Indians and Alaska natives recognizes toxic metals as a risk factor for CVD.\(^6^9\) These environmentally acquired metal contaminants may partially explain residual risk after traditional risk factors are taken into account. Past reductions in exposure to these metals have likely also contributed to reductions in cardiovascular mortality. However, as metal exposure remains widespread, additional efforts are needed.\(^7^0\) Funding for public health efforts is urgently needed to develop infrastructure, in particular for handling wastewater and producing metal-free drinking water, as ≈18 million people in the United States currently receive water through aged lead pipes,\(^7^1\) and to decrease urban lead exposure in neighborhoods affected by lead contamination in homes and residential soil. Preventing metal exposure in children and young adults is critical, given the long-term persistence of lead and cadmium in the body. As mentioned by Levin et al, new efforts are needed to rekindle government-wide surveillance, for instance through an interagency task force under the guidance of the Environmental Protection Agency and Centers for Disease Control and Prevention in monitoring and reporting lead exposures and trends.\(^7^2\) Clinical interventions and drug development are also needed to block the toxic effects or facilitate the elimination of persistent metals. In 2017, environmental cardiologist Aruni Bhatnagar stated "though heart disease rates have come down, the rate has slowed and flattened out in the recent past. That is why we thought we need..."
to try something different.⁷³ The evidence is strong that the time to recognize metal contaminants in the evaluation, treatment, and prevention of CVD is in the here and now.

ARTICLE INFORMATION

Affiliations
Department of Medicine (G.A.L.), and Columbia University Division of Cardiology (G.A.L.), Mount Sinai Medical Center, Miami Beach, FL; and Department of Environmental Health Sciences, Columbia University Mailman School of Public Health, New York, NY (A.N.).

Acknowledgments
We gratefully thank Nancy J. Lolocono, MPH, for her careful review and edits of our manuscript.

Disclosures
None.

REFERENCES

1. Brunier A, Muchnick A. WHO reveals leading causes of death and disability worldwide: 2000–2019. December 9, 2020. https://www.who.int/health-topics/cardiovascular-diseases#tab=tab. Accessed January 24, 2021.

2. U.S. EPA. Integrated Science Assessment (ISA) for Lead (Final Report, Jul 2013). U.S. Environmental Protection Agency, Washington, DC. EPA-600/R-13/007. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=255271. Accessed January 24, 2021.

3. Teilez-Plaza M, Navas-Acien A, Caldwell KL, Menke A, Muntner P, Guallar E. Reduction in cadmium exposure in the United States population, 1988–2008: the contribution of declining smoking rates. Environ Health Perspect. 2012;120:202–204. DOI: 10.1289/ehp.1104020.

4. Liu Y, Pan J, Fan C, Xu R, Wang Y, Xu C, Xie S, Zhang H, Cui X, Peng Z, et al. Short-term exposure to ambient air pollution and mortality from myocardial infarction. J Am Coll Cardiol. 2021;77:271–281. DOI: 10.1016/j.jacc.2020.11.033.

5. WHO Air Pollution: Fifth Report of the Expert Committee on Environmental Sanitation. Geneva, Switzerland: World Health Organization (WHO); 1998. Technical Report Series, No. 157. http://apps.who.int/iris/handle/10665/40416. Accessed February 2, 2020.

6. Wang C, Tu Y, Yu Z, Lu R. Pb and cardiovascular diseases in the elderly: an overview. Int J Environ Res Public Health. 2015;12:8187–8197. DOI: 10.3390/ijerph120708187.

7. Cakmak S, Dales R, Kauri LM, Mahmud M, Van Ryswyk K, Vanos J, Liu L, Kumarathasan P, Thompson E, Vincent R, et al. Metal composition of fine particulate air pollution and acute changes in cardiopulmonary physiology. Environ Pollut. 2014;189:208–214. DOI: 10.1016/j.envpol.2014.03.004.

8. Joint WHO/Convention Task Force on the Health Aspects of Ambient Air Pollution. Health risks of heavy metals from long-range transboundary air pollution. 2007. https://www.who.int/.../assets/pdf_file/0007/78549/E91044.pdf. Accessed January 24, 2021.

9. World Health Organization (WHO). Health Effects of Particulate Matter: Policy Implications for Countries in Eastern Europe, Caucasus and Central Asia. Copenhagen, Denmark: WHO Regional Office for Europe; 2013. http://www.who.int/.../data/assets/pdf_file/0006/189051/Health-effects-of-particulate-matter-final-Eng.pdf. Accessed January 21, 2021.

10. Caruso RV, O’Connor RJ, Stephens WE, Cummings KM, Fong GT. Toxic metals concentrations in cigarettes obtained from U.S. smokers in 2009: results from the International Tobacco Control (ITC) United States survey cohort. Int J Environ Res Public Health. 2014;11:202–217. DOI: 10.3390/ijerph11010202.

11. Vermeylen J, Nemmar A, Nemery B, Hoylaerts MF. Ambient air pollution and acute myocardial infarction. J Thromb Haemost. 2005;3:1955–1961. DOI: 10.1111/j.1538-7836.2005.01471.x.

12. Nemmar A, Hoet PH, Vermeylen J, Nemery B, Hoylaerts MF. Pharmacological stabilization of mast cells probably abrogates late thrombotic events induced by diesel exhaust particles in hamsters. Circulation. 2004;110:1670–1677. DOI: 10.1161/01.CIR.0000142053.13921.21.

13. Salvi S, Blomberg A, Rudell B, Kelly F, Sandström T, Holgate ST, Frew AJ. Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. Am J Respir Crit Care Med. 1999;159:702–709. DOI: 10.1164/ajrccm.159.3.9709083.

14. Liu K, Shang Q, Wan C, Song P, Ma C, Cao L. Characteristics and sources of heavy metals in PM2.5, during a typical haze episode in rural and urban areas in Taiyuan, China. Atmosphere. 2018;9:2. DOI: 10.3390/atoms9010002.

15. Fine LJ, Joubert B, Nadadur S. Stimulating intervention research to reduce cardiopulmonary impacts of particulate matter in air pollution among high-risk populations. October 5, 2020. Available at: https://grants.nih.gov/grants/guide-notice-files/NOTH-20-788.html. Accessed July 29, 2020.

16. Schroeder WH, Dobson M, Kane MD, Johnson ND. Toxic trace elements associated with airborne particulate matter: a review. JAPCA. 1997;37:1267–1285. DOI: 10.1080/08940639819870631.

17. Patterson C, Ericson J, Manea-Krichten M, Shirahata H. Natural skeletal levels of lead in Homo sapiens uncontaminated by technological lead. Sci Total Environ. 1991;107:203–236. DOI: 10.1016/0048-9697(91)90260-3.

18. Dignam T, Kaufmann RB, LeStourgeon L, Brown MJ. Control of lead sources in the United States, 1970–2017: public health progress and current challenges to eliminating lead exposure. J Public Health Manag Pract. 2019;25:S13–S22. DOI: 10.1097/PHH.0000000000000889.

19. Dowd TL, Rosen JP, Gundberg CM, Gupta RK. The displacement of calcium from osteoclast at submicromolar concentrations of free lead. Biochim Biophys Acta. 1994;1226:131–137. DOI: 10.1016/0925-4439(94)90020-5.

20. Barbosa F Jr, Tanus-Santos JE, Gerlach RF, Parsons PJ. A critical review of biomarkers used for monitoring human exposure to lead: advantages, limitations, and future needs. Environ Health Perspect. 2005;113:1669–1674. DOI: 10.1289/ehp.1171.

21. Hu H, Shih R, Rothenberg S, Schwartz BS. The epidemiology of lead toxicity in adults: measuring dose and consideration of other methodologic issues. Environ Health Perspect. 2007;115:455–462. DOI: 10.1289/ehp.9783.

22. Check L, Mertel-Parrish A. The fate and behavior of persistent, bio-accumulative, and toxic (PBT) chemicals: examining lead (Pb) as a PBT metal. Rev Environ Health. 2013;28:65–96. DOI: 10.1515/reveh-2013-0005.

23. Farah C, Michel LYM, Balligand JL. Nitric oxide signalling in cardiovascular health and disease. Nat Rev Cardiol. 2018;15:292–316. DOI: 10.1038/nrcardio.2017.224.

24. Tousoulis D, Kampoli AM, Tontoulis C, Papageorgiou N, Stefanadis C. The role of nitric oxide on endothelial function. Curr Vasc Pharmacol. 2012;10:104–118. DOI: 10.2174/157016110098829760.

25. Solenkova NV, Newman JD, Berger JS, Thurston G, Hochman JS, Lamas GA. Metal pollutants and cardiovascular disease: mechanisms and consequences of exposure. Am Heart J. 2014;168:812–822. DOI: 10.1016/j.ahj.2014.07.007.

26. Vaziri ND. Mechanisms of lead-induced hypertension and cardiovascular disease. Am J Physiol Heart Circ Physiol. 2008;295:H454–H465. DOI: 10.1152/ajphelp.00158.2008.

27. Heo Y, Parsons PJ, Lawrence DA. Lead differentially modifies cytokine production in vitro and in vivo. Toxicol Appl Pharmacol. 1996;138:149–157. DOI: 10.1006/taap.1996.0108.

28. Rodriguez-Iturbe B, Sindhu NK, Krioukov Y, Vaziri ND. Chronic exposure to low doses of lead results in renal infiltration of immune cells, apoptosis, NF-κB activation and overexpression of tubulointerstitial angiogenesis II. Antioxid Redox Signal. 2003;5:1269–1274.

29. Vaisiere T, Savan C, Hercberg Z. Epigenetic interplay between histone modifications and DNA methylation in gene silencing. Mutat Res. 2008;659:40–48. DOI: 10.1016/j.mrrev.2008.02.004.

30. Kovatli L, Georgiou E, Ioannou A, Haltioglu C, Tzimagiorkis G, Tsoukali H, Kouidiou S. p16 Promoter methylation in Pb2+ exposed individuals. Cln Toxicol (Phila). 2009;48:124–128. DOI: 10.3109/15563650903567091.
31. Li C, Yang X, Xu M, Zhang J, Sun N. Epigenetic marker (LINE-1 promoter) methylation level was associated with occupational lead exposure. Clin Toxicol (Phila). 2013;51:225–229. DOI: 10.3109/15565650.2013.782410.

32. Papanikolaou NC, Hatzidaki EG, Belianni S, Tzanakakis GN, Tsatsakis AM. Lead toxicity update: a brief review. Med Sci Monit. 2019;25:RA281–RA356.

33. Annest JL, Pirkle JL, Makuc D, Neese JW. Bayse DD, Kovar MG. Chronological trend in blood lead levels between 1976 and 1980. N Engl J Med. 1983;308:1373–1377. DOI: 10.1056/NEJM198309302301.

34. Lustberg M, Silbergeld E. Blood lead levels and mortality. Arch Intern Med. 2002;162:2434–2439. DOI: 10.1001/archie.162.21.2443.

35. Menke A, Munter P, Batuman V, Silbergeld EK, Guallar E. Blood lead below 0.48 μmol/L (10 μg/dL) and mortality among US adults. Circulation. 2006;114:1388–1394. DOI: 10.1161/CIRCULATIONAHA.106.628321.

36. Nawrot TS, Staessen JA. Low-level environmental exposure to lead unmasked as silent killer. Circulation. 2006;114:1347–1349. DOI: 10.1161/CIRCULATIONAHA.106.650440.

37. Langhein BP, Rauch S, Auinger P, Allen RW, Hornung RW. Low-level lead exposure and mortality in US adults: a population-based cohort study. Lancet Public Health. 2018;3:e177–e184. DOI: 10.1016/S2468-2667(18)30025-2.

38. Ruiz-Hernandez A, Navas-Acien A, Pastor-Barriuso R, Crainiceanu CM, Redon J, Guallar E, Tellez-Plaza M. Declining exposure to lead and cadmium contributed to explaining the reduction of cardiovascular mortality in the US population, 1988–2004. Int J Epidemiol. 2017;46:1903–1912. DOI: 10.1093/ije/dyx176.

39. Wang X, Mukherjee B, Kyun PS. Does information on blood heavy metals improve cardiovascular mortality prediction? J Am Heart Assoc. 2019;8:e013571. DOI: 10.1161/JAHA.119.013571.

40. Park SK, Zhao Z, Mukherjee B. Construction of environmental risk score beyond standard linear models using machine learning methods: application to metal mixtures, oxidative stress and cardiovascular disease in NHANES. Environ Health. 2017;16:102. DOI: 10.1186/s12940-017-0310-9.

41. Chowdhury R, Ramond A, O’Keeffe LM, Shahzad S, Kunutsor SK, Lattimore D, Wenne J, Schisterman EF. Association of cadmium, lead and mercury with paraoxonase 1 activity in women. PLoS One. 2014;9:e92152. DOI: 10.1371/journal.pone.0092152.

42. Domingo-Relloso A, Riffo-Campos AL, Haack K, Rentero-Garrido P, Ladd-Acosta C, Fallin DM, Tang WY, Herreros-Martinez M, Gonzalez JR, Bozak AK, et al. cadmium, smoking, and human blood DNA methylation profiles in adults from the Strong Heart Study. Environ Health Perspect. 2020;128:67005. DOI: 10.1289/EHP6345.

43. Bhattacharyya T, Nicholls SJ, Toopi EJ, Zhang R, Yang X, Schmutz D, Fu X, Shao M, Brennan DM, Ellis SG, et al. Relationship of paraoxonase 1 (PON1) gene polymorphisms and functional activity with systemic oxidative stress and cardiovascular risk. JAMA. 2008;299:1265–1276. DOI: 10.1001/jama.2008.11.1265.

44. Pollack AZ, Sjaarda L, Ahrens KA, Mumford SL, Brownie RW, Wactawski-Wende J, Schisterman EF. Association of cadmium, lead and mercury with paraoxonase 1 activity in women. PLoS One. 2014;9:e92152. DOI: 10.1371/journal.pone.0092152.

45. Wallace J, Schisterman EF. The relationship of cadmium in the air to cardiovascular disease rate. JAMA. 1996;276:267–271.

46. Nawrot TS, Van Hecke E, Thijs L, Richart T, Kuznetsova T, Jin Y, Vangronsense J, Roels HA, Staessen JA. Cadmium-related mortality and long-term secular trends in the cadmium body burden of an environmentally exposed population. Environ Health Perspect. 2008;116:1602–1628. DOI: 10.1289/ehp.111667.

47. Tellez-Plaza M, Guallar E, Fabitsz RR, Howard BV, Umanos JG, Francesconi KA, Goessliger W, Silbergeld EK, Devereux RB, Navas-Acien A. Cadmium exposure and incident peripheral arterial disease. Circ Cardiovasc Qual Outcomes. 2013;6:626–633. DOI: 10.1161/CIRCOUTCOM ES.112.000663.

48. Tellez-Plaza M, Jones MR, Dominguez-Lucas A, Guallar E, Navas-Acien A. Cadmium exposure and clinical cardiovascular disease: a systematic review. Curr Atheroscler Rep. 2013;15:356. DOI: 10.1007/s11883-013-0356-2.

49. Jeong J, Yun SM, Kim M, Koh YH. Association of blood cadmium with cardiovascular disease in Korea: from the Korea National Health and Nutrition Examination Survey 2008–2013 and 2016. Int J Environ Res Public Health. 2018;15:6288. DOI: 10.3390/ijerph15116288.

50. Ujetra F, Arenas IA, Diaz D, Yates T, Beasley R,Navas-Acien A, Lamas GA. Cadmium level and severity of peripheral artery disease in patients with coronary artery disease. Eur J Prev Cardiol. 2019;26:1456–1458. DOI: 10.1177/2047483819865858.

51. Lamadas et al Lead and Cardiac as Cardiovascular Risk Factors

52. Breathed K, Sims M, Gross M, Jackson EA, Jones EJ, Navas-Acien A, Taylor H, Thomas KL, Howard BV: American Heart Association Council on Epidemiology and Prevention; Council on Quality of Care and Outcomes Research; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Lifestyle and
Cardiometabolic Health. Cardiovascular health in American Indians and Alaska Natives: a scientific statement from the American Heart Association. Circulation. 2020;141:e948–e959. DOI: 10.1161/CIR.0000000000000773.

70. Lead and copper rule long-term revisions. Environmental Protection Agency (EPA). March 10, 2021. Available at:https://www.epa.gov/sdwa/lead-and-copper-rule-long-term-revisions. Accessed January 24, 2021.

71. Coursen DF. A neglected environmental justice issue: indoor plumbing. Hill; 2020. Available at:http://thehill.com/opinion/energy-environment/510857-a-neglected-environmental-justice-issue-indoor-plumbing. Accessed Jan 21, 2021.

72. Levin R, Zilli Vieira CL, Rosenbaum MH, Bischoff K, Mordarski DC, Brown MJ. The urban lead (Pb) burden in humans, animals and the natural environment. Environ Res. 2021;193:110377. DOI: 10.1016/j.envres.2020.110377.

73. Gulati V. Indian-born scientist attempts treating hearts via urban forests. Economic Times. Nov 1, 2017. Available at:https://economictimes.indiatimes.com/news/science/indian-born-scientist-attempts-treating-hearts-via-urban-forests-science-feature/articleshow/61396721.cms?from=mdr. Accessed June 14, 2020.