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VIEWPOINTS

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

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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 metal 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 ≤10 μm are generally indicated by the shorthand PM_{10}. Particles of ≤2.5 μm ($PM_{2.5}$) 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 $PM_{2\cdot5}$ 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,

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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]

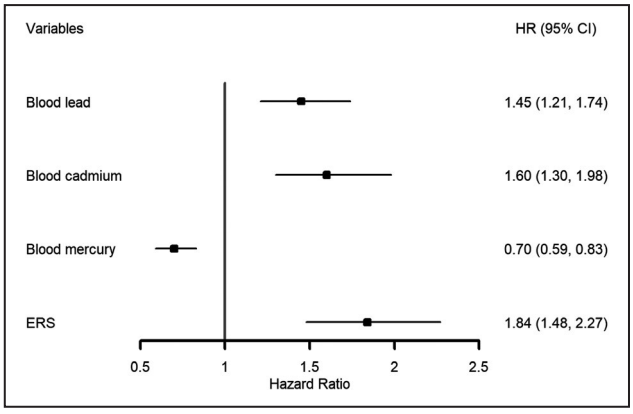

Figure 1. Contributions of lead and cadmium exposure reductions to cardiovascular disease mortality prevention in the US population comparing National Health and Nutrition Examination Survey 1988 to 1994 vs 1999 to 2004 after adjustment for established cardiovascular risk factors.
Hazard ratios (HRs) for death from cardiovascular disease, according to individual metal levels and Environmental Risk Score (ERS). HR (95% CI) comparing the 75th vs the 25th of each variable. Lead, cadmium, and mercury were log transformed. Each variable was included separately in each Cox model. (Source: Wang et al).[39]

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,

1.39; 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 to 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.[26,42] 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

tone.[51] Cadmium modulates calcium concentration, and as a result, interferes with multiple intracellular signaling pathways.[52,53] Cadmium-induced endoplasmic reticulum stress leads to cell death through activation of the apoptotic pathway[54]. Cadmium has also been related to increased oxidative stress through glutathione depletion.[55-57] Camidum 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.[58,59] Studies suggest that low levels of paraoxonase 1 activity may be associated with an increased prevalence of CVD.[60,61]

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.[62]

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).[63]

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.[64] 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.[45,65] The HR comparing the 80th with the 20th percentile (1.62 and 0.55 µg 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.[45] In the same population (n=2864), urine cadmium levels were independently associated with incident PAD.[65] 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.[66] This systematic review did not include the Korean NHANES study reported in 2020.[67]

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[68] 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.[69] 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.[70] 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,[71] 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.[72] 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 been coming 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

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Disclosures

None.

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