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Review

Environmental heavy metals and cardiovascular diseases: Status and future direction

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Abstract

Cardiovascular disease (CVD) and environmental degradation are leading global health problems of our time. Recent studies have linked exposure to heavy metals to the risks of CVD and diabetes, particularly in populations from low- and middle-income countries, where concomitant rapid development occurs. In this review, we 1) assessed the totality, quantity, and consistency of the available epidemiological studies, linking heavy metal exposures to the risk of CVD (including stroke and coronary heart disease); 2) discussed the potential biological mechanisms underlying some tantalizing observations in humans; and 3) identified gaps in our knowledge base that must be investigated in future work. An accumulating body of evidence from both experimental and observational studies implicates exposure to heavy metals, in a dose-response manner, in the increased risk of CVD. The limitations of most existing studies include insufficient statistical power, lack of comprehensive assessment of exposure, and cross-sectional design. Given the widespread exposure to heavy metals, an urgent need has emerged to investigate these putative associations of environmental exposures, either independently or jointly, with incident CVD outcomes prospectively in well-characterized cohorts of diverse populations, and to determine potential strategies to prevent and control the impacts of heavy metal exposure on the cardiometabolic health outcomes of individuals and populations.

Keywords: Heavy metal; Cardiovascular disease; Hypertension; Stroke; Coronary heart disease

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Introduction

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality globally. In 2017, approximately 18 million CVD deaths occurred worldwide, corresponding to 330 million years of life lost and another 35.6 million years lived with disability.[1] While in the United States, CVD remains the leading cause of death for both men and women, the disease has emerged as the leading cause of death (40% of all deaths) in rapidly developing countries such as China and Brazil.[2] Thus, identification of novel preventable risk factors is urgently needed particularly for populations in low- and middle-income countries.[3] Environmental degradation and exposure to heavy metals may have a direct impact on CVD development, which have become one of the most pressing nemeses of individual and population health globally.[4]

Heavy metals include toxic metals such as arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg), and some of the essential trace metals such as chromium (Cr), cobalt (Co), copper (Cu), magnesium (Mg), manganese (Mn), molybdenum (Mo), nickel (Ni), selenium (Se), tungsten (W), vanadium (V), and zinc (Zn). Evidence on the role of environmental exposure to heavy metals in CVD risk has rapidly increased over the past two decades.[5] Recent studies have provided provocative evidence linking environmental exposure to heavy metals to increased risks of diabetes and hypertension.[6,7] Diabetes and hypertension are strong CVD risk factors. Toxic As has been directly shown to cause gluconeogenesis and impairment of β-cell function,[8] and inhibit the expression of peroxisome proliferator-activated receptor γ, causing hyperglycemia and dyslipidemia.[9] Toxic metals (As, Cd, Pb, and Hg) and some of the essential metals (Co, Cu, Cr, Ni, and Se) are metalloestrogens and may also increase the risk of CVD through endocrine disruption.[10] However, few studies have directly and comprehensively investigated exposure to multiple heavy metals, particularly their joint effects on CVD risk. By contrast, prospective cohort studies have shown that higher levels of dietary and serum essential trace metals are directly associated with lower CVD risk and that supplementation of which may have potential benefits by mitigating the effects of toxic metals on the cardiovascular system.

In the US National Health and Examination Surveys (NHANES), biomonitoring of metals indicated a marked reduction in population mean exposure to several heavy metals (Pb and Cd) from 1988−1994 to 1999−2004, corresponding to a decrease in CVD mortality rates of 43% from the same period.[5] Benjamin and colleagues attributed 32% of the reduction to the decline in metal exposures of the US population.[11] However, exposure to environmental metals remains substantial, posing serious threat to public health that requires urgent study and action.[12] In this review, we 1) assessed the totality, quantity, and consistency of the available epidemiological studies that linked heavy metal exposures to CVD risk (including stroke and coronary heart disease, and CHD), 2) discussed potential biological mechanisms underlying some tantalizing observations in humans, and 3) identify gaps in our knowledge base that need to be investigated in future work.

Epidemiological studies linking metal exposures to CVD risk

Some studies have reported statistically significant associations between CVD and exposure to As, Cd, Hg, and Pb,[4] while other studies found no significant association between these toxic metals and CVD risk.[13−19] The available studies have also reported a significant association between imbalances in essential metals and CVD risk. Specifically, imbalanced levels of Zn,[20,21] Cu,[22−26] Cr,[27,28] Co,[29,30] Mg,[22,24,31−69] Se,[61,70−84] Ni,[85] and W[86−89] were associated with an increased CVD risk. Other studies, however, failed to establish a significant association between these essential metals and CVD risk.[22,44,58,61,65,85,88,90−94]

A recent meta-analysis of approximately 350,000 individuals from 37 countries showed that exposure to As, Pb, Cd, and Cu was directly associated with an increased risk of CVD incidence and mortality, having a linear-shaped dose−response curve.[4] However, no significant association was found between Hg exposure and CVD risk in the same meta-analysis. For Zn and CVD risk, the findings from prospective cohorts were also inconsistent, with the highest category of Se intake associated with lower CVD risk. Several meta-analyses also demonstrated how Mg exposure from diet and blood reduced the risks of CVD incidence and mortality.[95,96] Although the evidence has been updated in recent reviews, it is far from establishing causality. A major limitation of these studies is their cross-sectional in design, except for As, Cd, Pb, Mg, and Se, for which increasing prospective evidence generally consistently shows an increased risk (As, Cd, and Pb) of CVD risk (decreased risk from Mg[22,24,31−65] and Se[61,70−84]). Exposures to Ni and Mn have been associated with the risk of hypertension and CVD mortality.[97−101] The lack of high-quality and

comprehensive assessment of metal exposure coupled with limited prospective studies with inconsistent findings presents a large uncertainty on causal claims. To date, despite the numerous studies that assessed the association between individual metal exposure and CVD risk, no study in humans has comprehensively investigated the possible antagonistic effects of multiple toxic and essential metal exposures or established optimal levels of essential trace metals in mitigating the CVD risk induced by toxic metals.

Gaps in the current epidemiological studies linking heavy metals to CVD risk

Most previous studies were cross-sectional in design

The national NHANES studies of the United States contributed much to the body of evidence linking heavy metals to CVD risk.[87,102,103] While having representative samples, the NHANES studies are cross-sectional in nature and thus may be biased, known as "reverse causation." Toxic metals are well known to cause renal tubular dysfunction in patients with established type 2 diabetes (T2D) and CVD, and dysfunctional kidneys lose metals through increasing renal excretion, which results in their concomitant decrease in the blood.[8] Thus, findings from cross-sectional studies may actually reflect disease consequences rather than disease causes. A recent large cross-sectional study based on NHANES data concluded that prospective studies are urgently needed to further evaluate metals as risk factors of diabetes,[104] while another recent review of environmental factors of CVD called for high-quality prospective cohort studies in investigating the effects of metal exposure.[105]

Most previous studies focused on individual metals without consideration of the joint effects of multiple metals

Despite the experimental studies that have shown that heavy metal exposures may increase CVD risk and that essential metals at normal levels could counteract the toxicity from toxic metal exposures, few human studies have directly and comprehensively investigated the effects of multiple metal exposures and the alleged antagonistic effect between essential and toxic metals on CVD risk. Nevertheless, essential trace metals are recommended by some as potential beneficial supplements for the prevention of CVDs.[106−109] Nigra et al analyzed data from the Strong Heart Study and found that the association between tungsten and CVD incidence and mortality was positive though non-significant at lower urinary molybdenum levels and significant and inverse at higher urinary molybdenum levels.[86] Moreover, urinary cadmium was associated with increased risk of ischemic stroke but had a more pronounced association in participants in the lowest tertile of serum Zn levels.[86] The few studies conducted to date have had the power to study effect modification between essential trace metals and toxic metals in reducing CVD risk.

No previous studies examined the possible effects of essential metals/trace elements

No available epidemiological study has directly and comprehensively investigated the potential antagonistic effects of essential metals/trace elements on the reduction of toxic metal effects or the optimal levels of essential metals to mitigate the toxic metal effect. Thus, recommending mineral supplementation as a means of CVD prevention is considered by some to be immature at this stage. Regardless, additional and methodologically sound prospective studies are the only way to move the field forward, that is, to determine the significance and optimal levels of the cardiometabolic effects of essential metals.[104] If we can confirm the antagonistic effects between toxic and essential metals, and establish optimal body levels of essential metals that reduce the adverse effect of toxic metal exposure, our study could lead to simple, safe, readily available, acceptable, and highly affordable nutrition intervention for the prevention of CVD that will have both clinical, environmental, and public health significance worldwide.

Proposed biological mechanisms

Toxic metal-induced oxidative stress

Toxic metals (As, Cd, Hg, and Pb) can induce oxidative stress by generating reactive oxygen species (ROS), including superoxide radicals, hydrogen peroxide, and nitric oxide.[110,111] Many metals have been shown to increase lipid peroxidation,[112,113] or the free radical-driven oxidative modification of low-density lipoprotein (ox-LDL), a well-recognized causal event early in atherosclerosis development.[114,115] Cd can damage vascular tissues, induce endothelial dysfunction, and promote atherosclerosis by oxidative mechanisms.[116] Pb is known to induce ROS production,[106,110] and Pb-triggered oxidative stress can lead to the degradation of proteins, nucleic acids, and lipid peroxidation.[106,117] Cu together with Zn, for example, is essential for balanced oxidant-antioxidant mechanisms, and Cu and Zn imbalances can increase susceptibility to

toxic metal-induced oxidative damage to islet β-cells and thereby lead to the pathogenesis of insulin resistence.[118] Cr is a component or activator of some enzymes, mostly antioxidants. Se is a cofactor of the antioxidant enzyme glutathione peroxidase that enables the reduction of Cd/Pb-induced oxidative stress.[119−121]

Heavy metals linked to elevated systemic inflammation

Deficiency of essential and excess of toxic metals may lead to immune function impairment and accumulation of immune complexes, and through a series of interrelated processes, leads to CVD, including uncontrolled release of inflammatory cytokines, renal damage, and central nervous system stimulation.[122] In mouse experiments, metals increased oxidative stress and inflammation caused atherosclerotic lesion formation. As has been associated with increased intravascular inflammation by upregulating interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), monocyte chemotactic protein, vascular cell adhesion molecule 1 (VCAM-1), and intercellular adhesion molecule (ICAM).[123] Cd has also been associated with perturbations in inflammation and coagulation, including elevated blood C-reactive protein (CRP) and fibrinogen levels in a general US population,[124] and VCAM-1 in an animal study.[125] Both the oxidative stress and elevated systemic inflammation induced by exposure to toxic metals contribute to the progression of atherosclerosis.

Toxic metals compete with essential metals for various physiological functions and affect CVD risk

Toxic metals compete with essential metals for absorption and excretion; transport of metals in the body; binding to target proteins; and metabolism and sequestration of toxic metals.[126−128] Part of Pb toxicity, for example, comes from its ability to mimic other essential metals (e.g., Ca, Fe, and Zn), as it binds to and interacts with many of the same enzymes as these essential metals and thus interferes with the enzymes' ability to catalyze its normal reactions.[110] Cd and Pb have similar chemical and physical properties to Zn, and compete for the binding sites of metal absorptive and enzymatic proteins. Therefore, in case of Zn deficiency and increased exposure to these toxic metals, the body will use Cd and Pb instead of Zn.[129] Cd also competes with Fe for access to intestinal metal uptake transporters.[130] Deficiency of Fe can lead to greater absorption and toxicity of Cd and Pb.[131,132] Se at low concentrations can decrease As toxicity via excretion of As−Se compounds, but excessive Se can enhance As toxicity.[133] Ca and Mg also compete with Pb or Cd for intestinal absorption to reduce the toxic metal burden and prevent toxic metal-induced tissue damage by competitive binding to active sites of enzymes.[134,135] In summary, essential trace metals with their antioxidant properties at normal levels have the ability to counteract the oxidative stress induced by toxic metals, thus mitigating the toxicity of toxic metals.

Heavy metals affect CVD risk through body weight changes

Low-level Pb exposure during development resulted in later-life obesity in adult mice.[136] Pb intake during development caused higher food intake, higher body weight and body fat, and higher insulin response.[137] A study reported that Hg, Mn, and Co affect the lipid metabolism in adipose tissue, and Hg may accelerate the development of obesity-related diseases in mice.[138] Human studies also found that toxic metals could contribute to weight changes and were associated with obesity. A US NHANES study found that Ba and Tl were positively associated, while Cd, Co, and Pb were negatively associated with BMI and waist circumference.[139] The US adults who had a higher BMI had lower levels of Hg in their blood.[140] Cd levels in adults were found to be negatively associated with being overweight.[141] Overweight/obese women were found to have a high prevalence of Ni allergy, and a low-Ni diet could help with weight loss.[142]

Exposure to toxic metals increases the risk of hypertension

The effect of Pb on increased blood pressure has been consistently reported,[143−145] and As exposure has also been associated with hypertension in a dose-response assessment based on a recent systematic review.[146] Exposure to toxic metals may increase the risk of high blood pressure, which leads to CVD events such as stroke and CHD.

Potential directions for future studies

In addressing the major gaps and limitations of the current literature discussed earlier, targeting perspective research studies in occupationally exposed populations in industries such as mining and alloy manufacturing may be a most cost-effective approach

to investigate the role of heavy metal exposures in CVD development. We proposed several directions for future studies as follows: 1. simultaneous evaluation of the role of multiple heavy metal exposures on CVD risk; 2. assessment of the antagonistic effect of essential metals on the reduction of toxic metal effect on CVD; 3. determining the optimal body levels of essential metals that could mitigate CVD risk from toxic metals; and 4. conducting a nested case−control study in occupational populations or highly exposed general populations that include both cases and controls based on physical examinations and clinical biochemistry tests at baseline and during follow-up.

In summary, CVD and environmental degradation are major public health problems worldwide. Thus, understanding the preventable determinants of CVD is critical for establishing appropriate intervention strategies for prevention and control. Recent experimental and epidemiological studies indicate that heavy metal exposure deserves consideration as a risk factor of CVD, and this association is biologically plausible. Environmental exposure to heavy metals could also change the dynamic interplay with genetic, nutritional, and physical activity factors, and alter CVD risk. Owing to the inconclusive nature of the reported joint association and widespread exposure to heavy metals, large prospective cohort studies of diverse populations are urgently needed to investigate these alleged association and determine the optimal levels of essential metals for reducing the toxic metal impacts on CVD risk to improve both individual and population health outcomes.

Conflict of interest

None.

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