Clinica Chimica Acta 589 (2026) 121011

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Metal exposure in heart disease

Berthold Hocher [a,b,c,d,*,1]

[a] Department of Medicine, University Medical Centre Mannheim, University of Heidelberg, Heidelberg, Germany
[b] Clinical Research Center for Reproduction and Genetics in Hunan Province, Reproductive and Genetic Hospital of CITIC-Xiangya, Changsha, Hunan, China
[c] IMD Institut Für Medizinische Diagnostik Berlin-Potsdam GbR, Berlin, Germany
[d] Institute of Reproductive and Stem Cell Engineering, NHC Key Laboratory of Human Stem Cell and Reproductive Engineering, School of Basic Medical Science, Central South University, Changsha, China

ARTICLE INFO

Keywords:
Coronary heart disease
Heavy metals
Lead
Cadmium
Arsenic
Mercury
Chromium
Oxidative stress
Inflammation
Prevention
Environmental cardiology

ABSTRACT

Coronary heart disease (CHD) remains a leading cause of morbidity and mortality worldwide. In addition to classical risk factors, environmental exposures to toxic metals have been increasingly associated with cardiovascular risk in epidemiological studies. This narrative review summarizes current PubMed-indexed literature on the association of lead, cadmium, arsenic, mercury, and chromium with CHD, with emphasis on epidemiological evidence, mechanistic studies, and clinical implications. Literature was selected to cover major human observational studies, relevant experimental data, and translational reports addressing exposure pathways, biomarkers, vascular mechanisms, and prevention. Available epidemiological evidence suggests that chronic exposure to lead, cadmium, and arsenic is associated with higher risks of hypertension, atherosclerotic cardiovascular disease, and cardiovascular mortality, whereas the evidence for mercury and chromium is more heterogeneous and context-dependent. Mechanistic evidence, derived mainly from experimental and translational studies, indicates that these metals can promote oxidative stress, inflammation, endothelial dysfunction, disturbed lipid handling, mitochondrial injury, and, in some cases, epigenetic remodeling, thereby contributing to atherogenesis and plaque progression. However, the strength of evidence differs across metals and mechanisms, and causal interpretation remains strongest where experimental plausibility and human data converge. Clinically, heavy metal exposure should be considered in selected patients with CHD, particularly those with atypical risk profiles, relevant environmental or occupational exposure histories, or unexplained disease progression despite optimal standard management. Whole blood and urine measurements remain the preferred biomarkers in most settings, whereas hair analysis requires cautious interpretation. Prevention focuses on exposure reduction through water and food safety, emission control, smoking cessation, and targeted public health measures. Overall, toxic metals represent a plausible and likely underrecognized contributor to cardiovascular disease that deserves greater integration into cardiovascular prevention and environmental health research.

1. Introduction

Coronary heart disease (CHD) remains a major cause of death worldwide despite significant advances in prevention and therapy. Classical risk factors such as hypertension, dyslipidemia, diabetes, smoking, and obesity explain a large proportion of cases, yet a considerable residual risk persists despite optimal risk factor control. This gap has increasingly drawn attention to non-traditional determinants of cardiovascular disease (CVD), including environmental exposure. Among these, toxic heavy metals such as lead (Pb), cadmium (Cd), arsenic (As), mercury (Hg), and chromium (Cr) have emerged as important contributors to CV morbidity and mortality.

Recent consensus statements and scientific reports underscore the public health importance of environmental metal exposures. The American Heart Association (AHA) 2023 Scientific Statement on environmental contaminants concluded that chronic low-level exposure to Pb and Cd significantly increases CV risk, with no apparent safe threshold. Similarly, the World Health Organization (WHO) and the European Food Safety Authority (EFSA) highlight As in drinking water, Cd in agricultural soils, and Hg in seafood as major unresolved global

* Corresponding author at: University Medical Center Mannheim, University of Heidelberg, Theodor-Kutzer-Ufer 1–3, 68167 Mannheim, China.
E-mail address: berthold.hocher@medma.uni-heidelberg.de.
[1] ORCID: 0000–0001–8143-0579

https://doi.org/10.1016/j.cca.2026.121011
Received 14 February 2026; Received in revised form 14 April 2026; Accepted 15 April 2026
Available online 17 April 2026

health threats. These assessments emphasize that heavy metals are not only occupational hazards but also ubiquitous exposures affecting the general population, often through food, water, or air. Large population-based analyses have estimated a substantial CV mortality burden attributable to low-level Pb exposure [1].

The biological plausibility of metal-induced CV toxicity is supported by converging evidence from experimental, epidemiological, and clinical studies. Heavy metals can induce oxidative stress, chronic inflammation, disturbances in lipid metabolism, endothelial dysfunction, impairment of ion homeostasis, epigenetic alterations, and direct cellular toxicity—all recognized drivers of atherosclerosis and CV events. Importantly, these mechanisms interact with classical risk factors and may accelerate disease progression in susceptible individuals [2–6].

Given their persistence in the environment, bioaccumulation in the food chain, and very slow excretion from the human body, heavy metals represent a long-term and often underestimated CV risk factor. This review is intended as a narrative review with an integrated epidemiological, mechanistic, and clinical focus. Pb, Cd, As, Hg and Cr, were targeted in this study because these metals are among the most extensively studied and clinically relevant toxic exposures in CV and environmental health, with substantial evidence linking them to adverse CV outcomes and well-recognized public health exposure pathways. Although other metals, including nickel as well as essential trace elements such as copper, iron, manganese, and zinc at toxic concentrations, may also contribute to CV injury, a comprehensive treatment of all cardiotoxic metals is beyond the scope of the present review. Several systematic reviews and meta-analyses have already evaluated individual metals or overall toxic metal exposure in relation to CVD; however, an important gap remains in integrating these epidemiological findings with shared and metal-specific mechanisms of CV injury and with their practical implications for diagnosis, prevention, and patient management. Accordingly, this review aims to provide a translational synthesis of current knowledge on selected toxic metals in heart disease, spanning exposure pathways, mechanistic insights, and clinical relevance [7–17].

2. Literature search strategy

This article was designed as a narrative review. The literature search was conducted primarily in PubMed, focusing on studies addressing toxic metal exposure and CHD, atherosclerosis, endothelial dysfunction, oxidative stress, inflammation, biomarkers of exposure, and preventive strategies. Search terms included combinations of Cd, As, Hg, Cr, heavy metals, CHD, CVD, atherosclerosis, endothelial dysfunction, oxidative stress, inflammation, epigenetics, biomarkers, and prevention. Priority was given to human epidemiological studies, major reviews, meta-analyses, and translational or mechanistic studies directly relevant to CV injury. Additional references were identified through citation screening of relevant articles. The aim of the review was not to provide a formal systematic synthesis, but rather a structured narrative overview of current evidence and mechanistic concepts. Therefore, no formal risk-of-bias assessment was performed.

3. Sources and pathways of exposure

Human exposure to toxic metals occurs through multiple routes, including inhalation, ingestion, dermal absorption, and, in some cases, endogenous release from metallic implants or prosthetic materials, and spans a continuum from high-intensity occupational settings to chronic low-level environmental exposure. Occupational exposure is typically encountered in mining, smelting, battery manufacture, electroplating, leather processing, and related industrial activities, whereas environmental exposure in the general population more commonly occurs through contaminated drinking water, food, ambient air, tobacco smoke, seafood, and consumer products. Because many metals are environmentally persistent and bioaccumulate in the food chain, even long-term low-level exposure may lead to cumulative internal burdens relevant to CV risk. These exposure scenarios differ substantially in magnitude, duration, biomarker interpretation, and implications for CV risk assessment, and exposure patterns also vary geographically according to local geology, industrialization, agricultural contamination, dietary habits, and environmental regulation. Therefore, the CV relevance of metal exposure should be interpreted not only according to toxicological source, but also in relation to exposure intensity, population context, and regional distribution.

Exposure occurs through multiple pathways:

- **Pb** exposure can result from old water pipe seepage, Pb-based paints, foods such as wild mushrooms, game meat, offal, or contaminated teas, industrial emissions, waste incineration, as well as through tobacco and e-cigarette smoke or Pb-painted tableware.
- **Cd** is primarily found in phosphate fertilizers and consequently in contaminated foods (grains, vegetables, seeds and the oils pressed from them), fish and shellfish, tobacco plants, tobacco and e-cigarette smoke, and also tattoo inks.
- **As** may be ingested via contaminated groundwater, rice, mushrooms, fish and seafood, tobacco smoke, or emissions from waste incineration. In some world regions, As in drinking water constitutes a severe public health issue.
- **Hg** is mainly present as methyl-Hg in fish and seafood but can also be found in meat or vegetables grown on contaminated soils; industrial processes (e.g., chlor-alkali production) also contribute to exposure. Additional sources include dental amalgam and emissions from coal-fired power plants.
- **Cr** comes from natural sources like rocks and soil, and human activities such as industry and fossil fuel burning. Cr(III) is essential, but Cr(VI) is toxic and often results from industrial processes, contaminating water and soil. These sources and pathways are key to understanding human exposure and environmental impac

Toxic metals are environmentally persistent contaminants that can accumulate in ecosystems and enter the human food chain. Owing to their slow excretion, even chronic low-level exposure may, over time, result in substantial body burdens with potential CV relevance [18–25]. In this narrative review, we focus primarily on selected toxic metals with established or suspected roles in CVD, while also discussing Cr because of its distinct properties as both an essential trace element and a potential toxicant depending on chemical form and exposure level. We aim to integrate current knowledge on exposure pathways, epidemiological associations, underlying mechanisms, and clinical implications.

4. Heavy metals and CV risk

Although As, Pb, Cd, Hg and Cr share several downstream mechanisms of CV injury, including oxidative stress, inflammation, endothelial dysfunction, and acceleration of atherosclerosis, they differ substantially in exposure routes, toxicokinetics, relevant biomarkers, and the degree of epidemiological support for CHD. A clinically meaningful interpretation therefore requires more than listing generic toxicological pathways. It also requires distinguishing short-term from cumulative exposure markers, identifying major modifiers of susceptibility, and critically evaluating the strength of the available human evidence. Overall, the epidemiological evidence is strongest for Pb, Cd and As, more heterogeneous for Hg, and comparatively limited for Cr. This comparative perspective is important because the metals discussed here should not be viewed as interchangeable CV toxicants. This revision directly addresses the reviewer's request for greater mechanistic synthesis and more explicit clinical interpretation [26].

4.1. Arsenic (As)

As occurs in organic and inorganic forms, but CV toxicity is mainly

linked to inorganic As species, especially arsenite and arsenate, which are commonly derived from contaminated drinking water and certain foods. As has been associated with hypertension, endothelial dysfunction, atherosclerosis, and CV mortality. Mechanistically, As is notable not only for inducing oxidative stress and nitric oxide dysregulation, but also for interfering with mitochondrial energy metabolism, including phosphate substitution and impaired ATP production, thereby contributing to vascular and myocardial dysfunction. It also promotes thrombosis and epigenetic alterations that may contribute to persistent CV injury. A particularly important point is interindividual susceptibility: As toxicity depends partly on biotransformation efficiency, and individuals with less efficient As methylation may retain more toxic intermediates and therefore have greater CV vulnerability at similar exposure levels. From an epidemiological perspective, As has relatively strong support as a CV toxicant, especially in populations exposed through drinking water; however, interpretation should distinguish inorganic As exposure from total As measurements that may partly reflect less toxic seafood-derived organic forms [27–32]. Prospective cohort evidence in populations with low-to-moderate As exposure (e.g., the Strong Heart Study) supports associations with incident CVD and mortality [33,34].

4.2. Lead (Pb)

Pb remains highly relevant to CVD because its effects may persist long after external exposure has decreased. Pb promotes hypertension, endothelial dysfunction, oxidative stress, inflammation, and atherosclerosis, in part by displacing calcium (Ca) and zinc (Zn), inhibiting antioxidant enzymes, increasing reactive oxygen species (ROS) generation, and disturbing Ca-dependent signaling pathways. For CV interpretation, biomarker selection is crucial. Blood Pb is widely used but mainly reflects recent or ongoing exposure, whereas bone Pb better captures cumulative body burden over years to decades. This distinction is clinically important because Pb stored in bone can be remobilized during aging, osteoporosis, pregnancy, and chronic disease, thereby contributing to sustained endogenous exposure even when environmental sources decline. Among the metals discussed here, Pb has one of the most consistent epidemiological associations with CV mortality and hypertension-related outcomes, and cumulative exposure measures are likely more informative for long-term CV risk than blood Pb alone [35–38]. Even at low exposure, Pb has been associated with increased CV mortality in population-based analyses [1].

4.3. Mercury (Hg)

Hg occurs as elemental Hg, inorganic salts, and methyl-Hg, the latter being especially relevant for CV risk because it is highly bioavailable and bioaccumulates in the food chain, particularly in predatory fish. Mechanistically, Hg promotes oxidative stress, inflammation, thrombosis, endothelial dysfunction, and mitochondrial impairment. It binds to selenium and thiol groups, inhibits antioxidant enzymes, increases low density lipoprotein (LDL) oxidation, and may reduce the cardioprotective function of high density lipoprotein (HDL)-associated enzymes. These mechanisms support biological plausibility for atherosclerosis and coronary events. However, epidemiological interpretation is more complex than for Pb, Cd or As because Hg exposure through fish intake may coexist with potentially cardioprotective nutrients such as omega-3 fatty acids and selenium. This likely contributes to the more heterogeneous and context-dependent epidemiological evidence linking Hg to CHD [39,40].

4.4. Cadmium (Cd)

Cd is characterized by a very long biological half-life and progressive accumulation in the body, making it particularly relevant for chronic CV injury. It enters the body through food, fertilizers, industrial emissions, and especially tobacco smoke. However, Cd toxicity should not be interpreted merely as a marker of smoking. Although smoking is a major source of exposure, epidemiological studies indicate that associations between Cd and CVD persist after adjustment for smoking and are also observed among never-smokers, supporting a smoking-independent vascular effect. Mechanistically, Cd contributes to endothelial injury, oxidative stress, lipid peroxidation, nitric oxide dysregulation, renal damage, and interference with Zn-dependent antioxidant and repair systems. These pathways are highly relevant for both hypertension and atherosclerotic progression. Among the metals reviewed here, Cd has comparatively strong epidemiological support, including evidence linking chronic exposure to CVD, although interpretation remains influenced by biomarker choice, kidney function, and the long latency of exposure effects [41–47].

4.5. Chromium (Cr)

Cr requires particularly cautious interpretation because its CV relevance depends fundamentally on chemical speciation. Trivalent Cr has historically been considered metabolically relevant, whereas hexavalent Cr is a recognized toxicant with strong oxidative, inflammatory, and genotoxic potential. This distinction is essential in CV research, yet epidemiological studies do not always clearly differentiate Cr species. As a result, although Cr can plausibly contribute to vascular injury, the available evidence linking Cr specifically to CHD is less robust than for Pb, Cd, or As. Cr should therefore be discussed more cautiously as a potentially cardiotoxic exposure whose clinical interpretation depends strongly on valence state, exposure context, and the limitations of the current epidemiological literature [48–53].

5. Comparative interpretation of the evidence

Taken together, the metals discussed in this review should not be regarded as mechanistically or epidemiologically equivalent. Pb and Cd appear to have the most consistent evidence linking chronic exposure to hypertension, atherosclerosis, and CV events in the general population. As also has substantial support, particularly for inorganic exposure in populations affected by contaminated drinking water, with CV risk modified by differences in As metabolism. Hg is biologically plausible as a cardiotoxicant, but its epidemiological signal is more difficult to isolate because exposure often co-occurs with fish-derived nutrients that may exert opposing CV effects. Cr currently has the least conclusive evidence for CHD because CV effects depend strongly on chemical form and because the epidemiological literature remains comparatively limited. This graded interpretation strengthens the clinical relevance of the section and better addresses the reviewer's concern that the previous version did not critically evaluate the relative strength of the evidence across individual metals.

6. Mechanisms of heavy metal–induced cardiotoxicity

Heavy metals such as As, Cd, Pb, Hg and Cr contribute to CHD not through isolated toxic effects, but through an interconnected pathogenic cascade that promotes the initiation, progression, and destabilization of atherosclerotic plaques. In the revised conceptual framework, metal exposure is understood as a chronic environmental stressor that first disrupts cellular redox balance and mitochondrial function, then activates inflammatory and endothelial signaling, alters lipid handling and vascular tone, induces maladaptive epigenetic and transcriptional responses, and ultimately accelerates plaque development, plaque vulnerability, and thrombotic complications. Thus, oxidative stress, inflammation, endothelial dysfunction, lipid dysregulation, ion imbalance, apoptosis, and epigenetic remodeling should not be viewed as separate mechanisms, but as interdependent stages within a common atherogenic process. This integrated interpretation directly addresses the reviewer's concern that the previous version was too descriptive and

insufficiently organized around a coherent pathogenic model (Fig. 1). (See Table 1.)

6.1. Early molecular injury: Redox imbalance and mitochondrial dysfunction

A central initiating event in metal-induced vascular injury is the disruption of redox homeostasis. Many toxic metals bind sulfhydryl groups of glutathione, cysteine, and antioxidant enzymes, thereby weakening endogenous antioxidant defenses. Pb, Cd and Hg can displace essential metals such as Zn from critical enzymes, whereas hexavalent Cr generates reactive intermediates during intracellular reduction. The resulting overproduction of ROS promotes lipid peroxidation, protein oxidation, DNA damage, and mitochondrial dysfunction. In the context of atherosclerosis, this early oxidative injury is not merely a marker of toxicity; it serves as an upstream trigger that amplifies inflammatory signaling, reduces nitric oxide bioavailability, promotes LDL oxidation, and shifts vascular cells toward a proatherogenic phenotype [54–56].

6.2. Inflammatory response

Oxidative stress is closely linked to inflammatory activation. Heavy metals stimulate NF-κB, MAP kinase pathways, and inflammasome-related signaling, resulting in increased expression of cytokines, chemokines, and adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1). This converts the endothelium from a quiescent antithrombotic barrier into an activated surface that promotes leukocyte adhesion, monocyte recruitment, and vascular inflammation. Endothelial nitric oxide signaling is simultaneously impaired, leading to vasoconstriction, reduced vascular repair capacity, and a prothrombotic state. In pathogenic terms, these changes represent the transition from early molecular injury to vascular dysfunction, creating the conditions for intimal immune-cell infiltration and chronic plaque-promoting inflammation [57–60].

6.3. Lipid dysregulation, foam-cell formation, and plaque growth

Metals also contribute directly to atherogenesis by altering lipid metabolism and promoting the formation of lipid-laden foam cells. Pb interferes with lipase activity, Cd disrupts cholesterol regulation and antioxidant defenses, and Hg enhances LDL oxidation while impairing protective HDL-associated enzyme systems. These lipid abnormalities interact with endothelial activation and inflammation to increase retention and oxidation of atherogenic lipoproteins in the vessel wall. Oxidized LDL is then taken up by macrophages, promoting foam-cell formation and fatty streak development. Over time, persistent exposure sustains this proatherogenic milieu, favoring progression from early lesion formation to more complex plaques characterized by necrotic core expansion, oxidative damage, and chronic inflammatory cell recruitment [61–63].

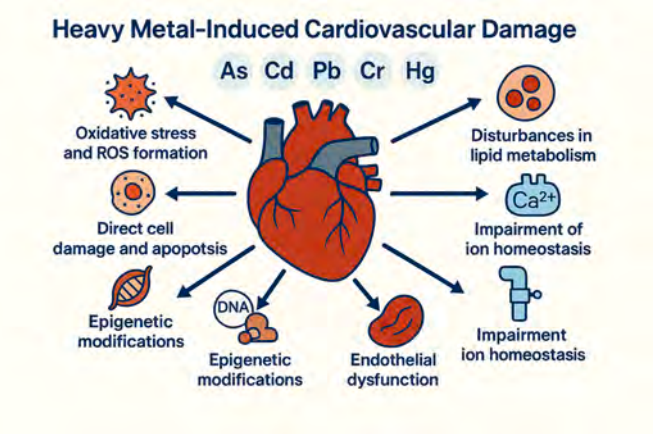

Fig. 1. Heavy Metal–Induced Cardiovascular Damage. Major mechanisms by which toxic metals including arsenic (As), cadmium (Cd), lead (Pb), chromium (Cr), and mercury (Hg) contribute to cardiovascular injury.

6.4. Vascular smooth muscle dysfunction, remodeling, and plaque instability

Beyond the endothelium and macrophages, toxic metals also affect vascular smooth muscle cells and extracellular matrix remodeling. Disturbed Ca signaling, mitochondrial injury, and apoptosis can impair smooth muscle cell viability and phenotype, while chronic oxidative and inflammatory stress favors matrix degradation and fibrotic remodeling. These processes influence plaque composition, cap integrity, arterial stiffness, and vascular calcification. In advanced lesions, the combination of endothelial dysfunction, oxidative lipid injury, macrophage activation, smooth muscle dysregulation, and matrix remodeling may promote plaque vulnerability, erosion, or rupture. Thus, the mechanistic relevance of heavy metals extends beyond plaque initiation to later stages of clinical importance, including thrombosis, myocardial infarction, and other acute coronary syndromes. This disease-sequence framing makes the section more clinically meaningful than a simple list of molecular pathways [64–68].

6.5. Impaired ion homeostasis

Disruption of Ca balance is another shared mechanism. Pb blocks Ca channels and alters intracellular release; Cd increases intracellular Ca^{2+} via channel activation; Hg perturbs Ca^{2+}-dependent enzyme function. These ion disturbances promote ROS production and mitochondrial dysfunction, further linking ion dysregulation to oxidative stress, apoptosis, and impaired vascular tone [69–71].

6.6. Epigenetic modifications

Epigenetic changes should also be interpreted within this pathogenic sequence rather than as an isolated mechanism. DNA methylation changes, histone modifications, and altered non-coding RNA regulation may stabilize proinflammatory, pro-oxidative, and metabolically adverse cellular states after exposure. In this way, epigenetic remodeling may help explain why the CV consequences of metal exposure can persist long after the exposure itself has declined, especially in the setting of cumulative body burden. It may also provide a mechanistic link between environmental exposure history and long-term vascular memory, thereby reinforcing progression from chronic exposure to persistent atherosclerotic risk. The reviewer's concern about excessive overlap among mechanisms is therefore best addressed by positioning epigenetic processes as mediators of persistence and biological embedding rather than as one more parallel pathway [72–76].

7. Emerging frameworks: Exposomics, systems toxicology, and multi-omics

To better understand how environmental exposures translate into CVD, emerging frameworks such as exposomics, systems toxicology, and multi-omics offer important conceptual advances. An exposomic perspective emphasizes that CV risk is shaped not by one isolated toxicant, but by the cumulative and time-varying totality of environmental exposures across the life course [77,78]. Systems toxicology extends this view by examining how toxicants perturb interconnected biological networks and adverse-outcome pathways rather than single linear mechanisms [79,80]. Multi-omics approaches, including epigenomics, transcriptomics, proteomics, metabolomics, and lipidomics, can help

Table 1
Exposure sources, biomarkers, and cardiovascular relevance of toxic metals in CHD.

Metal	Major exposure sources	Main route (s) of exposure	Common biomarker(s)	Representative cardiovascular relevance	Key notes
Lead (Pb)	Old water pipes, Pb-based paints, industrial emissions, waste incineration, contaminated food (eg, game meat, offal, wild mushrooms, tea), tobacco and e-cigarette smoke	Ingestion, inhalation	Whole blood; bone Pb where available	Hypertension, endothelial dysfunction, atherosclerosis, cardiovascular mortality	Persistent environmental toxicant; accumulates in bone and may be remobilized during aging, osteoporosis, or chronic disease
Cadmium (Cd)	Phosphate fertilizers, contaminated grains and vegetables, seeds and seed oils, shellfish, tobacco smoke, e-cigarettes, tattoo inks	Ingestion, inhalation	Whole blood; urine	Oxidative stress, endothelial injury, lipid peroxidation, hypertension, atherosclerotic cardiovascular disease	Long biological half-life; accumulates mainly in kidney and liver; smoking is a major source
Arsenic (As)	Contaminated groundwater, drinking water, rice and rice products, mushrooms, seafood, tobacco smoke, industrial emissions	Ingestion, inhalation	Urinary As species	Hypertension, endothelial dysfunction, atherosclerosis, cardiovascular disease, cardiovascular mortality	Cardiovascular toxicity is most relevant for inorganic As; speciation is important to distinguish seafood-derived organic forms
Mercury (Hg)	Fish and seafood, contaminated soil-derived food, coal combustion, mining and industrial processes, dental amalgam	Ingestion, inhalation	Whole blood; hair in selected settings	Oxidative stress, endothelial dysfunction, thrombosis, mitochondrial injury; epidemiological association with CHD remains heterogeneous	Bioaccumulates in the food chain; methylmercury is the most relevant environmental form; interpretation may be confounded by beneficial nutrients in fish
Chromium (Cr)	Natural sources, industrial processes, electroplating, stainless steel production, leather industry, fossil fuel combustion, contaminated water and soil	Ingestion, inhalation	Blood or urine in selected settings	Potential oxidative, inflammatory, and vascular toxicity, especially for hexavalent Cr	Toxicological relevance depends on speciation: trivalent Cr is an essential trace element, whereas hexavalent Cr is toxic

identify biological signatures linking metal exposure to endothelial activation, inflammatory reprogramming, mitochondrial dysfunction, lipid oxidation, and plaque vulnerability [81,82]. In the context of CHD, these approaches may be especially valuable for identifying exposure-response patterns at environmentally relevant low exposure levels, clarifying susceptible subgroups, and resolving the biological heterogeneity of metal-mixture effects [78,83]. Including these concepts strengthens the manuscript's translational relevance and aligns the mechanistic discussion with current directions in environmental cardiology research [77,78,81].

A further limitation of single-metal models is that real-world exposure usually occurs as mixtures rather than as isolated toxicants [78,83]. In epidemiologic studies of CV outcomes, mixture-based analyses using approaches such as Bayesian kernel machine regression and weighted quantile sum regression have increasingly shown that co-exposure to multiple metals may be associated with CV risk factors and disease in ways that are not well captured by single-exposure models [83–85]. Combined exposure to As, Pb, Cd, Hg, or Cr is biologically plausible as a driver of additive or synergistic toxicity because these metals converge on common pathogenic nodes, including oxidative stress, depletion of antioxidant defenses, mitochondrial dysfunction, impaired nitric oxide bioavailability, inflammatory signaling, dysregulation of lipid metabolism, endothelial dysfunction, and epigenetic remodeling [86–89]. Synergy is particularly plausible when different metals perturb complementary components of the same pathogenic network—for example, one weakening antioxidant defenses, another enhancing ROS generation, and another promoting endothelial activation or lipid oxidation [86–89]. The consequence may be a more sustained and amplified atherogenic response than predicted by single-exposure analyses alone [83–85]. This issue is especially relevant to population-based environmental exposure, where low-dose mixtures may exert cumulative vascular effects even when individual metals fall below traditional toxicological thresholds [77,78,83]. A mixture-based interpretation therefore provides a more realistic model of environmental cardiotoxicity than isolated pathway descriptions [78,83].

Taken together, the CV effects of toxic metals can be conceptualized as a progressive, multi-level process: chronic exposure promotes redox imbalance and mitochondrial stress; these changes activate inflammatory and endothelial pathways; endothelial dysfunction and lipid oxidation favor leukocyte recruitment and foam-cell formation; vascular smooth muscle cell dysfunction and matrix remodeling contribute to plaque progression; and persistent epigenetic and network-level changes, potentially reinforced by mixed exposures, may help sustain and amplify these processes over time [86–91]. This integrated model is more informative than a pathway-by-pathway list because it connects molecular injury to the natural history of atherosclerosis and provides a framework for interpreting both subclinical vascular damage and overt coronary events [89–91].

8. Clinical implications and prevention

The CV relevance of toxic metal exposure has important preventive implications, but translation into clinical practice should be cautious. Contaminant metals such as Pb, Cd, and As are increasingly recognized as CV risk factors, yet current major CHD guidelines do not recommend routine heavy-metal screening in all patients with CHD. Clinical use of metal testing should therefore be framed as a selective toxicological evaluation, guided by exposure history, symptom pattern, and clinical context, rather than as part of routine CV diagnostics [86,92,93].

8.1. Risk assessment and diagnostics

In clinical practice, the most appropriate first step is a structured exposure history, including occupational contact, contaminated water or food sources, smoking, supplements or traditional remedies, and other environmental risks (Fig. 2). When testing is clinically indicated, validated blood- and urine-based biomarkers remain the preferred approaches because they are better standardized and more clinically interpretable than alternative matrices [86,92,93]. Blood measurements are generally most useful for recent or ongoing exposure, whereas urine testing may be more informative for some metals or exposure settings, particularly when speciated analysis is available. However, biomarker interpretation depends strongly on the individual metal, exposure timing, and toxicokinetics, and results should ideally be assessed in collaboration with a clinical toxicology or occupational/environmental medicine service. [86,92,93].

Heavy-metal testing may be considered in selected situations such as documented occupational exposure, residence in contaminated areas, suspected As-contaminated drinking water, smoking-related Cd burden, or CVD that appears disproportionate to conventional risk factors. [86,92,93] Even in these settings, testing should not be presented as a consensus CHD screening framework, but rather as a targeted extension

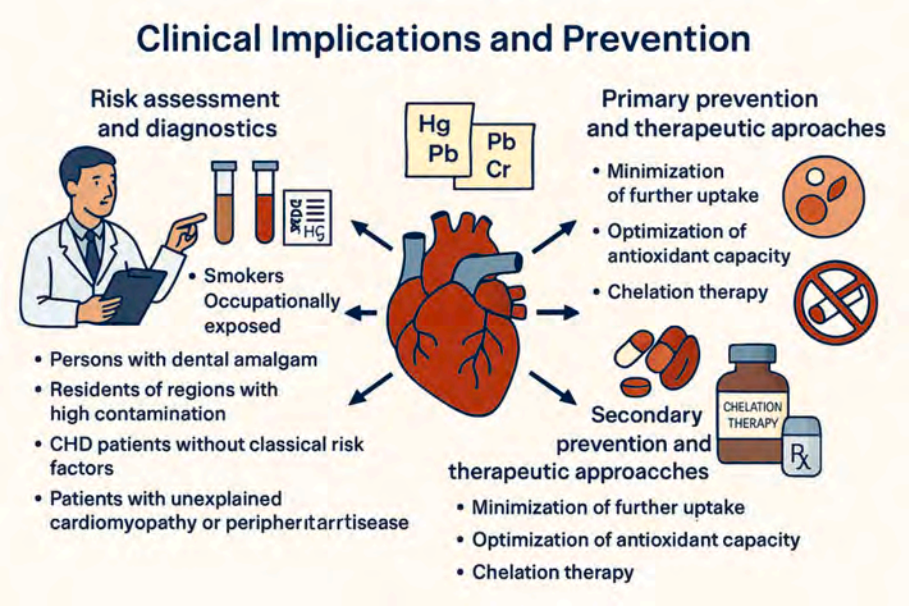

Fig. 2. Clinical Implications and Prevention of Heavy Metal–Induced Cardiovascular Damage.

of clinical evaluation when toxic exposure is plausible.

8.2. Hair analysis

Hair analysis is particularly challenging. Although hair can sometimes reflect longer-term exposure and has been used in research and selected environmental investigations, its clinical reliability is limited by external contamination, cosmetic treatment effects, laboratory variability, lack of standardized washing and preprocessing procedures, and uncertainty in relating measured concentrations to internal dose or disease ris. [92–94]. For this reason, hair analysis should not be recommended as a routine diagnostic tool in patients with CHD. At most, it may serve as an adjunctive exposure marker in highly selected circumstances and should, whenever possible, be corroborated by validated blood or urine biomarkers. A partial exception is methyl-Hg exposure, for which hair concentrations may have biomarker value in specific exposure settings, but this exception does not justify routine use of hair testing in CV practice. [92–94]

8.3. Primary prevention

The strongest current clinical implication remains prevention of exposure rather than downstream medical treatment. Primary prevention includes remediation of contaminated drinking water, reduction of industrial and agricultural emissions, control of contaminated food sources, smoking cessation, and avoidance of unregulated supplements or traditional preparations that may contain toxic metals [86,92,93]. These strategies are currently better supported at the population and risk-reduction level than any routine patient-level toxic-metal screening program in cardiology.

8.4. Chelation therapy and therapeutic limitations

Chelation therapy should be discussed primarily within a toxicological, not a routine CV, framework. Established indications relate to acute or clinically significant poisoning and require specialist supervision, careful agent selection, and monitoring for adverse effects such as nephrotoxicity, electrolyte abnormalities, redistribution phenomena, and depletion of essential trace elements [86,92,93]. In contrast, the use of EDTA-based chelation for prevention of CV events remains unproven. The original TACT trial in patients with prior myocardial infarction suggested a possible reduction in CV events [95], and a prespecified subgroup analysis reported greater apparent benefit among patients with diabetes [96]. However, the trial was controversial, and subsequent evidence from TACT2 showed that in patients with diabetes and prior myocardial infarction, edetate disodium-based chelation did not reduce major adverse CV events despite lowering blood Pb concentrations [97]. Accordingly, current randomized evidence does not support EDTA chelation as a routine strategy for secondary CV prevention [95–97].

Chelation should therefore not be recommended in this review as a standard treatment for CHD patients with suspected low-level environmental exposure alone. A more defensible clinical position is that suspected toxic-metal burden should prompt exposure reduction, targeted biomarker confirmation where appropriate, and referral to specialists in toxicology or occupational/environmental medicine when poisoning is clinically significant [86,92,93,97].

9. Summary and outlook

The role of heavy metals in the pathogenesis of CHD is increasingly being recognized. Even low-level exposures can significantly increase CV risk. Comprehensive risk assessment, primary prevention through exposure reduction, and targeted secondary prevention are crucial to minimize the burden of these environmental toxins and improve CV health.

Further research is needed to better understand the complex interactions between heavy metals, genetics, and lifestyle factors, and to develop more precise intervention strategies. Some toxic metals can impair kidney function even at very low blood concentrations. Reduced kidney function is itself an independent risk factor for CVD.

To assess chronic effects of toxic metals on the cardio-renal system, measurement of metals by mass spectrometry in whole blood samples is the method of choise, since this method provides the best information on mean metal exposure in the weeks prior to sample collection—similar to how HbA1c reflects long-term glycemic control [98,99].

CRediT authorship contribution statement

Berthold Hocher: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

[1] B.P. Lanphear, S. Rauch, P. Auinger, R.W. Allen, R.W. Hornung, Low-level lead exposure and mortality in US adults: a population-based cohort study, Lancet Public Health 3 (4) (2018) e177–e184, https://doi.org/10.1016/S2468-2667 [18]30025-2.

[2] A.J. Ferrari, D.F. Santomauro, A. Aali, Y.H. Abate, C. Abbafati, H. Abbastabar, et al., Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the global burden of disease study 2021, Lancet 403 (10440) (2024) 2133–2161, https://doi.org/10.1016/S0140-6736 [24]00757-8.

[3] B. Gholami, M.M. Bastan, S. Gholami, A. Nejati, S. Khosravi, M.R. Malekpour, et al., Disability-adjusted life years, years lived with disability, and years of life lost of diseases among children and adolescents in national and subnational levels of Iran, 1990-2021: a systematic analysis for the global burden of disease 2021, PLoS One 20 (6) (2025) e0325085, https://doi.org/10.1371/journal.pone.0325085.

[4] E.J. Benjamin, P. Muntner, A. Alonso, et al., Heart disease and stroke statistics—2019 update: a report from the american heart association, Circulation 139 (10) (2019) e56–e528.

[5] G.A. Roth, G.A. Mensah, C.O. Johnson, et al., Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study, J. Am. Coll. Cardiol. 76 (25) (2020) 2982–3021.

[6] R. Chowdhury, A. Ramond, G.A. Figtree, et al., Environmental toxic metal exposure and cardiovascular disease: a systematic review and meta-analysis, BMJ 362 (2018) k3310.

[7] A. Navas-Acien, A.R. Sharrett, E.K. Silbergeld, B.S. Schwartz, K.E. Nachman, T. A. Burke, E. Guallar, Arsenic exposure and cardiovascular disease: a systematic review of the epidemiologic evidence, Am. J. Epidemiol. 162 (11) (2005) 1037–1049, https://doi.org/10.1093/aje/kwi330.

[8] P. Verzelloni, T. Urbano, L.A. Wise, M. Vinceti, T. Filippini, Cadmium exposure and cardiovascular disease risk: a systematic review and dose-response meta-analysis, Environ. Pollut. 15 (345) (2024) 123462, https://doi.org/10.1016/j.envpol.2024.123462.

[9] A. Navas-Acien, E. Guallar, E.K. Silbergeld, S.J. Rothenberg, Lead exposure and cardiovascular disease–a systematic review, Environ. Health Perspect. 115 (3) (2007) 472–482, https://doi.org/10.1289/ehp.9785.

[10] G. Genchi, A. Carocci, G. Lauria, et al., Lead and cardiovascular disease: a systematic review, Environ. Res. 189 (2020) 109919.

[11] X.F. Hu, K. Singh, H.M. Chan, Mercury exposure, blood pressure, and hypertension: a systematic review and dose-response meta-analysis, Environ. Health Perspect. 126 (7) (2018) 076002, https://doi.org/10.1289/EHP2863.

[12] E. Sazakli, Human health effects of oral exposure to chromium: a systematic review of the epidemiological evidence, Int. J. Environ. Res. Public Health 21 (4) (2024) 406, https://doi.org/10.3390/ijerph21040406.

[13] R. Chowdhury, A. Ramond, L.M. O'Keeffe, S. Shahzad, S.K. Kunutsor, T. Muka, J. Gregson, P. Willeit, S. Warnakula, H. Khan, S. Chowdhury, R. Gobin, O. H. Franco, E. Di Angelantonio, Environmental toxic metal contaminants and risk of cardiovascular disease: systematic review and meta-analysis, BMJ 29 (362) (2018) k3310, https://doi.org/10.1136/bmj.k3310 (PMID: 30158148).

[14] M. Tellez-Plaza, M.R. Jones, A. Dominguez-Lucas, E. Guallar, A. Navas-Acien, Cadmium exposure and clinical cardiovascular disease: a systematic review, Curr. Atheroscler. Rep. 15 (10) (2013) 356, https://doi.org/10.1007/s11883-013-0356-2.

[15] J. Maiuolo, R. Bulotta, R. Mollace, F. Bosco, L. Guarnieri, F. Oppedisano, S. Ilari, C. Muscoli, E. Palma, V. Mollace, Non-essential heavy metal effects in cardiovascular diseases: an overview of systematic reviews, Front. Cardiovasc. Med. 23 (11) (2024) 1332339, https://doi.org/10.3389/fcvm.2024.1332339.

[16] S. Satarug, Dietary cadmium intake and its effects on kidneys, Toxics 6 (10) (2018) 15, https://doi.org/10.3390/toxics6010015.

[17] L. Järup, A. Akesson, Current status of cadmium as an environmental health problem, Toxicol. Appl. Pharmacol. 238 (3) (2009) 201–208, https://doi.org/10.1016/j.taap.2009.04.020.

[18] P.B. Tchounwou, C.G. Yedjou, A.K. Patlolla, D.J. Sutton, Heavy metal toxicity and the environment, Exp Suppl. 101 (2012) 133–164, https://doi.org/10.1007/978-3-7643-8340-4_6.

[19] K. Moon, E. Guallar, A. Navas-Acien, Arsenic exposure and cardiovascular disease: an updated systematic review, Curr. Atheroscler. Rep. 14 (6) (2012) 542–555, https://doi.org/10.1007/s11883-012-0280-x.

[20] J.C. States, S. Srivastava, Y. Chen, A. Barchowsky, Arsenic and cardiovascular disease, Toxicol. Sci. 107 (2) (2009) 312–323, https://doi.org/10.1093/toxsci/kfn236.

[21] Y. Chen, F. Wu, M. Liu, F. Parvez, V. Slavkovich, M. Eunus, A. Ahmed, M. Argos, T. Islam, M. Rakibuz-Zaman, R. Hasan, G. Sarwar, D. Levy, J. Graziano, H. Ahsan, A prospective study of arsenic exposure, arsenic methylation capacity, and risk of cardiovascular disease in Bangladesh, Environ. Health Perspect. 121 (7) (2013) 832–838, https://doi.org/10.1289/ehp.1205797.

[22] E.J. Buenz, Lead exposure through eating wild game, Am. J. Med. 129 (5) (2016) 457–458, https://doi.org/10.1016/j.amjmed.2015.12.022.

[23] K. Ertl, R. Kitzer, W. Goessler, Elemental composition of game meat from Austria, Food Addit. Contam. Part B Surveill. 9 (2) (2016) 120–126, https://doi.org/10.1080/19393210.2016.1151464.

[24] N.D. Vaziri, M. Khan, Interplay of reactive oxygen species and nitric oxide in the pathogenesis of experimental lead-induced hypertension, Clin. Exp. Pharmacol. Physiol. 34 (9) (2007) 920–925, https://doi.org/10.1111/j.1440-1681.2007.04644.x.

[25] G. Genchi, M.S. Sinicropi, A. Carocci, G. Lauria, A. Catalano, Mercury exposure and heart diseases, Int. J. Environ. Res. Public Health 14 (1) (2017) 74, https://doi.org/10.3390/ijerph14010074.

[26] X. Guo, N. Li, H. Wang, W. Su, Q. Song, Q. Liang, M. Liang, C. Sun, Y. Li, et al., Combined exposure to multiple metals on cardiovascular disease in NHANES under five statistical models, Environ. Res. 215 (Pt 3) (2022) 114435, https://doi.org/10.1016/j.envres.2022.114435.

[27] A.H. Smith, E.O. Lingas, M. Rahman, Contamination of drinking-water by arsenic in Bangladesh: a public health emergency, Bull. World Health Organ. 78 (9) (2000) 1093–1103 (PMID: 11019458).

[28] F.J. Zhao, S.P. McGrath, A.A. Meharg, Arsenic as a food chain contaminant: mechanisms of plant uptake and metabolism and mitigation strategies, Annu. Rev. Plant Biol. 61 (2010) 535–559, https://doi.org/10.1146/annurev-arplant-042809-112152.

[29] Y.J. Zavala, J.M. Duxbury, Arsenic in rice: I. Estimating normal levels of total arsenic in rice grain, Environ. Sci. Technol. 42 (10) (2008) 3856–3860, https://doi.org/10.1021/es702747y.

[30] M.F. Naujokas, B. Anderson, H. Ahsan, H.V. Aposhian, J.H. Graziano, C. Thompson, W.A. Suk, The broad scope of health effects from chronic arsenic exposure: update on a worldwide public health problem, Environ. Health Perspect. 121 (3) (2013) 295–302, https://doi.org/10.1289/ehp.1205875.

[31] A.E. Nigra, T.R. Sanchez, K.E. Nachman, D. Harvey, S.N. Chillrud, J.H. Graziano, A. Navas-Acien, The effect of the environmental protection agency maximum contaminant level on arsenic exposure in the USA from 2003 to 2014: an analysis of the national health and nutrition examination survey (NHANES), Lancet Public Health 11 (2017) e513–e521, https://doi.org/10.1016/S2468-2667 [17]30195-0.

[32] A. Kumar, P. Adak, P.L. Gurian, J.R. Lockwood, Arsenic exposure in US public and domestic drinking water supplies: a comparative risk assessment, J. Expo. Sci. Environ. Epidemiol. 20 (3) (2010) 245–254, https://doi.org/10.1038/jes.2009.24.

[33] K.A. Moon, E. Guallar, J.G. Umans, R.B. Devereux, L.G. Best, K.A. Francesconi, W. Goessler, J. Pollak, E.K. Silbergeld, B.V. Howard, A. Navas-Acien, Association between exposure to low to moderate arsenic levels and incident cardiovascular disease: a prospective cohort study, Ann. Intern. Med. 159 (10) (2013) 649–659, https://doi.org/10.7326/0003-4819-159-10-201311190-00719.

[34] C.C. Kuo, P. Balakrishnan, M.O. Gribble, L.G. Best, W. Goessler, J.G. Umans, A. Navas-Acien, The association of arsenic exposure and arsenic metabolism with all-cause, cardiovascular and cancer mortality in the strong heart study, Environ. Int. 159 (2022) 107029, https://doi.org/10.1016/j.envint.2021.107029.

[35] P. Dang, M. Tang, H. Fan, J. Hao, Chronic lead exposure and burden of cardiovascular disease during 1990-2019: a systematic analysis of the global burden of disease study, Front. Cardiovasc. Med. 9 (11) (2024) 1367681, https://doi.org/10.3389/fcvm.2024.1367681.

[36] J. Zhao, H. Yang, Burden of cardiovascular disease attributable to lead exposure in China: a comprehensive analysis of data from 1990 to 2019, Am. J. Transl. Res. 16 (9) (2024) 4959–4966, https://doi.org/10.62347/CJBO5822.

[37] J. He, W. Zhang, F. Zhao, et al., Investigation of the relationship between lead exposure in heavy metals mixtures and the prevalence of stroke: a cross-sectional study, BMC Public Health 24 (2024) 3474, https://doi.org/10.1186/s12889-024-21000-y.

[38] M.A. Mostafa, M.A. Abueissa, M.Z. Soliman, M.I. Ahmad, E.Z. Soliman, Association between blood lead levels and silent myocardial infarction in the general population, J. Clin. Med. 13 (6) (2024) 1582, https://doi.org/10.3390/jcm13061582.

[39] J.T. Salonen, K. Seppänen, K. Nyyssönen, H. Korpela, J. Kauhanen, M. Kantola, J. Tuomilehto, H. Esterbauer, F. Tatzber, R. Salonen, Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and any death in eastern finnish men, Circulation 91 (3) (1995) 645–655, https://doi.org/10.1161/01.CIR.91.3.645.

[40] J.K. Virtanen, S. Voutilainen, T.H. Rissanen, J. Mursu, T.P. Tuomainen, M. J. Korhonen, V.P. Valkonen, K. Seppänen, J.A. Laukkanen, J.T. Salonen, Mercury, fish oils, and risk of acute coronary events and cardiovascular disease, coronary heart disease, and all-cause mortality in men in eastern Finland, Arterioscler. Thromb. Vasc. Biol. 25 (1) (2005) 228–233, https://doi.org/10.1161/01.ATV.0000150040.20950.61.

[41] G. Genchi, M.S. Sinicropi, G. Lauria, A. Carocci, A. Catalano, The effects of cadmium toxicity, Int. J. Environ. Res. Public Health 17 (11) (2020) 3782, https://doi.org/10.3390/ijerph17113782.

[42] L. Järup, M. Berglund, C.G. Elinder, G. Nordberg, M. Vahter, Health effects of cadmium exposure–a review of the literature and a risk estimate, Scand. J. Work Environ. Health 24 (1) (1998) 1–51.

[43] M. Peana, A. Pelucelli, C.T. Chasapis, S.P. Perlepes, V. Bekiari, S. Medici, M. A. Zoroddu, Biological effects of human exposure to environmental cadmium, Biomolecules 13 (1) (2023) 36, https://doi.org/10.3390/biom13010036.
[44] J.L. Peters, T.S. Perlstein, M.J. Perry, E. McNeely, J. Weuve, Cadmium exposure in association with history of stroke and heart failure, Environ. Res. 110 (2) (2010) 199–206, https://doi.org/10.1016/j.envres.2009.12.004.
[45] G. Kuna, S. Gullipalli, V. Chintada, Health risks associated with cadmium toxicity, in: A.K. Jha (Ed.), Cadmium Toxicity in Water: Challenges and Solutions, Springer Nature Switzerland, Cham, 2024, pp. 47–60.
[46] B. Fagerberg, L. Barregard, Review of cadmium exposure and smoking-independent effects on atherosclerotic cardiovascular disease in the general population, J. Intern. Med. 290 (6) (2021) 1153–1179, https://doi.org/10.1111/joim.13350.
[47] B. Fagerberg, L. Barregard, G. Sallsten, N. Forsgard, G. Ostling, M. Persson, Y. Borné, G. Engström, B. Hedblad, Cadmium exposure and atherosclerotic carotid plaques–results from the Malmö diet and Cancer study, Environ. Res. 136 (2015) 67–74, https://doi.org/10.1016/j.envres.2014.11.004.
[48] W.T. Cefalu, F.B. Hu, Role of chromium in human health and in diabetes, Diabetes Care 27 (11) (2004) 2741–2751, https://doi.org/10.2337/diacare.27.11.2741.
[49] R.A. Anderson, Chromium in the prevention and control of diabetes, Diabetes Metab. 26 (1) (2000) 22–27.
[50] J.B. Vincent, The biochemistry of chromium, J. Nutr. 130 (4) (2000) 715–718, https://doi.org/10.1093/jn/130.4.715.
[51] V. Singh, N. Singh, M. Verma, R. Kamal, R. Tiwari, M. Sanjay Chivate, V. Mishra, Hexavalent-chromium-induced oxidative stress and the protective role of antioxidants against cellular toxicity, Antioxidants 11 (12) (2022) 2375.
[52] F. Carbone, F. Montecucco, S. Xu, M. Banach, T. Jamialahmadi, A. Sahebkar, Epigenetics in atherosclerosis: key features and therapeutic implications, Expert Opin. Ther. Targets 24 (8) (2020) 719–721, https://doi.org/10.1080/14728222.2020.1764535.
[53] N. Ercal, H. Gurer-Orhan, N. Aykin-Burns, Toxic metals and oxidative stress part i: mechanisms involved in metal-induced oxidative damage, Curr. Top. Med. Chem. 1 (6) (2001) 529–539, https://doi.org/10.2174/1568026013394831.
[54] K. Jomova, M. Valko, Advances in metal-induced oxidative stress and human disease, Toxicology 283 (2011) 65–87, https://doi.org/10.1016/j.tox.2011.03.001.
[55] M. Shahid, B. Pourrut, C. Dumat, M. Nadeem, M. Aslam, E. Pinelli, Heavy-metal-induced reactive oxygen species: Phytotoxicity and physicochemical changes in plants, Rev. Environ. Contam. Toxicol. 232 (2014) 1–44, https://doi.org/10.1007/978-3-319-06746-9.
[56] M.J. Smith, F. Yang, A. Griffiths, A. Morrell, S.J. Chapple, R.C.M. Siow, T. Stewart, W. Maret, G.E. Mann, Redox and metal profiles in human coronary endothelial and smooth muscle cells under hyperoxia, physiological normoxia and hypoxia: effects of NRF2 signaling on intracellular zinc, Redox Biol. 62 (2023) 102712, https://doi.org/10.1016/j.redox.2023.102712.
[57] M. Wagner, C.L. Klein, H. Kleinert, C. Euchenhofer, U. Förstermann, C. J. Kirkpatrick, Heavy metal ion induction of adhesion molecules and cytokines in human endothelial cells: the role of NF-kappaB, i kappaB-alpha and AP-1, Pathobiology 65 (5) (1997) 241–252, https://doi.org/10.1159/000164135.
[58] X. Zhang, G. Wang, M. Li, Y. Li, X. Luo, Y. Liu, X. Zhang, J.G. Hocher, B.K. Krämer, B. Hocher, X. Yang, Both partial inactivation as well as activation of NF-κB signaling lead to hypertension and chronic kidney disease, Nephrol. Dial. Transplant. 39 (12) (2024) 1993–2004, https://doi.org/10.1093/ndt/gfae090.
[59] B. Messner, A. Türkcan, C. Ploner, G. Laufer, D. Bernhard, Cadmium overkill: autophagy, apoptosis and necrosis signalling in endothelial cells exposed to cadmium, Cell. Mol. Life Sci. 73 (8) (2016) 1699–1713, https://doi.org/10.1007/s00018-015-2094-9.
[60] H. Deng, S. Zhu, H. Yang, H. Cui, H. Guo, J. Deng, et al., The dysregulation of inflammatory pathways triggered by copper exposure, Biol. Trace Elem. Res. 201 (2) (2023) 539–548, https://doi.org/10.1007/s12011-022-03171-0.
[61] E.M. Alissa, G.A. Ferns, Heavy metal poisoning and cardiovascular disease, J Toxicol. 2011 (2011) 870125, https://doi.org/10.1155/2011/870125.
[62] K. Park, D. Mozaffarian, Omega-3 fatty acids, mercury, and selenium in fish and the risk of cardiovascular diseases, Curr. Atheroscler. Rep. 12 (6) (2010) 414–422, https://doi.org/10.1007/s11883-010-0138-z.
[63] P. Ricketts, M. Voutchkov, H.M. Chan, Risk-benefit assessment for total mercury, arsenic, selenium, and omega-3 fatty acids exposure from fish consumption in Jamaica, Biol. Trace Elem. Res. 197 (1) (2020) 262–270, https://doi.org/10.1007/s12011-019-01965-3.
[64] M.B. Wolf, J.W. Baynes, Cadmium and mercury cause an oxidative stress-induced endothelial dysfunction, Biometals 20 (1) (2007) 73–81, https://doi.org/10.1007/s10534-006-9016-0.
[65] Omanwar S, Fahim M. Mercury exposure and endothelial dysfunction: an interplay between nitric oxide and oxidative stress. Int. J. Toxicol. 2015;34 [4]:300–7. doi: https://doi.org/10.1177/1091581815589766.
[66] A.E. Nigra, A. Ruiz-Hernandez, J. Redon, A. Navas-Acien, M. Tellez-Plaza, Environmental metals and cardiovascular disease in adults: a systematic review beyond lead and cadmium, Curr Environ Health Rep. 3 (4) (2016) 416–433, https://doi.org/10.1007/s40572-016-0117-9.
[67] A.M. Yang, K. Lo, T.Z. Zheng, J.L. Yang, Y.N. Bai, Y.Q. Feng, N. Cheng, S.M. Liu, Environmental heavy metals and cardiovascular diseases: status and future direction, Chronic Dis. Transl. Med. 6 (4) (2020) 251–259, https://doi.org/10.1016/j.cdtm.2020.02.005.
[68] R.P. Brandes, Endothelial dysfunction and hypertension, Hypertension 64 (5) (2014) 924–928, https://doi.org/10.1161/HYPERTENSIONAHA.114.03575.
[69] N.V. Solenkova, J.D. Newman, J.S. Berger, G. Thurston, J.S. Hochman, G.A. Lamas, Metal pollutants and cardiovascular disease: mechanisms and consequences of exposure, Am. Heart J. 168 (6) (2014) 812–822, https://doi.org/10.1016/j.ahj.2014.07.007.
[70] V. Kumar, S. H, L.K.D. Huligowda, M. Umesh, P. Chakraborty, B. Thazeem, A. P. Singh, Environmental pollutants as emerging concerns for cardiac diseases: a review on their impacts on cardiac health, Biomedicines 13 (1) (2025) 241, https://doi.org/10.3390/biomedicines13010241.
[71] Z.Y. Liu, Z.Y. Liu, L.C. Lin, K. Song, B. Tu, Y. Zhang, J.J. Yang, J.Y. Zhao, H. Tao, Redox homeostasis in cardiac fibrosis: focus on metal ion metabolism, Redox Biol. 71 (2024) 103109, https://doi.org/10.1016/j.redox.2024.103109.
[72] W. Lieberman-Cribbin, A. Domingo-Relloso, A. Navas-Acien, S. Cole, K. Haack, J. Umans, M. Tellez-Plaza, E. Colicino, A.A. Baccarelli, X. Gao, A. Kupsco, Epigenetic biomarkers of lead exposure and cardiovascular disease: prospective evidence in the strong heart study, J. Am. Heart Assoc. 11 (23) (2022) e026934, https://doi.org/10.1161/JAHA.122.026934.
[73] H. Wang, Y. Liu, S. Yan, C. Li, J. Tang, H. Hu, M. Wu, C. Tu, Heavy metals, epigenetic aging, and mortality: a cohort study, Ecotoxicol. Environ. Saf. 8 (303) (2025) 118826, https://doi.org/10.1016/j.ecoenv.2025.118826.
[74] P. Long, Q. Wang, Y. Zhang, X. Zhu, K. Yu, H. Jiang, X. Liu, M. Zhou, Y. Yuan, K. Liu, J. Jiang, X. Zhang, M. He, H. Guo, W. Chen, J. Yuan, L. Cheng, L. Liang, T. Wu, Profile of copper-associated DNA methylation and its association with incident acute coronary syndrome, Clin. Epigenetics 13 (1) (2021) 19, https://doi.org/10.1186/s13148-021-01004-w.
[75] Y. Wu, R. Wang, R. Liu, Y. Ba, H. Huang, The roles of histone modifications in metal-induced neurological disorders, Biol. Trace Elem. Res. 201 (1) (2023) 31–40, https://doi.org/10.1007/s12011-022-03134-5.
[76] W. Perng, M. Tamayo-Ortiz, L. Tang, B.N. Sánchez, A. Cantoral, J.D. Meeker, D. C. Dolinoy, E.F. Roberts, E.A. Martinez-Mier, H. Lamadrid-Figueroa, P.X.K. Song, A.S. Ettinger, R. Wright, M. Arora, L. Schnaas, D.J. Watkins, J.M. Goodrich, R. C. Garcia, M. Solano-Gonzalez, L.F. Bautista-Arredondo, A. Mercado-Garcia, H. Hu, M. Hernandez-Avila, M.M. Tellez-Rojo, K.E. Peterson, Early life exposure in mexico to ENvironmental toxicants (ELEMENT) project, BMJ Open 9 (8) (2019) e030427, https://doi.org/10.1136/bmjopen-2019-030427.
[77] T. Münzel, M. Sørensen, O. Hahad, M. Nieuwenhuijsen, A. Daiber, The contribution of the exposome to the burden of cardiovascular disease, Nat. Rev. Cardiol. 20 (10) (2023) 651–669, https://doi.org/10.1038/s41569-023-00873-3.
[78] I. Motairek, J. Wilder, F. Laden, B. Coull, J. Schwartz, I. Kloog, et al., The exposome and cardiovascular health, Can. J. Cardiol. 39 (11) (2023) 1573–1589, https://doi.org/10.1016/j.cjca.2023.05.020.
[79] S.J. Sturla, A.R. Boobis, R.E. FitzGerald, J. Hoeng, R.J. Kavlock, K. Schirmer, et al., Systems toxicology: from basic research to risk assessment, Chem. Res. Toxicol. 27 (3) (2014) 314–329, https://doi.org/10.1021/tx400410s.
[80] R. Barouki, K. Audouze, X. Coumoul, F. Demenais, D. Gauguier, et al., From the exposome to mechanistic understanding of chemical-induced disease: the role of systems toxicology and adverse outcome pathways, Toxicol. Sci. 186 (1) (2022) 5–15, https://doi.org/10.1093/toxsci/kfab149.
[81] P. Leon-Mimila, J. Wang, A. Huertas-Vazquez, Relevance of multi-omics studies in cardiovascular diseases, Front. Cardiovasc. Med. 6 (2019) 91, https://doi.org/10.3389/fcvm.2019.00091.
[82] F. Liu, Y. Gao, Y. Zhao, P. Wang, J. Wang, D. Liu, et al., Serum cardiovascular-related metabolites disturbance induced by heavy metal exposure, J. Hazard. Mater. 405 (2021) 124179, https://doi.org/10.1016/j.jhazmat.2020.124179.
[83] G. Yim, J. Khoury, G.R. Urquhart, A.R. Zota, Y. Oulhote, Exposure to metal mixtures in association with cardiovascular outcomes and risk factors in adults: a scoping review, Environ. Health 21 (1) (2022) 28, https://doi.org/10.1186/s12940-022-00848-z.
[84] B. Ibrahimou, Y. Jie, V. Cueto, J. Baek, W. Li, Y.V. Sun, Assessing the risk of heart attack: a bayesian kernel machine regression of multiple heavy metals in NHANES, J. Expo. Sci. Environ. Epidemiol. 34 (6) (2024) 1032–1042, https://doi.org/10.1038/s41370-024-00684-z.
[85] B. Mansouri, F. Zaheri, M.L. Najafi, M. Hadian, P.K. Hopke, Mixture effects of trace element levels on cardiovascular diseases and cancer: a systematic review, Biol. Trace Elem. Res. 202 (10) (2024) 4917–4940, https://doi.org/10.1007/s12011-024-04159-3.
[86] G.A. Lamas, A. Navas-Acien, D.B. Mark, K.L. Lee, Contaminant metals as cardiovascular risk factors, J. Am. Coll. Cardiol. 82 (3) (2023) 238–251, https://doi.org/10.1016/j.jacc.2023.05.040.
[87] H. Koyama, K. Uemura, T. Matsubara, Heavy metal exposure: molecular pathways, clinical consequences, and toxicological advances, Int. J. Mol. Sci. 25 (3) (2024) 1234, https://doi.org/10.3390/ijms25031234.
[88] M. Balali-Mood, K. Naseri, Z. Tahergorabi, M.R. Khazdair, M. Sadeghi, Toxic mechanisms of five heavy metals: mercury, lead, chromium, cadmium, and arsenic, Front. Pharmacol. 12 (2021) 643972, https://doi.org/10.3389/fphar.2021.643972.
[89] J. Huang, L. Tinker, C.B. Eaton, et al., Overview of the cardiovascular effects of environmental metals, Curr. Atheroscler. Rep. 24 (10) (2022) 847–858, https://doi.org/10.1007/s11883-022-01052-y.
[90] M. Batty, M.R. Bennett, E. Yu, et al., The role of oxidative stress in atherosclerosis, Cells 11 (23) (2022) 3843, https://doi.org/10.3390/cells11233843.
[91] M.G. Scioli, G. Storti, F. D'Amico, R. Rodriguez Guzman, F. Centofanti, E. Doldo, et al., Oxidative stress and new pathogenetic mechanisms in endothelial dysfunction: potential diagnostic biomarkers and therapeutic targets, J. Clin. Med. 9 (6) (2020) 1995, https://doi.org/10.3390/jcm9061995.

[92] Z. Pan, T. Gong, P. Liang, Heavy metal exposure and cardiovascular disease, Circ. Res. 134 (9) (2024) 1160–1178, https://doi.org/10.1161/CIRCRESAHA.123.323617.
[93] G.A. Lamas, A. Bhatnagar, M.R. Jones, K.K. Mann, K. Nasir, M. Tellez-Plaza, F. Ujueta, A. Navas-Acien, American Heart Association Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing, Council on Lifestyle and Cardiometabolic Health, Council on Peripheral Vascular Disease, Council on the Kidney in Cardiovascular Disease, Contaminant metals as cardiovascular risk factors: a scientific statement from the American Heart Association, J. Am. Heart Assoc. 12 (13) (2023) E029852, https://doi.org/10.1161/JAHA.123.029852.
[94] M. Frisch, B.S. Schwartz, The pitfalls of hair analysis for toxicants in clinical practice: three case reports, Environ. Health Perspect. 110 (4) (2002) 433–436, https://doi.org/10.1289/ehp.02110433.
[95] G.A. Lamas, C. Goertz, R. Boineau, D.B. Mark, T. Rozema, R.L. Nahin, L. Lindblad, E.F. Lewis, J. Drisko, K.L. Lee, et al., Effect of disodium EDTA chelation regimen on cardiovascular events in patients with previous myocardial infarction: the TACT randomized trial, JAMA 309 (12) (2013) 1241–1250, https://doi.org/10.1001/jama.2013.2107.
[96] E. Escolar, G.A. Lamas, D.B. Mark, R. Boineau, C. Goertz, Y. Rosenberg, R.L. Nahin, P. Ouyang, M. Jones, M. Levin, et al., The effect of an EDTA-based chelation regimen on patients with diabetes mellitus and prior myocardial infarction in the trial to assess chelation therapy (TACT), Circ. Cardiovasc. Qual. Outcomes 7 (2014) 15–24, https://doi.org/10.1161/CIRCOUTCOMES.113.000663.
[97] G.A. Lamas, K.J. Anstrom, A. Navas-Acien, R. Boineau, H. Nemeth, Z. Huang, J. Wen, Y. Rosenberg, M. Stylianou, T.L.Z. Jones, et al., Edetate disodium-based chelation for patients with a previous myocardial infarction and diabetes: TACT2 randomized clinical trial, JAMA 332 (10) (2024) 794–803, https://doi.org/10.1001/jama.2024.11463.
[98] J. Zuo, K. Huesker, X. Chen, Y. Liu, J.G. Hocher, C. Reichetzeder, S. Elitok, B. K. Krämer, V. von Baehr, B. Hocher, Association of arsenic, lead, and mercury with liver function markers in german outpatients, Food Chem. Toxicol. 207 (2026) 115837, https://doi.org/10.1016/j.fct.2025.115837.
[99] J. Zuo, K. Huesker, Y. Liu, J.G. Hocher, X. Zhang, V. von Baehr, B.K. Krämer, B. Hocher, Association of whole blood heavy metal concentrations with kidney function, Sci. Rep. 15 (11) (2025) 8370, https://doi.org/10.1038/s41598-025-93548-7.