THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Dirty Earth, Diseased Hearts: Soil, Water, and Plastic Pollution in the Cardiovascular Exposome

ABSTRACT

Healthy soils and clean water are essential for human survival, yet, both are increasingly compromised by chemical and plastic pollution. This preventable crisis causes an estimated 9 million premature deaths each year, including about 0.9 million linked to soil pollution and 1.3 million to water pollution. In 2019 alone, pollution contributed to 5.5 million cardiovascular deaths, underscoring its role in the global burden of non-communicable disease. A key under-recognized driver is the rapid rise in plastic production and plastic-associated chemicals. Global plastic output has increased more than 250-fold since 1950 and is projected to nearly triple by 2060, while less than 10% is effectively recycled. As highlighted by the Lancet Countdown on health and plastics, plastics threaten human health across their lifecycle, from fossil fuel extraction to waste, fragmentation, and environmental persistence. Soils and water systems are increasingly contaminated by heavy metals, pesticides, persistent synthetic chemicals, and micro- and nanoplastics. These pollutants degrade soil, reduce agricultural productivity, contaminate food chains, and spread through aquatic ecosystems, thereby amplifying disease risk. Micro- and nanoplastics have been detected in human blood, placenta, brain, and cardiovascular tissues, raising concern about biological effects. These exposures are drivers of cardiovascular disease. Despite their chemical diversity, they converge on shared mechanisms, including oxidative stress, inflammation, endocrine disruption, and circadian dysregulation. Their persistence reflects policy failure. Reducing soil, water, and plastic pollution must become a central pillar of cardiovascular prevention through enforceable, lifecycle-based policies that protect human health.

Keywords: Cardiovascular disease, endothelium, environment, oxidative stress, plastic pollution, soil pollution, water pollution

INTRODUCTION

Healthy soils and clean water are fundamental to human health and planetary stability. Soil, often overlooked in medicine, underpins food production, ecosystem integrity, water regulation, and carbon storage, thereby mitigating climate change. Yet, soil degradation already threatens the health and livelihoods of 3.2 billion people worldwide;[1] while more than 2 billion people live under conditions of water stress, a number projected to rise with climate change and population growth.[2]

Pollution of soil, water, and air is a major and escalating global health threat.[3] The Lancet Commission on Pollution and Health identified pollution as responsible for approximately 9 million premature deaths in 2019, 16% of all global deaths, and 268 million disability-adjusted life-years (DALYs).[4,5] Air pollution remains the leading contributor, causing up to 8.3 million deaths annually,[6,7] whereas water pollution disproportionately affects infant mortality.[4] Soil pollution contributes substantially to disease burden across the life course. [4,8]

An emerging and insufficiently addressed dimension is plastic pollution. As highlighted by the Lancet Countdown on health and plastics, plastic production has increased more than 250-fold since 1950, with profound health risks across its lifecycle, from fossil fuel extraction to waste accumulation. Micro- and nanoplastics, now detected in human tissues,[9] represent a new class of pervasive environmental contaminants.

INVITED REVIEW

Thomas Münzel[1]
Marin Kuntic[1,#]
Jos Lelieveld[2]
Michael Aschner[3]
Mark J. Nieuwenhuijsen[4]
Omar Hahad[1]
Andreas Daiber[1,#]
Philip J. Landrigan[5]

[1]*Department of Cardiology at the Johannes Gutenberg University, University Medical Center Mainz, Mainz, Germany*
[2]*Atmospheric Chemistry Department, Max Planck Institute for Chemistry, Mainz, Germany*
[3]*Molecular Pharmacology, Albert Einstein College of Medicine, New York, United States*
[4]*Center for Research in Environmental Epidemiology (CREAL), Barcelona, Spain*
[5]*Global Observatory on Planetary Health, Boston College, USA and Centre Scientifique de Monaco, Massachusetts, United States*

Corresponding author:
Thomas Münzel
✉ tmuenzel@uni-mainz.de

Received: April 24, 2026
Accepted: April 28, 2026
Available Online Date: June 15, 2026

Cite this article as: Münzel T, Kuntic M, Lelieveld J, *et al*. Dirty earth, diseased hearts: soil, water, and plastic pollution in the cardiovascular exposome. *Anatol J Cardiol.* 2026;30(7):411-434.

[#]These authors contributed equally and should be considered as joint first and joint last authors.

DOI: 10.14744/AnatolJCardiol.2026.6593

Notably, ~70% of pollution-related diseases are non-communicable, with cardiovascular diseases accounting for more than 60% of this burden.[10] Despite this, environmental drivers are largely neglected in global non-communicable disease (NCD) strategies. Across diverse exposures, shared mechanisms, including oxidative stress, inflammation, neuroendocrine activation, and circadian disruption—link pollution to cardiometabolic and neuropsychiatric disease.[5,11-15]

Soil and water pollution, though less visible than air pollution, involves complex mixtures of heavy metals, pesticides, synthetic chemicals, pathogens, and plastic waste originating from industry, agriculture, fossil fuels, and urbanization. More than 90% of pollution-related disease and deaths occur in low- and middle-income countries [16] (Figure 1).

This review examines the links between soil and water pollution and human health, with a focus on cardiovascular disease.

Soil and Water: The Living Foundations of Health and Survival

Healthy soil and water are foundational to human health, food security, and ecosystem stability. Soil underpins nearly 95% of global food production and provides about 78% of per capita caloric intake directly from crops, with an additional 20% derived from land-based systems dependent on soil. Beyond food, soil supplies essential nutrients, filters water, and supports biodiversity critical for nutrient cycling, carbon storage, and disease regulation. It is also the second-largest active carbon sink after the oceans and provides materials for infrastructure, fuel, and fiber. However, soil health is increasingly threatened by pollution, including heavy metals, pesticides, and macro- and microplastics, as well as by deforestation and overfertilization.

Oceans, covering more than 70% of Earth's surface and containing 97% of its water, are equally vital. They regulate climate by absorbing 90% of excess heat and about one-third of carbon dioxide emissions,[17] produce atmospheric oxygen through marine microorganisms,[18,19] and sustain global economies and food systems.[20] They are essential for human well-being, particularly in coastal and low-income regions.[21-23]

Despite their importance, oceans are increasingly threatened by climate change, acidification, biodiversity loss, and pollution.[20,24-27] Rising water demand, urbanization, and industrialization further degrade freshwater systems, with an estimated 80% of wastewater globally released untreated, disproportionately affecting low-income countries and posing major risks to human health and ecosystems.

HIGHLIGHTS

- Chemical and plastic pollution causes an estimated 9 million deaths per year,
- Global plastic output is projected to tiple by 2060 based on the actual levels.

CHEMICAL CONTAMINATION OF SOIL AND WATER: SHARED MOLECULAR PATHWAYS DRIVING CARDIOVASCULAR DISEASE

Chemical Contamination as a Systemic Health Hazard

Contamination of soil and water is a major but often underestimated determinant of human health. According to a WHO assessment, exposure to selected chemicals caused an estimated 2 million deaths and 53 million DALYs in 2019, exceeding the previous estimate of 1.6 million deaths and 45 million DALYs in 2016.[28] The substances involved include heavy metals, organic solvents, polycyclic aromatic hydrocarbons (PAHs), benzene, pesticides, and highly persistent "forever chemicals" such as perfluorinated and polyfluorinated alkyl substances (PFAS).[28] Although these chemicals are classically linked to cancer and respiratory disease, they also contribute importantly to cardiovascular morbidity and mortality.[28] This threat is not theoretical: biomonitoring studies have detected hundreds of such compounds, sometimes at concerning concentrations, in the general European population [29]and in the United States.[30]

Shared Molecular Pathways of Toxicity

Despite their diverse chemical structures, many pollutants act through a limited number of shared pathophysiological pathways, most prominently oxidative stress, inflammation, metabolic dysregulation, endothelial dysfunction, and circadian disruption (Figure 2).

Pesticides and Endocrine-Disrupting Chemicals

Pesticides activate the aryl hydrocarbon receptor, leading to the release of thromboinflammatory mediators such as interleukin-1β, plasminogen activator inhibitor-2, and transforming growth factor-α (Figure 2). More broadly, pesticides and other endocrine-disrupting chemicals promote chronic low-grade inflammation.[31] hydrocarbon receptor activation also induces xenobiotic-metabolizing enzymes, including cytochrome P450 1A1 and 1B1 and glutathione S-transferase A1. In parallel, altered glucose metabolism activates muscarinic receptor signaling and the citric acid cycle, increasing diacylglycerol generation and thereby activating protein kinase C and the phagocytic NADPH oxidase NOX2, with subsequent reactive oxygen species (ROS) formation.[32]

Pesticides additionally impair potassium homeostasis and ATP-sensitive potassium channel activity, leading to mitochondrial dysfunction, mitochondrial ROS formation, and altered calcium signaling. They may react with protein thiol groups, causing electrophile adduct formation and sulfoxidation that disrupt multiple enzymatic pathways. Disturbed insulin signaling, including altered expression of insulin receptor substrate 2, glucose transporter 2, and glucokinase, links pesticide exposure to metabolic disease. Some pesticides also form DNA adducts, cause strand breaks, induce mutagenic base modifications, and promote adverse epigenetic changes. Halogenated solvents may exert toxicity partly through disruption of cardiac ion channels.[33]

Metals and Metalloids

Cadmium, lead, and mercury alter antioxidant gene expression, including superoxide dismutase and catalase, and

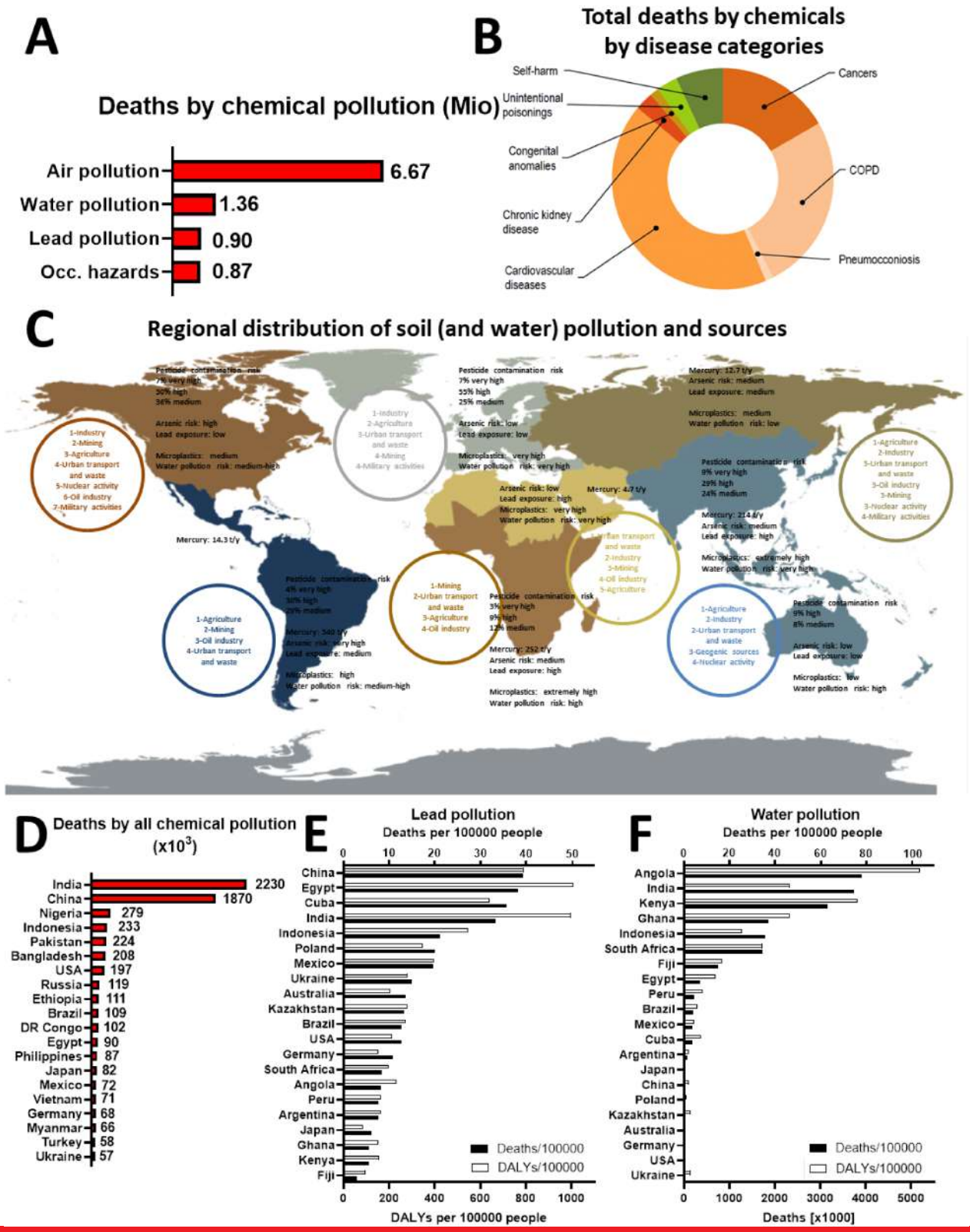

Figure 1. Estimated global annual deaths by all sources of chemical pollution (A)[3,4] and the disease entities being associated with these deaths (B).[28] (C) Regional distribution of chemical soil (and water pollution) with the major sources like industry, mining, and agriculture.[16] The chemical pollution levels and risk scores were summarized from different chemical pollution exposure maps (the sources can be provided by the authors at request). (D) Deaths by all chemical pollution—ranking by top 20 countries.[16] Population-related rates of death and disability-adjusted life-years for lead pollution as a typical soil pollutant (E) and for water pollution (unsafe water source including chemical hazards) (F), listed for 20 representative countries of different WHO regions.[198] With permission from[3,28] (CC BY-NC-ND, CC BY-NC-SA). Graph[8] modified with permission.

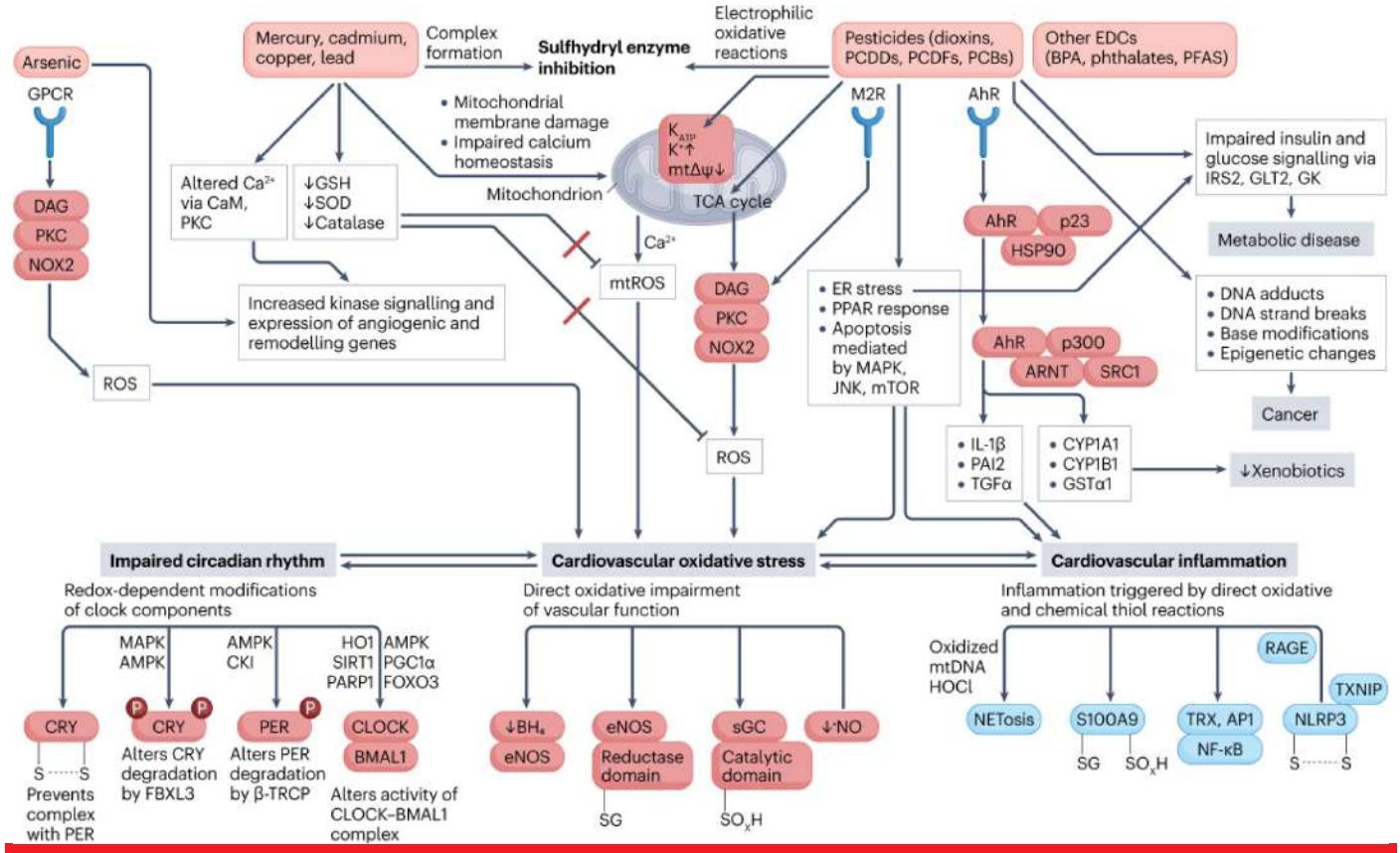

Figure 2. Cellular pathophysiology of metals/metalloids and pesticides. Details and explanation of abbreviations in the text. Pathomechanisms summarized[38] for arsenic, for lead,[35] for cadmium,[34] and[32] for pesticides. Oxidative mechanisms of endothelial/vascular dysfunction summarized.[40] Activating redox mechanisms for inflammation summarized.[41] Other pathomechanisms summarized[13] for heavy metals and[31] for pesticides or other endocrine-disrupting chemicals. PCDDs, polychlorinated dibenzodioxins; PCDFs, polychlorinated dibenzofurans; PCBs, polychlorinated biphenyls; -SG, S-glutathionylation; -SO_xH, sulfoxidation; -S-S-, disulfide bridge. Graph[8] modified with permission.

reduce intracellular glutathione levels, thereby weakening cellular antioxidant defenses and promoting oxidative stress through redox cycling, Fenton-like chemistry, and lipid peroxidation.[34,35] These mechanisms provide a plausible link to ferroptosis-associated cardiovascular injury.[36] Heavy metals also bind thiol groups in proteins and enzymes, thereby impairing enzymatic function.

For methylmercury, one of the earliest toxic processes is the reaction with endogenous thiol and selenol groups, producing stable complexes that impair protein function.[37] Lead also damages membranes, including mitochondrial membranes, and perturbs calcium homeostasis, thereby further increasing mitochondrial ROS formation. Arsenic, although technically a metalloid, behaves similarly to heavy metals and can activate G-protein-coupled receptors, leading to NOX2 activation and downstream oxidative injury.[38] Cadmium has also been shown to activate phosphoinositide 3-kinases/protein kinase B (PI3K/Akt) signaling, a pathway implicated in cardiotoxicity and remodeling.[39]

From Oxidative Stress to Vascular Injury

A central consequence of pollutant-induced ROS generation is vascular dysfunction. Oxidative depletion of tetrahydrobiopterin and S-glutathionylation of endothelial nitric oxide synthase (eNOS) can render the enzyme inactive or uncoupled, thereby reducing nitric oxide bioavailability and worsening endothelial dysfunction.[40] Protein kinase C (PKC)-dependent inhibition of eNOS phosphorylation may further contribute to its inactivity. In parallel, sulfoxidation of soluble guanylyl cyclase impairs vasodilatory signaling, while direct reaction of nitric oxide with superoxide forms peroxynitrite, a strong oxidant that amplifies oxidative damage in addition to depleting nitric oxide.

ROS also activate inflammatory signaling cascades.[41] Examples include neutrophil extracellular trap formation through hypochlorous acid generation and oxidation of mitochondrial DNA, a potent damage-associated molecular pattern. Thiol oxidation can activate nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) via thioredoxin oxidation or activator protein 1 (AP-1) activation. The NLR family pyrin domain containing 3 (NLRP3) inflammasome may be triggered by thiol oxidation, disulfide bridge formation, or activation of thioredoxin-interacting protein. Signaling through receptor for advanced glycation end products is likewise redox-sensitive. Toxic metals, metalloids, and

pesticides can therefore directly engage redox-sensitive inflammatory machinery.

Taken together, oxidative stress and inflammation represent the major mechanistic bridge between pollutant exposure and cardiovascular injury, as emphasized by previous reviews [5,13,31] and by meta-analytic evidence linking pesticide exposure to oxidative stress biomarkers.[42] Additional pathways include metallothionein-1 induction,[43] interleukin 6 (IL-6) release through mitogen-activated protein kinase 3/1 (ERK1/2) activation,[44] suppression of antioxidant enzymes, and uncoupling of mitochondrial respiration.[5] Methylmercury further promotes thrombosis and inflammatory activation.[45] Importantly, heavy metals and organic pollutants also disrupt circadian regulation; cadmium chronotoxicity is a notable example.[46,47] Antioxidant cotreatment can partly attenuate these effects, again underscoring the role of oxidative stress.[48] Copper, even at low concentrations, can also induce ROS generation and lipid peroxidation and may promote endothelial dysfunction through interaction with homocysteine.[49-51]

CHEMICAL POLLUTANTS AND THEIR DISEASE BURDEN

Broad Health Effects Beyond the Cardiovascular System

Chemical contaminants in soil and water can be broadly divided into inorganic pollutants, such as metals and metalloids, and organic pollutants, such as persistent industrial chemicals and pesticides. Both groups have major implications for human health.

Arsenic, cadmium, lead, and mercury are associated with cardiovascular disease, neurodevelopmental injury, and cancer.[4,52-54] Organic contaminants such as polychlorinated biphenyls (PCBs), PAHs, and volatile organic compounds are linked to cancer, reproductive toxicity, and neurological disease.[55-58] Dioxins remain a concern because of their persistence and toxicity.[59,60] PCBs, although banned in many settings, continue to persist in the environment and are linked to endocrine disruption and cancer.[61,62] PFAS are highly persistent and contribute to endocrine and neurodevelopmental effects.[63] Pesticides bioaccumulate and are increasingly associated with chronic diseases, including cancer and asthma.[64]

Metals as Cardiovascular Toxicants

Exposure to toxic metals such as arsenic, lead, cadmium, mercury, and copper has become a major public-health issue.[65-67] Arsenic and cadmium are classified as group I human carcinogens. Chronic exposure to these substances is linked not only to cancers of the bladder, kidney, liver, lung, and skin, but increasingly also to cardiovascular disease. Methylmercury is a potent neurotoxicant,[68] yet it also appears relevant to vascular disease. Arsenic and coexisting metals can independently increase cardiovascular risk.[49] The key point is that even low to moderate exposure levels, common in many populations, are increasingly associated with adverse cardiovascular outcomes.

Pesticides and Endocrine-Disrupting Chemicals

Organophosphate insecticides such as malathion, chlorpyrifos, diazinon, and parathion are designed to inhibit acetylcholinesterase and primarily target the nervous system. Yet, their adverse effects extend beyond neurotoxicity. Persistent organochlorines such as dichlorodiphenyltrichloroethane (DDT), chlorinated industrial chemicals such as PCBs, dioxins, PFAS, and related compounds remain important due to persistence, bioaccumulation, and endocrine disruption. The Stockholm Convention banned many persistent organic pollutants,[69] but legacy contamination remains widespread.

Dioxins are particularly toxic and have been associated with insulin resistance and type 2 diabetes.[70-72] Dioxin-like PCBs are linked to hypertension, hypertriglyceridemia, glucose intolerance, obesity, and diabetes.[5] Polybrominated diphenyl ethers can alter thyroid function and are associated with metabolic syndrome and diabetes.[73] PFAS act as endocrine disruptors and are increasingly implicated in obesity, dyslipidemia, and diabetes,[74-76] with occupational studies also suggesting increased mortality from diabetes and cerebrovascular disease.[77] Bisphenol A (BPA) and phthalates also disrupt endocrine function and may promote cardiovascular disease through adverse effects on lipids, obesity, and diabetes.[74,75]

CARDIOVASCULAR DISEASE AS A SENTINAL OUTCOME OF CHEMICAL EXPOSURE HIDDEN CARDIOTOXINS IN THE MODERN CHEMICAL ERA

A major concern is that known hazards likely represent only the tip of the iceberg. More than 300,000 synthetic chemicals have been introduced over the past decades, and many remain inadequately tested for cardiovascular toxicity.[78,79] These substances are present in consumer products, food chains, indoor environments, and ecosystems, resulting in widespread exposure.[80,81] Weak regulation and incomplete toxicity testing mean that many cardiotoxic effects may only become apparent through epidemiological observation. Figure 3 summarizes major cardiovascular complications linked to chemical exposure.

Epidemiological Evidence: Metals

Evidence linking metals to cardiovascular disease is extensive (Table 1). Historical observations described excess hypertension and stroke among lead-exposed workers.[67,82] Later studies confirmed that even low blood lead concentrations are associated with hypertension.[83,84] Cohort studies subsequently showed higher all-cause and cardiovascular mortality with elevated blood lead levels [85,86](Figure 4). In patients with type 2 diabetes, both blood lead and cadmium were associated with increased all-cause and cardiovascular mortality.[87] Blood selenium and cadmium were also associated with heart failure and mortality, indicating that mixtures of metals may modify risk.[88]

Cadmium exposure has been associated with coronary artery disease, peripheral arterial disease, atherosclerosis, stroke, and cardiovascular mortality.[67,89] Even low urinary cadmium concentrations have been linked to increased cardiovascular risk. Studies examining multiple metals together found associations with both all-cause and cardiovascular mortality.[90] Particularly striking is the estimate that lead exposure may

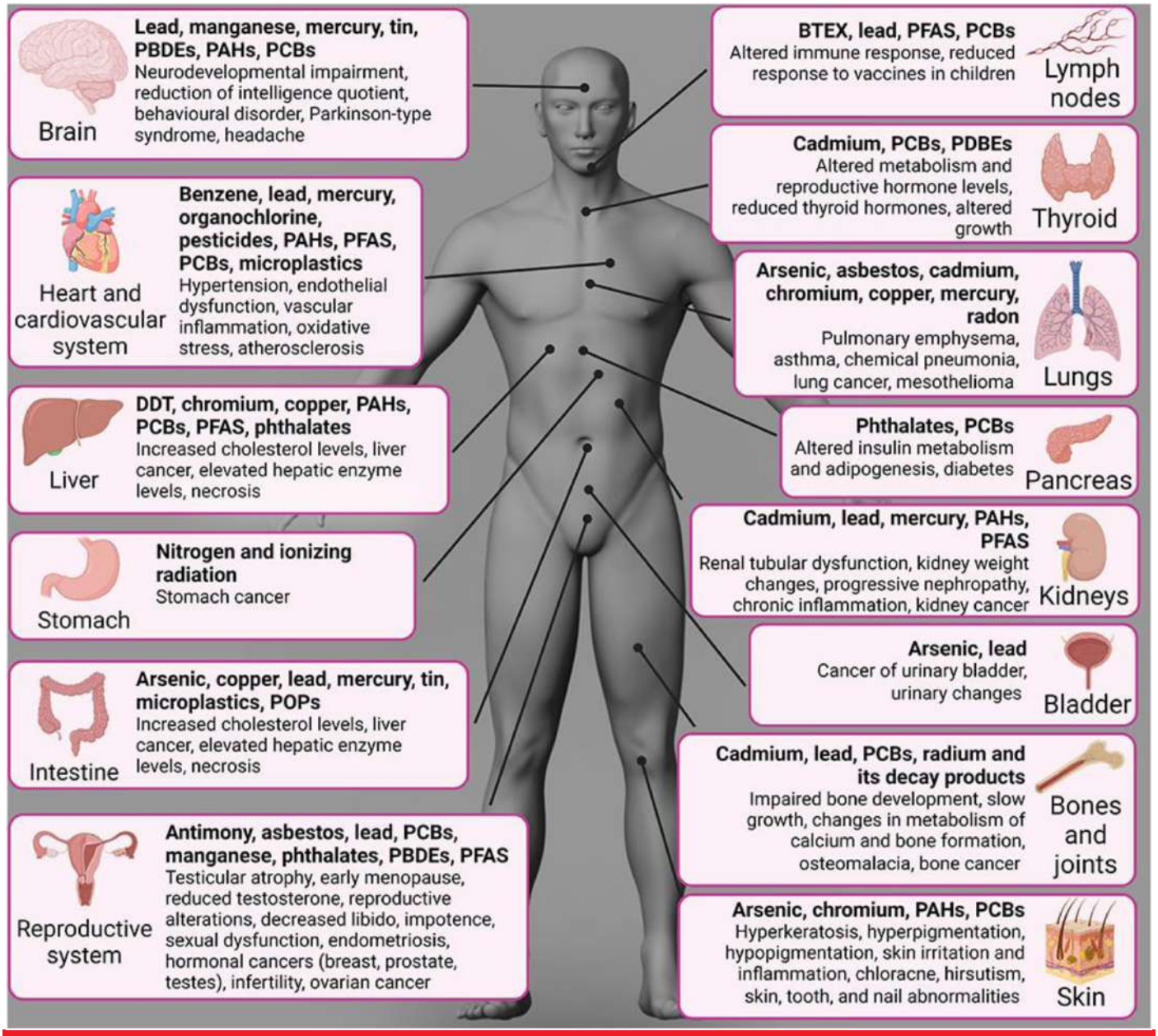

Figure 3. Main effects of soil contaminants on human health, indicating the organs or systems affected and the contaminants causing them. BTEX, refers to the chemicals benzene, toluene, ethylbenzene, and xylene; PBDEs, polybrominated diphenyl ethers; PCBs, polychlorinated biphenyls; PFAS, per- and polyfluoroalkyl substances; POPs, persistent organic pollutants. Adapted from the report of the Food and Agriculture Organization of the United Nations (created from data in the Agency for Toxic Substances and Disease Registry[199] and Campanale et al[200]), https://www.fao.org/3/cb4894en/online/src/html/chapter-04-3.html. Graph[8] modified with permission.

have been responsible for 5.5 million cardiovascular deaths worldwide in 2019.[91]

Mercury exposure has been linked to reduced heart rate variability, hypertension, carotid thickening, accelerated atherosclerosis, myocardial infarction, and cardiovascular mortality.[92] Cobalt toxicity has long been known from "beer drinkers cardiomyopathy" [93] and from occupational exposure in hard-metal industries.[94] Arsenic shows strong dose–response relationships with carotid atherosclerosis, hypertension, ischemic heart disease, diabetes, and peripheral vascular disease.[67,95-97] Copper has also been linked to cardiovascular disease.[98]

Epidemiological Evidence: Pesticides, Plastics, and Endocrine Disruptors

A growing number of epidemiological studies implicate BPA and related plastic chemicals in cardiovascular disease (Table 2). Higher urinary BPA has been associated with prevalent cardiovascular diagnoses,[99] and subsequent studies linked BPA, bisphenol F (BPF), and bisphenol S (BPS) with prevalent cardiovascular disease, hypertension, or

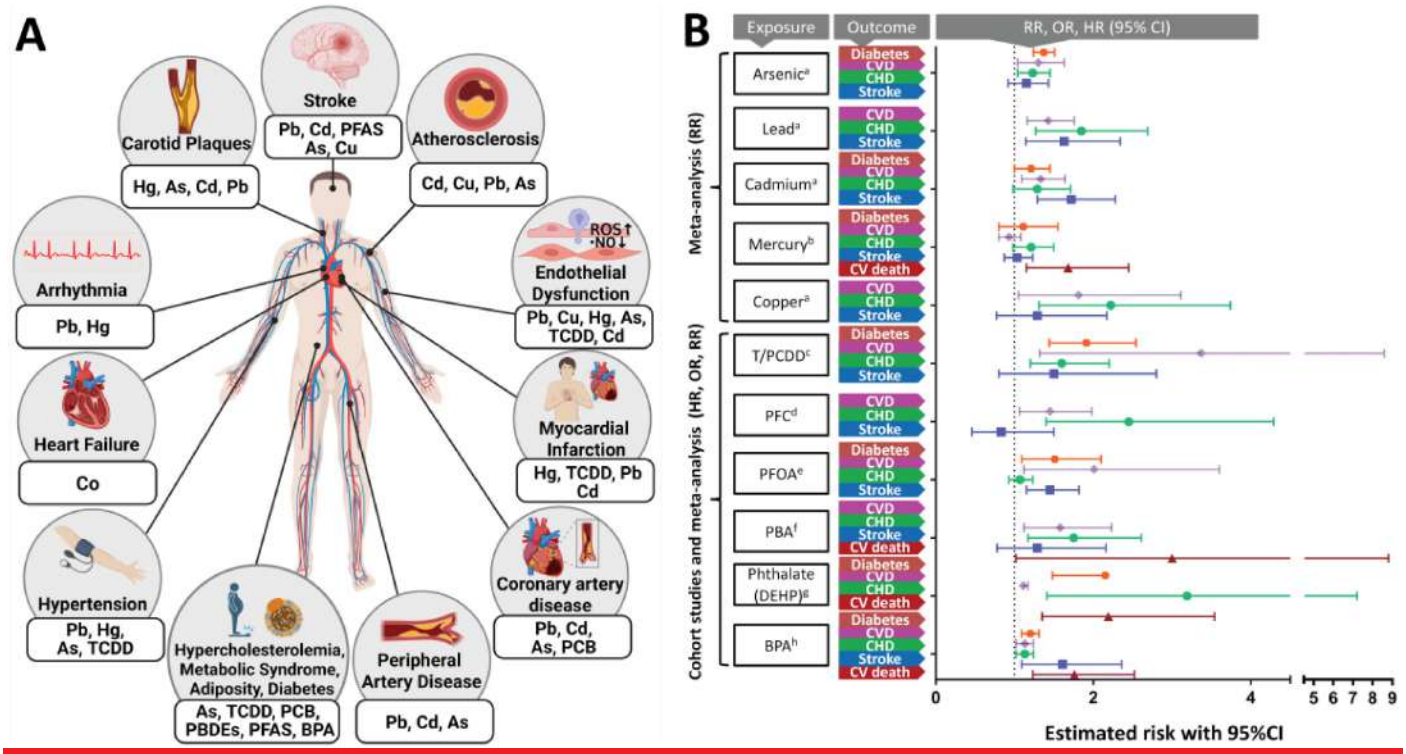

Figure 4. (A) Cardiovascular side effects of toxic chemicals. Graph[8] modified with permission using biorender.com. (B) Association of metals and pesticides with cardiovascular risk. Data taken from a meta-analysis for all metals[a] except mercury[b] (highest versus lowest tertile or highest versus lowest)[36,67] and from cohort studies for pesticides [c] (2nd highest versus lowest quartile, exposed versus unexposed),[201,202] [d] (highest versus lowest quartile),[203-205] [e] (highest versus lowest quartile or quintile),[193,206,207] [f] (highest versus lowest tertile).[208,209] T/PCDD, dioxins; PFC, per- and polyfluorinated chemicals; PFAS, per- and polyfluoroalkyl substances; PFOA, perfluorooctanoic acid; PBA, phenoxybenzoic acid; PCB, polychlorinated biphenyls; PBDE, polybrominated diphenyl ethers; BPA, bisphenol-A. Graph[210] modified with permission.

heart failure.[100-104] These findings suggest that replacement bisphenols may not be safer than BPA.

Additionally, PCBs, dioxins, and organophosphates were also associated with cardiac toxicity in epidemiological studies. Acute poisoning by organophosphates can cause profound cardiac toxicity, including bradycardia, ST-segment elevation, conduction abnormalities, QT prolongation, torsade de pointes, and ventricular arrhythmias.[105] High-level exposure to 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) has been associated with increased mortality from ischemic heart disease and other cardiovascular conditions.[106] Among PCBs, the most cardiotoxic appear to be dioxin-like congeners such as PCB-126.[72,106,107]

Summary Perspective

Chemical contamination of soil and water is not only an environmental problem but a major cardiovascular threat. Heavy metals, pesticides, persistent organic pollutants, and endocrine-disrupting chemicals act through shared mechanisms, especially oxidative stress, inflammation, endothelial dysfunction, and circadian disruption, to drive vascular injury and chronic disease. Although the evidence base is strongest for lead, cadmium, arsenic, mercury, BPA, PFAS, dioxins, and related compounds, many additional cardiotoxic chemicals likely remain unidentified. The burden is therefore likely underestimated, particularly in regions with weak regulation and high cumulative exposure.

MICRO- AND NANOPLASTICS AS EMERGING SOIL AND WATER CONTAMINANTS

A Rapidly Expanding Pollution Problem

Plastic production has increased dramatically over the past decades, from less than 2 million tons in 1950 to about 460 million tons today, with roughly half of all plastic ever produced manufactured since 2002. Without major policy change, production is projected to double by 2040 and triple by 2060, with especially steep growth expected in low- and middle-income countries.[108] At the same time, plastic leakage into the environment has risen sharply. Global plastic waste entering ecosystems is estimated at 44 million tons per year, while the accumulation of plastics in rivers, lakes, and oceans is expected to more than triple by 2060.[108] Most visible plastic waste initially appears as macroplastic debris, but this is only part of the problem. Environmental weathering, abrasion, oxidation, hydrolysis, and photodegradation progressively fragment larger plastic items into smaller particles that disperse widely through soil and water systems.

These particles are now classified according to size as plastic nanoparticles (≤100 nm), nanoplastics (100-1000 nm),

microplastics (1 μm to <1000 μm), mesoplastics, macroplastics, and megaplastics.[109] Of these, micro- and nanoplastics are of greatest toxicological concern because of their biological mobility, persistence, and capacity to interact with cells and tissues[110] (Figure 5). Their widespread presence in soils, inshore waters, rivers, and oceans has raised growing concern not only because of ecological damage but also because of their possible implications for human cardiovascular health. Plastic contamination of seafood and drinking water represents an important route of human exposure, especially for populations that depend heavily on marine food sources.[111] Recent work from the *Lancet Countdown on health and plastics* reinforces this concern by framing plastics as a life-cycle threat to human health, spanning fossil fuel extraction, polymer production, product use, waste generation, and environmental breakdown into micro- and nanoplastics. It also highlights that less than 10% of plastics are recycled and that plastic-related health losses now exceed US$1.5 trillion annually, underscoring the scale of the problem beyond purely environmental metrics.

Mechanisms of Micro- and Nanoplastic Toxicity

Micro- and nanoplastics are not inert particles. At high concentrations, they are directly cytotoxic and can induce cell death through necrosis or regulated pathways.[112] Surface-active agents and additives associated with these particles can disrupt plasma membranes and alter cell signaling. Small nanoparticles, in particular, are readily taken up by cells through endocytosis.[113,114] Once internalized, they may destabilize endosomal membranes, interfere with intracellular trafficking, and damage subcellular organelles such as mitochondria.[115,116] Their accumulation within endosomes and lysosomes can also impair macroautophagy, thereby disturbing cellular quality control mechanisms.[117] In some circumstances, micro- and nanoplastics may stimulate autophagic responses; in others, they may trigger autophagy-associated cell death.[118]

A recurring feature of particle toxicity is the induction of cellular stress. Experimental studies have shown activation of stress pathways such as adenosine monophosphate (AMP)-activated protein kinase in exposed organisms.[119,120] This response is closely linked to excess generation of reactive oxygen species,[121] derived either from damaged mitochondria or from activation of NADPH oxidases.[122] As with classical air pollutants and chemical toxicants, oxidative stress appears to be a central pathway by which micro- and nanoplastics impair vascular and metabolic homeostasis.

These particles also activate innate immune pathways. Damage-associated molecular patterns generated by cellular injury can stimulate Toll-like receptor signaling, resulting in sterile inflammation even in the absence of infection.[123,124] Local inflammatory responses can recruit immune cells, amplify cytokine release, and promote tissue damage. Evidence from aquatic species indicates that nanoparticles can activate innate immune defense systems,[125] and analogous processes are likely to occur in mammalian and human cells.

Plastic Particles as Carriers of Chemical Toxicity

An additional concern is that plastic particles are not only toxic in themselves but also function as carriers for a wide variety of hazardous chemicals. Approximately half of the weight of many manufactured plastics consists of additives, including phthalates, bisphenols, flame retardants, PFAS, PCBs, and heavy metals. These compounds are added to impart flexibility, durability, color, fire resistance, or water repellence, but many are carcinogenic, endocrine-disrupting, neurotoxic, or metabolically harmful. Because many additives are not covalently bound to the polymer matrix, they can leach from plastic particles into the surrounding environment or directly into biological tissues. Thus, micro- and nanoplastics act as mobile vectors for chemical exposure, potentially amplifying toxicity through combined particle and chemical effects.[126,127] This concern is emphasized in the *Lancet Countdown on health and plastics*, which describes plastics as complex chemical materials whose health effects extend far beyond visible debris and include systemic exposure to plastic-associated chemicals throughout the lifecycle.

Cardiovascular Effects of Micro- and Nanoplastics

Although human data remain limited, experimental evidence suggests that micro- and nanoplastics can adversely affect the cardiovascular system through several mechanisms. In vitro studies show that nanoplastics can induce premature endothelial senescence through upregulation of p53, p21, and p16, all key mediators of cell-cycle arrest and vascular aging.[128] Exposure of isolated pig coronary arteries to polystyrene nanoplastics caused endothelial dysfunction, downregulation of endothelial nitric oxide synthase, and increased oxidative stress, mediated in part through the NADPH oxidase/sirtuin (SIRT) pathway.[128] These findings strongly parallel the redox-dependent vascular injury observed with more established pollutants.

Animal studies support these observations. In mice, ingestion of polystyrene beads increased adiposity and promoted cardiometabolic disease.[129] In Wistar rats, microplastics triggered cardiomyocyte pyroptosis via oxidative stress and NLRP3/caspase-1 signaling and promoted cardiac fibrosis through activation of Wnt/β-catenin signaling and apoptosis.[130,131] Other studies have shown that polystyrene nanoplastics can cause vascular injury, structural endothelial damage, coagulation abnormalities, and prothrombotic changes mediated through Janus kinase 1/signal transducer and activator of transcription 3 (JAK1/STAT3)/tissue factor signaling.[132] Additional reported effects include altered heart rate, impaired cardiac function, hemolysis, pericardial effusion, myocardial fibrosis, and a prothrombotic phenotype.[109,133]

Taken together, these data suggest that micro- and nanoplastics can damage the cardiovascular system at multiple levels: by impairing endothelial function, promoting oxidative stress and inflammation, activating inflammasome signaling, accelerating vascular aging, and enhancing thrombosis. In mechanistic terms, they resemble a hybrid toxic exposure, part particle, part chemical mixture, part inflammatory trigger.

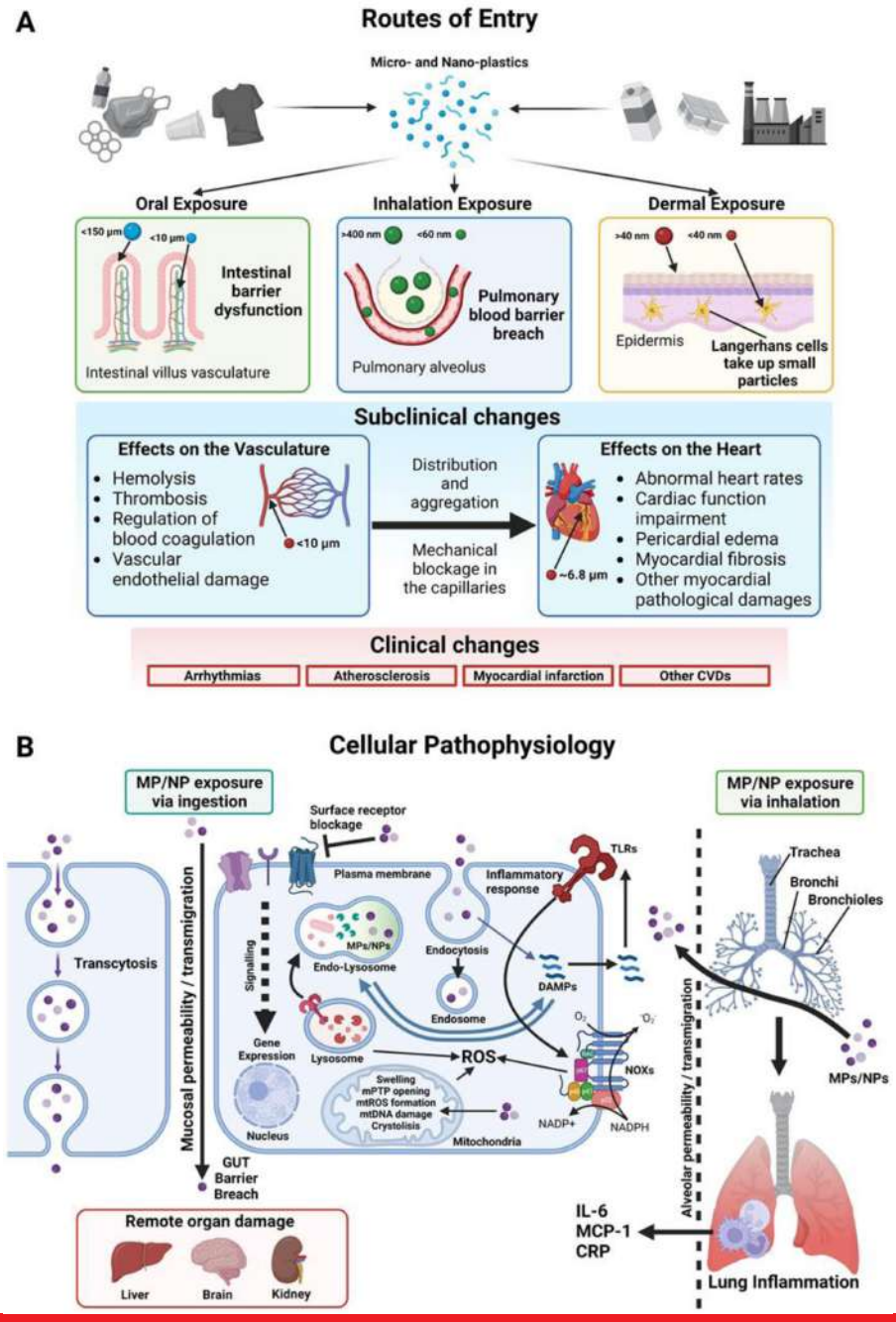

Figure 5. (A) The exposure routes, toxicological, subclinical, and clinical effects of MNPs on the cardiovascular system. Graph[8] modified with permission using biorender.com. (B) Scheme of pathomechanisms of micro- and nanoplastics (MP/NP) toxicity (combination of experimentally confirmed pathomechanisms of MP/NP as well as anticipated processes established for airborne ultrafine and fine particulate matter particles). MPs/NPs uptake is mainly based on ingestion and inhalation. MPs/NPs can, on one hand, increase mucosal and alveolar permeability, allowing transmigration of the particles (e.g. via gut barrier breach or transcytosis). On the other hand, severe lung inflammation caused by MP/NP interaction with phagocytic cells will cause the release of inflammatory cytokines such as IL-6, MCP-1, and CRP to the circulation. Once reaching the circulation and end organs, MPs/NPs can impair signaling via cell surface receptors and thereby cause changes in nuclear gene expression. Endocytosis of MPs/NPs will lead to the formation of endolysosomes, release of damage-associated molecular patterns (DAMPs), and thereby activation of Toll-like receptor (TLR)-mediated inflammatory signaling and oxidative stress. NPs can also directly penetrate into mitochondria and cause multiple functional damages via swelling, cristolysis, opening of the mitochondrial permeability transition pore (mPTP), mitochondrial DNA (mtDNA) damage, and mitochondrial reactive oxygen species formation. Oxidative stress may arise from the NADPH oxidases (NOXs) and damaged mitochondria. Redrawn and modified from Yong et al[112] with permission. © 2020 by the authors (Licensee MDPI, Basel, Switzerland). This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license. Graph[8] modified with permission using biorender.com.

Human Exposure and Translational Relevance

Direct evidence in humans is still emerging, but recent findings are troubling. Micro- and nanoplastics have now been detected in human blood,[134] supporting the view that these particles can cross biological barriers and enter the circulation. Human evidence has also advanced beyond exposure detection alone. A recent systematic review of in vivo human studies concluded that micro- and nanoplastics are detectable across multiple human organs and are already linked, albeit not yet definitively, to inflammation and functional impairment, while underscoring major methodological heterogeneity and the urgent need for standardized exposure assessment and prospective cohort studies.[135] Particularly relevant for cardiovascular medicine, Marfella and colleagues showed that the presence of micro- and nanoplastics in carotid atheromas was associated with a significantly increased risk of the composite endpoint of myocardial infarction, stroke, or death during follow-up, providing the first prospective human evidence linking plaque-associated plastic particles with adverse cardiovascular outcomes.[136] This clinical signal is reinforced by a paired-sample analysis showing that microplastics were detected in all blood and carotid plaque samples, with higher concentrations in plaques than in blood, and that several polymer types were associated with adverse lipid markers, providing further support for systemic exposure and vascular tissue accumulation.[137] The Lancet Countdown on health and plastics further documents that micro- and nanoplastics have been found in human breastmilk, liver, kidney, colon, placenta, lung, spleen, brain, heart, and great vessels, reinforcing the plausibility of direct cardiovascular effects and the need for a precautionary approach.[138] Broader recent reviews have also reinforced the view that exposure through ingestion and inhalation is widespread and that micro- and nanoplastics should increasingly be regarded as credible contributors to chronic disease risk, even though causal inference remains constrained by small study sizes, variable analytical methods, and the lack of large-scale longitudinal studies.[139,140]

ENVIRONMENTAL DRIVERS OF SOIL AND WATER DEGRADATION

Deforestation and Ecosystem Disruption

Deforestation, the large-scale removal of forests, is a major driver of environmental degradation with far-reaching implications for climate, biodiversity, and human health. It is primarily driven by agricultural expansion, logging, mining, and urbanization. Forests play a critical role in carbon sequestration, and their removal releases large amounts of stored carbon dioxide, thereby accelerating climate change. In addition, deforestation disrupts hydrological cycles, altering rainfall patterns and increasing the risk of both droughts and floods.

The ecological consequences are profound. Forest loss leads to biodiversity decline, threatening ecosystem services such as pollination, pest regulation, and soil fertility. These disruptions have direct implications for food security and agricultural productivity. Indigenous and local communities, particularly in regions such as the Amazon and Central Africa, are disproportionately affected, often facing displacement, loss of livelihoods, and erosion of cultural identity.

Although deforestation may yield short-term economic benefits through timber extraction and agricultural expansion, it undermines long-term ecosystem services, including water purification, soil stability, and climate regulation.[141] Increasingly, policy approaches emphasize sustainable forestry, land-use regulation, reforestation, and recognition of ecosystem services in economic decision-making.

Wildfires, particularly in South America, further amplify these effects. The Amazon region, which contains approximately 21% of the world's remaining forests, is increasingly affected by fires linked to deforestation and land degradation.[142] These fires not only release greenhouse gases but also reduce the capacity of forests to absorb them, creating a feedback loop that accelerates climate change.[143] Alarmingly, deforestation levels of 20%-25% may push the Amazon toward an irreversible tipping point, transforming it into a non-forest ecosystem and disrupting regional and global hydrological cycles.[143]

Deforestation also has direct health consequences. Biomass burning releases particulate matter and toxic gases, contributing to cardiovascular and respiratory disease. Moreover, increased human–wildlife contact raises the risk of zoonotic disease transmission, including Ebola and vector-borne diseases such as malaria and dengue.[144] Loss of forest resources further undermines nutrition, water access, and traditional medicine systems.

Airborne Dust and Soil-Derived Particles

Airborne soil particles represent an underappreciated pathway linking soil degradation to human health. Agricultural activities, construction, and unpaved surfaces release dust into the atmosphere, while natural sources, particularly desert regions, generate large quantities of wind-blown (aeolian) dust. The "dust belt" extending from North Africa through the Middle East to Central Asia is the largest global source,[145] contributing 30%-50% of atmospheric aerosol loading.[146]

Although often considered "natural," a substantial proportion of dust emissions is influenced by human activity, including land degradation and desertification. The relative contribution of anthropogenic sources varies geographically, ranging from ~8% in North Africa to ~75% in Australia.[147] Dust particles can be transported over long distances, affecting populations far from their origin (Figure 6).

Health impacts are significant. Assuming similar toxicity to urban particulate matter, desert dust contributes to approximately 1.8% of global cardiopulmonary mortality, rising to 15%-50% in regions close to major dust sources.[148] Climate change is expected to increase dust emissions, making it an increasingly important component of air pollution.[149]

Mechanistically, inhaled dust particles induce oxidative stress and inflammation in the respiratory system, damaging the air–blood barrier.[150] Smaller particles can enter the circulation, triggering systemic inflammatory responses

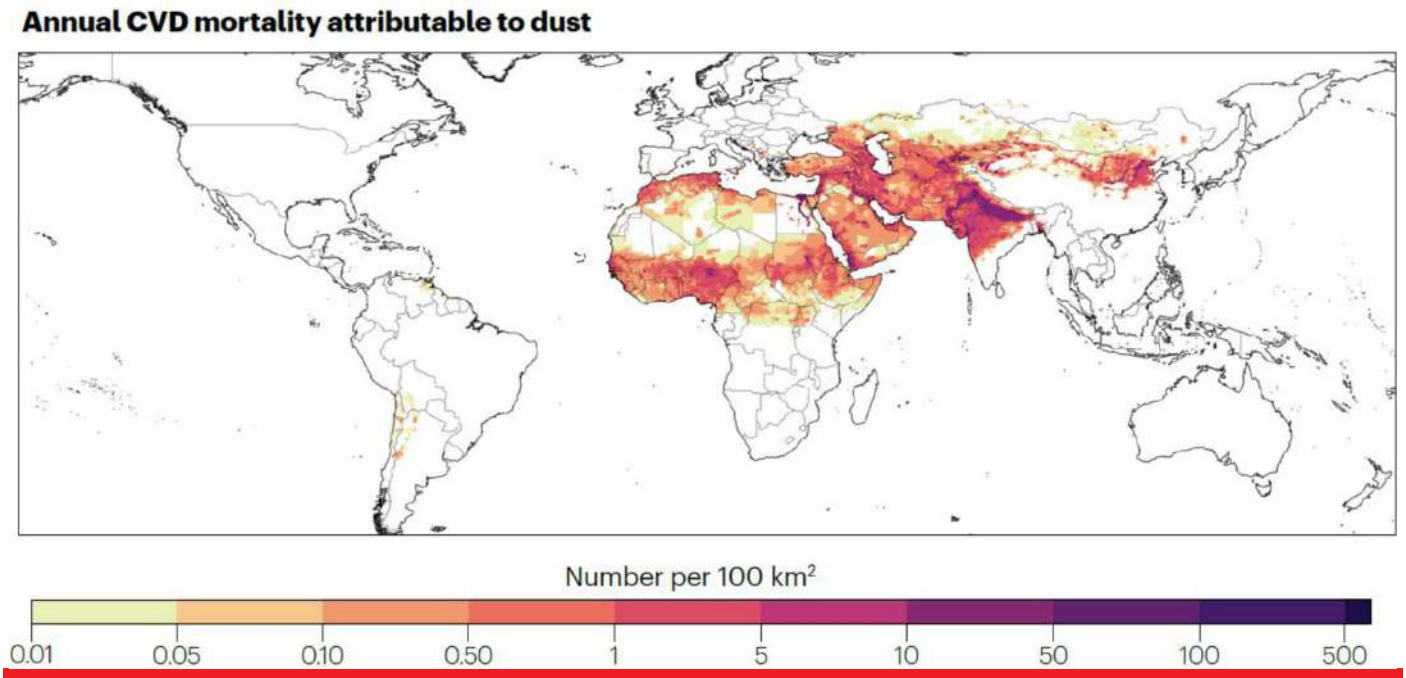

Figure 6. Annual cerebrovascular (stroke) plus ischemic heart disease mortality per area of 10 × 10 km² from exposure to aeolian dust (total CVD mortality). CVD, cardiovascular diseases. Graph[8] modified with permission.

and affecting cardiovascular and cerebrovascular systems.[151,152] Importantly, the toxicity of dust is enhanced by interaction with anthropogenic pollutants. During atmospheric transport, dust particles accumulate acids, metals, and secondary pollutants, increasing their oxidative potential.[153,154]

Epidemiological evidence supports these findings. Dust exposure has been associated with acute myocardial infarction,[155] and meta-analyses show increased cardiovascular mortality with rising dust concentrations.[152] A 10 μg/m³ increase in PM10 from desert dust is associated with a ~2% increase in cardiovascular mortality risk. However, most studies focus on short-term exposure, and long-term effects remain insufficiently understood.

Overfertilization and Nitrogen Cycle Disruption

Human activities have profoundly altered the global nitrogen cycle, primarily through synthetic fertilizer production (Haber–Bosch process), livestock farming, and fossil fuel combustion.[156,157] While reactive nitrogen is essential for plant growth, excessive inputs lead to widespread environmental and health impacts.

Overfertilization results in eutrophication of soils and water bodies, groundwater contamination with nitrates, and atmospheric release of ammonia (NH_3). Ammonia contributes to the formation of fine particulate matter (PM2.5) by reacting with sulfur and nitrogen oxides, particularly in regions with intensive agriculture. In Europe, East Asia, and parts of North America, agricultural ammonia emissions contribute substantially to PM2.5-related mortality, estimated at 20%-40%.[158,159] Given that nearly half of air pollution-related deaths are due to cardiovascular disease,[7] overfertilization indirectly contributes to CVD burden.

Excess nitrogen also leads to acidification, biodiversity loss, and emission of nitrous oxide (N_2O), a potent greenhouse gas that contributes to climate change and stratospheric ozone depletion.[160]

At the individual level, elevated nitrate and nitrite levels have been linked to cardiovascular mortality. Studies show that increased serum nitric oxides (NOx) concentrations are associated with a higher risk of cardiovascular death.[161,162] In a cohort study, elevated NOx levels were associated with nearly doubled cardiovascular mortality risk (HR 1.98, 95% CI=1.10-3.58).[163] These findings highlight the importance of nitrogen pollution as both an environmental and clinical concern.

Urban Design and Environmental Exposure

Urbanization is a defining feature of the modern exposome. Currently, 55% of the global population lives in cities, a proportion projected to reach 68% by 2050, with the majority residing in low- and middle-income countries.[164] While urban environments provide access to healthcare and infrastructure,[165] they also concentrate environmental exposures.

Unhealthy city design contributes to pollution through traffic emissions, industrial activity, and inadequate waste management.[13,166] High levels of nitrogen dioxide, sulfur dioxide, and particulate matter increase the risk of cardiovascular disease, cancer, and neurodegenerative conditions.[3,4]

The lack of green spaces exacerbates these risks. Vegetation improves air quality, reduces heat, and supports mental health, yet many urban areas remain heavily built-up with limited greenery.[167,168] Soil contamination from industrial activities introduces heavy metals and chemicals into urban environments, which can enter the food chain or groundwater.[169]

Urban heat islands, caused by heat absorption from buildings and asphalt—further increase cardiovascular risk, particularly during heatwaves.[168] Car-centric infrastructure reduces physical activity, contributing to obesity, diabetes, and CVD.[170]

Urban runoff carries pollutants, including microplastics and PFAS, into water systems.[5] In addition, noise, overcrowding, and lack of access to natural environments negatively affect mental health.[15]

Sustainable urban planning, emphasizing green spaces, active transport, public transit, and pollution control, is therefore a critical strategy for reducing environmental health risks.[171]

Climate Change as a Cross-Cutting Driver

Climate change acts as a multiplier of environmental risks, affecting soil, water, and air quality simultaneously. Soils are a major carbon reservoir, storing more carbon than the atmosphere,[172] but climate change is altering soil moisture, increasing erosion, and accelerating desertification.[173]

Rising temperatures and extreme weather events mobilize pollutants, increase water contamination, and promote the spread of pathogens. Floods can redistribute contaminants, while droughts concentrate pollutants in water sources.

Climate change also affects air quality. Higher temperatures promote the formation of ozone and secondary particulate matter, while drought conditions increase dust emissions and wildfire frequency.[174,175] Wildfires release large amounts of particulate matter and toxic metals, with significant cardiovascular impacts.

Heat itself is a major cardiovascular stressor. Non-optimal temperatures contribute to more than 7.6% of cardiovascular deaths in Europe.[176] Heat exposure increases heart rate, blood viscosity, and inflammatory responses, exacerbating existing cardiovascular and respiratory diseases.[177] Combined exposure to heat and air pollution further amplifies health risks.[178]

Urban populations are particularly vulnerable due to heat island effects, high pollution levels, and limited adaptive capacity.

Key Concept

Deforestation, airborne dust, overfertilization, urbanization, and climate change are interconnected drivers of soil and water degradation. Through shared pathways—including oxidative stress, inflammation, and ecosystem disruption—these environmental changes contribute substantially to cardiovascular disease and global health risk.

CURRENT GAPS AND FUTURE PRIORITIES

Despite growing recognition of environmental pollution as a major driver of cardiovascular disease, substantial knowledge gaps remain. Human exposure levels across different environmental compartments, soil and water, are still incompletely characterized, particularly for complex mixtures of pollutants. Dose–response relationships are often poorly defined, especially at low, chronic exposure levels that are most relevant for the general population. Moreover, while epidemiological evidence is robust for some exposures such as air pollution and toxic metals, it remains limited or heterogeneous for many other environmental contaminants and combined exposures.

A major limitation is that much of the current evidence base derives from experimental models, including cellular systems and animal studies, rather than large-scale human investigations. However, these studies consistently point toward a convergence of biological effects across diverse pollutants. Key mechanisms include oxidative stress, endothelial dysfunction, inflammation, metabolic dysregulation, pyroptosis, fibrosis, and prothrombotic signaling. The remarkable consistency of these pathways across different environmental stressors strongly supports their biological relevance and argues against considering any single pollutant in isolation.

Future research must move beyond single-exposure paradigms and address the complexity of real-world conditions. Priorities include:

- Quantification of environmentally realistic exposure levels across populations;
- Investigation of chronic low-dose and cumulative effects over the life course;
- Improved understanding of tissue distribution and bioaccumulation;
- Assessment of mixture effects and interactions between chemical and non-chemical stressors;
- Generation of long-term epidemiological data linking environmental exposures to cardiovascular outcomes;
- Development of advanced analytical tools for biomonitoring and exposome research.

Importantly, the absence of complete scientific certainty should not delay action. The history of environmental health repeatedly demonstrates that waiting for definitive causal proof at the population level can result in substantial and preventable disease burden. A precautionary approach is therefore warranted.

Key Concept

Environmental pollutants in soil and water, ranging from metals and pesticides to persistent synthetic chemicals and complex mixtures, act through shared biological pathways, including oxidative stress, inflammation, endothelial dysfunction, vascular aging, fibrosis, and thrombosis. These mechanisms provide a unifying framework linking environmental exposure to cardiovascular disease. Given their global prevalence, persistence, and capacity to interact within the human exposome, these pollutants represent a major, yet still under-recognized, modifiable cardiovascular risk factor.

INTERCONNECTED PATHWAYS: SOIL-WATER-AIR TRANASFER AND THE EXPOSOME

Environmental Compartments are Not Isolated

Soil, water, and air are tightly interconnected environmental compartments that continuously exchange pollutants. Contaminants released into soil rarely remain confined;

instead, they are mobilized through leaching, runoff, volatilization, and resuspension, thereby entering aquatic systems and the atmosphere. This dynamic exchange creates a complex and evolving mixture of exposures that shape the human exposome across the life course.

Agricultural practices represent a major pathway for such transfer. Pesticides, fertilizers, and industrial contaminants accumulate in soil and are transported into rivers, lakes, and groundwater through rainfall and irrigation. Similarly, contaminated sediments can release pollutants back into water systems under changing environmental conditions, prolonging exposure. Industrial emissions deposited onto soil surfaces can later be resuspended into the air as particulate matter, contributing to inhalational exposure.[3]

This continuous cycling of pollutants implies that exposure assessment based on a single environmental medium is inherently incomplete. Instead, individuals are exposed to mixtures of pollutants across multiple pathways: ingestion (food and water), inhalation (airborne particles), and dermal contact, often simultaneously and chronically.

The Exposome Framework: from Single Pollutants to Mixtures

The concept of the exposome provides a useful framework to understand these complex interactions. It captures the totality of environmental exposures across the lifespan, integrating chemical, physical, and biological stressors with social and behavioral determinants. Soil and water pollution are therefore not isolated phenomena but integral components of a broader environmental risk architecture that includes air pollution, noise, heat, and light exposure.

Importantly, co-exposure is the rule rather than the exception. Individuals living in urban or industrialized environments are often exposed simultaneously to heavy metals, endocrine-disrupting chemicals, microplastics, air pollutants, and non-chemical stressors. These combined exposures may interact in additive, synergistic, or even antagonistic ways, complicating risk assessment and potentially amplifying health effects.[5]

Recent epidemiological and experimental studies increasingly support the concept that mixtures of pollutants exert stronger biological effects than individual exposures. For example, combined exposure to metals and air pollution has been associated with enhanced oxidative stress and vascular dysfunction, suggesting convergence on shared mechanistic pathways.[179]

Shared Biological Pathways Across Environmental Stressors

A striking feature of environmental risk factors is the convergence of biological mechanisms across seemingly unrelated exposures. Whether triggered by chemical pollutants, particulate matter, noise, or psychosocial stress, a limited set of core pathways appears to mediate disease development.

Central among these are oxidative stress, inflammation, endothelial dysfunction, autonomic imbalance, and activation of the hypothalamic–pituitary–adrenal axis. Increased sympathetic activity and stress hormone release can further amplify vascular injury and metabolic dysregulation. These processes lead to impaired nitric oxide signaling, increased vascular tone, prothrombotic states, and structural vascular changes.

Circadian disruption represents another unifying mechanism. Environmental exposures, including heavy metals, endocrine disruptors, and artificial light, can interfere with circadian gene expression and biological rhythms, thereby affecting metabolism, blood pressure regulation, and inflammatory responses.[46,131] This may provide an additional link between environmental stressors and cardiometabolic disease.

The convergence of these pathways supports the concept of a "final common pathway" of environmental cardiotoxicity, in which diverse exposures ultimately lead to similar vascular and systemic outcomes.

Vulnerable Populations and Environmental Injustice

The burden of environmental exposure is not equally distributed. More than 90% of pollution-related disease and death occurs in low- and middle-income countries.[16] Rapid urbanization, weak regulatory frameworks, and limited infrastructure for waste management and pollution control contribute to disproportionately high exposure levels in these regions.

Within countries, vulnerable populations, including children, the elderly, and socioeconomically disadvantaged groups, are often more heavily exposed and more susceptible to adverse health effects. Occupational exposures further increase risk in specific groups, such as agricultural workers, miners, and industrial laborers.

Early-life exposure is of particular concern. Developmental windows represent periods of heightened vulnerability during which environmental insults can have long-lasting effects on organ systems, including the cardiovascular and nervous systems. Evidence suggests that prenatal and early childhood exposure to pollutants may predispose individuals to cardiovascular disease later in life.

Climate Change as an Amplifier of Pollution Exposure

Climate change interacts with soil and water pollution in multiple ways, often exacerbating exposure and health risks. Rising temperatures can increase the volatilization of chemicals and accelerate the degradation of plastics into micro- and nanoplastics. Extreme weather events, such as floods and droughts, can mobilize pollutants from contaminated soils into water systems or concentrate them in shrinking water supplies.

Drought conditions may increase reliance on contaminated groundwater, while flooding can disperse industrial and agricultural contaminants over wide areas. In addition, climate-driven changes in ecosystems can alter the distribution and bioaccumulation of pollutants in food chains.

Heat stress itself is a cardiovascular risk factor and may act synergistically with chemical exposures to increase disease risk. Thus, climate change does not represent a separate challenge but rather an amplifier of existing environmental health threats.

Implications for Risk Assessment and Prevention

The interconnected nature of environmental exposures has important implications for both research and policy. Traditional risk assessment approaches, which focus on single pollutants in isolation, are insufficient to capture the complexity of real-world exposures. There is a need for integrated approaches that consider mixtures, multiple exposure pathways, and cumulative risk over time.

From a prevention perspective, this implies that effective strategies must address the broader environmental system rather than individual pollutants alone. Reducing emissions, improving waste management, regulating chemical production, and redesigning urban environments are all necessary components of a comprehensive approach.

Importantly, environmental interventions often yield co-benefits. Measures that reduce pollution, such as transitioning to clean energy, promoting sustainable agriculture, and improving urban design, can simultaneously mitigate climate change, enhance biodiversity, and reduce cardiovascular risk.

Key Concept

Soil, water, and air pollution are interconnected components of a unified environmental exposome. Their combined effects, mediated through shared biological pathways such as oxidative stress and inflammation, drive cardiovascular and systemic disease. Addressing these risks requires integrated, multisectoral strategies that move beyond single-exposure paradigms.

POLICY PREVENTION, AND CLINICAL IMPLICATIONS

Environmental Pollution as a Preventable Cardiovascular Risk Factor

The evidence presented in this Review makes clear that soil, water, and plastic pollution are not only environmental concerns but major, modifiable drivers of cardiovascular disease. Despite this, environmental exposures remain largely absent from clinical guidelines and global prevention strategies for NCDs. Current frameworks continue to prioritize individual lifestyle factors while underestimating structural and environmental determinants of health.[10]

This imbalance represents a critical gap. Unlike many traditional risk factors, environmental exposures are largely involuntary and unequally distributed. As such, they require population-level interventions rather than individual behavioral change. Addressing pollution is therefore not only a matter of environmental protection but a central pillar of cardiovascular prevention.

Policy Failure and the Need for Systemic Change

The persistence of widespread chemical and plastic pollution reflects systemic policy failures. More than 300,000 synthetic chemicals are in global use, yet only a small fraction have been adequately tested for long-term toxicity, including cardiovascular effects.[78,126] Regulatory frameworks are often fragmented, slow to respond, and insufficiently precautionary.

In addition, the true health costs of pollution are largely externalized. Industrial production, fossil fuel use, and plastic manufacturing generate substantial economic benefits for producers while shifting health and environmental costs onto societies, particularly vulnerable populations. The *Lancet Countdown on health and plastics* highlights that plastics alone are associated with health-related economic losses exceeding US$1.5 trillion annually, underscoring the magnitude of these hidden costs. (Figure 7)

A paradigm shift is urgently needed, from reactive regulation to proactive, precautionary governance. This includes stricter chemical safety testing, transparency regarding chemical composition, and lifecycle-based regulation of pollutants from production to disposal.

Priority Actions for Policy and Public Health

Effective prevention of pollution-related cardiovascular disease requires coordinated, multisectoral action. Key priorities include:

- **Reducing emissions at the source** through stricter regulation of industrial chemicals, pesticides, and plastic production.
- **Transitioning to clean energy systems**, thereby simultaneously reducing air, soil, and water contamination.
- **Improving waste management and circular economy strategies**, particularly for plastics.
- **Protecting water resources** through improved monitoring, filtration, and infrastructure.
- **Strengthening international agreements**, including implementation of the European Union Zero Pollution Action Plan and the development of a legally binding Global Plastics Treaty (see the following).

These measures are not only technically feasible but also highly cost-effective when considering the substantial healthcare costs associated with pollution-related disease.

The Role of Clinicians and the Healthcare System

Healthcare professionals have a critical role in addressing environmental determinants of cardiovascular disease. Clinicians should recognize pollution as a major cardiovascular risk factor, comparable in importance to smoking, hypertension, and diabetes, and incorporate environmental exposure into risk assessment and patient counseling.

At the individual level, clinicians can:

- Educate patients about environmental risks and mitigation strategies
- Identify vulnerable populations, including those with high occupational or residential exposure.
- Advocate for preventive measures, such as improved indoor air quality and reduced exposure to contaminated food and water.

At the collective level, healthcare professionals and scientific societies should:

- Advocate for stronger environmental policies
- Integrate environmental risk factors into clinical guidelines
- Support research on environmental determinants of disease

Figure 7. Quantifiable economic losses due to soil pollution. Adapted.[172]

- Engage with policymakers to promote evidence-based regulation

Healthcare systems themselves must also reduce their environmental footprint, as they contribute significantly to greenhouse gas emissions and waste generation.

RESEARCH PRIORITIES AND RESEARCH GAPS

Despite growing evidence, important gaps remain. These include limited data on long-term, low-dose exposure, insufficient understanding of mixture effects, and a lack of large-scale epidemiological studies linking soil and water pollutants to cardiovascular outcomes.

Future Research Should Prioritize

- Improved exposure assessment using biomonitoring and exposome approaches
- Mechanistic studies linking environmental exposures to cardiovascular endpoints
- Longitudinal cohort studies assessing cumulative exposure and disease risk
- Interventional studies evaluating the impact of pollution reduction on cardiovascular outcomes

Bridging these gaps will be essential to strengthen causal inference and inform policy.

A Call to Action: From Evidence to Implementation

The science is now sufficiently robust to justify immediate action. Waiting for absolute certainty risks perpetuating preventable disease and death. The history of public health, from tobacco control to air pollution regulation, demonstrates that early intervention saves lives.

Environmental pollution represents a global cardiovascular risk factor of unprecedented scale. Addressing it requires coordinated action across sectors, disciplines, and political boundaries. Policies that reduce pollution will yield substantial co-benefits, including improved cardiovascular health, reduced healthcare costs, climate mitigation, and enhanced ecosystem resilience.

Policy Frameworks and Economic Burden of Pollution Control

The scale of soil and water pollution poses not only a major health threat but also a profound economic challenge. In the European Union alone, soil degradation is estimated to cost more than €50 billion annually.[180] Approximately 2.8 million potentially contaminated sites have been identified, many of them legacy "brownfield" areas with unclear ownership, suggesting that the true burden is likely underestimated.[181]

Table 1. Cardiovascular Diseases and Outcomes Associated with Metal Exposure in Epidemiological Studies

First Author, Year	Total Sample Size	Exposure	Outcome	Risk Estimate
Schober, 2006 [85]	n = 9,757	Blood lead	All-cause and CVD mortality	Using blood lead levels < 5 microg/dL as the referent, RR of mortality from all causes was 1.24 (95% CI 1.05-1.48) for those with blood levels of 5-9 microg/dL and 1.59 (95% CI, 1.28-1.98) for those with blood levels > or = 10 microg/dL. The magnitude of risk was similar for deaths due to cardiovascular disease.
Lanphear, 2018 [86]	n = 14,289	Blood lead	All-cause, CVD, ischemic heart disease mortality	An increase in the concentration of lead in blood from 1.0 μg/dL to 6.7 μg/dL was associated with all-cause mortality (HR 1.37, 95% CI 1.17-1.60), CVD mortality (1.70, 1.30-2.22), and ischemic heart disease mortality (2-08, 1.52-2.85).
Tsoi, 2021[185]	n = 39,477	Blood lead	Prevalent hypertension	Using quartile 1 as reference, higher blood lead levels were associated with increased odds of hypertension (Quartile 4 OR 1.22, 95% CI 1.09-1.36).
Cook, 2022[186]	n = 15,036	Blood lead	CVD and heart disease mortality	Participants with high lead level (vs. low level) had an increased risk of death from all CVD (HR 1.35, 95% CI 1.03-1.77). Moderate and high lead levels showed an increased risk of death from heart disease (1.37, 1.04-1.81 and 1.60, 1.21- 2.13, respectively). A linear association with all CVD and heart disease deaths was observed (1.08, 1.00- 1.16 and 1.09, 1.02-1.16, respectively, per 1-unit increase in lead levels).
Zhu, 2022 [87]	n = 7,420 for blood lead and n = 5,113 for blood cadmium	Blood lead and cadmium	All-cause and CVD mortality	The geometric mean (interquartile range) concentrations of blood lead and cadmium were 19.6 (11.8, 35.0) μg/L and 0.39 (0.21, 0.60) μg/L, respectively, among patients with type 2 diabetes. Comparing extreme quartiles, the HR of all-cause mortality were 1.51 (1.25-1.82) for blood lead and 1.58 (1.22-2.03) for blood cadmium. The HRs of CVD mortality were 2.27 (1.54-3.34) for blood lead and 1.78 (1.04-3.03) for blood cadmium.
Lee, 2011[187]	n = 1,908	Blood cadmium	Prevalent ischemic heart disease, stroke, and hypertension	An interquartile range (IQR) increase in blood cadmium was found to be associated with an increased risk for ischemic heart disease (OR 2.1, 95% CI 1.3-3.4), and hypertension only among men (OR 1.4, 95% CI 1.1-1.8). No association was observed with stroke.
Tellez-Plaza, 2013 [89]	n = 3,348	Urine cadmium	Incident CVD	HRs comparing the 80th to the 20th percentile of urine cadmium concentrations were 1.43 for cardiovascular mortality (95% CI 1.21-1.70) and 1.34 for CHD mortality (1.10-1.63). HRs for incident cardiovascular disease, coronary heart disease, stroke, and heart failure were 1.24 (1.11-1.38), 1.22 (1.08-1.38), 1.75 (1.17-2.59), and 1.39 (1.01-1.94), respectively.
Li, 2022 [188]	n = 39,865	Blood cadmium	All-cause and CVD mortality	Compared with the lowest quantile of cadmium exposure level group, the HRs in the highest quantile cadmium exposure level group were 1.73 (95% CI 1.52-1.97) for all-cause mortality and 1.72 (95% CI 1.28-2.30) for CVD mortality.
Tellez-Plaza, 2012 [189]	n = 8,989	Blood and urine cadmium	All-cause and CVD mortality	HRs for blood and urine cadmium were 1.50 (95% CI 1.07-2.10) and 1.52 (95% CI 1.00-2.29), respectively, for all-cause mortality, 1.69 (95% CI 1.03- 2.77) and 1.74 (95% CI 1.07- 2.83) for CVD mortality, 1.98 (95% CI 1.11- 3.54) and 2.53 (95% CI 1.54-4.16) for heart disease mortality, and 1.73 (95 CI 0.88-3.40) and 2.09 (95% CI 1.06-4.13) for CHD mortality.
Xing, 2023 [88]	n = 15,689	Blood selenium and cadmium	Prevalent heart failure and CVD and all-cause mortality	Low blood selenium (OR 0.952) and high blood cadmium (OR 1.345) were associated with heart failure. HRs for all-cause mortality was 0.76 (95% CI 0.65-0.88)for high selenium levels compared to low selenium levels. Taking the low cadmium levels as reference, HR for all-cause mortality among high cadmium levels was 1.68 (95% CI 1.44-1.96). Association between selenium, cadmium, and cardiovascular mortality was similar to that of all-cause mortality.

(*Continued*)

Table 1. Cardiovascular Diseases and Outcomes Associated with Metal Exposure in Epidemiological Studies (Continued)

First Author, Year	Total Sample Size	Exposure	Outcome	Risk Estimate
Nigra, 2021[190]	n = 4,990	Urinary total arsenic	Heart disease mortality	HR of heart disease mortality for an increase in urinary total arsenic was 1.20 (0.83-1.74).
Sun, 2021[191]	n = 17,294	Blood mercury	All-cause and CVD mortality	Mean (SD) blood mercury concentration was 1.62 (2.46) μg/L. Comparing the highest with the lowest quartile of blood mercury concentration, the HRs were 0.82 (0.66-1.05) for all-cause mortality and 0.90 (0.53-1.52) for CVD related mortality.
Isiozor, 2023[192]	n = 1,911	Serum copper	CVD mortality	Copper concentrations (mg/l) were categorized into quartiles (<1.0; 1 to <1.1; 1.1 to <1.21; ≥1.21). Using the first quartile as reference, the HR for CVD death in second, third and fourth quartiles were 1.45 (1.05-2.01), 1.69 (1.25-2.27), and 1.68(1.23-2.29), respectively.
Duan, 2020[90]	n = 26,056	Blood lead, cadmium, and mercury and urine barium, cadmium, cobalt, cesium, molybdenum, lead, antimony, titanium, tungsten, and uranium	All-cause and CVD mortality	The blood metal mixture was associated with all-cause mortality (RR 1.38, 95% CI 1.25-1.51) and CVD mortality (RR 1.43, 95% CI 1.06-1.94). The urinary metal mixture was associated with an increased risk of all-cause mortality (RR 1.48, 95% CI 1.30-1.68).

Globally, the financial gap for restoring and protecting ecosystems remains substantial. Achieving Sustainable Development Goal 14—focused on conserving oceans and marine resources—will require approximately US$174.5 billion annually, compared with current investments of only US$25.5 billion, leaving a funding gap of nearly US$149 billion per year.[182] This underscores the urgent need for increased investment in pollution prevention, particularly targeting plastic contamination at its source.

In response, the European Commission has introduced the Zero Pollution Action Plan as a core element of the European Green Deal.[183] Its 2050 vision aims to reduce pollution to levels no longer harmful to human health or ecosystems. Interim 2030 targets include reducing premature deaths from air pollution by 55%, cutting plastic waste at sea by 50% and environmental microplastics by 30%, halving pesticide use and nutrient losses, improving biodiversity by 25%, reducing noise exposure by 30%, and significantly lowering waste generation.[183]

A comparable regulatory framework exists in the United States through the Environmental Protection Agency (EPA), which implements major legislative instruments such as the Clean Air Act, Clean Water Act, Toxic Substances Control Act, Resource Conservation and Recovery Act, and Superfund program to regulate pollutants, manage hazardous waste, and remediate contaminated sites.[184]

Together, these frameworks highlight both progress and persistent gaps. Closing the implementation and funding deficits will be essential to reduce pollution exposure and achieve meaningful health gains.

CONCLUSIONS

Soil, water, and plastic pollution represent a largely invisible but profoundly important driver of global cardiovascular disease. This Review highlights that these environmental exposures are not isolated ecological concerns but central determinants of human health, contributing substantially to the global burden of NCD. The evidence is now compelling: pollutants originating from industrial, agricultural, and urban sources permeate ecosystems, enter the human body through multiple pathways, and converge on a limited set of biological mechanisms, including oxidative stress, inflammation, endothelial dysfunction, and metabolic disruption, that ultimately promote cardiovascular injury.

A key insight is the interconnected nature of environmental compartments. Soil, water, and air continuously exchange contaminants, creating complex exposure mixtures that define the human exposome. This interconnectedness challenges traditional single-exposure frameworks and underscores the need for integrated, systems-level approaches in both research and prevention. Importantly, emerging contaminants such as micro- and nanoplastics exemplify how modern environmental changes introduce new and poorly understood risks with potentially far-reaching cardiovascular implications.

Despite these advances, environmental determinants remain underrepresented in cardiovascular prevention

Table 2. Cardiovascular Diseases and Outcomes Associated with Pesticides and Other Endocrine-Disrupting Exposures in Epidemiological Studies

Lang, 2008[99]	n = 1,455	Urinary BPA	Prevalent CVD	Higher urinary BPA concentrations were associated with cardiovascular diagnoses (OR per 1-SD increase in BPA concentration, 1.39; 95% CI 1.18-1.63).
Shankar, 2012[193]	n = 745	Urinary BPA	Peripheral arterial disease	OR for peripheral arterial disease associated with the highest versus lowest tertile of urinary BPA was 2.69 (95% CI 1.02-7.09).
Sturgeon, 2016[194]	n = 5,080	Urinary phthalate metabolite	CVD mortality	No association between CVD mortality and individual urinary phthalate metabolites was observed. HRs comparing the highest to lowest quartile ranged from 0.73 (0.5-1.2) for mono-ethyl phthalate to 1.4 (0.8-2.5) for mono-(2-ethyl-5-hydroxyhexyl) phthalate.
Bao, 2020[195]	n = 3,883	Urinary BPA	All-cause and CVD mortality	HRs comparing highest vs lowest tertile of urinary BPA levels were 1.49 (95% CI 1.01-2.19) for all-cause mortality and 1.46 (95% CI 0.67-3.15) for cardiovascular disease mortality.
Cai, 2020[196]	n = 9,139	Urinary BPA	Prevalent CVD	In quartile analysis, highest level of urinary BPA was associated with increased prevalence of myocardial infarction (OR 1.73, 95% CI 1.11-2.69) and stroke (1.61, 1.09-2.36), when compared with those at the lowest quartile. Per unit (μg/g creatinine) increment in ln-transformed BPA concentration was shown to be significantly associated with 19%, 19%, 25%, 29%, 20%, and 16% increased ORs of prevalence of congestive heart failure, CHD, angina pectoris, MI, stroke and total CVD among total participants, respectively.
Moon, 2021[100]	n = 11,857	Urinary BPA	Prevalent CVD	OR between BPA and CVD was 1.13 (95% CI 1.02-1.24).
Wang, 2022[101]	n = 1,267	Urinary BPF and BPS	Prevalent CVD	The third tertile concentration of BPS increased the risk of total CVD (OR: 1.99, 1.16-3.40). BPS was positively associated with the risk of coronary heart disease, and the third tertile concentration of BPS increased the CHD risk by 2.22 times (1.04-4.74). No significant association was observed between BPF and CVD.
Chen, 2022[102]	n = 8,164	Urinary BPA, BP-3, and triclosan	Prevalent CVD	OR of CVD 1.09 (95% CI 1.01-1.18) per 1-unit increasement in log-transformed urinary BPA. Compared with the lowest quartile (< 0.9), the OR was 1.30 (1.03-1.65) in the highest quartile (> 3.8). No associations were found for BP-3 and triclosan.
Moreno-Gómez-Toledano, 2022[103]	n = 3,701	Urinary BPF and BPS	Prevalent congestive heart failure and hypertension	BPF showed a statistically significant relationship with congestive heart failure (OR 1.15, 95% CI 1.01-1.30). BPS was positively correlated with hypertension (OR 1.09, 95% CI 1.02-1.17).
Lu, 2023[104]	n = 3,502	Urinary BPA, BPF, and BPS	Prevalent CVD	The highest level of urinary BPA (≥2.5 ng/ml) was significantly associated with a higher CVD prevalence (OR 1.58; 95% CI 1.08-2.3) among all participants in the quartile analysis. Higher levels of urinary BPF were positively associated with CVD prevalence in females (Q2: 1.81, 1.03-3.18; Q4: 1.73, 1.07-2.79) and in the elderly population (Q3: 1.7, 1.16-2.48). No associations were found between urinary BPS levels and CVD.
Chen, 2023[42]	n = 1,467	Urinary BPA	Prevalent blood pressure and hypertension	When the concentration of BPA was in Q4, diastolic blood pressure was increased by 2.08 mm Hg. At the same time, compared to participants in the first quartile (Q1), those from the fourth quartile (Q4) of BPA concentrations had 21% higher odds of hypertension (compared to the lowest quartile, Q1).
Chen, 2023[197]	n = 9,243	Urinary BPA	Cardiovascular and all-cause mortality	Compared to the lowest BPA quartile group, HRs of the highest BPA quartile group were 1.76 (95% CI, 1.23-2.52) for cardiovascular mortality and 1.21 (95% CI, 0.98-1.49) for all-cause mortality.

BP-3, benzophenone-3; BPA, bisphenol A; BPF, bisphenol F; bisphenol S; CHD, coronary heart disease.

strategies and clinical guidelines. This gap reflects not a lack of evidence, but a lag in translation from science to policy and practice. Unlike traditional risk factors, environmental exposures are largely involuntary, unequally distributed, and driven by structural forces, necessitating population-level interventions and strong regulatory action.

The implications are clear. Reducing pollution is one of the most powerful and cost-effective strategies to prevent cardiovascular disease on a global scale. Measures targeting emissions, chemical safety, waste management, and sustainable urban and agricultural practices offer substantial co-benefits for climate, ecosystems, and human health.

At the same time, clinicians and scientific societies must play a more active role in recognizing, communicating, and addressing environmental risks.

Ultimately, protecting soil and water quality is not only an environmental imperative but a medical one. Cardiovascular health cannot be achieved without a healthy environment. Integrating environmental protection into the core of cardiovascular prevention represents a critical step toward a more comprehensive, equitable, and future-oriented approach to global health.

Peer-Review: Internally peer-reviewed.

Author Contributions: Concept – T.M., P.L.; Design – not applicable; Supervision – not applicable; Resources – T.M., A.D.; Materials – not applicable.; Data Collection and/or Processing – not applicable; Analysis and/or Interpretation – not applicable; Literature Search – T.M., M.K., O.H., A.D.; Writing – T.M., P.L., M.K., O.H., A.D., J.L., M.A., M.N.; Critical Review – T.M., P.L., M.K., O.H., A.D., J.L., M.A., M.N.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: T.M. is a principal investigator and O.H., M.K. and A.D. are (Young) Scientists of the DZHK (German Center for Cardiovascular Research), Partner Site Rhine-Main, Mainz, Germany. Continuous structural funding by the DZHK is highly appreciated. Collaborations of the authors were supported by the environmental network EXPOHEALTH funded by the state of Rhineland-Palatinate, Germany. M.A. was supported in part by grants from the National Institute of Environmental Health Sciences (NIEHS), R01ES07331 and R01ES10563. We gratefully acknowledge financial support through vascular biology research grants from the Foundation Heart of Mainz (to O.H., M.K. and A.D.) and the Mainzer Wissenschaftsstiftung.

REFERENCES

1. UNITED NATIONS. *Soil Pollution a Risk to Our Health and Food Security 2020*. https://www.unep.org/news-and-stories/story/soil-pollution-risk-our-health-and-food-security
2. *WHO Global Air Quality Guidelines: Particulate Matter (PM(25) and PM(10)), Ozone, Nitrogen Dioxide, Sulfur Dioxide and Carbon Monoxide. Geneva2021*.https://www.who.int/publications/i/item/9789240034228/
3. Fuller R, Landrigan PJ, Balakrishnan K, et al. Pollution and health: a progress update. *Lancet Planet Health*. 2022;6(6):e535-e547. [CrossRef]
4. Landrigan PJ, Fuller R, Acosta NJR, et al. The Lancet Commission on pollution and health. *Lancet*. 2018;391(10119):462-512. [CrossRef]
5. Münzel T, Hahad O, Daiber A, Landrigan PJ. Soil and water pollution and human health: what should cardiologists worry about? *Cardiovasc Res*. 2023;119(2):440-449. [CrossRef]
6. Lelieveld J, Haines A, Burnett R, et al. Air pollution deaths attributable to fossil fuels: observational and modelling study. *BMJ*. 2023;383:e077784. [CrossRef]
7. Lelieveld J, Klingmüller K, Pozzer A, et al. Cardiovascular disease burden from ambient air pollution in Europe reassessed using novel hazard ratio functions. *Eur Heart J*. 2019;40(20):1590-1596. [CrossRef]
8. Münzel T, Hahad O, Lelieveld J, et al. Soil and water pollution and cardiovascular disease. *Nat Rev Cardiol*. 2024;22(2):71-89. [CrossRef]
9. Xu H, Dong C, Yu Z, et al. Detection and analysis of microplastics in tissues and blood of human cervical cancer patients. *Environ Res*. 2024;259:119498. [CrossRef]
10. WORLD HEALTH ORGANIZATION. *Global Action Plan for the Prevention and Control of Non-communicable Diseases 2013-2020*. Geneva, Switzerland, 2013. https://www.who.int/publications/i/item/9789241506236
11. Münzel T, Sørensen M, Daiber A. Transportation noise pollution and cardiovascular disease. *Nat Rev Cardiol*. 2021;18(9):619-636. [CrossRef]
12. Frumkin H, Haines A. Global environmental change and noncommunicable disease risks. *Annu Rev Public Health*. 2019;40(1):261-282. [CrossRef]
13. Cosselman KE, Navas-Acien A, Kaufman JD. Environmental factors in cardiovascular disease. *Nat Rev Cardiol*. 2015;12(11):627-642. [CrossRef]
14. Münzel T, Gori T, Al-Kindi S, et al. Effects of gaseous and solid constituents of air pollution on endothelial function. *Eur Heart J*. 2018;39(38):3543-3550. [CrossRef]
15. Münzel T, Hahad O, Sørensen M, et al. Environmental risk factors and cardiovascular diseases: a comprehensive review. *Cardiovasc Res*. 2021;118(14):2880-2902. [CrossRef]
16. GAHP. *Report by the Global Alliance on Health and Pollution. Pollution and Health Metrics*; 2019. https://gahp.net/wp-content/uploads/2019/12/PollutionandHealthMetrics-final-12_18_2019.pdf Accessed 19/12/2023
17. Gruber N, Clement D, Carter BR, et al. The oceanic sink for anthropogenic CO(2) from 1994 to 2007. *Science*. 2019;363(6432):1193-1199. [CrossRef]
18. Cerezo MI, Agustí S. PAHs reduce DNA synthesis and delay cell division in the widespread primary producer Prochlorococcus. *Environ Pollut*. 2015;196:147-155. [CrossRef]
19. Echeveste P, Agustí S, Dachs J. Cell size dependent toxicity thresholds of polycyclic aromatic hydrocarbons to natural and cultured phytoplankton populations. *Environ Pollut*. 2010;158(1):299-307. [CrossRef]
20. Whitmee S, Haines A, Beyrer C, et al. Safeguarding human health in the Anthropocene epoch: report of the Rockefeller Foundation-Lancet Commission on planetary health. *Lancet*. 2015;386(10007):1973-2028. [CrossRef]
21. Rockström J, Steffen W, Noone K, et al. A safe operating space for humanity. *Nature*. 2009;461(7263):472-475. [CrossRef]
22. Depledge MH, Harvey AJ, Brownlee C, Frost M, Moore MN, Fleming LE. Changing views of the interconnections between the oceans and human health in Europe. *Microb Ecol*. 2013;65(4):852-859. [CrossRef]
23. Ercolano G, De Cicco P, Ianaro A. New drugs from the sea: pro-apoptotic activity of sponges and algae derived compounds. *Mar Drugs*. 2019;17(1):31. [CrossRef]
24. Keeling RF, Körtzinger A, Gruber N. Ocean deoxygenation in a warming world. *Annu Rev Mar Sci*. 2010;2(1):199-229. [CrossRef]
25. IPCC. Intergovernmental Panel on Climate Change; 2019. https://www.ipcc.ch/site/assets/uploads/sites/3/2019/12/SROCC_FullReport_FINAL.pdf
26. Pauly D, Zeller D. Catch reconstructions reveal that global marine fisheries catches are higher than reported and declining. *Nat Commun*. 2016;7(1):20160119. [CrossRef]
27. Cuyvers LBW, Gjerde K. *Deep Seabed Mining*; 2018. https://portals.iucn.org/library/node/47761.
28. WORLD HEALTH ORGANIZATION. *The Public Health Impact of Chemicals: Knowns and Unknowns - Data Addendum for 2019*; 2021.
29. HBM4EU. The European human biomonitoring initiative; 2016. https://www.hbm4eu.eu/.

30. CENTERS FOR DISEASE CONTROL AND PREVENTION (U.S.), Centers for Disease Control and Prevention (US). National biomonitoring survey. https://www.cdc.gov/biomonitoring/index.html ed2018.
31. Liu Z, Lu Y, Zhong K, Wang C, Xu X. The associations between endocrine disrupting chemicals and markers of inflammation and immune responses: a systematic review and meta-analysis. *Ecotoxicol Environ Saf*. 2022/03/12;234:113382. [CrossRef]
32. Sule RO, Condon L, Gomes AV. A common feature of pesticides: oxidative stress-the role of oxidative stress in pesticide-induced toxicity. *Oxid Med Cell Longev*. 2022;2022(1):20220119. [CrossRef]
33. Himmel HM. Mechanisms involved in cardiac sensitization by volatile anesthetics: general applicability to halogenated hydrocarbons? *Crit Rev Toxicol*. 2008;38(9):773-803. [CrossRef]
34. Rasin P, Sreekanth A. Cadmium exposure and cardiovascular diseases. *Chem Res Toxicol*. 2023;36(9):1441-1443. [CrossRef]
35. Singh N, Kumar A, Gupta VK, Sharma B. Biochemical and molecular bases of lead-induced toxicity in mammalian systems and possible mitigations. *Chem Res Toxicol*. 2018;31(10):1009-1021. [CrossRef]
36. Hu XF, Lowe M, Chan HM. Mercury exposure, cardiovascular disease, and mortality: A systematic review and dose-response meta-analysis. *Environ Res*. 2021;193:110538. [CrossRef]
37. Farina M, Aschner M, Rocha JBT. Oxidative stress in MeHg-induced neurotoxicity. *Toxicol Appl Pharmacol*. 2011;256(3):405-417. [CrossRef]
38. Ellinsworth DC. Arsenic, reactive oxygen, and endothelial dysfunction. *J Pharmacol Exp Ther*. 2015;353(3):458-464. [CrossRef]
39. Shen J, Wang X, Zhou D, et al. Modelling cadmium-induced cardiotoxicity using human pluripotent stem cell-derived cardiomyocytes. *J Cell Mol Med*. 2018;22(9):4221-4235. [CrossRef]
40. Daiber A, Steven S, Weber A, et al. Targeting vascular (endothelial) dysfunction. *Br J Pharmacol*. 2016;174(12):1591-1619. [CrossRef]
41. Wenzel P, Kossmann S, Münzel T, Daiber A. Redox regulation of cardiovascular inflammation - Immunomodulatory function of mitochondrial and Nox-derived reactive oxygen and nitrogen species. *Free Radic Biol Med*. 2017;109:48-60. [CrossRef]
42. Chen JC, Baumert BO, Li Y, et al. Associations of per- and polyfluoroalkyl substances, polychlorinated biphenyls, organochlorine pesticides, and polybrominated diphenyl ethers with oxidative stress markers: a systematic review and meta-analysis. *Environ Res*. 2023;239:117308. [CrossRef]
43. Westbury S, Ghosh I, Jones HM, et al. The influence of the urban food environment on diet, nutrition and health outcomes in low-income and middle-income countries: a systematic review. *BMJ Glob Health*. 2021;6(10):e006358. [CrossRef]
44. Paniagua L, Diaz-Cueto L, Huerta-Reyes M, Arechavaleta-Velasco F. Cadmium exposure induces interleukin-6 production via ROS-dependent activation of the ERK1/2 but independent of JNK signaling pathway in human placental JEG-3 trophoblast cells. *Reprod Toxicol*. 2019;89:28-34. [CrossRef]
45. Kempuraj D, Asadi S, Zhang B, et al. Mercury induces inflammatory mediator release from human mast cells. *J Neuroinflammation*. 2010;7(1):20100311. [CrossRef]
46. Parmalee NL, Aschner M. Metals and circadian rhythms. *Adv Neurotoxicol*. 2017;1:119-130. [CrossRef]
47. Li H, Kilgallen AB, Münzel T, et al. Influence of mental stress and environmental toxins on circadian clocks: implications for redox regulation of the heart and cardioprotection. *Br J Pharmacol*. 2020;177(23):5393-5412. [CrossRef]
48. Lafuente A. The hypothalamic-pituitary-gonadal axis is target of cadmium toxicity. An update of recent studies and potential therapeutic approaches. *Food Chem Toxicol*. 2013;59:395-404. [CrossRef]
49. Jomova K, Jenisova Z, Feszterova M, et al. Arsenic: toxicity, oxidative stress and human disease. *J Appl Toxicol*. 2011;31(2):95-107. [CrossRef]
50. Gaetke LM, Chow CK. Copper toxicity, oxidative stress, and antioxidant nutrients. *Toxicology*. 2003;189(1-2):147-163. [CrossRef]
51. Kang YJ. Copper and homocysteine in cardiovascular diseases. *Pharmacol Ther*. 2011;129(3):321-331. [CrossRef]
52. WORLD HEALTH ORGANIZATION. Mercury and health. World Health Organization [online]. Accessed 22 September 2020. https://www.who.int/news-room/fact-sheets/detail/mercury-and-health; 2017.
53. WORLD HEALTH ORGANIZATION. Water-related diseases: Arsenicosis [online]; 2020. https://www.who.int/news-room/fact-sheets/detail/arsenic
54. Prüss-Ustün A, Wolf J, Corvalán C, Bos R, Neira M. *Preventing Disease through Healthy Environments. A Global Assessment of the Burden Disease from Environmental Risk*. Geneva, Switzerland, World Health Organization; 2016:176. (also https://apps.who.int/iris/bitstream/handle/10665/204585/9789241565196_eng)
55. AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY. *Interaction Profile for Benzene, Toluene, Ethylbenzene, and Xylenes (BTEX)*. Agency for Toxic Substances and Disease Registry; 2004:154. (also https://www.atsdr.cdc.gov/interactionprofiles/ip-btex/ip05.pdf)
56. Drwal E, Rak A, Gregoraszczuk EL. Review: polycyclic aromatic hydrocarbons (PAHs)-Action on placental function and health risks in future life of newborns. *Toxicology*. 2019;411:133-142. [CrossRef]
57. EUROPEAN CENTRAL BANK. *JRC. European Union Risk Assessment Report: phenol*. No. EUR 22522 EN/1. European Chemical Bureau - Joint Research Centre, 2006; p. 240. (also available at https://echa.europa.eu/documents/10162/1ca68f98-878f-4ef6-914a-9f21e9ad2234)
58. Galbraith D, Gross SA, Paustenbach D. Benzene and human health: A historical review and appraisal of associations with various diseases. *Crit Rev Toxicol*. 2010;40(sup2):1-46. [CrossRef]
59. Knutsen HK, Alexander J, Barregård L, et al. Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food. *EFSA J*. 2018;16(11):20181120. [CrossRef]
60. Who. *An Estimated 12.6 Million Deaths Each Year Are Attributable to Unhealthy Environments*. Geneva: World Health Organization; 2016.
61. Carpenter DO. Exposure to and health effects of volatile PCBs. *Rev Environ Health*. 2015;30(2):81-92. [CrossRef]
62. Klocke C, Lein PJ. Evidence implicating non-dioxin-like congeners as the key mediators of polychlorinated biphenyl (PCB) developmental neurotoxicity. *Int J Mol Sci*. 2020;21(3):1013. [CrossRef]
63. Brusseau ML, Anderson RH, Guo B. PFAS concentrations in soils: background levels versus contaminated sites. *Sci Total Environ*. 2020;740:140017. [CrossRef]
64. Kim KH, Kabir E, Jahan SA. Exposure to pesticides and the associated human health effects. *Sci Total Environ*. 2017;575:525-535. [CrossRef]
65. Fawell J, Nieuwenhuijsen MJ. Contaminants in drinking water. *Br Med Bull*. 2003;68(1):199-208. [CrossRef]
66. Järup L. Hazards of heavy metal contamination. *Br Med Bull*. 2003;68(1):167-182. [CrossRef]
67. Chowdhury R, Ramond A, O'Keeffe LM, et al. Environmental toxic metal contaminants and risk of cardiovascular disease:

systematic review and meta-analysis. *BMJ*. 2018;362:k3310. [CrossRef]
68. National_Academy_of_Sciences. *Toxicological Effects of Methyl Mercury*. Washington DC: National Academies Press; 2000.
69. United_Nations_Environment. *The Stockholm Convention on Persistent Organic Pollutants*; 2001.
70. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for chlorinated dibenzo-p-dioxins (CDDs). Atlanta GCfDCaP. http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=366&tid=63
71. Consonni D, Pesatori AC, Zocchetti C, et al. Mortality in a population exposed to dioxin after the Seveso, Italy, accident in 1976: 25 years of follow-up. *Am J Epidemiol*. 2008;167(7):847-858. [CrossRef]
72. Lee DH, Lee IK, Song K, et al. A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes. *Diabetes Care*. 2006;29(7):1638-1644. [CrossRef]
73. Lim JS, Lee DH, Jacobs DR, Jr. Association of brominated flame retardants with diabetes and metabolic syndrome in the U.S. population, 2003-2004. *Diabetes Care*. 2008;31(9):1802-1807. [CrossRef]
74. Gore AC, Chappell VA, Fenton SE, et al. EDC-2: the Endocrine Society's Second Scientific Statement on endocrine-disrupting chemicals. *Endocr Rev*. 2015;36(6):E1-E150. [CrossRef]
75. Kahn LG, Philippat C, Nakayama SF, Slama R, Trasande L. Endocrine-disrupting chemicals: implications for human health. *Lancet Diabetes Endocrinol*. 2020;8(8):703-718. [CrossRef]
76. Timmermann CAG, Rossing LI, Grøntved A, et al. Adiposity and glycemic control in children exposed to perfluorinated compounds. *J Clin Endocrinol Metab*. 2014;99(4):E608-E614. [CrossRef]
77. Lundin JI, Alexander BH, Olsen GW, Church TR. Ammonium perfluorooctanoate production and occupational mortality. *Epidemiology*. 2009;20(6):921-928. [CrossRef]
78. Landrigan PJ, Goldman LR. Children's vulnerability to toxic chemicals: a challenge and opportunity to strengthen health and environmental policy. *Health Aff*. 2011;30(5):842-850. [CrossRef]
79. Wang Z, Walker GW, Muir DCG, Nagatani-Yoshida K. Toward a global understanding of chemical pollution: A first comprehensive analysis of national and regional chemical inventories. *Environ Sci Technol*. 2020;54(5):2575-2584. [CrossRef]
80. Centers_for_Disease_Control_and_Prevention_(US). National Biomonitoring Survey. 2022. https://www.cdc.gov/biomonitoring/index.html
81. Jamieson AJ, Malkocs T, Piertney SB, Fujii T, Zhang Z. Bioaccumulation of persistent organic pollutants in the deepest ocean fauna. *Nat Ecol Evol*. 2017;1(3):20170213. [CrossRef]
82. Lancereaux E. Nephrite et arthrite saturnine: coincidences de ces affections; parallele avec la nephrite etl'arthrite gouttesses. *Transact Int Med Congr*; 1881;2:193-202
83. Schwartz J. Lead, Blood pressure, and cardiovascular disease in men. *Arch Environ Health Int J*. 1995;50(1):31-37. [CrossRef]
84. Navas-Acien A, Guallar E, Silbergeld EK, Rothenberg SJ. Lead exposure and cardiovascular disease--a systematic review. *Environ Health Perspect*. 2007;115(3):472-482. [CrossRef]
85. Schober SE, Mirel LB, Graubard BI, Brody DJ, Flegal KM. Blood lead levels and death from all causes, cardiovascular disease, and cancer: results from the NHANES III mortality study. *Environ Health Perspect*. 2006;114(10):1538-1541. [CrossRef]
86. Lanphear BP, Rauch S, Auinger P, Allen RW, Hornung RW. Low-level lead exposure and mortality in US adults: a population-based cohort study. *Lancet Public Health*. 2018;3(4):e177-e184. [CrossRef]
87. Zhu K, Zhang Y, Lu Q, et al. Associations of exposure to lead and cadmium with risk of all-cause and cardiovascular disease mortality among patients with type 2 diabetes. *Environ Sci Pollut Res*. 2022;29(51):76805-76815. [CrossRef]
88. Xing X, Xu M, Yang L, et al. Association of selenium and cadmium with heart failure and mortality based on the National Health and Nutrition Examination Survey. *J Hum Nutr Diet*. 2023;36(4):1496-1506. [CrossRef]
89. Tellez-Plaza M, Guallar E, Howard BV, et al. Cadmium exposure and incident cardiovascular disease. *Epidemiology*. 2013;24(3):421-429. [CrossRef]
90. Duan W, Xu C, Liu Q, et al. Levels of a mixture of heavy metals in blood and urine and all-cause, cardiovascular disease and cancer mortality: a population-based cohort study. *Environ Pollut*. 2020;263(A):114630. [CrossRef]
91. Larsen B, Sánchez-Triana E. Global health burden and cost of lead exposure in children and adults: a health impact and economic modelling analysis. *Lancet Planet Health*. 2023/09/16;7(10):e831-e840. [CrossRef]
92. Lim KM, Kim S, Noh JY, et al. Low-level mercury can enhance procoagulant activity of erythrocytes: a new contributing factor for mercury-related thrombotic disease. *Environ Health Perspect*. 2010;118(7):928-935. [CrossRef]
93. Morin Y, Daniel P. Quebec beer-drinkers' cardiomyopathy: etiological considerations. *Can Med Assoc J*. 1967;97:926-928
94. Perez AL, Tang WHW. Contribution of environmental toxins in the pathogenesis of idiopathic cardiomyopathies. *Curr Treat Options Cardiovasc Med*. 2015;17(5):381. [CrossRef]
95. Stea F, Bianchi F, Cori L, Sicari R. Cardiovascular effects of arsenic: clinical and epidemiological findings. *Environ Sci Pollut Res*. 2014;21(1):244-251. [CrossRef]
96. Moon K, Guallar E, Navas-Acien A. Arsenic exposure and cardiovascular disease: an updated systematic review. *Curr Atheroscler Rep*. 2012;14(6):542-555. [CrossRef]
97. Tseng WP. Black foot disease in Taiwan: a 30-year follow-up study. *Angiology*. 1989;40(6):547-558. [CrossRef]
98. Kinsman GD, Howard AN, Stone DL, Mullins PA. Studies in copper status and atherosclerosis. *Biochem Soc Trans*. 1990;18(6):1186-1188. [CrossRef]
99. Lang IA, Galloway TS, Scarlett A, Henley WE, Depledge M, Wallace RB. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. *JAMA*. 2008;300(11):1303-1310. [CrossRef]
100. Moon S, Yu SH, Lee CB, Park YJ, Yoo HJ, Kim DS. Effects of bisphenol A on cardiovascular disease: an epidemiological study using National Health and Nutrition Examination survey 2003-2016 and meta-analysis. *Sci Total Environ*. 2021;763:142941. [CrossRef]
101. Wang R, Fei Q, Liu S, et al. The bisphenol F and bisphenol S and cardiovascular disease: results from NHANES 2013-2016. *Environ Sci Eur*. 2022;34(1):4. [CrossRef]
102. Chen Z, He J, Shi W. Association between urinary environmental phenols and the prevalence of cardiovascular diseases in US adults. *Environ Sci Pollut Res*. 2022;29(28):42947-42954. [CrossRef]
103. Moreno-Gómez-Toledano R. Relationship between emergent BPA-substitutes and renal and cardiovascular diseases in adult population. *Environ Pollut*. 2022;313:120106. [CrossRef]
104. Lu Y, Chen S, Jin H, Tang L, Xia M. Associations of bisphenol F and S, as substitutes for bisphenol A, with cardiovascular disease in American adults. *J Appl Toxicol*. 2023;43(4):500-507. [CrossRef]
105. Bar-Meir E, Schein O, Eisenkraft A, et al. Guidelines for treating cardiac manifestations of organophosphates poisoning with

special emphasis on long QT and torsades de pointes. *Crit Rev Toxicol*. 2007;37(3):279-285. [CrossRef]
106. Humblet O, Birnbaum L, Rimm E, Mittleman MA, Hauser R. Dioxins and cardiovascular disease mortality. *Environ Health Perspect*. 2008;116(11):1443-1448. [CrossRef]
107. Gustavsson P, Hogstedt C. A cohort study of Swedish capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). *Am J Ind Med*. 1997;32(3):234-239. (doi:10.1002/(sici)1097-0274(199709)32:3<234::aid-ajim8>3.0.co;2-x)
108. ORGANIZATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT. Global Plastics Outlook OECD Publishing, Paris; 2022
109. Ali N, Katsouli J, Marczylo EL, Gant TW, Wright S, Bernardino de la Serna J. The potential impacts of micro-and-nano plastics on various organ systems in humans. *EBiomedicine*. 2024;99:104901. [CrossRef]
110. Wright SL, Thompson RC, Galloway TS. The physical impacts of microplastics on marine organisms: a review. *Environ Pollut*. 2013;178:483-492. [CrossRef]
111. Landrigan P, Symeonides C, Raps H, Dunlop S. The global plastics treaty: why is it needed? *Lancet*. 2023;402(10419):2274-2276. [CrossRef]
112. Yong CQY, Valiyaveettil S, Tang BL. Toxicity of microplastics and nanoplastics in mammalian systems. *Int J Environ Res Public Health*. 2020;17(5):1509. [CrossRef]
113. Oh N, Park JH. Endocytosis and exocytosis of nanoparticles in mammalian cells. *Int J Nanomedicine*. 2014;9(suppl 1):51-63. [CrossRef]
114. Zhang S, Gao H, Bao G. Physical principles of nanoparticle cellular endocytosis. *ACS Nano*. 2015;9(9):8655-8671. [CrossRef]
115. Horstmann H, Ng CP, Tang BL, Hong W. Ultrastructural characterization of endoplasmic reticulum--Golgi transport containers (EGTC). *J Cell Sci*. 2002;115(22):4263-4273. [CrossRef]
116. Treyer A, Pujato M, Pechuan X, Müsch A. Iterative sorting of apical and basolateral cargo in Madin-Darby canine kidney cells. *Mol Biol Cell*. 2016;27(14):2259-2271. [CrossRef]
117. Lim SL, Ng CT, Zou L, et al. Targeted metabolomics reveals differential biological effects of nanoplastics and nanoZnO in human lung cells. *Nanotoxicology*. 2019;13(8):1117-1132. [CrossRef]
118. Cordani M, Somoza Á. Targeting autophagy using metallic nanoparticles: a promising strategy for cancer treatment. *Cell Mol Life Sci*. 2019;76(7):1215-1242. [CrossRef]
119. Besseling E, Wang B, Lürling M, Koelmans AA. Nanoplastic affects growth of S. obliquus and reproduction of D. magna. *Environ Sci Technol*. 2014;48(20):12336-12343. [CrossRef]
120. Liu Z, Cai M, Yu P, et al. Age-dependent survival, stress defense, and AMPK in Daphnia pulex after short-term exposure to a polystyrene nanoplastic. *Aquat Toxicol*. 2018;204:1-8. [CrossRef]
121. Jeong J, Choi J. Adverse outcome pathways potentially related to hazard identification of microplastics based on toxicity mechanisms. *Chemosphere*. 2019;231:249-255. [CrossRef]
122. Bedard K, Krause KH. The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology. *Physiol Rev*. 2007;87(1):245-313. [CrossRef]
123. Gong T, Liu L, Jiang W, Zhou R. DAMP-sensing receptors in sterile inflammation and inflammatory diseases. *Nat Rev Immunol*. 2020;20(2):95-112. [CrossRef]
124. Shen H, Kreisel D, Goldstein DR. Processes of sterile inflammation. *J Immunol*. 2013;191(6):2857-2863. [CrossRef]
125. Greven AC, Merk T, Karagöz F, et al. Polycarbonate and polystyrene nanoplastic particles act as stressors to the innate immune system of fathead minnow (Pimephales promelas). *Environ Toxicol Chem*. 2016;35(12):3093-3100. [CrossRef]
126. Wang YL, Lee YH, Chiu IJ, Lin YF, Chiu HW. Potent impact of plastic nanomaterials and micromaterials on the food chain and human health. *Int J Mol Sci*. 2020;21(5):1727. [CrossRef]
127. De-la-Torre GE. Microplastics: an emerging threat to food security and human health. *J Food Sci Technol*. 2020;57(5):1601-1608. [CrossRef]
128. Shiwakoti S, Ko JY, Gong D, et al. Effects of polystyrene nanoplastics on endothelium senescence and its underlying mechanism. *Environ Int*. 2022;164:107248. [CrossRef]
129. Zhao J, Gomes D, Jin L, et al. Polystyrene bead ingestion promotes adiposity and cardiometabolic disease in mice. *Ecotoxicol Environ Saf*. 2022;232:113239. [CrossRef]
130. Wei J, Wang X, Liu Q, et al. The impact of polystyrene microplastics on cardiomyocytes pyroptosis through NLRP3/Caspase-1 signaling pathway and oxidative stress in Wistar rats. *Environ Toxicol*. 2021/01/07;36(5):935-944. [CrossRef]
131. Li Z, Zhu S, Liu Q, et al. Polystyrene microplastics cause cardiac fibrosis by activating Wnt/beta-catenin signaling pathway and promoting cardiomyocyte apoptosis in rats. *Environ Pollut*. 2020;265(A):115025. [CrossRef]
132. Wang X, Jia Z, Zhou X, et al. Nanoplastic-induced vascular endothelial injury and coagulation dysfunction in mice. *Sci Total Environ*. 2023;865:161271. [CrossRef]
133. Zhu X, Wang C, Duan X, Liang B, Genbo Xu E, Huang Z. Micro- and nanoplastics: A new cardiovascular risk factor? *Environ Int*. 2023;171:107662. [CrossRef]
134. Leslie HA, van Velzen MJM, Brandsma SH, Vethaak AD, Garcia-Vallejo JJ, Lamoree MH. Discovery and quantification of plastic particle pollution in human blood. *Environ Int*. 2022;163:107199. [CrossRef]
135. Tran HAA, Ng JJ, Tang DH, Yong CT, Ho AFW. Health impacts of micro- and nanoplastics in humans: systematic review of in vivo evidence. *Environ Health*. 2026;25(1):20260227. [CrossRef]
136. Marfella R, Prattichizzo F, Sardu C, et al. Microplastics and nanoplastics in atheromas and cardiovascular events. *N Engl J Med*. 2024;390(10):900-910. [CrossRef]
137. Cui C, Guo Z, Liu Y, et al. Tissue-specific distribution of microplastics in human blood and carotid plaques: a paired sample analysis. *Environ Int*. 2025;203:109743. [CrossRef]
138. Landrigan PJ, Dunlop S, Treskova M, et al. The Lancet Countdown on health and plastics. *Lancet*. 2025;406(10507):1044-1062. [CrossRef]
139. Ali N, Katsouli J, Auyang E, Bernardino de la Serna J. Microplastic and nanoplastic pollution and associated potential disease risks. *Lancet Planet Health*. 2025;9(12):101390. [CrossRef]
140. Rehman MFU, Khan MM, Khan MM. Impact of microplastics and nanoplastics on human health: mechanistic insights and exposure pathways. *Toxicol Lett*. 2025;414:111769. [CrossRef]
141. UNITED NATIONS. *The Global Forest Goals Report* https://www.un.org/esa/forests/wp-content/uploads/2021/08/Global-Forest-Goals-Report-2021.pdf; 2021
142. Armenteras D, Dávalos LM, Barreto JS, et al. Fire-induced loss of the world's most biodiverse forests in Latin America. *Sci Adv*. 2021;7(33):20210813. [CrossRef]
143. UNDRR. *Wildfires in Latin America: A Preliminary Analysis, Messages and Resources* https://www.undrr.org/publication/wildfires-latin-america-preliminary-analysis-messages-and-resources. 2022
144. Morand S, Lajaunie C. Outbreaks of vector-borne and zoonotic diseases are associated with changes in forest cover and oil palm expansion at global scale. *Front Vet Sci*. 2021;8:20210324. [CrossRef]
145. Prospero JM, Ginoux P, Torres O, Nicholson SE, Gill TE. Environmental characterization of global sources of atmospheric soil

dust identified with the nimbus 7 total ozone mapping spectrometer (TOMS) absorbing aerosol product. *Rev Geophys*. 2002;40(1). [CrossRef]
146. Chen W. MH, Song H, Zheng H. Progress in dust modelling, global dust budgets, and soil organic carbon dynamics. *Land*. 2022; *11*(2), 176; https://doi.org/10.3390/land11020176.
147. Ginoux P, Prospero JM, Gill TE, Hsu NC, Zhao M. Global-scale attribution of anthropogenic and natural dust sources and their emission rates based on MODIS Deep Blue aerosol products. *Rev Geophys*. 2012;50(3). [CrossRef]
148. Giannadaki DP, Pozzer A, Lelieveld J. Modeled global effects of airborne desert dust on air quality and premature mortality. *Atmos Chem Phys*. 2014;14(2):957-968. [CrossRef]
149. Gomez JGJ, Turnock ST, Horowitz LW, et al. The projected future degradation in air quality is caused by more abundant natural aerosols in a warmer world. *Communications Earth & Environment* 2023; 4:22 |https://doi.org/10.1038/s43247-023-00688-7.
150. Fussell JC, Kelly FJ. Mechanisms underlying the health effects of desert sand dust. *Environ Int*. 2021;157:106790. [CrossRef]
151. Miller MR, Newby DE. Air pollution and cardiovascular disease: car sick. *Cardiovasc Res*. 2019;116(2):279-294. [CrossRef]
152. Lwin KS, Tobias A, Chua PL, et al. Effects of desert dust and sandstorms on human health: A scoping review. *GeoHealth*. 2023;7(3):20230301:e2022. [CrossRef]
153. Yu Y, Paul K, Arah OA, et al. Air pollution, noise exposure, and metabolic syndrome - A cohort study in elderly Mexican-Americans in Sacramento area. *Environ Int*. 2020;134:105269. [CrossRef]
154. Karydis VA, Tsimpidi AP, Pozzer A, Astitha M, Lelieveld J. Effects of mineral dust on global atmospheric nitrate concentrations. *Atmos Chem Phys*. 2016;16(3):1491-1509. [CrossRef]
155. Kojima S, Michikawa T, Ueda K, et al. Asian dust exposure triggers acute myocardial infarction. *Eur Heart J*. 2017;38(43):3202-3208. [CrossRef]
156. Galloway JN, Townsend AR, Erisman JW, et al. Transformation of the nitrogen cycle: recent trends, questions, and potential solutions. *Science*. 2008;320(5878):889-892. [CrossRef]
157. Fowler D, Coyle M, Skiba U, et al. The global nitrogen cycle in the twenty-first century. *Phil Trans R Soc B*. 2013;368(1621):20130164. [CrossRef]
158. McDuffie EE, Martin RV, Spadaro JV, et al. Source sector and fuel contributions to ambient PM(2.5) and attributable mortality across multiple spatial scales. *Nat Commun*. 2021;12(1):20210614. [CrossRef]
159. Lelieveld J, Evans JS, Fnais M, Giannadaki D, Pozzer A. The contribution of outdoor air pollution sources to premature mortality on a global scale. *Nature*. 2015;525(7569):367-371. [CrossRef]
160. Zhang X, Ward BB, Sigman DM. Global nitrogen cycle: critical enzymes, organisms, and processes for nitrogen budgets and dynamics. *Chem Rev*. 2020;120(12):5308-5351. [CrossRef]
161. Gumanova NG, Deev AD, Zhang W, Kots AY, Shalnova SA. Serum nitrite and nitrate levels, NOx, can predict cardiovascular mortality in the elderly in a 3-year follow-up study. *BioFactors*. 2017;43(1):82-89. [CrossRef]
162. Gumanova NG, Deev AD, Kots AY, Shalnova SA. Elevated levels of serum nitrite and nitrate, NOx, are associated with increased total and cardiovascular mortality in an 8-year follow-up study. *Eur J Clin Investigation*. 2019;49(3):20190111. [CrossRef]
163. Bahadoran Z, Mirmiran P, Tahmasebinejad Z, Azizi F, Ghasemi A. Serum nitric oxide metabolites and hard clinical endpoints: a population-based prospective study. *Scand Cardiovasc J*. 2019;53(4):176-182. [CrossRef]
164. UN. World. *Population Prospects 2019: Highlights* https://population.un.org/wpp/Publications/Files/wpp2019_10KeyFindings.pdf. 2019.
165. Dye C. Health and urban living. *Science*. 2008;319(5864):766-769. [CrossRef]
166. Ezzati M, Webster CJ, Doyle YG, Rashid S, Owusu G, Leung GM. Cities for global health. *BMJ*. 2018;363:k3794. [CrossRef]
167. Hunter RF, Nieuwenhuijsen M, Fabian C, et al. Advancing urban green and blue space contributions to public health. *Lancet Public Health*. 2023;8(9):e735-e742. [CrossRef]
168. Münzel T, Sørensen M, Lelieveld J, et al. Heart healthy cities: genetics loads the gun but the environment pulls the trigger. *Eur Heart J*. 2021;42(25):2422-2438. [CrossRef]
169. Baumgartner J, Brauer M, Ezzati M. The role of cities in reducing the cardiovascular impacts of environmental pollution in low- and middle-income countries. *BMC Med*. 2020;18(1):20200224. [CrossRef]
170. Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1.9 million participants. *Lancet Glob Health*. 2018;6(10):e1077-e1086. [CrossRef]
171. Nieuwenhuijsen MJ. New urban models for more sustainable, liveable and healthier cities post Covid19; reducing air pollution, noise and heat island effects and increasing green space and physical activity. *Environ Int*. 2021;157:106850. [CrossRef]
172. FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS. *Soil Organic Carbon, the Hidden Potential* https://www.fao.org/3/i6937e/i6937e.pdf; 2017.
173. EXECUTIVE OFFICE OF ENERGY AND ENVIRONMENTAL AFFAIRS. *Soil Moisture Deficit* https://www.eea.europa.eu/en/analysis/indicators/soil-moisture-deficit; 2021.
174. Doherty RM, Heal MR, O'Connor FM. Climate change impacts on human health over Europe through its effect on air quality. *Environ Health*. 2017/12/09;16(suppl 1). [CrossRef]
175. Liu J, Chen Y, Chao S, Cao H, Zhang A, Yang Y. Emission control priority of PM(2.5)-bound heavy metals in different seasons: A comprehensive analysis from health risk perspective. *Sci Total Environ*. 2018;644:20-30. [CrossRef]
176. Alahmad B, Khraishah H, Royé D, et al. Associations between extreme temperatures and cardiovascular cause-specific mortality: results from 27 countries. *Circulation*. 2023;147(1):35-46. [CrossRef]
177. Ebi KL, Capon A, Berry P, et al. Hot weather and heat extremes: health risks. *Lancet*. 2021;398(10301):698-708. [CrossRef]
178. WORLD HEALTH ORGANIZATION. Heat and health in the WHO European Region: updated evidence for effective prevention. World Health Organization Regional Office for Europe, Copenhagen, Denmark. https://wwwwhoint/europe/publications/i/item/97892890554062021
179. Sule RO, Rivera GDT, Vaidya T, Gartrell E, Gomes AV. Environmental toxins and oxidative stress: the link to cardiovascular diseases. *Antioxidants*. 2025;14(5):604. [CrossRef]
180. EXECUTIVE OFFICE OF ENERGY AND ENVIRONMENTAL AFFAIRS. Soil. https://wwweeaeuropaeu/en/topics/in-depth/soil#2023.
181. EXECUTIVE OFFICE OF ENERGY AND ENVIRONMENTAL AFFAIRS. Progress in the management of contaminated sites in Europe. https://wwweeaeuropaeu/en/analysis/indicators/progress-in-the-management-of2022.
182. Johansen DF, Vestvik RA. The cost of saving our ocean - estimating the funding gap of sustainable development goal 14. *Mar Policy*. 2020;112:103783. [CrossRef]
183. EUROPEAN UNION. *Zero Pollution Action Plan Towards Zero Pollution for Air, Water and Soil*; 2021. https://leap.unep.org/en/countries/eu/national-legislation/eu-action-plan-towards-zero-pollution-air-water-and-soil

184. Goldsborough III EGM, McEvoy JW, Blumenthal RS, Jacobsen AP. Pollution and cardiovascular health: A contemporary review of morbidity and implications for planetary health American Heart Journal Plus. *Cardiol Res Pract*. 2023;25:1-8.
185. Tsoi MF, Lo CWH, Cheung TT, Cheung BMY. Blood lead level and risk of hypertension in the United States National Health and Nutrition Examination survey 1999-2016. *Sci Rep OrigPap*. 2021;11(1):1-6. [CrossRef]
186. Cook MK, Zhang J, Wei Y. Blood Lead Levels and risk of deaths from cardiovascular disease. *Am J Cardiol*. 2022;173:132-138. [CrossRef]
187. Lee MS, Park SK, Hu H, Lee S. Cadmium exposure and cardiovascular disease in the 2005 Korea National Health and Nutrition Examination Survey. *Environ Res*. 2011;111(1):171-176. [CrossRef]
188. Li Z, Fan Y, Tao C, et al. Association between exposure to cadmium and risk of all-cause and cause-specific mortality in the general US adults: a prospective cohort study. *Chemosphere*. 2022;307(4):136060. [CrossRef]
189. Tellez-Plaza M, Navas-Acien A, Menke A, Crainiceanu CM, Pastor-Barriuso R, Guallar E. Cadmium exposure and all-cause and cardiovascular mortality in the U.S. general population. *Environ Health Perspect*. 2012;120(7):1017-1022. [CrossRef]
190. Nigra AE, Moon KA, Jones MR, Sanchez TR, Navas-Acien A. Urinary arsenic and heart disease mortality in NHANES 2003-2014. *Environ Res*. 2021;200:111387. [CrossRef]
191. Sun Y, Liu B, Rong S, et al. Association of seafood consumption and mercury exposure with cardiovascular and all-cause mortality among US adults. *JAMA Netw Open*. 2021;4(11):e2136367. [CrossRef]
192. Isiozor NM, Kunutsor SK, Vogelsang D, Isiozor I, Kauhanen J, Laukkanen JA. Serum copper and the risk of cardiovascular disease death in Finnish men. *Nutr Metab Cardiovasc Dis*. 2023;33(1):151-157. [CrossRef]
193. Shankar A, Teppala S, Sabanayagam C. Bisphenol A and peripheral arterial disease: results from the NHANES. *Environ Health Perspect*. 2012;120(9):1297-1300. [CrossRef]
194. Sturgeon SR, Flynn D, Kaiser AB, Reeves KW. Urinary levels of phthalate metabolites and cardiovascular disease mortality (NHANES, 1999-2008). *Int J Hyg Environ Health*. 2016;219(8):876-882. [CrossRef]
195. Bao W, Liu B, Rong S, Dai SY, Trasande L, Lehmler HJ. Association between bisphenol A exposure and risk of all-cause and cause-specific mortality in US adults. *JAMA Netw Open*. 2020;3(8):e2011620. [CrossRef]
196. Cai S, Rao X, Ye J, et al. Relationship between urinary bisphenol A levels and cardiovascular diseases in the U.S. adult population, 2003-2014. *Ecotoxicol Environ Saf*. 2020;192:110300. [CrossRef]
197. Chen S, Tao Y, Wang P, et al. Association of urinary bisphenol A with cardiovascular and all-cause mortality: National Health and Nutrition Examination Survey (NHANES) 2003-2016. *Environ Sci Pollut Res*. 2023;30(17):51217-51227. [CrossRef]
198. GBD. Tool for access to GBD data. IHME global health data exchange tool. *GHDx*; 2023. http://ghdx.healthdata.org/gbd-results-tool Accessed 19/12/2023
199. Agency for Toxic Substances and Disease Registry [annual report]; 2018. https://www.atsdr.cdc.gov/2018atsdrannualreport/index.html.
200. Campanale C, Dierkes G, Massarelli C, Bagnuolo G, Uricchio VF. A relevant screening of organic contaminants present on freshwater and pre-production microplastics. *Toxics*. 2020;8(4):100. [CrossRef]
201. Chang JW, Chen HL, Chang CC, Su HJ, Liao PC, Lee CC. Predicting the risk of cardiovascular disease in people exposed to moderate to high levels of dioxin. *J Hazard Mater*. 2011;198:317-322. [CrossRef]
202. Vena J, Boffetta P, Becher H, et al. Exposure to dioxin and nonneoplastic mortality in the expanded IARC international cohort study of phenoxy herbicide and chlorophenol production workers and sprayers. *Environ Health Perspect*. 1998;106(suppl 2):645-653. [CrossRef]
203. Huang M, Jiao J, Zhuang P, Chen X, Wang J, Zhang Y. Serum polyfluoroalkyl chemicals are associated with risk of cardiovascular diseases in national US population. *Environ Int*. 2018;119:37-46. [CrossRef]
204. Mattsson K, Rignell-Hydbom A, Holmberg S, et al. Levels of perfluoroalkyl substances and risk of coronary heart disease: findings from a population-based longitudinal study. *Environ Res*. 2015;142:148-154. [CrossRef]
205. Schillemans T, Donat-Vargas C, Lindh CH, et al. Per- and polyfluoroalkyl substances and risk of myocardial infarction and stroke: a nested case-control study in Sweden. *Environ Health Perspect*. 2022;130(3). [CrossRef]
206. Simpson C, Winquist A, Lally C, Steenland K. Relation between perfluorooctanoic acid exposure and strokes in a large cohort living near a chemical plant. *Environ Res*. 2013;127:22-28. [CrossRef]
207. Winquist A, Steenland K. Modeled PFOA exposure and coronary artery disease, hypertension, and high cholesterol in community and worker cohorts. *Environ Health Perspect*. 2014;122(12):1299-1305. [CrossRef]
208. Bao W, Liu B, Simonsen DW, Lehmler HJ. Association between exposure to pyrethroid insecticides and risk of all-cause and cause-specific mortality in the general US adult population. *JAMA Intern Med*. 2020;180(3):367-374. [CrossRef]
209. Xue Q, Pan A, Wen Y, et al. Association between pyrethroid exposure and cardiovascular disease: A national population-based cross-sectional study in the US. *Environ Int*. 2021;153:106545. [CrossRef]
210. Münzel T, Sørensen M, Lelieveld J, et al. A comprehensive review/expert statement on environmental risk factors of cardiovascular disease. *Cardiovasc Res*. 2025;121(11):1653-1678. [CrossRef]