

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

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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 countries¹⁶ (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 triple 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 population²⁹ 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 thrombin-inflammatory mediators such as interleukin-1 β , 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

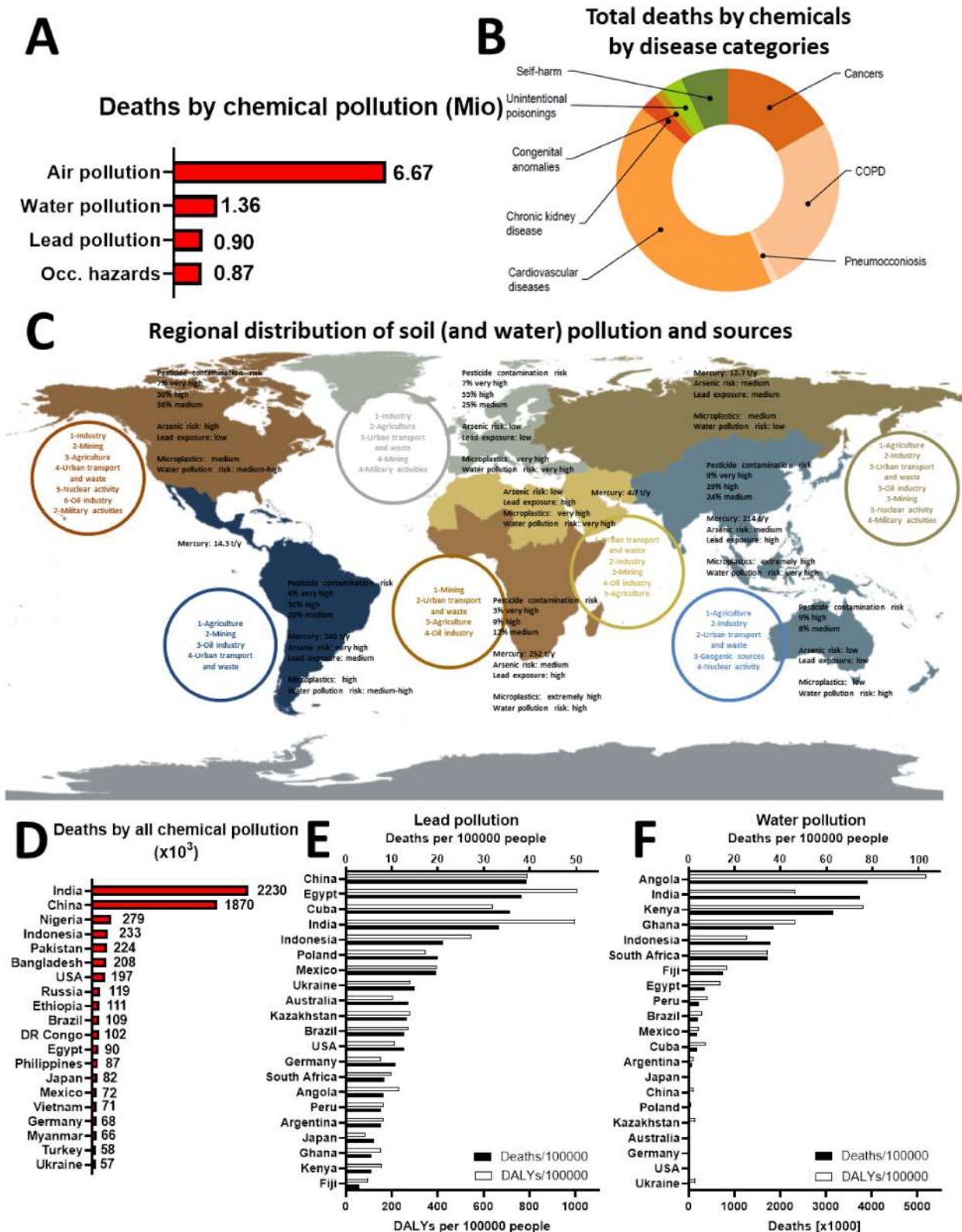


Figure 1. Estimated global annual deaths by all sources of chemical pollution (A)^{3,4} and the disease entities being associated with these deaths (B).²⁸ (C) Regional distribution of chemical soil (and water) pollution with the major sources like industry, mining, and agriculture.¹⁶ The chemical pollution 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). Graph⁸ modified with permission.

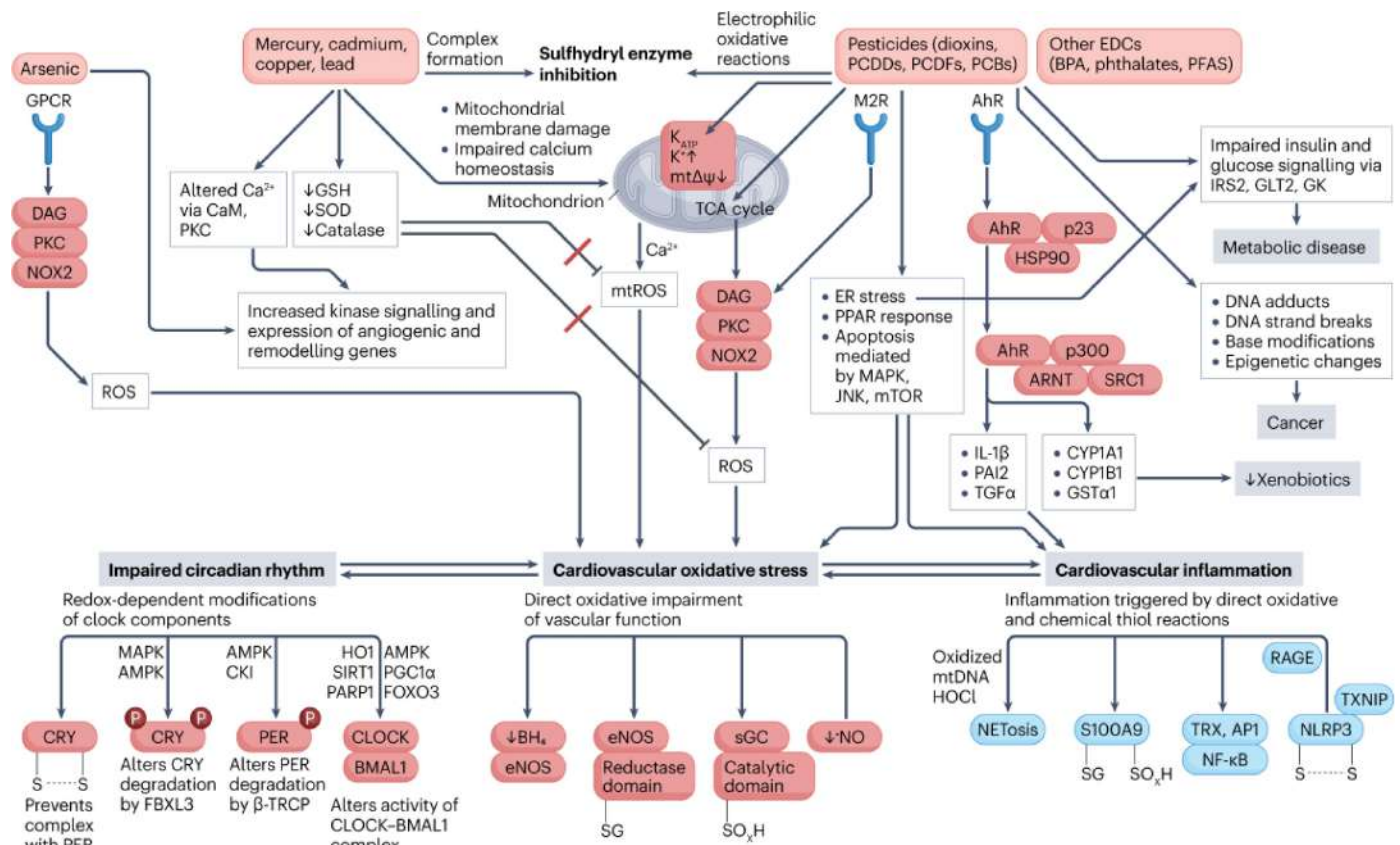


Figure 2. Cellular pathophysiology of metals/metalloids and pesticides. Details and explanation of abbreviations in the text. Pathomechanisms summarized³⁸ for arsenic, for lead,³⁵ for cadmium,³⁴ and³² for pesticides. Oxidative mechanisms of endothelial/vascular dysfunction summarized.⁴⁰ Activating redox mechanisms for inflammation summarized.⁴¹ Other pathomechanisms summarized¹⁵ for heavy metals and³¹ 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. Graph⁸ 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 SENTINEL 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

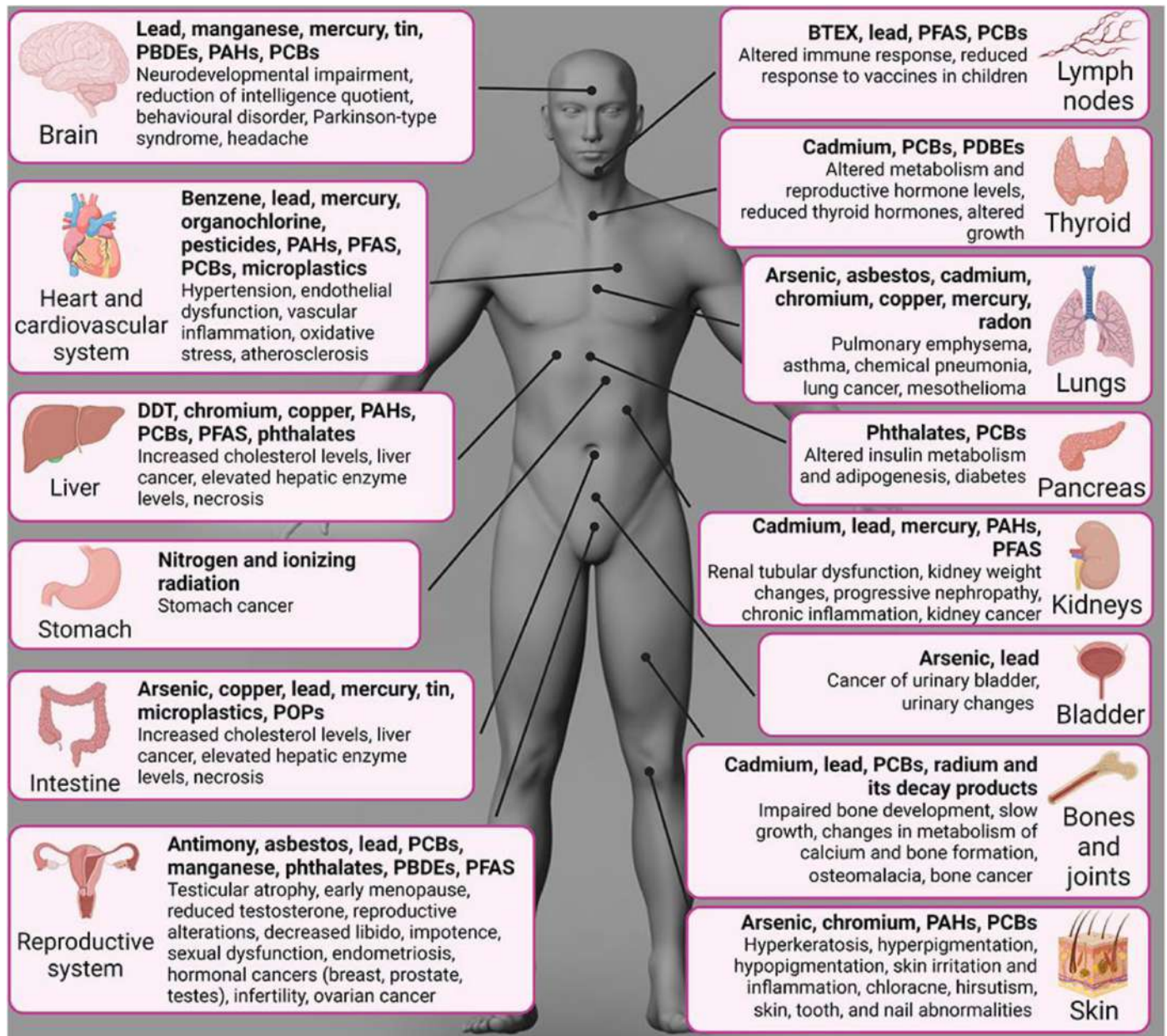


Figure 3. Main effects of soil contaminants on human health, indicating the organs or systems affected and the contaminants causing them. BTEX, refers to the chemicals benzene, toluene, ethylbenzene, and xylene; PBDEs, polybrominated diphenyl ethers; PCBs, polychlorinated biphenyls; PFAS, per- and polyfluoroalkyl 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>. Graph⁹ 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

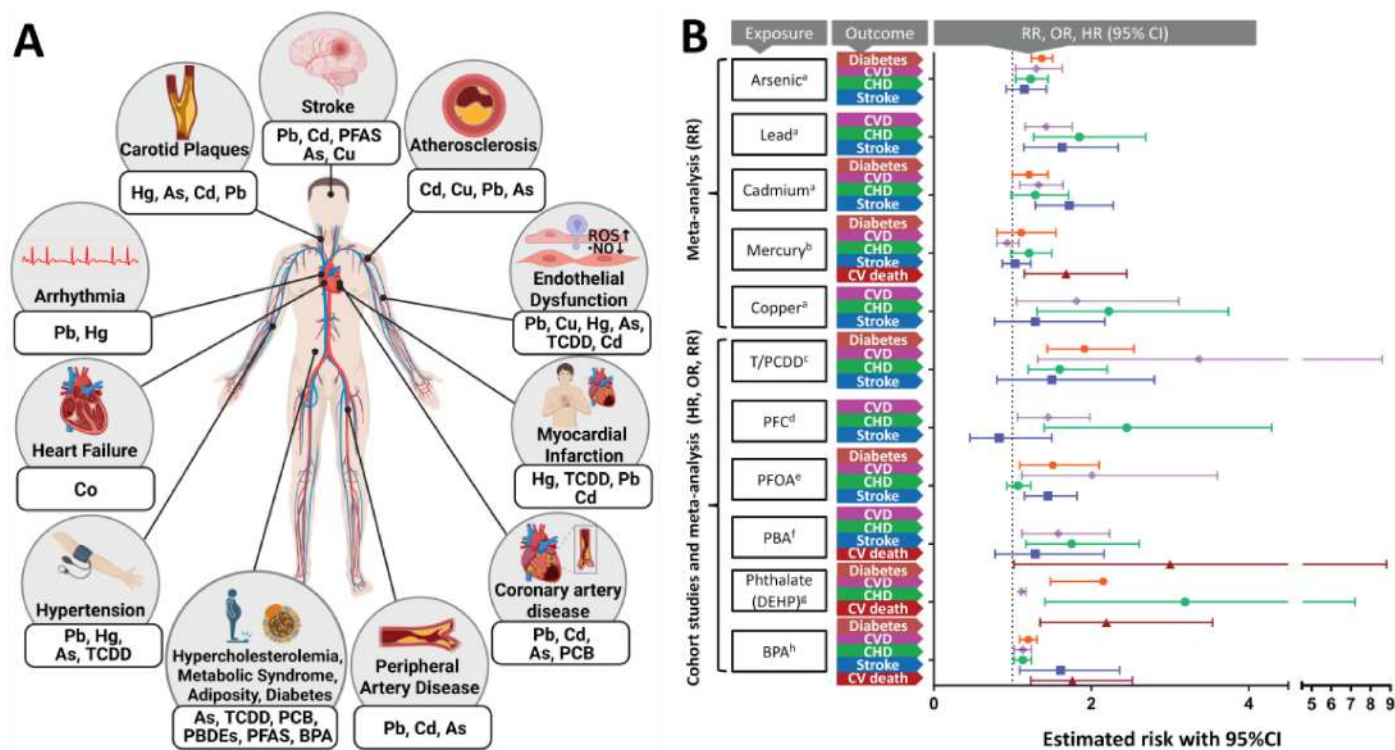


Figure 4. (A) Cardiovascular side effects of toxic chemicals. Graph⁸ modified with permission using biorender.com. (B) Association of metals and pesticides with cardiovascular risk. Data taken from a meta-analysis for all metals ^a except mercury ^b (highest versus lowest tertile or highest versus lowest)^{36,67} 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. Graph²¹⁰ 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 $<1000 \mu\text{m}$), mesoplastics, macroplastics, and megoplastics.¹⁰⁹ Of these, micro- and nanoplastics are of greatest toxicological concern because of their biological mobility, persistence, and capacity to interact with cells and tissues¹¹⁰ (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 inflammatory signaling, accelerating vascular aging, and enhancing thrombosis. In mechanistic terms, they resemble a hybrid toxic exposure, part particle, part chemical mixture, part inflammatory trigger.

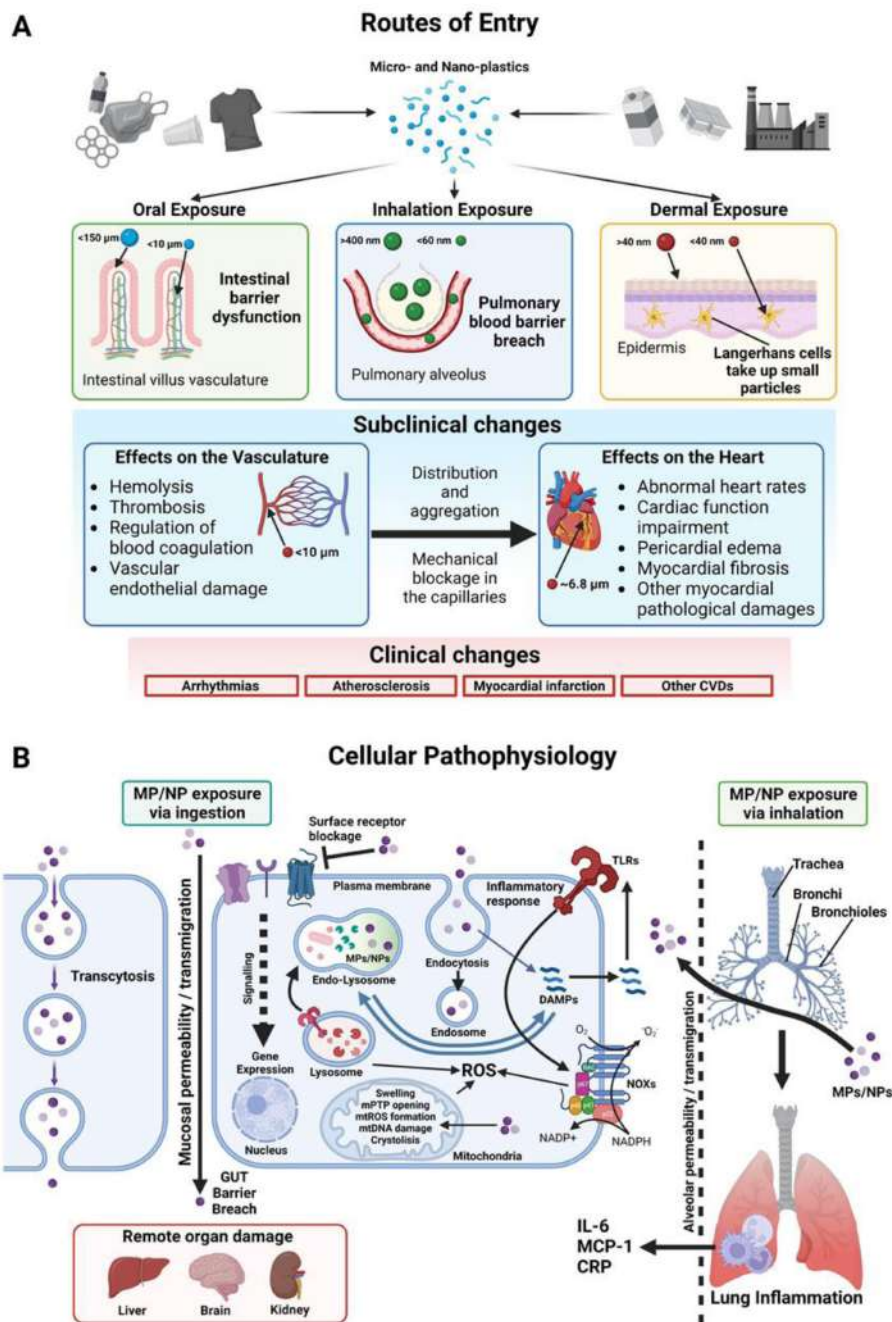


Figure 5. (A) The exposure routes, toxicological, subclinical, and clinical effects of MNPs on the cardiovascular system. Graph⁸ modified with permission using biorender.com. **(B)** Scheme of pathomechanisms of micro- and nanoplastics (MP/NP) toxicity (combination of experimentally confirmed pathomechanisms 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 al¹¹² 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. Graph⁸ 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 Alarming, 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

Annual CVD mortality attributable to dust

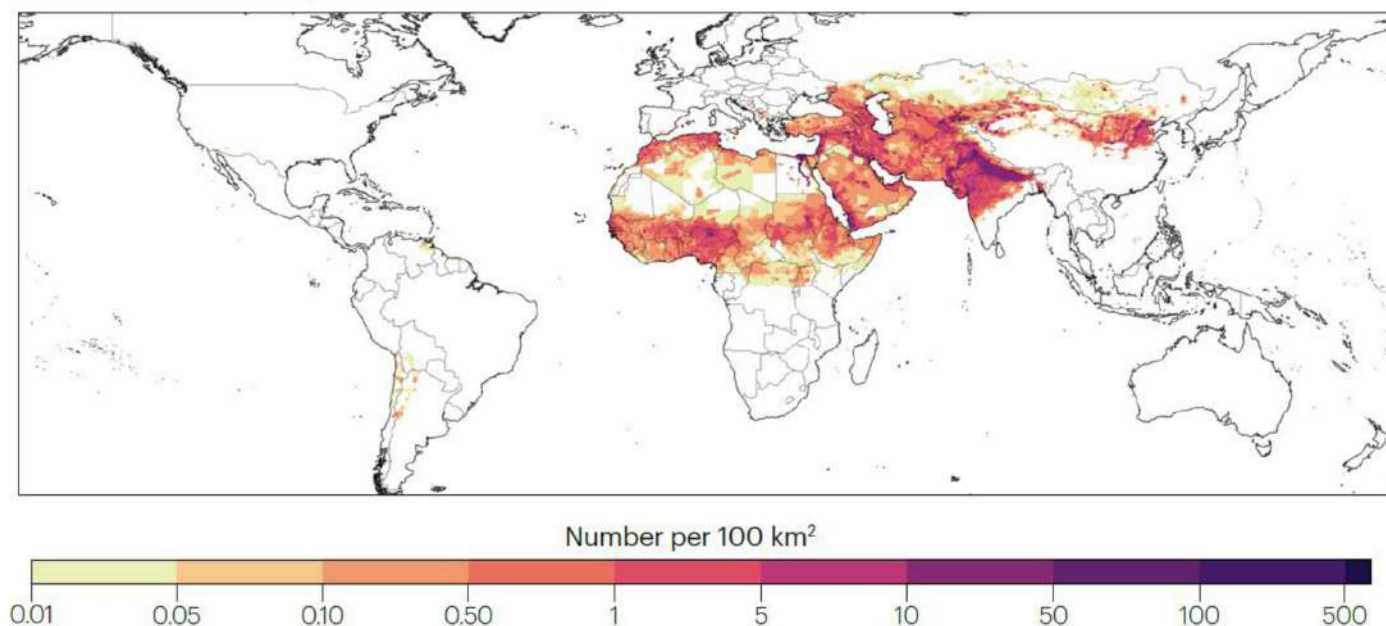


Figure 6. Annual cerebrovascular (stroke) plus ischemic heart disease mortality per area of 10 × 10 km² from exposure to aeolian dust (total CVD mortality). CVD, cardiovascular diseases. Graph⁸ modified with permission.

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 (NH₃). Ammonia contributes to the formation of fine particulate matter (PM_{2.5}) 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 PM_{2.5}-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 (N₂O), 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 (NO_x) concentrations are associated with a higher risk of cardiovascular death.^{161,162} In a cohort study, elevated NO_x 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 TRANSFER 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

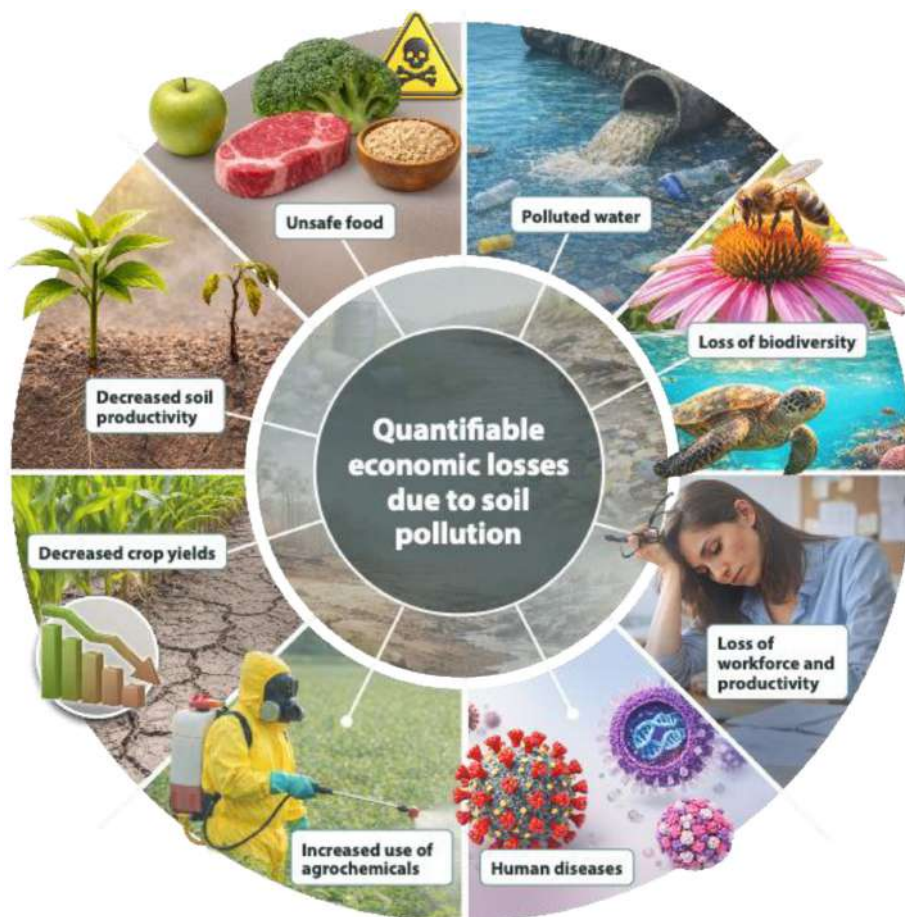


Figure 7. Quantifiable economic losses due to soil pollution. Adapted.¹⁷²

- 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 ($\mu\text{g/g}$ 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 increase 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.

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