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Birjand University of Medical Sciences

Contaminant Metals as Cardiovascular Risk Factors: A Scientific Statement From the American Heart Association

Presented by

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AHA SCIENTIFIC STATEMENT

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Introduction

Cardiovascular disease (CVD) is the predominant cause of death worldwide, leading to at least **18 million** lives lost per year worldwide

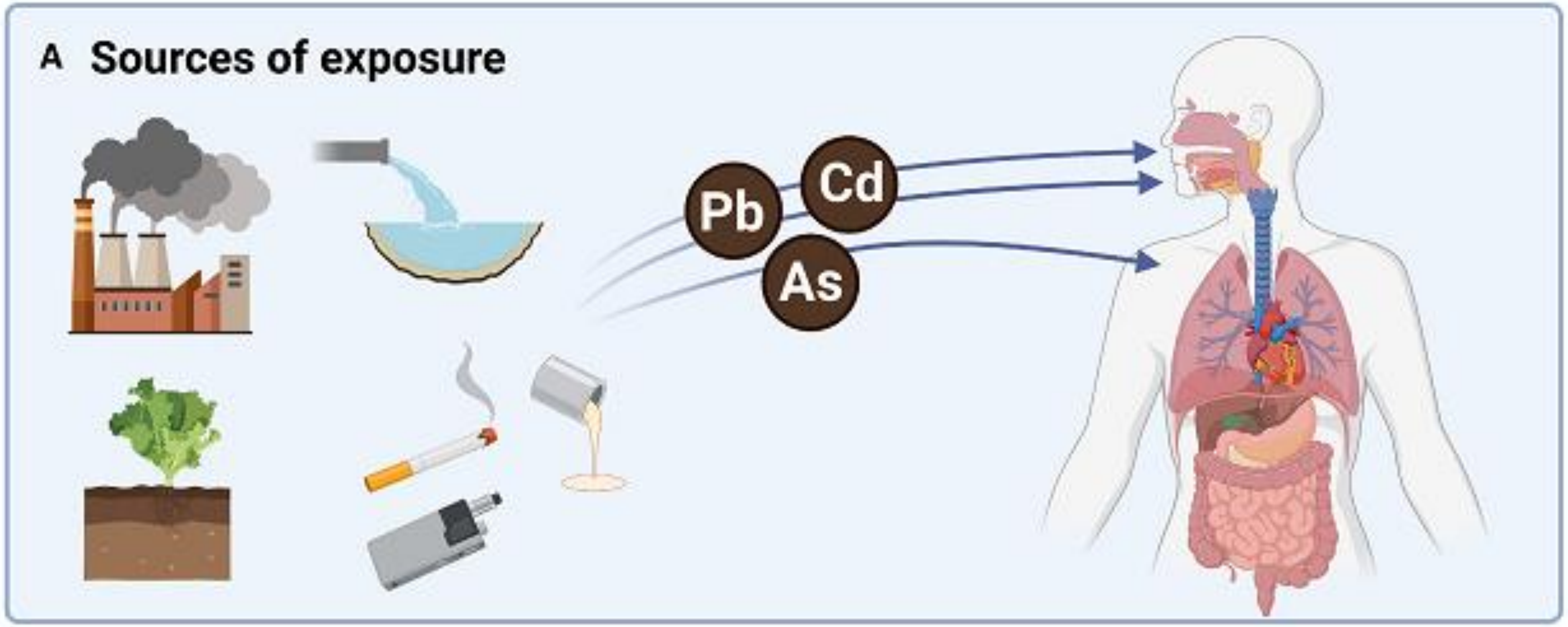
Rapid industrialization, urbanization and economic growth have increased **heavy metal** exposure.

- **Lead** exposure is due to **gasoline**, **cigarette** smoke, **manufacturing** processes, and **domestic** lead-based paints.
- **Cadmium** exposure can be attributed to **cigarette** smoke and **contaminated** food or water
- **Mercury**, the primary source is contaminated **seafood** (e.g., fish, shellfish)

-**Inorganic Arsenic** is a potent toxic and carcinogenic metalloid (intermediate properties between metals and nonmetals) found in water, soil, food (rice), and air.

- **Lead** and **cadmium** may disturb **blood clotting** and increase the risk of CVDs

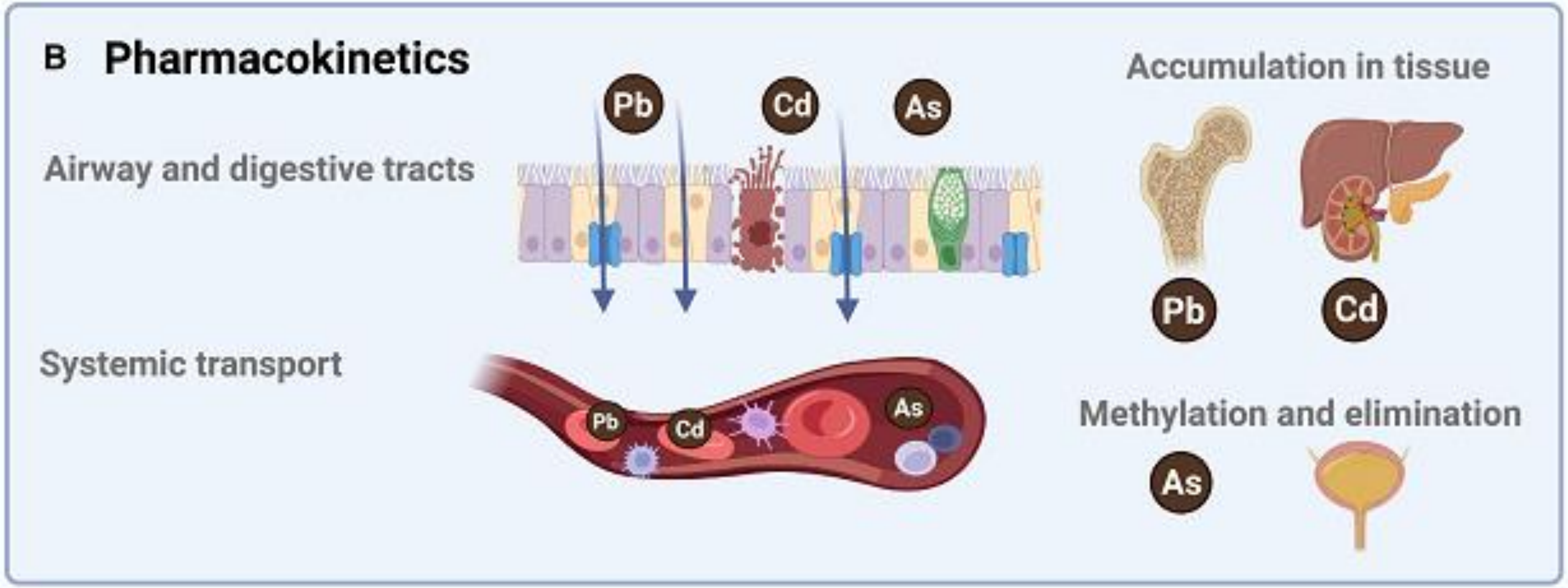
  Heavy metals catalyzes the production of reactive oxygen species (ROS) and induces infammatory mediators leading to damage to endothelial vascular cells.



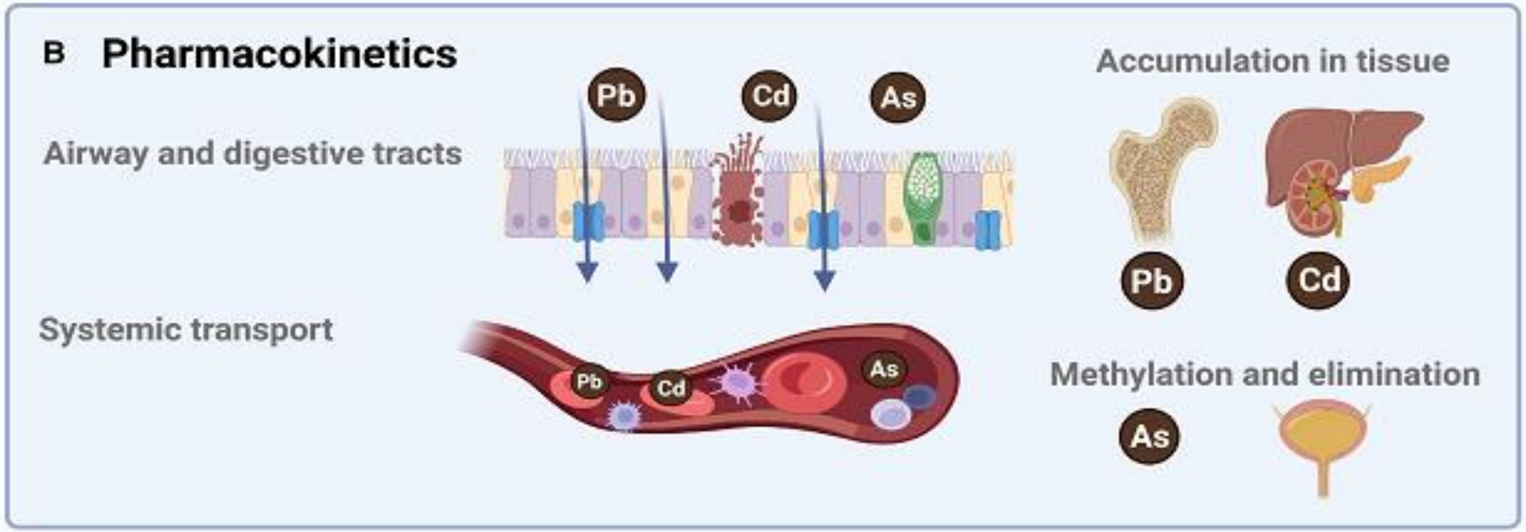
Sources of Exposure and Pharmacokinetics

- Lead production has continued to grow, from **8** million tons globally in 2006 to **12** million tons in 2018.
- Exposed **sources** of **lead and cadmium** including **old paint**, **tobacco** products (conventional cigarettes and **e- cigarettes**), secondhand smoke, acid- lead batteries, contaminated foods.

- Divalent cations and both can be efficiently **absorbed** through the **respiratory** and **gastrointestinal** tracts
- Both metals gain intracellular access **via transporters** of essential metals
- Excretion of these metals has **half-lives** of decades.



- **Arsenic.** Known as a poison for centuries, it was widely used in **medicine** before the introduction of **antibiotics**.
- Inorganic arsenic in water is completely absorbed through the **gastrointestinal** tract using water channels (**aquaporins**)
- After exposure, inorganic arsenic is methylated into **mono- and dimethyl arsenic** compounds, metabolites that are excreted in the **urine**.
- Women, in general, are more efficient arsenic methylators than men.



Biological Mechanisms

❑Endothelial Injury

Cadmium and arsenic enhance endothelial cell expression of adhesion molecules, altering signaling, increasing permeability, and inducing oxidative stress and inflammation, all proatherosclerotic stimuli

❑Inflammatory Mediators

Increased release of proinflammatory cytokines and inflammatory mediators, such as cyclooxygenase-2, lipoxygenases, prostaglandins, and acute phase proteins, such as C-reactive protein

Biological Mechanisms

❑Oxidative Stress

Lead and cadmium **compete** with copper and zinc, essential elements that play a fundamental role on cellular transport and redox balance maintenance. Increased levels of **reactive oxygen** species can increase oxidized lipids/lipoproteins, promoting **atherosclerotic plaque** formation.

❑Lipid Metabolism

Lead and cadmium levels in the body have been associated with differential circulating **lipid profiles.** Arsenic alters cellular lipid homeostasis, such that

macrophages retain lipids resulting in foam cell formation and increased **atherosclerotic plaque**

Biological Mechanisms

❑Heart Rhythm and the ECG

Chronic arsenic exposure interfering with intracellular calcium accumulation in myocardial tissues via reduced surface expression of the cardiac potassium channel human. Increased risk of QT prolongation

❑Epigenomic Effects

Lead, cadmium, and arsenic have epigenomic effects, including effects on DNA methylation and histone modifications, influencing gene expression and downstream transcription. macrophages retain lipids resulting in foam cell formation and increased **atherosclerotic plaque**

Biological Mechanisms

❑Ischemic Heart Disease and Stroke

In general population from Spain, urinary cadmium was associated with incident CVD

In China, cadmium and arsenic were associated with increased incidence of ischemic heart disease, ischemic stroke, and overall stroke

United States, urinary cadmium as well as monomethylarsonate, a metabolite of inorganic arsenic, were positively associated with incident ischemic stroke.

❑Heart Failure

Blood lead has been associated with left ventricular hypertrophy in several studies

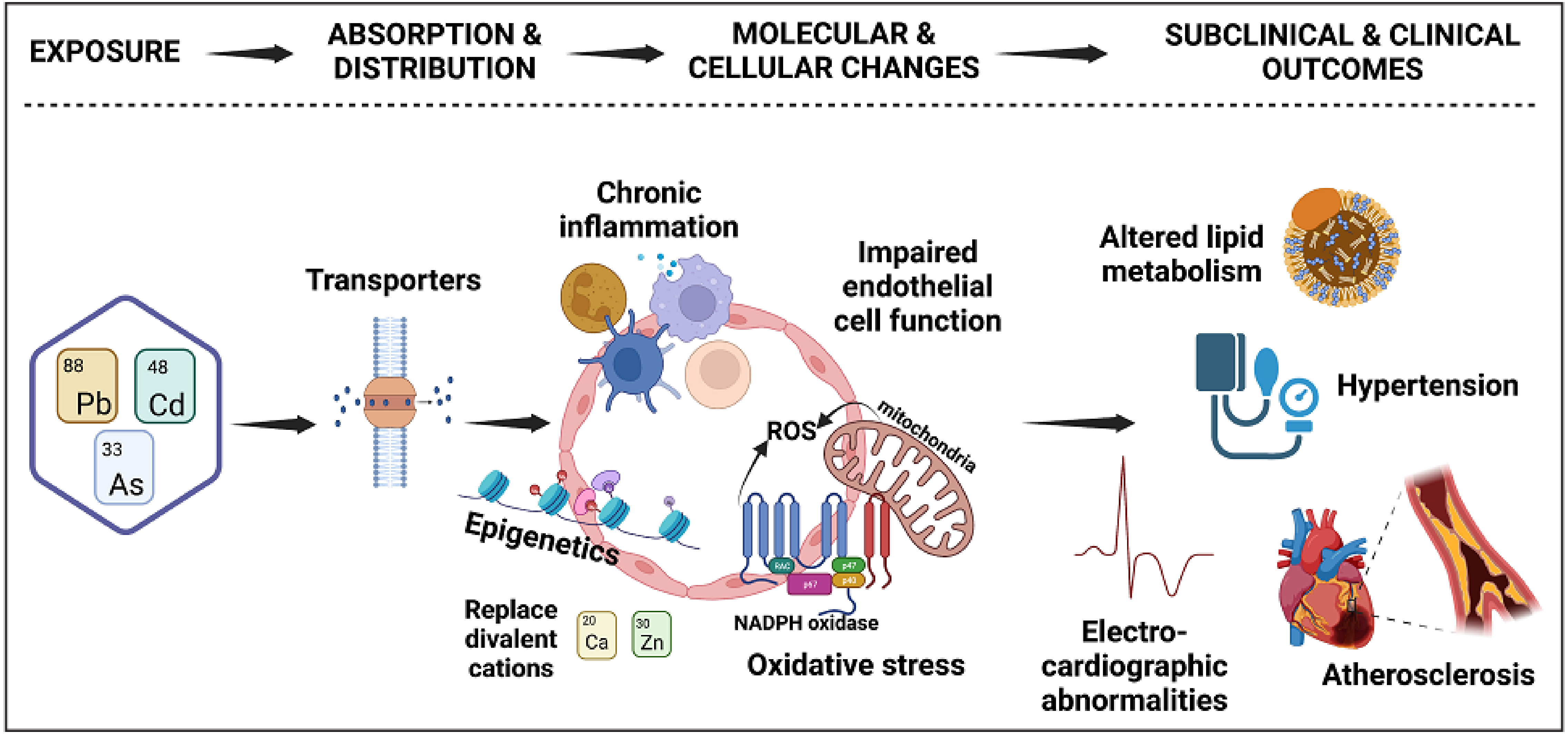
Urinary arsenic and cadmium was positively associated with heart failure incidence

Biological Mechanisms

❑Death

lead, cadmium, and arsenic are associated with premature death, attributable in large part to increased CVD risk.

Studies in Taiwan, Chile, and Bangladesh have consistently shown that arsenic levels in drinking Water **>50 μg/L** are associated with increased all-cause and cardiovascular death.


EXPOSURE
ABSORPTION & DISTRIBUTION
MOLECULAR & CELLULAR CHANGES
SUBCLINICAL & CLINICAL OUTCOMES
88 Pb
48 Cd
33 As
Transporters
Chronic inflammation
Impaired endothelial cell function
Epigenetics
ROS
mitochondria
NADPH oxidase
Replace divalent cations
20 Ca
30 Zn
Oxidative stress
Altered lipid metabolism
Hypertension
Electro-cardiographic abnormalities
Atherosclerosis

Metals	No. studies	No. participants	No. events	Relative risk (95% CI)
Lead				
Cardiovascular disease	10	110 382	4970	1.43 (1.16–1.76)
Coronary heart disease	8	91 779	2228	1.85 (1.27–2.69)
Stroke	6	89 494	518	1.63 (1.14–2.34)
Cadmium				
Cardiovascular disease	6	50 674	3756	1.33 (1.09–1.64)
Coronary heart disease	5	32 070	1654	1.29 (0.98–1.71)
Stroke	3	9123	601	1.72 (1.29–2.28)
Arsenic				
Cardiovascular disease	7	135 943	3208	1.30 (1.04–1.63)
Coronary heart disease	8	190 816	4640	1.23 (1.04–1.45)
Stroke	4	134 526	961	1.15 (0.92–1.43)

Relative risk (95% CI)

Relative risk for top *v* bottom third of baseline level of each contaminant

Interventions

❑Public Health Interventions

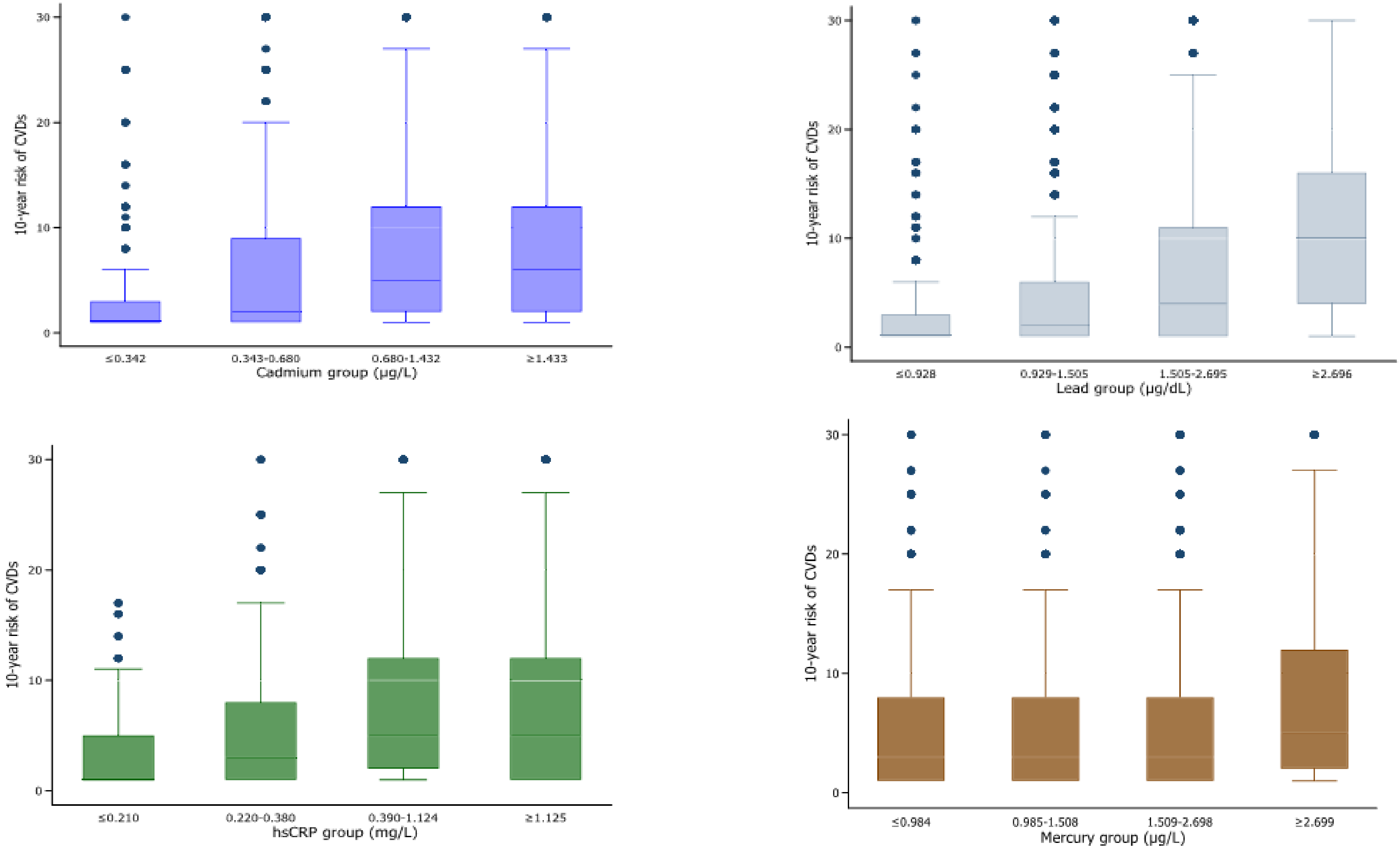
Minimize metal contamination of air, water, food, and soil

Tobacco control

❑Medical Interventions

Chelating agents with high affinity for toxic metals, particularly the edetates (EDTA and its salts), and dimercaptosuccinic acid (succimer) remove contaminant metals, especially lead and cadmium, from the human body.

Healthy diet/lifestyle and nutritional supplementation such as folate (vitamin B-9) and N-Acetyl cysteine.


10-year risk of CVDs
0
10
20
30
≤0.342
0.343-0.680
0.680-1.432
≥1.433
Cadmium group (μg/L)
10-year risk of CVDs
0
10
20
30
≤0.928
0.929-1.505
1.505-2.695
≥2.696
Lead group (μg/dL)
10-year risk of CVDs
0
10
20
30
≤0.210
0.220-0.380
0.390-1.124
≥1.125
hsCRP group (mg/L)
10-year risk of CVDs
0
10
20
30
≤0.984
0.985-1.508
1.509-2.698
≥2.699
Mercury group (μg/L)

Variables	Males (n = 4724) Lead quartiles Quartile 1 ≤ 0.984 (μg/dL)	Quartile 2 0.984–1.509 (μg/dL)	Quartile 3 1.509–2.698 (μg/dL)	Quartile 4 ≥ 2.699 (μg/dL)	p-values	Females (n = 4878) Lead quartiles Quartile 1 ≤ 0.984 (μg/dL)	Quartile 2 0.984–1.509 (μg/dL)	Quartile 3 1.509–2.698 (μg/dL)	Quartile 4 ≥ 2.699 (μg/dL)	p-values
(C) Cardiometabolic factors according to the quartiles of serum lead levels by gender										
Age (year)	35.53 ± 15.82	39.46 ± 15.33	45.56 ± 15.24	51.66 ± 13.20	<0.001	37.35 ± 13.94	44.04 ± 15.53	49.49 ± 14.69	54.93 ± 12.09	<0.001
BMI (Kg/m^2)	24.29 ± 3.86	24.37 ± 3.45	24.35 ± 3.22	24.18 ± 2.95	0.343	22.80 ± 3.69	23.16 ± 3.69	23.65 ± 3.51	24.04 ± 3.31	<0.001
Waist circumference (cm)	84.19 ± 10.61	84.90 ± 9.44	85.32 ± 9.00	85.42 ± 8.38	0.430	76.66 ± 10.96	77.53 ± 10.24	79.29 ± 9.74	80.66 ± 9.29	<0.001
Total cholesterol (mg/dL)	181.31 ± 30.45	185.89 ± 34.47	189.18 ± 37.61	192.27 ± 36.67	0.002	187.84 ± 35.04	187.69 ± 36.53	191.83 ± 37.63	201.15 ± 38.03	<0.001
LDL-C (mg/dL)	108.81 ± 29.29	111.76 ± 28.78	113.85 ± 32.57	114.14 ± 32.48	0.558	106.80 ± 31.20	109.00 ± 32.77	113.03 ± 32.50	123.23 ± 32.99	<0.001
Triglyceride (mg/dL) †	110.5 (37.5–191)	109 (44–168)	126 (52–190)	139 (54–210)	<0.001	81 (36–122)	88 (40–130)	96 (42–142)	112 (45–164.5)	<0.001
HDL-C (mg/dL)	46.68 ± 10.92	46.54 ± 10.85	46.28 ± 11.27	47.02 ± 11.95	0.245	55.37 ± 13.07	53.53 ± 12.30	52.67 ± 12.64	51.08 ± 11.64	<0.001
HbA1c (%)	5.65 ± 1.00	5.71 ± 0.99	5.86 ± 1.06	5.92 ± 0.99	0.0007	5.52 ± 0.79	5.66 ± 0.82	5.77 ± 0.85	5.86 ± 0.79	<0.001
Fasting glucose (mg/dL)	100.68 ± 31.07	98.85 ± 26.08	101.74 ± 27.49	102.21 ± 23.79	0.055	93.03 ± 19.67	96.01 ± 20.16	97.25 ± 21.26	97.54 ± 21.58	0.001
Energy intake (Kcal)	2151.62 ± 978.46	2385.41 ± 981.32	2369.51 ± 961.48	2404.58 ± 969.45	0.177	1781.22 ± 729.61	1726.66 ± 713.00	1701.55 ± 665.56	1622.86 ± 652.54	0.002
Serum creatinine (μmol/L)	0.95 ± 0.16	0.97 ± 0.36	0.97 ± 0.20	0.97 ± 0.21	0.976	0.67 ± 0.10	0.70 ± 0.11	0.71 ± 0.11	0.73 ± 0.20	<0.001
ALT (U/L) †	18 (10–31)	21 (10–33)	22 (11–32)	22 (11–31)	0.699	12 (7–18)	14 (7–19)	15 (8–21)	16 (9–22)	0.009
AST (U/L) †	19.5 (13–24)	21 (13–26)	22 (15–27)	22 (15–28)	0.076	17 (13–20)	18 (13–21)	19 (13–23)	20 (14–24)	<0.001
SBP (mmHg)	118.25 ± 13.33	118.00 ± 13.33	120.05 ± 14.01	124.46 ± 16.57	<0.001	109.70 ± 13.95	112.95 ± 16.21	117.55 ± 17.72	121.92 ± 17.72	<0.001
DBP (mmHg)	75.91 ± 9.48	77.42 ± 9.54	79.20 ± 10.20	81.03 ± 10.85	<0.001	71.51 ± 8.98	72.51 ± 9.23	74.90 ± 9.76	77.43 ± 9.86	<0.001
Serum cotinine (ng/mL) †	2.50 (0.27–512.02)	4.39 (0.18–817)	13.20 (0.24–1135.96)	97.82 (0.33–1330.00)	<0.001	0.674 (0.06–3.08)	0.84 (0.07–4.56)	1.79 (0.01–8.49)	3.15 (0.01–10.83)	0.002

Conclusions:

Exposure to metals constitutes a significant risk factor for CVD, including ischemic heart disease, stroke, and peripheral artery disease (PAD). Contaminant metals may replace biologically essential metals bound to critical proteins and that such protein dysfunction contributes to tissue oxidative stress as well as local and systemic inflammation.

Prevent and treat water, air, soil, and food pollution incorporating cost– benefit analyses that estimate the cardiovascular benefits.

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Toxic Mechanisms of Five Heavy Metals: Mercury, Lead, Chromium, Cadmium, and Arsenic

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Thank you for your attention

Metal	Specimen (half-life)	Method	Additional information	Possible reference value for adults
Lead	Blood (30–100 d)* Bone (decades) Postchelation urine (decades)†	ICPMS K-shell XRF ICPMS	Blood is the common marker Postchelation urine is an established measure of total body burden	3.5 μg/dL (similar to children) ... ...
Cadmium	Blood (30–100 d)* Urine (decades) Postchelation urine (unknown)†	ICPMS ICPMS ICPMS	Smokers have markedly high levels	1.0 μg/L both blood and urine‡ (based on NHANES)
Arsenic	Urine (1–30 d) Toenail (weeks of exposure 6 prior mo)	ICPMS ICPMS or nuclear activation analysis	Avoid seafood for 7 d before sample Measurement error is large	5 μg/L (based on water standards)‡ ...

ICPMS indicates inductively coupled plasma mass spectrometry; NHANES, National Health and Nutrition Examination Survey; and XRF, x-ray fluorescence.

*Reflects both exogenous and endogenous exposure from bone and other tissues.

†Chelating agents for lead are intravenous (EDTA) or oral (dimercaptosuccinic acid [succimer]); the chelatable urine lead is considered a marker of lead body burden. Intravenous EDTA also chelates cadmium, however, whether postchelation urine cadmium reflects total cadmium body burden is not established.

‡First morning urine void (for spot urine samples, report per gram of creatinine). For cadmium, this limit is around 3 times the geometric mean in urine in NHANES (similar for blood). For arsenic, the measure of total arsenic requires no seafood in the preceding 7 days or using arsenic speciation (sum inorganic and methylated species). The possible guideline is proposed on the basis of the drinking water standard in New Jersey and New Hampshire and that the ratio in water and urine is 1.