Environment, Health and Justice: The Power of Community and Inter-disciplinary Science

Ana Navas-Acien, MD, PhD
Environmental Health Sciences
Columbia University Mailman School of Public Health
Mission: integrate **systems science**, **innovative technology** and **Indigenous knowledge** to protect the Northern Plains water resources and communities from hazardous metals.
Indigenous principles that motivate our work and partnership

• Collective leadership

• Value traditional knowledge
  - Water is life (Mní wičhóni)
  - 7 generations principle
  - Relationality – connections in a circular rather than linear process

• Accept research codes the tribes have developed:
  - Sovereignty and data ownership
  - Tribes RRBs and Indian Health Service IRBs
    - Protocols, publications, lay summaries
  - Communication of study findings (individuals, community)
Data ownership and data sharing

• Who owns the data?

• Who allows data sharing and in which terms?

• Who profits from research
Data ownership and data sharing

“Data are not a gift. At best, they are ‘on loan’, and hence revocable if misused. Data are a responsibility. Not an entitlement.”

– Tsosie, Fox and Yracheta.

Nature 2021

Krystal Tsosie
Keolu Fox
Joseph Yracheta
El Ejido, Almeria, South East Spain

Aljibe in El Ejido, Almeria
Traditional water collection system
Occupation, Exposure to Chemicals and Risk of Gliomas and Meningiomas in Sweden

Ana Navas-Acien, MD, MPH, Marina Pollan, MD, PhD, Per Gustavsson, MD, PhD, and Nils Plato, PhD

<table>
<thead>
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<td>12</td>
<td>1.68</td>
<td>1.76 0.99–3.14</td>
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</tbody>
</table>

Madrid, Spain
Eliseo Guallar

Ellen Silbergeld

Cardiovascular and Metal Epidemiology

Baltimore, MD, USA
Lead, Cadmium, Smoking, and Increased Risk of Peripheral Arterial Disease

Ana Navas-Acien, MD, MPH; Elizabeth Selvin, MPH; A. Richey Sharrett, MD, DrPH; Emma Calderon-Aranda, PhD, MD; Ellen Silbergeld, PhD; Eliseo Guallar, MD, DrPH

*Circulation.* 2004;109:3196-3201

Blood Lead and PAD – Odds Ratio (95% CI) NHANES 1999-2000

- Adjusted for age, sex, race, education, body mass index, alcohol intake, hypertension, diabetes, hypercholesterolemia, glomerular filtration rate and C-reactive protein
- Further adjusted for smoking status (never/former/current) and serum cotinine

Baltimore, MD, USA
Indigenous communities in the US suffer from an epidemic of cardiovascular disease and diabetes

• Highest coronary heart disease rates in the US
  • Over 1/3 of deaths occur before the age of 65 years
  • Diabetes burden is 3x higher than in White communities

• European colonization and US policies have contributed to these inequalities

• Sovereignty, cultural resilience, and traditional knowledge: core values and positive influences

Breathett et al. Circulation 2020
Arsenic in US drinking water

Groundwater

Community Water Systems

Private well probability arsenic > 10 µg/L

Community water system arsenic concentration

Nigra et al. EHP 2020
Spaur et al. STOTEN 2021
Mining and metal exposures in Indigenous Communities

County average uranium levels (µg/L) in public water systems, 2000-2011

Lewis et al. Current Environmental Health Reports 2017

Ravalli et al. Lancet Public Health 2022
Arsenic and uranium spatially correlate in water samples in Strong Heart Water Study communities in South Dakota.

Sobel et al. Environ Polluton 2021
Conceptual framework

Water → Metal biomarkers → Mechanistic markers → Clinical disease

Air → Metal biomarkers

Food → Metal biomarkers

Genetics, metabolism, nutrition, co-exposures, co-morbidities
Strong Heart Study

Funded by the National Heart, Lung and Blood Institute since 1988 and the National Institute of Environmental Health Sciences since 2012

N = 7,600 adults
13 tribes and communities

http://strongheart.ouhsc.edu/

SHS field team, South Dakota

SHS annual Steering Committee meeting, Eagle Butte, SD 2015
Metal mixtures in urban and rural populations in the US: The Multi-Ethnic Study of Atherosclerosis and the Strong Heart Study


- Arsenic, tungsten and uranium levels higher in SHS participants than MESA participants
- Cluster of these 3 metals in the SHS supports water as a source of contamination
- Private well and community water systems in the SHS contribute to 46% of variation in urinary As levels in SHS (Spaur et al. 2023)
- Community water systems As and U in MESA contribute to 30% and 49% of variation in As in U, respectively (Spaur et al. 2023)
Prospective cohort study

Original Strong Heart Study
4,549 adults 45-74 y

Phase 1
1989-91

Phase 2
1993-95

Phase 3
1998-99

64% baseline response rate

89% retention rate

Ongoing Surveillance: Morbidity & Mortality

Phase 3 pilot
1998-99

Phase 4
2001-03

Phase 5
2006-09

Phase 6
2014-16

Phase 7
2022-24

Strong Heart Family Study
3,050 participants ≥14 y

NIH National Heart, Lung, and Blood Institute

NIH NIEHS

COLUMBIA Mailman School of Public Health
ENVIRONMENTAL HEALTH SCIENCES
Arsenic and Cardiovascular Disease

- Strong Heart Study participants 45-74 y.o. at baseline (Moon et al. 2013)
Arsenic and Cardiovascular Disease

• Strong Heart Study participants 45-74 y.o. at baseline (Moon et al. 2013)

• Strong Heart Family Study participants 14-49 y.o. at baseline (Pichler et al. 2019)
Arsenic and Cardiovascular Disease

- Strong Heart Study participants 45-74 y.o. at baseline (Moon et al. 2013)
- Consistent findings in rural Colorado: San Luis Valley Diabetes Study (James et al. EHP 2015)
- Strong Heart Family Study participants 14-49 y.o. at baseline (Pichler et al. 2019)
- Consistent findings in a ApoE-/- model

Consistent findings in rural Colorado: San Luis Valley Diabetes Study (James et al. EHP 2015)

Strong Heart Family Study participants 14-49 y.o. at baseline (Pichler et al. 2019)

Tap water arsenic for 13 weeks
Impact of reducing lead exposure in systolic blood pressure

- 278 participants with repeated blood lead measures
- Lead modeled as changes from 1997-1999 to 2006-2009
- Primary outcome: changes in systolic blood pressure levels from 2001-2003 to 2006-2009
- Adjusted for sex, age, center, BMI, years of education, smoking status, estimated glomerular filtration rate, hypertension treatment, and baseline systolic blood pressure levels

Change in systolic blood pressure by changes in blood lead from 1997-99 to 2006-2009 (n=278)

Lieberman-Cribbin et al. JAHA In press
Temporal changes in lead and cadmium exposure and the reduction in CVD mortality observed in the US


Figure 1. Age-, sex- and race-adjusted geometric mean blood lead and urine cadmium concentrations and cardiovascular disease (CVD) mortality rates across 1988–2004 National Health and Nutrition Examination Survey phases. Vertical bars show 95% confidence intervals based on 15000 bootstrap re-samples.
Temporal changes in lead and cadmium exposure and the reduction in CVD mortality observed in the US

Prevention and control strategies

Main objective:
• Prevent / reduce exposure to metals in the environment

Other strategies:
• Mitigate health effects of toxic metals: nutrition
  • Folic acid and arsenic
  • Zinc and cadmium
  • Calcium and lead
  • Selenium and arsenic

• Eliminate metals from the body: chelation
Mni Wiconi water reaching Pine Ridge reservation

Gathering heralds arrival of lines that carry clean water

Mary Garrigan, Journal staff  Aug 19, 2008

Workers for S&L Louis, a construction company out of St. Paul, Minn., dig a trench Wednesday for pipe west of Wanblee. When finished, this pipeline will bring water from the Missouri River to Potato Creek, Kyle and Red Shirt. (Photo by Ryan Soderlin, Journal staff)

WANBLEE - Words of congratulations and gratitude for the arrival of Missouri River water to the Pine Ridge Indian Reservation flowed freely at a Mni Wiconi connection dedication here Wednesday. But the people who live in this small community on the reservation's northeastern edge will have to wait a few more months for the water itself to begin flowing into their homes.

About 250 people gathered in the Crazy Horse School gymnasium to mark a milestone for the rural water project, whose Lakota name translates to "Water is life."
Mission: integrate systems science, innovative technology and Indigenous knowledge to protect the Northern Plains water resources and communities from hazardous metals.
Strong Heart Water Study for Private Wells

• Participatory randomized trial in South Dakota
• Filters installed to eliminate arsenic in drinking water
• Education intervention vs. standard information

Thomas et al. Sci Tot Environ 2019
George et al. EHP under 3rd review
Metallomics

Collective characterization and quantification of metal and metalloid molecules that translate into the structure, dynamics and function of an organism or system.

**Elements**
- ICPMS

**Species**
- HPLC-ICPMS

**Isotopes**
- MC-ICPMS

ICPMS: Inductively couple plasma mass spectrometry
HPLC: High performance chromatography
MC: multi-collector to measure ions
### The metallome in the human body

#### Essential Elements

<table>
<thead>
<tr>
<th>Element</th>
<th>g-level</th>
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<tbody>
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<td>Phosphorus</td>
<td>780</td>
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<tr>
<td>Potassium</td>
<td>140</td>
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<tr>
<td>Sulfur</td>
<td>140</td>
</tr>
<tr>
<td>Sodium</td>
<td>100</td>
</tr>
<tr>
<td>Chlorine</td>
<td>95</td>
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<tr>
<td>Magnesium</td>
<td>19</td>
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<td>Iron</td>
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<tr>
<td>Fluorine</td>
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<td>Zinc</td>
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<td>Silicon</td>
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#### Non-essential Elements

<table>
<thead>
<tr>
<th>Element</th>
<th>mg-level</th>
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<tbody>
<tr>
<td>Rubidium</td>
<td>680</td>
</tr>
<tr>
<td>Strontium</td>
<td>320</td>
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<tr>
<td>Bromine</td>
<td>260</td>
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<tr>
<td>Lead</td>
<td>120</td>
</tr>
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<td>Copper</td>
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<td>Aluminum</td>
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<tr>
<td>Cadmium</td>
<td>60</td>
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<tr>
<td>Barium</td>
<td>22</td>
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<tr>
<td>Iodine</td>
<td>20</td>
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<tr>
<td>Nickel</td>
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<td>Selenium</td>
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<td>Chromium</td>
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<td>Manganese</td>
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<td>Arsenic</td>
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<tr>
<td>Lithium</td>
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<td>Cesium</td>
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<td>Mercury</td>
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<tr>
<td>Molybdenum</td>
<td>5</td>
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<td>Cobalt</td>
<td>3</td>
</tr>
<tr>
<td>Antimony</td>
<td>2</td>
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</tbody>
</table>

#### Others (essential and non-essential)

- Tellurium: 800 µg-level
- Lanthanum: 700 µg-level
- Uranium: 100 µg-level
- Vanadium: 100 µg-level
- Tungsten: 200 µg-level

#### Biological samples
- Urine
- Whole blood
- Serum

*Courtesy: Kathrin Schilling*
Metal analysis in MESA urine

Exam 1: n = 6,814 (collected in 2000-2002)
Exam 5: n = 943 (collected in 2010-2011)

Elements: As, Ba, Cd, Co, Cs, Cu, Gd, Mn, Mo, Ni, Pb, Se, Sr, Tl, U, W, Zn

Arsenic species: inorganic As (iAs), methylarsonate (MMA), dimethylarsinate (DMA), arsenobetaine (AB), unknown species

Selenium species: trimethylselenonium ion (TMSe), selenite, other

HPLC-ICP-QQQ-MS

ICPMS

Columbia METALab Team
Kathrin Schilling
Chiugo Izuchukwu
Rony Glabonjat
Olgica Balac

R01ES028758
Urinary metals and incident cardiovascular disease

**Non-essential metals**

- Inorganic arsenic, ug/g
- Cadmium, ug/g
- Cobalt, ug/g
- Tungsten, ug/g
- Uranium, ug/g
- Selenium, ug/g
- Zinc, ug/g

**Essential metals**

- Metals modeled as restricted cubic splines with 10th percentile as the reference

- Adjusted for age, sex, race, eGFR, smoking status, BMI and strata for study center

- Further adjusted for diabetes status, SBP, antihypertensive treatment, total cholesterol, HDL, lipid-lowering medication

Metals modeled as restricted cubic splines with 10th percentile as the reference

Adjusted for age, sex, race, eGFR, smoking status, BMI and strata for study center

Further adjusted for diabetes status, SBP, antihypertensive treatment, total cholesterol, HDL, lipid-lowering medication
Urinary metals and total mortality

Non-essential metals

Essential metals

Metals modeled as restricted cubic splines with 10\textsuperscript{th} percentile as the reference

- Adjusted for age, sex, race, eGFR, smoking status, BMI and strata for study center
- Further adjusted for diabetes status, SBP, antihypertensive treatment, total cholesterol, HDL, lipid-lowering medication
Cadmium-Metallothionein Complex

Cadmium Toxicity

Figure by Koren Mann

Ujueta et al. Tox Sci 2021
Conceptual framework

Water

Air

Food

Metal biomarkers → Mechanistic markers → Clinical disease

Genetics, metabolism, nutrition, co-exposures, co-morbidities
Arsenic and cardiovascular disease: mediation via epigenetic mechanisms

- N=2321 participants
- 847 (36.4%) cases of incident CVD through 2009

21 CpGs associated with As-related CVD in the Strong Heart Study

Domingo-Relloso et al. *Circ Res* 2022
Arsenic and cardiovascular disease: mediation via epigenetic mechanisms

- N=2321 participants
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21 CpGs associated with As-related CVD in the Strong Heart Study

Association DNAm & CVD: Replicated in FHS, WHI & MESA for 6 CpGs

Association As & DNAm: Replicated in MESA for 2 CpGs

Gene functions related to: Diabetes & redox signaling

Domingo-Relloso et al. Circ Res 2022
Arsenic and cardiovascular disease: mediation via epigenetic mechanisms

- N=2321 participants
- 847 (36.4%) cases of incident CVD through 2009

Inter-species comparison:

CpGs associated with As and As-mediated CVD with supportive mouse liver DNAm data from Koren Mann’s lab

<table>
<thead>
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<th>Tagged gene</th>
<th>Function</th>
<th>As</th>
<th>As-med. CVD</th>
<th>Exp. data</th>
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<td>SLC7A11</td>
<td>GSH biosynthesis</td>
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<td>CSNK1D</td>
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<td>ATG16L2</td>
<td>Autophagy pathway (diabetes)</td>
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<td>APBB2</td>
<td>Beta cell function (diabetes)</td>
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<td>TYMP</td>
<td>Angiogenesis, endothelial cell growth</td>
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<td>Type 1 collagen</td>
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<td>TXNIP</td>
<td>Thioredoxin interacting protein</td>
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<td>MAPK8</td>
<td>Mitogen-activated protein kinase 8</td>
<td>X</td>
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</table>

*Other models different from K. Mann’s lab.

Association DNAm & CVD: Replicated in FHS, WHI & MESA for 6 CpGs

Association As & DNAm: Replicated in MESA for 2 CpGs

Gene functions related to: Diabetes & redox signaling

Domingo-Relloso et al. Circ Res 2022
Metals and epigenetic age acceleration

Change in epigenetic age acceleration for the joint distribution of urinary metals using Bayesian kernel machine regression

Adjusted for sex, estimated cell type proportions (CD4T, CD8T, NK, Monocytes, and B cells), genetic principal components, education level, smoking status, EpiSmokEr probability values, study center, BMI, estimated glomerular filtration rate and fasting plasma glucose.
Prevention and control strategies

Main objective:
• Prevent / reduce exposure to metals in the environment

Other strategies:
• Mitigate health effects of toxic metals: nutrition
  • Folic acid and arsenic
  • Zinc and cadmium
  • Calcium and lead
  • Selenium and arsenic

• Eliminate metals from the body: chelation
Can chelation reduce cardiovascular disease by increasing the elimination of divalent toxic metals?

Ethylenediaminetetraacetic acid (EDTA)
Effect of Disodium EDTA Chelation Regimen on Cardiovascular Events in Patients With Previous Myocardial Infarction

The TACT Randomized Trial

Gervasio A. Lamas, MD
Christine Goertz, DC, PhD
Robin Boineau, MD, MA
Daniel B. Mark, MD, MPH
Theodore Rosen, MD
Richard L. Nabin, PhD, MPH
Lauren Lindblad, MS
Eldrin F. Lewis, MD, MPH
Jeanne Drisko, MD
Kerry L. Lee, PhD
for the TACT Investigators

Importance Chelation therapy with disodium EDTA has been used for more than 50 years to treat atherosclerosis without proof of efficacy.

Objective To determine if an EDTA-based chelation regimen reduces cardiovascular events.

Design, Setting, and Participants Double-blind, placebo-controlled, 2 x 2 factorial randomized trial enrolling 1708 patients aged 50 years or older who had experienced a myocardial infarction (MI) at least 6 weeks prior and had serum creatinine levels of 2.0 mg/dL or less. Participants were recruited at 134 US and Canadian sites. Enrollment began in September 2003 and follow-up took place until October 2011 (median, 55 months). Two hundred eighty-nine patients (17% of total; n=115 in the EDTA group and n=174 in the placebo group) withdrew consent during the trial.

Interventions Patients were randomized to receive 40 infusions of a 500-mL chelation solution (3 g of disodium EDTA, 7 g of ascorbate, 8 vitamins, electrolytes, pro- caine, and heparin) (n=839) vs placebo (n=869) and an oral vitamin-mineral regimen vs an oral placebo. Infusions were administered weekly for 30 weeks, followed by 10 infusions 2 to 8 weeks apart. Fifteen percent discontinued infusions (n=38 [16%] in the chelation group and n=41 [15%] in the placebo group) because of adverse events.

Main Outcome Measures The prespecified primary end point was a composite of total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for angina. This report describes the intention-to-treat comparison of EDTA chelation vs placebo. To account for multiple interim analyses, the significance threshold required at the final analysis was $P = 0.036$.
Effect of Disodium EDTA Chelation Regimen on Cardiovascular Events in Patients With Previous Myocardial Infarction
The TACT Randomized Trial

Gervasio A. Lamas, MD
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Theodore Rosen, MD
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**EDTA: Placebo**

<table>
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<tr>
<th>HR (95% CI)</th>
<th>P = 0.035</th>
</tr>
</thead>
<tbody>
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<td>0.82 (0.69, 0.99)</td>
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**With Diabetes:**

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>P = 0.002 (Bonferroni adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.59 (0.44, 0.79)</td>
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</table>
• 1000 participants randomized
• Study will be unblinded in the next few months
• **Blood and urine metals measured at the CDC at infusions 1, 5, 20, and 40:**
  • Evaluate their role as potential mechanisms for the cardiovascular benefits of EDTA
  • Conduct risk stratification pre-specified analyses
ABCDE for CVD prevention

Focused on life styles and clinical care

Add E for Environment:

Credit: Roger Blumenthal (based on the American College of Cardiology and American Heart Association Primary Prevention Guidelines)

Arnett et al. Circulation 2019
ABCDE for CVD prevention

Focused on life styles and clinical care

Add E for Environment:

Credit: Roger Blumenthal (based on the American College of Cardiology and American Heart Association Primary Prevention Guidelines)

Arnett et al. Circulation 2019
CLINICAL STATEMENTS AND GUIDELINES

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

Gervasio A. Lamas, MD, FAHA; Aruni Bhatnagar, PhD, FAHA; Miranda R. Jones, MHS, PhD; Koren K. Mann, PhD; Khurram Nasir, MD, MPH, FAHA; Maria Tellez-Plaza, MD, PhD; Francisco Ujueta, MD, MS; Ana Navas-Acien, MD, PhD; the American Heart Association Council on Epidemiology and Prevention; Council on Cardiovascular and Stroke Nursing; Council on Lifestyle and Cardiometabolic Health; Council on Peripheral Vascular Disease; and Council on the Kidney in Cardiovascular Disease
Summary

• Contaminant metal exposures are widespread affecting all populations
  • Disproportionately affect rural and Indigenous communities near abandoned mines

• Metals are cardiovascular risk factors
  • Full characterization is pending
  • Gene-metal interaction and –omics analyses require large consortia and experimental work

• Caution: interpretation of metal biomarkers is complex

• Metallomics provide exciting new opportunities for prevention, interventions, and diagnosis to improve patients and populations’ health
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