

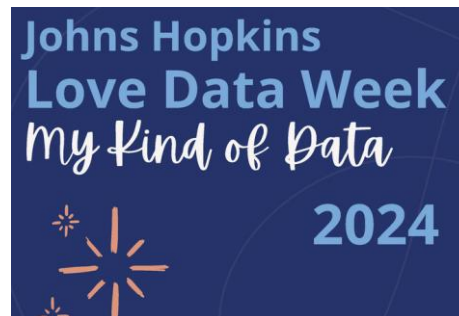


Environment, Health and Justice: The Power of Community and Inter-disciplinary Science

Ana Navas-Acien, MD, PhD

Environmental Health Sciences

Columbia University Mailman School of Public Health





Design: Tammy Granados

Mission: integrate **systems science**,
innovative technology and
Indigenous knowledge to protect the
Northern Plains water resources and
communities from hazardous metals

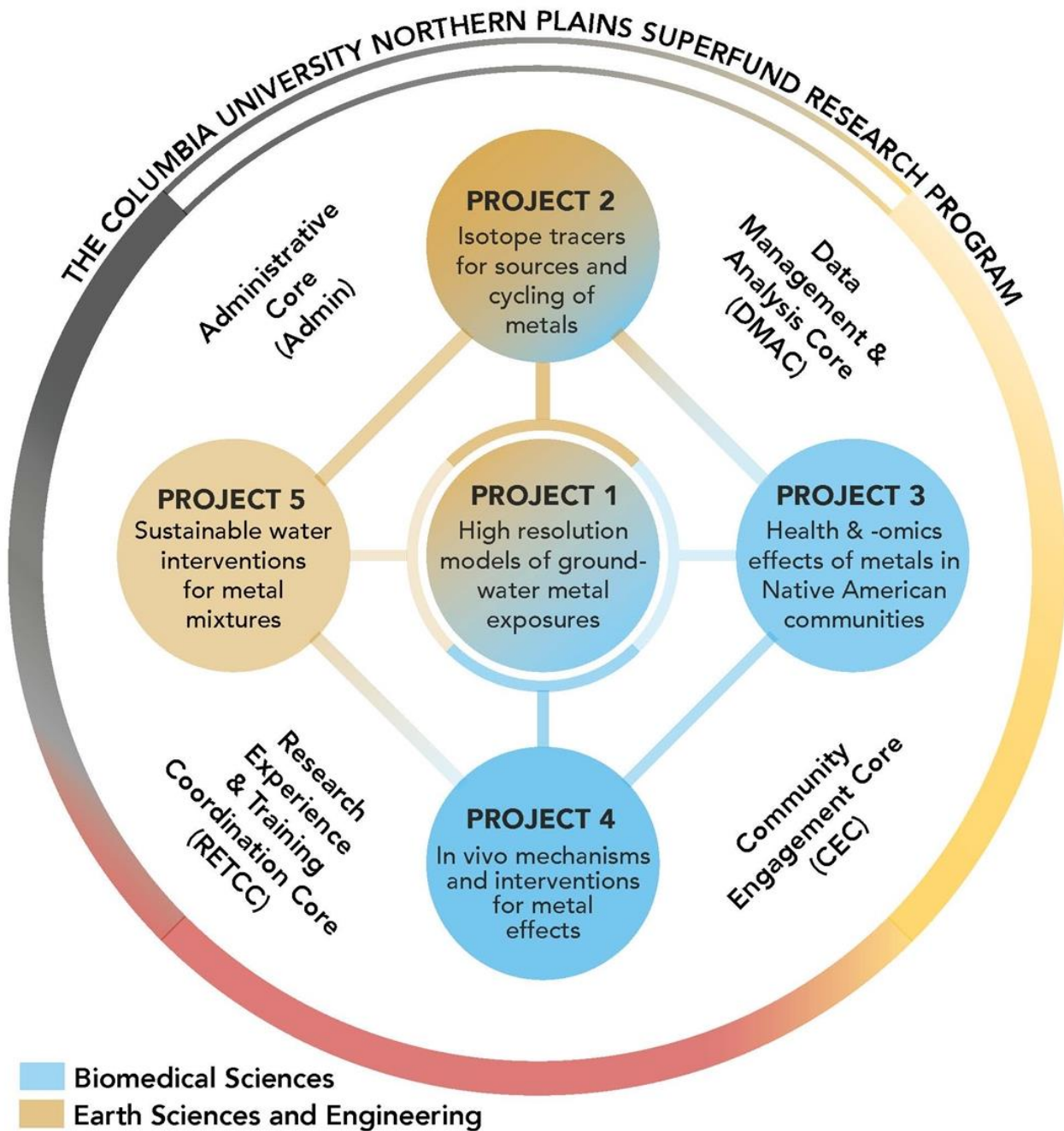


National Institute of
Environmental Health Sciences
Superfund Research Program
P42ES033719

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)



MISSOURI BREAKS
Creating Opportunities for Health



COLUMBIA

MAILMAN SCHOOL OF PUBLIC HEALTH

LAMONT-DOHERTY EARTH OBSERVATORY
COLUMBIA CLIMATE SCHOOL
Climate, Earth, and Society



P42ES033719



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ENVIRONMENTAL HEALTH SCIENCES

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



Marina Pollán

Cancer and
Environmental
Epidemiology



Madrid, Spain

Occupation, Exposure to Chemicals and Risk of Gliomas and Meningiomas in Sweden

Ana Navas-Acién, MD, MPH,¹ Marina Pollán, MD, PhD,^{1*} Per Gustavsson, MD, PhD,^{2,3}
and Nils Plato, PhD^{2,3}

Occupational exposure factors ^{a,b}	OC	Not adjusted for other chemicals		Adjusted for other chemical exposures	
	2,465	RR	95%CI	RR ^c	95%CI
Arsenic^d					
No exposure	2,401	1.00		1.00	
Possible	34	1.62	1.15–2.27	1.61	1.12–2.32
Probable	—			—	
Asbestos					
No exposure	2,233	1.00		1	
Possible	194	0.91	0.79–1.06	0.91	0.75–1.11
Probable	38	0.78	0.56–1.07	0.78	0.56–1.07
Chromium/nickel					
No exposure	2,382	1.00		1.00	
Possible/probable ^e	83	1.12	0.90–1.39	1.17	0.86–1.60
Lead					
No exposure	2,455	1.00		1.00	
Possible	10	1.08	0.58–2.01	1.08	0.58–2.01
Probable	—	—		—	
Mercury					
No exposure	2,453	1.00		1.00	
Possible	—	—		—	
Probable	12	1.68	0.95–2.96	1.76	0.99–3.14

First first author paper



Eliseo Guallar



Ellen Silbergeld

Cardiovascular and Metal
Epidemiology



Baltimore, MD, USA



Eliseo Guallar



Ellen Silbergeld

Cardiovascular and Metal
Epidemiology



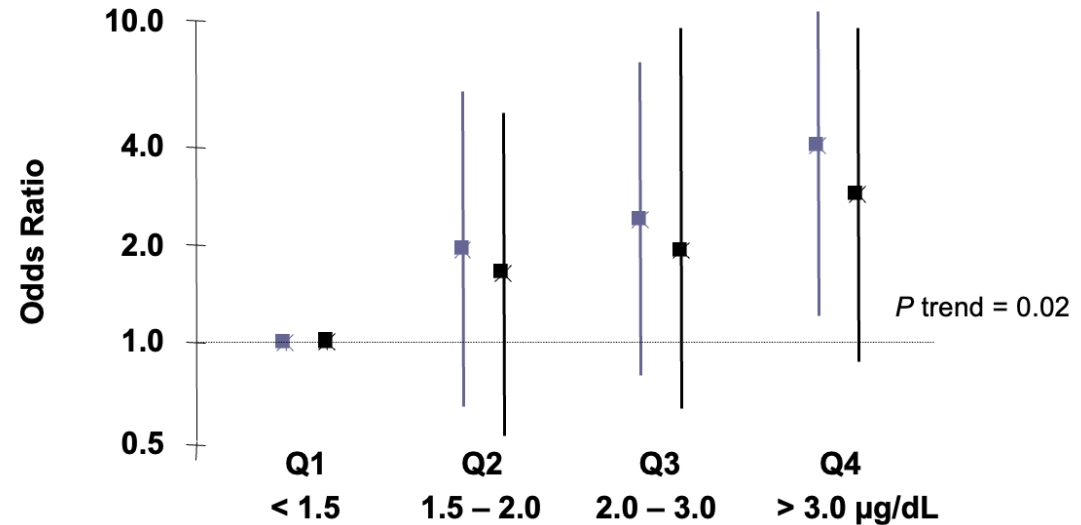
Baltimore, MD, USA

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

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



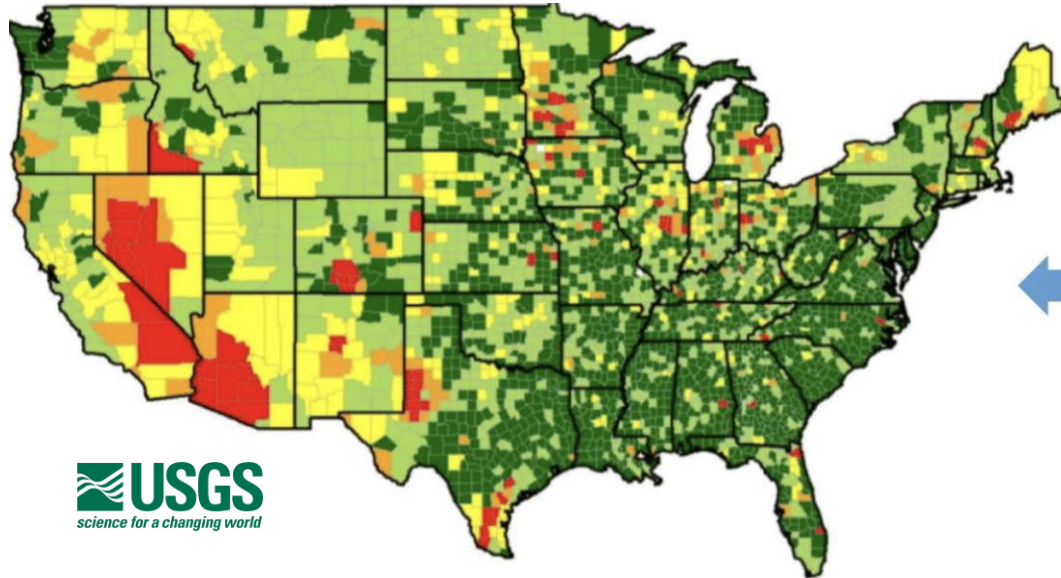
Annie Nigra



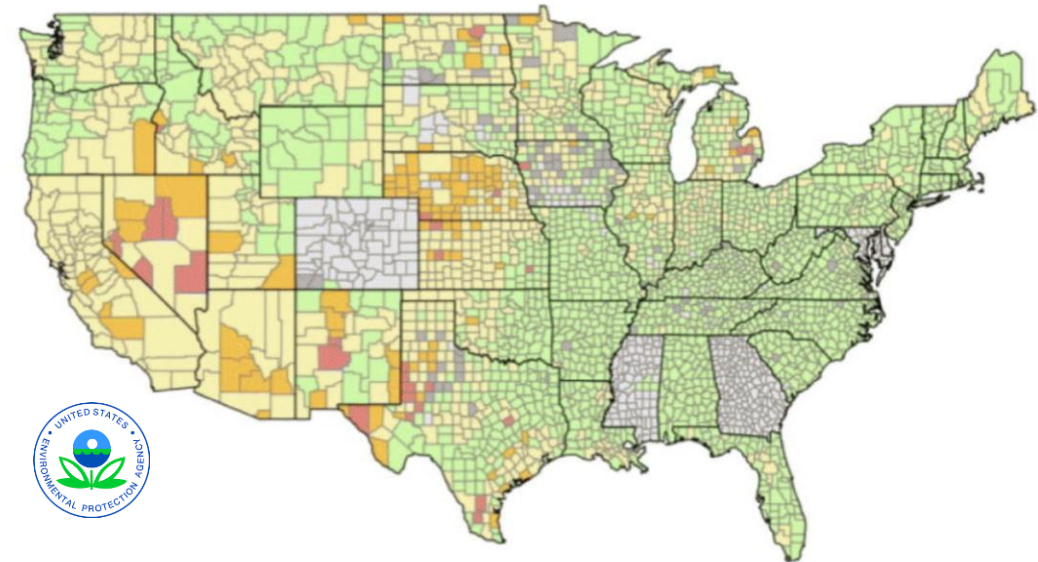
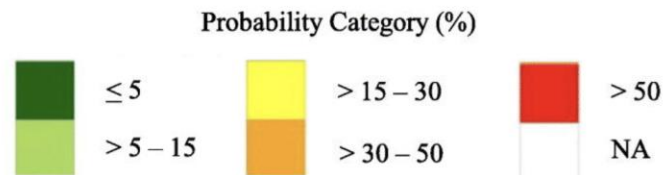
Maya Spaur

Groundwater

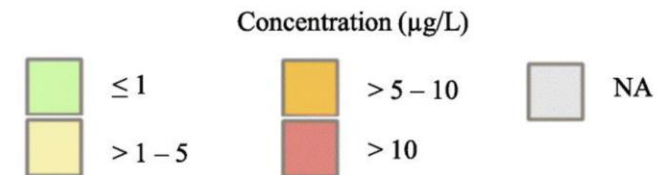
Community Water Systems



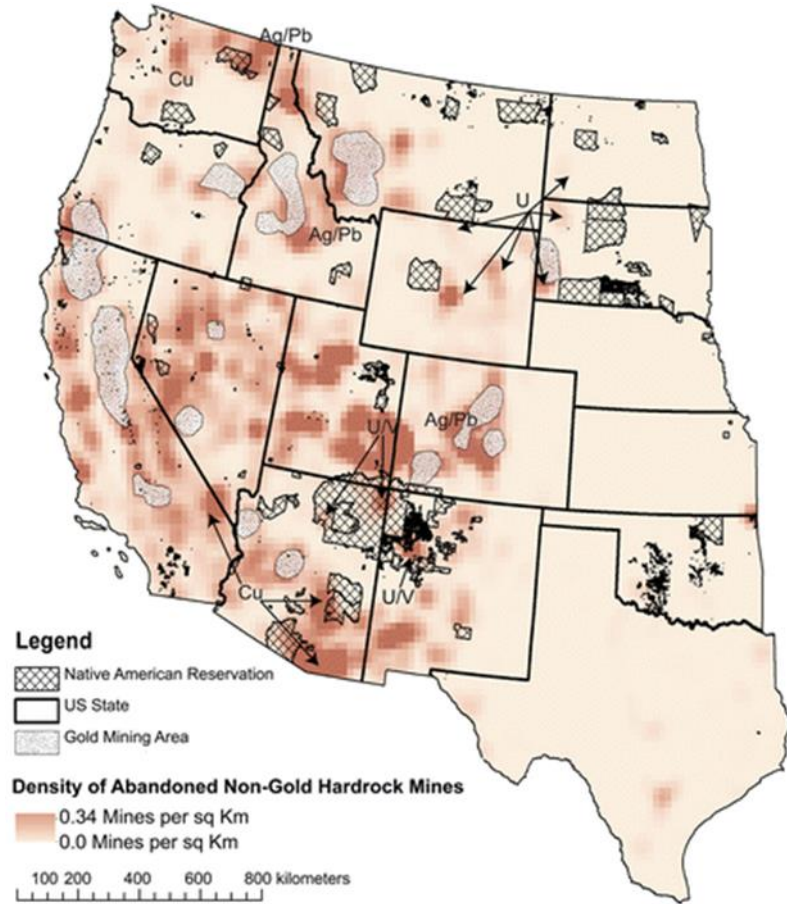
Private well probability arsenic > 10 µg/L



Community water system arsenic concentration

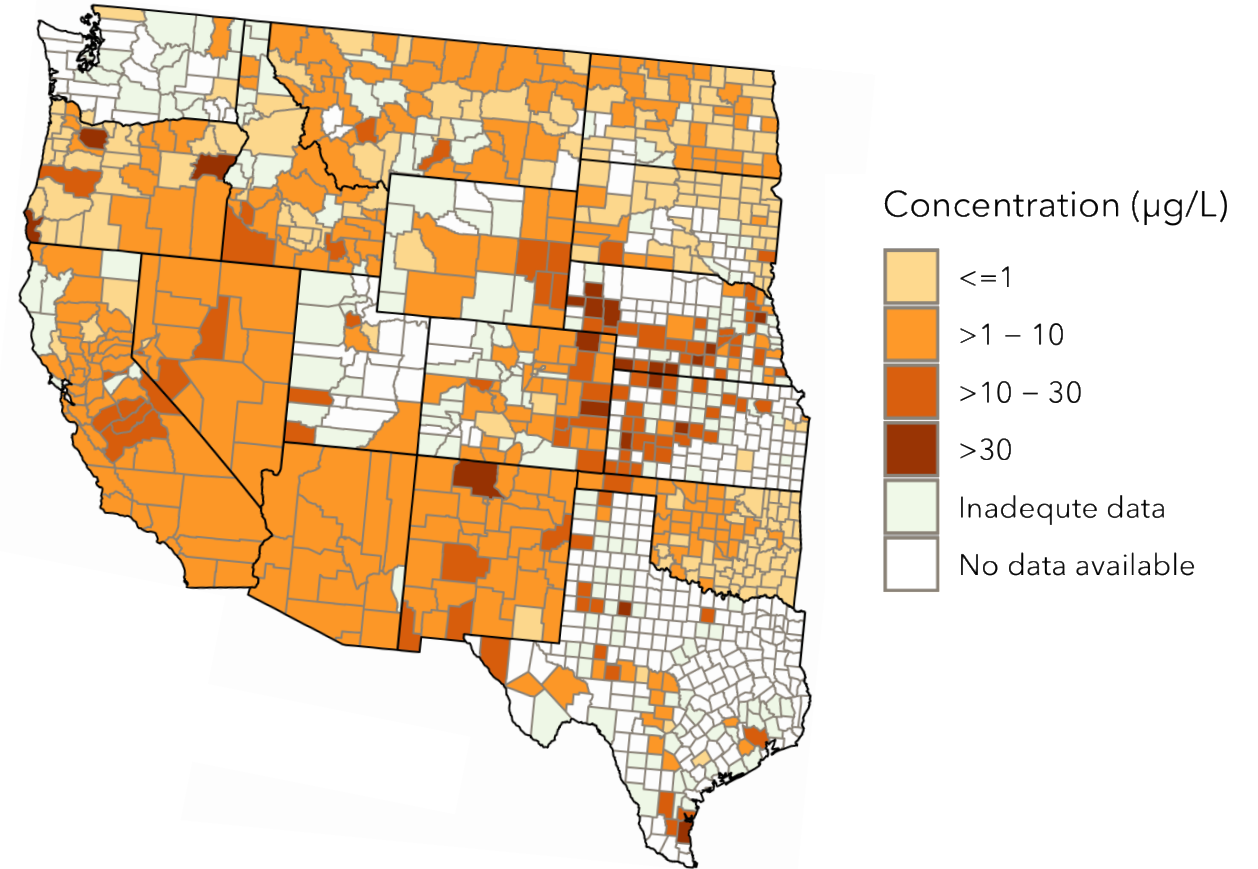


Mining and metal exposures in Indigenous Communities



Lewis et al. Current Environmental Health Reports 2017

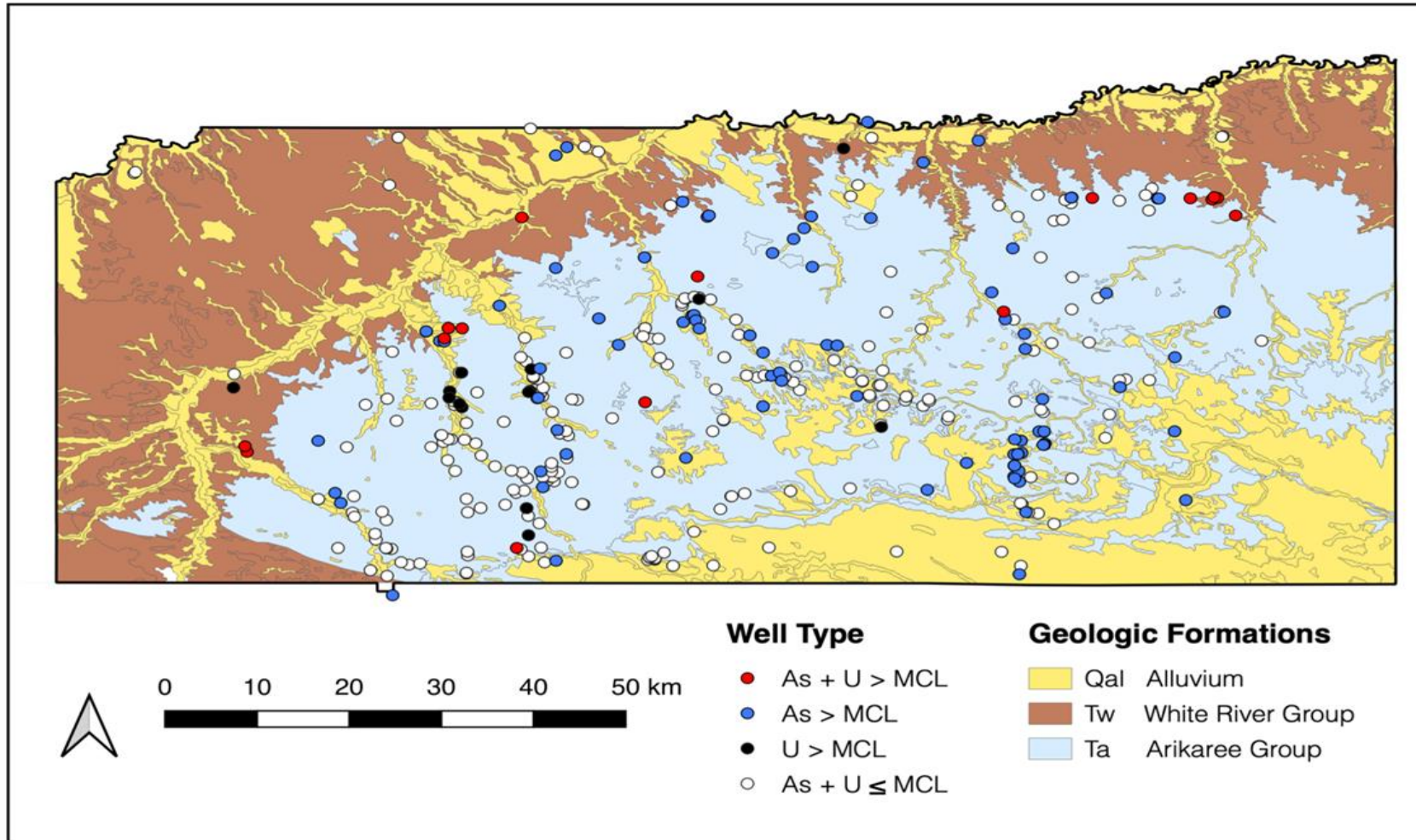
County average uranium levels ($\mu\text{g/L}$) in public water systems, 2000-2011



Ravalli et al. Lancet Public Health 2022



Arsenic and uranium spatially correlate in water samples Strong Heart Water Study communities in South Dakota

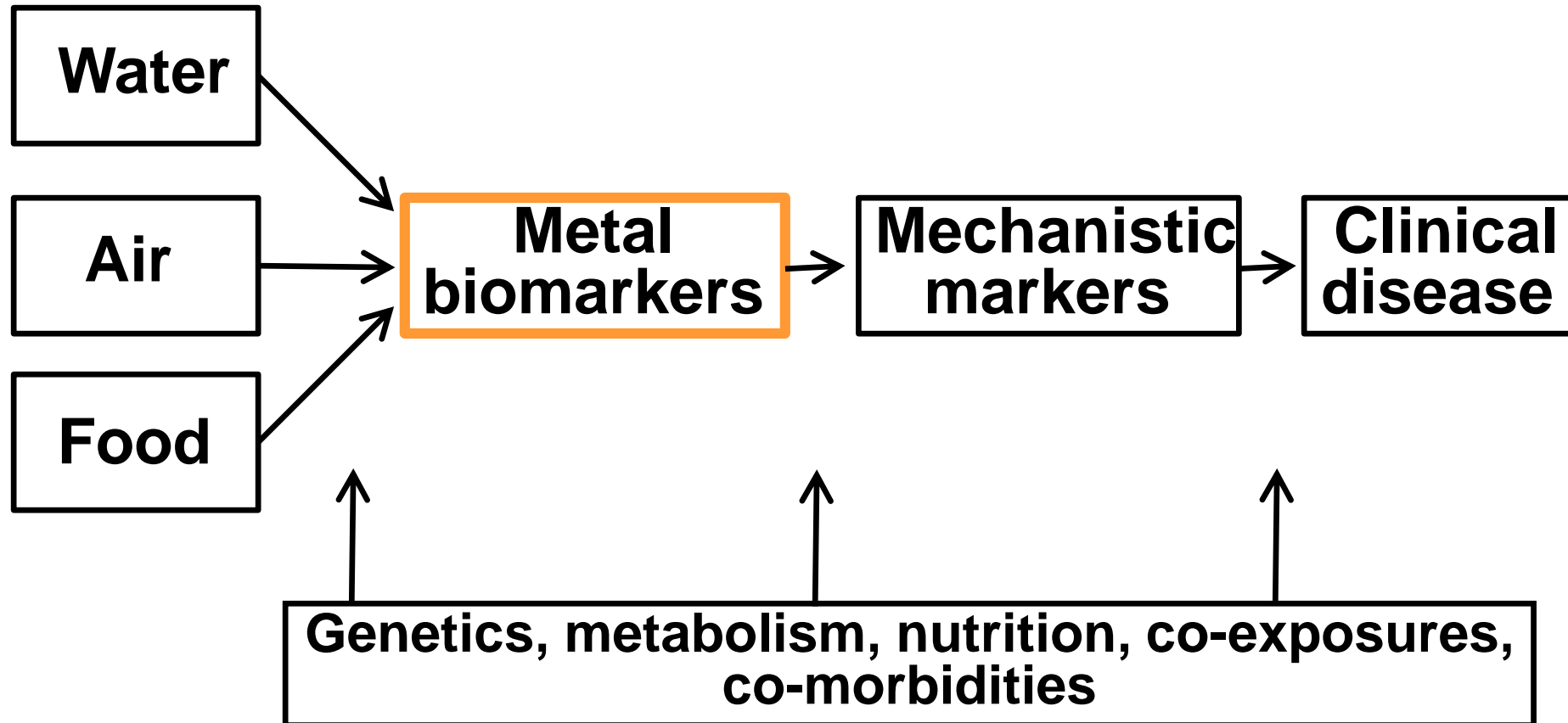


Marisa Sobel



Ben Bostick

Conceptual framework

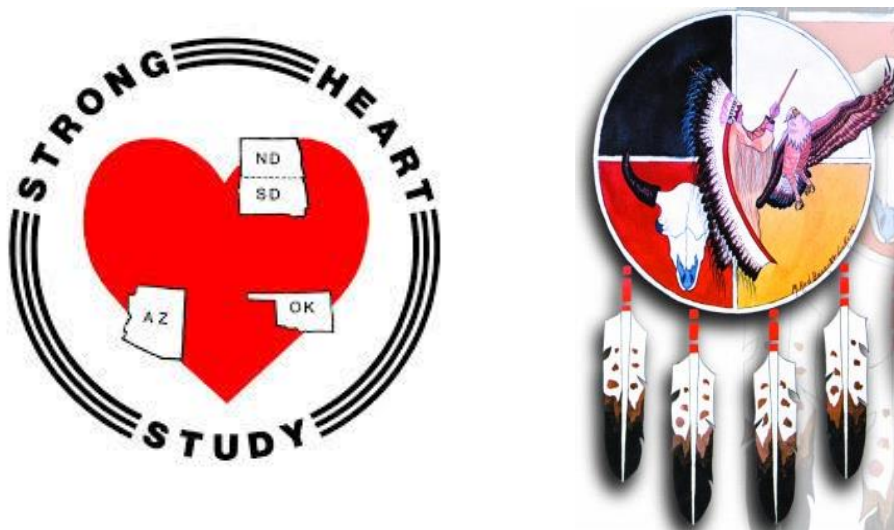


Strong Heart Study

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



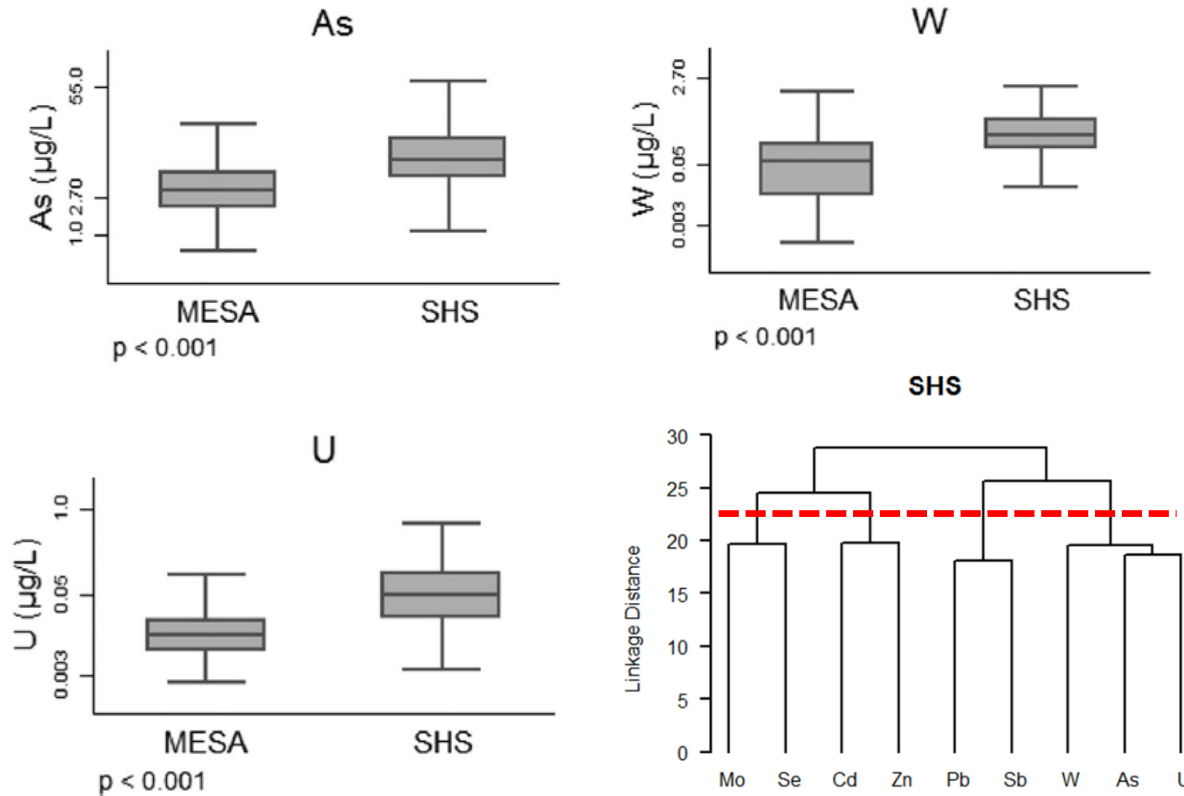
SHS annual Steering Committee meeting, Eagle Butte, SD 2015

Metal mixtures in urban and rural populations in the US: The Multi-Ethnic Study of Atherosclerosis and the Strong Heart Study [☆]



Yuanjie Pang ^{a,*}, Roger D. Peng ^b, Miranda R. Jones ^a, Kevin A. Francesconi ^c, Walter Goessler ^c, Barbara V. Howard ^{d,e}, Jason G. Umans ^{d,e}, Lyle G. Best ^f, Eliseo Guallar ^{a,g,h}, Wendy S. Post ^{a,g,h}, Joel D. Kaufman ⁱ, Dhananjay Vaidya ^h, Ana Navas-Acien ^{a,g,j}

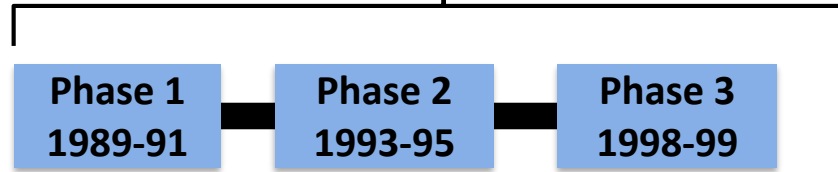
- Arsenic, tungsten and uranium levels higher in SHS participants than MESA participants
- Cluster of these 3 metals in the SHS supports water as a source of contamination
- Private well and community water systems in the SHS contribute to **46% of variation** in urinary As levels in SHS (Spaur et al. 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



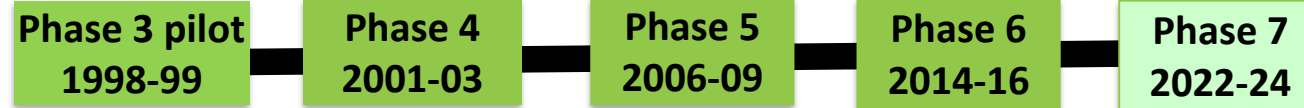
Original Strong Heart Study
4,549 adults 45-74 y



64% baseline
response rate

89%
retention rate

88%



Strong Heart *Family* Study
3,050 participants ≥ 14 y



National Heart, Lung,
and Blood Institute

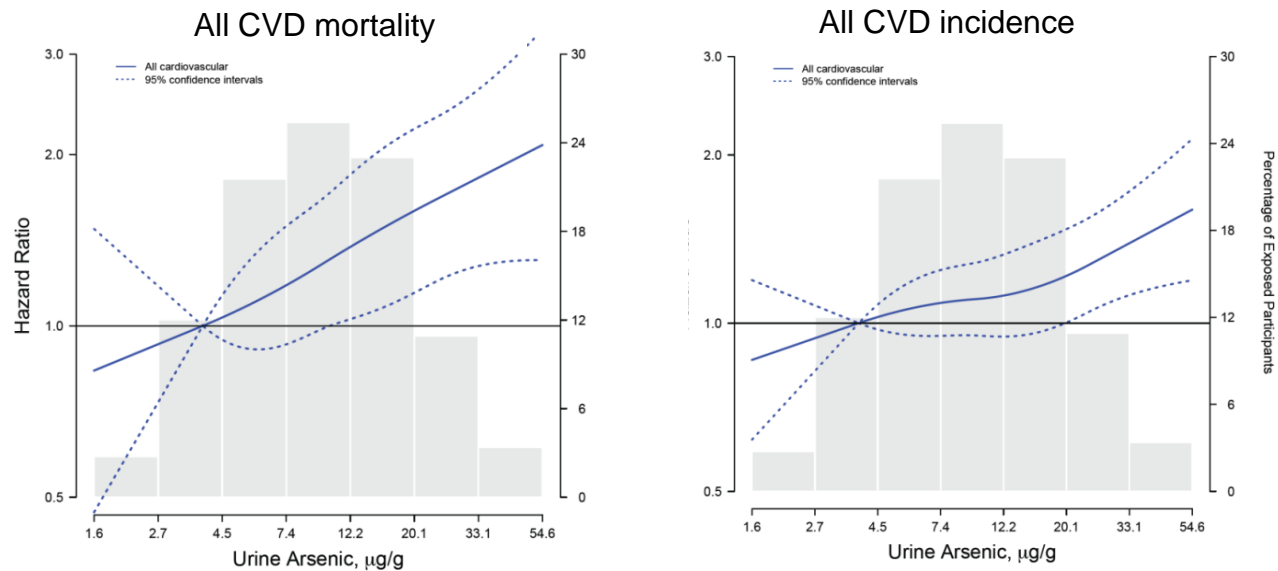


NIEHS

Arsenic and Cardiovascular Disease



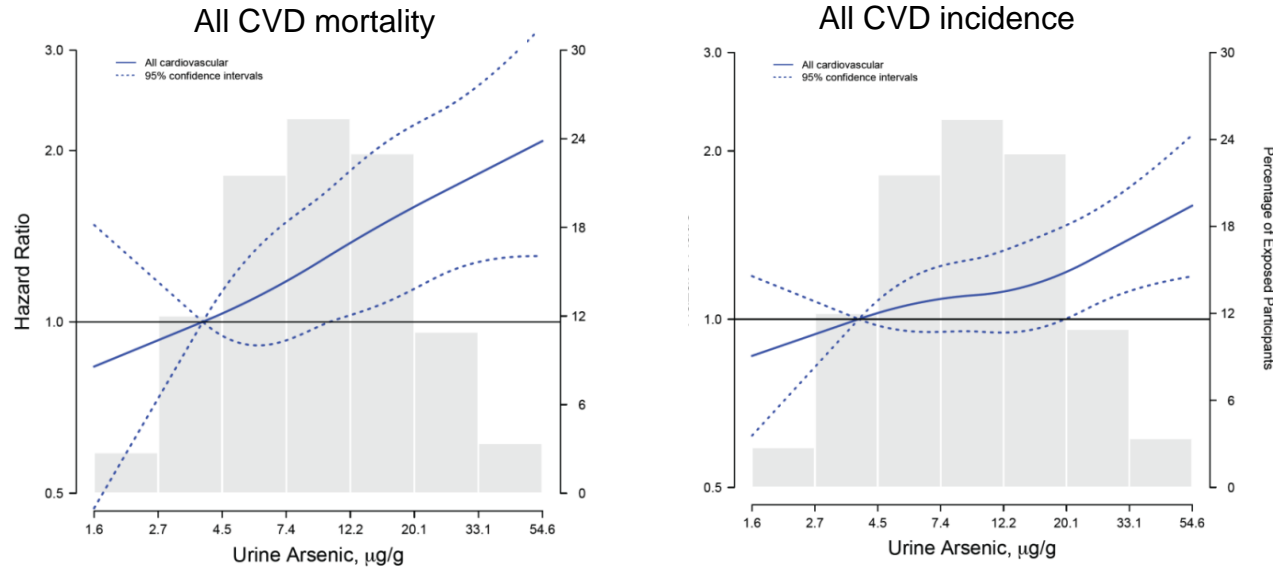
- Strong Heart Study participants 45-74 y.o. at baseline (Moon et al. 2013)



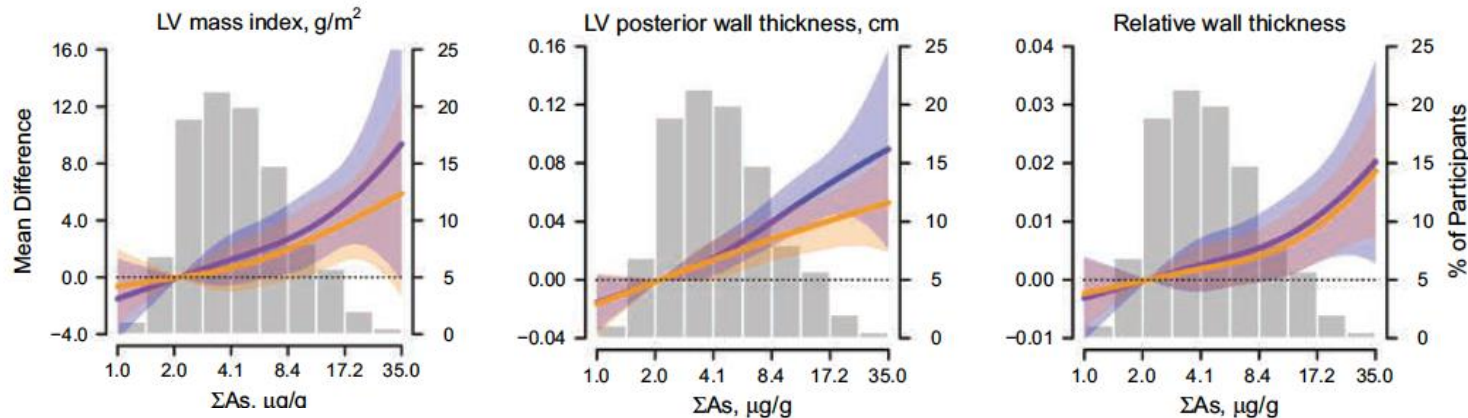


Arsenic and Cardiovascular Disease

- 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)

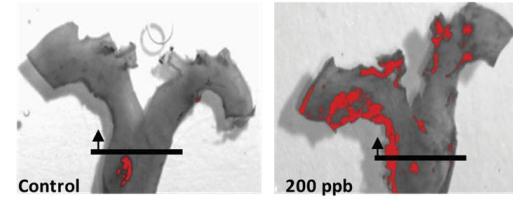
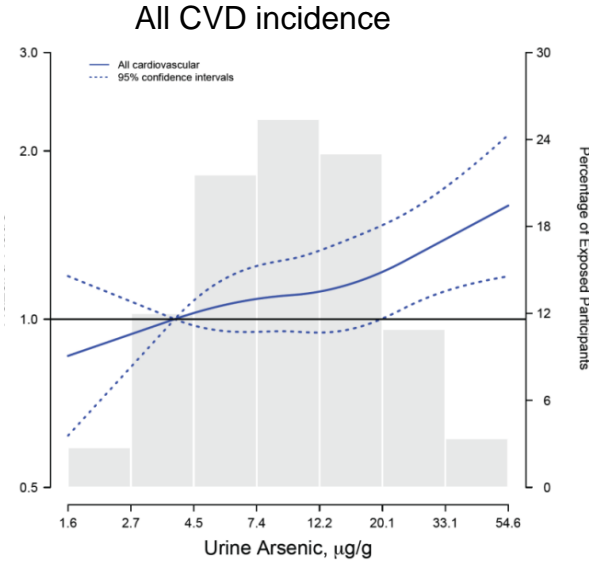
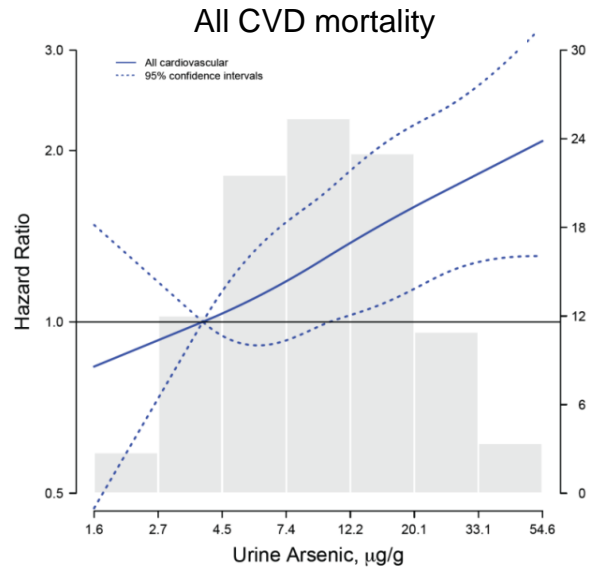


Arsenic and Cardiovascular Disease

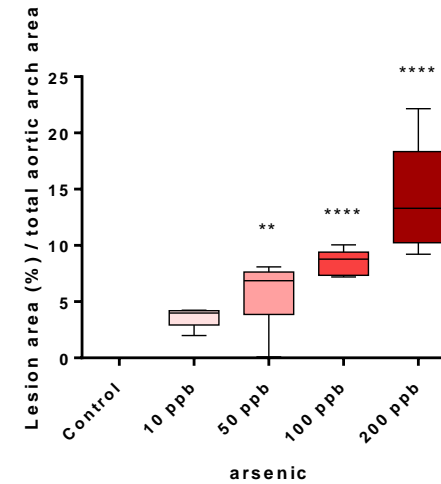


- Strong Heart Study participants 45-74 y.o. at baseline (Moon et al. 2013)

- Consistent findings in rural Colorado: San Luis Valley Diabetes Study (James et al. EHP 2015)
- Consistent findings in a ApoE-/- model

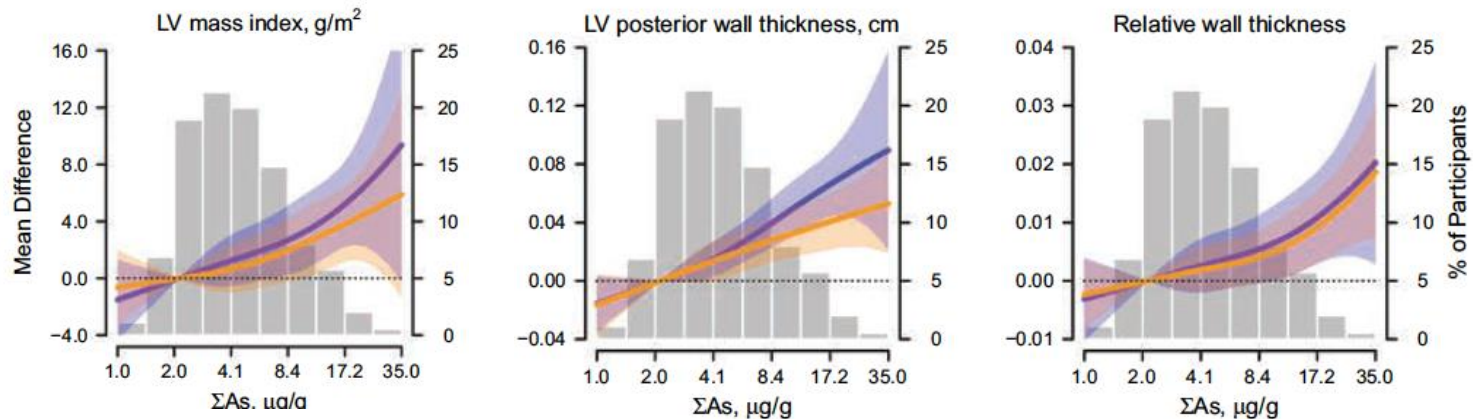


Koren Mann



Tap water arsenic for 13 weeks

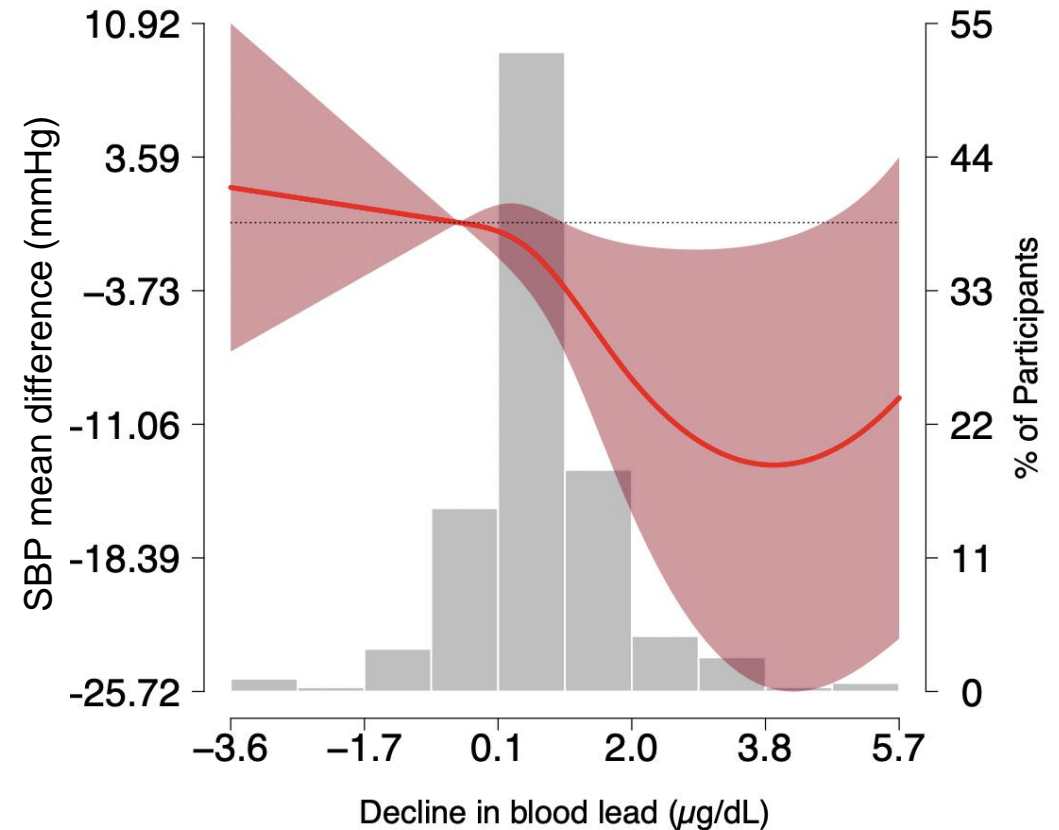
- Strong Heart Family Study participants 14-49 y.o. at baseline (Pichler et al. 2019)



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



Maria Tellez Plaza

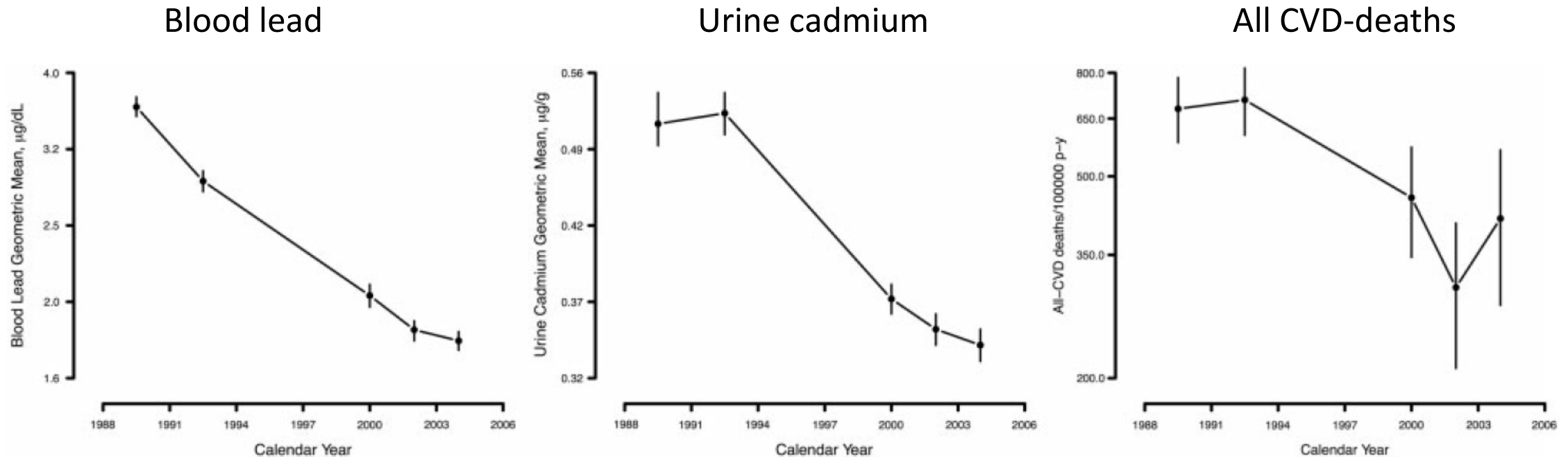
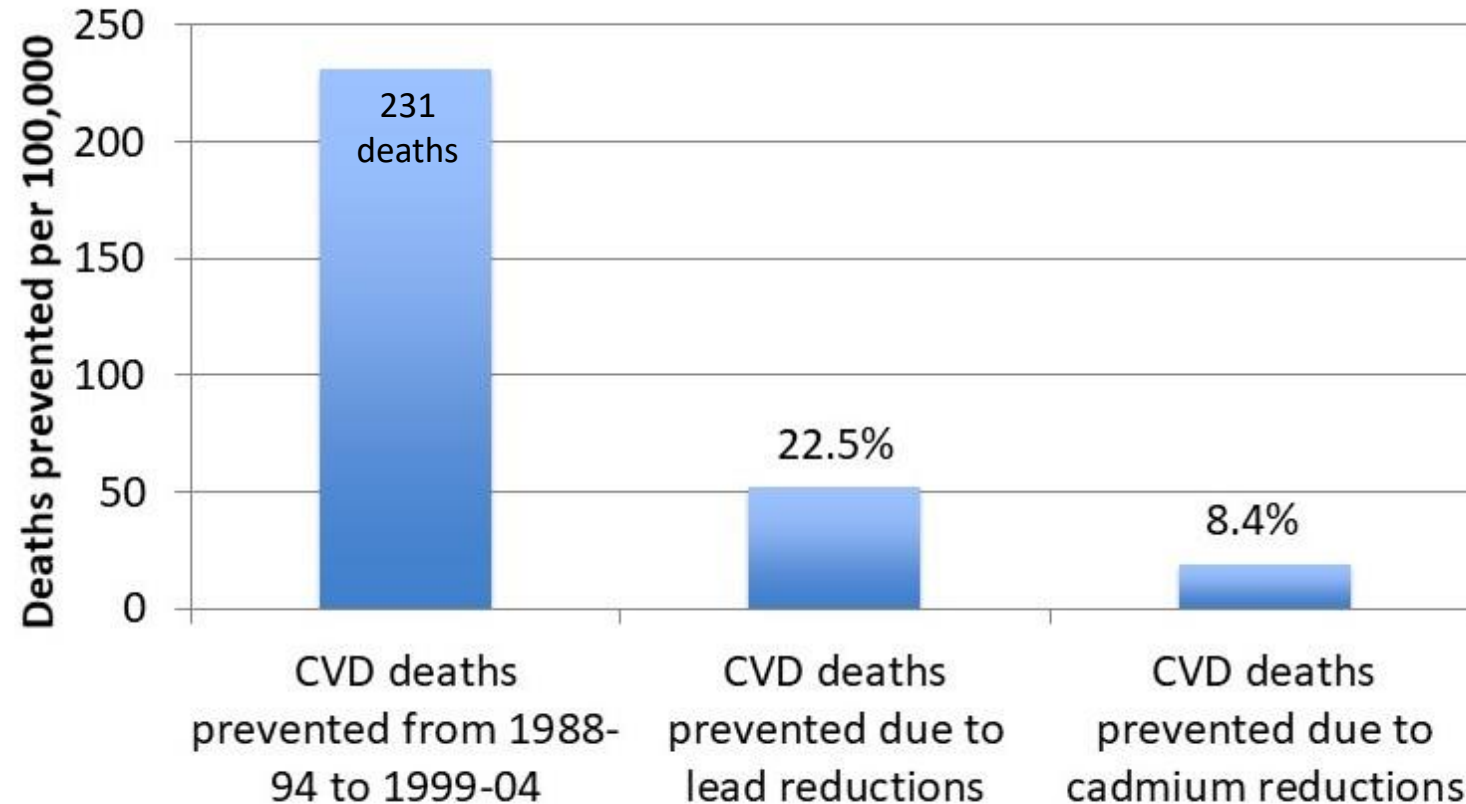


Figure 1. Age-, sex- and race-adjusted geometric mean blood lead and urine cadmium concentrations and cardiovascular disease (CVD) mortality rates across 1988–2004 National Health and Nutrition Examination Survey phases. Vertical bars show 95% confidence intervals based on 15 000 bootstrap re-samples.

Temporal changes in lead and cadmium exposure and the reduction in CVD mortality observed in the US



Maria Tellez Plaza



Prevention and control strategies

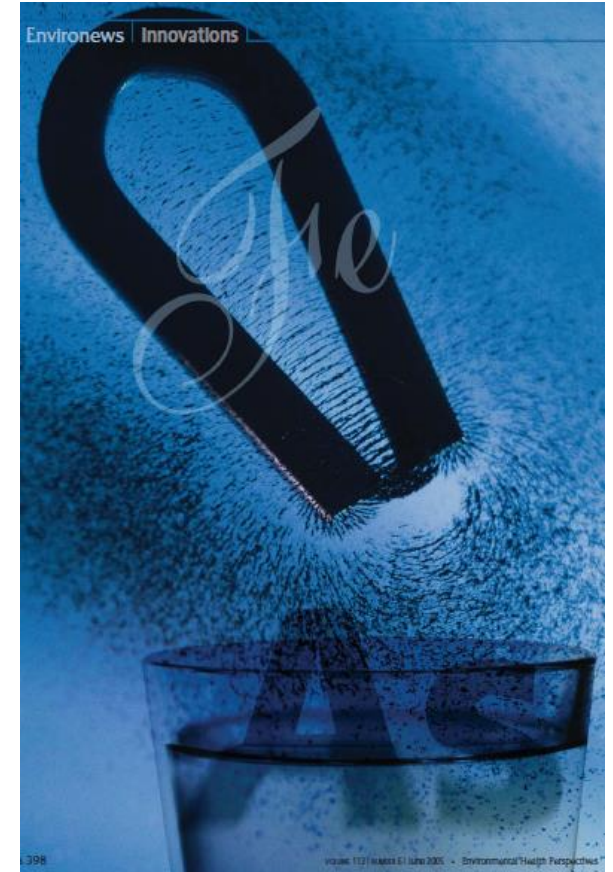
Main objective:

- 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.J. 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."

Superfund Research Program



National Institute of
Environmental Health Sciences
Superfund Research Program



Design: Tammy Granados

Mission: integrate **systems science**,
innovative technology and
Indigenous knowledge to protect the
Northern Plains water resources and
communities from hazardous metals

P42ES033719

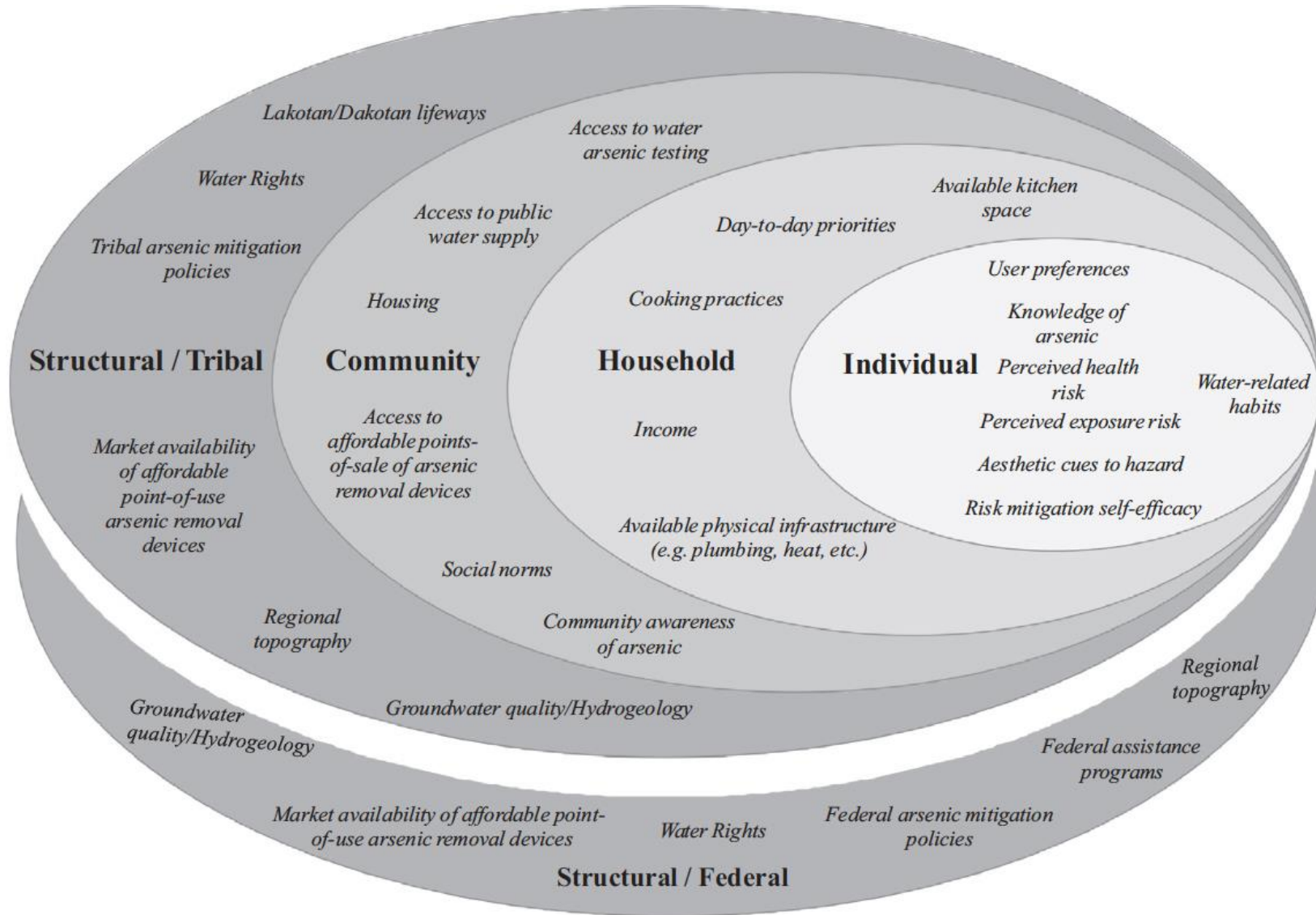
Strong Heart Water Study for Private Wells

- 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

The Strong Heart Water Study Multi-Level Conceptual Framework

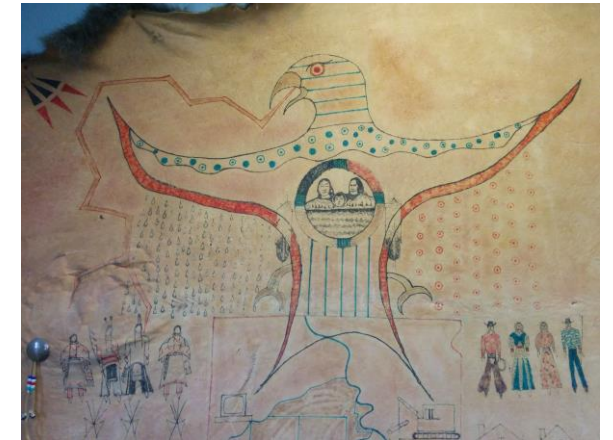




**Christine
George**



Design: Annie Chasing Hawk

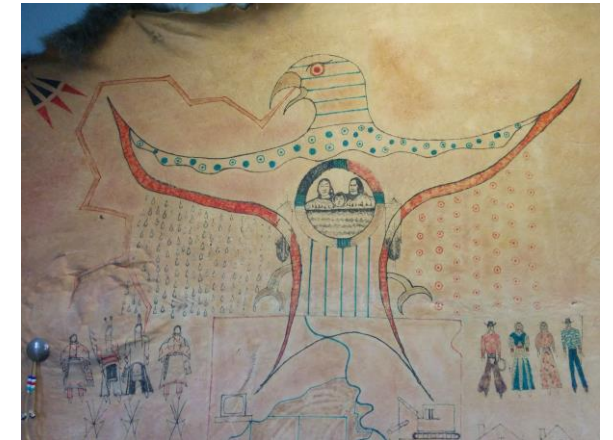




Christine George



Design: Annie Chasing Hawk



Marcia O'Leary



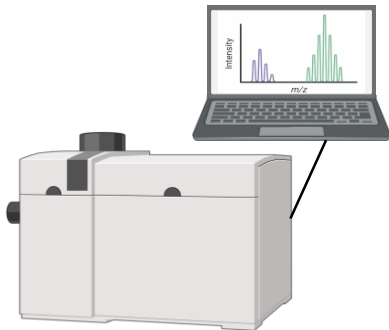
Tracy Zacher

Metallomics

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

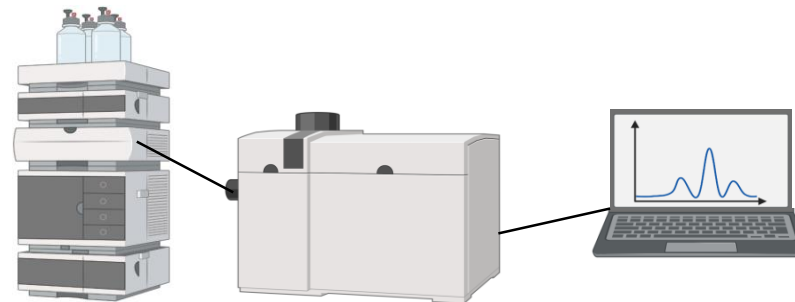
Elements

ICPMS



Species

HPLC-ICPMS



Isotopes

MC-ICPMS



ICPMS: Inductively couple plasma mass spectrometry

HPLC: High performance chromatography

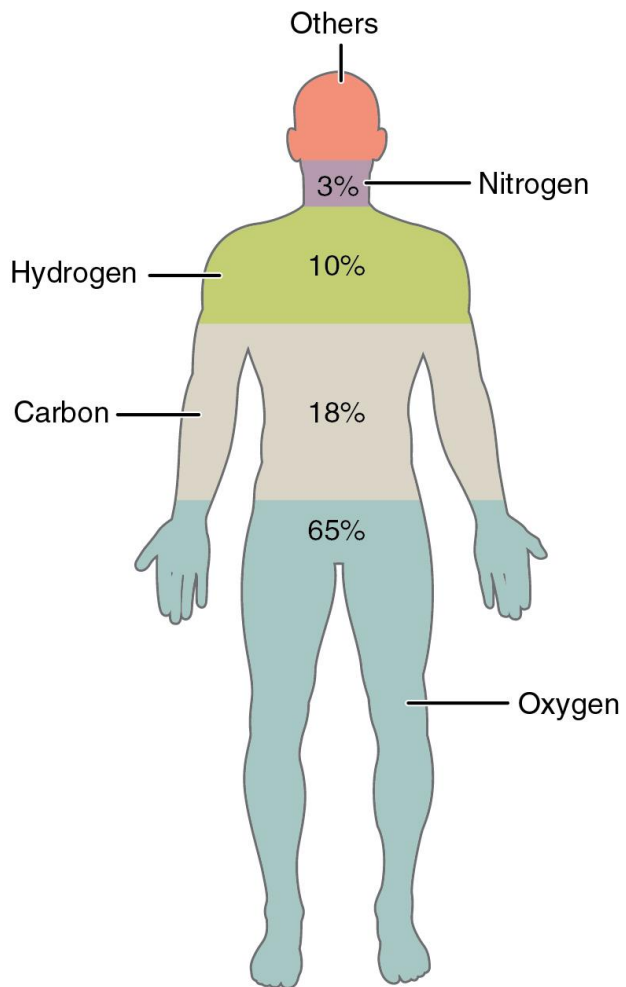
MC: multi-collector to measure ions

Periodic Table of Elements

H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba		Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra		Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Cn	Nh	Fl	Mc	Lv	Ts	Og
			La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
			Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr

- Alkali Metals
- Alkali Earth Metals
- Transition Metals
- Post-transition Metals
- Metalloids
- Reactive Nonmetals
- Noble Gases
- Lanthanides & Actinides

The metallome in the human body



**Others = 36 elements
(essential and non-essential)**

Element	g-level
Phosphorus	780
Potassium	140
Sulfur	140
Sodium	100
Chlorine	95
Magnesium	19
Iron	4.2
Fluorine	2.6
Zinc	2.3
Silicon	1

**Essential
Non-essential**

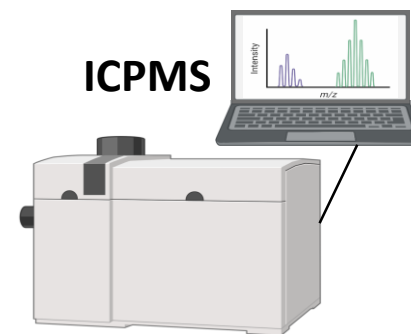
Element	mg-level
Rubidium	680
Strontium	320
Bromine	260
Lead	120
Copper	72
Aluminum	60
Cadmium	60
Barium	22
Iodine	20
Nickel	15
Selenium	15
Chromium	14
Manganese	12
Arsenic	7
Lithium	7
Cesium	6
Mercury	6
Molybdenum	5
Cobalt	3
Antimony	2

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

Biological samples

- Urine
- Whole blood
- Serum

Metal analysis in MESA urine



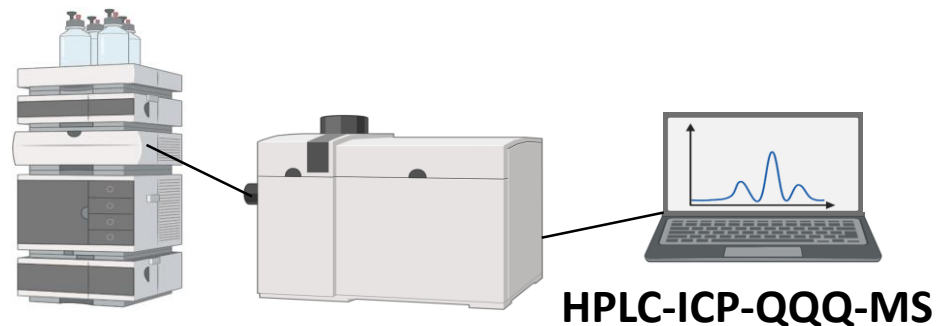
Exam 1: n = 6,814 (collected in 2000-2002)

Exam 5: n = 943 (collected in 2010-2011)

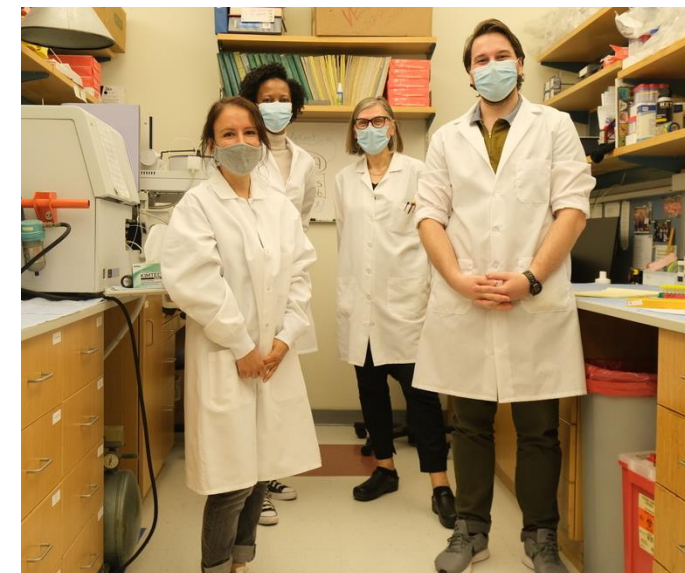
Elements: As, Ba, Cd, Co, Cs, Cu, Gd, Mn, Mo, Ni, Pb, Se, Sr, Tl, U, W, Zn

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

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



Columbia METALab Team



Kathrin Schilling

Chiugo Izuchukwu

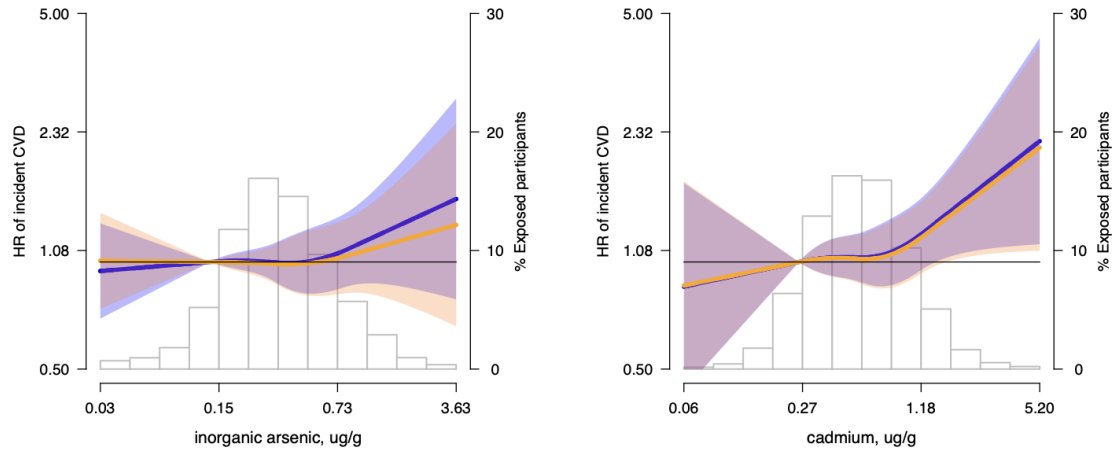
Rony Glabonjat

Olgica Balac

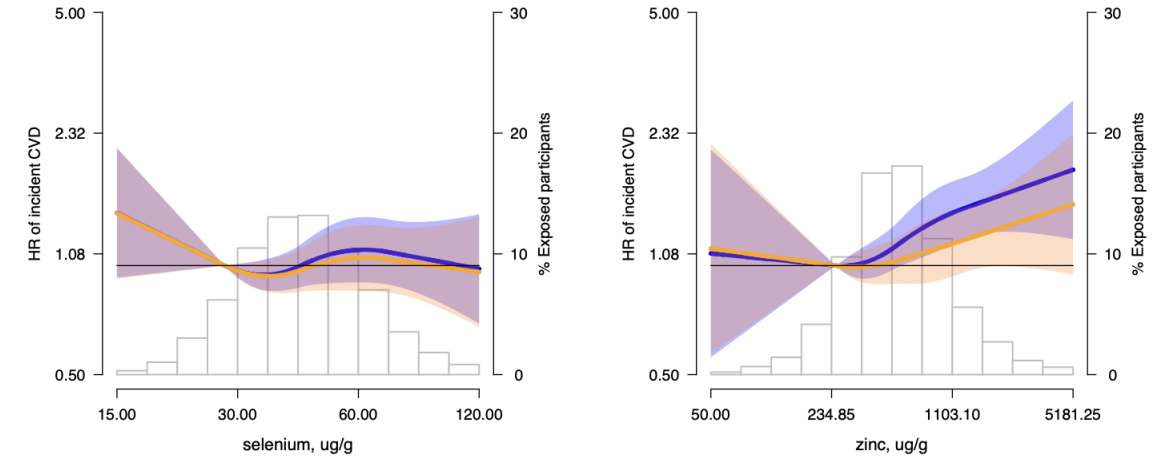
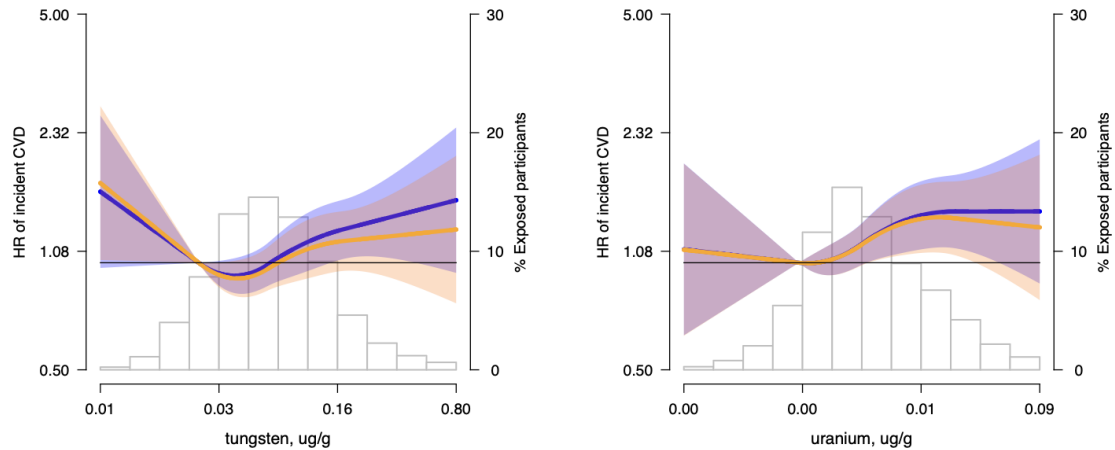
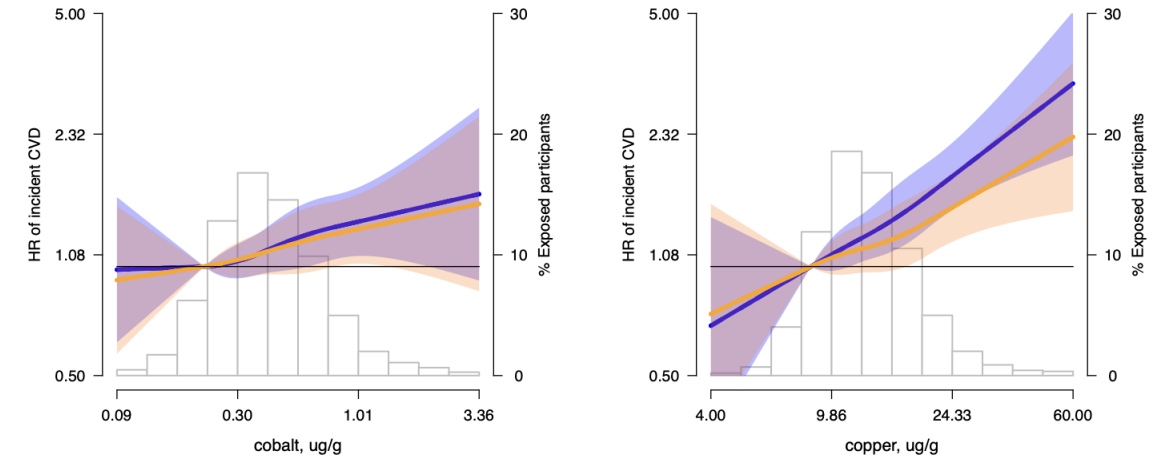
Urinary metals and incident cardiovascular disease

Do not distribute

Non-essential metals



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

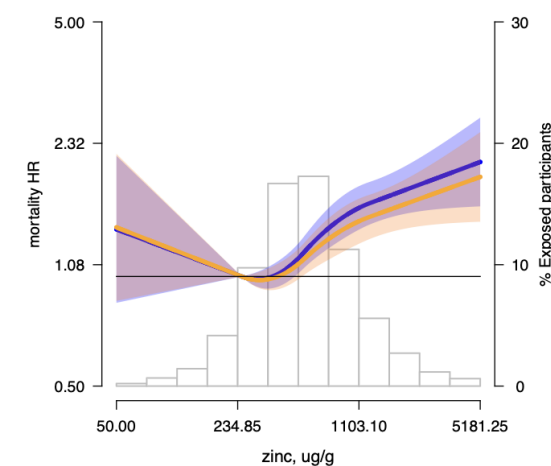
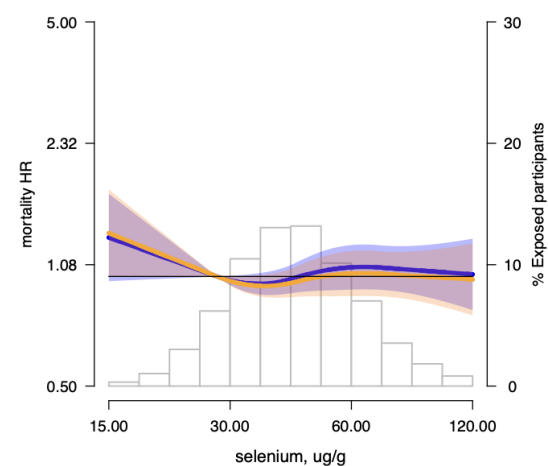
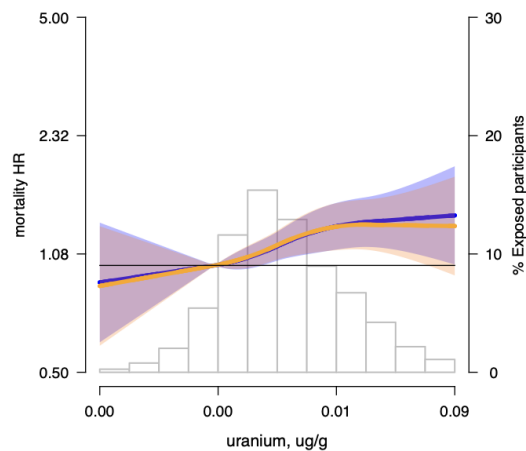
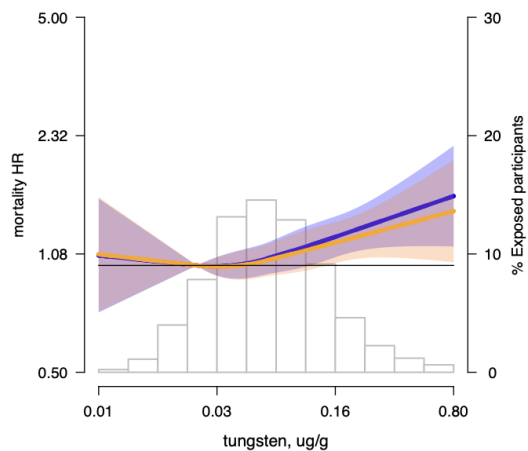
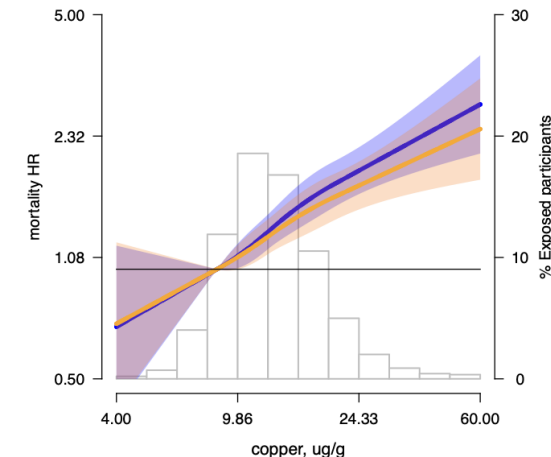
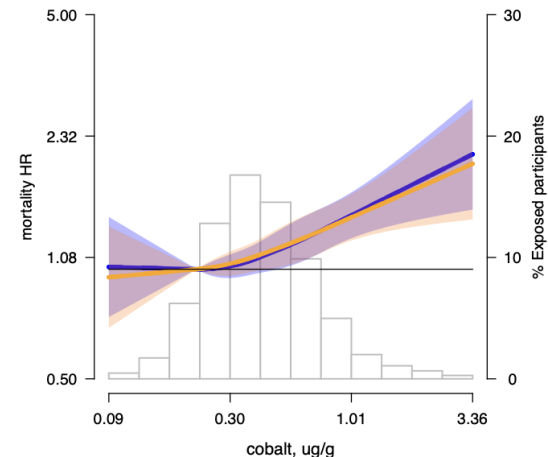
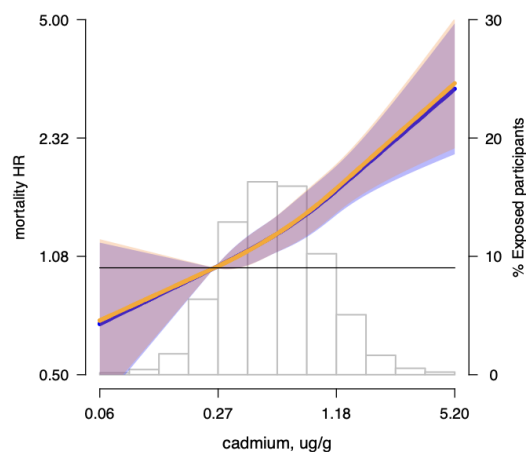
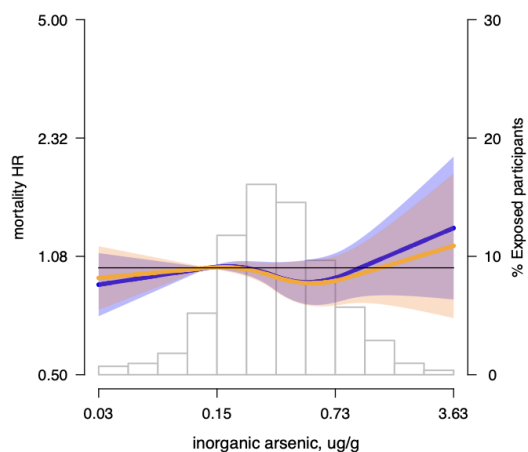
Further adjusted for diabetes status, SBP, antihypertensive treatment, total cholesterol, HDL, lipid-lowering medication

Urinary metals and total mortality

Do not distribute

Non-essential metals

Essential metals

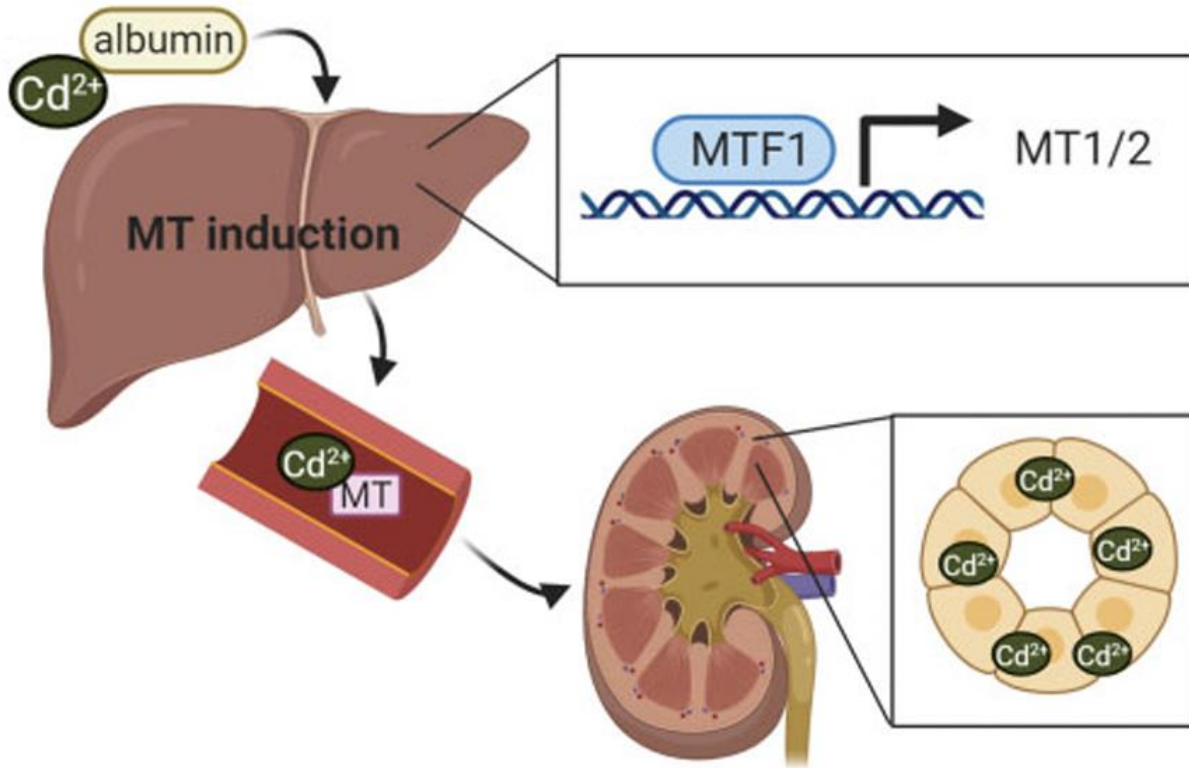


Metals modeled as restricted cubic splines with 10th percentile as the reference

— 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

Cadmium-Metallothionein Complex



Cadmium Toxicity

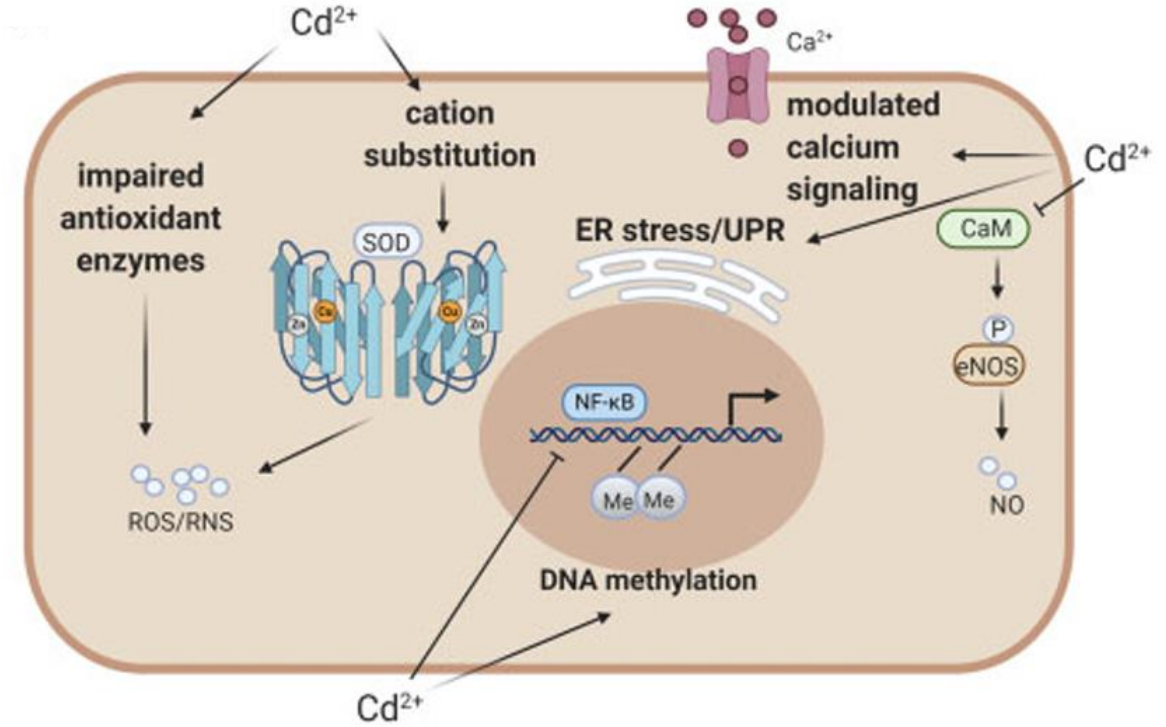
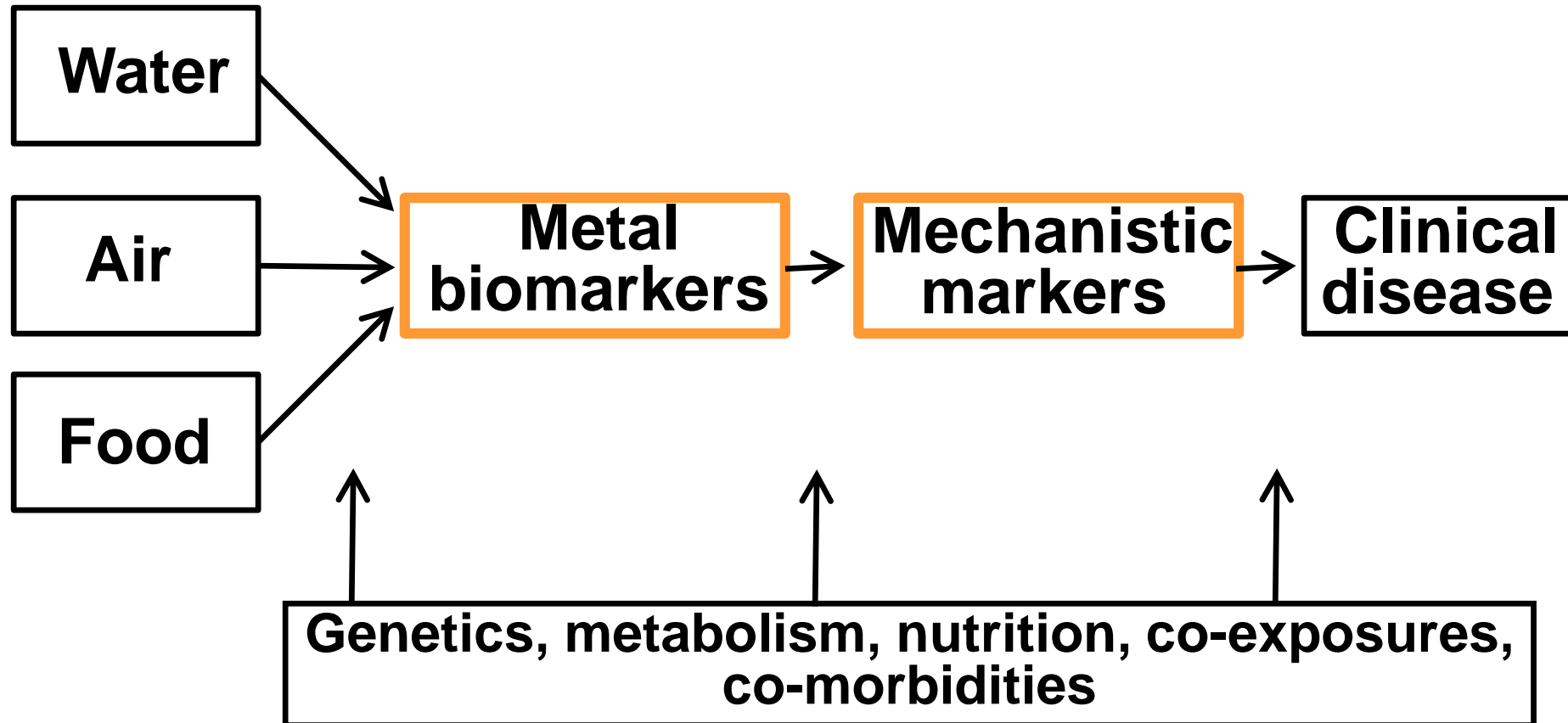


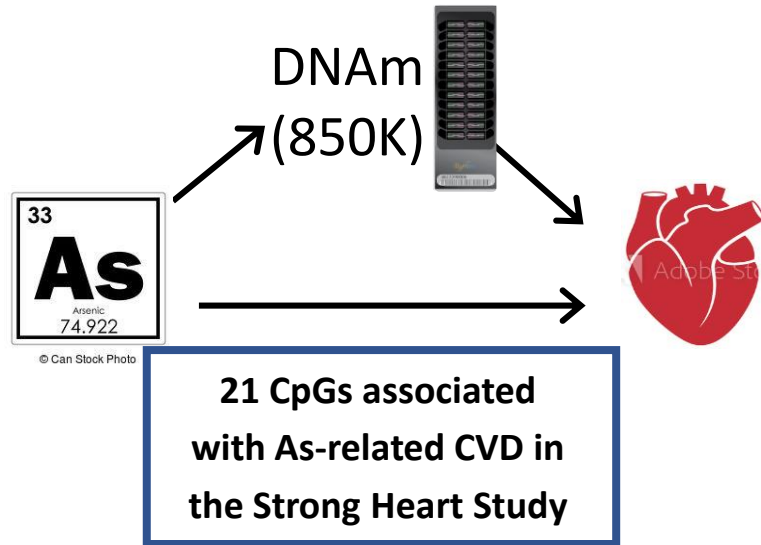
Figure by Koren Mann

Ujueta et al. Tox Sci 2021

Conceptual framework



Arsenic and cardiovascular disease: mediation via epigenetic mechanisms



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

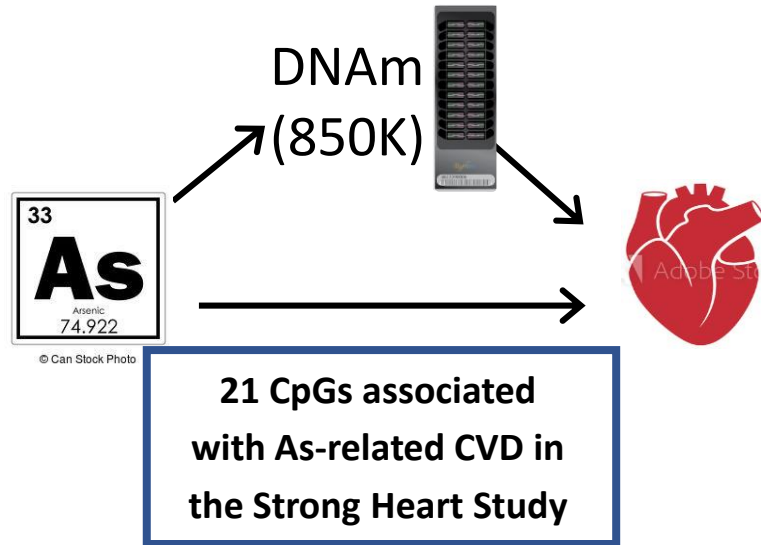


Arce Domingo

Arsenic and cardiovascular disease: mediation via epigenetic mechanisms



Arce Domingo



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



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

Association **As & DNAm**:
Replicated in MESA
for 2 CpGs

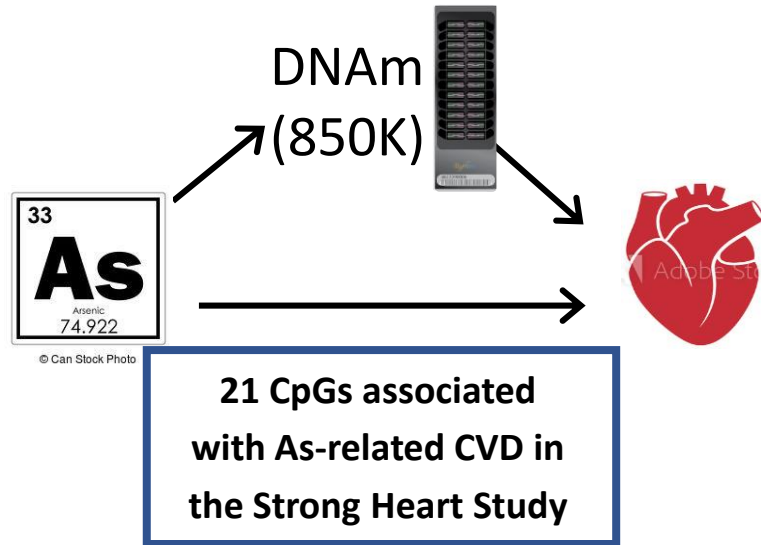


Gene functions related to:
Diabetes & redox signaling

Arsenic and cardiovascular disease: mediation via epigenetic mechanisms



Arce Domingo



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



Inter-species comparison:



APO E-/- model exposed to arsenic in drinking water in utero onwards

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

Tagged gene	Function	As	As-med. CVD	Exp. data
SLC7A11	GSH biosynthesis	X	X	
SLC7A5	GSH biosynthesis	X		X
PKN3	DNA repair and apoptosis	X	X	X
CSNK1D	DNA repair and apoptosis	X		*
ATG16L2	Autophagy pathway (diabetes)	X	X	X
APBB2	Beta cell function (diabetes)	X	X	X
TYMP	Angiogenesis, endothelial cell growth	X	X	X
COL1A1	Type 1 collagen	X	X	*
TXNIP	Thioredoxin interacting protein	X	X	X
MAPK8	Mitogen-activated protein kinase 8	X	X	X

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

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

Association **As & DNAm**:
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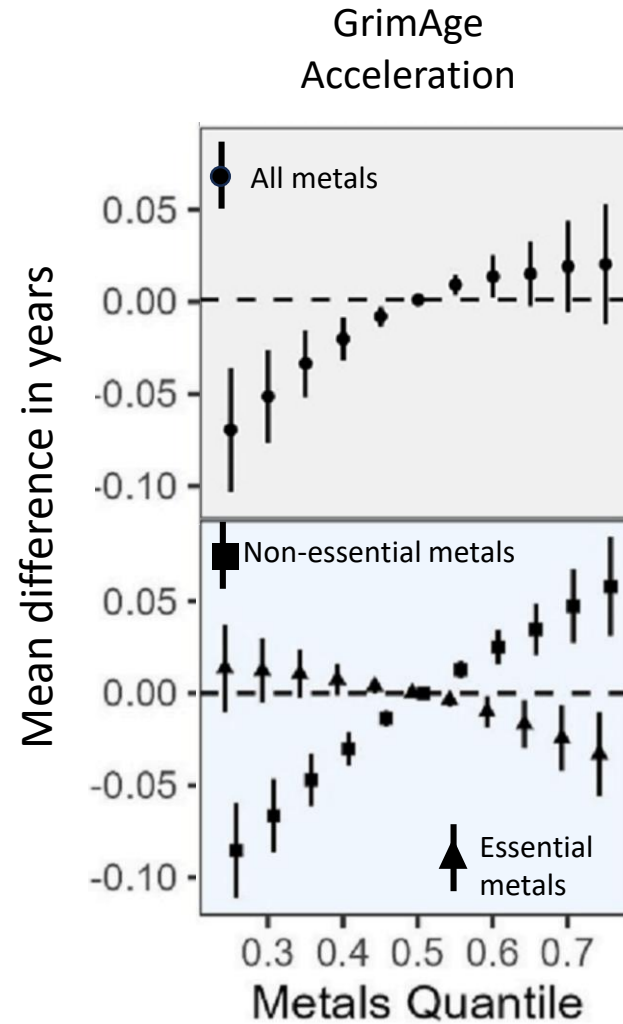


Gene functions related to:
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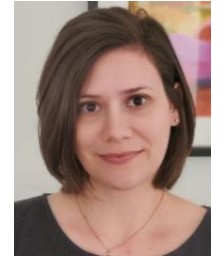
Metals and epigenetic age acceleration

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.



Kaila Boyer



Allison Kupsco



October 2023



R01ES032638
R25ES025505

Prevention and control strategies

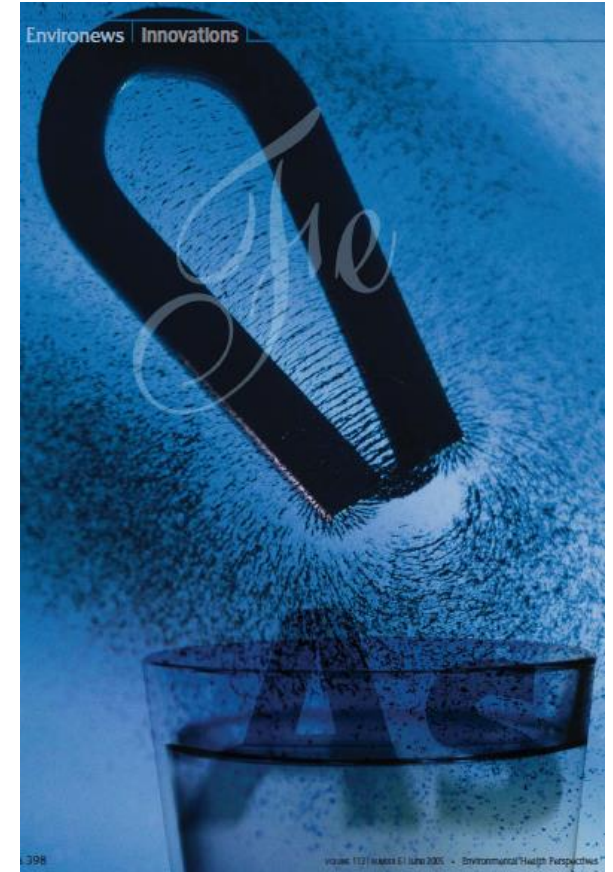
Main objective:

- 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



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 Rozema, MD
Richard L. Nahin, PhD, MPH
Lauren Lindblad, MS
Eldrin F. Lewis, MD, MPH
Jeanne Drisko, MD
Kerry L. Lee, PhD
for the TACT Investigators

TREATMENT OF LEAD TOXICITY with chelation was first reported with EDTA in the early 1950s.¹ Apparent success in reducing metastatic calcium deposits² led Clarke et al³ in 1956 to treat angina pa-

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.

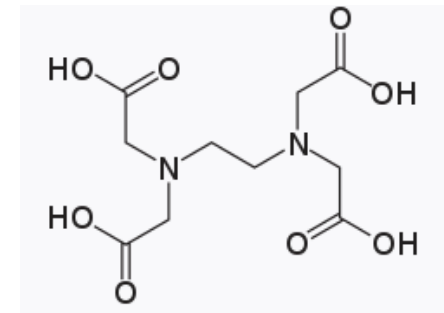
Design, Setting, and Participants Double-blind, placebo-controlled, 2 × 2 factorial randomized trial enrolling 1708 patients aged 50 years or older who had experienced a myocardial infarction (MI) at least 6 weeks prior and had serum creatinine levels of 2.0 mg/dL or less. Participants were recruited 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, B vitamins, electrolytes, procaine, 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.

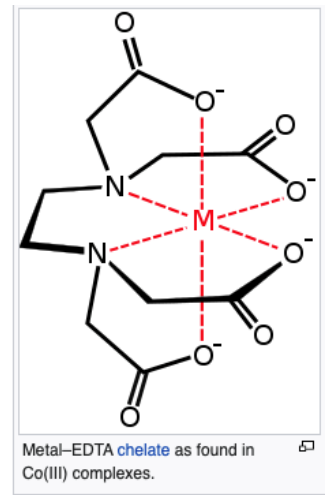
Main Outcome Measures The prespecified primary end point was a composite of total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for angina. This report describes the intention-to-treat comparison of EDTA chelation vs placebo. To account for multiple interim analyses, the significance threshold required at the final analysis was $P=.036$.



Gervasio (Tony)
Lamas
TACT2 PI



Ethylenediaminetetraacetic acid (EDTA)



EDTA: Placebo

HR (95% CI)
0.82 (0.69, 0.99)

$P = 0.035$

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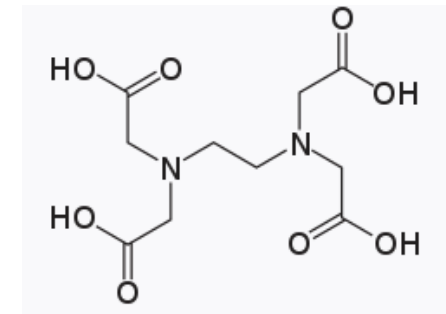
With Diabetes:

HR (95% CI)
 0.59 (0.44, 0.79)

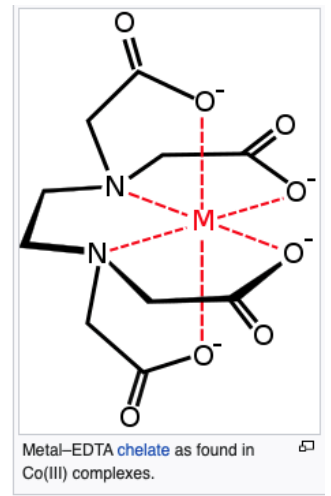
$P = 0.002$
 (Bonferroni adjusted)



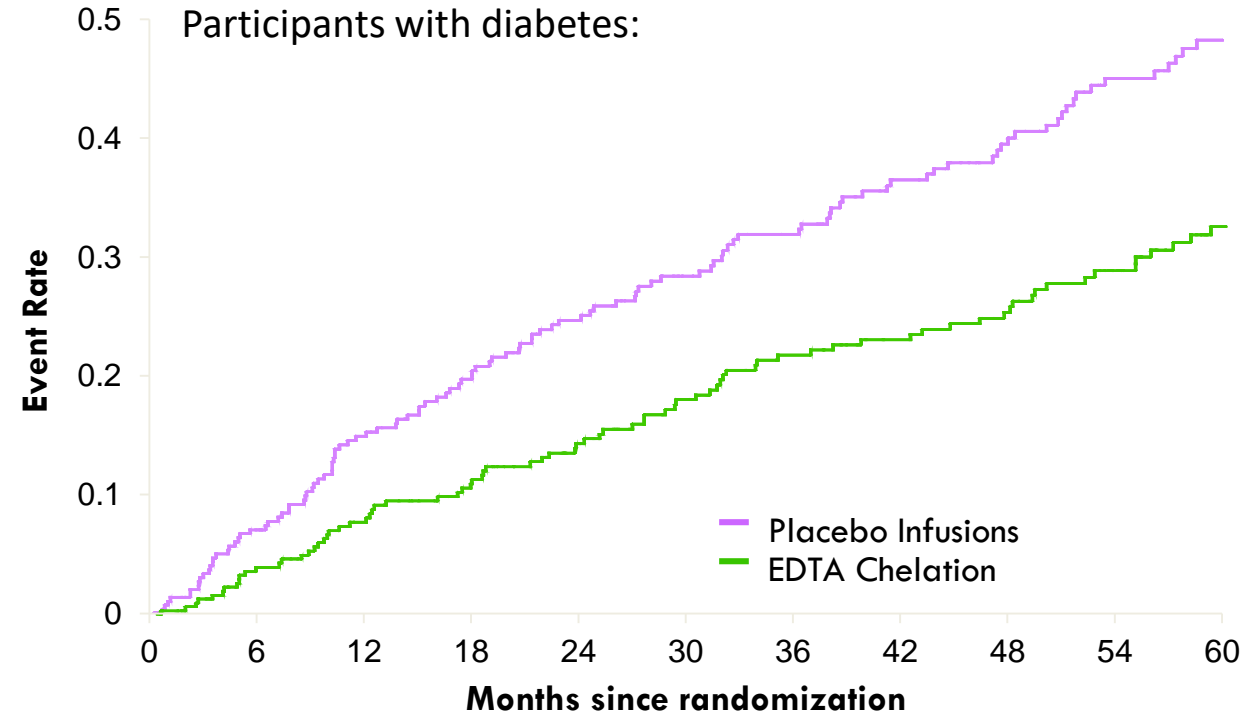
Gervasio (Tony)
 Lamas
 TACT2 PI



Ethylenediaminetetraacetic acid (EDTA)



Metal-EDTA chelate as found in Co(III) complexes.



TACT₂

TRIAL TO ASSESS CHELATION THERAPY



Gervasio (Tony) Lamas
Mount Sinai Medical Center
Miami, USA, TACT2 PI



Regina Santella
Columbia University



National Center for
Complementary and
Integrative Health



National Heart, Lung,
and Blood Institute



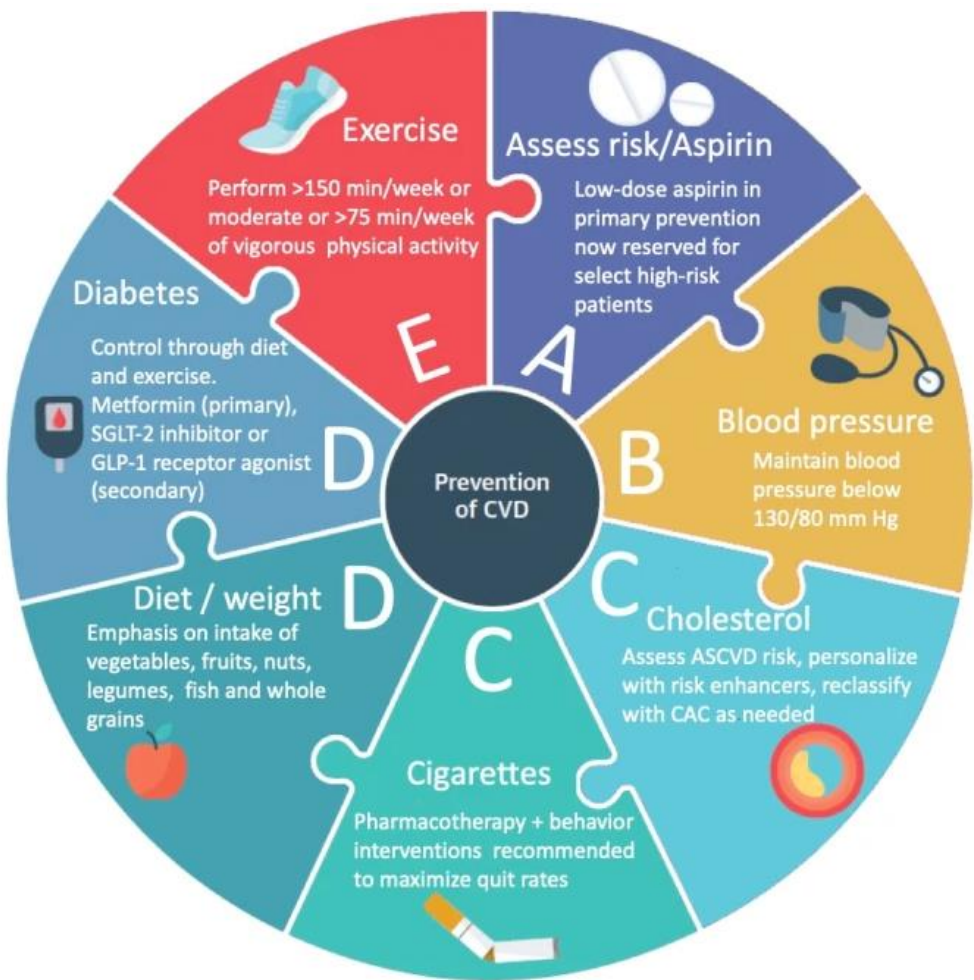
- 1000 participants randomized
- Study will be unblinded in the next few months
- **Blood and urine metals measured at the CDC at infusions 1, 5, 20, and 40:**
 - Evaluate their role as potential mechanisms for the cardiovascular benefits of EDTA
 - Conduct risk stratification pre-specified analyses

ABCDE for CVD prevention



Focused on life styles and clinical care

Add E for *Environment*:

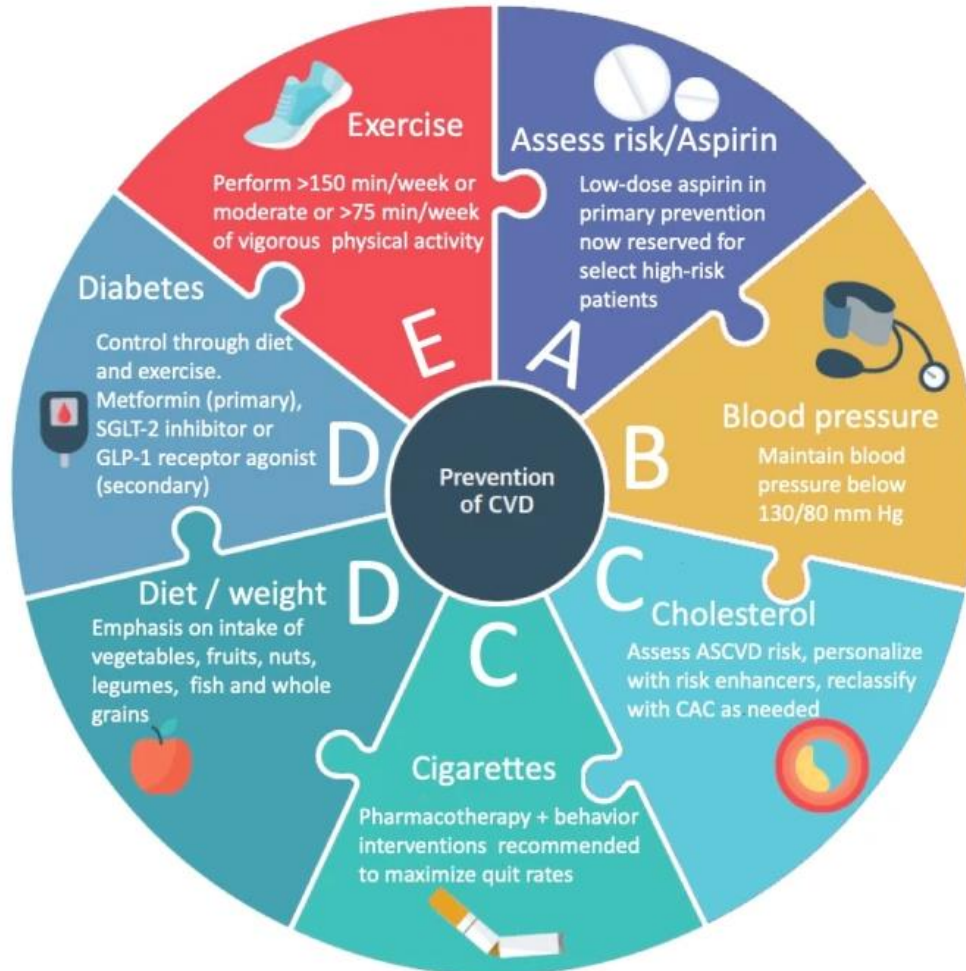


Credit: Roger Blumenthal (based on the American College of Cardiology and American Heart Association Primary Prevention Guidelines)

ABCDE for CVD prevention



Focused on life styles and clinical care



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Add E for *Environment*:





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

Acknowledgements:

- Study participants, communities, and funding organizations that make research possible



R01HL090863 (completed)
R01ES021367 (completed)
R01ES025216 (completed)
R01ES032638
75N92019D00023



R01ES025135



P42ES033719



P30ES009089



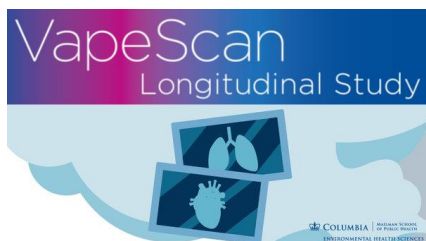
R01ES028758



U01DK130058



R01AT009273
UH3AT009149



R01ES029967
R01HL155576

Drive, talent and creativity move science and public health forward



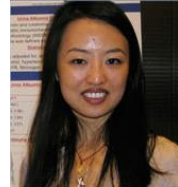
Maria Tellez-Plaza,
Scientist, ISCIII



Miranda Jones,
Assist. Prof.,
Hopkins



Matt Gribble
Assoc. Prof.,
U. Alabama



Laura Zheng Data
Scientist, Aetna



Chin-Chi Kuo Prof.,
China Medical U.,
Taiwan



**Esther Garcia-
Esquinas**
Scientist, ISCIII



Kat Moon
Assist. Prof
BU



Farrah Mateen
Assoc. Prof.,
Harvard



Poojitha Balakrishnan
Resident, U. Alabama



Pablo Olmedo
Assoc. Professor,
U. Granada



Maria Grau, Data
Scientist,
U. Valencia



Miranda Spratlen,
Assoc.
Res Scientist, CU



Martha Powers,
IRIS, EPA



Anne Nigra,
Assist. Prof, CU



Tiffany Sanchez,
Assist. Prof., CU



Joseph Yracheta,
Scientist,
NativeBio



**Katherine
Crocker,** Assist.
Prof U. Puget
Sound



Arce Domingo,
Assoc. Res Scientist,
Biostat, CU



Anne Bozack,
Post-doc Stanford U



Ahlam Abuawad,
Post-doc, Dartmouth
School of Medicine



Di Zhao, Assist
Prof
Nanjing
Agricultural U



Maya Spaur,
Post-doc NCI



Marisa Sobel,
PhD student CU



Kevin Patterson,
PhD student CU



Monique Slowly,
Scientist ICF



Will Lieberman-Cribbin
PhD student CU



Lizbeth Gomez
PhD student Drexel



Irene Martinez-Morata
PhD student CU



Enoch Jiang
Medical student
NYU



Filippo Ravalli
Medical student
CU



Kaila Boyer
Medical student
SUNY Downstate



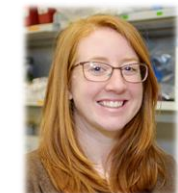
Marilyn Santo,
MPH student CU



Marta Galvez,
Scientist, Pfizer



Christian Dye
Post-doc CU



Katlyn McGraw
Post-doc CU