Metals and Cardiovascular Disease: Evidence, Mechanisms, and Opportunities for Prevention

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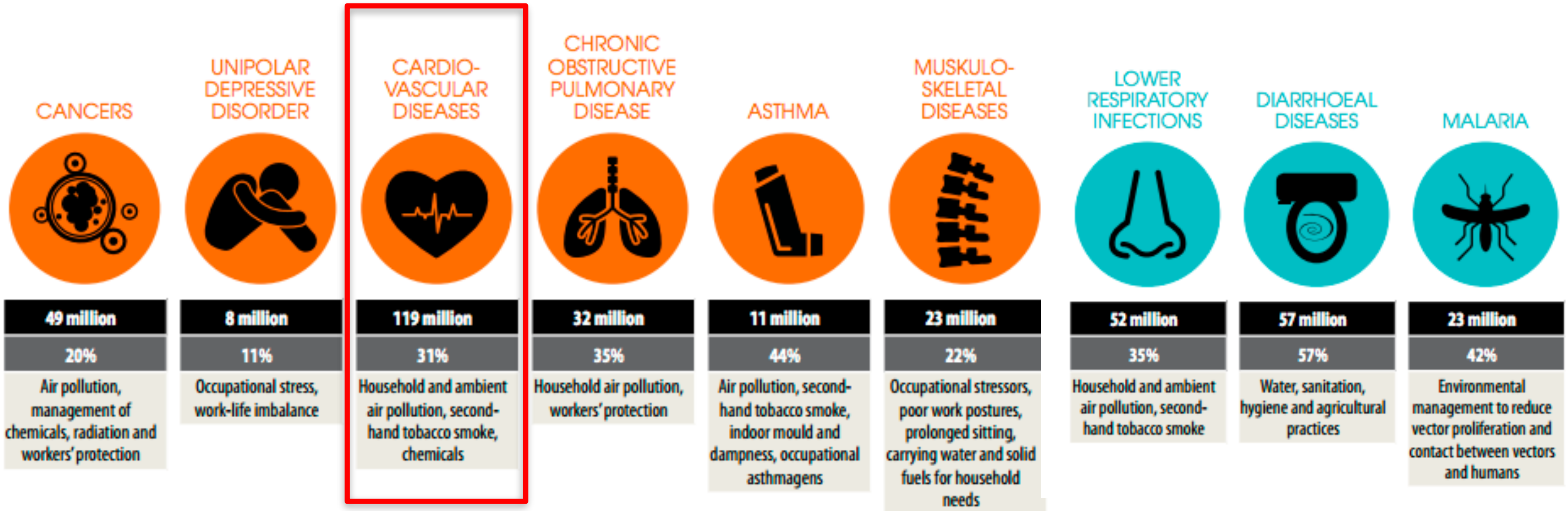
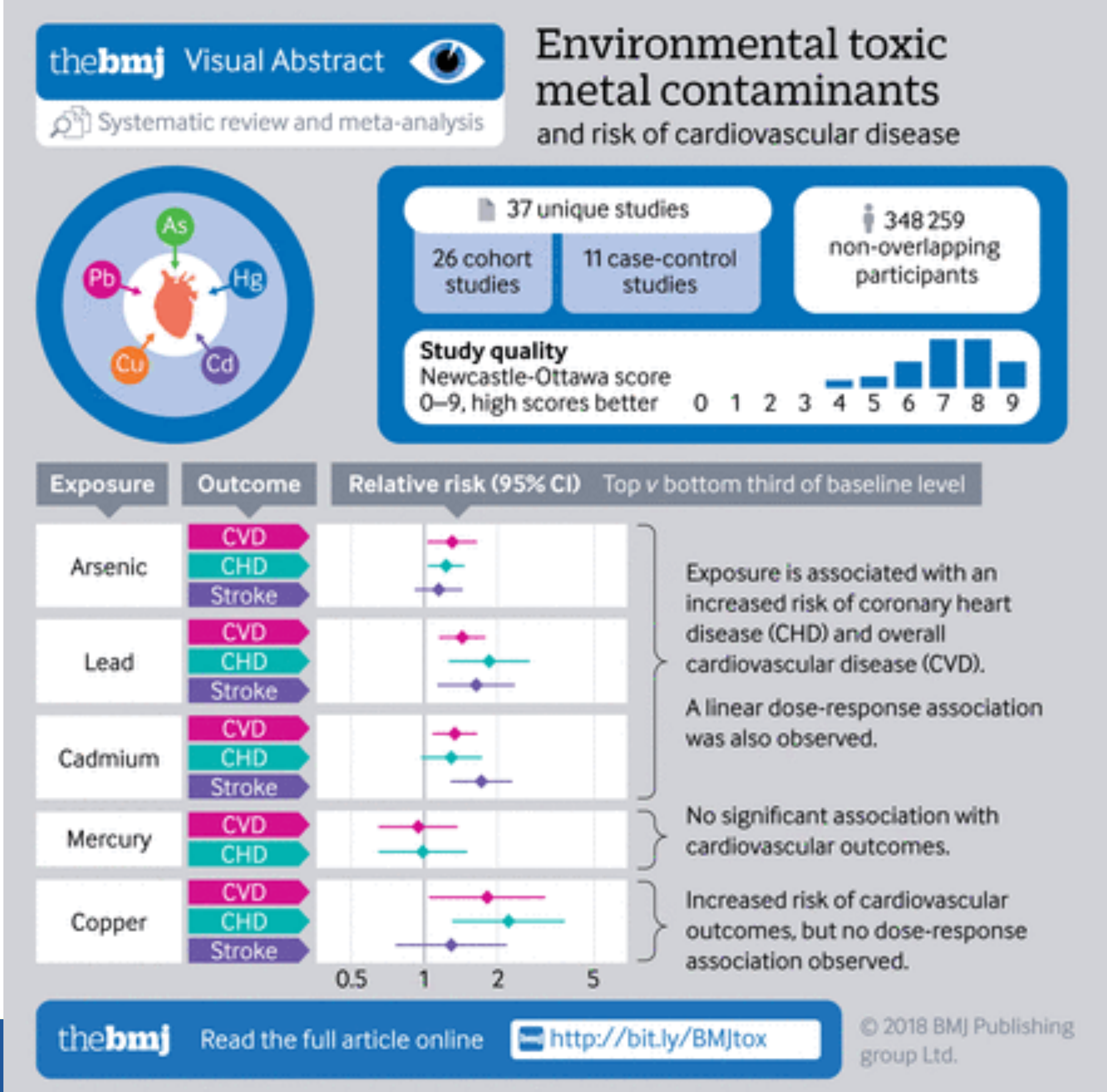
Environment and burden of disease



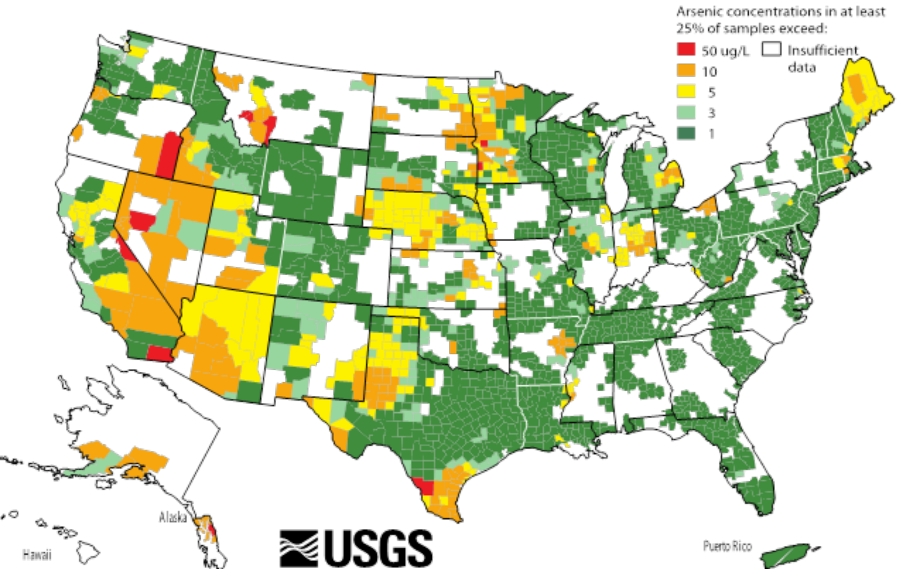
31% of the burden of disease from fatal CVD globally could be avoided if environmental risks were removed (*World Health Organization*, 2016)



Chowdhury et al.
BMJ 2018

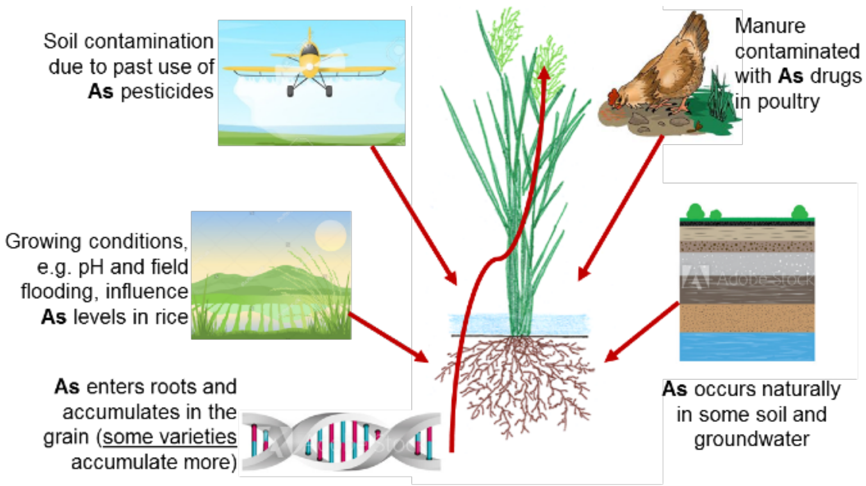
Arsenic is widespread in water and food

Arsenic in groundwater



US EPA standard is 10 µg/L

Arsenic accumulates in rice grain



Standard for FDA is pending

Inorganic arsenic

- Water, food (rice, juice, other grains), air
- Excreted through the urine in 3 phases
- Half life 3 to 38 days
- Health effects: best known for cancer and cardiovascular effects
- Seafood: source of organic arsenicals that are non-toxic

Arsenic and CVD – epidemiological evidence

1930s 1980s	**Case series / Ecological studies** • German vintners (As in pesticides, PAD) • Taiwan & Chile (water As, PAD & other CVD)
1990s	**Cohort studies in Taiwan** • Ecological water As assessment • CVD mortality (all, CHD, stroke)
2007	**Ecological study in Chile** • Natural experiment before & after water As • Myocardial infarction mortality
2011 2013	**HEALS cohort in Bangladesh** • Water and urine As • CVD incidence & mortality (all, CHD, stroke)

As levels:	> 500 µg/L	100 µg/L	10-100 µg/L	< 10 µg/L

Children and young adults exposed to arsenic in drinking water at 900 µg/L in Chile showed thickening of the arterial intima and myocardial infarction

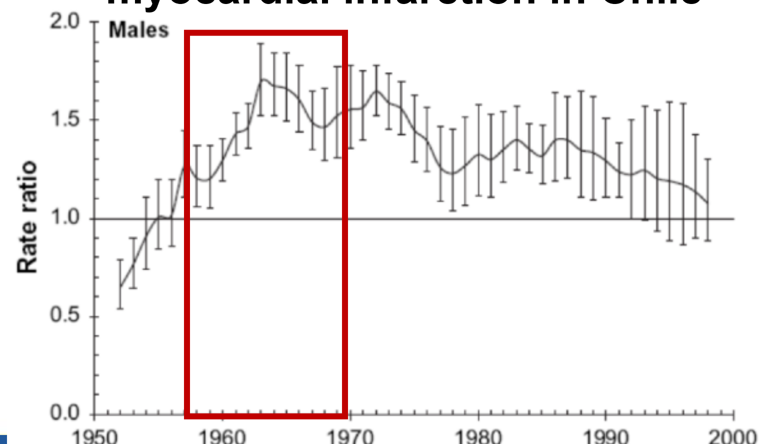
Rosenberg HG. Arch Pathol 1974;97:360-365

Fig 1.—Cross section of epicardial branch of left coronary artery. Note fibrous intimal thickening, replication of elastic fibers internal to lamina elastica. Medial coat and adventitia show slight changes (case 1) (Verhoff-van Giesson,

Black Foot Disease Taiwan

Tromboangeitis obliterans
+ arteriosclerosis

Ecological study of myocardial infarction in Chile



Yuan Y et al. Am J Epidemiol 2007

Health Effects and Geochemistry of Arsenic: The Columbia University NIEHS Superfund Research Program

NIEHSSRP

Columbia University

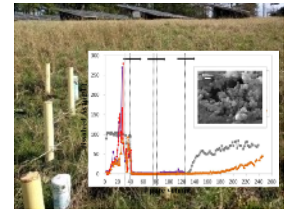
http://superfund.ciesin.columbia.edu **Follow us on Twitter: @Columbia_SRP**

Habibul Ahsan, Lex van Geen and local team at the HEALS clinic in Araihazar, Bangladesh

Joe Graziano with Bangladesh Children Study Participants

Administrative Core

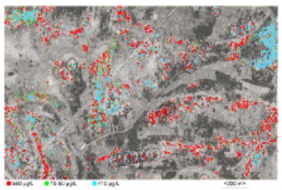
Director Ana Navas-Acien
Co-Director Alexander van Geen



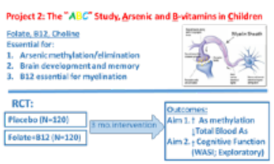
CU SRP Scientists establishing the efficacy of magnetite-based As groundwater remediation (inset graph and micrograph), a tool we hope to apply at the Lot 86 NPL site (shown in photo).

CU SRP Scientists with HEALS Field Staff in Bangladesh at 12-year Anniversary Celebration of Study

Research Projects



As Concentrations in Tubewells Araihazar, Bangladesh



Project 1: Health Effects of As Longitudinal Study (HEALS)
PI: Habibul Ahsan

Evaluate health effects from As in drinking water in Araihazar, Bangladesh

- 35,000 men & women interviewed every 2-3 years
- Dedicated medical clinic
- Study impact of As exposures on:
  - Cardiovascular disease and diabetes
  - Non-malignant respiratory disease
- Contribute to the dose-response assessment through a pooled analysis with 11 other cohorts worldwide

Project 2: Arsenic and B-vitamins in Children (ABC study)
PI: Mary Gamble

Placebo-controlled RCT of folate plus B12 supplementation on As internal dose and cognitive function in children

- Elucidate the effect of folate+vitamin B12 on As methylation and blood As levels in children (Aim 1)
- Explore their effect on cognitive function (Aim 2)
- Assess the association of choline on Aim 1 and 2 outcomes
- Replicate association of dietary folate, B12 and choline on As methylation in adolescents from the Strong Heart Study

Project 3: Enhanced Remediation at US As-contaminated Sites
PI: Benjamin Bostick

Examine different As remediation approaches

- To understand the mechanisms of arsenic dissolution and retention in environments affected by arsenic contamination.
- To develop, optimize and pilot arsenic remediation in groundwater
  1. Oxalate-based enhanced pump-and-treat remediation of arsenic
  2. Magnetite-based arsenic immobilization
- Piloting biogenic magnetite immobilization at Lot86 NPL site (NC) and Yinchuan, China.

Project 4: Resilience of Low-As Aquifers and their Role in Reducing Human Exposure
PI: Alexander van Geen

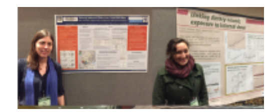
Lower As exposure in HEALS

- Test hh wells within study area using both lab measurements & field kits
- Monitor 110 deep community wells

Understand processes that threaten quality of GW in current low As aquifers

- Investigate a handful of community well failures using geophysical, hydrological, & biogeochemical approaches

Educational Interventions with health education clowns

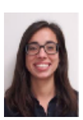


Trainees Sara Flanagan and Tiffany Sanchez presenting at NIEHS Fest

Outreach with health care providers to launch As monitoring in medical practices in Hunterdon New Jersey

Cores

Anne Bozack, 2017 K.C. Donnelly Externship Award



Anne Nigra, PhD student and CU SRP trainee

Core A: Training Core
PIs: Joseph Graziano
Brian Mailloux

Educate trainees in the interdisciplinary research methods and strategies for environmental health and engineering sciences

Core B: Integrated Science Support Core
PIs: Joseph Graziano
Richard Buchsbaum

Precisely measure metals & metabolites in biospecimens

Provide safe, secure relational data management

Core C: Biogeochemistry
PI: Alexander van Geen

Measure metals, dissolved organic carbon, reactive organic acids & more in groundwater and sediment samples

Core D: Hydrogeology
PI: Peter Schlosser

Provide the tools and expertise to collect and interpret hydrogeological data

Core E: Community Engagement
PI: Yan Zheng

Develop tools, resources & strategies to build the capacity of individuals, communities & government partners to reduce exposure to As from private wells in ME, NJ & MN

Core F: Research Translation Core (RTC)
PIs: Sandra Baptista
Steven Chillrud

Augmenting & accelerating the impact of our Center's basic & applied science on public policies, regulations & human behavior

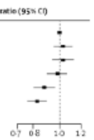
Barnard College Arsenic Awareness Student Videos

Trace metal core at Columbia University Mailman School of Public Health

Estimated urinary DMA concentrations in NHANES

Year	N	Geometric mean	Geometric mean ratio (95% CI)
2003–04	1275	3·01 (2·97–3·05)	1·00 (reference)
2005–06	1406	3·10 (3·06–3·15)	1·03 (0·95–1·12)
2007–08	1595	3·11 (3·07–3·15)	1·03 (0·94–1·13)
2009–10	1763	2·93 (2·89–2·97)	0·98 (0·90–1·06)
2011–12	1472	2·64 (2·61–2·68)	0·88 (0·80–0·96)
2013–14	1644	2·49 (2·45–2·52)	0·83 (0·76–0·90)

p value for trend p<0·001

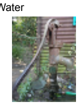


Source: Nigra et al. Lancet Public Health 2017

Data server in Araihazar, Bangladesh

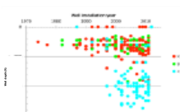
As Testing in Maine Well Water

Transdisciplinary Data Entry

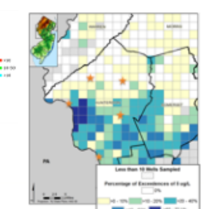


Safe well

Field kit testing and e-data entry in Araihazar by study staff



Well Installations by Year Depth Distribution of As



★ Participating medical practices in As monitoring in Hunterdon, NJ

Brochure to offer As testing in medical practices in Hunterdon, NJ

BMJ

BMJ 2011;342:d2431 **RESEARCH**

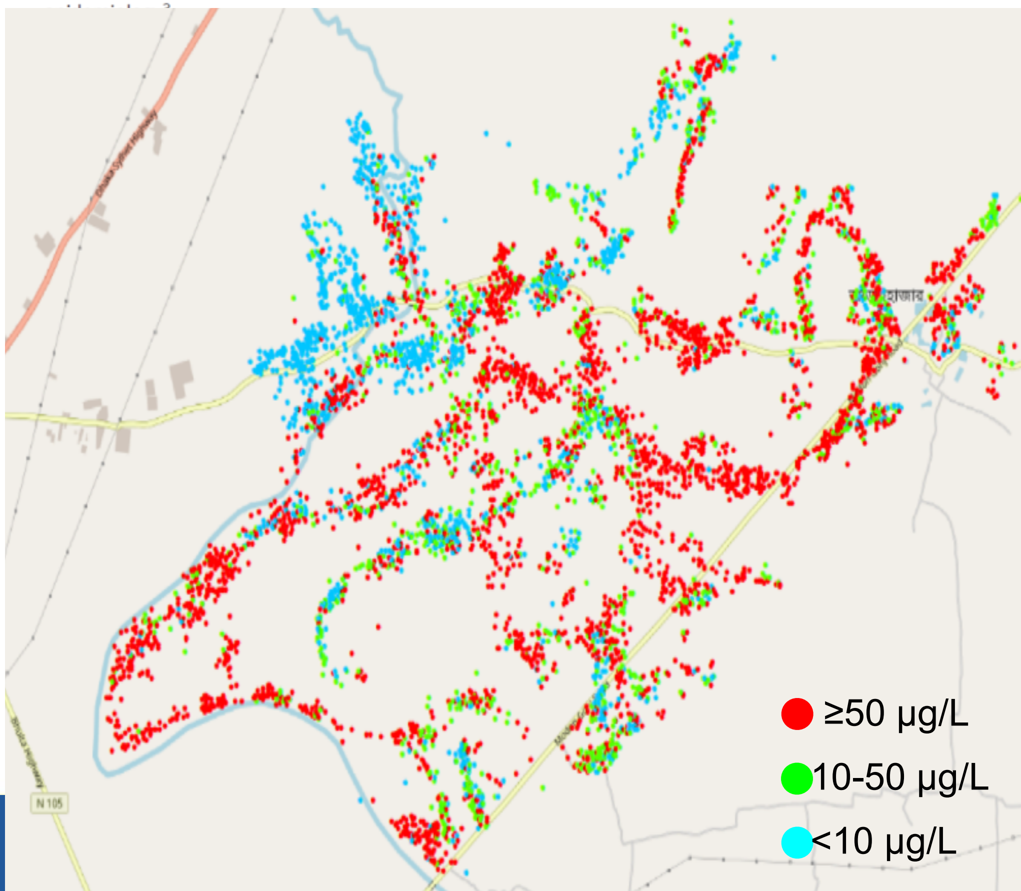
Arsenic exposure from drinking water and mortality from cardiovascular disease in Bangladesh: prospective cohort study

Yu Chen, associate professor of epidemiology,[1] Joseph H Graziano, professor of environmental health sciences,[2] Faruque Parvez, associate research scientist ,[2] Mengling Liu, associate professor of biostatistics,[1] Vesna Slavkovich, associate research scientist ,[2] Tara Kalra, project coordinator/data analyst,[3] Maria Argos, project coordinator/data analyst,[3] Tariqul Islam, project director ,[4] Alauddin Ahmed, field coordinator ,[4] Muhammad Rakibuz-Zaman, study physician/laboratory manager ,[4] Rabiul Hasan, assistant field coordinator ,[4] Golam Sarwar, informatics manager ,[4] Diane Levy, senior staff associate ,[2] Alexander van Geen, Lamont research professor in Lamont-Doherty Earth Observatory ,[5] Habibul Ahsan, professor of

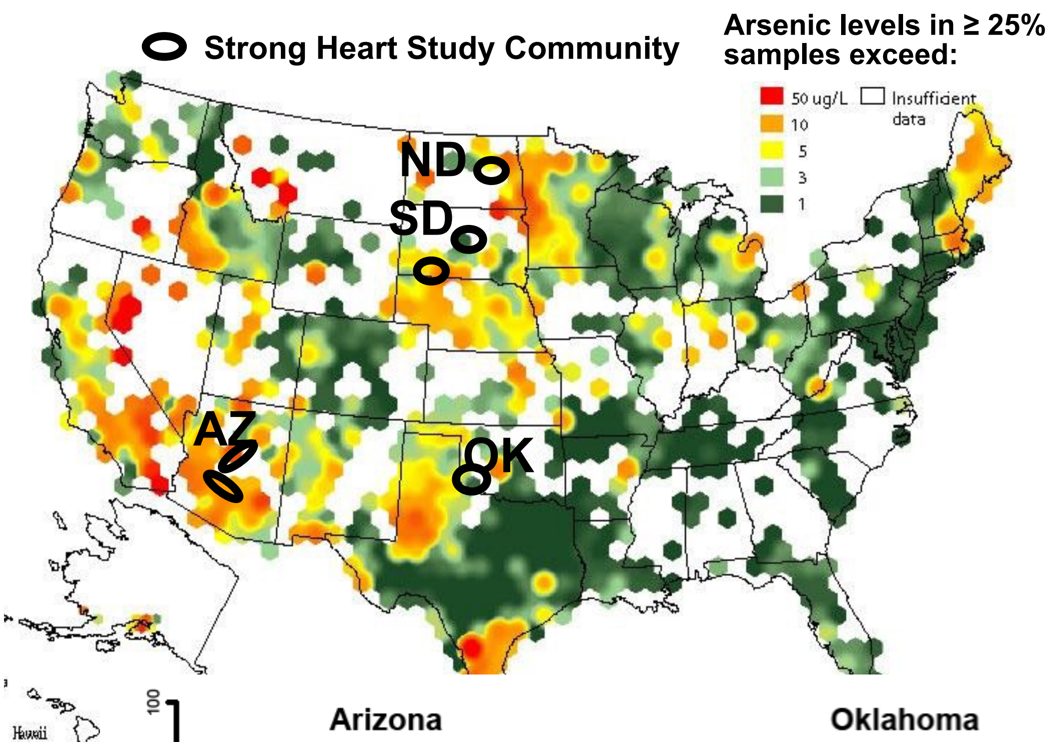
HEALS cohort recruited and followed 12,000 participants since 2000-2001 in Araihazar, Bangladesh

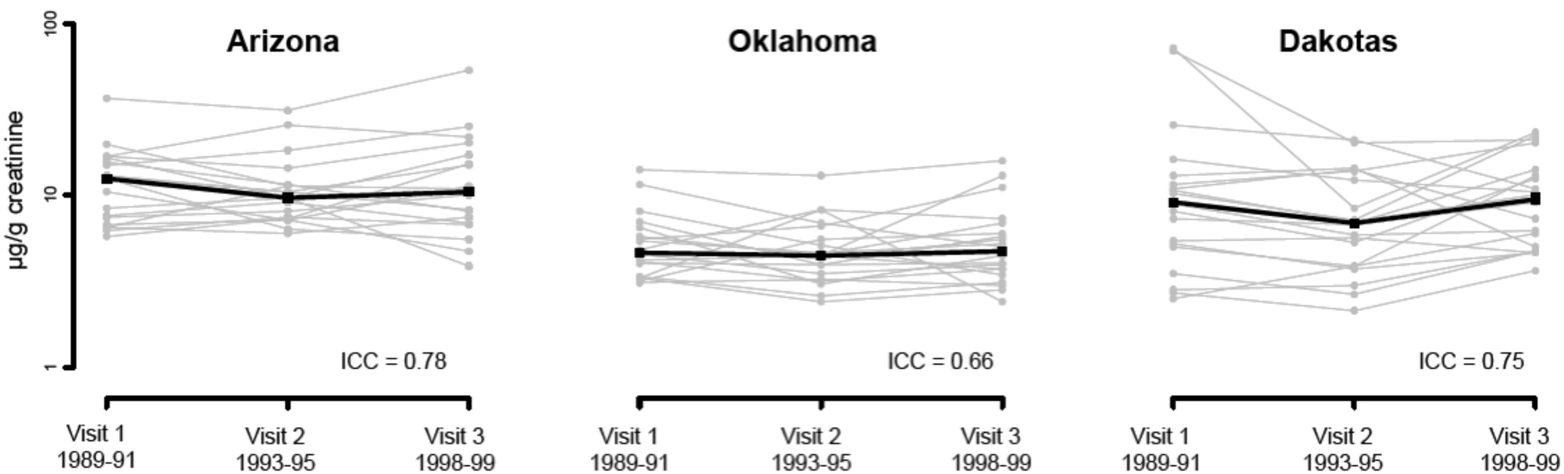
Water As	HR (95%CI)
<12.0 µg/L	1.00 (ref)
12.1-62.0	1.22 (0.65, 2.32)
62.1-148.0	1.35 (0.71, 2.57)
>148.1	1.92 (1.07, 3.43)
Per SD (115 µg/L)	1.29 (1.10, 1.52)

Adjusted for age, sex, BMI, smoking status, education



Arsenic exposure disproportionately affects rural areas in the US, including American Indian communities





ICC = Intraclass correlation coefficient

Study Population

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

Visit 1	Visit 2	Visit 3
1989-91	1993-95	1998-99

64% baseline response rate

89% 88%
retention rate

Ongoing Surveillance: Morbidity & Mortality

Visit 3 pilot	Visit 4	Visit 5	Visit 6
1998-99	2001-03	2006-09	2014-16

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

Arsenic funding: NHLBI (R01HL090863) and NIEHS (R01ES021367, R01ES025216, R01ES025135)

Team Science and Community Partnership

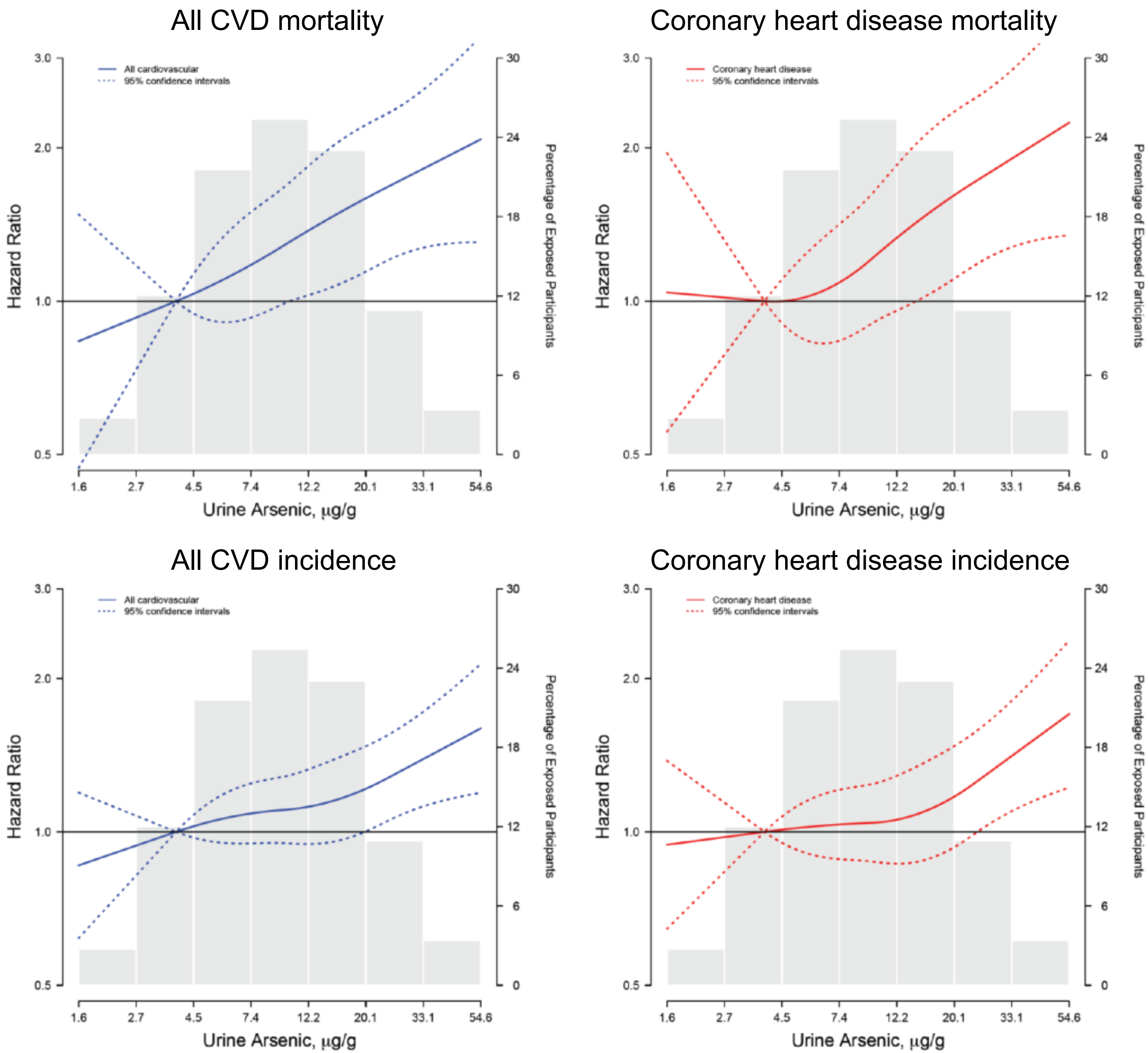
Hazard ratio (95% CI) for CVD by urine arsenic in the Strong Heart Study


Kat Moon

	Cases/ Non-cases	CVD mortality	CVD incidence
Sum inorganic and methylated arsenic			
Q1 (< 5.8 µg/g)	86/809	1.00 (referent)	1.00 (referent)
Q2 (5.8–9.7)	95/797	1.06 (0.78, 1.44)	1.13 (0.95, 1.34)
Q3 (9.7–15.7)	114/778	1.24 (0.90, 1.70)	1.02 (0.84, 1.23)
Q4 (>15.7)	143/752	1.52 (1.10, 2.11)	1.24 (1.02, 1.50)
p trend		<0.001	0.008

Stratified by study region and age-adjusted (age at baseline treated as staggered entries) and further adjusted for sex, education, alcohol, smoking, and body mass index, total cholesterol, HDL-cholesterol, hypertension medication, systolic blood pressure, diabetes and estimated glomerular filtration rate

Arsenic and incident CVD



Moon et al. Annals Intern Medicine 2013

Lines represent hazard ratios (95% CI) based on restricted cubic splines and adjusted for age, sex, education, alcohol, smoking, body mass index, total cholesterol, HDL-cholesterol, hypertension medication, SBP, diabetes eGFR, and stratified by region

A Section 508–conformant HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1307839.

Association between Lifetime Exposure to Inorganic Arsenic in Drinking Water and Coronary Heart Disease in Colorado Residents

Katherine A. James,[1] Tim Byers,[1] John E. Hokanson,[1] Jaymie R. Meliker,[2] Gary O. Zerbe,[1] and Julie A. Marshall[1]

[1]Colorado School of Public Health, University of Colorado Denver, Aurora, Colorado, USA; [2]Department of Preventive Medicine, State University of New York, Stony Brook, New York, USA

Hazard ratio (95%CI) for incident coronary heart disease by water arsenic levels in the San Luis Valley Diabetes Study

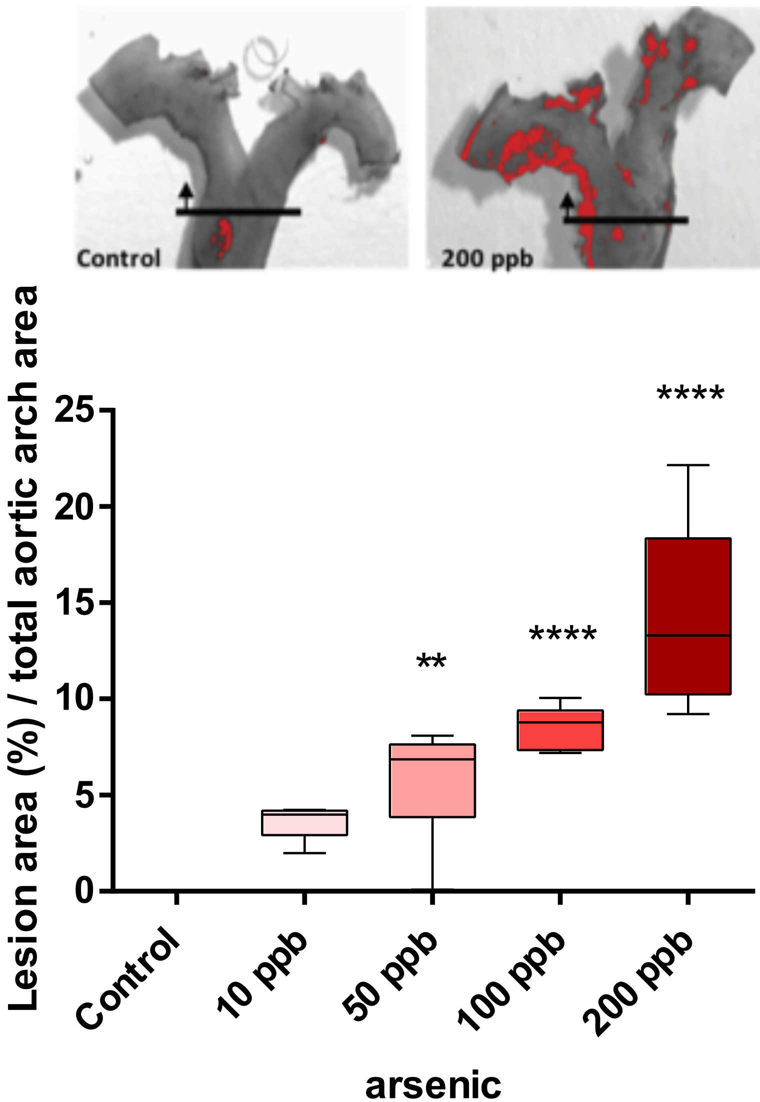
Variable	Univariate model HR (95% CI)	Full model HR (95% CI)
Arsenic exposure		
1–20 µg/L	1.0	1.0
20–30 µg/L	1.24 (0.70, 2.31)	1.25 (0.60, 2.61)
30–45 µg/L	2.14 (1.22, 3.98)	2.08 (1.11, 3.92)
45–88 µg/L	3.12 (1.11, 9.02)	3.34 (1.15, 9.30)

Adjusted for age, sex, ethnicity, income, family history CHD, diabetes, BMI, physical activity, LDL-cholesterol, triglycerides, HDL-cholesterol, folate, selenium

VOLUME 123 | NUMBER 2 | February 2015 • Environmental Health Perspectives

ApoE$^{-/-}$ Model of Arsenic-induced Atherosclerosis

Tap water arsenic
for 13 weeks



N=6/group

Mann K et al. EHP 2017

Summary of cardiovascular relevant findings in Strong Heart Study

Low-to-moderate **arsenic exposure** associated with:

- **Cardiovascular disease** incidence and mortality (coronary heart disease and stroke)
- **Peripheral artery disease**, **carotid atherosclerosis**, prolonged **QT interval**, **cardiac geometry**
- Prevalent / incident **diabetes** and diabetes control
- Prevalent and incident **albuminuria**
- Incident **chronic kidney disease**

EBioMedicine 28 (2018) 311–315

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Paper

Disconnect Between Genes Associated With Ischemic Heart Disease and Targets of Ischemic Heart Disease Treatments

C.M. Schooling [a,b,*], J.V. Huang [b], J.V. Zhao [b], M.K. Kwok [b], S.L. Au Yeung [b], S.L. Lin [b]

[a] CUNY Graduate School of Public Health and Health Policy, New York, USA
[b] School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

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Keywords:
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Gene
Treatment

_AS3MT_ is associated with Coronary Heart Disease in Cardiogram

ABSTRACT

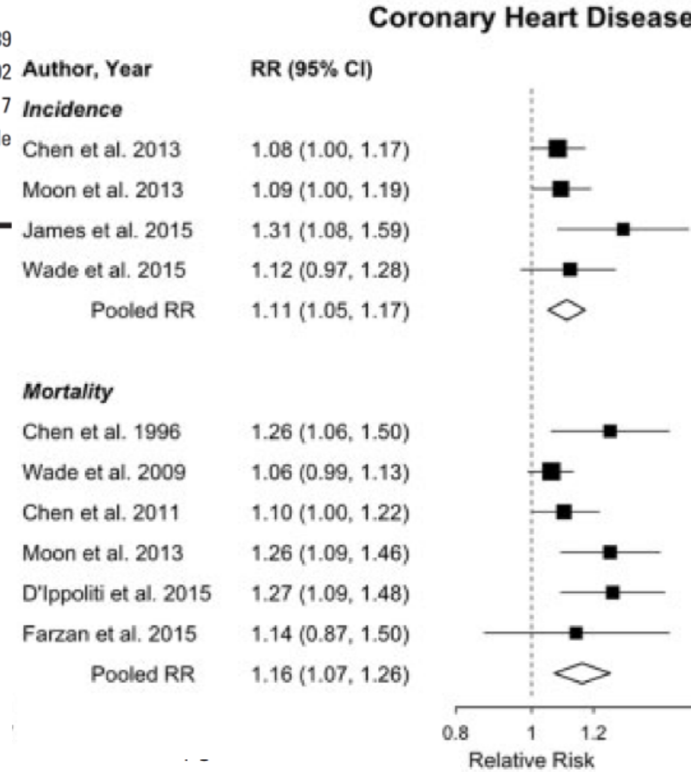
Background: Development of pharmacological treatments to mitigate ischemic heart disease (IHD) has encompassed disappointing results and expensive failures, which has discouraged investment in new approaches to prevention and control. New treatments are most likely to be successful if they act on genetically validated targets. We assessed whether existing pharmacological treatments for IHD reduction are acting on genetically validated targets and whether all such targets for IHD are currently being exploited.
Methods: Genes associated with IHD were obtained from the loci of single nucleotide polymorphisms reported in either of two recent genome wide association studies supplemented by a gene-based analysis (accounting for linkage disequilibrium) of CARDIoGRAMplusC4D 1000 Genomes, a large IHD case (n = 60,801)-control (n = 123,504) study. Treatments targeting the products of these IHD genes and genes with products targeted by current IHD treatments were obtained from Kyoto Encyclopedia of Genes and Genomes and Drugbank. Cohen's kappa was used to assess agreement.
Results: We identified 173 autosomal genes associated with IHD and 236 autosomal genes with products targeted by current IHD treatments, only 8 genes (*PCSK9*, *EDNRA*, *PLG*, *LPL*, *CXCL12*, *LRP1*, *CETP* and *ADORA2A*) overlapped, i.e. were both associated with IHD and had products targeted by current IHD treatments. The Cohen's kappa was 0.03. Interventions related to another 29 IHD genes exist, including dietary factors, environmental exposures and existing treatments for other indications.
Conclusions: Closer alignment of IHD treatments with genetically validated physiological targets may represent a major opportunity for combating a leading cause of global morbidity and mortality through repurposing existing interventions.

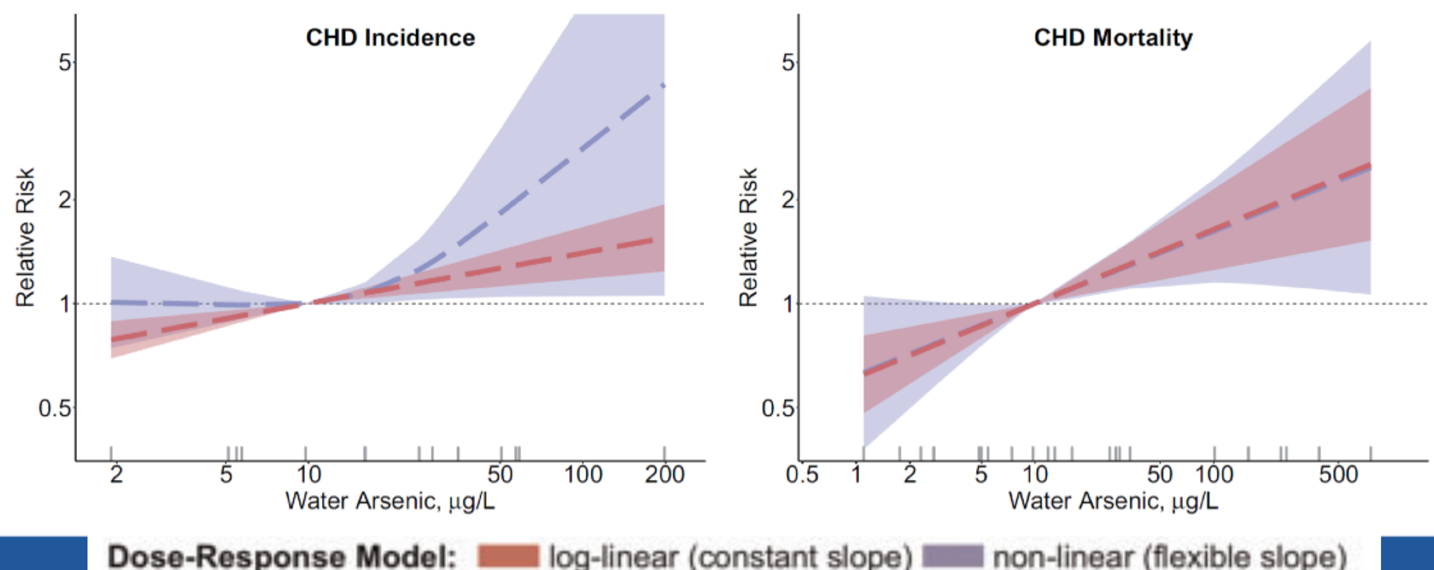
International Journal of Epidemiology, 2017, 1924–1939
doi: 10.1093/ije/dyx202
Advance Access Publication Date: 23 September 2017
Original article

Hazardous Substances

A dose-response meta-analysis of chronic arsenic exposure and incident cardiovascular disease

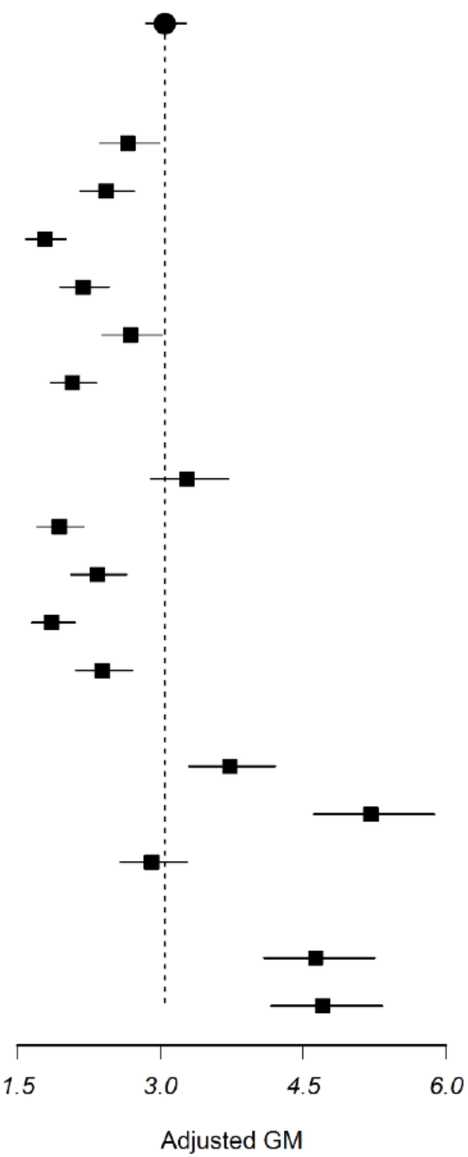
Katherine A Moon,[1,2*] Shilpi Oberoi,[3] Aaron Barchowsky,[3] Yu Chen,[4] Eliseo Guallar,[1] Keeve E Nachman,[2] Mahfuzar Rahman,[5] Nazmul Sohel,[6] Daniela D'Ippoliti,[7] Timothy J Wade,[8] Katherine A James,[9] Shohreh F Farzan,[10] Margaret R Karagas,[11] Habibul Ahsan[12] and Ana Navas-Acien[1,2,13]





Urine arsenic by city and race in MESA (n=310)

	N	Adjusted GM (95% CI)
Overall	310	3.05 (2.85, 3.27)
White		
Los Angeles, CA	15	2.66 (2.37, 2.99)
Winston−Salem, NC	15	2.43 (2.16, 2.73)
New York, NY	15	1.79 (1.59, 2.01)
Baltimore, MD	15	2.19 (1.95, 2.46)
St Paul, MN	15	2.69 (2.39, 3.02)
Chicago, IL	15	2.08 (1.85, 2.33)
Black		
Los Angeles, CA	15	3.28 (2.90, 3.72)
Winston−Salem, NC	15	1.94 (1.71, 2.20)
New York, NY	15	2.34 (2.06, 2.65)
Baltimore, MD	15	1.86 (1.65, 2.11)
Chicago, IL	15	2.39 (2.11, 2.71)
Hispanic		
Los Angeles, CA	25	3.73 (3.30, 4.21)
New York, NY	25	5.21 (4.61, 5.88)
St Paul, MN	25	2.91 (2.58, 3.28)
Chinese		
Los Angeles, CA	35	4.63 (4.09, 5.25)
Chicago, IL	35	4.71 (4.16, 5.33)



Adjusted for urine creatinine, sex, age, education and body mass index

Miranda Jones

Jones et al. Am J Epidemiol 2016

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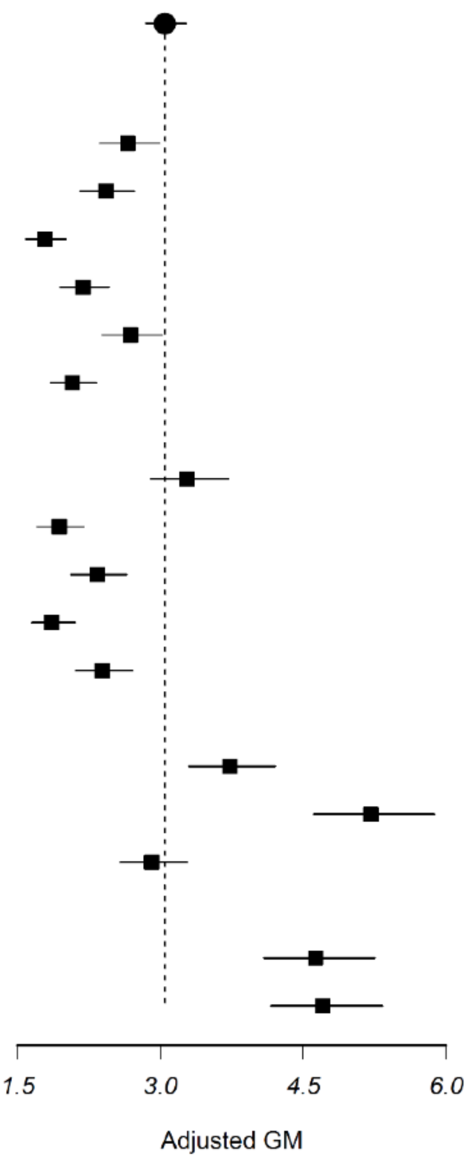


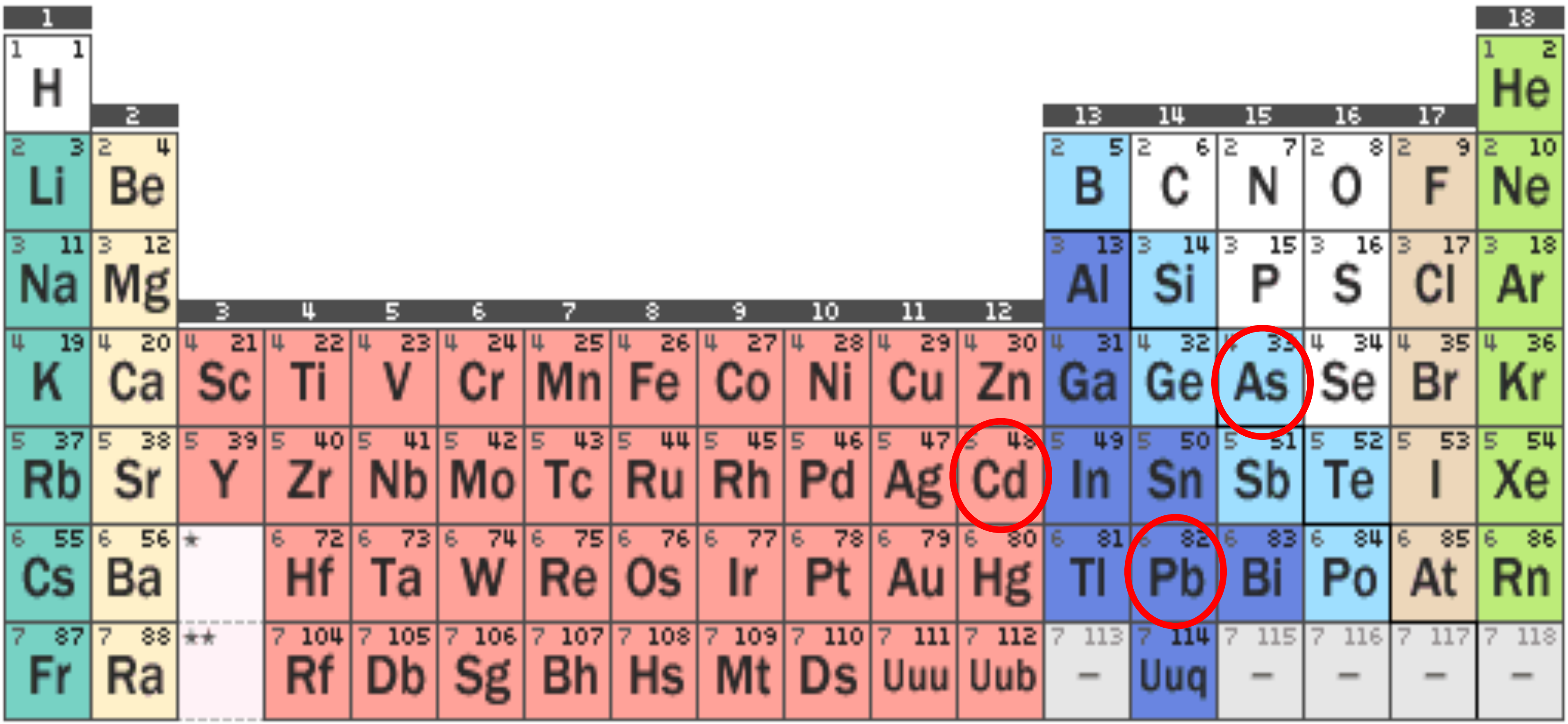
Adjusted for urine creatinine, sex, age, education and body mass index

Miranda Jones

Arsenic and other metals/ metalloids ongoing in ~6,000 MESA participants (R01ES028758)

Jones et al. Am J Epidemiol 2016

Metals with evidence in support of potential cardiovascular effects



Evidence at low-moderate levels is increasing

SATURNINE GOUT, AND ITS DISTINGUISHING MARKS.

By G. LORIMER, M.A., M.D.Edin., Buxton.

The conclusions arrived at are based upon an analysis of 107 cases of gout due to plumbism, which have occurred in the writer's experience, and the subsequent remarks constitute a record of facts so observed.

6. *Arterial Thickening and Degeneration.*—This condition, noted in sixty-nine cases, consists of a sclerosis of the arterial coats, along with atheromatous changes. It is, in fact, a premature ageing of the arterial system. *a.* It may be due to the action of lead, which causes contraction of the muscular walls of the arteries, and raises arterial tension. *b.* It may be connected with the renal changes which arise in saturnine arthritis. *c.* It may depend on the condition of the blood in gout, which gives rise to increased arterial tension, and predisposes to atheroma. Cardiac hypertrophy is observed in saturnine gout, especially at the advanced period of the disease. The arterial changes, however, may occur independently of the cardiac. Pericarditis has been noted by Charcot and Gumbolt. One instance only was noted by the writer in the cases referred to.

Lead and cadmium: sources of exposure

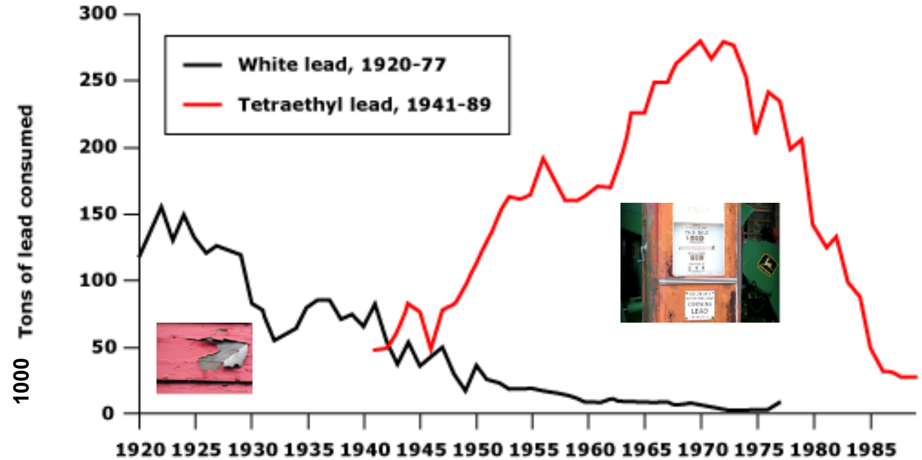
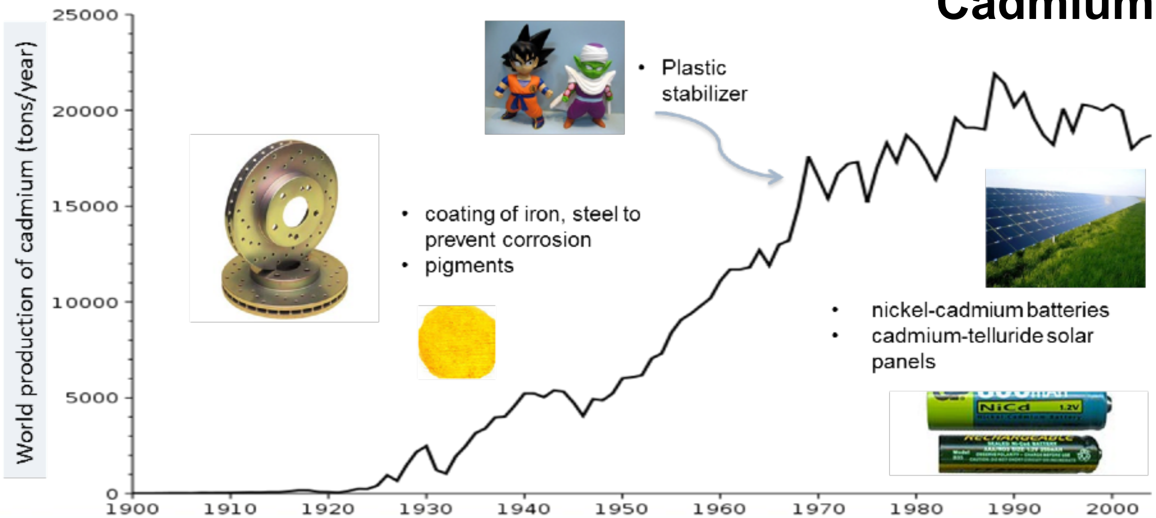


FIGURE 2-1
Falling Consumption of White Lead; Rising Consumption of Leaded Gasoline
U.S. Department of the Interior, Bureau of Mines, "Lead," in *Minerals Yearbook* 1920–89 (Washington: GPO, 1921–90). No statistics for tetraethyl lead were published prior to 1941.

Lead

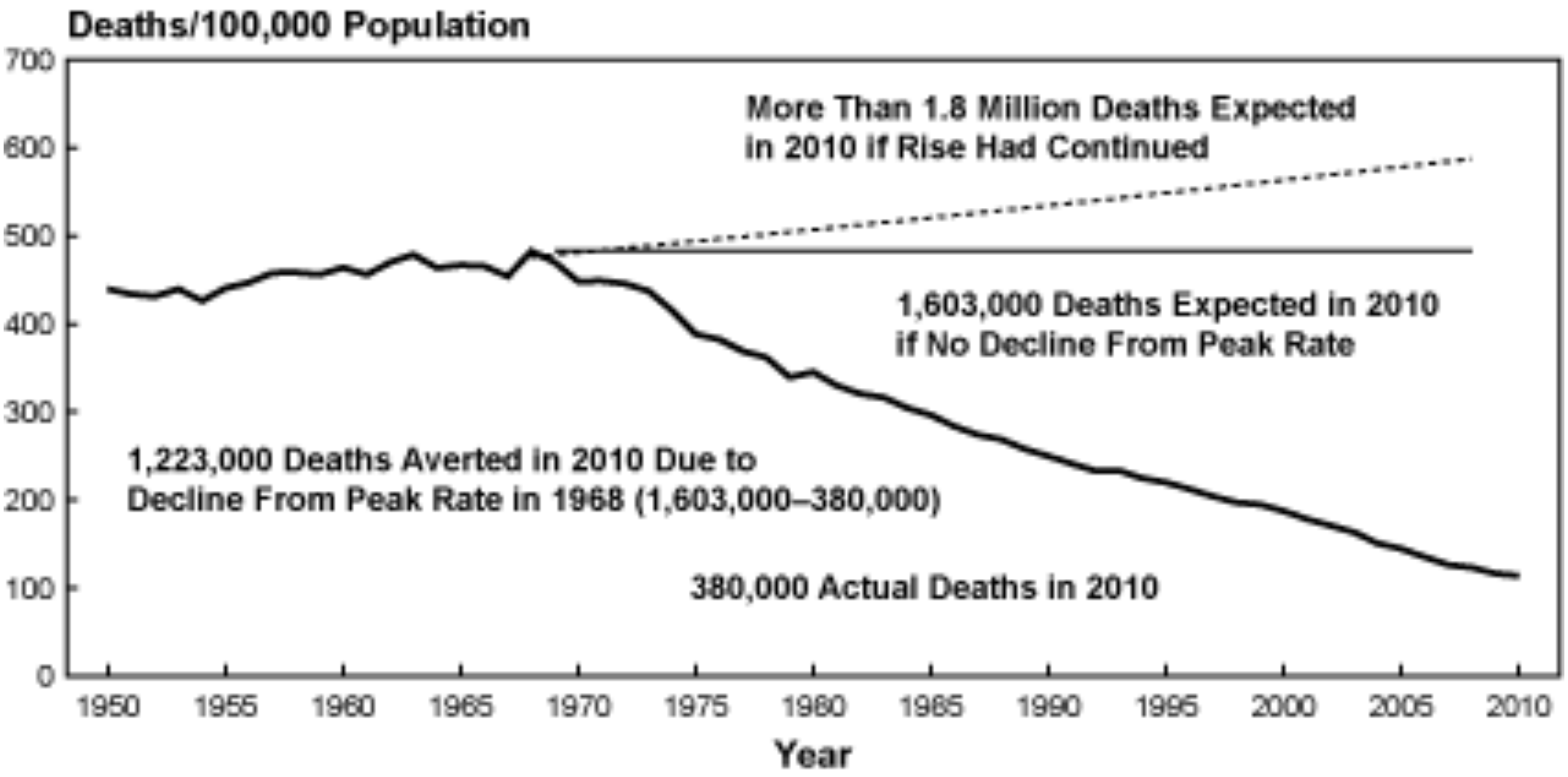
- Air, food, water, smoking, dust, soil
- Stored in bones
- Half life decades
- Health effect: best known for neurocognitive effects



Cadmium

- Smoking, food, soil, air
- Stored in soft tissues
- Half life decades
- Health effects: best known for carcinogenic effects

More than 1 million CVD deaths prevented in 2010 compared to 1968 in the US



http://www.nhlbi.nih.gov/about/documents/factbook/2012/chapter4

International Journal of Epidemiology, 2017, 1903–1912
doi: 10.1093/ije/dyx176
Advance Access Publication Date: 30 August 2017
Original article

Maria
Tellez Plaza

Hazardous Substances

Declining exposures to lead and cadmium contribute to explaining the reduction of cardiovascular mortality in the US population, 1988–2004

Adrian Ruiz-Hernandez,[1,2] Ana Navas-Acien,[3–5] Roberto Pastor-Barriuso,[6,7] Ciprian M Crainiceanu,[8] Josep Redon,[1,2,9] Eliseo Guallar[3,5,10] and Maria Tellez-Plaza[2,4]*

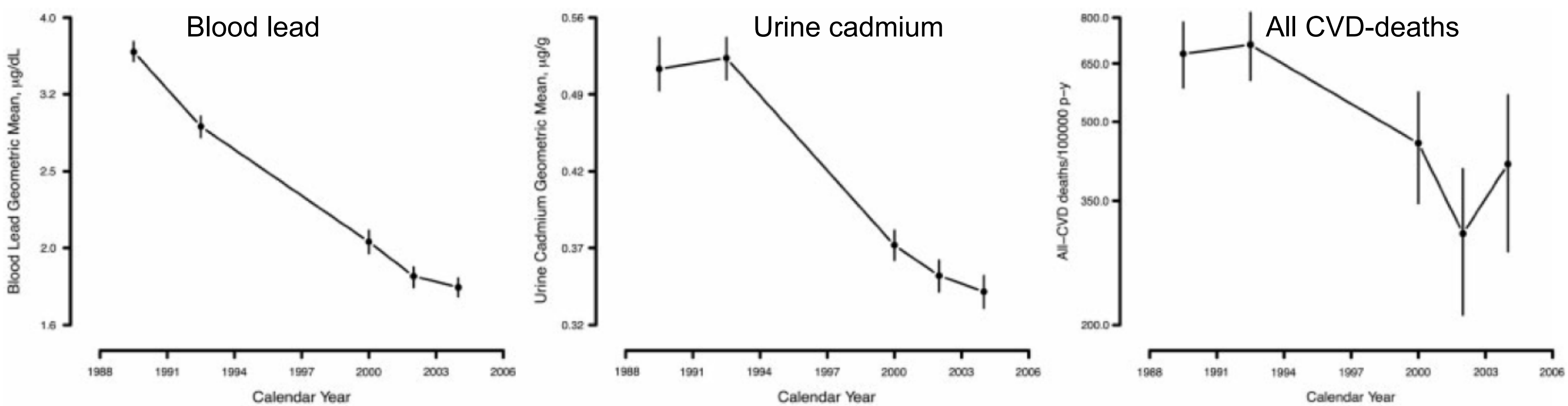
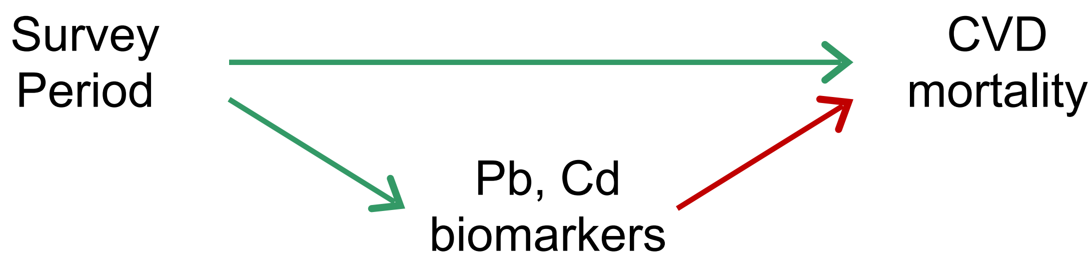


Figure 1. Age-, sex- and race-adjusted geometric mean blood lead and urine cadmium concentrations and cardiovascular disease (CVD) mortality rates across 1988–2004 National Health and Nutrition Examination Survey phases. Vertical bars show 95% confidence intervals based on 15 000 bootstrap re-samples.

Can the effect of period in CVD mortality be explained (i.e. mediated) by temporal changes in lead and cadmium exposure?



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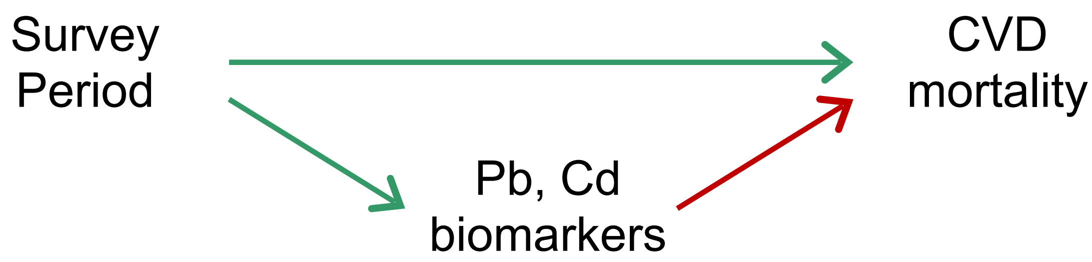

- Nested Aalen additive hazard models for CVD deaths with the same set of confounders (age, sex, race, smoking status, physical activity, obesity, hypertension, diabetes, total cholesterol, low HDL cholesterol, lipid-lowering medication) one adjusting for metals and one not (Jiang and VanderWeele. AJE 2015;182:105-08; WanderWeele. Epidemiology 2011;22:582-85).
- Among **230.7 CVD deaths/100,000 person-year avoided** in the US comparing 1999-2004 to 1988-1994:
  - **52.0 (22.5%)** deaths were attributable to changes in lead and
  - **19.4 (8.4%)** deaths were attributable to cadmium
  - after adjustment for sociodemograhic, CVD risk factors and changes in medication use over the 2 periods

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Key Messages

- Blood lead and urine cadmium have been associated with a broad range of cardiovascular endpoints in multiple epidemiologic studies. However, the contribution of lead and cadmium changes over time to cardiovascular mortality trends has not been formally investigated.
- Our findings suggest that reducing lead and cadmium exposures may be an overlooked public health achievement by preventing a substantial amount of cardiovascular deaths in the USA.
- Since both metals remain associated with cardiovascular disease at relatively low levels of exposure, primary prevention strategies minimizing avoidable lead and cadmium exposures could further contribute to the prevention and control of cardiovascular disease in general populations.

Low-level lead exposure and mortality in US adults: a population-based cohort study

Bruce P Lanphear, Stephen Rauch, Peggy Auinger, Ryan W Allen, Richard W Hornung

nhanes

oa OPEN ACCESS

Lancet Public Health 2018

Published Online
March 12, 2018

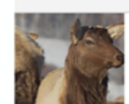
Summary

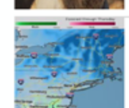
Background Lead exposure is a risk factor for cardiovascular disease mortality, but the number of deaths in the USA attributable to lead exposure is poorly defined. We aimed to quantify the relative contribution of environmental lead exposure to all-cause mortality, cardiovascular disease mortality, and ischaemic heart disease mortality.

US deaths from lead exposure 10 times higher than thought, study suggests

By Mark Lieber, CNN
Updated 9:19 PM ET, Mon March 12, 2018

More from CNN


Russians soak up the 'power' of Siberian red deer blood


Keep out the snow shovel. Another nor'easter, 'bomb cyclone...

TACT2
TRIAL TO ASSESS CHELATION THERAPY

- Replicative trial of EDTA chelation and high-dose oral vitamins in 1200 post-MI diabetic patients
- Funded by NIH
- Storing biospecimens for measuring metals and testing future mechanistic hypotheses (biorepository at Columbia University)
- Metals at infusions 1, 5, 20, and 40 (or 1 year) assessed at the CDC
    - **Pre-infusion blood Pb** together with Cd, Co, Cr, Hg, Mn, Se
    - **Pre- and post-infusion urine Cd** together with Pb, Ba, Be, Cs, Co, Cu, Mn, Mo, Ni, Pt, Sb, Sn, Sr, Tl, U, W, Zn

TACT2 provides a unique opportunity to understand the causal role of metals in CVD

R01AT009273 (NCCIH)

Effect of Disodium EDTA Chelation Regimen on Cardiovascular Events in Patients With Previous Myocardial Infarction

The TACT Randomized Trial

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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

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 $P=.036$.

Results Qualifying previous MIs occurred a median of 4.6 years before enrollment. Median age was 65 years, 18% were female, 9% were nonwhite, and 31% were diabetic. The primary end point occurred in 222 (26%) of the chelation group and 261 (30%) of the placebo group (hazard ratio [HR], 0.82 [95% CI, 0.69-0.99]; $P=.035$). There was no effect on total mortality (chelation: 87 deaths [10%]; placebo, 93 deaths [11%]; HR, 0.93 [95% CI, 0.70-1.25]; $P=.64$), but the study was not powered for this comparison. The effect of EDTA chelation on the components of the primary end point other than death was of similar magnitude as its overall effect (MI: chelation, 6%; placebo, 8%; HR, 0.77 [95% CI, 0.54-1.11]; stroke: chelation, 1.2%; placebo, 1.5%; HR, 0.77 [95% CI, 0.34-1.76]; coronary revascularization: chelation, 15%; placebo, 18%; HR, 0.81 [95% CI, 0.64-1.02]; hospitalization for angina: chelation, 1.6%; placebo, 2.1%; HR, 0.72 [95% CI, 0.35-1.47]). Sensitivity analyses examining the effect of patient dropout and treatment adherence did not alter the results.

Conclusions and Relevance Among stable patients with a history of MI, use of an intravenous chelation regimen with disodium EDTA, compared with placebo, modestly reduced the risk of adverse cardiovascular outcomes, many of which were revascularization procedures. These results provide evidence to guide further research but are not sufficient to support the routine use of chelation therapy for treatment of patients who have had an MI.

Trial Registration clinicaltrials.gov Identifier: NCT00044213

JAMA. 2013;309(12):1241-1250 www.jama.com

Treatment of lead toxicity with chelation was first reported with EDTA in the early 1950s.[1] Apparent success in reducing metastatic calcium deposits[2] led Clarke et al[3] in 1956 to treat angina patients with EDTA, and others to use chelation for various forms of atherosclerotic disease.[4-6] Chelation therapy evolved to constitute infusions of vitamins and disodium EDTA, a drug that binds divalent and some trivalent cations, including calcium, magnesium, lead, cadmium, zinc, iron, aluminum, and copper, facilitating their urinary excretion.[7,8]

Over the next decades, based on favorable anecdotal and case report experience, chelation practitioners increased their use of EDTA for coronary and peripheral artery disease. The 2007 National Health Statistics Report compared chelation use since 2002 and noted

For editorial comment see pp 1291 and 1293.

Author Video Interview available at www.jama.com.

Author Affiliations are listed at the end of this article.
A complete list of the TACT Investigators appears in the eAppendix.

Corresponding Author: Gervasio A. Lamas, MD, Columbia University Division of Cardiology, Mount Sinai Medical Center, 4300 Alton Rd, Miami Beach, FL 33140 (gervasio.lamas@msmc.com).

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

EDTA: Placebo

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

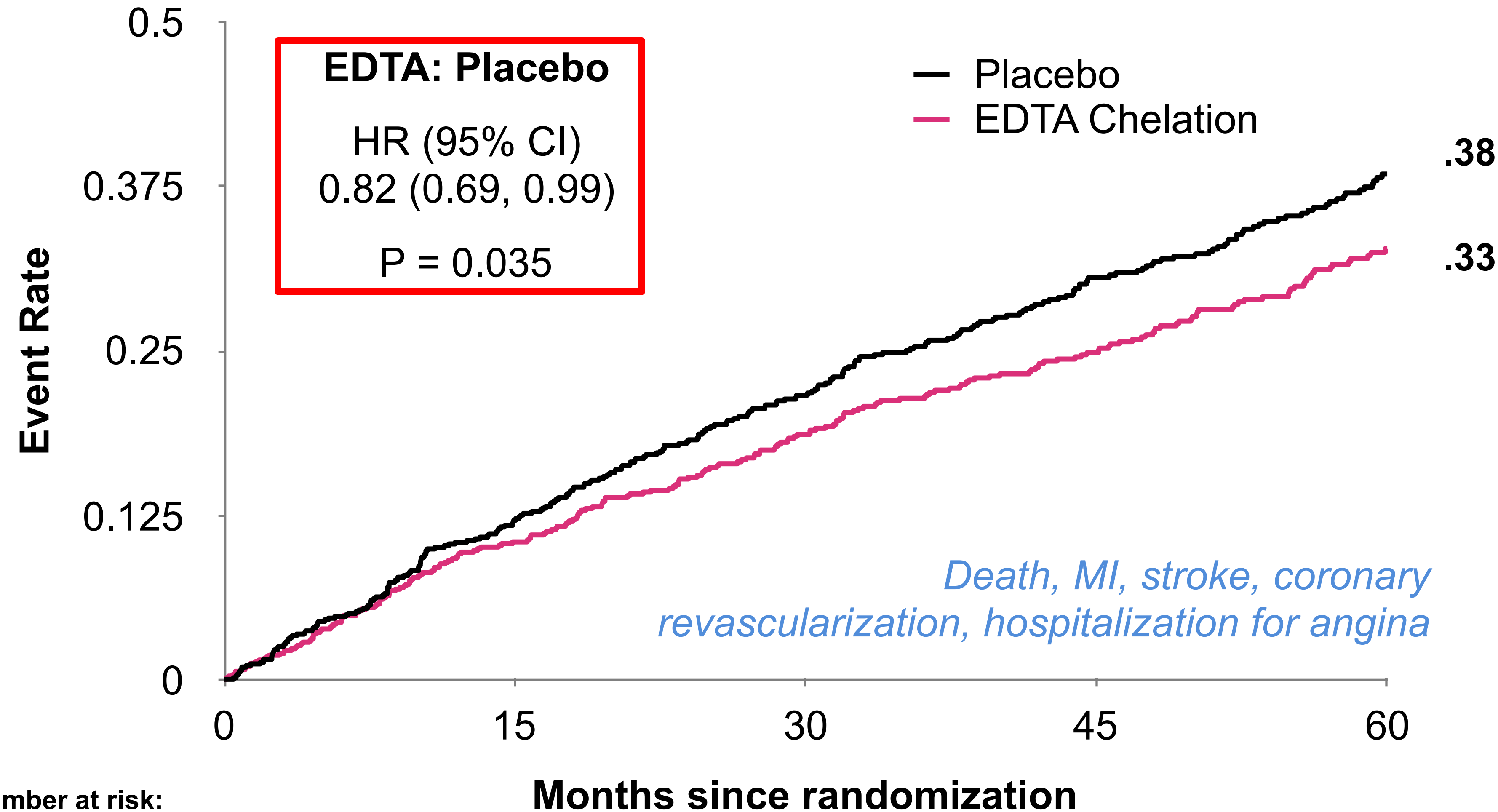
P = 0.035

With Diabetes:

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

P = 0.002
(Bonferroni adjusted)

TACT Primary Endpoint Results

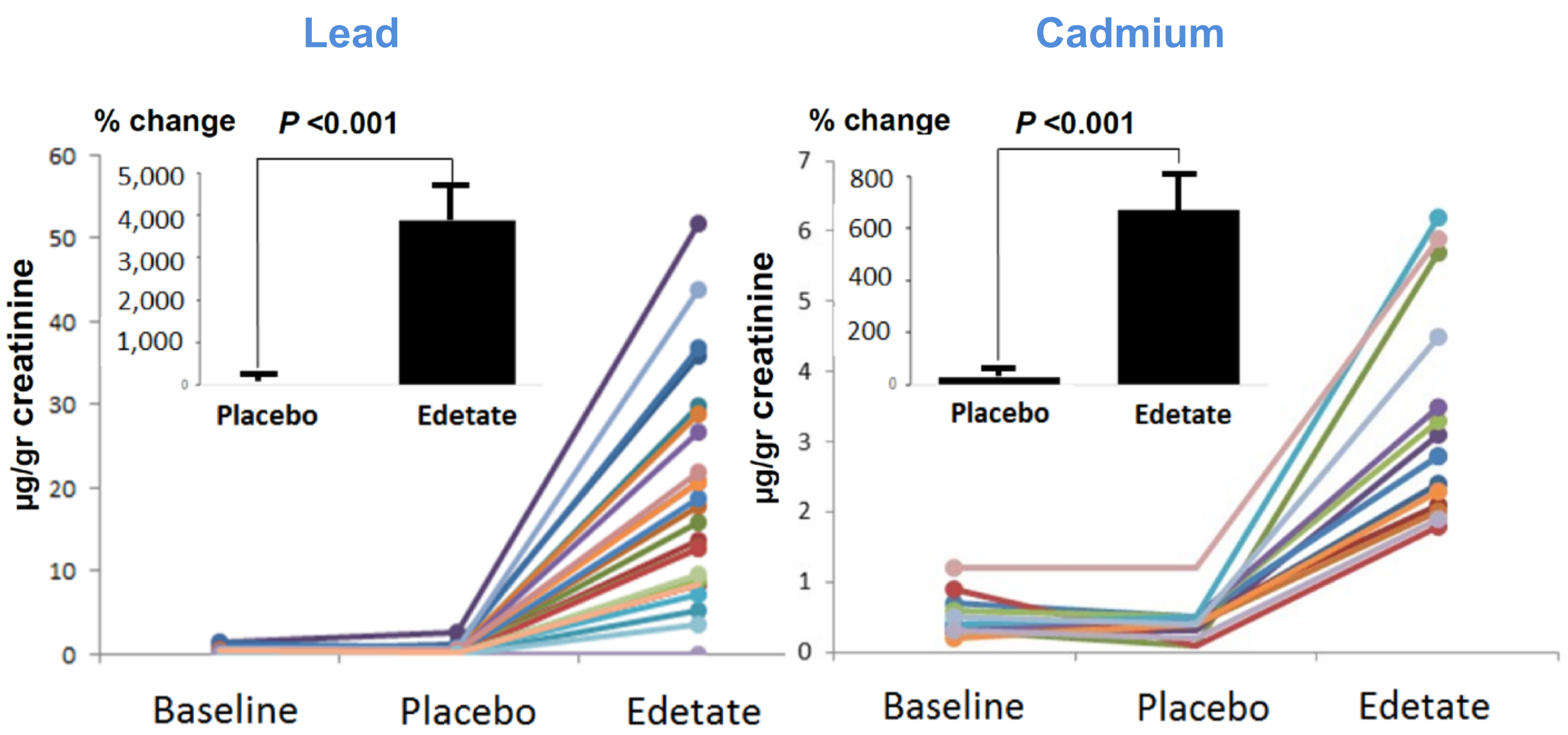


Number at risk:

Placebo	**869**	**776**	**701**	**638**	**566**	**515**	**475**	**429**	**384**	**322**	**205**
EDTA chelation		**839**	**760**	**703**	**650**	**588**	**537**	**511**	**476**	**427**	**358**
	229										

Lamas G, Goertz C, Boineau R et al. Effect of Disodium EDTA Chelation Regimen on Cardiovascular Events in Patients with Previous Myocardial Infarction. *JAMA*. 2013;309(12):1246.

What does the TACT infusion (Na_2EDTA) chelate?



Lines represent individual data points (N=24)
Bar graphs are mean (SD) of % change from baseline with placebo and Na_2EDTA infusions

Arsenic Prevention Intervention: Strong Heart Water Study in North/South Dakota

Christine George

Marcia O'Leary

Strong Heart Water Study

Cluster Randomized Controlled Trial

Tribal Level Intervention
Policy planning and sustainability

Community Level Intervention
Community promoter training program
Water arsenic testing program

Household and Individual Level Interventions

Standard Program
150 Households
300 Participants (2 per home)

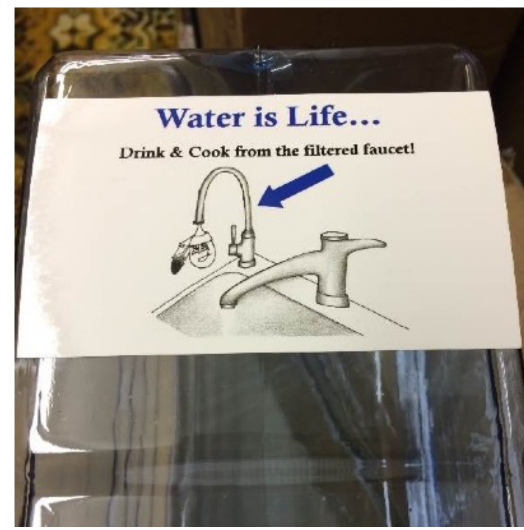
- Arsenic removal device
- Written maintenance instructions (1 visit)

Intensive Health Promotion Program
150 Households
300 Participants (2 per home)

- Arsenic removal device
- Health promotion program including maintenance instructions (5 visits)

R01ES025135

SHWS Intervention Pilot



- 5 filters installed in a pilot study in Feb and Mar 2017 followed for 9 months
- Pilot test of study materials
- RTC started this summer (17 homes and 35 participants recruited so far)

Heating coils in e-cigarettes

Ana Rule

JHU

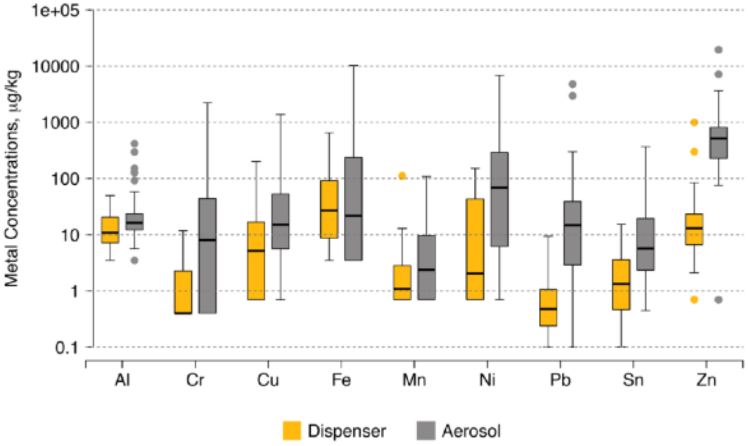
Markus Hilpert

Columbia University

Metal alloys

- Kanthal (Al, Fe and Cr)
- Nichrome (Ni and Cr)
- Combinations

Joints and other parts of the device (e.g. tin)



Olmedo et al. Environ Health Perspect 2018

New coil

Used coil

Summary

- Metal exposure is widespread through air, water and food
- Evidence supports the role of arsenic, lead and other metals in CVD at relevant levels of exposure for general populations
- Research is needed to evaluate the impact of metals in general populations and to understand the potential benefits of reducing metal exposure and internal dose in CVD prevention
- Public health and clinical strategies that prevent metal exposure and its health effects in aging populations are needed
- The impact of early life exposures on adult onset disease must be evaluated in epidemiologic settings

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- Jason Umans, MedStar Health Research Institute
- Shelley Cole, Texas Biomed Research Institute
- Lyle Best, Missouri Breaks Industry Research
- Marcia O'Leary, Missouri Breaks Industry Research
- Gervasio (Tony) Lamas, Mount Sinai Medical Center
- Regina Santella, Columbia University
- Joseph Graziano, Columbia University
- Mary Gamble, Columbia University
- Lex van Geen, Columbia University
- Marianthi Kioumourtzoglou, Columbia University
- Daniele Fallin, Johns Hopkins University
- Christine George, Johns Hopkins University
- Ana Rule, Johns Hopkins University
- Markus Hilpert, Columbia University

NIH NIEHS

NIH National Heart, Lung, and Blood Institute

Srp Superfund Research Program

- Students and Trainees
- Communities and participants

Funding: NHLBI (R01HL090863, 1R01HL134149), NIEHS (R01ES021367, R01ES025216, R01ES025135, P30ES009089, P42ES010349) and NCCIH (R01AT009273)