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

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31% of the burden of disease from fatal CVD globally could be avoided if environmental risks were removed (World Health Organization, 2016)
Environmental toxic metal contaminants and risk of cardiovascular disease

- **Exposure**: Arsenic, Lead, Cadmium, Mercury, Copper
- **Outcome**: CVD, CHD, Stroke
- **Relative risk (95% CI)**
- **Top vs bottom third of baseline level**

**Exposure is associated with an increased risk of coronary heart disease (CHD) and overall cardiovascular disease (CVD).**

- **Arsenic**
  - CVD: Increased risk
  - CHD: Increased risk
  - Stroke: Increased risk

- **Lead**
  - CVD: Increased risk
  - CHD: Increased risk
  - Stroke: Increased risk

- **Cadmium**
  - CVD: Increased risk
  - CHD: Increased risk
  - Stroke: Increased risk

- **Mercury**
  - CVD: Increased risk
  - CHD: Increased risk

- **Copper**
  - CVD: Increased risk
  - CHD: Increased risk

**No significant association with cardiovascular outcomes.**

- **Increased risk of cardiovascular outcomes, but no dose-response association observed.**

**Study quality**
- Newcastle-Ottawa score: 0–9, high scores better
- 37 unique studies
- 26 cohort studies
- 11 case-control studies
- 348,259 non-overlapping participants

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Arsenic is widespread in water and food

**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

US EPA standard is 10 µg/L

Standard for FDA is pending

- Soil contamination due to past use of As pesticides
- Growing conditions, e.g. pH and field flooding, influence As levels in rice
- As enters roots and accumulates in the grain (some varieties accumulate more)
- As occurs naturally in some soil and groundwater
- Manure contaminated with As drugs in poultry

Arsenic in groundwater

Arsenic accumulates in rice grain
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)

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**Black Foot Disease Taiwan**

*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 Giessen,*

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**Ecological study of myocardial infarction in Chile**

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

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Tromboangeitis obliterans + arteriosclerosis

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

<table>
<thead>
<tr>
<th>Water As</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12.0 µg/L</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>12.1-62.0</td>
<td>1.22 (0.65, 2.32)</td>
</tr>
<tr>
<td>62.1-148.0</td>
<td>1.35 (0.71, 2.57)</td>
</tr>
<tr>
<td>&gt;148.1</td>
<td>1.92 (1.07, 3.43)</td>
</tr>
<tr>
<td>Per SD (115 µg/L)</td>
<td>1.29 (1.10, 1.52)</td>
</tr>
</tbody>
</table>

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

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, ³ Mengling Liu, associate professor of biostatistics, ⁴ Vesna Slavkovich, associate research scientist, ⁵ Tara Katra, project coordinator/data analyst, ⁶ Maria Argos, project coordinator/data analyst, ⁷ Tarik Islam, project director, ⁸ Alauddin Ahmed, field coordinator, ⁹ Muhammad Rakibuz-Zaman, study physician/laboratory manager, ¹⁰ Rabiu Hasan, assistant field coordinator, ¹¹ Golam Sarwar, informatics manager, ¹² Diane Levy, senior staff associate, ¹³ Alexander van Geen, Lamont research professor in Lamont-Doherty Earth Observatory, ¹⁴ Habibul Ahsan, professor of

≥50 µg/L
10-50 µg/L
<10 µg/L
Arsenic exposure disproportionately affects rural areas in the US, including American Indian communities.
Study Population

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

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

64% baseline response rate
89% retention rate
88%

Ongoing Surveillance: Morbidity & Mortality

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

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

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

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

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

Adjusted for age, sex, ethnicity, income, family history CHD, diabetes, BMI, physical activity, LDL-cholesterol, triglycerides, HDL-cholesterol, folate, selenium
ApoE<sup>−/−</sup> Model of Arsenic-induced Atherosclerosis

Tap water arsenic for 13 weeks

Lesion area (%) / total aortic arch area

Control  10 ppb  50 ppb  100 ppb  200 ppb

N=6/group

Mann K et al. EHP 2017
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**
AS3MT is associated with Coronary Heart Disease in Cardiogram
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 Mahfuizar 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 Ahsan12 and Ana Navas-Acien1,2,13

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**CHD Incidence**

<table>
<thead>
<tr>
<th>Water Arsenic, μg/L</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
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<tr>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>100</td>
<td>5</td>
</tr>
<tr>
<td>200</td>
<td>10</td>
</tr>
</tbody>
</table>

**CHD Mortality**

<table>
<thead>
<tr>
<th>Water Arsenic, μg/L</th>
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<tbody>
<tr>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
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<tr>
<td>2</td>
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<tr>
<td>5</td>
<td>3</td>
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<tr>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>500</td>
<td>50</td>
</tr>
</tbody>
</table>

**Dose-Response Model:**
- log-linear (constant slope)
- non-linear (flexible slope)
Urine arsenic by city and race in MESA (n=310)

<table>
<thead>
<tr>
<th>Race</th>
<th>City</th>
<th>N</th>
<th>Adjusted GM (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>310</td>
<td>3.05 (2.85, 3.27)</td>
</tr>
<tr>
<td>White</td>
<td>Los Angeles, CA</td>
<td>15</td>
<td>2.66 (2.37, 2.99)</td>
</tr>
<tr>
<td></td>
<td>Winston-Salem, NC</td>
<td>15</td>
<td>2.43 (2.16, 2.73)</td>
</tr>
<tr>
<td></td>
<td>New York, NY</td>
<td>15</td>
<td>1.79 (1.59, 2.01)</td>
</tr>
<tr>
<td></td>
<td>Baltimore, MD</td>
<td>15</td>
<td>2.19 (1.95, 2.46)</td>
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<tr>
<td></td>
<td>St Paul, MN</td>
<td>15</td>
<td>2.69 (2.39, 3.02)</td>
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<tr>
<td></td>
<td>Chicago, IL</td>
<td>15</td>
<td>2.08 (1.85, 2.33)</td>
</tr>
<tr>
<td>Black</td>
<td>Los Angeles, CA</td>
<td>15</td>
<td>3.28 (2.90, 3.72)</td>
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<td>1.94 (1.71, 2.20)</td>
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<tr>
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<td>25</td>
<td>3.73 (3.30, 4.21)</td>
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Adjusted for urine creatinine, sex, age, education and body mass index.
Urine arsenic by city and race in MESA (n=310)

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

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
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 Guallar3,5,10 and Maria Tellez-Plaza2,4*

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

- 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 sociodemographic, CVD risk factors and changes in medication use over the 2 periods
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 Guallar3,5,10 and Maria Tellez-Plaza2,4*

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.
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
• 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, Ti, U, W, Zn

TACT2 provides a unique opportunity to understand the causal role of metals in CVD
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 Linblad, 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, 8 vitamins, electrolytes, procaaine, and heparin) (n=859) 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, 16% were female, 9% were nonwhite, and 31% were diabetic. The primary end point occurred in 22% (26%) of the chelation group and 26% (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, 0.70-1.23]; 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

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For editorial comment see pp 1291 and 1293.

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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

EDTA: Placebo

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

P = 0.035

Death, MI, stroke, coronary revascularization, hospitalization for angina

What does the TACT infusion (Na$_2$EDTA) chelate?

Lines represent individual data points (N=24)
Bar graphs are mean (SD) of % change from baseline with placebo and Na$_2$EDTA infusions

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

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)

Jason George
Marcia O’Leary

Strong Heart Water Study

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

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

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