Arsenic Research at Low Exposure Levels: Exposure Assessment Challenges and Possible Solutions

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Arsenic and health: what is known

- Poison: median lethal dose at 1-4 mg/kg
- Chronic effects > 100 µg/L in drinking water well established
- Evidence at levels 10 – 100 µg/L increasing
- Few studies available at levels < 10 µg/L
  - New Jersey drinking water standard is at 5 µg/L
  - The Netherlands 1st country to set a drinking water standard at 1 µg/L
  - Information at low levels critical to understand the health effects of arsenic in food
Association Between Exposure to Low to Moderate Arsenic Levels and Incident Cardiovascular Disease

A Prospective Cohort Study

Katherine A. Moon, MPH; Eliseo Guallar, MD, DrPH; Jason G. Umans, MD, PhD; Richard B. Devereux, MD; Lyle G. Best, MD; Kevin A. Francesconi, PhD; Walter Goessler, PhD; Jonathan Pollak, MPP; Ellen K. Silbergeld, PhD; Barbara V. Howard, PhD; and Ana Navas-Acien, MD, PhD

Background: Long-term exposure to high levels of arsenic is associated with increased risk for cardiovascular disease, whereas risk from long-term exposure to low to moderate arsenic levels (<100 μg/L in drinking water) is unclear.

Objective: To evaluate the association between long-term exposure to low to moderate arsenic levels and incident cardiovascular disease.

Design: Prospective cohort study.


Patients: 3575 American Indian men and women aged 45 to 74 years living in Arizona, Oklahoma, and North and South Dakota.

Measurements: The sum of inorganic and methylated arsenic species in urine at baseline was used as a biomarker of long-term arsenic exposure. Outcomes were incident fatal and nonfatal cardiovascular disease.

Results: A total of 1184 participants developed fatal and nonfatal cardiovascular disease. When the highest- and lowest-quartile arsenic concentrations (>15.7 vs. <5.8 μg/g creatinine) were compared, the hazard ratios for cardiovascular disease, coronary heart disease, and stroke mortality after adjustment for sociodemographic factors, smoking, body mass index, and lipid levels were 1.65 (95% CI, 1.20 to 2.27; P for trend < 0.001), 1.71 (CI, 1.19 to 2.44; P for trend < 0.001), and 3.03 (CI, 1.08 to 8.50; P for trend = 0.061), respectively. The corresponding hazard ratios for incident cardiovascular disease, coronary heart disease, and stroke were 1.32 (CI, 1.09 to 1.59; P for trend = 0.002), 1.30 (CI, 1.04 to 1.62; P for trend = 0.006), and 1.47 (CI, 0.97 to 2.21; P for trend = 0.032), respectively. These associations varied by study region and were attenuated after further adjustment for diabetes, hypertension, and kidney disease measures.

Limitations: Direct measurement of individual arsenic levels in drinking water was unavailable.

Conclusion: Long-term exposure to low to moderate arsenic levels was associated with cardiovascular disease incidence and mortality.

Primary Funding Source: National Heart, Lung, and Blood Institute and National Institute of Environmental Health Sciences.
Arsenic and incident CVD

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.
Dietary sources of inorganic arsenic exposure

- Rice
- Granola bars
- Apple and apple juice
- Chicken
Major challenge for epidemiologic studies at low-arsenic levels: exposure assessment

- Need to integrate complex and multiple exposure sources: primarily food, also water, air, dust and soil

- Biomarkers essential
  - Urine arsenic species: assess both arsenic exposure and metabolism (for genetics and susceptibility)

  Challenges:
  - Organic arsenicals from seafood
  - Correction for urine dilution

  - Toenail arsenic: reflects mostly inorganic arsenic species

  Limitations:
  - Arsenic metabolism difficult to assess
  - Determinants of toenail growth likely to be important
Seafood intake: major challenge for inorganic arsenic assessment in general populations

Other sources of inorganic arsenic (occupational settings and air pollution) are not represented.

**Bolded:** arsenic species commonly measured in urine in epidemiologic studies
Seafood intake: major challenge for inorganic arsenic assessment in general populations

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Other sources of inorganic arsenic (occupational settings and air pollution) are not represented. **Bolded:** arsenic species commonly measured in urine in epidemiologic studies
Arsenic species ($\mu$g/L) in urine after eating blue mussels

After 3 days of seafood restriction, all subjects had 16 mussels (160 g wet weight)
Urine arsenic metabolites after 1 mg of oxoarsenosugars

Volunteer 2 had only excreted 15% of initial dose at 90 hours after ingestion while volunteer 3 had excreted 88% of initial dose.
Arsenobetaine, total arsenic and DMA in NHANES

- Total arsenic vs. Arsenobetaine: $r=0.79$
- DMA vs. Arsenobetaine: $r=0.45$
- Total arsenic minus AB vs. Arsenobetaine: $r=0.51$
Urine arsenic concentrations by self-reported seafood intake in the past 24-h
Can we “reestimate” arsenic concentrations in urine not derived from seafood?

Idea from the nutritional epidemiology literature:

- Estimate urinary arsenic not derived from seafood by regressing urinary arsenic on arsenobetaine concentrations and extracting the model residuals

- Advantages of using arsenobetaine:
  • Specific to seafood
  • Objective biomarker of seafood intake
  • Not metabolized into other species
  • Reflects other seafood arsenicals
Seafood intake: major challenge for inorganic arsenic assessment in general populations

Other sources of inorganic arsenic (occupational settings and air pollution) are not represented.

**Bolded:** arsenic species commonly measured in urine in epidemiologic studies
Seafood intake: major challenge for inorganic arsenic assessment in general populations

Other sources of inorganic arsenic (occupational settings and air pollution) are not represented.

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Seafood intake: major challenge for inorganic arsenic assessment in general populations

Other sources of inorganic arsenic (occupational settings and air pollution) are not represented.

Bolded: arsenic species commonly measured in urine in epidemiologic studies

Other sources of inorganic arsenic (occupational settings and air pollution) are not represented.
Arsenobetaine, total arsenic and DMA in NHANES

- **Total arsenic (μg/L)** vs. Arsenobetaine (μg/L) with a correlation coefficient (r) of 0.79.
- **DMA (μg/L)** vs. Arsenobetaine (μg/L) with a correlation coefficient (r) of 0.45.
- **Total arsenic minus AB (μg/L)** vs. Arsenobetaine (μg/L) with a correlation coefficient (r) of 0.51.
Let’s test it

Population: Multi-Ethnic Study of Atherosclerosis

- Study funded by NHLBI
- N=6,814 men and women 45-74 years of age followed since 2000-02
- 4 racial/ethnic groups: White, Black, Hispanic and Chinese
- **Subset for this study: N=310**
- Arsenic species measured at University of Graz, Austria
- Seafood consumption:
  - 19.4% rare or never
  - 51.3% 2-4 times/month
  - 29.4% ≥2 times/week
Proposed method

We estimated urinary concentrations of iAs, DMA and MMA by

- Regressing the original concentrations by arsenobetaine
  \[ \log(\text{arsenical}_i) = \beta_0 + \beta_1 \cdot \log(\text{arsenobetaine}_i) + \varepsilon_i \]

- Extracting model residuals: inorganic and methylated arsenic species from exposure to As not related to recent seafood intake

- Adding to the residuals the mean levels of the corresponding arsenic species among participants with low arsenobetaine levels (<1 µg/L)

We compared the association of the original biomarker and the estimated biomarker with self-reported seafood intake and rice intake and with measured n-3 fatty acids

Hypothesis

Arsenic biomarker corrected for arsenobetaine will:

• Remain associated with rice intake, a source of iAs and DMA

• No longer be associated with seafood intake, as arsenobetaine, which is not metabolized, can remove at least a large part of the contribution of seafood arsenicals to arsenic estimates in urine
Arsenic speciation

HPLC/ICPMS chromatograms before (grey) and after (black) adding H$_2$O$_2$

Fig. 1  Anion-exchange HPLC/ICPMS chromatograms of a urine sample (grey line) and the same sample after treatment with H$_2$O$_2$ (black line). The expanded regions show the two areas where changes occurred. HPLC conditions were: PRP-X100 column (4.6 mm × 150 mm, 5 μm particles) at 40°C with a mobile phase of 20 mM aqueous phosphoric acid adjusted with aqueous ammonia to pH 6.0 at a flow rate of 1 mL min$^{-1}$. Injection volume was 20 μL.

<table>
<thead>
<tr>
<th>Study and Arsenic Measure</th>
<th>Measured Concentration&lt;sup&gt;a&lt;/sup&gt; (µg/L), median (IQR)</th>
<th>Calibrated Concentration&lt;sup&gt;b&lt;/sup&gt; (µg/L), median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MESA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arsenobetaine</td>
<td>5.2 (1.1–18.7)</td>
<td></td>
</tr>
<tr>
<td>iAs</td>
<td>0.2 (0.1–0.5)</td>
<td>0.1 (0.05–0.3)</td>
</tr>
<tr>
<td>MMA</td>
<td>0.7 (0.3–1.3)</td>
<td>0.3 (0.2–0.6)</td>
</tr>
<tr>
<td>DMA</td>
<td>6.7 (3.4–13.6)</td>
<td>2.5 (1.4–4.3)</td>
</tr>
<tr>
<td>∑As</td>
<td>8.1 (3.8–15.5)</td>
<td>3.1 (1.7–5.5)</td>
</tr>
<tr>
<td>Arsenic species %&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>iAs %</td>
<td>3.1 (1.6–5.0)</td>
<td>4.2 (2.2–6.7)</td>
</tr>
<tr>
<td>MMA %</td>
<td>8.4 (5.2–12.4)</td>
<td>10.3 (6.5–14.8)</td>
</tr>
<tr>
<td>DMA %</td>
<td>87.5 (83.2–91.9)</td>
<td>85.4 (79.6–89.6)</td>
</tr>
<tr>
<td><strong>NHANES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arsenobetaine</td>
<td>1.6 (0.3–6.9)</td>
<td></td>
</tr>
<tr>
<td>DMA</td>
<td>3.5 (2.0–5.9)</td>
<td>2.5 (1.6–4.1)</td>
</tr>
</tbody>
</table>

Abbreviations: DMA, dimethylarsinate; iAs, inorganic arsenic; IQR, interquartile range; MESA, Multi-Ethnic Study of Atherosclerosis; MMA, methylarsonate; NHANES, National Health and Nutrition Examination Survey; ∑As, sum of inorganic and methylated arsenic species.

<sup>a</sup> Measured concentrations represent originally measured urine arsenic concentrations.

<sup>b</sup> Calibrated concentrations represent urine arsenic concentrations corrected for arsenobetaine concentrations.

<sup>c</sup> iAs %, MMA %, and DMA % are estimated as their concentrations divided by the sum of the inorganic and methylated arsenic species.
## Ratio of GM (95% CI) of urine arsenic concentrations by frequency of self-reported seafood intake

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Measured Biomarker</th>
<th>Estimated Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DMA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1x/month</td>
<td>60</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>2-4x/ month</td>
<td>159</td>
<td>1.27 (1.01, 1.59)</td>
<td>0.95 (0.78, 1.16)</td>
</tr>
<tr>
<td>≥2x/ week</td>
<td>91</td>
<td>1.93 (1.50, 2.48)</td>
<td>1.04 (0.83, 1.30)</td>
</tr>
<tr>
<td><strong>ΣAs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1x/month</td>
<td>60</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>2-4x/ month</td>
<td>159</td>
<td>1.26 (1.02, 1.57)</td>
<td>0.97 (0.80, 1.18)</td>
</tr>
<tr>
<td>≥2x/ week</td>
<td>91</td>
<td>1.91 (1.50, 2.43)</td>
<td>1.08 (0.87, 1.33)</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, body mass index and urine creatinine
Ratio of GM (95% CI) of ΣAs in urine by measured and estimated n-3 fatty acids (PUFAs)

Shaded areas represent confidence intervals

Ratio of GM (95% CI) of urine arsenic concentrations by frequency of self-reported rice intake

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Measured Biomarker</th>
<th>Estimated Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DMA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1x/month</td>
<td>42</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>2-4x/ month</td>
<td>105</td>
<td>1.28 (0.99, 1.67)</td>
<td>1.32 (1.05, 1.66)</td>
</tr>
<tr>
<td>≥2x/ week</td>
<td>162</td>
<td>2.21 (1.72, 2.85)</td>
<td>1.78 (1.43, 2.22)</td>
</tr>
<tr>
<td><strong>ΣAs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1x/month</td>
<td>42</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>2-4x/ month</td>
<td>105</td>
<td>1.27 (0.98, 1.63)</td>
<td>1.30 (1.04, 1.63)</td>
</tr>
<tr>
<td>≥2x/ week</td>
<td>162</td>
<td>2.16 (1.70, 2.75)</td>
<td>1.77 (1.43, 2.19)</td>
</tr>
</tbody>
</table>

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

• Arsenic estimated biomarker ($\Sigma$As) provides an assessment of arsenic exposure that no longer reflects seafood intake
• Method can facilitate research about low-level arsenic exposure in general populations with seafood intake
Arsenic by race in MESA

Ratio of geometric mean (95%CI) of e∑As in urine by race/ethnicity

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>90</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Chinese</td>
<td>70</td>
<td>1.94 (1.61, 2.35)</td>
<td>1.84 (1.48, 2.28)</td>
<td>1.72 (1.34, 2.21)</td>
</tr>
<tr>
<td>Black</td>
<td>75</td>
<td>0.91 (0.76, 1.09)</td>
<td>0.90 (0.74, 1.09)</td>
<td>0.89 (0.73, 1.07)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>75</td>
<td>1.51 (1.26, 1.82)</td>
<td>1.45 (1.18, 1.77)</td>
<td>1.38 (1.11, 1.72)</td>
</tr>
</tbody>
</table>

Model 1: Adjusted for age, sex, body mass index and urine creatinine
Model 2: Model 1 + city
Model 3: Model 2 + frequency of rice intake
## Arsenic by city in MESA

<table>
<thead>
<tr>
<th>City</th>
<th>N</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winston-Salem, NC</td>
<td>30</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>New York, NY</td>
<td>55</td>
<td>1.44 (1.08, 1.93)</td>
<td>1.15 (0.87, 1.54)</td>
<td>1.11 (0.83, 1.49)</td>
</tr>
<tr>
<td>Baltimore, MD</td>
<td>30</td>
<td>0.93 (0.67, 1.28)</td>
<td>0.92 (0.68, 1.24)</td>
<td>0.90 (0.67, 1.22)</td>
</tr>
<tr>
<td>St. Paul, MN</td>
<td>40</td>
<td>1.30 (0.96, 1.76)</td>
<td>0.97 (0.71, 1.32)</td>
<td>0.96 (0.71, 1.31)</td>
</tr>
<tr>
<td>Chicago, IL</td>
<td>65</td>
<td>1.47 (1.10, 1.95)</td>
<td>1.06 (0.80, 1.40)</td>
<td>1.04 (0.78, 1.37)</td>
</tr>
<tr>
<td>Los Angeles, CA</td>
<td>90</td>
<td>1.67 (1.27, 2.20)</td>
<td>1.15 (0.88, 1.52)</td>
<td>1.13 (0.86, 1.49)</td>
</tr>
</tbody>
</table>

- **Model 1**: Adjusted for age, sex, body mass index and urine creatinine
- **Model 2**: Model 1 + race/ethnicity
- **Model 3**: Model 2 + frequency of rice intake

*Jones et al. Under review*
Urine arsenic by city and race in MESA

**Model 1**

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

**Model 2**

<table>
<thead>
<tr>
<th></th>
<th>Adjusted GM (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>3.05 (2.85, 3.26)</td>
</tr>
<tr>
<td><strong>White</strong></td>
<td></td>
</tr>
<tr>
<td>Los Angeles, CA</td>
<td>2.70 (2.42, 3.01)</td>
</tr>
<tr>
<td>Winston–Salem, NC</td>
<td>2.41 (2.16, 2.69)</td>
</tr>
<tr>
<td>New York, NY</td>
<td>1.73 (1.55, 1.93)</td>
</tr>
<tr>
<td>Baltimore, MD</td>
<td>2.30 (2.06, 2.57)</td>
</tr>
<tr>
<td>St Paul, MN</td>
<td>2.71 (2.42, 3.02)</td>
</tr>
<tr>
<td>Chicago, IL</td>
<td>2.01 (1.80, 2.24)</td>
</tr>
<tr>
<td><strong>Black</strong></td>
<td></td>
</tr>
<tr>
<td>Los Angeles, CA</td>
<td>3.32 (2.93, 3.76)</td>
</tr>
<tr>
<td>Winston–Salem, NC</td>
<td>1.89 (1.67, 2.14)</td>
</tr>
<tr>
<td>New York, NY</td>
<td>2.36 (2.09, 2.68)</td>
</tr>
<tr>
<td>Baltimore, MD</td>
<td>1.86 (1.64, 2.10)</td>
</tr>
<tr>
<td>Chicago, IL</td>
<td>2.40 (2.12, 2.72)</td>
</tr>
<tr>
<td><strong>Hispanic</strong></td>
<td></td>
</tr>
<tr>
<td>Los Angeles, CA</td>
<td>3.85 (3.41, 4.34)</td>
</tr>
<tr>
<td>New York, NY</td>
<td>5.25 (4.66, 5.92)</td>
</tr>
<tr>
<td>St Paul, MN</td>
<td>2.79 (2.48, 3.15)</td>
</tr>
<tr>
<td><strong>Chinese</strong></td>
<td></td>
</tr>
<tr>
<td>Los Angeles, CA</td>
<td>4.70 (4.20, 5.27)</td>
</tr>
<tr>
<td>Chicago, IL</td>
<td>4.64 (4.14, 5.20)</td>
</tr>
</tbody>
</table>

Model 1: Adjusted for urine creatinine, sex, age, education and body mass index
Model 2: Further adjusted for frequency of rice intake
Summary of findings in MESA

- Seafood intake is a major contributor to urine As in a multi-ethnic population from 6 US cities.

- We estimated As not derived from seafood (eΣAs) correcting for arsenobetaine using a residual based strategy.

- eΣAs levels were higher with increasing rice intake.

- eΣAs levels were higher in Chinese and Hispanic Americans compared to White and Black participants.

- Chinese participants from LA and Chicago and Hispanics from NY had the highest eΣAs levels.

- Within White participants, eΣAs levels were higher in LA and St Paul.

- Within Black participants, eΣAs levels were higher in LA.
Research and public health needs

• Better surveillance of As exposure across the US
  - Lack of adequate geographical and race/ethnic information on arsenic exposure at the national level
  - NHANES limited by high % undetectable for inorganic arsenic and MMA and geographical information of the study participants not publically available

• Research on the health effects of low-level As exposure
  - MESA represents an excellent population to conduct such research
MESA Exams (N=6,814 men and women 45-74 y)

Phone surveillance every 6-9 months for clinical events

Exam 1 2000-2002
- Demographics
- Blood pressure
- ECG
- Anthropometry
- Urine sample
- Blood sample
- Carotid US
- Brachial US
- Carotid distensibility
- Arterial wave form
- Medical history
- Medications
- Diet
- Physical activity
- Psychosocial
- Cardiac MRI scan
- Chest CT scan

Exam 2 2002-2004
- Demographics
- Blood pressure
- Anthropometry
- Urine sample
- Blood sample
- Carotid US
- Medical history
- Medications
- Family history
- Sleep history
- Physical activity
- Psychosocial
- Cardiac MRI scan (n=600)
- Chest CT scan (n=1/2 cohort)

Exam 3 2004-2005
- Demographics
- Blood pressure
- Anthropometry
- Urine sample
- Blood sample
- Carotid US
- Medical history
- Medications
- Sleep history
- Physical activity
- Psychosocial
- Chest CT scan (n=1/2 cohort)
- Spirometry (n=1/2 cohort)

Exam 4 2005-2007
- Demographics
- Blood pressure
- Anthropometry
- Blood sample
- Carotid US
- Medical history
- Medications
- Sleep history
- Psychosocial
- Cardiac MRI (n=1/4 cohort)
- Chest CT scan (n=1/4 cohort)
- Spirometry (n=1/2 cohort)

Exam 5 2010-2012
- Demographics
- Blood pressure
- ECG
- Anthropometry
- Urine sample
- Blood sample
- Carotid US
- Medical history
- Medications
- Family history
- Sleep history
- Psychosocial
- Cognitive function
- Cardiac MRI scan
- Chest CT scan
- Spirometry

Multiple measures are already available in MESA biospecimens including genetic information (GWAS and Metabochip), 450K DNA methylation, biomarkers of oxidative stress, inflammation and endothelial dysfunction, neighborhood characteristics, air pollution estimated at the household level, etc.

More than 1000 peer-reviewed publications
Hypotheses

1. **Association**: Arsenic exposure at water arsenic <10 µg/L is associated with increased clinical CVD (coronary heart disease and stroke incidence and mortality) and burden of atherosclerosis (carotid intima-media thickness, coronary artery calcification, arterial distensibility, and peripheral artery disease).

2. **Modification**: The association of arsenic with cardiovascular outcomes is modified by smoking, genetic variants and nutritional factors related to arsenic metabolism and toxicity. Investigating modification at low-arsenic levels is important, as health effects may be observed only in susceptible sub-groups.

3. **Mediation**: The association between arsenic and cardiovascular outcomes are mediated, at least in part, by oxidative stress and inflammation pathways, cardiac electrophysiology alterations, endothelial dysfunction, blood pressure, diabetes, and/or epigenetic modifications. These mediation hypotheses are informed by data at moderate-high arsenic exposure, although formal mediation analyses have been limited.
Figure 5 | Possible mechanisms for the cardiovascular effects of exposure to arsenic. Ingestion of food and water containing arsenic constitutes the main source of exposure to arsenic in most populations, although occupational exposure and inhalation are also routes. Abbreviations: ECG, electrocardiograph; GFR, glomerular filtration rate.
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