Arsenic and Health Effects in the Strong Heart Study: Opportunities for Prevention

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Arsenic and CVD – epidemiological evidence

1930s
- Case series / Ecological studies
  - German vintners (As in pesticides, PAD)
  - Taiwan & Chile (water As, PAD & other CVD)

1980s
- Cohort studies in Taiwan
  - Ecological water As assessment
  - CVD mortality (all, CHD, stroke)

1990s
- Ecological study in Chile
  - Natural experiment before & after water As
  - Myocardial infarction mortality

2007
- 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

Black Foot Disease Taiwan

Tromboangeitis obliterans + arteriosclerosis

Ecological study of myocardial infarction in Chile

Prospective Cohort Studies in Taiwan


Arsenic in water measured at the village level and incident coronary heart disease mortality in Southwestern Taiwan

<table>
<thead>
<tr>
<th>Arsenic (μg/L)</th>
<th>N</th>
<th>No. cases</th>
<th>Hazard Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.01</td>
<td>467</td>
<td>3</td>
<td>1.0</td>
<td>Ref.</td>
</tr>
<tr>
<td>0.01-500 μg/L</td>
<td>211</td>
<td>2</td>
<td>2.5</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;500 μg/L</td>
<td>922</td>
<td>11</td>
<td>3.9</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, smoking, body mass index, cholesterol, triglycerides, hypertension, diabetes
HEALS cohort recruited and followed 12,000 participants since 2000-2001 in Araihazar, Bangladesh

<table>
<thead>
<tr>
<th>Primary well water As</th>
<th>HR (95%CI)</th>
<th>Urine As</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12.0 µg/L</td>
<td>1.00 (ref)</td>
<td>&lt;106 µg/g</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>12.1-62.0</td>
<td>1.22 (0.65, 2.32)</td>
<td>106-199</td>
<td>1.29 (0.74, 2.27)</td>
</tr>
<tr>
<td>62.1-148.0</td>
<td>1.35 (0.71, 2.57)</td>
<td>200-351</td>
<td>1.53 (0.83, 2.82)</td>
</tr>
<tr>
<td>&gt;148.1</td>
<td>1.92 (1.07, 3.43)</td>
<td>&gt;351</td>
<td>2.06 (1.24, 3.72)</td>
</tr>
<tr>
<td>Per 115 µg/L (SD)</td>
<td>1.29 (1.10, 1.52)</td>
<td>Per 282 µg/g (SD)</td>
<td>1.26 (1.12, 1.42)</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, BMI, smoking status, education
EPA Standard 10 µg/L As in drinking water

Arsenic levels in ≥ 25% samples exceed:

- 50 ug/L
- 10
- 5
- 3
- 1
- Insufficient data

No. Samples: 31,000

EPA Standard 10 µg/L As in drinking water

Tribally owned community water systems (CWS) with arsenic > 10 µg/L in year 2000

<table>
<thead>
<tr>
<th>US EPA Region</th>
<th>Comm. Water Systems</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>% As &gt;10µg/L</td>
</tr>
<tr>
<td>1 (Ct, Ma, Me, Nh, Ri, Vt)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2 (Nj, Ny)</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>3 (Dc, De, Md, Pa, Va, Wv)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>4 (Al, Fl, Ga, Ms, Nc, Sc, Tn)</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>5 (Il, In, Mi, Wi, Oh)</td>
<td>79</td>
<td>4</td>
</tr>
<tr>
<td>6 (Ar, La, Nm, Ok, Tx)</td>
<td>47</td>
<td>23</td>
</tr>
<tr>
<td>7 (Ia, Ks, Mo, Ne)</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>8 (Co, Mt, Nd, Sd, Ut, Wy)</td>
<td>104</td>
<td>8</td>
</tr>
<tr>
<td>9 (Az, Ca, Nv, Hi, islands)</td>
<td>192</td>
<td>30</td>
</tr>
<tr>
<td>10 (Id, Or, Wa)</td>
<td>82</td>
<td>12</td>
</tr>
<tr>
<td>Navajo nation</td>
<td>95</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>630</td>
<td>16</td>
</tr>
</tbody>
</table>

16% of tribally owned community water systems above > 10 µg/L vs. 4% for the overall US population

Source: David Harvey MPH Capstone project, 2007
Tribally owned community water systems (CWS) with arsenic > 10 µg/L in year 2000

<table>
<thead>
<tr>
<th>US EPA Region</th>
<th>Comm. Water Systems</th>
<th>Population</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>% As &gt;10µg/L</td>
<td>No.</td>
</tr>
<tr>
<td>1 (Ct, Ma, Me, Nh, Ri, Vt)</td>
<td>1</td>
<td>0</td>
<td>41,000</td>
</tr>
<tr>
<td>2 (Nj, Ny)</td>
<td>7</td>
<td>0</td>
<td>8,425</td>
</tr>
<tr>
<td>3 (Dc, De, Md, Pa, Va, Wv)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>4 (Al, Fl, Ga, Ms, Nc, Sc, Tn)</td>
<td>15</td>
<td>0</td>
<td>19,326</td>
</tr>
<tr>
<td>5 (Il, In, Mi, Wi, Oh)</td>
<td>79</td>
<td>4</td>
<td>87,687</td>
</tr>
<tr>
<td>6 (Ar, La, Nm, Ok, Tx)</td>
<td>47</td>
<td>23</td>
<td>60,413</td>
</tr>
<tr>
<td>7 (La, Ks, Mo, Ne)</td>
<td>8</td>
<td>0</td>
<td>4,468</td>
</tr>
<tr>
<td>8 (Co, Mt, Nd, Sd, Ut, Wy)</td>
<td>104</td>
<td>8</td>
<td>87,342</td>
</tr>
<tr>
<td>9 (Az, Ca, Nv, Hi, islands)</td>
<td>192</td>
<td>30</td>
<td>201,391</td>
</tr>
<tr>
<td>10 (Id, Or, Wa)</td>
<td>82</td>
<td>12</td>
<td>45,918</td>
</tr>
<tr>
<td>Navajo nation</td>
<td>95</td>
<td>14</td>
<td>116,227</td>
</tr>
<tr>
<td>Total</td>
<td>630</td>
<td>16</td>
<td>672,197</td>
</tr>
</tbody>
</table>

16% of tribally owned community water systems above > 10 µg/L vs. 4% for the overall US population

Source: David Harvey MPH Capstone project, 2007
Arsenic exposure disproportionately affects rural areas in the US, including American Indian communities.
Strong Heart Study: Team Science
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

Ongoing Surveillance: Morbidity & Mortality

Visit 3 pilot
1998-99

Visit 4
2001-03

Visit 5
2006-09

Visit 6
2014-16

Visit 7
2021-23

Strong Heart Family Study
3,050 participants ≥14 y

Continuous funding critical to maintain sustainable research projects
Coronary Heart Disease (45-64 y)

ARIC: Atherosclerosis Risk in Communities
Prevalence of Atherosclerosis Plaque

![Graph showing prevalence of atherosclerosis plaque across different age groups for ARIC and CHS studies.](image-url)
<table>
<thead>
<tr>
<th>Variables</th>
<th>SHS</th>
<th>SHFS</th>
<th>SHSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD and sociodemographic RFs</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Clinical data</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical exams</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ultrasound / echocardiography</td>
<td>X</td>
<td>X</td>
<td>subset</td>
</tr>
<tr>
<td>Brain MRI</td>
<td>subset</td>
<td>subset</td>
<td>X</td>
</tr>
<tr>
<td>Laboratory data</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Genetic data (including stored DNA)</td>
<td>X</td>
<td>X</td>
<td>subset</td>
</tr>
<tr>
<td>Telomere length</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urine metals (including As speciation)</td>
<td>X</td>
<td>subset</td>
<td>(80%)</td>
</tr>
<tr>
<td>Epigenetic data (850K + validation)</td>
<td>X</td>
<td>subset</td>
<td>subset</td>
</tr>
<tr>
<td>Phthalates</td>
<td>pilot</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent organic pollutants</td>
<td>pilot</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolomics</td>
<td>pilot</td>
<td>pilot</td>
<td>pilot</td>
</tr>
</tbody>
</table>

SHS: Strong Heart Study; SHFS: Strong Heart Family Study; SHSS: Strong Heart Stroke Study
## Data contributed to the SHS

<table>
<thead>
<tr>
<th>Variables</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Phase III pilot</th>
<th>Phase IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic species in urine</td>
<td>3973</td>
<td>311</td>
<td>311</td>
<td>143</td>
<td>2310</td>
</tr>
<tr>
<td>Total metals in urine (As, Cd, Mo, Pb, Sb, Se, W, Zn)</td>
<td>3973</td>
<td>311</td>
<td>311</td>
<td>143</td>
<td>2310</td>
</tr>
<tr>
<td>Urine uranium</td>
<td>311</td>
<td>311</td>
<td>311</td>
<td>143</td>
<td>2310</td>
</tr>
<tr>
<td>Metabochip</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2251</td>
</tr>
<tr>
<td>AS3MT sequencing</td>
<td>1,200</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illumina 850K (DNA methylation)</td>
<td>2,351</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P180 metabolomic panel</td>
<td></td>
<td></td>
<td></td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>OCM custom panel 13 metabolites</td>
<td></td>
<td></td>
<td></td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

Extensive phenotyping available as part of the SHS examination and follow-up

Other data available: telomere, exome chip, untargeted metabolomics
Overall framework

Water → Metal biomarkers → Mechanistic markers → Clinical disease

Air → Metal biomarkers

Food → Metal biomarkers

Susceptibility factors (genetics, nutrition, co-exposures, co-morbidities, etc.)
Diet explained less than 4% of the variability in urinary As in Arizona, Oklahoma, and North/South Dakota.

Nigra et al. Under tribal review
Summary of arsenic health 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 and functioning
- Prevalent and incident **diabetes** and diabetes control
- Prevalent and incident **albuminuria**
- Incident **chronic kidney disease**
- **Neurocognitive outcomes**
- **Cancer** mortality of the lung, prostate and pancreas
- **Non-malignant lung disease** (under review)
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></td>
<td>&lt;0.001</td>
<td>0.008</td>
</tr>
</tbody>
</table>

**Model 1** stratified by study region and age-adjusted (age at baseline treated as staggered entries)

**Model 2** 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

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.

Moon et al. Annals Intern Medicine 2013
**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. Marshall¹*

¹Colorado School of Public Health, University of Colorado Denver, Aurora, Colorado, USA; ²Department 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**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate model</th>
<th>Full model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic exposure</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</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−/− Model of Arsenic-induced Atherosclerosis

Tap water arsenic for 13 weeks

Mann K et al. EHP 2017
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 Keeeve 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 Ahsan12 and Ana Navas-Acien1,2,13
Urine arsenic by city and race in MESA (n=310)

<table>
<thead>
<tr>
<th>Race</th>
<th>City, State</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>
</tr>
<tr>
<td></td>
<td>St Paul, MN</td>
<td>15</td>
<td>2.69 (2.39, 3.02)</td>
</tr>
<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>
</tr>
<tr>
<td></td>
<td>Winston-Salem, NC</td>
<td>15</td>
<td>1.94 (1.71, 2.20)</td>
</tr>
<tr>
<td></td>
<td>New York, NY</td>
<td>15</td>
<td>2.34 (2.06, 2.65)</td>
</tr>
<tr>
<td></td>
<td>Baltimore, MD</td>
<td>15</td>
<td>1.86 (1.65, 2.11)</td>
</tr>
<tr>
<td></td>
<td>Chicago, IL</td>
<td>15</td>
<td>2.39 (2.11, 2.71)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>Los Angeles, CA</td>
<td>25</td>
<td>3.73 (3.30, 4.21)</td>
</tr>
<tr>
<td></td>
<td>New York, NY</td>
<td>25</td>
<td>5.21 (4.61, 5.88)</td>
</tr>
<tr>
<td></td>
<td>St Paul, MN</td>
<td>25</td>
<td>2.91 (2.58, 3.28)</td>
</tr>
<tr>
<td>Chinese</td>
<td>Los Angeles, CA</td>
<td>35</td>
<td>4.63 (4.09, 5.25)</td>
</tr>
<tr>
<td></td>
<td>Chicago, IL</td>
<td>35</td>
<td>4.71 (4.16, 5.33)</td>
</tr>
</tbody>
</table>

Adjusted for urine creatinine, sex, age, education and body mass index.
Role of genetics

- Heritability estimates:
  - 50-53% iAs, 16-50% MMA, 33-63% DMA

- Genomewide association study in Bangladesh, positive selection study in South America, and candidate gene studies highlight AS3MT variants

- AS3MT (10q24) encodes enzyme arsenic (III) methyltransferase
  - Role in methylating iAs to MMA and DMA
Manhattan plot for DMA% in Strong Heart Family Study

AS3MT (10q24) encodes enzyme arsenic (III) methyltransferase

Analysis based on ~200,000 SNPs from common variants in GWAS and less common variants associated with cardiometabolic traits

As species % by rs12768205 (index SNP)
homozygous dominant AA
heterozygous AG
homozygous recessive GG

GMR: geometric mean ratio

Balakrishnan et al. Environ Health Perspect 2017
Grau-Perez et al. Environ Health Perspect 2018
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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Gene
Treatment

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, PLGL, LPL, CXCL12, LRPL1, 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.

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Arsenic and diabetes

- Arsenic exposure was associated with prevalent diabetes and with diabetes control
- Arsenic metabolism associated with incident diabetes and with markers of insulin resistance

Kuo et al Diabetes Care 2015
Relative Risk for Metabolic Syndrome and its individual components per IQR increase in $\Sigma$As and 5% increase in arsenic metabolism biomarkers

- **A)** $\Sigma$As
- **B)** iAs%
- **C)** MMA%
- **D)** DMA%

Spratlen et al. Am J Epidemiol. 2018
Figure 7. Correlation chord plots of plasma OCM and other metabolites with As, diabetes and mtDNA biomarkers (n=60). We show correlations ≥0.15 (A) and ≤-0.15 (B). Those at p<0.05 are plot with darker colors (r>0.25). The correlations of LysoPC a C18:2 with DMA% and of glutamate with HOMA2-IR were significant after Bonferroni correction (α=0.05/276). Correlations within classes of biomarkers are not shown.
Shared Associations between Arsenic and Diabetes Metabolites

**Diabetes**
- SAM
- SAH
- Glutamate
- Cysteine
- LysoPC 18:2
- PC ae 40:6
- PC ae 34:3
- PC aa 38:3

**Arsenic Metabolism**

Spratlen et al. Environ Res 2018
One carbon metabolism

Methionine Synthase – Vitamin B_{12} dependent

Serine

Vitamin B_{6}

Glycine

Vitamin B_{2}

5,10-methylene tetrahydrofolate

S-adenosyl methionine (SAM)

Dimethylglycine

Betaine

Choline

LysoPCs

Phosphatidylcholines (PCs)

Homocysteine

Ceramide

DAG

Lysophosphatidylcholines (LysoPCs)

Cystathionine

Vitamin B_{6}

Cysteine + Glycine + Glutamate

GSH

Cysteine

Methyltransferases

S-adenosyl homocysteine (SAH)

PCs

LysoPCs

Ceramide

SMs

DAG

Homocysteine

Cystathionine

GSH

Cysteine + Glycine + Glutamate

Methionine

Vitamin B_{6}

Dietary Folate

5-methyl tetrahydrofolate

MTHFR

As^{III}

MMA^{III}

As^{V}

MMA^{V}

DMA^{V}

As^{III}

As^{V}
Arsenic, epigenetics and cardiovascular disease

Aim 1

Arsenic \rightarrow \text{DNAm} \rightarrow \text{CVD}

Aim 2a

As genes \rightarrow \text{DNAm} \rightarrow \text{CVD}

Aim 2b

Arsenic \rightarrow \text{DNAm} \rightarrow \text{CVD}

CVD genes

Grey line: established association between arsenic and CVD in the SHS. Other CVD risk factors are not shown.
850K DNA methylation analysis

- 2351 DNA samples from visit 1 analyzed
- 8 excluded because of low median intensity

Density Plots of the DNA methylation proportions estimated from the raw (unprocessed proportions)

**Preliminary results:**
- After Bonferroni correction, 12 CpGs were associated with arsenic exposure \((P<0.05)\), located in 10 genes:
  - ANKS3, CSNK1D (2 CpGs), LINGO3, PRPF8, DNAH1, EIF2C2, SLC7A5, ADAMTS14, SLC7A11, and DHX16 (2 CpGs)
- We identified eight differentially methylated regions, including the genes CSNK1D, FOXG-1, BAIAP2, and ABAT.
- Differential methylation in these sites has been previously associated with kidney and liver function and the regulation of apoptosis, cellular adhesion and angiogenesis.
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, Jason G. Umans d, Lyle G. Best f, Eliseo Guallar a, g, h, Wendy S. Post a, g, h, Joel D. Kaufman l, Dhananjay Vaidya l, Ana Navas-Acien a, g, j

Results:
All nine urinary metals were higher in SHS compared to MESA participants. PCA and CA revealed significant between-group mixtures. LDA showed that the As-U-W cluster and PC might reflect a similar mixture pattern between MESA and SHS. Compared to MESA, the Cd-Mo, As-Mo-Sb-U-W, and Cd-Pb-Se-Zn clusters were more similar in SHS.

Discussion:
The different metal-mixtures between MESA and SHS could be due to differences in exposure sources and/or metabolic pathways of different urinary metals.
Manuscripts on metals in the SHS

- 59 manuscripts approved by P&P committee
  - 34 published
  - 3 under review (Chest, Environ Pollution, Circulation Cardiovasc Imaging)
  - 1 approved by tribes and IRB and close to submission
  - 2 pending tribal approval
  - 14 actively ongoing (at different stages, many on epigenetics with exciting findings)
  - 5 dormant
- 2 manuscripts pending to be submitted to P&P committee
Doctoral Theses

- 8 completed
  - Maria Tellez-Plaza
  - Matt Gribble
  - Esther Garcia-Esquinas
  - Farrah Mateen
  - Chin-Chi Kuo
  - Laura Zheng
  - Katherine Moon
  - Miranda Spratlen

- 5 in progress
  - Martha Powers (orals passed)
  - Anne Nigra (orals passed)
  - Anne Bozack (orals passed)
  - Di Zhao (orals passed)
  - Joe Yracheta (orals pending)
Grants

Funded:
• R01HL090863: Arsenic, CVD and diabetes SHS (complete)
• R01ES021367: Arsenic, genetics, diabetes SHFS (complete)
• R01ES025216: Arsenic, epigenetics and CVD SHS (ongoing) + supplement to support Joe Yracheta’s DrPH
• R01ES025135: Participatory interventions to reduce arsenic (Strong Heart Water Study) (ongoing)
• R01ES028805: Principal component pursuit to assess exposure to environmental mixtures in epidemiologic studies (PI: Marianthi Kioumourtzoglou, ongoing)
• R35ES028379: Arsenic and the human genome: susceptibility and response to exposure (PI: Brandon Pierce, ongoing)
• CDC/ATSDR internal grant to measure blood metals (just started)

F31
• Miranda Spratlen (As, metabolism and metabolic syndrome)
• Martha Powers (As and lung disease)
• Anne Nigra (As and CVD)

Planning:
• Mercury grant (pilot ongoing)
Research data relevant at multiple levels

- **Local level**: prevention and intervention
  
  provide control data

- **Regional level**: increase resources, prevention strategies

- **Country and global level**: policy
  - EPA risk assessment
  - IARC: cancer evaluation
  - WHO: drinking water standards
SHS contributed to EPA arsenic risk assessment

- EPA recently requested data from the Strong Heart Study to improve their pharmacokinetic modeling for the ongoing As risk assessment.

- We consulted with the Strong Heart Study steering committee and approval to provide the aggregated data and support the EPA was granted (we run analyses exactly as requested by the EPA and provided tabulated results to them).

- EPA agreed that if a publication is prepared, it will be submitted to the tribes for approval.
SHS has directly contributed to EPA arsenic risk assessment

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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."

After 15 years of construction and nearly half a billion dollars in federal funds, the 24-inch core pipeline and its clean, safe, high-quality drinking water from the Missouri River has finally crossed the reservation's border.
The effect of the Environmental Protection Agency maximum contaminant level on arsenic exposure in the USA from 2003 to 2014: an analysis of the National Health and Nutrition Examination Survey (NHANES)

Anne E Nigra, Tiffany R Sanchez, Keeve E Nachman, David E Harvey, Steven N Chillrud, Joseph H Graziano, Ana Navas-Acien

**Summary**

**Background** In 2006, the current US Environmental Protection Agency (EPA) maximum contaminant level for arsenic in public water systems (10 µg/L) took effect. We aimed to assess national trends in water arsenic exposure in the USA, hypothesising that urinary arsenic concentrations would decrease over time in individuals using public water systems but not in those using well water (which is not federally regulated). We further estimated the expected number of avoided skin or lung and bladder cancer cases.

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>Geometric mean</th>
<th>Geometric mean ratio (95% CI)</th>
<th>N</th>
<th>Geometric mean</th>
<th>Geometric mean ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003-04</td>
<td>1275</td>
<td>3.01 (2.97-3.05)</td>
<td>1.00 (reference)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2005-06</td>
<td>1406</td>
<td>3.10 (3.06-3.15)</td>
<td>1.03 (0.95-1.12)</td>
<td>125</td>
<td>2.38 (2.28-2.47)</td>
<td></td>
</tr>
<tr>
<td>2007-08</td>
<td>1595</td>
<td>3.11 (3.07-3.15)</td>
<td>1.03 (0.94-1.13)</td>
<td>292</td>
<td>2.99 (2.88-3.11)</td>
<td>1.26 (1.04-1.51)</td>
</tr>
<tr>
<td>2009-10</td>
<td>1763</td>
<td>2.93 (2.89-2.97)</td>
<td>0.98 (0.90-1.06)</td>
<td>192</td>
<td>2.63 (2.53-2.73)</td>
<td>1.10 (0.91-1.34)</td>
</tr>
<tr>
<td>2011-12</td>
<td>1472</td>
<td>2.64 (2.61-2.68)</td>
<td>0.88 (0.80-0.96)</td>
<td>248</td>
<td>2.63 (2.53-2.73)</td>
<td>1.11 (0.94-1.30)</td>
</tr>
<tr>
<td>2013-14</td>
<td>1644</td>
<td>2.49 (2.45-2.52)</td>
<td>0.83 (0.76-0.90)</td>
<td>182</td>
<td>2.27 (2.18-2.36)</td>
<td>0.95 (0.80-1.13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>161</td>
<td>2.59 (2.50-2.70)</td>
<td>1.09 (0.79-1.52)</td>
</tr>
</tbody>
</table>

*p value for trend* p<0.001

![Graph showing trends in arsenic exposure](Lancet Public Health 2017; 2: e513-21 Published Online October 22, 2017 http://dx.doi.org/10.1016/S2468-2667(17)30195-0)
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)
SHWS Intervention Pilot

- 5 filters installed in a pilot study Feb and Mar 2017 followed for 9 months
- Pilot test of study materials
- RTC started summer 2018 (17 homes and 35 participants recruited so far)
Communities and participants make research possible

- Engagement and participation
- Support of science
- Contributions to research questions
- Contribution to conduction of research

- Research can and must benefit communities
  - Benefits are sometime slow
  - Researchers need to be actively engaged
Acknowledgements

- Eliseo Guallar, Johns Hopkins University
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- Jason Umans, MedStar Health Research Institute
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- Christine George, Johns Hopkins University
- David Harvey, Indian Health Service

**Funding:** NHLBI (R01HL090863), NIEHS (R01ES021367, R01ES025216, R01ES025135, P30ES009089, P42ES010349)

- Students and Trainees
- Communities and participants
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
Visit 7 2021-23

Continuous funding critical to maintain sustainable research projects

Urine metals available
Urine metals in a subset

Strong Heart Family Study
3,050 participants ≥14 y