Environment and Cardiovascular Disease: Opportunities for Prevention in the Strong Heart Study Communities

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Strong Heart Study: Team Science
Collective effort

- Exposure Sciences
- Epidemiology and medicine
- Trust
- Partnership
- Toxicology
- Genomics
- Sustainability
- Social Sciences
- Intervention Research
Strong Heart Study

Population-based prospective cohort study funded since 1988 by the National Heart, Lung and Blood Institute and the Indian Health Service

N = 7,600 adults
13 tribes and communities

http://strongheart.ouhsc.edu/
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% retention rate

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

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

ARIC: Atherosclerosis Risk in Communities

SHS

ARIC
Prevalence of Atherosclerosis Plaque

ARIC: Atherosclerosis Risk in Communities / CHS: Cardiovascular Health Study
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><strong>Total</strong></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 2006
Arsenic exposure disproportionately affects rural areas in the US, including American Indian communities.
Arsenic exposure disproportionately affects rural areas in the US, including American Indian communities.
31% of the burden of disease from fatal CVD globally could be avoided if all environmental risks were removed (household and ambient air pollution, secondhand tobacco smoke, and chemicals) (World Health Organization, 2016)
Elevated Concentrations of U and Co-occurring Metals in Abandoned Mine Wastes in a Northeastern Arizona Native American Community

Johanna M. Blake,† Sumant Avasarala,‡ Kateryna Artyushkova,§ Abdul-Mehdi S. Ali,‖ Adrian J. Brearley,‖ Christopher Shuey,† Wm. Paul Robinson,† Christopher Nez,§ Sadie Bill,§ Johnnye Lewis,‖ Chris Hirani,‖ Juan S. Lezama Pacheco,◆ and José M. Cerrato*,†
Metal mixtures in urban and rural populations in the US: The Multi-Ethnic Study of Atherosclerosis and the Strong Heart Study

Yuanjie Pang\textsuperscript{a,\textsuperscript{b}}, Roger D. Peng\textsuperscript{b}, Miranda R. Jones\textsuperscript{a}, Kevin A. Francesconi\textsuperscript{c}, Walter Goessler\textsuperscript{c}, Barbara V. Howard\textsuperscript{d,e}, Jason G. Umans\textsuperscript{d,e}, Lyle G. Best\textsuperscript{f}, Eliseo Guallar\textsuperscript{a,g,h}, Wendy S. Post\textsuperscript{a,g,h}, Joel D. Kaufman\textsuperscript{i}, Dhananjay Vaidya\textsuperscript{b}, Ana Navas-Acien\textsuperscript{a,g,j}
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
- Highly toxic and carcinogenic, affects many organs and systems
- Seafood: source of organic arsenicals that are non-toxic

US EPA standard in public water is 10 µg/L
FDA standard for rice is pending
Arsenic is pleiotropic

- Brain
- Heart (CVD)
- Hypertension
- Liver
- Kidneys
- Lungs (function, cancer, bronchiectasis)
- Bone Marrow (cellular maturation)
- Diabetes
- Skin Lesions
- Bladder cancer

Slide courtesy of Mary Gamble
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

Ecological study of myocardial infarction in Chile


BMJ

HEALS cohort

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,3 Vesna Slavkovich, associate research scientist,7 Tara Kalra, project coordinator/data analyst,3 Maria Argos, project coordinator/data analyst,4 Taril Islam, project director,5 Aleaveen Ahmed, field coordinator,2 Muhammad Rakibuzz-Zaman, study physician/laboratory manager,6 Rabiul Hasan, assistant field coordinator,6 Golam Sanwar, informatics manager,6 Diane Levy, senior staff associate,2 Alexander van Geen, Lamont research professor in Lamont-Doherty Earth Observatory,6 Habibul Ahsan, professor of epidemiology5

BMJ 2011;342:d2431
Arsenic exposure and metabolism

Other sources of arsenic (occupational settings and air pollution) are not shown. Urine As species commonly measured in epidemiologic studies are marked in blue.

Water → iAs → MMA → DMA → Total urine arsenic

Recent rice, other foods → iAs

Recent Seafood → Arsenosugars, Arsenolipids → Arsenobetaine

Other metabolites
Risk of cardiovascular mortality over 20 years by urine arsenic quartiles

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
ApoE−/− Model of Arsenic-induced Atherosclerosis

Tap water arsenic for 13 weeks

Lesion area (%) / total aortic arch area

N=6/group

Slide courtesy of Koren Mann
Association between Lifetime Exposure to Inorganic Arsenic in Drinking Water and Coronary Heart Disease in Colorado Residents

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

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 HR (95% CI)</th>
<th>Full model HR (95% CI)</th>
</tr>
</thead>
<tbody>
<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
Summary of the 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)

2011
- 2013
- SHS and SLVDS in rural US
  - Water (SLVDS) and urine (SHS) As
  - CVD incidence & mortality (all, CHD, stroke)

As levels: $> 500 \, \mu g/L$ $100 \, \mu g/L$ $10-100 \, \mu g/L$ $< 10 \, \mu g/L$
Dose-response meta-analysis

- Compared to 5 µg/L, the pooled relative risks (95% CI) for 10 µg/L water arsenic based on a log-linear model were:
  - 1.11 (1.05, 1.17) (N=4) for CHD incidence
  - 1.16 (1.07, 1.26) (N=6) for CHD mortality,
- No evidence of non-linearity, although these tests had low statistical power
- Meta-analysis limited by the small number of studies and availability of published data

Moon et al. Int J Epidemiol under revision
Need to combine studies - sharing

• A single study is unlikely to cover the full range of the relevant exposures, different genetic backgrounds, different characteristics – combining studies allows to compare across studies: look for consistencies and differences

• By combining epidemiologic studies of arsenic and CVD
  1) We extend the range of arsenic exposure levels
  2) Increase statistical power to evaluate dose-response, gene-environment interactions, nutrition-environment interactions, mediation analyses

• Consortium efforts are needed in environmental health

• Address and respect communities conditions for data sharing
Data ownership and data sharing

• Who owns the data?

• Who allows data sharing and in which terms?

• Who profits from research?
Recommendations

• Build relationships
• Use a participatory approach
• Accept research codes that tribes have developed to regulate the collection and circulation of information about their members
  - Tribes and Indian Health Service IRBs
  - Data ownership
  - Review of publications and lay summaries
  - Communication of study findings (individuals, community)
  - Anonymity of individuals and tribes
  - Value traditional knowledge

Moreno-John et al. J Aging Health 2004
Goins et al. Gerontologist 2011
Indigenous peoples must benefit from science

To drive sustainable development, Dyna Rochmyaningsih argues, science must empower rural communities — not just serve industry and governments.

**MITIGATION**

**MUST BE THE RESPONSIBILITY OF EVERYONE ON THE PLANET, NOT JUST SCIENTISTS, BUSINESSMEN AND POLICYMAKERS.**
Arsenic and diabetes

- Arsenic exposure was associated with prevalent diabetes and with diabetes control (Gribble et al. AJE 2012)
- Arsenic metabolism associated with incident diabetes and with markers of insulin resistance (Kuo et al. Diabetes Care 2015)

![Diagram of arsenic metabolism]

Inorganic arsenic → MMA → DMA → Urine

- Inorganic Arsenic: 10 - 20%
- MMA: 10 - 20%
- DMA: 60 - 80%
Arsenic and incident diabetes in the Strong Heart Family Study

Hazard Ratio for incident diabetes by arsenic exposure in all participants and in participants with normal fasting glucose (NFG), stratified by center and adjusted for age, sex, education, smoking, body mass index, waist circumference, kidney function, estimated dietary vitamin B2, vitamin B6 and folate and AS3MT genotype.

Grau et al. Under tribal review
Arsenic exposure and metabolism and the metabolic syndrome (MetS)

Relative risk (RR) for MetS, waist circumference (WC), triglycerides (TG), HDL-cholesterol, hypertension (HT) and fasting plasma glucose (FPG) per interquartile range (IQR) of arsenic exposure (iAs+MMA+DMA levels) and arsenic metabolism (iAs%, MMA%, DMA%). Models adjusted for age, sex, center, education, smoking, alcohol, body mass index, kidney function, urine creatinine, ΣAs (for As metabolism).
Insulin resistance (HOMA-IR) by arsenic metabolism biomarkers in the SHFS (n=1548)

Model was adjusted age, sex, center, education, BMI, smoking, waist circumference, glomerular filtration rate, fasting glucose levels at baseline, estimated dietary vitamin B2, vitamin B6 and folate and AS3MT genotype.
Role of genetics

- Inorganic arsenic is methylated into MMA, then DMA and excreted in urine
- Heritability estimates proportion of total variability attributed to genetics
  - 53% iAs, 50% MMA, 63% DMA (Tellez-Plaza et al EHP 2013)
- Genomewide association study in Bangladesh (HEALS), and candidate gene studies highlight AS3MT variants
- AS3MT (10q24) encodes enzyme arsenic (III) methyltransferase
  - Possible role in methylating iAs to MMA and DMA
Illumina MetaboChip

- Approximately 200,000 SNPs

- Common variants from previous GWAS studies of diabetes, obesity and cardiometabolic diseases and less common variants not on GWAS chips

- We also fine mapped candidate genes

<table>
<thead>
<tr>
<th>Panel</th>
<th>Total SNPs</th>
<th>Correction Bonferroni</th>
<th>Effective SNPs</th>
<th>Correction LD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MetaboChip</td>
<td>120,975</td>
<td>4.1330e-7</td>
<td>64374.845</td>
<td>7.7670e-7</td>
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<tr>
<td>Candidate (arsenic)</td>
<td>670</td>
<td>7.4626e-5</td>
<td>549.389</td>
<td>9.3359e-5</td>
</tr>
</tbody>
</table>

LD: linkage disequilibrium
Manhattan plot for arsenic metabolism biomarkers (DMA%) in Strong Heart Family Study (n=2,428)

*AS3MT*(10q24) encodes enzyme arsenic (III) methyltransferase
Arsenic species % by rs12768205 (index SNP)

Balakrishnan et al. Environ Health Perspect 2017
One carbon metabolism and methylation

Nutrients/nutrient intermediates are marked in **red**, antioxidants in **blue**. Some enzymes are shown in **italic**. The box includes reactions that also occur in the mitochondria.
Effects of Folic Acid Supplementation on Arsenic Metabolites in Urine

*P < 0.01; **P < 0.0001

14% decline in blood arsenic concentrations

HOMA-IR by arsenic metabolism biomarkers interaction analyses

Vitamin B2 (mg)
- \( \leq 1.7 \):
  - \( N = 793 \)
  - GMR (95% CI) = 1.11 (1.03, 1.19)
  - \( P \text{ int.} = 0.35 \)
  - GMR of HOMA-IR by iAs% vs MMA% = 0.96 (0.90, 1.02)
  - \( P \text{ int.} = 0.01 \)
  - GMR of HOMA-IR by MMA% vs DMA% = 0.99 (0.95, 1.03)
  - \( P \text{ int.} = 0.04 \)
- \( >1.7 \):
  - \( N = 755 \)
  - GMR (95% CI) = 1.07 (1.00, 1.16)
  - GMR of HOMA-IR by iAs% vs MMA% = 0.88 (0.83, 0.92)
  - GMR of HOMA-IR by MMA% vs DMA% = 1.02 (0.98, 1.06)

Vitamin B6 (mg)
- \( \leq 1.6 \):
  - \( N = 835 \)
  - GMR (95% CI) = 1.12 (1.04, 1.20)
  - \( P \text{ int.} = 0.10 \)
  - GMR of HOMA-IR by iAs% vs MMA% = 0.96 (0.90, 1.03)
  - \( P \text{ int.} = 0.001 \)
  - GMR of HOMA-IR by MMA% vs DMA% = 0.98 (0.94, 1.02)
  - \( P \text{ int.} = 0.002 \)
- \( >1.6 \):
  - \( N = 713 \)
  - GMR (95% CI) = 1.07 (0.99, 1.15)
  - GMR of HOMA-IR by iAs% vs MMA% = 0.86 (0.81, 0.91)
  - GMR of HOMA-IR by MMA% vs DMA% = 1.03 (0.99, 1.07)

Folate (mg)
- \( \leq 335.5 \):
  - \( N = 764 \)
  - GMR (95% CI) = 1.11 (1.03, 1.19)
  - \( P \text{ int.} = 0.37 \)
  - GMR of HOMA-IR by iAs% vs MMA% = 0.96 (0.89, 1.03)
  - \( P \text{ int.} = 0.04 \)
  - GMR of HOMA-IR by MMA% vs DMA% = 0.99 (0.94, 1.03)
  - \( P \text{ int.} = 0.05 \)
- \( >335.5 \):
  - \( N = 784 \)
  - GMR (95% CI) = 1.07 (1.00, 1.16)
  - GMR of HOMA-IR by iAs% vs MMA% = 0.88 (0.84, 0.92)
  - GMR of HOMA-IR by MMA% vs DMA% = 1.02 (0.98, 1.06)

rs12768205
- G/G:
  - \( N = 788 \)
  - GMR (95% CI) = 1.13 (1.04, 1.21)
  - \( P \text{ int.} = 0.03 \)
  - GMR of HOMA-IR by iAs% vs MMA% = 0.93 (0.89, 0.99)
  - \( P \text{ int.} = 0.11 \)
  - GMR of HOMA-IR by MMA% vs DMA% = 0.98 (0.94, 1.02)
  - \( P \text{ int.} = 0.02 \)
- G/A:
  - \( N = 627 \)
  - GMR (95% CI) = 1.04 (0.97, 1.12)
  - GMR of HOMA-IR by iAs% vs MMA% = 0.90 (0.83, 0.96)
  - GMR of HOMA-IR by MMA% vs DMA% = 1.03 (0.99, 1.07)
- A/A:
  - \( N = 135 \)
  - GMR (95% CI) = 1.03 (0.90, 1.17)
  - GMR of HOMA-IR by iAs% vs MMA% = 0.80 (0.71, 0.91)
  - GMR of HOMA-IR by MMA% vs DMA% = 1.07 (0.98, 1.16)
- Overall:
  - \( N = 1548 \)
  - GMR (95% CI) = 1.09 (1.02, 1.17)
  - GMR of HOMA-IR by iAs% vs MMA% = 0.91 (0.87, 0.96)
  - GMR of HOMA-IR by MMA% vs DMA% = 1.00 (0.97, 1.04)
Arsenic and Cancer

- Cancer was not originally included in the consent forms in all study sites, maybe in some broad sentences about studying health and disease in general, not specifically
- Special community approval was needed to conduct this research
- Study participants are currently being reconsented for cancer and other outcomes
Comments from a community member

“The SHS has been here a long time,” LeBeau observes. “That relationship is established. I think that’s the way it should be. It fits well within the community.”

Among the stubborn stereotypes swirling around American Indians is that they won’t participate in or comply with scientific studies—a notion the SHS has been disproving for a quarter century.

“Understanding requires data,” LeBeau reasons. “Without that, you can’t change things. Maybe this won’t help me, but [it might help] my kids, my grandkids.”

LeBeau is woven into his community. Entwined with his people’s past. Unwilling to say the heck with the future.

“Our culture is here, our language, our elders, our ceremonies,” he says, alluding to men whose prayers emanate from sweat lodges, women who piece together star quilts and children whose elders are buried at Wounded Knee. “It’s happening here.”

Ryman LeBeau, Chair of the Environment and Natural Resource Committee
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
Contribute to EPA arsenic risk assessment

- EPA recently requested urine arsenic data from the Strong Heart Study to improve their pharmacokinetic modeling for the ongoing arsenic risk assessment
- We consulted with the Strong Heart Study steering committee, which includes community members
- Approval to provide the data and support the EPA was granted (provide aggregated data not raw data)
- EPA agreed that if a publication is prepared, it will be submitted to the tribes for approval
Urinary DMA corrected for dietary and tobacco sources of arsenic and adjusted for age, race/ethnicity, education and body mass index.

### Public water

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>Geometric Means</th>
<th>GMR (95% CI)</th>
<th>Public water</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003/2004</td>
<td>1275</td>
<td>2.39 (2.15, 2.65)</td>
<td>1.00 (reference)</td>
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<tr>
<td>2005/2006</td>
<td>1406</td>
<td>2.46 (2.38, 2.54)</td>
<td>1.03 (0.95, 1.12)</td>
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<tr>
<td>2007/2008</td>
<td>1595</td>
<td>2.47 (2.38, 2.56)</td>
<td>1.03 (0.94, 1.13)</td>
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<tr>
<td>2009/2010</td>
<td>1763</td>
<td>2.33 (2.25, 2.41)</td>
<td>0.98 (0.90, 1.06)</td>
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<tr>
<td>2011/2012</td>
<td>1472</td>
<td>2.10 (2.01, 2.19)</td>
<td>0.88 (0.80, 0.96)</td>
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</tr>
<tr>
<td>2013/2014</td>
<td>1644</td>
<td>1.97 (1.89, 2.06)</td>
<td>0.83 (0.76, 0.90)</td>
<td></td>
</tr>
</tbody>
</table>

### Well water

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>Geometric Means</th>
<th>GMR (95% CI)</th>
<th>Well water</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>125</td>
<td>1.68 (1.09, 2.57)</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>292</td>
<td>2.10 (1.92, 2.29)</td>
<td>1.26 (1.04, 1.51)</td>
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</tr>
<tr>
<td></td>
<td>192</td>
<td>1.85 (1.66, 2.05)</td>
<td>1.10 (0.91, 1.34)</td>
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</tr>
<tr>
<td></td>
<td>248</td>
<td>1.86 (1.70, 2.02)</td>
<td>1.11 (0.94, 1.30)</td>
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<tr>
<td></td>
<td>182</td>
<td>1.60 (1.43, 1.77)</td>
<td>0.95 (0.80, 1.13)</td>
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<tr>
<td></td>
<td>161</td>
<td>1.83 (1.50, 2.16)</td>
<td>1.09 (0.79, 1.52)</td>
<td></td>
</tr>
</tbody>
</table>

**P for trend p < 0.001**  

Findings support the critical role of federal drinking water regulations in reducing toxic exposures and protecting human health.
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.
Planning a prevention intervention study in South and North Dakota

Meeting at Eagle Butte, SD

Meeting at Martin, SD
Planning a prevention intervention study in South and North Dakota

Making those meetings possible is Marcia O’Leary, RN, Manager of Missouri Breaks Research, the institution that runs the Strong Heart Study
Strong Heart Water Study for private wells

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)

Funded by National Institute Environmental Health Sciences (R01ES025135)
The Ecological Model for Strong Heart Water Study

**Tribal Nations**
- **Environmental Factors**
  - Arsenic mitigation policies for private well users
- **Target Behaviors**
  - Developing sustainable arsenic mitigation policies

**Community**
- **Environmental Factors**
  - Access to water arsenic testing
  - Target Behaviors
    - Building local capacity to implement arsenic mitigation programs

**Family/Household**
- **Environmental Factors**
  - Access to arsenic mitigation options for private well users
  - **Target Behaviors**
    - Maintaining arsenic removal devices

**Individual**
- **Environmental Factors**
  - Resources on the health implications of arsenic
- **Target Behaviors**
  - Using 100% arsenic-safe water for drinking and cooking
  - Building knowledge on arsenic health implications
SHWS Intervention Pilot

- 6 filters installed during the pilot study in February and March 2017
- Pilot testing of the study materials
Intervention Evaluation

Baseline
• Urine arsenic
• Water arsenic
• Water Qx
• ICAM-1, VCAM-1
• HbA1c
• Lung function
• Blood pressure

1 Month Visit
• Urine arsenic
• Water arsenic
• Water Qx
• Water meter

6 Month Visit
• Urine arsenic
• Water arsenic
• Water Qx
• Water meter
• ICAM-1, VCAM-1
• HbA1c
• Lung function
• Blood pressure

Long Term 1-3 Years Visit
• Urine arsenic
• Water arsenic
• Water Qx
• Water meter
Replicative trial of EDTA chelation and high-dose oral vitamins in 1200 post-MI diabetic patients

Selecting the population that showed the greatest benefit

Storing biospecimens for measuring metals and testing future mechanistic hypotheses

Funded by NHLBI and NCCIH (National Center for Complementary and Integrative Health)
Lead, cadmium and cardiovascular disease

What we know:

• Increased blood pressure levels
• Increased CVD mortality (several studies including NHANES)
• Increased CVD incidence in several populations, although the number of studies is small:
  - Normative Aging Study (lead)
  - Strong Heart Study and other studies (cadmium)
• Increased subclinical cardiovascular disease (carotid atherosclerosis, peripheral artery disease)
• Experimental studies support these cardiovascular effects
Urgent need for high quality air pollution assessment in North Dakota

Where Oil and Politics Mix

After an unusual land deal, a giant spill and a tanker-train explosion, anxiety began to ripple across the North Dakota prairie.

Deborah Sontag, NYT, 11/22/14
Jim Wilson, photographer
In the picture: Dr. Lyle Best and his dog
300 yards from a home

A Belch from the porch

Oil tank explosion on 3/7/2015
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
Funding

- R01HL090863: Arsenic, CVD and diabetes SHS (completed)
- R01ES021367: Arsenic, genetics, diabetes SHFS (NCE, renewal submitted)
- R01ES025216: Arsenic, epigenetics and CVD SHS (ongoing)
- R01ES025135: Participatory interventions to reduce arsenic (ongoing)
Strong Heart Study

Strong Heart Study co-investigators and community members
Barbara Howard, Jason Umans, Darren Calhoun, Cynthia West (*MedStar/Arizona*)
Lyle Best, Marcia O’Leary, Joseph Yracheta, Marie Gross, Stacey Jolly (*North/South Dakota*)
Elisa Lee, Everett Rhoades, Fawn Yeh, Ying Zhang, Tauqeer Ali, Julie Stoner (*Oklahoma*)
Shelley Cole, Karin Haack, Jean MacCluer (*Texas Biomed*)
Nora Franceschini, Saroja Vorungati, Kari North (*UNC*)
Richard Devereux, Mary Roman, Peter Okin (*Cornell U*)
Jinying Zhao (*U of Florida*)

Mentors
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Richey Sharrett

Hopkins co-investigators
Winnie Tang, Zhibin Wang, Virginia Weaver, Kellogg Schwab, Luke McDonald (*EHS*)
Linda Kao, Dani Fallin (*Epi*)
Dhananjay Vaidya (*GIM*)
Ciprian Crainiceanu, Karen Bandeen-Roche (*Biostats*)

Indian Health Service
David Harvey

Graz Laboratory
Kevin A. Francesconí, Walter Goessler
Strong Heart Water Study

Community Consultants
• Reno Red Cloud
• Carlyle Ducheneaux
• Robert Thompson

Strong Heart Study Investigators
• Marcia O’ Leary
• Joseph Yracheta
• Lyle Best
• Jason Umans
• Fawn Yeh
• Amanda Fretts

Indian Health Service
• CAPT David Harvey

Johns Hopkins University
• Christine George
• Allison Barlow
• Kellogg Schwab
• Luke MacDonald
• Lawrence Moulton
• Joel Gittelsohn

Columbia University
• Maria Grau
Students and trainees move the science forward – drive and creativity
Collective Competence

• Authority is rooted in collective competence
• Decision making is horizontal, precedent oriented and consensual
• Process is fluid, iterative, recorded orally, benchmarked by key events (not chronologically)
• Leadership is shared, diffused and ascribed
• Tribal communities are sociocentric

Spiro Manson, PhD
University Colorado Denver
NHLBI Forum, Aug 2, 2016
Metal chelation

Ethylene Diamine Tetra Acetate Anion (EDTA)

- Administered intravenously (slow infusion)
- Distributed across bone and soft tissues where it binds metal cations (“organic coating”)
- EDTA-metal complex is stable, non-toxic and excreted through the kidneys
- FDA approved uses:
  - Lead poisoning (CaNa₂EDTA)
  - Hypercalcemia (Na₂EDTA)
- Historically, controversial role in CVD prevention