Strong Heart Study: Moving forward our understanding on the role of arsenic and other metals in cardiovascular disease

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Strong Heart Study: Team Science
Arsenic exposure disproportionately affects rural areas in the US, including American Indian communities.
Elevated Concentrations of U and Co-occurring Metals in Abandoned Mine Wastes in a Northeastern Arizona Native American Community

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Metal mixtures in urban and rural populations in the US: The Multi-Ethnic Study of Atherosclerosis and the Strong Heart Study

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%

Continuous funding critical to maintain sustainable research projects
Arsenic and Other Chronic Diseases

Cardiovascular Mortality

- Hazard Ratio vs % Exposed Participants
- Urine arsenic, μg/g
- Moon et al Ann Intern Med 2013

Incident Chronic Kidney Disease

- Hazard Ratio vs % Exposed Participants
- Urine arsenic, μg/g
- Zheng et al Epidemiology 2015

Arsenic Metabolism

- iAs% ↔ DMA%
- MMA% ↔ DMA%

Incident Diabetes

- Hazard Ratio
-DMA%
-Kuo et al Diabetes Care 2015

R01HL090863 and R01ES021367
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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Model HR(95%CI)</th>
<th>Full Model HR(95%CI)</th>
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</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>
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
- Genomewide association study in Bangladesh, and candidate gene studies highlight \( AS3MT \) variants
- \( AS3MT \) (10q24) encodes enzyme arsenic (III) methyltransferase
  - Possible role in methylating iAs to MMA and DMA
Arsenic Genetics in the Strong Heart Family Study: Manhattan plot for arsenic metabolism biomarkers

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

Balalrikshnan et al. Environ Health Perspect 2016

R01ES021367
Arsenic species % by rs12768205 (top signal)

- homozygous dominant AA
- heterozygous AG
- homozygous recessive GG
Grey line: established association between arsenic and CVD in the SHS. Other CVD risk factors are not shown.
Navajo Birth Cohort Study

- Collaborative effort to better understand developmental health effects of environmental exposures, in particular uranium on the Navajo Nation
- Top metals found in dust: arsenic, antimony, lead, manganese, uranium
- Importance of cohorts recruited during early life and childhood for CVD

http://www.sric.org/nbcs/docs/NBCS_overview_063014.pdf
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
Reducing Environmental Exposures can Decrease the Burden of CVD

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)
Arsenic Prevention Intervention: 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)
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
Environmental research – partnership is essential

Meeting at Cheyenne River

Meeting at Oglala Sioux
Study team

Students, fellows, staff
Maria Tellez-Plaza, Matt Gribble, Laura Zheng, Esther Garcia, Kat Moon, Farrah Mateen, CC Kuo, Jon Pollak, Ching-Wei Tsai, Poojitha Balakrishnan, Maria Grau, Anne Nigra, Pablo Olmedo, Jolie Susan

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Eliseo Guallar, Linda Kao (Epi)
Dani Fallin (Mental health)
Dhananjay Vaidya (GIM)
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Strong Heart Study co-investigators
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Elisa Lee, Everett Rhoades, Fawn Yeh, Ying Zhang (Oklahoma)
Shelley Cole, Karin Haack, Jean MacCluer (Texas Biomed)
Nora Franceschini, Saroja Vorungati, Kari North (UNC)
Jonathan Newman (NYU)

Indian Health Service
David Harvey

Graz Laboratory
Kevin A. Francesconio, Walter Goessler

Funding: P30ES03819, R01HL090863, R01ES021367, R01ES025216, R01ES025135
Students and trainees move the science forward – drive and creativity

Maria Tellez-Plaza Ass. Professor, Spain
Matt Gribble Ass. Professor, Emory
Miranda Jones, Ass. Professor, Hopkins
Laura Zheng Post-doc, Mt Sinai NY
Chin-Chi Kuo Ass. Professor, Taiwan
Esther Garcia-Esquinas Instructor, Spain
Kat Moon PhD student, Hopkins
Ching-Wei Tsai Ass. Professor, Taiwan

Farrah Mateen Ass. Professor, Harvard
Poojitha Balakrishnan Post-doc, Hopkins
Pablo Olmedo Post-doc, Hopkins
Maria Grau, Visitor Scholar, Hopkins
Miranda Spratlen, PhD student Hopkins
Martha Powers, PhD student Hopkins
Yuanjie Pang, PhD student Oxford
Anne Nigra, ScM student Hopkins
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 and...

- R01HL090863: Arsenic, CVD and diabetes SHS (completed)
- R01ES021367: Arsenic, genetics, diabetes SHFS (NCE)
- R01ES025216: Arsenic, epigenetics and CVD SHS (ongoing)
- R01ES025135: Participatory interventions to reduce arsenic (ongoing)
- P42ES10349: Superfund Research Program Columbia University (pending)

...communities and participants make science possible