COLUMBIA | OF PUBLIC HEALTH
ENVIRONMENTAL HEALTH SCIENCES

SRP Globally Reducing Arsenic Exposure | Columbia Superfund Research Program

STRONG HEART STUDY

STRONG HEART Water Study

Environmental Justice and GxE Research: Experiences from Working with Indigenous Communities

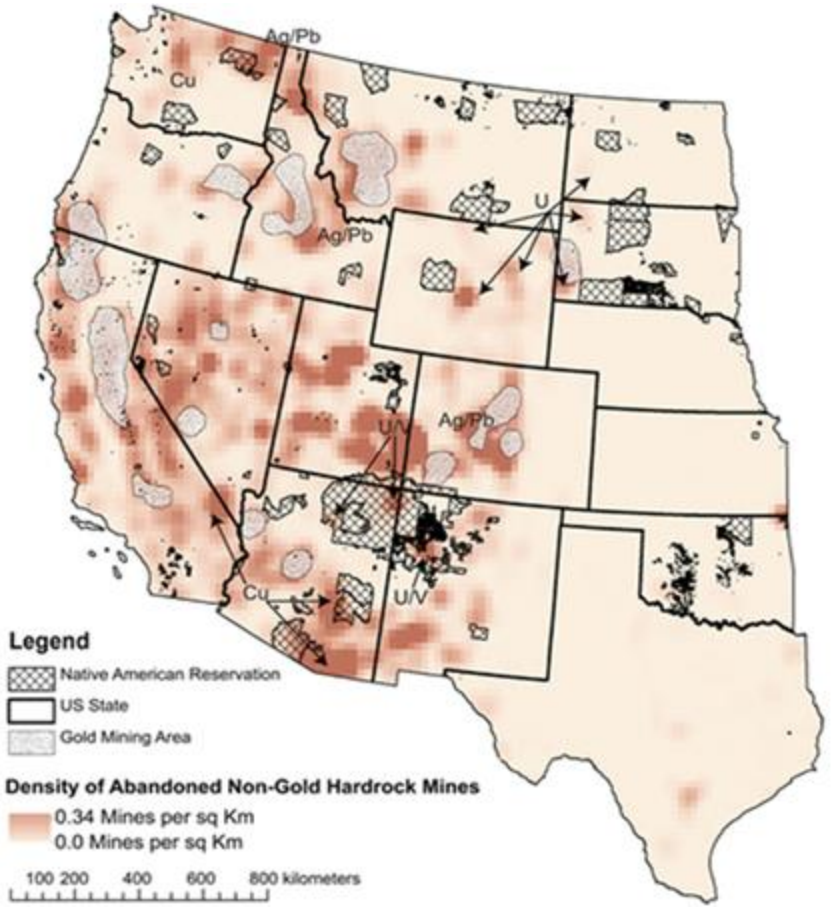
Ana Navas-Acien, MD, PhD

Environmental Health Sciences

Columbia University Mailman School of Public Health

Ethical, Legal, and Social Implications of Gene-Environment Interaction Research, Virtual Workshop January 11-12, 2022

Environmental justice in Indigenous communities



Source: Lewis et al. 2017

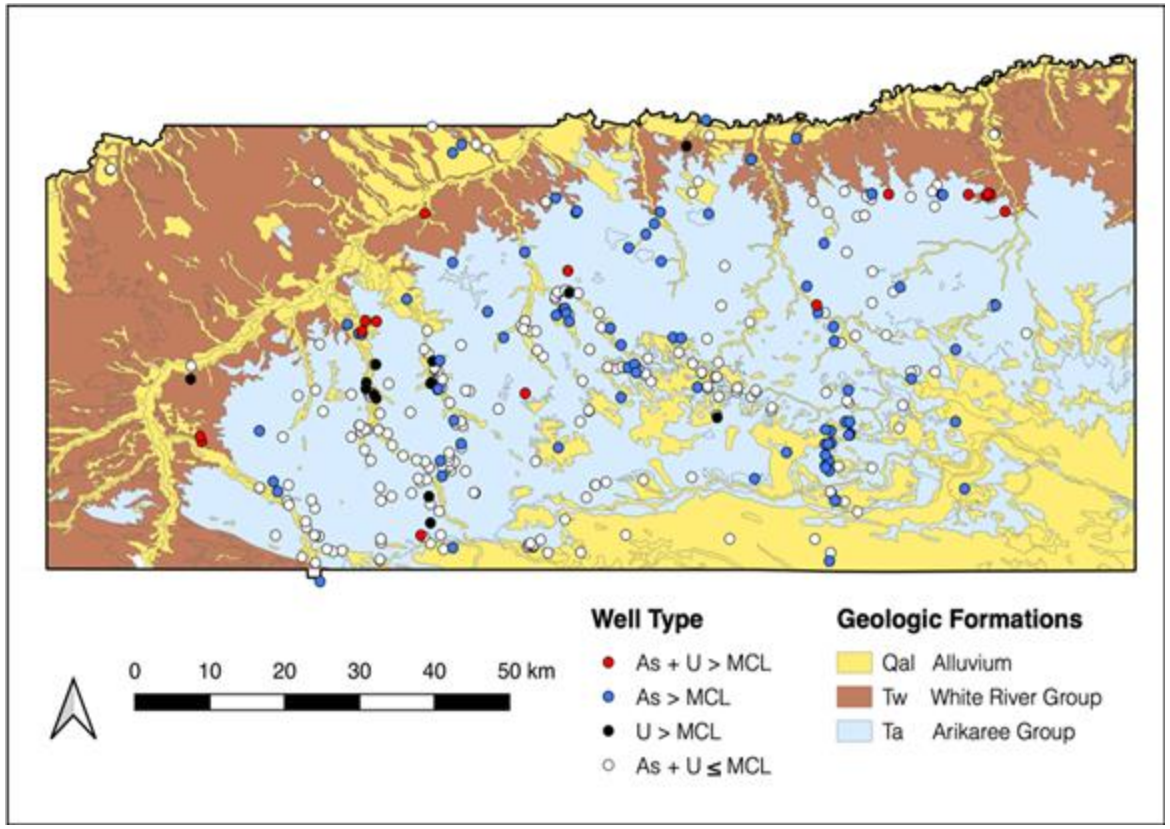
Dakota Access Pipeline protest, Standing Rock, SD

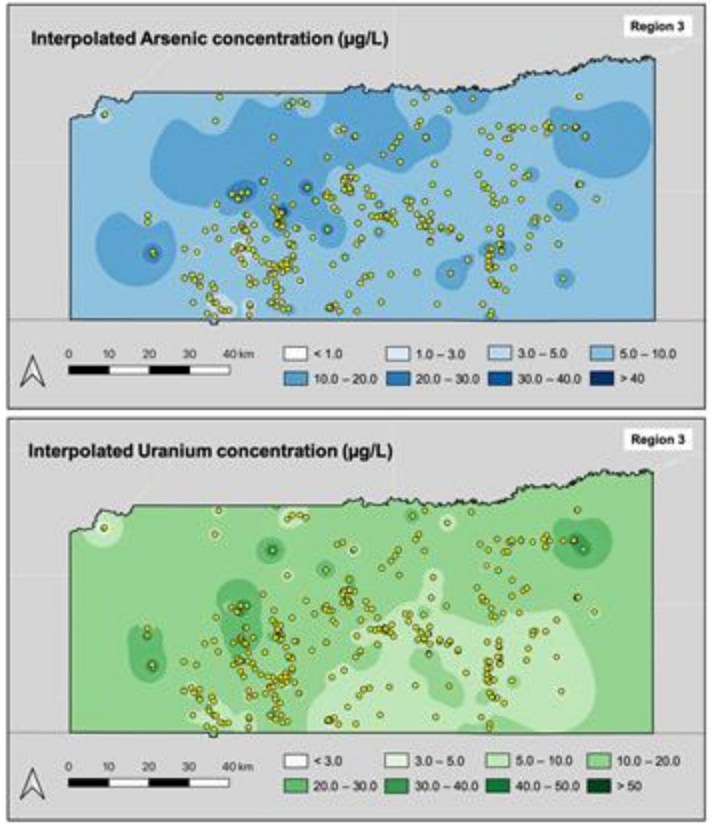
Source: NoDAPL Archive

Arsenic and uranium spatially correlate in water samples in a Indigenous community in South Dakota


Marisa Sobel


Ben Bostick





STRONG HEART Water Study

R01ES025135

Sobel et al. Environ Pollution 2021

Strong Heart Study

Population-based longitudinal study funded by NHLBI since 1988 and also supported by NIEHS since 2012

- **N = 7,600 adults**
- **13 tribes and communities**

http://strongheart.ouhsc.edu/

Arizona

North/South Dakota

Oklahoma

Strong Heart Study: Participatory Science

Eagle Butte, South Dakota,
Strong Heart Study
Steering Committee meeting
October 2015

Strong Heart Study: Participatory Science

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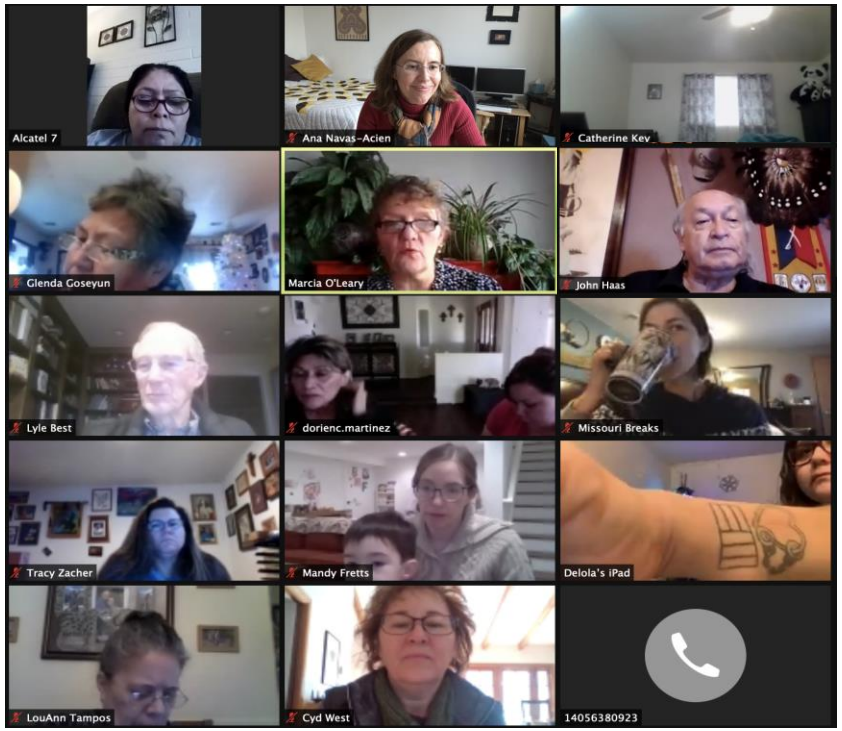

Local research team in South Dakota

MISSOURI BREAKS
Creating Opportunities for Health

Marcia O'Leary
Missouri Breaks Director

Indigenous principles that motivate our work and partnership

- Collective leadership
- Value traditional knowledge
  - Water is life (Mní wičhóni)
  - 7 generations principle
  - Relationality – connections in a circular rather than linear process

Indigenous principles that motivate our work and partnership

- Collective leadership
- Value traditional knowledge
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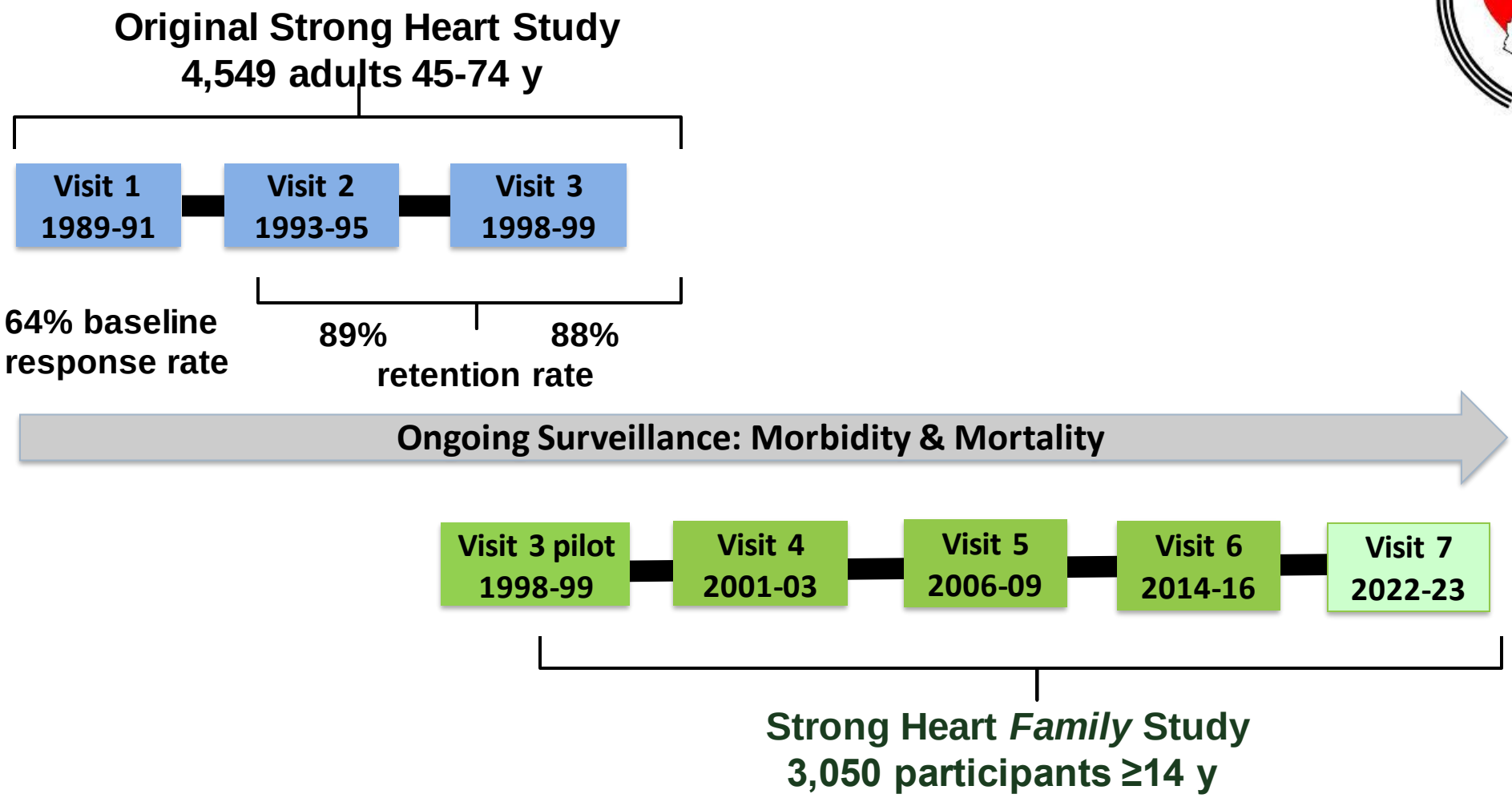
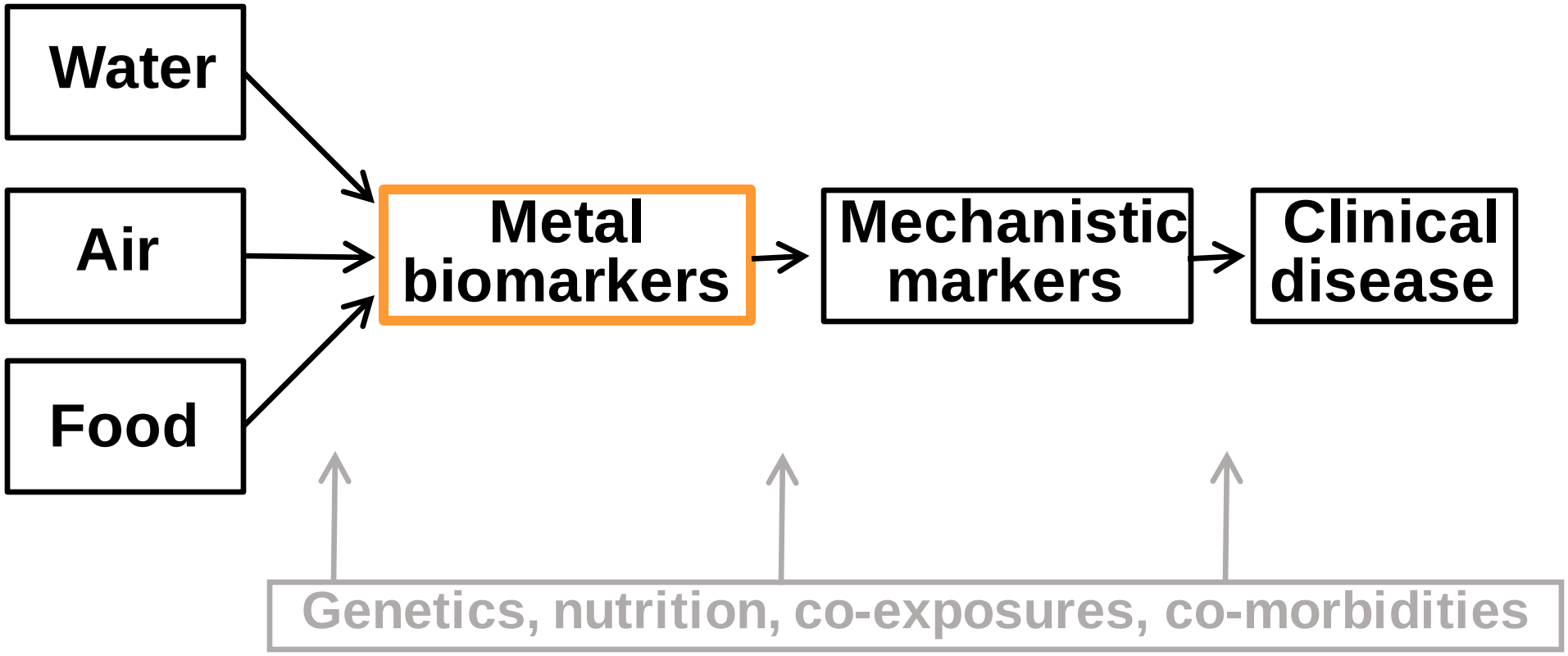
  - Relationality – connections in a circular rather than linear process
- Accept research codes the tribes have developed:
  - Sovereignty and data ownership
  - Tribes RRBs and Indian Health Service IRBs
    - Protocols, publications, lay summaries
  - Communication of study findings (individuals, community)

Prospective cohort study

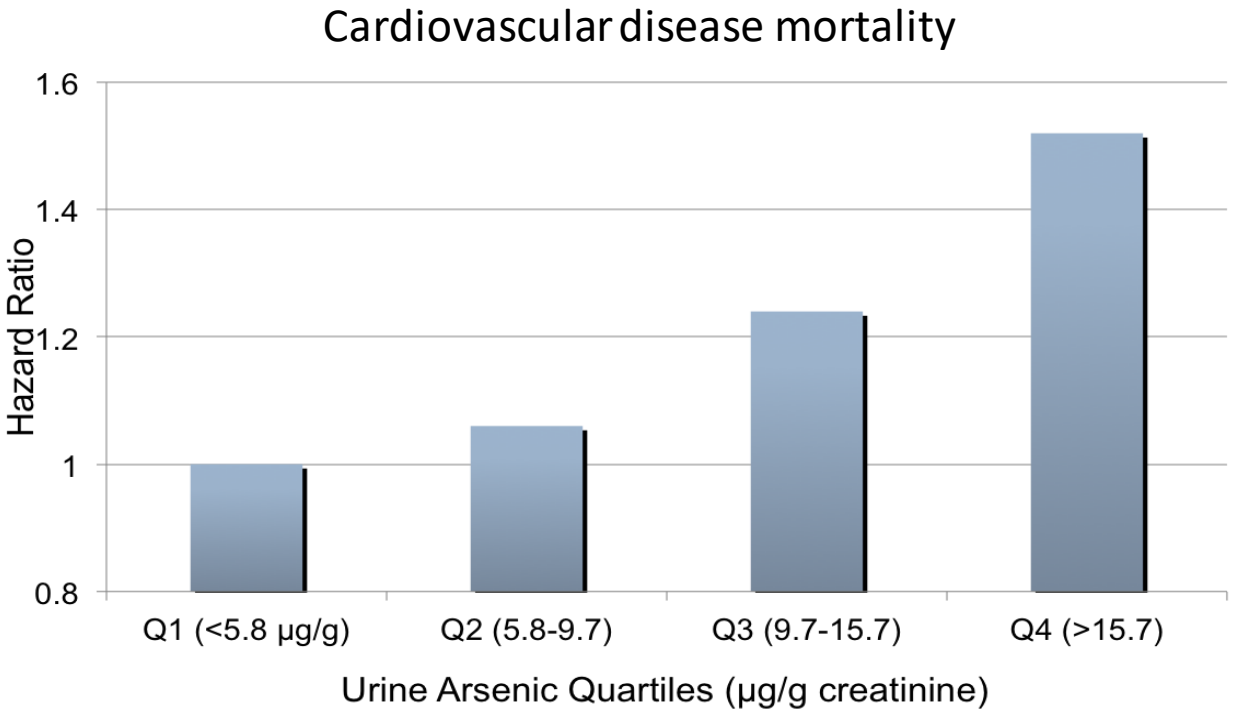


Continuous funding critical to maintain sustainable research projects

Conceptual framework

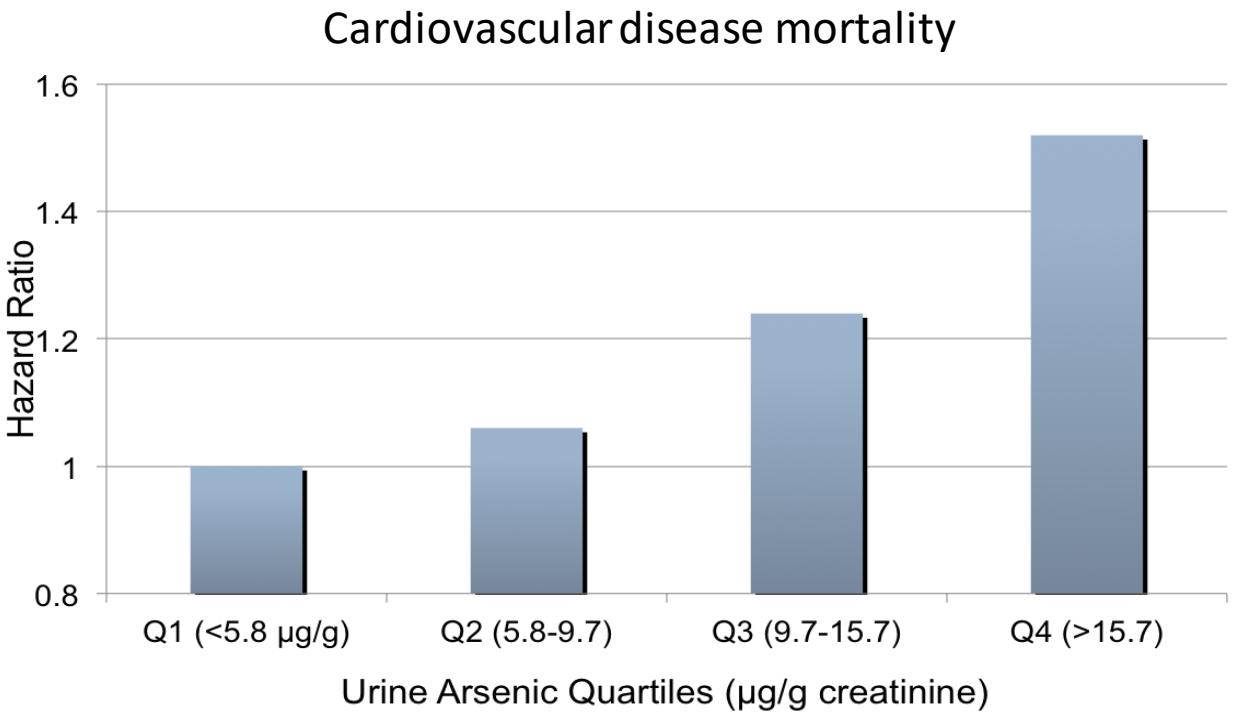


Arsenic and incident CVD over 20 years



Moon et al. Annals Intern Medicine 2013

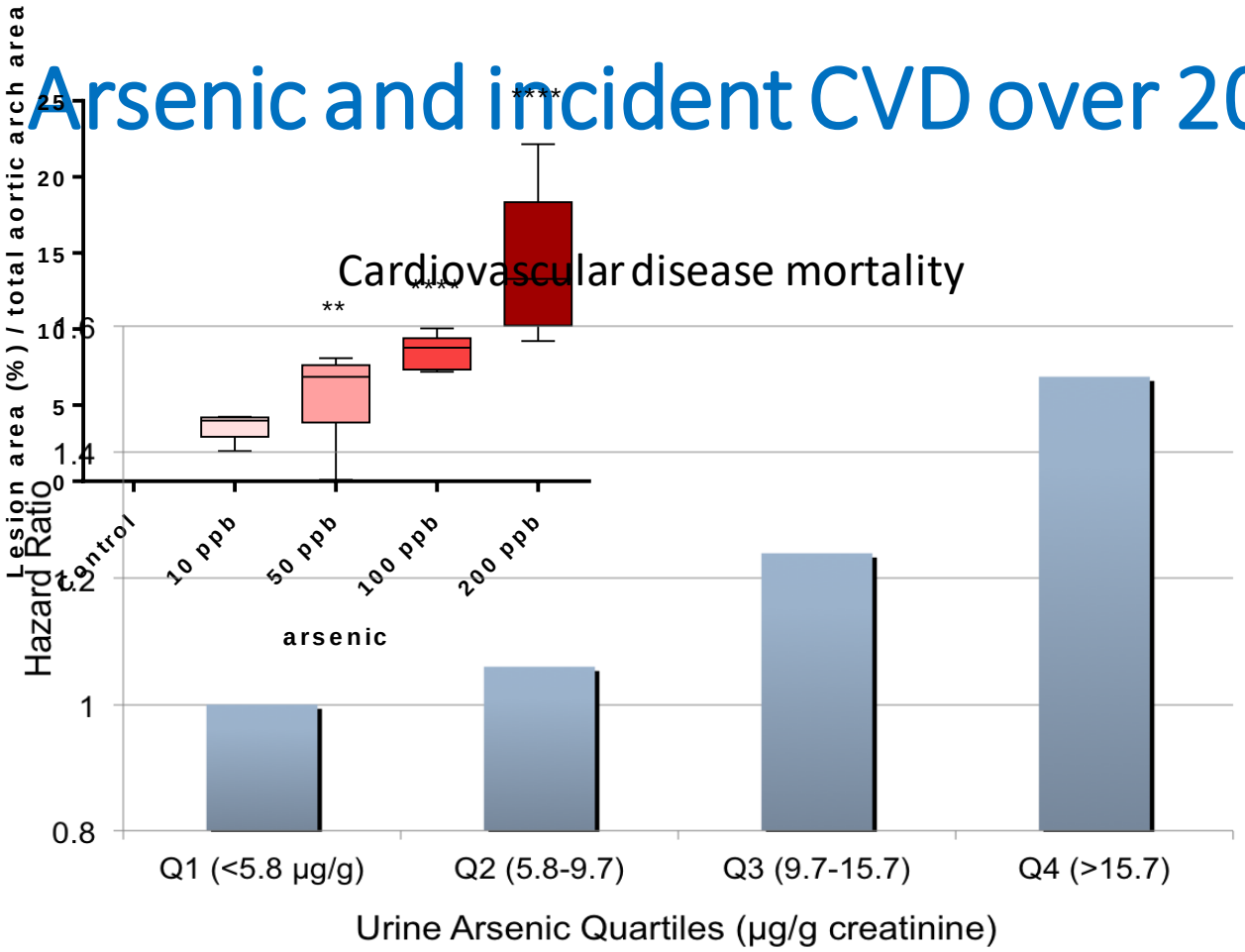
Arsenic and incident CVD over 20 years



- Consistent findings in rural Colorado San Luis Valley Diabetes Study (James et al. EHP 2015)

Moon et al. Annals Intern Medicine 2013

Arsenic and incident CVD over 20 years



- Consistent findings in rural Colorado San Luis Valley Diabetes Study (James et al. EHP 2015)
- Consistent findings in a ApoE-/- model

Koren Mann

Tap water arsenic for 13 weeks

Moon et al. Annals Intern Medicine 2013

Arsenic and Cancer

Dorothy Rhoades
U. Oklahoma

Hazard ratios (95% confidence interval) comparing 80th vs. 20th percentile for the sum of inorganic and methylated arsenic species

	Cases/ Non-cases	Model 1	Model 2
Lung	**80 / 3606**	**1.59 (1.05, 2.42)**	**1.56 (1.02, 2.39)**
Prostate	**16 / 1483**	**1.91 (0.82, 4.41)**	**3.30 (1.28, 8.48)**
Liver	**21 / 3665**	**1.50 (0.76, 2.97)**	**1.34 (0.66, 2.73)**
Kidney	**26 / 3660**	**0.69 (0.25, 1.90)**	**0.44 (0.14, 1.90)**
Pancreas	**24 / 3662**	**2.26 (1.04, 4.88)**	**2.46 (1.09, 5.58)**
Lymphatic/hematopoietic	**35 / 3651**	**0.59 (0.29, 1.17)**	**0.46 (0.22, 0.96)**
Total cancer	**385/ 3546**	**1.16 (0.94, 1.42)**	**1.14 (0.92, 1.42)**

Model 1 stratified by region and age adjusted (staggered entries)

Model 2 further adjusted for sex, education, body mass index, and smoking status (kidney cancer also adjusted for eGFR)

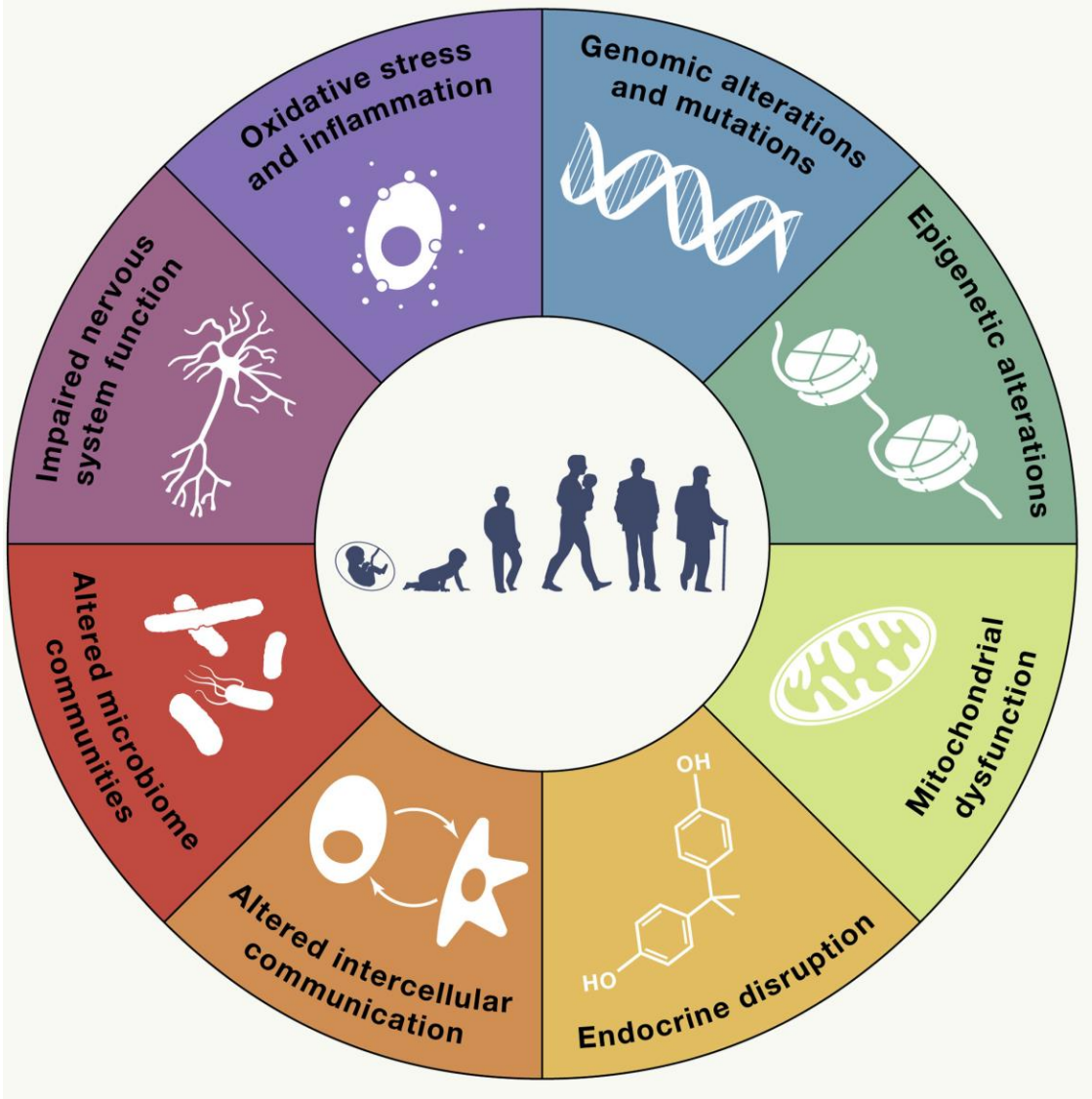
- No association with cancers of the breast, esophagus, stomach, colon/rectum
- Insufficient number of cases to evaluate bladder and skin cancer

Cell *184*, March 18, 2021

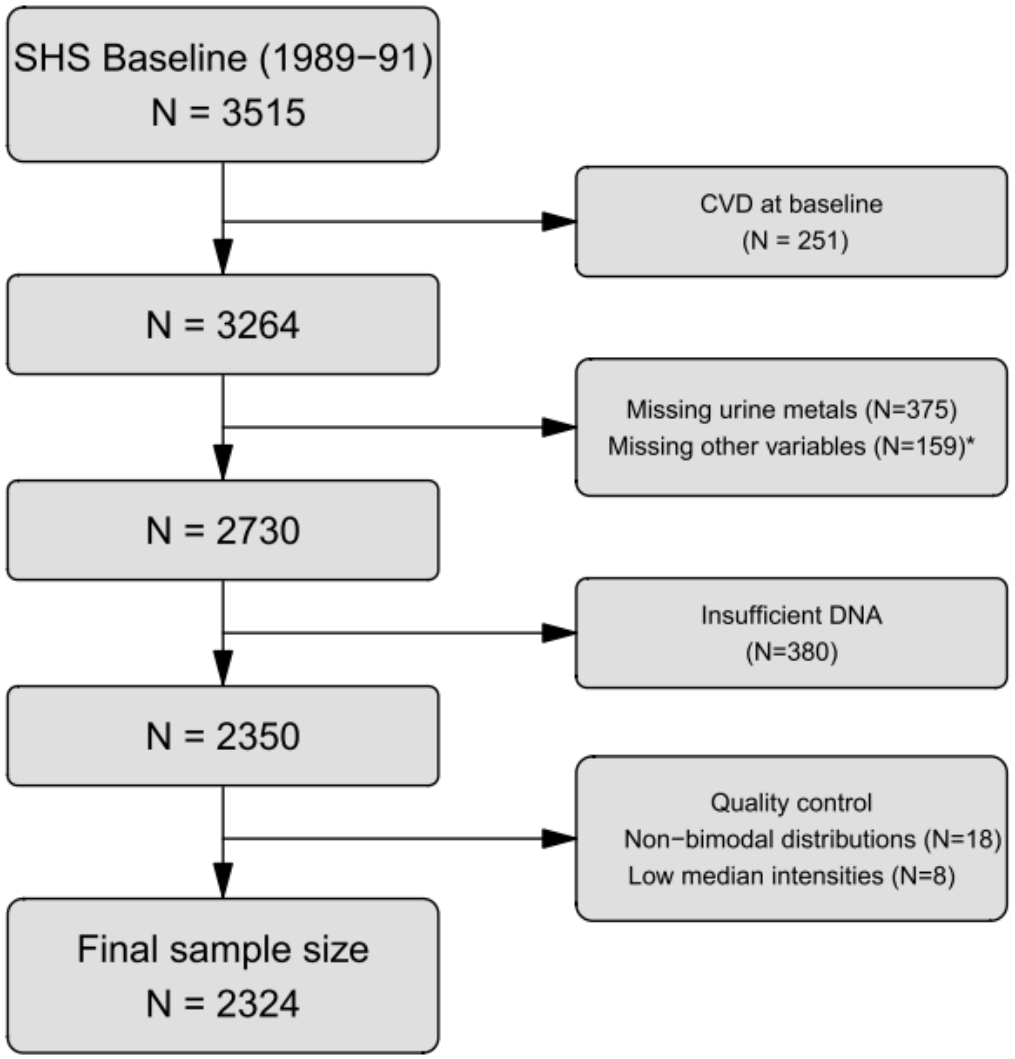
CellPress

What are the possible mechanisms?

s,[1,2,3,*] Tim S. Nawrot,[4,5] and Andrea A. Baccarelli[6]
lemiology, Helmholtz Zentrum München, German Research Center for Environmental Heal
iology, Institute for Medical Information Processing, Biometry and Epidemiology, Medical
ans-Universität München, 81377 Munich, Germany
Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA
onmental Sciences, Hasselt University, Hasselt, Belgium
Health Unit, Leuven University, Leuven, Belgium
Environmental Health Sciences, Mailman School of Public Health, Columbia University, Ne
e: peters@helmholtz-muenchen.de
0.1016/j.cell.2021.01.043



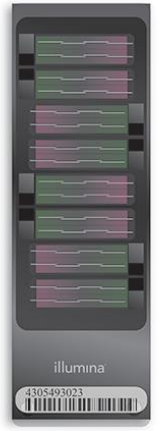
Blood DNA methylation (DNAm)

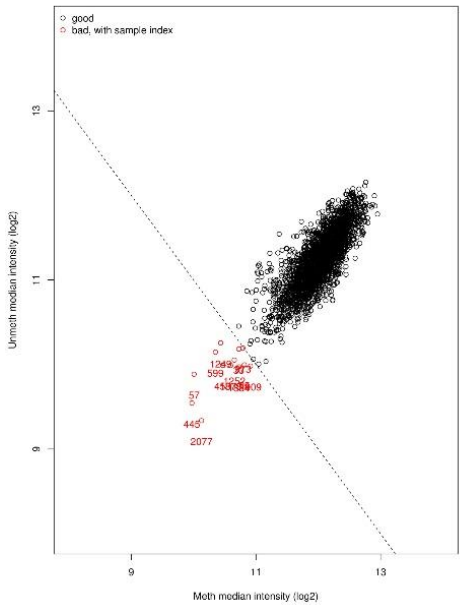


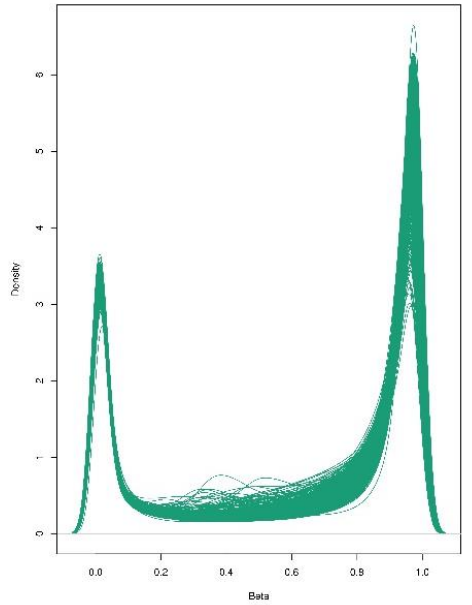
* 5 participants missing education, 2 smokings status, 11 BMI,

52 LDL cholesterol, 14 hypertension treatment, 111 eGFR, 30 diabetes

Illumina's
MethylationEPIC Array







788,368 CpGs available for analysis

R01ES025216

Strong Heart Study Newsletter

Investigating Cardiovascular Disease in American Indians

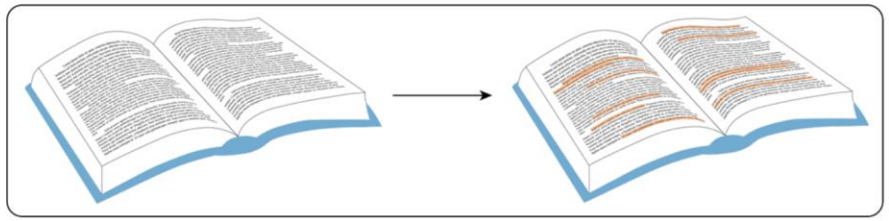
Updates for Community Members and Strong Heart Study Participants

Volume 29, Issue 1 Winter 2019

WHAT IS EPIGENETICS?

DNA is made up of a sequence of bases (called A, T, G, and C). All cells in your body contain the same, unique DNA sequence. Epigenetics is the study of changes to a person's DNA that are not due to changes in the DNA sequence. So, what does that mean? The DNA sequence provides instructions for cells. The instructions are communicated through gene expression. However, not all cells follow the same set of instructions. For example, some cells become muscle cells and some cells become brain cells. Epigenetic markers provide instructions to turn some genes on and to turn some genes off so they become what they were meant to be. It is similar to highlighting in a book showing which parts are important to read.

Like highlighting, epigenetic markers tell a cell which parts of DNA are important.



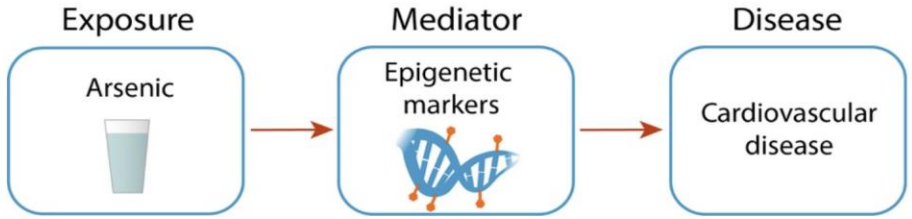
Epigenetic markers include DNA methylation. – *Anne Bozack, Doctoral Student, and Ana Navas-Acien, MD, MPH, PhD, Professor, Columbia University*

EPIGENETICS AND THE ENVIRONMENT

The environment around us and our experiences can cause changes to epigenetic markers. These changes can help our bodies adjust to stress. For example, they allow muscles to grow when you exercise. However, these changes can also lead to problems and to disease. Environmental exposures such as diet, tobacco, and arsenic can change epigenetic markers. – *Anne Bozack, Doctoral Student, and Ana Navas-Acien, MD, MPH, PhD, Professor, Columbia University*

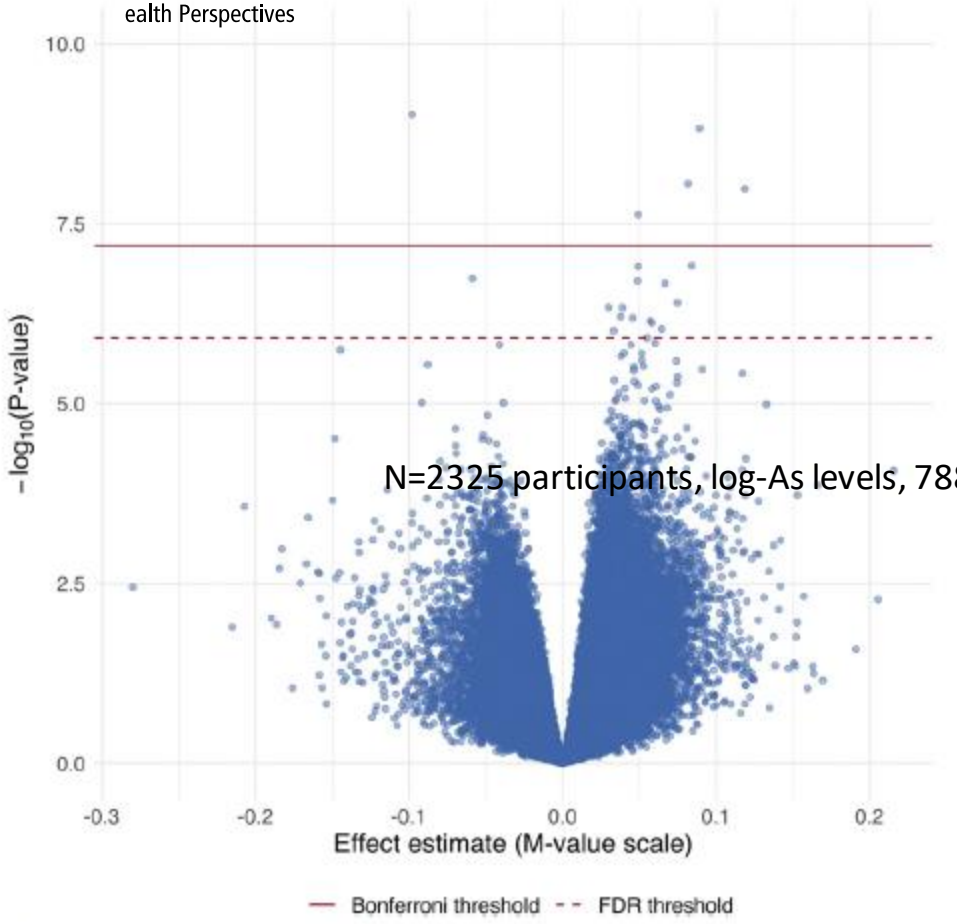
WHAT CAN WE LEARN ABOUT EPIGENETICS FROM THE STRONG HEART STUDY?

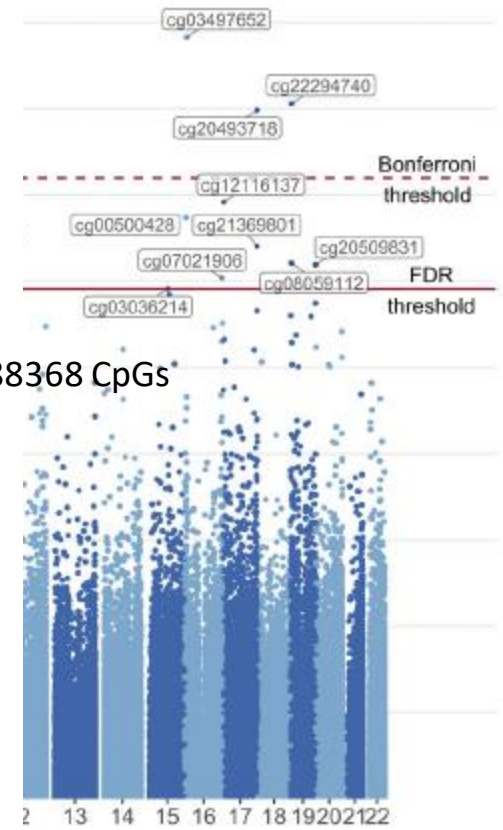
Exposure to arsenic through water and food may increase the risk of cardiovascular disease. We have measured epigenetic markers in the form of DNA methylation in blood samples from participants in the Strong Heart Study. We are using these data to investigate if epigenetics is a factor that acts between arsenic exposure and CVD. We are asking the following questions: (1) does arsenic change epigenetic markers? (2) Do these epigenetic changes affect heart disease? We hope the answers to these questions will lead to new ways to prevent heart disease. – *Anne Bozack, Doctoral Student, and Ana Navas-Acien, MD, MPH, PhD, Professor, Columbia University*



DO BEHAVIORS CHANGE GENE FUNCTION? SMOKING AND GENE FUNCTION

Early data from the Strong Heart Study (SHS) confirms the effects of smoking on our genes. The SHS has collected data on changes that smoking can make to genes in the DNA collected from SHS participants. These are chemical changes that can occur to any of our many genes. These changes cause the DNA to be "methylated", and can turn genes on and off. This is called epigenetic modification. There are a number of studies that have reported that two genes in particular get this modification, or change, in smokers. Using early data from the SHS we were able to identify these same changes in the DNA of current cigarette smokers. One gene has been known to be associated with increased risk of heart disease (F2RL3), Another gene is associated with processes that get rid of toxins from cigarette smoke (AHRR). Confirming these results in the SHS data means that our SHS data are of high quality. We are analyzing the data for additional, unique findings regarding the impact of our behavior on our genes. – *Shelley Cole, PhD, Associate Professor and Program Co-lead Population Health, Texas Biomedical Research Institute*





N=2325 participants, log-As levels, 788368 CpGs

Figure 2. Volcano plot for the epigenome-wide association of log(total urinary arsenic levels) and DNA methylation levels. Limma models adjusted for age, sex, BMI, self-reported smoking status, education (<high school, high school graduate or GED, >high school), study center (Arizona, Oklahoma, North and South Dakota), estimated glomerular filtration rate, and cell-type proportion estimates. The solid line represents the Bonferroni threshold and the dashed line represents the FDR threshold for significance. Note: BMI, body mass index; FDR, false discovery rate; GED, General Education Diploma.

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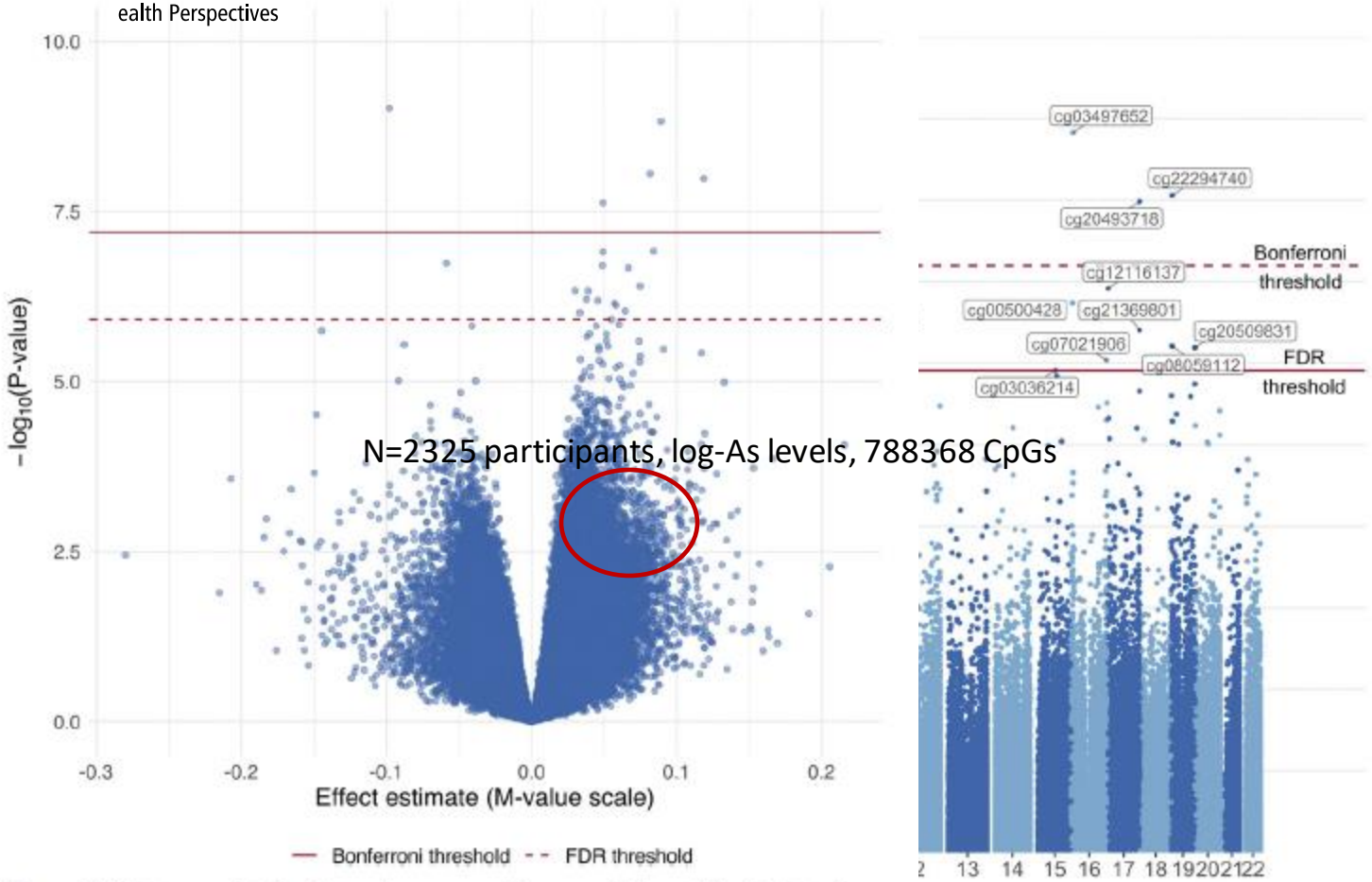
2,3 *Jason G. Umans,*[5,6]
0 *Walter Goessler,*[10]

Anne Bozack

Bozack et al. Environ Health Perspect 2020



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nic:
with

2,3 *Jason G. Umans,*[5,6]
0 *Walter Goessler,*[10]

Anne Bozack

Top CpG annotated to *SLC7A11A*, gene involved in cysteine/glutamate transport and glutathione biosynthesis

Bozack et al. Environ Health Perspect 2020

Domingo-Relloso *et al. Clin Epigenet* (2021) 13:43
https://doi.org/10.1186/s13148-021-01030-8

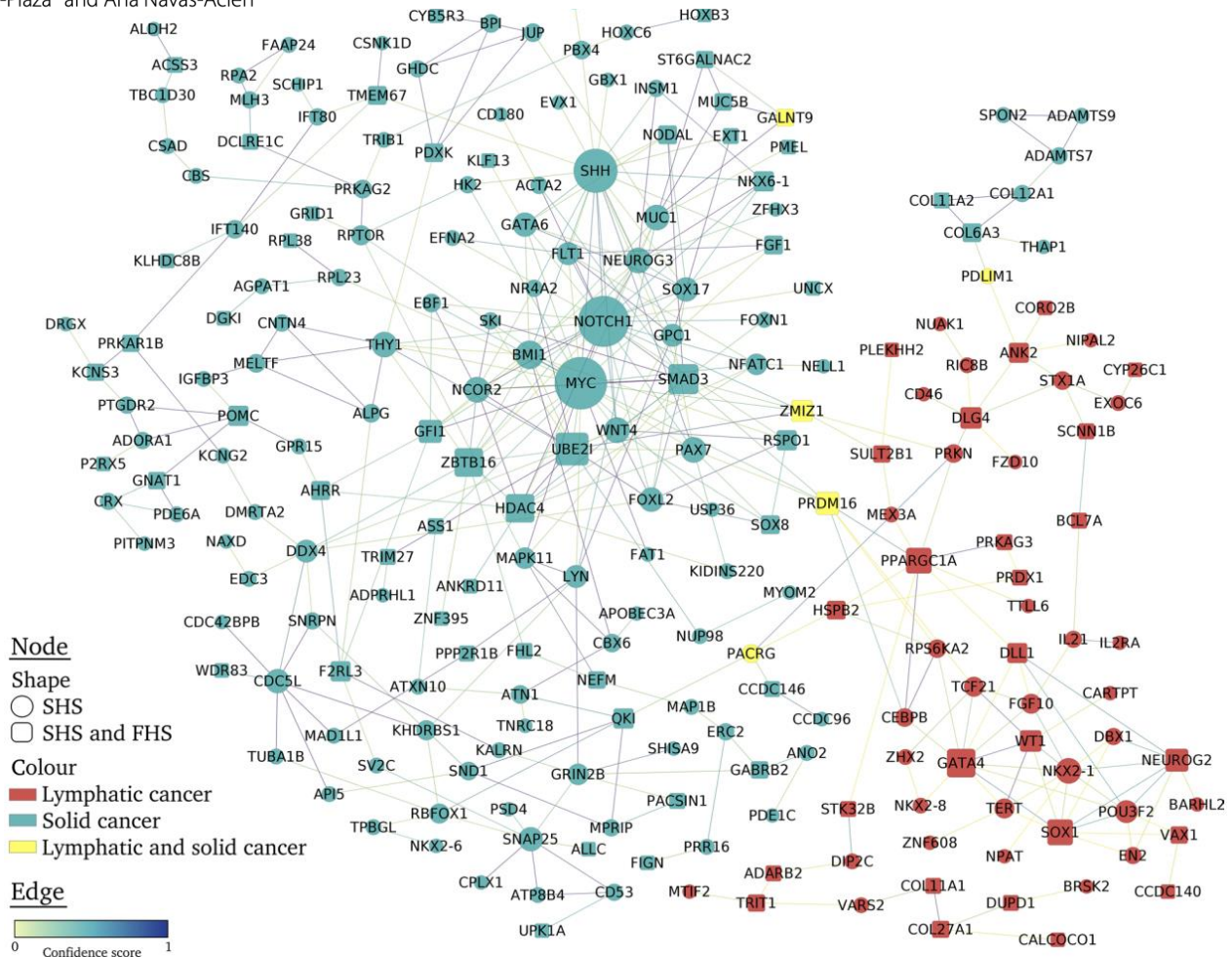
Clinical Epigenetics

RESEARCH Open Access

DNA methylation and cancer incidence: lymphatic–hematopoietic versus solid cancers in the Strong Heart Study

Arce Domingo-Relloso[1,2,3*], Tianxiao Huan[4,5], Karin Haack[6], Angela L. Riffo-Campos[7], Daniel Levy[4,5], M. Daniele Fallin[8,9], Mary Beth Terry[10], Ying Zhang[11], Dorothy A. Rhoades[12], Miguel Herreros-Martinez[13], Esther Garcia-Esquinas[14,15], Shelley A. Cole[6], Maria Tellez-Plaza[2] and Ana Navas-Acien[1*]

Protein-protein interaction network of differentially methylated positions (DMPs)



Arce Domingo, PhD student

Collaboration in consortium projects

Christiansen *et al. Clin Epigenet* (2021) 13:36
https://doi.org/10.1186/s13148-021-01018-4

Clinical Epigenetics

RESEARCH Open Access

Novel DNA methylation signatures of tobacco smoking with trans-ethnic effects

C. Christiansen[1], J. E. Castillo-Fernandez[1], A. Domingo-Relloso[2,3,4], W. Zhao[5], J. S. El-Sayed Moustafa[1], P.-C. Tsai[1,12,13], J. Maddock[6], K. Haack[7], S. A. Cole[7], S. L. R. Kardia[5], M. Molokhia[8], M. Suderman[9], C. Power[10], C. Relton[9,10], A. Wong[6], D. Kuh[6], A. Goodman[11], K. S. Small[1], J. A. Smith[5], M. Tellez-Plaza[3], A. Navas-Acien[2], G. B. Ploubidis[11], R. Hardy[6] and J. T. Bell[1*]

and diverse populations

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-021-27234-3 OPEN

Meta-analyses identify DNA methylation associated with kidney function and damage

Environmental Health Perspectives

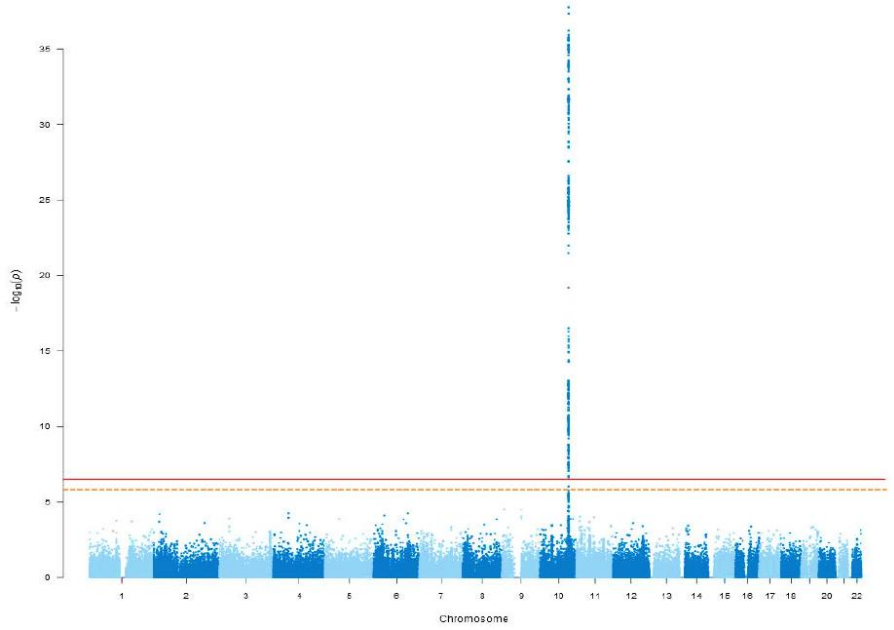
Research

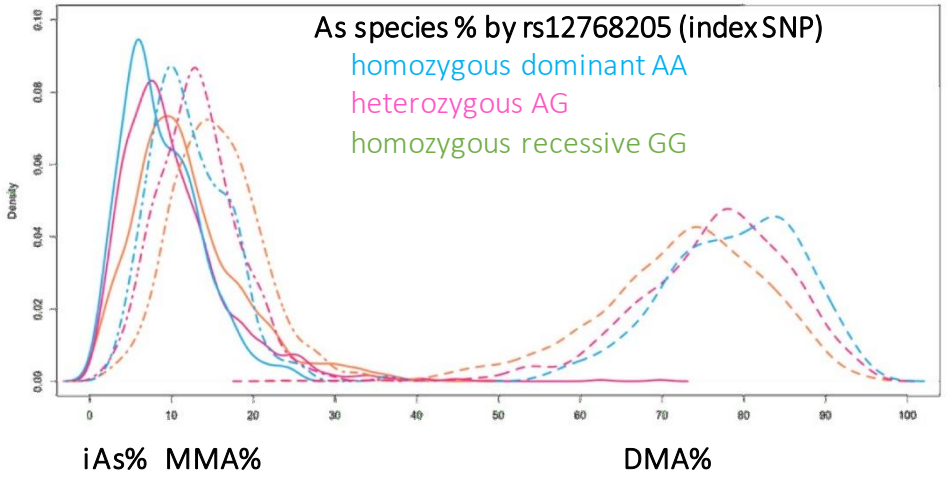
Rare, Protein-Altering Variants in *AS3MT* and Arsenic Metabolism Efficiency: A Multi-Population Association Study

Dayana A. Delgado,[1] Meytal Chernoff,[1] Lei Huang,[2] Lin Tong,[1] Lin Chen,[1] Farzana Jasmine,[1] Justin Shinkle,[1] Shelley A. Cole,[3] Karin Haack,[3] Jack Kent,[3] Jason Umans,[4] Lyle G. Best,[5] Heather Nelson,[6] Donald Vander Griend,[7] Joseph Graziano,[8] Muhammad G. Kibriya,[1] Ana Navas-Acien,[8] Margaret R. Karagas,[9] Habibul Ahsan,[1,10,11,12] and Brandon L. Pierce[1,10,11]

Manhattan plot for DMA% in Strong Heart Family Study

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



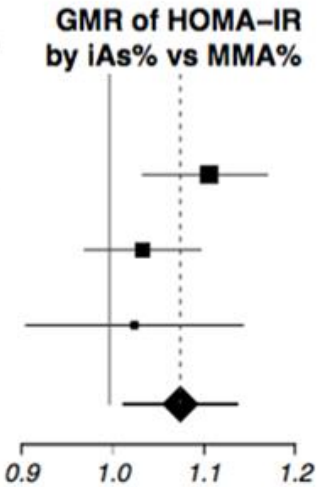


Metabochip

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

Arsenic-*AS3MT* index SNP interaction on HOMA-IR

	N	GMR (95% CI)	P int.
rs12768205			
G/G	786	1.13 (1.04, 1.21)	0.03
G/A	627	1.04 (0.97, 1.12)	
A/A	135	1.03 (0.90, 1.17)	
Overall	1548	1.09 (1.02, 1.17)	

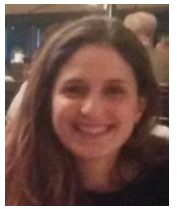


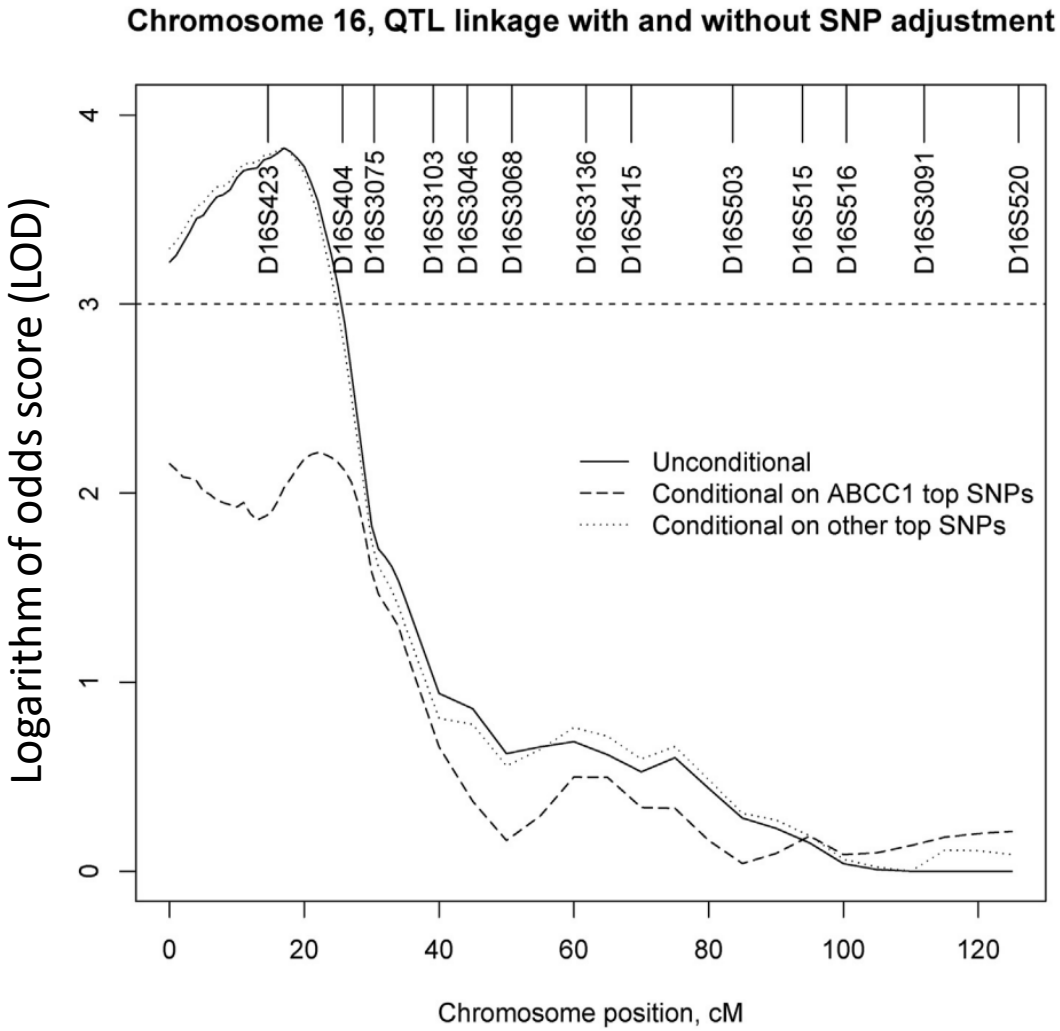
GMR: geometric mean ratio

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

Role of genetics in urine cadmium levels


Maria Tellez


Maria Grau



- Evidence of a genetic locus on Chromosome 16 associated with urinary cadmium in a linkage analysis (N=1936)
- Peak reduced by 40% after adjustment for the top 20 SNPs annotated to *ABCC1*

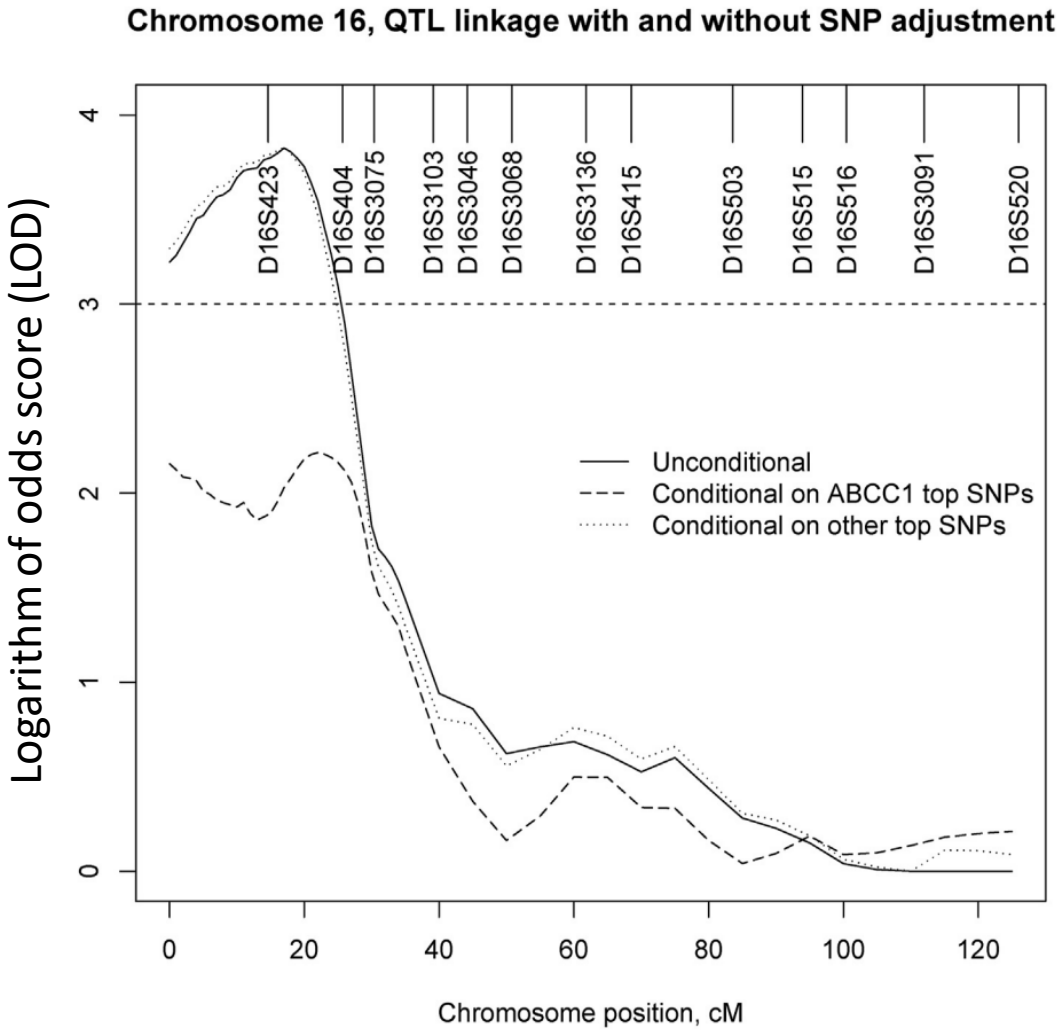
Adjusted for age, age^2, sex, age*sex, age^2*sex, smoking status (never, former, current), location and urine zinc (log mg/g creatinine). In conditional QTL linkage analysis statistical models were additionally adjusted for SNPs annotated to ABCC1 and genes other than ABCC1 among the top 20 significant SNPs.

R01ES021367

Role of genetics in urine cadmium levels


Maria Tellez


Maria Grau



- Evidence of a genetic locus on Chromosome 16 associated with urinary cadmium in a linkage analysis (N=1936)
- Peak reduced by 40% after adjustment for the top 20 SNPs annotated to *ABCC1*
- Urgent need: Metal-GWAS Initiative

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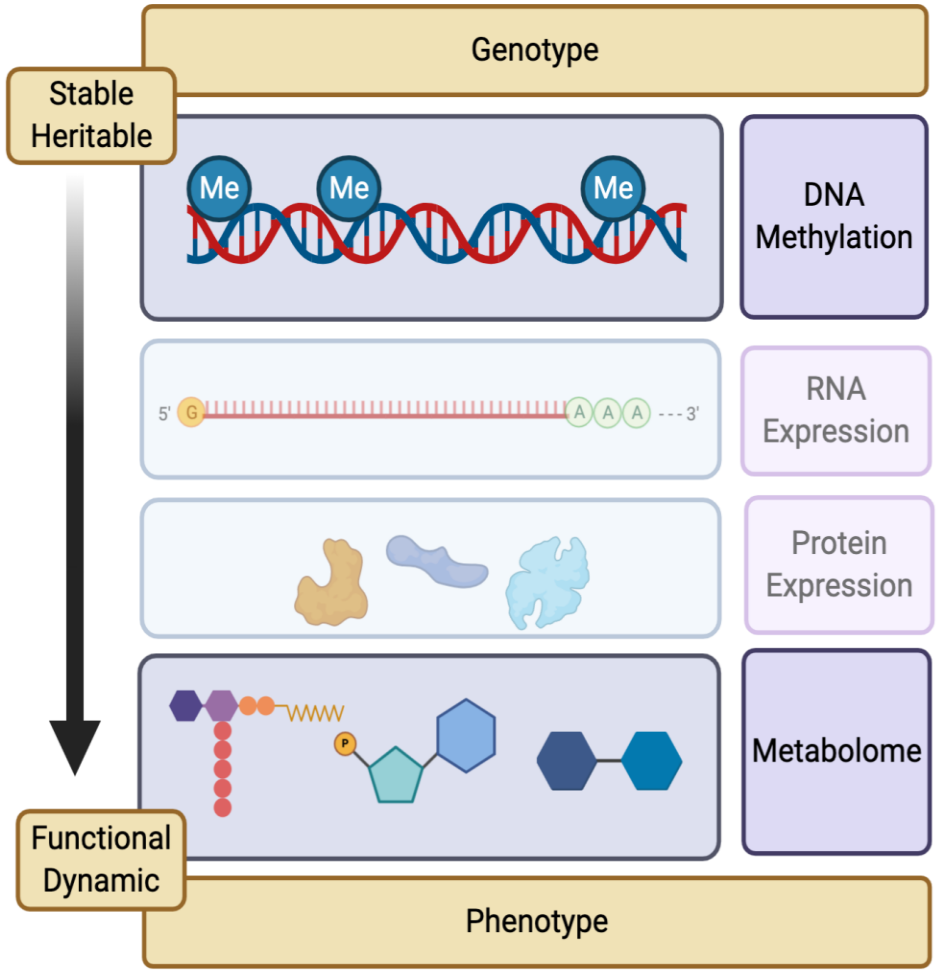
R01ES021367

Possible molecular mechanisms for metal-related disease

- Increasing evidence that metals effects involve a dynamic and interactive system of molecular layers
- Multi-omics approaches can help us characterize metal-induced disease, including cardiovascular disease



Credit: Allison Kupsco

strongheartstudy.org

Strong Heart Study

The largest epidemiologic study of cardiovascular disease in American Indians

HOME | ABOUT | COMMUNITY | RESEARCH | EDUCATION | MEDICAL PROVIDERS | INTERNAL | CONTACT US

RESEARCH

EDUCATION

COMMUNITY

ANNOUNCEMENTS

Strong Heart Study is conducting Virtual Public Health Training Sessions from March - June 2021

Please click this link for more details.

Phase VII exam planning phase

Click here for more details.

The Strong Heart Study is a study of cardiovascular disease and its risk factors among American Indians. Field Centers are located in Arizona, North and South Dakotas, and Oklahoma.

Strong Heart Study website: source of information for multiple stakeholders

Data ownership and data sharing

- Who owns the data?

- Who allows data sharing and in which terms?

Tribal communities are resisting unrestricted data sharing

http://countercurrentnews.com/2016/11/dakota access pipeline builders admit protests cost 100 million/

Data ownership and data sharing

- Who owns the data?
- Who allows data sharing and in which terms?
- Who profits from research

nature

Genomics data: the broken promise is to Indigenous people

In lamenting the "broken promise that undermines human genome research", this journal implies that researchers have a right to access information across databases (see *Nature* **590**, 198–201; 2021). In our view, this problematically frames 'equity' and 'progress' for scientists and dismisses the rights of those who contributed the DNA. As Indigenous geneticists, we remind researchers of the broken promise to extend medical benefits to communities whose genomic data are publicly available.

The genomes of Indigenous people are sought for their unique variation: new genotype–phenotype associations in isolated, small populations are used to advance precision medicine. We take issue with the fact that the Human Genome Diversity Project publicly shares with industries that profit from the 'big data' economy genomic information gleaned from central-south American Indigenous individuals (K. Fox *N. Engl. J. Med.* **383**, 411–413; 2020). Meanwhile, wide disparities persist in the health of Indigenous people, owing to intractable power inequities, including in research, that precision medicine is unlikely to address (K. S. Tsosie *et al. Nature Rev. Genet.* **20**, 497–498; 2019).

We contend that the FAIR Principles (see go.nature.com/2nqzcxo) for data sharing grant too much decision-making authority to researchers outside of tribal governances. To understand the duty to steward data, look instead to the CARE Principles (collective benefit, authority to control, responsibility and ethics; see go.nature.com/3vsenhk). Data are not a gift. At best, they are 'on loan', and hence revocable if misused. Data are a responsibility not an entitlement.

Krystal S. Tsosie, **Keolu Fox**, **Joseph M. Yracheta** Native BioData Consortium, Eagle Butte, South Dakota, USA.
krystal@nativebio.org

nature

Genomics data: the broken promise is to Indigenous people

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WORLD VIEW *A personal take on events*

Indigenous peoples must benefit from science

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

22 OCTOBER 2015 | VOL 526 | NATURE | 477

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

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

http://rapidcityjournal.com/news/local/mni-wiconi-water-reach

Mni Wiconi water reaching Pine Ridge

Gathering heralds arrival of lines that carry clean water

Mary Garrigan, Journal staff Aug 19, 2008

Planning a participatory intervention study in South Dakota

Meeting at Eagle Butte, SD

Meeting at Martin, SD

Making those meetings and work possible is Marcia O'Leary, RN
Director of Missouri Breaks Industry Research, the local organization that conducts the Strong Heart Study in North and South Dakota

Strong Heart Water Study for Private Wells

- Participatory randomized trial in South Dakota
- Filters installed to eliminate arsenic in drinking water
- Education intervention vs. standard information

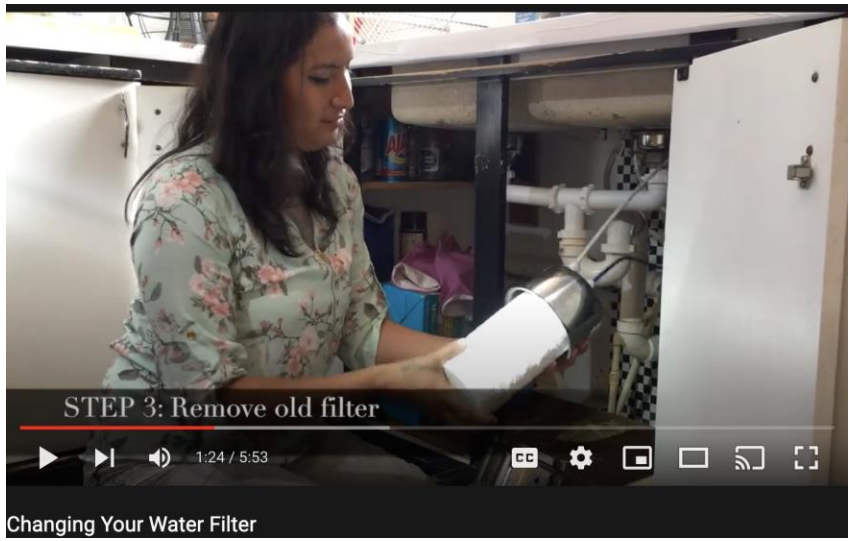
Christine George

Marcia O'Leary

Tracy Zacher

R01ES025135

Strong Heart Water Study for Private Wells: Tools for Communities



Rae O'Leary
Indigenous Health
Communication Specialist

R01ES025135

Communities and participants make research possible

- Engagement and participation
- Support of science
- Contributions to research questions
- Contribution to conduction of research
- Data access and decision-making
- Research can and must benefit communities
  - Benefits are sometime slow
  - Researchers need to be actively engaged

Funding sources

R01HL090863 (completed)
R01ES021367 (completed)
R01ES025216 (completed)
R01ES032638
75N92019D00023

R01ES025135

P42ES010349

P30ES009089

Students and trainees move the science forward: drive and creativity

Arce Domingo
PhD student

Ahlam Abuawad
PhD student CU

Maya Spaur
PhD student CU

Marisa Sobel
PhD student CU

Joseph Yracheta
DrPH student
Johns Hopkins

Will Lieberman-Cribbin
PhD student CU

Irene Martinez-Morata
PhD CU

Christian Dye
Post-doc CU

Kevin Patterson
Year gap

Enoch Jiang
Year gap

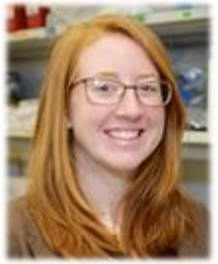
Filippo Ravalli
MPH student CU

Kaila Boyer
MPH student CU

Monique Slowl,
4+1 MPH CU

Marilyn Santo,
CU undergrad
PrIMER

Marta Galvez,
Prev. Medicine
resident



Katlyn McGraw
Post-doc CU