Exposures and Latent Disease Risk: Session III – Arsenic as a Case Study

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Arsenic exposure in the US and abroad

Arsenic exposure in the world

Smedley PL & Kinniburgh DG *Appl Geochem* 2002

Arsenic exposure in the U.S.

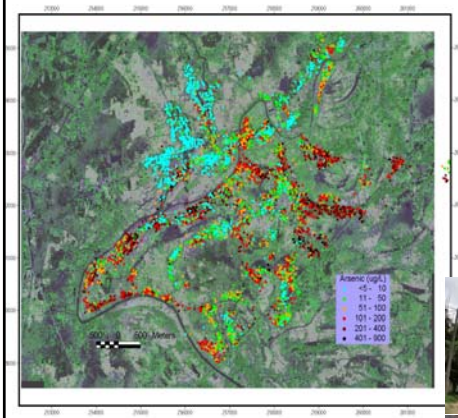
- Nearly 800 public water systems serving 1.8 million people (USGS estimate) and unknown number of private water wells.
- Arsenic in chicken meat, especially after cooking (EHP, 2013)
- Urinary arsenic is correlated with rice consumption in US children (EHP, 2012).
- Arsenic in juices (consumer report , 2012) and wine (2015)

Long-term Health Effects

Skin lesions
Non-melanoma skin cancers
Internal cancers:
- Bladder
- Kidney
- Lung
- Liver
- Prostate?

Developmental effects
Neurological effects
Hypertension
Cardiovascular disease
Pulmonary disease
Peripheral vascular disease
Mortality
Reproductive effects
Diabetes

Health Effects of Arsenic Longitudinal Study (HEALS) Araihazar, Bangladesh



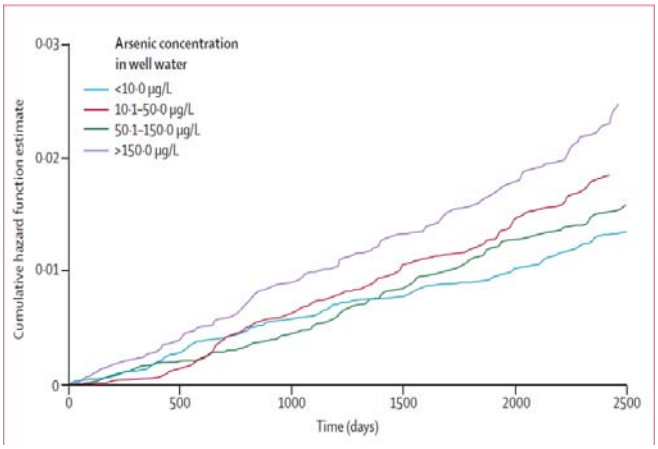
- 11,746 recruited in 2000, expanded to 35,000
- 96% response rate
- Water samples from 12,000 wells
- Urine samples collected every two years for 96-98%
- Blood samples at baseline for 94%
- In-person interview every two years
- Field clinics





Columbia Superfund Research Program

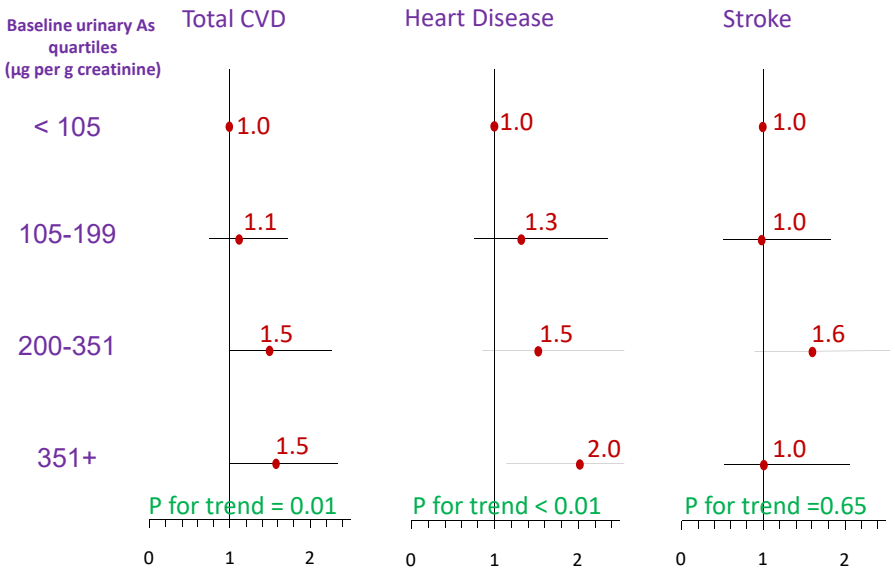
Arsenic Exposure and Chronic Disease Mortality in HEALS, 2000-2009



23.5% deaths could be attributed to As exposure > 10 µg/L

Argos *et al*, *The Lancet* 2010

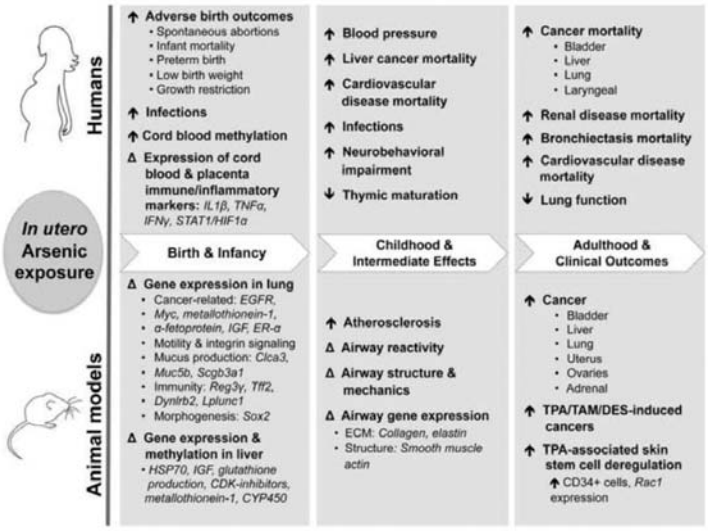
Baseline Urinary Arsenic and CVD Mortality



Adjusted for age, gender, BMI, education level, smoking status, and visit-to-visit changes in urinary As

Chen Y *et al BMJ* 2011, *EHP* 2013a, *EHP* 2013b, *AJE* 2013; Wu F, *et al EHP* 2015, Wu F, *et al AJE* 2013.

Health effects of *in utero* and early life arsenic exposure



Farzan SF, *TAPP*, 2013

Windows of susceptibility

- Periods of time in the lifecourse when individuals may be more susceptible to the adverse effects of a toxic exposure
  - Pregnancy
  - Fetal life
  - Infancy
  - Childhood
  - Adolescence

Farzan SF, *TAPP*, 2013

Baseline water As (n = 10,853) and urinary As (n = 10,549) with adjusted annual changes in systolic blood pressure (SBP) over 7 years of follow-up in HEALS

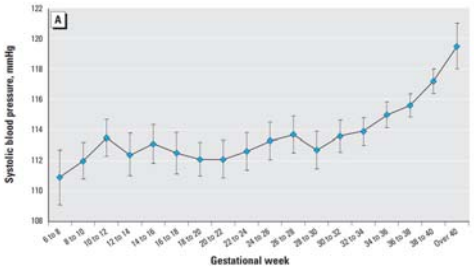
Baseline exposure	Range	Model 1 change/year (mmHg)	Model 2 change/year (mmHg)	Model 3 change/year (mmHg)
Water arsenic (μg/L)				
Q1	< 12	Reference	Reference	Reference
Q2	12–62	0.45 (0.32, 0.58)	0.42 (0.29, 0.56)	0.43 (0.29, 0.56)
Q3	62–148	0.60 (0.46, 0.73)	0.55 (0.42, 0.68)	0.54 (0.40, 0.67)
Q4	> 148	0.51 (0.38, 0.65)	0.48 (0.34, 0.61)	0.48 (0.35, 0.61)
Urinary creatinine-adjusted arsenic (μg/g creatinine)				
Q1	< 106	Reference	Reference	Reference
Q2	106–199	0.40 (0.26, 0.53)	0.38 (0.25, 0.52)	0.39 (0.25, 0.52)
Q3	199–352	0.45 (0.32, 0.59)	0.43 (0.30, 0.57)	0.44 (0.30, 0.58)
Q4	> 352	0.45 (0.31, 0.58)	0.41 (0.27, 0.54)	0.43 (0.29, 0.56)

Abbreviations: Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4. Model 1: controlled for baseline age and sex. Model 2: controlled for model 1 covariates plus BMI, smoking status, educational status, and history of diabetes. Model 3: controlled for model 2 covariates plus change of urinary creatinine-adjusted arsenic since baseline.

Jiang J *et al. EHP*, 2015 paper of year, the Society of Toxicology (SOT).

Pregnancy urinary As and changes in BP (mmHg) per month over pregnancy among 514 women in the New Hampshire Birth Cohort Study

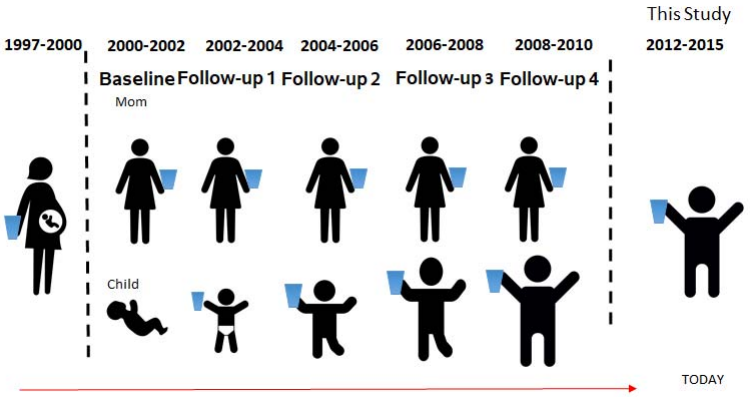
As exposure measure (per 5 μg/L)	No. of BP measurements	SBP	
		β_{12} (95% CI)[a]	*p*-Value[b]
Total As	5,032	0.15 (0.02, 0.29)	0.022
MMA	5,016	1.28 (–0.27, 2.83)	0.11
DMA	5,032	0.18 (0.02, 0.33)	0.022
iAs	5,031	1.11 (–0.23, 2.44)	0.10



Abbreviations: SBP, systolic blood pressure. [a]**Coefficient in relation to interaction between a 5-μg/L increase in total urinary arsenic, MMA, DMA, or iAs and each month of gestation**; adjusted for age at enrollment, pre-pregnancy BMI, educational level, marital status, maternal smoking, parity, gestational diabetes, and number of blood pressure measurements per participant. [b]p-Values for β12 effect estimates.

Farzan SF *et al. EHP*, 2015

HEALS adolescents study



Correlation between mother's urine As and water As = 0.75
Correlation between mother urine As and children's urine As = 0.75

Slide courtesy of T. Sanchez

Lifetime exposure and BP in adolescents (n = 720)

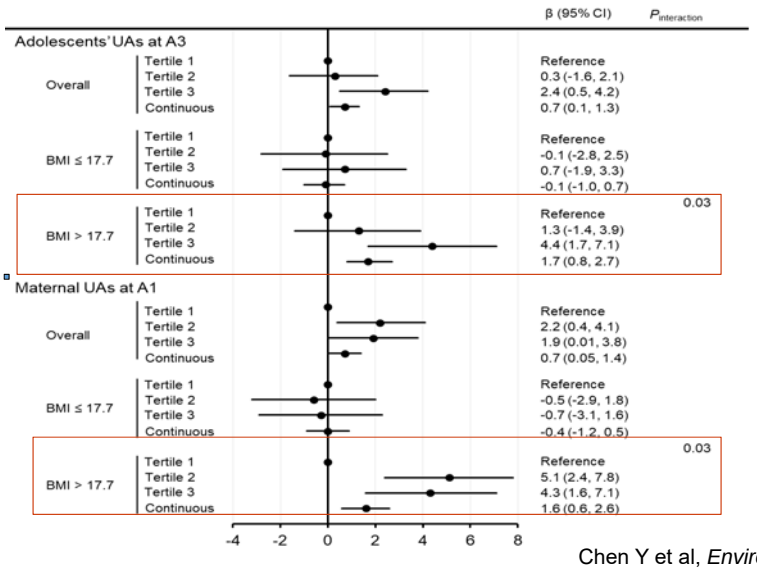
		SBP (mmHg)	DBP (mmHg)
	N	β[a] (95% CI)	β[a] (95% CI)
Adolescent's current urinary arsenic, µg/g creatinine			
Tertile 1 (15.8-71.2)	239	Ref	Ref
Tertile 2 (71.3-145.1)	240	0.3 (-1.6, 2.1)	-0.7 (-2.3, 1.0)
Tertile 3 (145.2-2886.9)	240	**2.4 (0.5, 4.2)**	1.0 (-0.6, 2.6)
Early childhood exposure (average maternal urinary arsenic *in urtero* to 5 years of age, A1)			
Tertile 1 (20.0-132.4)	231	Ref	Ref
Tertile 2 (132.5-272.3)	232	**2.2 (0.4, 4.1)**	1.0 (-0.7, 2.6)
Tertile 3 (272.4-3073.8)	232	**1.9 (0.01, 3.8)**	0.6 (-1.1, 2.3)
Childhood exposure (average maternal urinary arsenic at 5-12 years of age, A2)			
Tertile 1 (26.6-117.5)	240	Ref	Ref
Tertile 2 (117.6-239.6)	240	1.2 (-0.7, 3.0)	-0.3 (-1.9, 1.4)
Tertile 3 (239.7-3221.0)	240	1.2 (-0.7, 3.0)	0.2 (-1.5, 1.8)

[a]Adjusted for sex, age (years), BMI, and adolescent's education

Results were similar using BAs or with additional control for BCd, Bse, BPb, and BMn

Chen Y et al, *Environmental Research*, 2019

SBP in relation to adolescents' current urinary arsenic and maternal urinary arsenic at A1 (<5 years old)



Chen Y et al, *Environmental Research*, 2019

Models were adjusted for sex, age (years), and BMI.

Associations of weighted quantile sum regression index with SBP in overall and by BMI status

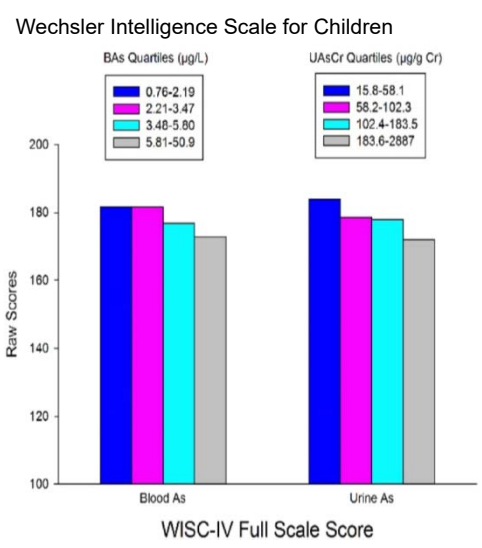
	WQS		Weight		
	β[a] (95% CI)	P	Current UAs	Maternal UAs at T1	Maternal UAs at T2
All	1.5 (0.3, 2.6)	0.01	0.53	0.35	0.12
BMI > 17.7	3.7 (1.9, 5.4)	<0.01	0.40	0.45	0.16
BMI ≤ 17.7	-0.2 (-1.7, 1.3)	0.78	-[b]	-[b]	-[b]

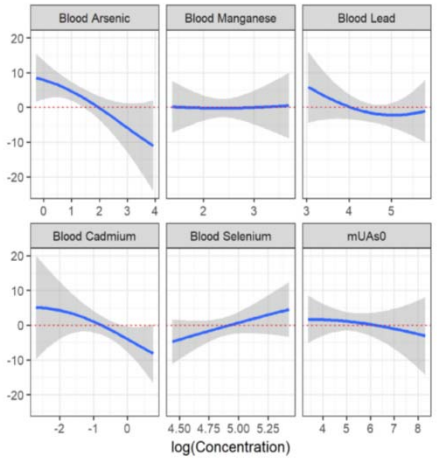
[a]β was estimated mean change in SBP for a-unit increase in the WQS index, adjusted for sex, age (years), and BMI.

[b] Weights were not given because the association between the weighted index and SBP was not statistically significant.

Chen Y et al, *Environmental Research*, 2019

Arsenic exposure and intellectual function in adolescents





Wasserman GA et al, *Environ Int, 2018*
Wasserman GA et al, *EHP*. 2007
Wasserman GA et al, *EHP*. 2011
Parvez F, et al, *EHP*, 2011
Wasserman GA, et al, *EHP* 2014

Arsenic and Pregnancy Outcomes in Bangladesh

Crude and adjusted odds ratios (95% CIs) for the associations between prenatal arsenic exposure and adverse pregnancy outcomes.

Model	Urinary total arsenic (µg/g creatinine)		
	17 – 555	556 – 3712	P-value
Any adverse pregnancy outcome			
Unadjusted	1 (ref)	1.53 (1.00, 2.35)	0.05
Adjusted for maternal age	1 (ref)	1.58 (1.02, 2.42)	0.04
Fully adjusted[a]	1 (ref)	1.59 (1.02, 2.46)	0.04
Stillbirth/spontaneous abortion			
Unadjusted	1 (ref)	1.50 (0.92, 2.45)	0.10
Adjusted for maternal age	1 (ref)	1.51 (0.93, 2.47)	0.10
Fully adjusted[a]	1 (ref)	1.57 (0.96, 2.56)	0.07
Stillbirth			
Unadjusted	1 (ref)	2.41 (1.00, 5.85)	0.05
Adjusted for maternal age	1 (ref)	2.41 (0.99, 5.85)	0.05
Fully adjusted[b]	1 (ref)	2.50 (1.04, 6.01)	0.05
Spontaneous abortion			
Unadjusted	1 (ref)	1.26 (0.72, 2.20)	0.41
Adjusted for maternal age	1 (ref)	1.27 (0.72, 2.24)	0.42
Fully adjusted[a]	1 (ref)	1.33 (0.76, 2.32)	0.32
Therapeutic/elective abortion			
Unadjusted	1 (ref)	1.67 (0.75, 3.73)	0.21
Adjusted for maternal age	1 (ref)	1.69 (0.75, 3.81)	0.21
Fully adjusted[a]	1 (ref)	1.58 (0.70, 3.56)	0.27

[a] Adjusted for maternal age (years), maternal education (years), BEST treatment assignment, and skin lesion severity.
[b] Adjusted for maternal age (years), maternal education (years), BEST treatment assignment, skin lesion severity, parity, and previous stillbirth.

Shih et al. *Environmental Research* 2017. 158: 456–461

Arsenic and Birth Outcomes in the US

Table 2
Adjusted expected change (95% confidence interval) for birth outcomes in relation to maternal 3rd-trimester urinary arsenic.

Arsenic exposure (μg/L)	n	Gestational age (weeks)[a]	Birthweight (g)[b]	Birth length (cm)[b]	Head circumference (cm)[b]	Ponderal index (kg/m^3)[b]
Total arsenic (n = 114)						
Per IQR (8.27) increase		0.06 (−0.03, 0.16)	1.95 (−21.75, 25.65)	0.28 (0.14, 0.42)	0.12 (0.04, 0.21)	−0.37 (−0.58, −0.17)
Q1 (≤4.00)	32	Ref	Ref	Ref	Ref	Ref
Q2 (4.01–7.55)	24	0.03 (−0.86, 0.92)	94.58 (−125.17, 314.33)	1.30 (−0.03, 2.63)	0.37 (−0.43, 1.17)	−1.19 (−3.14, 0.76)
Q3 (7.56–12.26)	33	0.08 (−0.76, 0.92)	85.79 (−121.21, 292.79)	1.66 (0.40, 2.91)	0.67 (−0.08, 1.43)	−1.94 (−3.78, −0.10)
Q4 (> 12.26)	25	0.24 (−0.66, 1.14)	87.71 (−133.66, 309.08)	2.21 (0.87, 3.55)	0.97 (0.16, 1.77)	−2.41 (−4.37, −0.44)
p for trend		0.61	0.45	0.001	0.02	0.01
DMA (n = 212)						
Per IQR (3.79) increase		−0.01 (−0.16, 0.14)	−10.67 (−64.31, 24.97)	0.40 (0.13, 0.66)	0.18 (0.02, 0.33)	−0.63 (−1.02, −0.25)
Q1 (≤1.93)	51	Ref	Ref	Ref	Ref	Ref
Q2 (1.94–3.50)	55	0.28 (−0.28, 0.83)	77.28 (−88.73, 243.29)	0.26 (−0.74, 1.26)	0.51 (−0.08, 1.10)	0.10 (−1.34, 1.55)
Q3 (3.51–5.72)	62	0.21 (−0.40, 0.81)	73.72 (−107.36, 254.80)	0.58 (−0.52, 1.67)	0.56 (−0.08, 1.20)	0.48 (−2.06, 1.10)
Q4 (> 5.72)	44	−0.08 (−0.74, 0.57)	−13.51 (−208.29, 181.27)	1.25 (0.07, 2.42)	0.65 (−0.04, 1.34)	−1.99 (−3.68, −0.29)
p for trend		0.69	0.81	0.03	0.09	0.01

[a] Models adjusted for urinary creatinine, maternal age, race/ethnicity, maternal education, income, pre-pregnancy BMI, infant sex, and number of live births.
[b] Model additionally adjusted for gestational age.

Shih et al. *Environmental Research* 2020. e109182

Arsenic and Birth Outcomes in the US

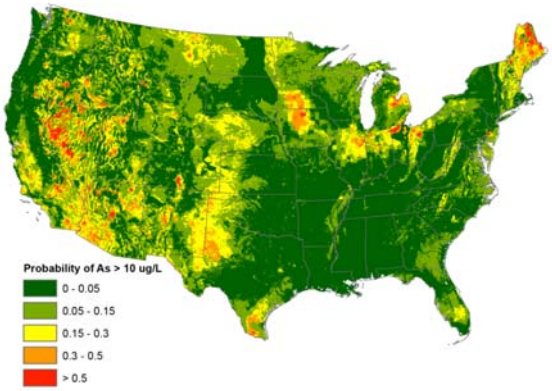
Table 3
Adjusted expected change (95% confidence interval) for birth outcomes in relation to maternal 3rd-trimester urinary arsenic, stratified by infant sex.

Per IQR (μg/L) increase	Gestational age (weeks)[a]	Birth weight (g)[b]	Birth length (cm)[b]	Head circumference (cm)[b]	Ponderal index (kg/m^3)[b]
Total arsenic (n = 114)					
Male infants (n = 57)	0.07 (−0.03, 0.16)	3.36 (−20.69, 27.41)	0.27 (0.13, 0.41)	0.11 (0.03, 0.20)	−0.34 (−0.55, −0.14)
Female infants (n = 57)	−0.05 (−0.46, 0.37)	−30.61 (−132.90, 71.67)	0.59 (−0.02, 1.19)	0.29 (−0.07, 0.66)	−1.14 (−2.01, −0.26)
p for interaction	*0.59*	*0.52*	*0.31*	*0.35*	*0.08*
DMA (n = 212)					
Male infants (n = 114)	0.05 (−0.10, 0.21)	−20.27 (−67.40, 26.88)	0.39 (0.11, 0.67)	0.19 (0.03, 0.36)	−0.60 (−1.01, −0.19)
Female infants (n = 98)	−0.44 (−0.84, −0.05)	−15.28 (−136.54, 105.98)	0.48 (−0.25, 1.20)	0.07 (−0.36, 0.49)	−0.89 (−1.94, 0.16)
p for interaction	*0.02*	*0.94*	*0.82*	*0.59*	*0.61*

[a] Models adjusted for urinary creatinine, maternal age, race/ethnicity, maternal education, income, pre-pregnancy BMI, infant sex, and number of live births.
[b] Model additionally adjusted for gestational age.

Shih et al. *Environmental Research* 2020. e109182

Arsenic Exposure in the United States



- Approximately 44.1 M people in the conterminous US use water from domestic wells
- Subset of this population with estimated arsenic concentration >10 µg/L is 2.1 M (4.8% of domestic well users)

Ayotte et al. Environ. Sci. Technol. 2017, 51, 12443−12454

Linking environmental and public health data to evaluate health effects of arsenic exposure from domestic and public supply wells

Powell Center

- Working Group supported by the John Wesley Powell Center for Analysis and Synthesis, funded by the U.S. Geological Survey
- Collaboration between USGS geologists/geochemists and public health researchers to evaluate the health effects of arsenic exposure in the United States (PIs: Argos, Ayotte, Gribble)
  - Goal 1: Update arsenic map for conterminous US
  - Goal 2: Evaluate health effects of arsenic exposure in US population
    - Individual-level birth outcomes (gestational age, birthweight) based on National Center for Health Statistics Birth Data for more than 10 million births in the US between 2014-2016

BiRCH cohort

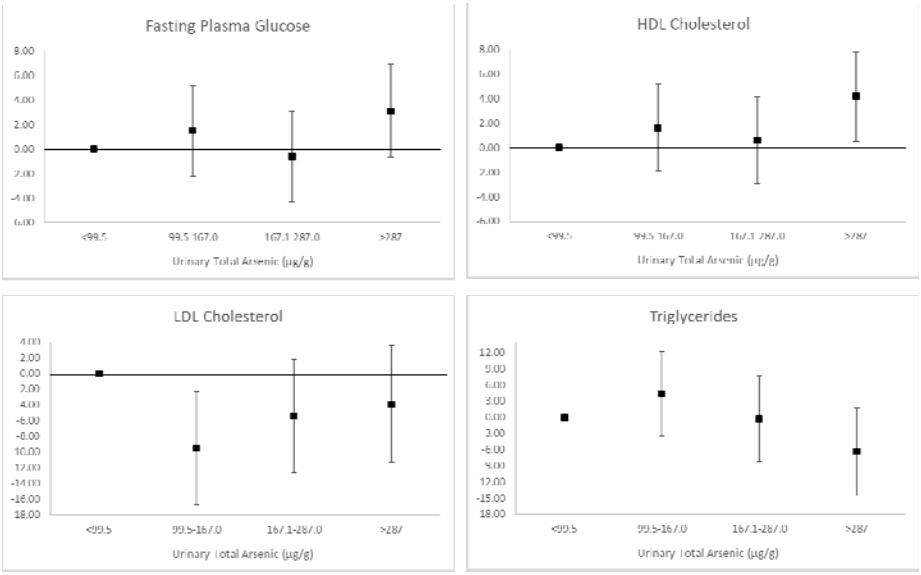
- **B**angladesh Env**i**ronmental **R**esearch in **C**hildren's **H**ealth (BiRCH; NIEHS R01 ES024423)
- Investigate the effects of in utero and early life arsenic exposure on thyroid and steroid levels, clinical characteristics, and DNA methylation in children
- 500 mother-child pairs enrolled
  - Pregnancies documented in the Health Effect of Arsenic Longitudinal Study (HEALS) cohort beginning in 2011
  - Children of HEALS females were formally enrolled into BiRCH at age 5-7 years (2014 -2016)
  - Clinical evaluation, laboratory-based evaluation, and baseline questionnaire implemented
    - Blood, spot urine, toenail clippings, saliva (including from both biological parents), naturally shed teeth

Selected Characteristics of BiRCH Cohort

Maternal Characteristics:	
Age, mean + SD	24.07 + 4.73
Educational status, n (%)	
No education	58 (11.6)
Up to primary	157 (31.4)
S.S.C	258 (51.6)
> H.S.C	27 (5.4)
Own land, n (%)	250 (50.0)
Own TV, n (%)	335 (67.0)
Delivery type, n (%)	
Natural delivery	379 (75.8)
Caesarean section	117 (23.4)
Forceps/instrumental delivery	4 (0.8)
Delivery place, n (%)	
Home, no trained attendant present	177 (35.4)
Home, trained midwife present	146 (29.2)
Medical facility	177 (35.4)
Spouse smoking during pregnancy, n (%)	211 (42.2)
Number of pregnancy, mean ± SD	3.14 ± 1.37
Ever had miscarriages, n (%)	124 (24.8)
Ever had stillbirth, n (%)	36 (7.2)

Child Characteristics:	
Age, mean ± SD	6.19 ± 0.68
Gender	
Male	254 (50.8)
Female	246 (49.2)
Twin pregnancy, n (%)	3 (0.6)
Breastfed, n (%)	500 (100.0)
Delivery size, n (%)	
Very small	15 (3.0)
Small	110 (22.0)
Usual/typical	336 (67.2)
Large	39 (7.8)
Health of child, n (%)	
Very healthy, no problems	8 (1.6)
Healthy, but a few minor problems	373 (74.6)
Sometimes quite ill	57 (11.4)
Almost always ill	62 (12.4)
Even been hospitalized, n (%)	77 (15.4)

Fasting Plasma Glucose and Blood Lipids



Genetic Susceptibility to Arsenic Exposure

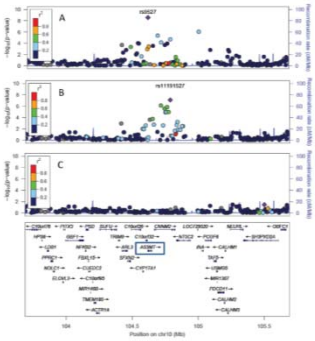


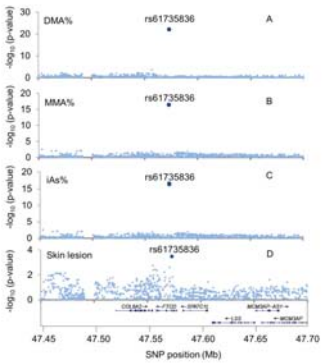
Table 2. Association between the 10q24.32 genotyped variants and arsenical skin lesion risk and SNP-arsenic interaction estimates.

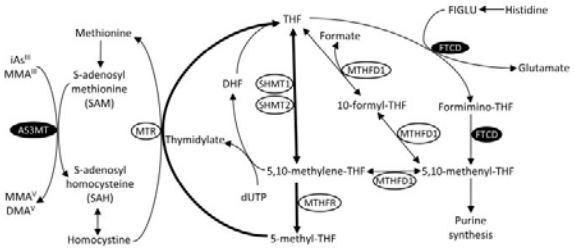
		MAF		Logistic regression[b]			ROADTRIPS[c]	Interaction with arsenic[d]	
SNP (MA[a])	Association with arsenic metabolite	Cases (n = 1,085)	Controls (n = 1,794)	OR	CI	P-value	P-value	Water arsenic P-value	Urine arsenic P-value
rs9527 (A)	↓ DMA%	0.108	0.076	1.42	1.16–1.72	0.0005	0.0005	0.004	0.02
rs1191527 (A)	↑ DMA%	0.152	0.163	0.96	0.89–1.29	0.38	0.33	0.72	0.38
rs4919694 (G)	↑ MMA%	0.103	0.098	1.07	0.89–1.29	0.46	0.60	0.87	0.34
rs4290163 (A)	↓ MMA%	0.427	0.434	0.96	0.82–112	0.59	0.62	0.99	0.23
rs11191659 (A)	↑ MMA%	0.058	0.042	1.32	1.02–1.72	0.04	0.02	0.001	<0.0001

[a]MA, minor allele.
[b]Each Logistic Regression model includes one SNP, adjusting for age and sex.
[c]The ROADTRIPS case-control test does not allow multivariate modeling (i.e., no adjustments), but accounts for cryptic relatedness.
[d]Interaction P-values are from mixed linear models that account for relatedness among subjects. Interactions are on the additive scale and are calculated using data on 69 cases and incident 700 controls.
doi:10.1371/journal.pgen.1002522.t002

Pierce et al. (2012) *PLOS Genet* 8(2):e1002522

Genetic Susceptibility to Arsenic Exposure





Pierce et al. (2019) *PLOS Genet* 15(3):e1007984.

Arsenic and DNA Methylation

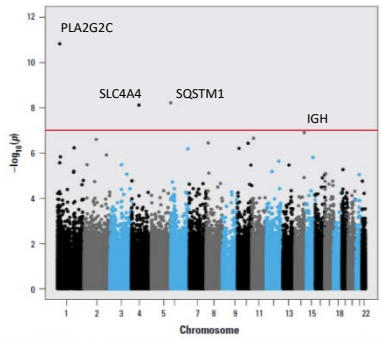


Figure 1. Manhattan plot for epigenome-wide association results for blood arsenic concentration. The horizontal red line corresponds to the significance threshold $p = 1 \times 10^{-7}$. Colors are used only to differentiate chromosomes.

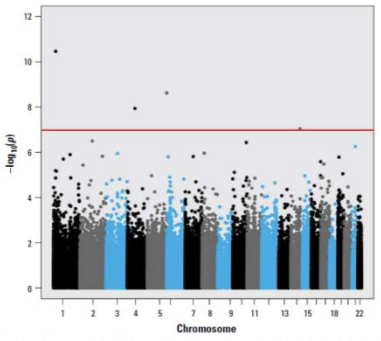
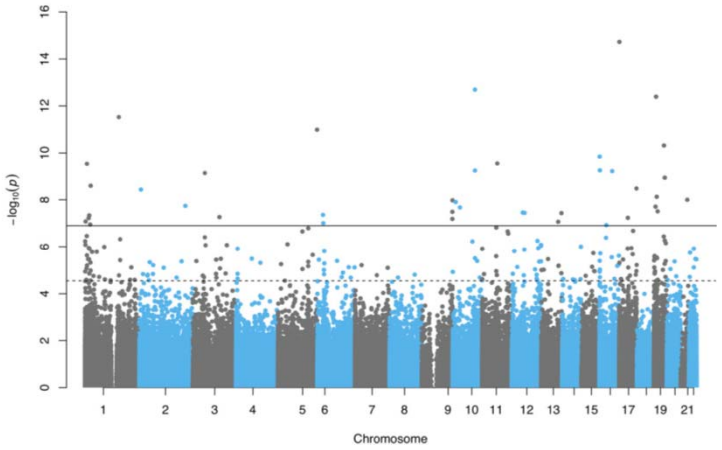


Figure 2. Manhattan plot for epigenome-wide association results for urinary total arsenic concentration. The horizontal red line corresponds to the significance threshold $p = 1 \times 10^{-7}$. Colors are used only to differentiate chromosomes.

Argos et al. (2015) *Environ Health Perspect* 123:64-71.

Meta-Analysis of Arsenic and DNA Methylation



Demanelis et al. (2019) *Environ Health Perspect* 127:57011.

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