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Arsenic, Blood Pressure, and Hypertension in the Strong Heart Family Study

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Environmental Health
2017

Abstract

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By Claire Mattison

Purpose: Arsenic is a well-known carcinogen and has been associated with adverse health effects, including cardiovascular disease. However, the association of arsenic with blood pressure at moderate exposure levels, such as those that occur in the Western United States, remains unclear. The aim of this study was to assess the cross-sectional associations between biomarkers of arsenic exposure and systolic blood pressure (SBP), diastolic blood pressure (DBP), and hypertension prevalence (defined as SBP ≥140 mm Hg, DBP ≥90 mm Hg, or taking hypertension medication) in the Strong Heart Family Study, a family-based cohort of American Indians.

Methods: We included 2,086 Strong Heart Family Study participants at their baseline visit (1998-1999 or 2001-2003) who had complete data on urine arsenic species, urine creatinine, blood pressure, hypertension medication use, sex, age, body mass index (BMI), smoking status, drinking status, diabetes status, educational attainment, study center (Arizona, Oklahoma, or North and South Dakota), and recent physical activity. Our biomarker of inorganic arsenic exposure was the sum of inorganic and methylated arsenic species in urine. We used generalized estimating equations with exchangeable correlation structure conditional on family membership to estimate the association of a doubling of arsenic exposure biomarker levels with SBP or DBP (linear regressions) or hypertension prevalence (Poisson regressions), adjusting for urine creatinine, urine arsenobetaine, and measured confounders.

Results: The associations of a two-fold increase in inorganic and methylated urine arsenic species were +0.74 mm Hg (95% CI: +0.05, +1.44) for SBP, +0.49 mm Hg (95% CI: -0.03, +1.01) for DBP, and a prevalence ratio of 1.10 (95% CI: 0.99, 1.23) for hypertension, after adjustment for urine creatinine, urine arsenobetaine, and potential confounders, and accounting for clustering by family.

Conclusions: This study suggests a modest cross-sectional association of arsenic exposure biomarkers with blood pressure. However, potential for residual confounding, particularly from dietary determinants of blood pressure associated with routes of arsenic exposure, cannot be ruled out. A prospective study taking into account the effect of diet on both arsenic exposure and blood pressure is needed to better quantify any association that may exist between arsenic and blood pressure within this population.

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Acknowledgements

I would like to acknowledge the Strong Heart Study and the Strong Heart Family Study, particularly to the participating tribes, for allowing me to analyze this data. I am especially grateful to Ana Navas-Acien, Fawn Yeh, Ying Zhang, Mandy Fretts, and Shelley Cole who helped me develop this project and provided advice and feedback throughout this process. I would like to thank my thesis advisor, Dr. Matthew Gribble, for guiding me through the process of working with data from the Strong Heart Family Study and his assistance with my analyses. As well, I would like to thank my faculty advisor, Dr. Yang Liu. Finally, I want to thank my friends and family who have given me their support and advice throughout this entire process.

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Introduction

Arsenic is a well-known human carcinogen and may be a risk factor for diabetes and other adverse health outcomes (IARC, 2004; Moon et al., 2012; Navas-Acien et al., 2005; States et al., 2009). Many studies have found an association between arsenic and cardiovascular disease (Moon et al., 2012; Moon et al., 2013; Tsuji et al., 2014). People can be exposed to arsenic through drinking water, food, dust, air, and occupational exposures (Agency for Toxic Substances and Disease Registry, 2007; O'Rourke et al., 1999a).

The current United States arsenic drinking water standard is 10 µg/L (parts per billion), which was lowered from 50 µg/L in 2001. At that time, about 10% of US water systems had levels >10 µg/L and less than half of the systems had levels <1 µg/L (EPA, 2001; Welch, 2000). Much of the Western United States, and some areas of the Midwest and Northeast, have naturally occurring high levels of arsenic in their groundwater (USGS, 2000). Worldwide, about 100 million people are exposed to drinking water that contains >50 µg/L arsenic ((WHO), 2001; Alaerts et al., 2001).

In the United States, populations with >10 µg/L arsenic in their tap water obtain about 30% of their arsenic exposure from their diet, and those with tap water ≤10 µg/L obtain about 54-85% of their arsenic intake from their diet (Kurzius-Spencer et al., 2014). Populations in the Western United States have the highest exposure to arsenic from their diets (Moschandreas et al., 2002).

Hypertension, or high blood pressure, is a risk factor for both heart disease and stroke, the first and fourth leading causes of death in the United States, respectively (Gillespie and Hurvitz, 2013). In the United States, 29.6% of adults have hypertension.

The prevalence of hypertension is higher in those who are older, diabetic, or overweight. In 2009 alone, high blood pressure was the primary cause of death for nearly 62,000 Americans (Go et al., 2013).

Many cross sectional and ecologic studies have found significant associations between arsenic and blood pressure and hypertension (Bosnjak et al., 2008; Dastgiri et al., 2010; Hossain et al., 2012; Kwok et al., 2007; Mazumder et al., 2012; Mordukhovich et al., 2012). In Taiwan and Bangladesh, studies have described a dose-response relationship between higher levels of long-term arsenic exposure and increased hypertension risk (Chen et al., 2007; Rahman et al., 1999). Prospective cohorts have found associations between arsenic exposure and increased systolic and diastolic blood pressure (Jiang et al., 2015; Wang et al., 2011). Hypertension and increased systolic blood pressure have been associated with low-level arsenic exposure from drinking water and occupational exposure (Chen et al., 2007; Jensen and Hansen, 1998). A person's genetics (Ameer et al., 2015; Chen et al., 2012; Farzan et al., 2015; Gong and O'Bryant, 2012; Hsueh et al., 2005) and their ability to metabolize arsenic (Huang et al., 2007; Li et al., 2013b; Li et al., 2015) have been found to modify the relationship between arsenic exposure and blood pressure.

Despite these findings, the association between arsenic exposure, hypertension, and blood pressure is not clear. In 2011, a systematic literature review found an increased odds of hypertension between the highest and lowest arsenic exposures, but a null association for moderate to high arsenic exposure and the review was limited by the small number (11) of studies identified (Abhyankar et al., 2012). In 2012, a meta-analysis on chronic arsenic exposure and hypertension found similarly mixed results but only

analyzed eight studies due to its restriction to studies on chronic arsenic exposure and its exclusion of two studies where the full text was unavailable. (Abir et al., 2012). Other studies have found no relationship between arsenic and blood pressure or hypertension (Butts et al., 2015; T. Casale and R. Giubilati, 2015). An examination of NHANES data from 2003-2008, examining low to moderate levels of arsenic exposure, found no relationship between arsenic and blood pressure (Jones et al., 2011). Other cross sectional analyses of NHANES data from 2009-2012 and 2011-2012 found associations only between dimethylarsinic acid (a metabolite of arsenic) and blood pressure (Shiue, 2014a; Shiue, 2014b).

Within the Strong Heart Study, a cohort study among participating American Indian communities in Arizona, Oklahoma, and North and South Dakota (Lee et al., 1990), arsenic has been associated with cancer and cardiovascular disease (García-Esquinas et al., 2013; Moon et al., 2013) as well as diabetes in cross-sectional, (Gribble et al., 2012) but not prospective, analyses (Kuo et al., 2015). The Strong Heart Family Study is an expansion of the Strong Heart Study (North et al., 2003). The primary objective of this analysis was to determine if there is a cross-sectional relationship between arsenic and arsenic metabolism exposures, and systolic blood pressure, diastolic blood pressure, or hypertension outcomes in the Strong Heart Family Study.

Methods

Study Population

The Strong Heart Study (SHS) is a long-term cohort study of cardiovascular disease in participating American Indian communities from Arizona, Oklahoma and North and South Dakota funded by the National Heart, Lung, and Blood Institute. The study began in 1989 and recruited 4,549 participants. The Strong Heart Family Study (SHFS) is an extension of the original cohort that began in 1998 (North et al., 2003). Extended families, including parents, spouses, offspring, spouses of offspring, and grandchildren, of original SHS cohort members were recruited into the SHFS. To ensure the families were sufficiently large, only families with at least 5 living siblings and at least 12 living offspring ≥18 years old were recruited (North et al., 2003). Methods for recruitment and protocols for the visits, which included a personal interview, physical examination, and laboratory tests, have been previously described (Lee et al., 1990; North et al., 2003). The data analyzed was collected at participants' baseline SHFS visit (1998-1999 or 2001-2003). All participants gave informed consent, and the study and protocols were reviewed by the participating tribes, the Indian Health Service, and Institutional Review Boards (Lee et al., 1990; North et al., 2003).

Exposure Assessment

Arsenic was measured by high performance liquid chromatography-inductively coupled mass spectrometry (HPLC-ICMPS) from urine collected at clinical visits. Inorganic arsenic (iAs), monomethylarsonous acid (MMA), and dimethylarsinous acid (DMA), are metabolites of arsenic measured in urine (Scheer et al., 2012). The percentage of each metabolite from total arsenic was calculated (%iAs, %MMA, %DMA), and principal component analysis was used to group participants based on

similar arsenic toxicokinetics. Urine creatinine information was collected to allow for adjustment for urine dilution. Blood pressure was measured 3 times at the clinical visit, and the average of the last 2 measurements was used for analyses. Demographic characteristics, lifestyle, and medical history were collected during the interviews using a standard questionnaire (North et al., 2003).

Confounder and Moderator Measures

Hypertension status was defined as systolic blood pressure (SBP) ≥140 mm Hg, diastolic blood pressure (DBP) ≥90 mm Hg, or taking hypertension medication. Hypertension treatment status was defined as no hypertension, hypertension with treatment, and hypertension without treatment. Diabetes was defined as HbA1c ≥6.5, fasting glucose ≥126, history of diabetes, taking oral hypoglycemic medications, or taking insulin. Our physical activity index was the mean across 7 days of pedometer readings for participants with ≥3 days of pedometer data. We recoded the family ID variable for clustering.

We considered both total urine arsenic and a more specific biomarker of inorganic arsenic exposure (i.e., the sum of inorganic and methylated arsenic species in urine) as our exposure variables. We used the first principal component of %iAs, %MMA, and %DMA as a single-number index to summarize inter-individual differences in inorganic arsenic toxicokinetics.

Potential confounders included sex (male/female), age (in years), body mass index (BMI), physical activity (mean 7-day pedometer usage), smoking status (current/ever/never), drinking status (current/ever/never), diabetes status (yes/no/pre or gestational diabetes), educational attainment (less than high school, some high school,

high school diploma, more than high school), study center (Arizona, Oklahoma, or North and South Dakota), kidney function, measured by estimated glomerular filtration rate (eGFR) using original creatinine, arsenobetaine (µg/L), and urine creatinine (mg/dL).

Analyses

Members of the source population with missing data on exposure, confounders, blood pressure, or hypertension outcomes were excluded from analyses. Our data set contained complete data from n=2424 people, n=141 from Phase III and n=2283 from Phase IV of the SHFS. Physical activity was only measured in Phase IV, and n=2086 participants were available for complete case analyses including physical activity measures.

Statistics were performed in Stata-SE,14.2, (StataCorp, LP, College Station, Texas). We analyzed the associations among participants at their respective baseline visit with available urine arsenic species measurements. We fit generalized estimating equation (GEE) models, with exchangeable correlation structure conditional on family membership, to model arsenic's cross-sectional relationships with systolic and diastolic blood pressure (linear regression) and hypertension prevalence (Poisson regression).

Arsenic exposure measurements included a doubling of inorganic and methylated arsenic, quartiles of inorganic and methylated arsenic, a doubling of total arsenic, quartiles of total arsenic, a measure of arsenic toxicokinetics (the first principal component summarizing %iAs, %MMA, and %DMA), and the interaction between the measure of arsenic toxicokinetics and a doubling of total arsenic. The outcomes were analyzed individually against systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), and hypertension prevalence.

For all three outcomes measures (systolic blood pressure, diastolic blood pressure, and hypertension), we ran 5 sequentially adjusted models. Model 1 was adjusted only for urine creatinine (for all exposures except arsenic toxicokinetics measure) and arsenobetaine (both coded as restricted cubic splines), to account for urine dilution and seafood consumption. In Model 2, we controlled for additional potential confounders including sex, age, BMI, educational attainment, diabetes status, smoking status, drinking status, and kidney function. In Model 3, we further adjusted for study center (Arizona, Oklahoma, North and South Dakota). In Model 4, we further adjusted for physical activity. Model 5 controlled for the same confounders as Model 4, but did not adjust for urine creatinine. In all models, all continuous confounders (urine creatinine, arsenobetaine, age, BMI, kidney function, physical activity) were fit as restricted cubic splines. We used Wald tests of interaction terms (α=0.05, df=2) to examine heterogeneity of the arsenic-blood pressure association by hypertension medication status (no hypertension, hypertension with treatment, or hypertension without treatment), diabetes status (yes/no/pre or gestational diabetes), and study center (Arizona, Oklahoma, or North and South Dakota). Where significant interactions were detected, stratified models were run.

Results

Demographics

Our final sample had n=699 participants from Arizona, n=813 participants from Oklahoma, and n=912 participants from North and South Dakota for a total of n=2,424. The prevalence of hypertension was 21.62%. The population was 60.6% female and 39.4% male, and 26.5% of males had hypertension as compared to only 18.4% of females. Participants with hypertension tended to be older, have a higher fasting glucose, have a higher BMI, exercise less, and have a lower eGFR (Table 1).

Males tended to have higher arsenic concentrations, and those ≥50 years old had lower levels of arsenic (Table 2). Participants from Arizona had higher levels of arsenic than those from Oklahoma or the Dakotas (Table 2). Arsenic decreased as education increased, increased with BMI, and those with diabetes had higher arsenic than those without. Arsenobetaine, a measure of arsenic from seafood, did not vary according to demographic factors in our population (Navas-Acien et al., 2011). Tables 3 and 4 break down arsenic metabolism measures and systolic and diastolic blood pressure by various demographic factors, respectively.

Systolic Blood Pressure

In the fully adjusted GEE model controlling for all confounders and accounting for clustering by family, a doubling of total arsenic was associated with a 0.91 mm Hg increase in systolic blood pressure (95% CI: 0.18, 1.65, Table 7), and a doubling of inorganic and methylated arsenic species was associated with a 0.74 mm Hg increase in systolic blood pressure (95% CI: 0.05, 1.44, Table 7). The highest quartile of total arsenic was associated with a 3.61 mm Hg increase in systolic blood pressure when compared to the lowest quartile (95% CI: 1.40, 5.82, Table 7). After controlling for confounders,

quartiles of the sum of inorganic and methylated arsenic and the principal component summarizing arsenic toxicokinetics were not associated with systolic blood pressure (Table 7). When stratified by study center, inorganic arsenic quartiles were not associated with systolic blood pressure (Table 9).

Diastolic Blood Pressure

In the fully adjusted GEE model controlling for all confounders and accounting for clustering by family, a doubling of total arsenic was associated with a 0.75 mm Hg increase in diastolic blood pressure (95% 0.19, 1.30, Table 8) and a doubling of inorganic arsenic was associated with a 0.49 mm Hg increase in diastolic blood pressure (95% CI: -0.03, 1.01, Table 8). Diastolic blood pressure increased 1.35 mm Hg (95% CI: -0.04, 2.78) when comparing the 3rd quartile of total arsenic to the 1st quartile and increased 2.85 (95% CI: 1.19, 4.51) mm Hg when comparing the 4th quartile of total arsenic to the 1st quartile (Table 8). Inorganic and methylated arsenic quartiles were not associated with diastolic blood pressure. A higher principle component score for arsenic toxicokinetics was associated with a lower diastolic blood pressure (-0.31 mm Hg, 95% CI: -0.61, -0.003, Table 8). When stratified by study center, the 2nd quartile of inorganic and methylated arsenic was associated with a -2.58 mm Hg (95% CI: -4.26, -0.91) decrease in diastolic blood pressure when compared to the 1st quartile in North and South Dakota (Table 10).

Hypertension

In the fully adjusted GEE model controlling for all confounders and accounting for clustering by family, a doubling of total arsenic in urine was associated with a hypertension prevalence ratio of 1.11 (95% CI: 0.98, 1.24, Table 5). A doubling of the

sum of inorganic and methylated arsenic species was associated similarly with a hypertension prevalence ratio of 1.10 (95% CI: 0.99, 1.23, Table 5). Quartiles of the inorganic exposure biomarker (e.g., the sum of inorganic and methylated arsenic species) were not significantly associated with hypertension prevalence. The principal component score reflecting arsenic toxicokinetics was also not associated with hypertension prevalence (Table 5).

When stratified by study center, there was no association between arsenic exposure and hypertension prevalence in Oklahoma (Table 6). However, the prevalence ratios comparing the 4^{th} quartile of inorganic arsenic to the 1^{st} quartile in Arizona (PR: 2.64, 95% CI: 0.88, 7.92, Table 6) and North and South Dakota (PR: 1.64, 95% CI: 0.94, 2.86, Table 6) were stronger than the pooled estimate (PR: 1.23, 95% CI: 0.87, 1.73, Table 5).

Discussion

The cross-sectional associations of a doubling of inorganic and methylated arsenic species in urine were +0.74 mm Hg (95% CI: +0.05, +1.44) for systolic blood pressure, +0.49 mm Hg (95% CI: -0.03, +1.01) for diastolic blood pressure, and a prevalence ratio of 1.10 (95% CI: 0.99, 1.23) for hypertension, after adjustment for urine creatinine, urine arsenobetaine, and potential confounders, and accounting for clustering by family. Our measure of arsenic metabolism was associated with lower diastolic blood pressure but not with systolic blood pressure or hypertension. There was no evidence for effect modification by blood pressure medication use or diabetes status. When stratified by study center, the associations were generally stronger in Arizona and the Dakotas, and not apparent in Oklahoma. These results suggest a modest cross-sectional association of arsenic exposure biomarkers with blood pressure.

This study has many limitations. For one, it is only a cross-sectional study and does not address the temporality of the participant's arsenic exposure as it relates to their development of hypertension or blood pressure. The urine arsenic measures were from a single urine sample. We did not control for diet, which is both a potential route of arsenic exposure, and a factor that can affect blood pressure. Our physical activity variable was only measured for one-week in Phase IV, leaving out members whose baseline visit was at Phase III and the presence of a pedometer could have increased participants' physical activity. These limitations leave open the possibility of residual confounding. When we accounted for clustering by family using an exchangeable covariance structure, we treated family members as if they were all equally related (e.g., siblings were treated the same as cousins). Our index (principal component of the % arsenic species) of arsenic

toxicokinetics was a rough measure of arsenic metabolism groupings and was limited in its ability to measure arsenic metabolism and its potential modification of the relationship between arsenic and blood pressure. Finally, we do not have any direct information on the sources of arsenic exposure in this population.

In this study, there may only be a positive association of arsenic exposure and blood pressure at higher levels of arsenic. In our analyses, only the highest quartiles of inorganic or total arsenic showed an association with blood pressure, and when stratified, the prevalence ratios and coefficients were higher in Arizona, the study center with the highest arsenic exposure levels. Other studies have found a similar pattern. A study in China found a significant correlation between arsenic and blood pressure at all arsenic levels, but a relationship with hypertension only above 50 µg/L of arsenic (Li et al., 2013a). Another cross sectional study found a relationship between arsenic and hypertension and blood pressure, only after 50 years of exposure to <50µg/L of arsenic (Zhang et al., 2013).

This pattern may be due to the mechanism through which arsenic exposure impacts blood pressure. Proposed mechanisms for an arsenic-blood pressure association include: oxidative stress, reduction of anti-oxidative defense systems, and vasoconstriction (Balakumar and Kaur, 2009) and a study in Taiwan found that genes that destroy reactive oxygen species modify the dose-response relationship between arsenic and hypertension (Chen et al., 2012). It may be that there is a threshold level of arsenic exposure or time exposed to arsenic that is necessary for these adverse impacts on the circulatory system to result in higher blood pressure or hypertension.

One way populations are exposed to inorganic arsenic is through natural arsenic contamination of drinking water (Agency for Toxic Substances and Disease Registry, 2007). In the United States, drinking water contains >10 µg/L arsenic (the EPA threshold) in parts of the Southwest, Midwest, and Northeast (Focazio, 2000). The National Human Exposure Assessment Survey in Arizona (NHEXAS –AZ) study found arsenic in 100% of tap water samples taken but also found that food, soil, and dust were other possible routes of exposure in populations in Arizona (O'Rourke et al., 1999a; O'Rourke et al., 1999b).

An analysis of the NHEXAS-AZ population and the Arizona Border Survey found that in households with tap water ≤10 µg/L, 93% of the arsenic exposure came from dietary intake (Kurzius-Spencer et al., 2013). Seafood is a major source of dietary arsenic exposure. However, in our study population, concentrations of arsenobetaine (arsenic from seafood intake) were low, indicating low seafood consumption. Other food items that could contribute to arsenic exposure in our population include coffee, tea, rice, legumes, seeds, nuts, meat, poultry, and grain products (Moschandreas et al., 2002; Rey deCastro et al., 2014; Tao and Michael Bolger, 1999).

This population is likely exposed to inorganic arsenic through both their drinking water and their diets, and this study shows that inorganic arsenic exposure may have a modest impact on their blood pressure and hypertension prevalence. This study can help inform tribal leadership on drinking water quality standards and diet recommendations within their communities to reduce inorganic arsenic exposure.

Conclusions

Our study shows a modest relationship between arsenic exposure and increased blood pressure and hypertension prevalence. As well, our results suggest that these associations may be seen at higher levels of arsenic exposure. However, our study was limited by its cross-sectional design and the potential for residual confounding, particularly from dietary determinants of blood pressure and arsenic exposure.

To better understand the relationship between arsenic and blood pressure in the Strong Heart Family study, a prospective study that takes into account potential confounding by dietary variables should be conducted. This would help ascertain the temporality of the relationship between arsenic exposure and changes to blood pressure and hypertension and address the potential residual confounding from our lack of data on diet.

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Tables:

	Without Hypertension			With Hypertension			
	No.	**%**	**Mean (SD)**	**No.**	**%**	**Mean (SD)**	**p-value**
Sex*							<0.0001
Male	702	36.95		253	48.28		
Female	1198	63.05		271	51.71		
Age, years*			32.85 (13.69)			47.01 (16.21)	<0.0001
Region*							<0.0001
Arizona	567	29.84		132	25.19		
Oklahoma	585	30.79		228	43.51		
North and South Dakota	748	39.37		164	31.30		
Education*							<0.0001
Less than High School	127	6.68		33	6.30		
Some High School	616	32.42		110	20.99		
High School Diploma	645	33.95		205	39.12		
Some College	512	26.95		176	33.59		
Smoking*							0.001
Never	828	43.58		232	44.27		
Former	355	18.68		132	25.19		
Current	717	37.74		160	30.53		
Drinking							0.177
Never	208	10.95		54	10.31		
Former	461	24.26		148	28.24		
Current	1231	64.79		322	61.45		
Diabetes Status*							0.002
Yes	1809	95.21		488	93.13		
Gestational/Pre-Diabetes	50	2.63		10	1.91		
No	41	2.16		26	4.96		
Fasting Glucose*			92.95 (10.21)			98.11 (10.95)	<0.0001
BMI*			31.19 (7.86)			33.36 (7.08)	<0.0001
Urine Creatinine			1.59 (0.93)			1.53 (0.97)	0.1514
Blood Pressure							
Systolic*			115.73 (10.62)			138.53 (16.21)	<0.0001
Diastolic*			73.48 (8.89)			85.97 (11.99)	<0.0001
Pedometer Steps*			6341 (3962)			5433 (3605)	<0.0001
eGFR *			98.22 (21.85)			87.98 (23.26)	<0.0001
TOTAL	**1900**	**78.38**	--	**524**	**21.62**	--	--

Table 1. Demographic Characteristics by Hypertension Status at Baseline
* Denotes statistical difference between groups either by 2 sample t-test or Pearson's chi-square (α=0.05)

	Total Arsenic			Sum Inorganic Arsenic and Methylated Arsenic			Arsenobetaine			
Percentile	**25th**	**Median**	**75th**	**25th**	**Median**	**75th**	**25th**	**Median**	**75th**	**TOTAL (N)**
Sex										
Male	5.9	9.98	17.28	4.17	6.9	11.94	0.33	0.51	1.03	955
Female	5.64	9.49	16.43	3.76	6.54	11.2	0.30	0.47	1.04	1469
Age										
<18	6.49	9.9	17.68	4.47	7.57	13.19	0.33	0.45	0.69	273
18-35	6.32	10.46	18.46	4.53	7.55	12.53	0.31	0.50	1.00	974
35-50	5.58	9.66	15.69	3.71	6.40	10.97	0.29	0.51	1.24	748
>50	4.53	7.96	13.40	2.94	5.28	8.93	0.29	0.47	1.26	429
Region										
Arizona	8.87	14.73	24.84	6.31	10.46	17.40	0.32	0.51	1.15	699
Oklahoma	5.10	7.94	12.23	3.33	5.32	8.32	0.34	0.53	1.11	813
North and South Dakota	5.25	8.465	14.82	3.53	5.99	10.18	0.28	0.44	0.88	912
Education										
Less than High School	6.67	11.62	22.45	4.73	8.92	16.51	0.29	0.46	0.85	160
Some High School	6.35	10.91	19.57	4.41	7.81	14.07	0.31	0.46	0.83	726
High school Diploma	5.74	9.16	15.21	3.9	6.26	10.56	0.29	0.49	1.00	850
Some College	5.32	8.85	14.07	3.41	5.90	9.57	0.34	0.54	1.33	688
Smoking										
Never	5.98	9.65	16.81	4.04	6.70	11.51	0.32	0.50	1.08	1060
Former	5.66	9.09	16.14	3.53	5.95	10.69	0.33	0.53	1.31	487
Current	5.64	9.96	17.09	3.98	6.90	11.81	0.28	0.46	0.93	877
Drinking										
Never	6.00	9.50	16.24	3.65	6.45	11.10	0.31	0.50	0.90	262
Former	5.56	9.22	14.83	3.79	6.23	10.36	0.30	0.49	1.15	609
Current	5.87	9.84	17.83	4.05	6.90	11.99	0.31	0.49	1.02	1553
Diabetes Status										
Yes	6.35	11.50	20.1	5.08	8.89	13.33	0.31	0.44	0.98	67
Gestational/Pre-Diabetes	6.03	10.87	19.51	3.69	7.475	13.48	0.37	0.58	1.87	60
No	5.77	9.57	16.52	3.91	6.60	11.41	0.31	0.49	1.01	2297
BMI										
Normal (<25)	5.19	8.54	14.59	3.31	5.78	10.23	0.29	0.47	0.77	478
Overweight (25-30)	5.61	8.97	15.63	3.77	6.16	10.56	0.31	0.51	1.06	635
Obese (>30)	6.20	10.32	18.60	4.18	7.40	12.69	0.31	0.50	1.17	1311
TOTAL	**5.78**	**9.66**	**16.78**	**3.93**	**6.64**	**11.53**	**0.31**	**0.49**	**1.04**	**2424**

Table 2. Arsenic Biomarkers according to Demographic Characteristics at Baseline

	Percent Inorganic Arsenic			Percent MMA			Percent DMA			
Percentile	**25th**	**Median**	**75th**	**25th**	**Median**	**75th**	**25th**	**Median**	**75th**	**TOTAL (N)**
Sex										
Male	7.94	11.26	16.00	12.31	15.66	19.13	65.74	72.35	78.55	955
Female	5.71	8.72	12.53	9.83	12.99	16.53	71.32	77.39	83.37	1469
Age										
<18	7.79	11.61	15.92	12.51	16.07	19.81	64.84	74.73	78.57	273
18-35	7.39	10.66	14.86	11.18	14.48	18.08	67.28	74.23	79.73	974
35-50	6.22	9.26	13.38	10.16	13.12	16.74	69.92	76.92	82.87	748
>50	4.61	7.28	11.21	9.52	13.13	16.98	72.37	79.05	84.29	429
Region										
Arizona	7.63	10.76	15.20	9.97	12.88	16.26	69.08	75.23	81.09	699
Oklahoma	5.45	8.29	12.35	10.48	13.77	17.91	70.34	76.96	83.27	813
North and South Dakota	6.73	10.04	14.46	11.56	14.96	18.44	67.42	74.40	80.58	912
Education										
Less than High School	7.27	11.01	14.17	10.15	13.93	18.01	69.20	74.91	80.19	160
Some High School	6.92	10.61	15.54	10.99	14.51	18.15	67.03	74.35	80.49	726
High School Diploma	6.65	9.78	13.77	10.84	14.09	17.87	69.07	75.17	81.19	850
Some College	5.79	8.51	12.20	10.13	13.24	16.93	70.73	77.55	83.41	688
Smoking										
Never	6.31	9.51	13.33	10.74	13.92	17.79	69.49	75.92	81.67	1060
Former	6.18	9.06	13.61	9.87	13.05	16.98	69.71	76.97	83.46	487
Current	6.93	10.37	14.92	10.95	14.39	18.04	67.42	74.21	80.65	877
Drinking										
Never	5.84	9.44	14.38	10.97	14.25	18.51	67.51	75.05	82.18	262
Former	6.01	8.89	12.41	10.14	13.65	17.20	70.76	76.96	82.94	609
Current	6.87	10.16	14.48	10.79	14.07	17.79	68.09	74.89	80.88	1553
Diabetes Status										
Yes	5.89	9.08	13.26	9.23	11.27	14.92	72.75	78.07	84.21	67
Gestational/Pre-Diabetes	6.13	8.85	12.87	10.66	12.78	15.07	71.00	77.39	81.82	60
No	6.52	9.81	14.01	10.64	14.06	17.87	68.53	75.38	81.57	2297
BMI										
Normal (<25)	7.71	11.43	16.80	13.12	17.16	20.66	63.26	71.12	77.05	478
Overweight (25-30)	6.25	9.78	14.21	10.98	14.81	18.18	67.71	74.87	81.09	635
Obese (>30)	6.29	9.18	13.03	9.85	12.80	15.88	81.31	77.40	83.02	1311
TOTAL	**6.49**	**9.78**	**13.98**	**10.58**	**13.95**	**17.71**	**68.65**	**75.57**	**81.65**	**2424**

Table 3. Measures of arsenic toxicokinetics, according to participant demographics

	Systolic Blood Pressure			Diastolic Blood Pressure			
Percentile	**25th**	**Median**	**75th**	**25th**	**Median**	**75th**	**TOTAL (N)**
Sex							
Male	115	124	133	71	79	86	955
Female	108	115	126	68	74	81	1469
Age							
<18	107	112	119	61	68	74	273
18-35	109	116	125	68	75	82	974
35-50	111	120	131	73	79	86	748
>50	119	130	140	71	77	84	429
Region							
Arizona	109	117	126	69	76	83	699
Oklahoma	113	124	134	69	77	85	813
North and South Dakota	109	117	127	69	75	82	912
Education							
Less than High School	108	118	129	67	75	83	160
Some High School	108	115.5	126	66	73	80	726
High School Diploma	112	121	131	71	77	85	850
Some College	111	120	132	70.5	77	85	688
Smoking							
Never	109	118	128	68	76	83	1060
Former	112	122	132	70	78	85	487
Current	110	118	129	69	76	83	877
Drinking							
Never	108	117	128	65	72	80	262
Former	111	119	130	69	76	82	609
Current	110	118	129	69	76	84	1553
Diabetes							
Yes	112	125	134	72	79	86	67
Gestational/Pre-Diabetes	108	116.5	125.5	69.5	74.5	82	60
No	110	118	129	69	76	83	2297
BMI							
Normal (<25)	106	112	122	63	70	78	478
Overweight (25-30)	110	118	130	70	77	83	635
Obese (>30)	112	121	131	71	78	85	1311
TOTAL	**110**	**119**	**129**	**69**	**76**	**83**	**2424**

Table 4. Blood Pressure measures by Demographic Characteristics at Baseline

	Model 1		Model 2		Model 3		Model 4		Model 5	
	PR	**95 % CI**	**PR**	**95% CI**	**PR**	**95% CI**	**PR**	**95% CI**	**PR**	**95% CI**
All Study Centers										
Total Arsenic Quartiles										
1	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
2	0.93	0.72, 1.21	0.97	0.75, 1.26	0.99	0.77, 1.29	1.02	0.78, 1.35	1.01	0.77, 1.32
3	0.91	0.68, 1.21	0.95	0.71, 1.26	0.99	0.74, 1.32	1.03	0.76, 1.41	1.01	0.75, 1.34
4	1.15	0.84, 1.59	1.22	0.88, 1.68	1.32	0.95, 1.85	1.39	0.97, 1.98	1.38	1.01, 1.89
Doubling of Total Arsenic	1.08	0.98, 1.20	1.06	0.95, 1.18	1.10	0.98, 1.23	1.11	0.98, 1.24	1.10	0.99, 1.21
Inorganic and Methylated Arsenic Quartiles										
1	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
2	0.98	0.76, 1.27	0.99	0.77, 1.27	1.00	0.77, 1.30	0.97	0.74, 1.28	0.96	0.74, 1.24
3	0.95	0.71, 1.26	0.97	0.73, 1.28	1.01	0.76, 1.35	0.99	0.73, 1.34	0.97	0.73, 1.28
4	1.13	0.83, 1.53	1.13	0.83, 1.54	1.22	0.88, 1.68	1.23	0.87, 1.72	1.24	1.07, 1.66
Doubling of Inorganic and Methylated Arsenic	1.09	0.99, 1.20	1.06	0.96, 1.17	1.10	0.99, 1.22	1.10	0.99, 1.23	1.09	0.99, 1.19
Measure of Arsenic Toxicokinetics**	0.87	0.82, 0.93	0.97	0.91, 1.04	0.98	0.91, 1.05	0.99	0.93, 1.07	---	----
Doubling of Inorganic Arsenic and Arsenic Toxicokinetics Interaction	0.97	0.95, 0.99	1.00	0.98, 1.02	1.00	0.98, 1.02	1.00	0.98, 1.02	1.00	0.98, 1.02

Table 5. Prevalence ratios of hypertension by arsenic exposure. Models are generalized estimating equation Poisson models for prevalent hypertension defined as (defined as SBP≥140 mm Hg, DBP≥90 mm Hg, or taking hypertension medication), with exchangeable covariance conditional on family membership.
Model 1: crude PR, adjusted only for arsenobetaine and log creatinine (n=2424)
Model 2: Further adjusted for age, sex, education, drinking status, smoking status, BMI, kidney function, diabetes, hypertension medication use, arsenobetaine, and urine creatinine (n=2424)
Model 3: Further adjusted for study center (n=2424)
Model 4: Further adjusted for exercise (n=2086)
Model 5: Model 4, without adjustment for urine creatinine (n=2086)
**Principle Component analysis score, not adjusted for urine creatinine.

	Model 1		Model 2		Model 4		Model 5	
	PR	**95% CI**	**PR**	**95% CI**	**PR**	**95% CI**	**PR**	**95% CI**
Arizona								
Inorganic and Methylated Arsenic Quartiles								
1	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
2	2.61	1.06, 6.40	2.30	0.93, 5.67	2.66	0.97, 7.33	2.24	0.90, 5.58
3	2.74	1.07, 6.99	2.25	0.88, 5.80	2.25	0.78, 6.44	1.61	0.68, 3.82
4	3.16	1.21, 8.27	2.41	0.90, 6.43	2.64	0.88, 7.92	1.76	0.74, 4.19
Oklahoma								
Inorganic and Methylated Arsenic Quartiles								
1	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
2	1.05	0.74, 1.50	0.89	0.63, 1.28	0.85	0.58, 1.24	0.88	0.62, 1.27
3	1.07	0.70, 1.62	0.86	0.57, 1.32	0.84	0.53, 1.32	0.89	0.59, 1.36
4	1.17	0.69, 1.96	0.84	0.49, 1.44	0.86	0.49, 1.51	0.94	0.58, 1.55
North and South Dakota								
Inorganic and Methylated Arsenic Quartiles								
1	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
2	0.66	0.41, 1.07	0.74	0.46, 1.21	0.67	0.40, 1.14	0.71	0.43, 1.16
3	0.67	0.40, 1.13	0.75	0.44, 1.28	0.67	0.38, 1.18	0.74	0.44, 1.23
4	1.14	0.70, 1.86	1.55	0.92, 2.61	1.64	0.94, 2.86	1.86	1.16, 2.98

Table 6. Prevalence ratios of hypertension by inorganic and methylated arsenic exposure, stratified by study center. Models are generalized estimating equation Poisson models for prevalent hypertension defined as (defined as SBP≥140 mm Hg, DBP≥90 mm Hg, or taking hypertension medication), with exchangeable covariance conditional on family membership.
Model 1: crude PR, adjusted only for arsenobetaine and log creatinine (n=2424)
Model 2: Further adjusted for age, sex, education, drinking status, smoking status, BMI, kidney function, diabetes, hypertension medication use, arsenobetaine, and urine creatinine (n=2424)
Model 3: Not included because stratified by study center
Model 4: Further adjusted for exercise
Model 5: Model 4, without adjustment for urine creatinine

	Model 1		Model 2		Model 3		Model 4		Model 5	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
All Study Centers										
Doubling of Total Arsenic	0.76	-0.01, 1.53	0.40	-0.28, 1.09	0.96	0.26, 1.65	0.91	0.18, 1.65	0.49	-0.10, 1.09
Doubling of Inorganic and Methylated Arsenic	0.60	-0.11, 1.32	0.24	-0.40, 0.88	0.78	0.13, 1.43	0.74	0.05, 1.44	0.35	-0.19, 0.90
Total Arsenic Quartiles										
1	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent
2	-0.12	-1.98, 1.75	0.41	-1.19, 2.01	0.83	-0.76, 2.41	0.75	-0.92, 2.42	0.24	-1.35, 1.82
3	-0.21	-2.24, 1.81	0.05	-1.70, 1.79	0.84	-0.90, 2.59	0.76	-1.09, 2.61	-0.04	-1.72, 1.64
4	1.73	-0.63, 4.09	2.00	-0.08, 4.07	3.31	1.22, 5.39	3.61	1.40, 5.82	2.55	0.61, 4.49
Inorganic and Methylated Arsenic Quartiles										
1	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent
2	-0.63	-2.50, 1.25	-0.56	-2.16, 1.04	-0.14	-1.73, 1.45	-0.26	-1.94, 1.42	-0.70	-2.26, 0.86
3	-0.63	-2.66, 1.39	-0.69	-2.44, 1.07	0.15	-1.60, 1.91	0.05	-1.80, 1.91	-0.54	-2.18, 1.10
4	0.42	-1.83, 2.67	0.04	-1.95, 2.02	1.36	-0.65, 3.36	1.42	-0.70, 3.55	0.69	-1.11, 2.48
Measure of Arsenic Toxicokinetics **	-0.95	-1.37, -0.54	-0.32	-0.71, 0.07	-0.24	-0.63, 0.14	-0.17	-0.57, 0.24		
Doubling of Inorganic Arsenic and Arsenic Toxicokinetics Interaction	-0.22	-0.34, -0.10	-0.06	-0.17, 0.05	-0.05	-0.15, 0.06	-0.04	-0.16, 0.07	-0.04	-0.15, 0.08

Table 7. Changes in systolic blood pressure by arsenic exposure. Models are generalized estimating equation Linear regression models for systolic blood pressure, with exchangeable covariance conditional on family membership.
Model 1: crude PR, adjusted only for arsenobetaine and log creatinine (n=2424)
Model 2: Further adjusted for age, sex, education, drinking status, smoking status, BMI, kidney function, diabetes, hypertension medication use, arsenobetaine, and urine creatinine (n=2424)
Model 3: Further adjusted for study center (n=2424)
Model 4: Further adjusted for exercise (n=2086)
Model 5: Model 4, without adjustment for urine creatinine (n=2086)
**Principle Component analysis score, not adjusted for urine creatinine.

	Model 1		Model 2		Model 3		Model 4		Model 5	
	β	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
All Study Centers										
Doubling of Total Arsenic	0.73	0.20, 1.27	0.63	0.14, 1.13	0.75	0.24, 1.27	0.75	0.19, 1.30	0.73	0.29, 1.18
Doubling of Inorganic and Methylated Arsenic	0.60	0.10, 1.09	0.39	-0.07, 0.86	0.49	0.01, 0.98	0.49	-0.03, 1.01	0.54	0.13, 0.95
Total Arsenic Quartiles										
1	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent
2	-0.18	-1.52, 1.16	0.25	-0.92, 1.42	0.34	-0.83, 1.52	0.22	-1.03, 1.47	0.15	-1.04, 1.33
3	1.33	-0.12, 2.77	1.35	0.08, 2.62	1.54	0.25, 2.83	1.35	-0.04, 2.73	1.30	0.05, 2.56
4	2.10	0.44, 3.76	2.37	0.86, 3.87	2.69	1.14, 4.23	2.85	1.19, 4.51	2.92	1.47, 4.38
Inorganic and Methylated Arsenic Quartiles										
1	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent
2	-1.06	-2.40, 0.29	-1.07	-2.24, 0.10	-0.99	-2.17, 0.18	-1.23	-2.48, 0.03	-1.18	-2.34, -0.01
3	0.34	-1.11, 1.78	0.08	-1.20, 1.36	0.25	-1.05, 1.55	-0.08	-1.47, 1.30	0.09	-1.13, 1.32
4	1.37	-0.22, 2.95	1.06	-0.38, 2.51	1.33	-0.15, 2.82	1.31	-0.28, 2.90	1.70	0.35, 3.04
Measure of Arsenic Toxicokinetics **	-0.68	-0.98, -0.39	-0.33	-0.62, -0.05	-0.33	-0.61, -0.04	-0.31	-0.61, -0.01		
Doubling of Inorganic Arsenic and Arsenic Toxicokinetics Interaction	-0.19	-0.28, -0.11	-0.09	-0.17, -0.01	-0.09	-0.17, -0.01	-0.09	-0.17, 0.01	-0.09	-0.18, 0.01

Table 8. Changes in diastolic blood pressure by arsenic exposure. Models are generalized estimating equation Linear regression models for diastolic blood pressure, with exchangeable covariance conditional on family membership.
Model 1: crude PR, adjusted only for arsenobetaine and log creatinine (n=2424)
Model 2: Further adjusted for age, sex, education, drinking status, smoking status, BMI, kidney function, diabetes, hypertension medication use, arsenobetaine, and urine creatinine (n=2424)
Model 3: Further adjusted for study center (n=2424)
Model 4: Further adjusted for exercise (n=2086)
Model 5: Model 4, without adjustment for urine creatinine (n=2086)
**Principle Component analysis score, not adjusted for urine creatinine.

	Model 1		Model 2		Model 4		Model 5	
	β	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Arizona								
Inorganic and Methylated Arsenic Quartiles								
1	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent
2	5.59	0.94, 10.24	3.52	-0.03, 7.06	3.59	-0.39, 7.58	3.56	0.03, 7.09
3	3.53	-1.17, 8.24	0.74	-2.82, 4.30	1.41	-2.50, 5.32	1.25	-1.95, 4.45
4	6.23	1.38, 11.07	2.00	-1.67, 5.67	2.67	-1.40, 6.74	2.54	-0.63, 5.72
Oklahoma								
Inorganic and Methylated Arsenic Quartiles								
1	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent
2	1.31	-1.77, 4.41	0.05	-2.04, 2.13	-0.06	-2.23, 2.12	-0.63	-2.65, 1.40
3	1.61	-1.92, 5.14	0.60	-1.79, 2.98	-0.10	-2.59, 2.38	-0.97	-3.19, 1.25
4	4.40	0.02, 8.79	1.64	-1.36, 4.65	1.32	-1.78, 4.43	0.15	-2.57, 2.87
North and South Dakota								
Inorganic and Methylated Arsenic Quartiles								
1	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent
2	-2.59	-5.42, 0.24	-0.85	-2.97, 1.26	-0.72	-2.89, 1.44	-1.79	-3.76, 0.19
3	0.76	-2.26, 3.78	1.65	-0.68, 3.99	2.05	-0.33, 4.43	0.63	-1.49, 2.76
4	-0.41	-3.60, 2.79	0.26	-2.28, 2.80	0.67	-1.91, 3.26	-0.80	-3.10, 1.50

Table 9. Changes in systolic blood pressure by inorganic and methylated arsenic exposure, stratified by study center. Models are generalized estimating equation Linear regression models for systolic blood pressure, with exchangeable covariance conditional on family membership.
Model 1: crude PR, adjusted only for arsenobetaine and log creatinine (n=2424)
Model 2: Further adjusted for age, sex, education, drinking status, smoking status, BMI, kidney function, diabetes, hypertension medication use, arsenobetaine, and urine creatinine (n=2424)
Model 3: Not included because stratified on study center
Model 4: Further adjusted for exercise (n=2086)
Model 5: Model 4, without adjustment for urine creatinine (n=2086

	Model 1		Model 2		Model 4		Model 5	
	β	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Arizona								
Inorganic and Methylated Arsenic Quartiles								
1	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent
2	2.12	-1.61, 5.86	0.80	-2.11, 3.72	0.31	-2.89, 3.51	0.72	-2.11, 3.56
3	2.04	-1.74, 5.82	-0.11	-3.04, 2.83	-0.40	-3.54, 2.75	0.11	-2.47, 2.68
4	4.35	0.46, 8.24	1.61	-1.43, 4.64	1.62	-1.66, 4.90	2.27	-0.28, 4.83
Oklahoma								
Inorganic and Methylated Arsenic Quartiles								
1	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent
2	0.25	-1.89, 2.39	-0.37	-2.01, 1.27	-0.48	-2.22, 1.26	-0.52	-2.13, 1.10
3	1.85	-0.60, 4.30	0.82	-1.06, 2.69	0.49	-1.49, 2.48	0.61	-1.16, 2.38
4	3.19	0.15, 6.23	1.53	-0.83, 3.89	1.30	-1.18, 3.79	1.61	-0.56, 3.79
North and South Dakota								
Inorganic and Methylated Arsenic Quartiles								
1	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent
2	-3.42	-5.43, -1.40	-2.43	-3.98, -0.87	-2.58	-4.26, -0.91	-2.60	-4.12, -1.07
3	-0.68	-2.84, 1.49	0.47	-1.27, 2.21	0.26	-0.61, 2.13	0.35	-1.29, 2.00
4	-0.60	-2.92, 1.71	0.14	-1.80, 2.07	0.34	-1.73, 2.40	0.67	-1.13, 2.46

Table 10. Changes in diastolic blood pressure by inorganic and methylated arsenic exposure, stratified by study center. Models are generalized estimating equation Linear regression models for diastolic blood pressure, with exchangeable covariance conditional on family membership.
Model 1: crude PR, adjusted only for arsenobetaine and log creatinine (n=2424)
Model 2: Further adjusted for age, sex, education, drinking status, smoking status, BMI, kidney function, diabetes, hypertension medication use, arsenobetaine, and urine creatinine (n=2424)
Model 3: Not included because stratified on study center
Model 4: Further adjusted for exercise (n=2086)
Model 5: Model 4, without adjustment for urine creatinine (n=2086