HHS Public Access

Author manuscript

Environ Res. Author manuscript; available in PMC 2022 April 01.

Published in final edited form as:

Environ Res. 2021 April ; 195: 110864. doi:10.1016/j.envres.2021.110864.

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

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Description of the process by which someone else could obtain the data and computing code required to replicate the results reported in your submission (or explanation why data or code are not available): Data from the Strong Heart Study and Strong Heart Family Study are owned by the participating tribes and communities. Requests for the data for specific uses must be submitted for consideration by the communities via standard procedures (e.g., application to the Strong Heart Study Steering Committee, Publications & Presentations Committee). All research reports based on Strong Heart Study data require approval by tribal institutional review boards prior to submission for publication.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abstract

Background: Arsenic has been associated with hypertension, though it is unclear whether associations persist at the exposure concentrations (e.g. <100 μg/L) in drinking water occurring in parts of the Western United States.

Methods: We assessed associations between arsenic biomarkers and systolic blood pressure (SBP), diastolic blood pressure (DBP), and hypertension in the Strong Heart Family Study, a family-based cohort of American Indians from the Northern plains, Southern plains, and Southwest. We included 1,910 participants from three study centers with complete baseline visit data (2001–2003) in the cross-sectional analysis of all three outcomes, and 1,453 participants in the prospective analysis of incident hypertension (follow-up 2006–2009). We used generalized estimating equations with exchangeable correlation structure conditional on family membership to estimate the association of arsenic exposure biomarker levels with SBP or DBP (linear regressions) or hypertension prevalence and incidence (Poisson regressions), adjusting for urine creatinine, urine arsenobetaine, and measured confounders.

Results: We observed cross-sectional associations for a two-fold increase in inorganic and methylated urine arsenic species of 0.64 (95% CI: −0.07, 1.35) mm Hg for SBP, 0.49 (95% CI: −0.03, 1.02) mm Hg for DBP, and a prevalence ratio of 1.10 (95% CI: 1.01, 1.21) for hypertension in fully adjusted models. During follow-up, 14% of subjects developed hypertension. We observed non-monotonic relationships between quartiles of arsenic and incident hypertension. Effect estimates were null for incident hypertension with continuous exposure metrics. Stratification by study site revealed elevated associations in Arizona, the site with the highest arsenic levels, while results for Oklahoma and North and South Dakota were largely null. Blood pressure changes with increasing arsenic concentrations were larger for those with diabetes at baseline.

Conclusions: Our results suggest a modest cross-sectional association of arsenic exposure biomarkers with blood pressure, and possible non-linear effects on incident hypertension.

Keywords

Strong Heart Study; cohort study; cardiovascular diseases; arsenicals; Indians; North American

Introduction

Arsenic is a widespread, naturally occurring metalloid. It is an established human carcinogen and may be a risk factor for diabetes and other adverse health outcomes.[1–4] Worldwide, tens of millions of people are exposed to drinking water containing >50 μg/L arsenic, a level considered unsafe by the World Health Organization and most countries.[5] The current U.S. arsenic drinking water standard is 10 μg/L, lowered from 50 μg/L in 2001. At that time, about 10% of U.S. water systems had levels >10 μg/L.[6,7] Much of the Western U.S., and some areas of the Midwest and Northeast, have naturally occurring elevated levels (e.g. >10 μg/L) of arsenic in groundwater.[8] Within the U.S., populations with >10 μg/L

arsenic in their drinking water obtain about 30% of their arsenic exposure from their diet, and those with drinking water concentrations ≤10 μg/L obtain about 54–85% of their arsenic intake from their diet.[9] Populations in the Western U.S. and from certain race/ethnic subgroups have the highest exposure to dietary arsenic.[10,11] In American Indians, diet appears to be a minor source of arsenic.[12]

Many studies have found an association between arsenic and cardiovascular disease,[2,13–15] with some evidence for increased hypertension risk.[15,16] Humans can be exposed to arsenic through drinking water, food, dust, air, and occupational activities.[17,18] 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 (U.S.), respectively.[19] In the U.S., nearly 30% of adults have hypertension, with a higher prevalence among those who are older, overweight, or have diabetes. Several studies suggest an association between arsenic and hypertension, but the relationship remains unclear due to limited assessment of temporality and the exposure-response relationship. Two prospective cohort studies in Taiwan and Bangladesh reported associations between arsenic exposure and increased systolic and diastolic blood pressure.[20,21] Several cross-sectional and ecologic studies reported associations between arsenic and blood pressure and hypertension,[22–27] with studies in Taiwan and Bangladesh describing dose-response relationships between high long-term arsenic exposure levels and increased hypertension risk.[28,29] Hypertension and increased systolic blood pressure have also been associated with low-level arsenic exposure from drinking water and occupational tasks.[28,30] A 2011 systematic review calculated pooled odds ratios for hypertension of 1.27 (95% CI: 1.09, 1.47; based on eight studies) comparing the highest and lowest arsenic exposure groups, and 1.15 (95% CI: 0.96, 1.37; based on five studies) comparing moderate to low exposures.[16] A 2012 meta-analysis of chronic arsenic exposure and hypertension found mixed results based on eight studies. [31] Other studies have found no relationship between arsenic and blood pressure or hypertension,[32,33] including an examination of 2003–2008 NHANES data on low to moderate arsenic exposure levels and blood pressure.[34] Other cross-sectional analyses of NHANES data from 2009–2010 and 2011–2012 found associations only between dimethylarsinic acid (a metabolite of arsenic) and blood pressure.[35,36]

Within the Strong Heart Study, a cohort study among participating American Indian communities in Arizona, Oklahoma, and North and South Dakota,[37] arsenic has been associated with cancer and cardiovascular disease[13,38] as well as diabetes in cross-sectional, [39] but not prospective, analyses.[40] One analysis examined incident metabolic syndrome and its components, including hypertension, in the Strong Heart Family Study, an expansion of the Strong Heart Study, and reported a null adjusted risk ratio estimate for arsenic and incident hypertension of 1.03 (95% CI: 0.88, 1.20).[15,41] However, the hypertension component used a more restricted sample and fewer exposure metrics than the analysis herein. The primary objective of our analysis was to contribute to the evidence determining a causal relationship between arsenic exposure and elevated blood pressure by assessing associations of arsenic and arsenic metabolism exposure metrics with prevalent systolic blood pressure, diastolic blood pressure, and hypertension, as well as with incident hypertension, 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 that began in 1989 with funding from the National Heart, Lung, and Blood Institute. The Strong Heart Family Study (SHFS), an extension of the original cohort, began in 1998.[41] Extended families, including parents, spouses, offspring, spouses of offspring, and grandchildren of original SHS cohort members were recruited into the SHFS. To ensure the family units were sufficiently large, only families with at least 5 living siblings and at least 12 living offspring ≥18 years old were recruited.[41] Methods for recruitment and protocols for study visits, which included a personal interview, physical examination, and laboratory tests, have been previously described.[37,41] For our cross-sectional analyses, we used data collected at participants' baseline SHFS visit (2001–2003). For the incidence analysis we used data from one wave of follow-up (2006–2009). All participants gave informed consent, and the study and protocols were reviewed by the participating tribes, the Indian Health Service, and Institutional Review Boards.[37,41]

Exposure Assessment

Total urinary arsenic was measured by inductively coupled plasma mass spectrometry, and arsenic species were measured by high performance liquid chromatography-inductively coupled mass spectrometry from morning spot urine samples collected at the baseline clinical visit. Inorganic arsenic (iAs), monomethylarsonic acid (MMA), and dimethylarsinic acid (DMA) are metabolites of arsenic measured in urine.[42] Limits of detection were 0.1 μg/L for all species; concentrations below the limit of detection were imputed as 0.1 μg/L divided by the square-root of 2 (<5% for all species). Detailed laboratory analysis methods and quality assurance/quality control procedures have been described elsewhere. All samples from the three study sites were randomly analyzed using the same procedures at University of Graz, Austria in batches of 79 samples; prior analyses have confirmed that no batch effects were present.[42] 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 (proportion of variance explained by PC1=0.77). Factor loadings for PC1 and PC2 for %iAs were 0.55 and −0.66, for %DMA were −0.66 and 0.04, and for %MMA were 0.52 and 0.75. We focus our analyses on PC1 as it describes the majority of inter-individual variability in toxicokinetics, and is useful to distinguish broad differences between participants' toxicokinetic profiles. Urine creatinine information was collected to allow for adjustment for urine dilution. We considered both total urine arsenic and a more specific biomarker of inorganic arsenic exposure (i.e., the sum of inorganic and methylated arsenic [MMA, DMA] 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.

Outcome Assessment

Blood pressure was measured 3 times on the right arm after 5 minutes' rest at the morning clinical visit, with the participant seated.[43] The average of the last 2 measurements was used

for analyses. 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.

Confounder and Moderator Measures

Demographic characteristics, lifestyle, and medical history were collected during baseline interviews using a standard questionnaire.[41] 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. Our diet index is adapted from the American Heart Association's Life's Simple Seven guidelines and incorporates 5 dietary components: fruits & vegetables, fish, whole grains, sodium, and sugar-sweetened beverage consumption.[44] The index gives one point for meeting the specified goal for each category (total range: 0–5): ≥4.5 cups per day of vegetables and fruit, two or more 3.5 ounce servings per week of fish, ≥3 servings per day of whole grains, <1500 mg/day of sugar, and ≤450 calories per week from sugar-sweetened beverages. Daily caloric intake was estimated at baseline through an interviewer-administered Block 119-item food frequency questionnaire. Arsenobetaine was measured by the same methods as the other arsenic species, described under Exposure Assessment above.

Potential confounders included sex (male/female), age (in years), body mass index (BMI), physical activity (mean 7-day pedometer usage), self-reported smoking status (current/former/never), self-reported alcohol drinking status (current/former/never), diabetes status (yes [including pre- or gestational diabetes]/no), 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), estimated daily total caloric intake, arsenobetaine (μg/L), urine creatinine (mg/dL), and kidney function measured by estimated glomerular filtration rate (eGFR) using serum creatinine.

Analyses

We excluded observations with missing data on exposure, confounders, blood pressure, or hypertension from analyses. From the initial sample of 2,424 with baseline data available, a total of 514 were excluded for missing data on physical activity and/or dietary components. The cross-sectional prevalence dataset contained complete data from 1,910 people. For the prospective incidence analysis, we excluded an additional 420 observations with hypertension at baseline and 37 with missing follow-up data, for a sample size of 1,453 for the prospective incidence analysis. We used covariates measured at baseline in all analyses.

Arsenic exposure metrics included $\log_2$-transformed (i.e. doubling of) inorganic and methylated arsenic (the more toxic forms of arsenic, often ingested via water), quartiles of inorganic and methylated arsenic (<1.34, 1.34–<1.86, 1.86–<2.40, ≥2.40 μg/L), $\log_2$-transformed total arsenic (which includes inorganic and methylated arsenic, as well as less toxic organic arsenic, generally ingested via seafood), quartiles of total arsenic (<5.70, 5.70–<9.38, 9.38–<16.06, ≥16.06 μg/L), a measure of arsenic toxicokinetics (the first principal

component summarizing %iAs, %MMA, and %DMA), and the interaction between the measure of arsenic toxicokinetics and $\log_2$-transformed total arsenic.

We performed statistical analyses in SAS, 9.4 (Cary, NC). We analyzed the associations among participants at their respective baseline visit with available urine arsenic species measurements. We used generalized estimating equation (GEE) models with exchangeable correlation structure conditional on family membership to estimate arsenic's cross-sectional relationships with systolic and diastolic blood pressure (linear regression), prevalence ratios for prevalent hypertension at baseline (Poisson regression), and risk ratios for incident hypertension at follow-up (Poisson regression).

We ran four sequentially adjusted models for all outcomes (SBP, DBP, and prevalent and incident hypertension). Model 1 was adjusted only for urine creatinine (for all exposures except the arsenic toxicokinetics measure, which is based on percent arsenic species and therefore conditions on overall urine dilution by dividing by the sum of species) and arsenobetaine, to account for urine dilution and seafood consumption,[45] respectively. In Model 2, we controlled for the following potential confounders recorded at baseline: sex, age, BMI, educational attainment, smoking status, drinking status, kidney function, diabetes status, physical activity, diet index, and total caloric intake. In Model 3, we further adjusted for study center. Model 4 controlled for the same covariates as Model 3 except for the exclusion of urine creatinine, as urine creatinine may be a surrogate for body composition and may therefore introduce collider stratification bias if included as a regression covariate (i.e. urine creatinine is a descendant of hydration and body composition, which are in turn ancestors of arsenic intake and cardiovascular outcomes).[46] As a further sensitivity analysis, Model 5 controlled for the same covariates as Model 3 except for the exclusion of arsenobetaine.

In all models, the following continuous confounders were fit as restricted cubic splines: urine creatinine, arsenobetaine, age, BMI, kidney function, and physical activity. Baseline estimated daily caloric intake was included as a continuous variable. We used Wald tests of interaction terms (α=0.05, df=2) to examine heterogeneity of the arsenic-blood pressure association by sex (female/male), hypertension medication status (no hypertension, hypertension with treatment, or hypertension without treatment), diabetes status (yes [including pre- or gestational diabetes]/no), and study center (Arizona, Oklahoma, or North and South Dakota). We ran stratified models for factors with significant interaction.

Results

Demographics

Our final sample for the cross-sectional analysis had 511 participants from Arizona, 713 participants from Oklahoma, and 686 participants from North and South Dakota, for a total of 1,910. The median age in years was 34.6 (IQR: 23.0–45.6; range: 14.1–93.3); the median (IQR) among those with hypertension at baseline was 45.4 (36.0–59.5) and among those without hypertension at baseline was 31.0 (21.0–41.7). For both total arsenic and inorganic and methylated arsenic, males tended to have higher concentrations, and those ≥50 years old had lower concentrations (Table 1), though this could reflect selection bias due to higher

mortality and morbidity prior to recruitment. Participants from Arizona had higher levels of total and inorganic/methylated arsenic than those from Oklahoma or North and South Dakota. Total and inorganic/methylated arsenic concentrations decreased as education increased, increased with BMI, and those with prevalent diabetes had higher concentrations than those without. Arsenobetaine, a measure of arsenic from seafood, did not vary according to demographic factors in our population.[47]

The prevalence of hypertension was 22.5% (n=430, with 212 taking blood pressure medication and 218 without medication). The population was 61.5% female and 38.5% male, and 27.9% of males had hypertension as compared to 19.2% of females. Participants with hypertension tended to be older, have a higher fasting glucose, have a higher BMI, have fewer daily steps, and have a lower eGFR (Table 2). There were 203 incident cases of hypertension between baseline and follow-up (n=97 taking blood pressure medication and 106 without medication), with incidences of 12.2% among females (n=113 cases) and 17.2% among males (n=90 cases) (Supplemental Table 1). Supplemental Tables 2 and 3 display arsenic metabolism measures and systolic and diastolic blood pressure, respectively, by various demographic factors.

Prevalent Hypertension

In the fully adjusted model (Model 3), a doubling of total arsenic in urine was associated with a hypertension prevalence ratio of 1.11 (95% CI: 1.00, 1.23, Table 3). A doubling of the sum of inorganic and methylated arsenic species (iAs, MMA, DMA) was associated similarly with a hypertension prevalence ratio of 1.10 (95% CI: 1.01, 1.21, Table 3). Prevalence ratios were elevated for the highest quartiles of total arsenic (PR=1.38; 95% CI: 1.04, 1.82) and the sum of inorganic and methylated arsenic (PR=1.19; 95% CI: 1.04, 1.82) compared to the lowest quartile, but were close to the null for the 2nd and 3rd quartiles. The principal component score reflecting arsenic toxicokinetics was not associated with hypertension prevalence (Table 3).

When stratified by study center, there was no association between inorganic and methylated arsenic exposure and hypertension prevalence in Oklahoma (Table 4). The prevalence ratio estimates comparing the 4th quartile of inorganic and methylated arsenic to the 1st quartile in Arizona (PR=3.71; 95% CI: 1.41, 9.77) and North and South Dakota (PR=1.54; 95% CI: 0.87, 2.72) were higher than the estimate for all three study centers combined (PR=1.19; 95% CI: 1.04, 1.82). Associations of hypertension prevalence and arsenic biomarkers did not significantly differ by sex, baseline hypertension treatment status, or baseline diabetes status.

Systolic Blood Pressure

In the fully adjusted model (Model 3), a doubling of total arsenic was associated with a 0.79 mm Hg increase in SBP (95% CI: 0.02, 1.56, Table 5), and a doubling of inorganic and methylated arsenic species was associated with a 0.64 mm Hg increase in SBP (95% CI: −0.07, 1.35). The highest quartile of total arsenic was associated with a 2.42 mm Hg increase in SBP when compared to the lowest quartile (95% CI: 0.18, 4.66). After controlling for possible confounders, quartiles of the sum of inorganic and methylated arsenic and the principal component summarizing arsenic toxicokinetics were not associated

with SBP. When stratified by study center, beta estimates for SBP were elevated for the 2nd, 3rd, and 4th quartiles of inorganic and methylated arsenic in Arizona and for the 4th quartile in North and South Dakota, but were not statistically significant (Supplemental Table 4). When stratified by baseline diabetes status, those with diabetes had stronger associations between arsenic biomarkers and SBP than those without diabetes. Associations of SBP and arsenic biomarkers did not significantly differ by sex or baseline hypertension treatment status (Supplemental Table 7).

Diastolic Blood Pressure

In the fully adjusted model (Model 3), a doubling of total arsenic was associated with a 0.73 mm Hg increase in DBP (95% 0.17, 1.28, Table 6) and a doubling of inorganic and methylated arsenic was associated with a 0.49 mm Hg increase in DBP (95% CI: −0.03, 1.02). We observed a positive exposure-response relationship between DBP and quartiles of total arsenic, with a beta estimate of 2.64 (95% CI: 0.98, 4.30) mm Hg when comparing the 4th and 1st quartiles of total arsenic. Inorganic and methylated arsenic quartiles were not associated with DBP, except for the 4th quartile when not adjusting for urine creatinine (Model 4). A higher principle component score for arsenic toxicokinetics was associated with a slightly lower DBP (-0.29 mm Hg, 95% CI: −0.60, 0.02). When stratified by study center, the 2nd quartile of inorganic and methylated arsenic was associated with a −3.59 mm Hg (95% CI: −5.49, −1.69; Supplemental Table 5) decrease in DBP when compared to the 1st quartile in North and South Dakota; quartiles were elevated in Arizona, with a beta estimate for the highest quartile of 4.65 (95% CI: 0.89, 8.41). When stratified by baseline diabetes status, those with diabetes had stronger associations between arsenic biomarkers and DBP than those without diabetes. Associations of DBP and arsenic biomarkers did not significantly differ by sex or baseline hypertension treatment status (Supplemental Table 7).

Incident Hypertension

We observed slightly elevated, non-monotonic relationships between quartiles of total arsenic and incident hypertension, with risk ratios of 1.34 (95% CI: 0.92, 1.94), 1.19 (95% CI: 0.82, 1.73), and 1.09 (95% CI: 0.66, 1.80) for the 2nd, 3rd, and 4th quartiles compared to the 1st quartile, respectively (Table 7). Associations between incident hypertension and quartiles of methylated and inorganic arsenic followed a similar pattern, with risk ratios in fully adjusted models of 1.43 (95% CI: 0.99, 2.06), 1.10 (95% CI: 0.75, 1.61), and 1.10 (95% CI: 0.69, 1.74) for the 2nd, 3rd, and 4th quartiles compared to the 1st quartile, respectively. Associations were null for exposure metrics modeled as continuous, i.e. per doubling of total arsenic, per doubling of methylated and inorganic arsenic, the principle component analysis score measure of arsenic toxicokinetics, and for the interaction of doubling of inorganic arsenic and arsenic toxicokinetic index. No patterns emerged for quartiles of inorganic and methylated arsenic with incident hypertension when stratified by site, with the highest detected risk ratios for the 2nd quartile in Arizona (2.53; 95% CI: 1.08, 5.93) and 3rd quartile in the Dakotas (1.62; 95% CI: 0.85, 3.09) compared to the 1st quartile (Supplemental Table 6). Associations of hypertension incidence and arsenic biomarkers did not significantly differ by sex, hypertension treatment status at follow-up, or baseline diabetes status.

Discussion

Our cross-sectional results suggest moderate positive relationships between arsenic exposure and hypertension, SBP, and DBP in models accounting for urine creatinine, urine arsenobetaine, potential confounders, and family clustering. There was no evidence for effect modification by blood pressure medication use or sex, but we did detect differences in the association of arsenic biomarkers with blood pressure (SBP and DBP) by diabetes status such that those with baseline diabetes had stronger associations. When stratified by study center, the associations were generally strongest in Arizona, slightly elevated in North and South Dakota, and not apparent in Oklahoma.

We estimated a prevalence ratio for hypertension per doubling of total arsenic of 1.11 (95% CI: 1.00, 1.23) in fully adjusted models, and of 1.38 (95% CI: 1.04, 1.82) comparing the highest to lowest exposure quartiles (≥16.06 vs <5.70 μg/L) of total arsenic. Our risk ratio estimates for incident hypertension were generally null except for the 2nd versus 1st quartile of inorganic and methylated arsenic in Arizona. A meta-analysis of eight studies estimated a risk ratio for hypertension of 1.23 (95% CI: 1.04, 1.45) for chronic exposure to drinking water arsenic concentrations of 10 μg/L compared to a referent of 1 μg/L.[48] However, a separate analysis of 851 SHFS participants reported a risk ratio for incident hypertension of 1.03 (95% CI: 0.88, 1.20) per interquartile range increase in total arsenic in a subset of 851 participants in a model adjusted for urinary creatinine concentration, age, sex, study center, education, alcohol intake, smoking status, kidney function, and BMI.[15] This estimate from an overlapping sample is similar to our risk ratio estimate of 0.98 (95% CI: 0.84, 1.14) for incident hypertension per doubling of total arsenic in fully adjusted models based on 1431 participants. Our findings generally support those of an analysis of cardiac function in the SHFS that reported an association between increased inorganic and methylated arsenic exposure and left ventricular hypertrophy, which was strongest among individuals with preexisting hypertension.[49]

In this study population, there may only be a positive association of arsenic exposure and blood pressure at higher levels of arsenic. It may be that there is a threshold level of arsenic exposure or time exposed to arsenic that is necessary for adverse impacts on the circulatory system to result in higher blood pressure or hypertension. In our analyses, only the highest quartiles of inorganic or total arsenic showed an association with blood pressure in cross-sectional analyses, 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.[50] Another cross-sectional study found a relationship between arsenic and hypertension and blood pressure only after 50 years of exposure to <50 μg/L of arsenic.[51] The urinary arsenic concentrations in this study (median [IQR] of 9.4 μg/L [5.7–16.1] for total arsenic, 4.8 μg/L [2.8–8.2] for DMA, and 0.5 [0.3–1.1] for arsenobetaine) are generally similar to U.S.-wide estimates (median [IQR] of 8.3 μg/L [4.2–17.1] for total arsenic, 3.6 μg/L [2.0– 6.0] for DMA, and 1.4 μg/L [0.3– 6.3] for arsenobetaine) from a study that used 2003–2008 NHANES data and which reported largely null associations of arsenic with hypertension and blood pressure.[34] The differences between our results and those based on

NHANES could be due to the lower levels of relatively non-toxic arsenobetaine in the SHFS (and therefore a higher proportion of total arsenic comprised or more toxic species), or due to the stronger associations we observed for the SHFS' Arizona study site, where exposures to toxic arsenic species were higher (median [IQR] of 14.1 μg/L [8.5–24.4] for total arsenic, 7.4 μg/L [4.4–12.2] for DMA, and 0.51 μg/L [0.31–1.17] for arsenobetaine).

In addition to differences in exposure levels and timeframes, variations in results across studies may stem from biological factors not considered in our analysis. A person's genetics[52–56] and their ability to metabolize arsenic[57–59] have been found to modify the relationship between arsenic exposure and blood pressure. A study in Taiwan found that genes that modulate reactive oxygen species modify the dose-response relationship between arsenic and hypertension.[53] Oxidative stress, reduction of anti-oxidative defense systems, and vasoconstriction have been proposed as mechanisms for a causal relationship between arsenic and blood pressure.[60]

One route through which populations are exposed to inorganic arsenic is via natural arsenic contamination of drinking water.[17] In the U.S., drinking water contains >10 μg/L naturally-occurring arsenic (the U.S. Environmental Protection Agency threshold) in parts of the Southwest, Midwest, and Northeast.[61] The National Human Exposure Assessment Survey in Arizona (NHEXAS –AZ, 1999–2002) study found arsenic in 100% of tap water samples taken, and also found that food, soil, and dust were additional possible routes of exposure.[18,62] 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.[63] 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.[10,64,65] This population is likely exposed to inorganic arsenic primarily through drinking water, and this study shows that inorganic arsenic exposure may have a modest impact on blood pressure and hypertension prevalence. This study can potentially help inform tribal leadership on drinking water quality standards and diet recommendations within their communities to reduce inorganic arsenic exposure.

This study has several limitations. The cross-sectional analysis does not address the temporality of the participant's arsenic exposure as it relates to their development of hypertension or blood pressure, i.e. it is not known whether arsenic exposure preceded hypertension in this analysis. The incident hypertension analysis is not subject to this limitation, however. A possible source of information bias is that the urine arsenic measures were from a single urine sample, which may not accurately reflect more biologically relevant long-term exposures. However, these exposure markers may be reasonable surrogates for average exposures, as there is evidence from a 10-year longitudinal analysis in the Strong Heart Study (predecessor of the SHFS) that arsenic concentrations vary relatively little over time.[66] This relative consistency is likely because consistent groundwater exposures account for most of the total arsenic in this population. Our metric of ambulatory physical activity was only measured for one-week in Phase IV, leaving out SHFS participants whose baseline visit was at Phase III, thus our sample was restricted to

participants with Phase IV baseline data. Additionally, the presence of a pedometer to measure ambulatory activity could have increased participants' physical activity, leaving open the possibility of residual confounding. By accounting 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. Potential for residual confounding from dietary determinants of blood pressure associated with routes of arsenic exposure cannot be ruled out. Though we included a dietary index based on American Heart Association guidelines, this index captured only a moderate degree of dietary variation across five dietary domains. Diet is both a potential route of arsenic exposure and a factor that can affect blood pressure. Finally, we do not have any direct information on the sources of arsenic exposure in this population.

While the prospective hypertension incidence analysis addresses the temporality of exposure preceding outcome, measurement error likely results from the fact that the precise timing of incidence is unknown, and instead we use assessment of the outcome at the follow-up study visit. While any incident hypertension occurred at some point between study visits, we use the assessment of incident hypertension only at the latter end of this timeline, i.e. the 2nd study visit. If indeed arsenic exposure increases the risk of hypertension, then on average individuals with higher arsenic exposure would be expected to have earlier incidence. In our analysis, however, the actual person-time from baseline to incidence is unknown, and the outcome is assessed at the same time for everyone, thus inflating the person-time in the denominator and biasing the estimates of a positive association towards the null. Additionally, while the cross-sectional analyses cannot establish temporality, a key feature of causality, the prospective analysis may be prone to survival bias, which would likely bias results towards the null if a positive causal relationship exists between arsenic exposure and blood pressure. This would occur if the individuals with the highest exposures that did not already have hypertension at baseline (i.e. those who were not excluded from the incidence analysis) were healthier on average than those with lower exposures and therefore less likely to develop hypertension during the 2.8–8.6 years (median 5.2 years) of follow-up.

Despite these limitations, our study shows a modest relationship between arsenic exposure and increased blood pressure and hypertension prevalence. Our cross-sectional results suggest that these associations may be seen at relatively moderate levels of arsenic exposure, while the prospective analyses suggested higher risks at lower levels. These findings may improve understanding of risk factors for hypertension in American Indian communities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Sources of financial support:

This work was sponsored by the National Institute of Environmental Health Sciences of the National Institutes of Health (P30 ES019776, R01ES028758, 1R01ES025216, P42 ES010349, P30ES009089, and T32 ES012870), and

by cooperative agreement U54AG062334. The Strong Heart Study has been funded in whole or in part with federal funds from the National Heart, Lung, and Blood Institute, National Institute of Health, Department of Health and Human Services, under contract numbers 75N92019D00027, 75N92019D00028, 75N92019D00029, & 75N92019D00030. The study was previously supported by research grants: R01HL109315, R01HL109301, R01HL109284, R01HL109282, and R01HL109319 and by cooperative agreements: U01HL41642, U01HL41652, U01HL41654, U01HL65520, and U01HL65521. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Highlights

- Arsenic was positively associated with prevalent hypertension and blood pressure
- Associations were strongest in the study site with the highest exposure levels
- Blood pressure associations were stronger for participants with baseline diabetes
- Arsenic and incident hypertension had a non-monotonic relationship

Table 1.

Arsenic biomarkers by demographic characteristics at baseline

	Total Arsenic (g/L)				Inorganic and Methylated Arsenic (μg/L)				Arsenobetaine (μg/L)			
Percentile	**25**	**50**	**75**		**25**	**50**	**75**		**25**	**50**	**75**	**Total (N)**
Sex												
Female	5.61	9.21	16.11		1.29	1.84	2.38		0.30	0.49	1.08	1175
Male	5.72	9.74	15.97		1.37	1.88	2.44		0.33	0.51	1.08	735
Age												
<18	6.41	10.12	17.15		1.50	2.03	2.58		0.34	0.46	0.71	225
18–35	6.23	10.15	17.65		1.49	1.97	2.46		0.32	0.51	1.03	741
35–50	5.30	9.07	15.41		1.22	1.78	2.37		0.29	0.51	1.23	596
>50	4.64	7.95	13.41		1.09	1.65	2.16		0.30	0.49	1.44	348
Region												
Arizona	8.51	14.06	24.38		1.83	2.33	2.80		0.31	0.51	1.17	511
Oklahoma	4.99	7.76	12.17		1.20	1.65	2.10		0.33	0.52	1.07	713
North and South Dakota	5.19	8.39	14.79		1.22	1.78	2.30		0.29	0.46	0.98	686
Education												
Less than high school	6.67	12.36	24.29		1.53	2.27	2.81		0.32	0.50	1.08	114
Some high school	6.35	10.34	18.42		1.46	2.01	2.60		0.32	0.47	0.83	547
High school diploma	5.73	8.68	14.85		1.35	1.81	2.32		0.29	0.49	0.96	674
Some college	5.11	8.58	13.79		1.18	1.74	2.23		0.33	0.55	1.36	575
Smoking status												
Never	5.88	9.42	16.06		1.37	1.88	2.39		0.32	0.51	1.14	825
Forsmer	5.49	8.31	14.51		1.21	1.71	2.27		0.33	0.54	1.22	393
Current	5.59	9.94	16.99		1.37	1.91	2.47		0.29	0.46	0.98	692
Alcohol												
Never	6.27	9.58	15.52		1.29	1.89	2.41		0.31	0.50	0.85	205
Former	5.41	8.71	14.40		1.26	1.80	2.28		0.30	0.48	1.11	489
Current	5.80	9.63	17.23		1.37	1.89	2.45		0.32	0.51	1.07	1216
Diabetes status												
Yes	5.82	10.31	13.94		1.39	1.97	2.25		0.28	0.45	1.17	78
No	5.70	9.31	16.09		1.34	1.86	2.40		0.31	0.50	1.07	1832
Body Mass Index												
<25	5.11	8.36	14.45		1.19	1.75	2.29		0.30	0.47	0.77	390
25–<30	5.61	9.18	15.58		1.29	1.80	2.36		0.32	0.52	1.16	514
≥30	6.03	9.89	17.80		1.39	1.93	2.48		0.31	0.51	1.22	1006

Table 2.

Demographic and health characteristics by hypertension status at baseline

	Without hypertension, n=1480	With hypertension, n=430	
	n (%) or mean (SD)	% or mean (SD)	p-value
Sex			<0.0001
Female	950 (64.2%)	225 (52.3%)	
Male	530 (35.8%)	205 (47.7%)	
Age, years	32.91 (13.62)	47.13 (16.18)	<0.0001
Region			<0.0001
Arizona	415 (28.0%)	96 (22.3%)	
Oklahoma	510 (34.5%)	203 (47.2%)	
North and South Dakota	555 (37.5%)	131 (30.5%)	
Education			<0.0001
Less than high school	91 (6.1%)	23 (5.3%)	
Some high school	462 (31.2%)	85 (19.8%0	
High school diploma	505 (34.1%)	169 (39.3%)	
Some college	422 (28.5%)	153 (35.6%)	
Smoking			0.0030
Never	635 (42.9%)	190 (44.2%)	
Former	284 (19.2%)	109 (25.3%)	
Current	561 (37.9%)	131 (30.5%)	
Alcohol			0.3300
Never	161 (10.9%)	44 (10.2%)	
Former	367 (24.8%)	122 (28.4%)	
Current	952 (64.3%)	264 (61.4%)	
Diabetes status			0.0100
Yes	54 (3.6%)	24 (5.6%)	
No	1426 (96.4%)	406 (94.4%)	
Fasting glucose	92.44 (9.82)	97.76 (10.35)	<0.0001
BMI	30.85 (7.53)	33.23 (7.06)	<0.0001
Urine creatinine	1.59 (0.94)	1.52 (0.96)	0.1440
Blood pressure			
Systolic	115.55 (10.56)	138.06 (15.79)	<0.0001
Diastolic	73.49 (8.84)	85.74 (11.76)	<0.0001
Pedometer steps	6321.94 (3978.16)	5496.91 (3585.24)	0.0001
Estimated glomerular filtration rate (eGFR)	97.08 (21.65)	87.43 (23.18)	<0.0001

* Denotes statistical difference between groups either by 2 sample t-test or Pearson's chi-square (α=0.05)

Table 3.

Prevalence ratios of hypertension by arsenic exposure, all study centers.

	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**
Total Arsenic Quartiles										
1	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
2	0.94	0.73, 1.21	1.00	0.81, 1.23	1.02	0.83, 1.27	1.01	0.82, 1.25	1.02	0.83, 1.26
3	0.92	0.70, 1.21	0.95	0.77, 1.19	1.01	0.81, 1.28	1.00	0.81, 1.23	1.01	0.80, 1.27
4	1.13	0.85, 1.50	1.24	0.96, 1.61	1.38	1.04, 1.82	1.39	1.08, 1.77	1.29	0.97, 1.72
Doubling of Total Arsenic										
	1.08	0.98, 1.18	1.06	0.97, 1.17	1.11	1.00, 1.23	1.10	1.02, 1.20	1.07	0.98, 1.17
Inorganic and Methylated Arsenic Quartiles										
1	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
2	1.00	0.79, 1.27	1.00	0.80, 1.24	1.01	0.81, 1.27	0.99	0.81, 1.22	1.01	0.80, 1.26
3	1.00	0.78, 1.28	0.98	0.78, 1.24	1.04	0.82, 1.32	1.03	0.84, 1.26	1.03	0.81, 1.31
4	1.07	0.82, 1.40	1.08	0.83, 1.42	1.19	1.04, 1.82	1.21	0.96, 1.54	1.18	0.89, 1.57
Doubling of Inorganic and Methylated Arsenic										
	1.08	0.99, 1.17	1.06	0.97, 1.16	1.10	1.01, 1.21	1.09	1.02, 1.17	1.10	1.00, 1.20
Measure of Arsenic Toxicokinetics **										
	0.87	0.83, 0.92	0.98	0.92, 1.04	0.99	0.93, 1.05	--	--	0.99	0.93, 1.05
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

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: Adjusted only for arsenobetaine and log urine creatinine

Model 2: Further adjusted for age, sex, education, drinking status, smoking status, BMI, kidney function, diabetes status, physical activity, diet index, total daily caloric intake

Model 3: Further adjusted for study center

Model 4: Model 3, without adjustment for urine creatinine

Model 5: Model 3, without adjustment for arsenobetaine

** Principle Component analysis score, not adjusted for urine creatinine.

Table 4.

Prevalence ratios of hypertension by quartiles of inorganic and methylated arsenic exposure, stratified by study center.

	Model 1		Model 2		Model 4		Model 5	
	PR	**95% CI**	**PR**	**95% CI**	**PR**	**95% CI**	**PR**	**95% CI**
Arizona								
1	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
2	4.12	1.54, 10.97	3.66	1.39, 9.64	2.78	1.18, 6.57	3.36	1.29, 8.73
3	4.52	1.53, 13.40	3.96	1.54, 10.19	2.47	1.16, 5.29	3.81	1.50, 9.66
4	4.48	1.34, 14.95	3.71	1.41, 9.77	2.18	1.05, 4.53	3.39	1.29, 8.89
Oklahoma								
1	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
2	1.00	0.75, 1.33	0.83	0.61, 1.12	0.87	0.68, 1.11	0.84	0.62, 1.14
3	1.02	0.73, 1.44	0.87	0.59, 1.28	0.94	0.70, 1.26	0.89	0.59, 1.33
4	1.06	0.74, 1.53	0.85	0.59, 1.23	0.95	0.69, 1.29	0.88	0.60, 1.29
North and South Dakota								
1	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
2	0.66	0.43, 1.02	0.72	0.45, 1.15	0.73	0.47, 1.12	0.71	0.44, 1.14
3	0.69	0.46, 1.06	0.70	0.47, 1.05	0.77	0.53, 1.10	0.70	0.47, 1.04
4	1.16	0.71, 1.91	1.54	0.87, 2.72	1.70	1.09, 2.66	1.52	0.87, 2.64

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: Adjusted only for arsenobetaine and log urine creatinine

Model 2: Further adjusted for age, sex, education, drinking status, smoking status, BMI, kidney function, diabetes status, physical activity, diet index, total daily caloric intake

Model 4: Model 2, without adjustment for urine creatinine

Model 5: Model 2, without adjustment for arsenobetaine

Table 5.

Changes in systolic blood pressure by arsenic exposure, all study centers

	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
Total Arsenic Quartiles										
1	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent
2	−0.86	−3.03, 1.31	−0.35	−2.00, 1.31	0.04	−1.66, 1.74	−0.23	−1.87, 1.41	−0.15	−1.83, 1.53
3	−1.07	−3.50, 1.35	−1.03	−2.95, 1.31	−0.29	−2.28, 1.70	−0.76	−2.45, 0.92	−0.67	−2.63, 1.29
4	0.79	−1.82, 3.40	1.27	−0.93, 3.47	2.42	0.18, 4.66	1.74	−0.22, 3.70	1.36	−0.63, 3.35
Doubling of Total Arsenic										
	0.62	−0.22, 1.45	0.30	−0.46, 1.06	0.79	0.02, 1.56	0.43	−0.18, 1.04	0.36	−0.23, 0.95
Inorganic and Methylated Arsenic Quartiles										
1	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent
2	−1.03	−3.01, 0.96	−1.20	−2.89, 0.50	−0.84	−2.52, 0.85	−1.08	−2.66, 0.50	−0.85	−2.54, 0.84
3	−0.77	−3.06, 1.52	−1.27	−3.17, 0.62	−0.50	−2.42, 1.43	−0.80	−2.30, 0.70	−0.58	−2.52, 1.36
4	−0.23	−2.65, 2.18	−0.80	−2.88, 1.27	0.40	−1.70, 2.49	−0.01	−1.72, 1.69	0.22	−1.89, 2.34
Doubling of Inorganic and Methylated Arsenic										
	0.53	−0.22, 1.27	0.16	−0.54, 0.85	0.64	−0.07, 1.35	0.31	−0.21, 0.82	0.58	−0.11, 1.27
Measure of Arsenic Toxicokinetics **										
	−1.03	−1.43, −0.63	−0.24	−0.62, 0.15	−0.16	−0.54, 0.23	--	--	−0.13	−0.51, 0.25
Doubling of Inorganic Arsenic and Arsenic Toxicokinetics Interaction										
	−0.26	−0.38, −0.14	−0.07	−0.18, 0.04	−0.05	−0.16, 0.06	−0.04	−0.16, 0.07	−0.03	−0.14, 0.08

Models are generalized estimating equation linear regression models for systolic blood pressure, with exchangeable covariance conditional on family membership.

Model 1: Adjusted only for arsenobetaine and log urine creatinine

Model 2: Further adjusted for age, sex, education, drinking status, smoking status, BMI, kidney function, diabetes status, physical activity, diet index, total daily caloric intake

Model 3: Further adjusted for study center

Model 4: Model 3, without adjustment for urine creatinine

Model 5: Model 3, without adjustment for arsenobetaine

** Principle Component analysis score, not adjusted for urine creatinine.

Table 6.

Changes in diastolic blood pressure by arsenic exposure, all study centers

	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
Total Arsenic Quartiles										
1	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent
2	−0.37	−2.04, 1.29	0.22	−1.20, 1.65	0.29	−1.16, 1.75	0.35	−1.04, 1.74	0.04	−1.41, 1.50
3	0.70	−0.87, 2.27	0.72	−0.63, 2.08	0.87	−0.52, 2.25	0.99	−0.24, 2.22	0.49	−0.90, 1.88
4	1.85	0.04, 3.65	2.41	0.76, 4.05	2.64	0.98, 4.30	2.92	1.53, 4.32	1.83	0.34, 2.32
Doubling of Total Arsenic										
	0.69	0.14, 1.24	0.64	0.08, 1.20	0.73	0.17, 1.28	0.76	0.32, 1.20	0.41	−0.02, 0.84
Inorganic and Methylated Arsenic Quartiles										
1	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent
2	−1.53	−3.15, 0.08	−1.64	−3.03, −0.25	−1.59	−2.98, −0.19	−1.43	−2.77, −0.09	−1.65	−3.03,−0.26
3	0.18	−1.48, 1.85	−0.38	−1.85, 1.09	−0.26	−1.73, 1.21	0.09	−1.19, 1.37	−0.33	−1.82, 1.15
4	0.89	−0.79, 2.56	0.61	−1.08, 2.29	0.80	−0.86, 2.46	1.42	0.09, 2.74	0.66	−1.00, 2.32
Doubling of Inorganic and Methylated Arsenic										
	0.57	0.08, 1.06	0.42	−0.11, 0.95	0.49	−0.03, 1.02	0.59	0.17, 1.00	0.44	−0.07, 0.95
Measure of Arsenic Toxicokinetics **										
	−0.70	−1.01, −0.39	−0.29	−0.60, 0.01	−0.29	−0.60, 0.02	--	--	−0.28	−0.59, 0.04
Doubling of Inorganic Arsenic and Arsenic Toxicokinetics Interaction										
	−0.20	−0.30, −0.11	−0.08	−0.17, 0.00	−0.08	−0.17, 0.00	−0.09	−0.17, 0.00	−0.08	−0.16, 0.01

Models are generalized estimating equation Linear regression models for diastolic blood pressure, with exchangeable covariance conditional on family membership.

Model 1: Adjusted only for arsenobetaine and log urine creatinine

Model 2: Further adjusted for age, sex, education, drinking status, smoking status, BMI, kidney function, diabetes status, physical activity, diet index, total daily caloric intake

Model 3: Further adjusted for study center

Model 4: Model 3, without adjustment for urine creatinine

Model 5: Model 3, without adjustment for arsenobetaine

** Principle Component analysis score, not adjusted for urine creatinine.

Table 7.

Risk Ratios (95% Confidence Intervals) for Incident Hypertension in the Strong Heart Family Study

	Model 1		Model 2		Model 3		Model 4		Model 5	
	RR	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Total Arsenic Quartiles										
1	1.00	referent	1.00	referent	1.00	referent	1.00	referent	1.00	referent
2	1.15	0.79, 1.67	1.31	0.90, 1.91	1.34	0.92, 1.94	1.38	0.94, 2.05	1.34	0.92, 1.94
3	1.16	0.80, 1.69	1.13	0.78, 1.64	1.19	0.82, 1.73	1.24	0.85, 1.81	1.21	0.82, 1.77
4	0.92	0.58, 1.48	1.00	0.62, 1.62	1.09	0.66, 1.80	1.16	0.72, 1.87	1.07	0.69, 1.66
Doubling of total arsenic										
	0.96	0.84, 1.10	0.94	0.82, 1.09	0.97	0.84, 1.13	1.02	0.90, 1.17	0.98	0.87, 1.10
Inorganic and Methylated Arsenic Quartiles										
1	1.00	referent	1.00	Referent	1.00	referent	1.00	Referent	1.00	referent
2	1.25	0.87, 1.78	1.41	0.99, 2.03	1.43	0.99, 2.06	1.50	1.04, 2.17	1.42	0.97, 2.07
3	1.09	0.74, 1.62	1.06	0.73, 1.54	1.10	0.75, 1.61	1.16	0.80, 1.68	1.07	0.72, 1.58
4	1.00	0.65, 1.54	1.02	0.66, 1.59	1.10	0.69, 1.74	1.17	0.76, 1.80	1.06	0.67, 1.67
Doubling of Inorganic and Methylated Arsenic										
	0.99	0.88, 1.11	0.97	0.85, 1.11	1.00	0.87, 1.15	1.04	0.93, 1.16	0.99	0.86, 1.14
Measure of Arsenic Toxicokinetics (principle component analysis score)										
	0.90	0.81, 0.98	0.97	0.88, 1.06	0.97	0.88, 1.07	--	--	0.98	0.89, 1.07
Doubling of Inorganic Arsenic and Arsenic Toxicokinetics Interaction										
	0.97	0.94, 1.00	0.99	0.96, 1.01	0.99	0.96, 1.01	0.99	0.96, 1.01	0.99	0.97, 1.01

Models are generalized estimating equation Poisson regression models for incident hypertension (defined as SBP ≥140 mm Hg, DBP ≥90 mm Hg, or taking hypertension medication), with exchangeable covariance conditional on family membership

Model 1: Adjusted only for arsenobetaine and log urine creatinine

Model 2: Further adjusted for age, sex, education, drinking status, smoking status, BMI, kidney function, diabetes status, physical activity, diet index, total daily caloric intake

Model 3: Further adjusted for study center

Model 4: Model 3, without adjustment for urine creatinine

Model 5: Model 3, without adjustment for arsenobetaine

** Principle Component analysis score, not adjusted for urine creatinine.