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Original Contribution

Arsenic Exposure, Diabetes Prevalence, and Diabetes Control in the Strong Heart Study

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This study evaluated the association of arsenic exposure, as measured in urine, with diabetes prevalence, glycated hemoglobin, and insulin resistance in American Indian adults from Arizona, Oklahoma, and North and South Dakota (1989–1991). We studied 3,925 men and women 45–74 years of age with available urine arsenic measures. Diabetes was defined as a fasting glucose level of 126 mg/dL or higher, a 2-hour glucose level of 200 mg/dL or higher, a hemoglobin A1c (HbA1c) of 6.5% or higher, or diabetes treatment. Median urine arsenic concentration was 14.1 μg/L (interquartile range, 7.9–24.2). Diabetes prevalence was 49.4%. After adjustment for sociodemographic factors, diabetes risk factors, and urine creatinine, the prevalence ratio of diabetes comparing the 75th versus 25th percentiles of total arsenic concentrations was 1.14 (95% confidence interval: 1.08, 1.21). The association between arsenic and diabetes was restricted to participants with poor diabetes control (HbA1c ≥8%). Arsenic was positively associated with HbA1c levels in participants with diabetes. Arsenic was not associated with HbA1c or with insulin resistance (assessed by homeostatic model assessment to quantify insulin resistance) in participants without diabetes. Urine arsenic was associated with diabetes control in a population from rural communities in the United States with a high burden of diabetes. Prospective studies that evaluate the direction of the relation between poor diabetes control and arsenic exposure are needed.

American Indians; arsenic; diabetes; glycated hemoglobin; insulin resistance

Abbreviations: CI, confidence interval; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment to quantify insulin resistance; SHS, Strong Heart Study.

Inorganic arsenic is a widespread toxicant and carcinogen found in groundwater, food, dust, and ambient air (1). High-chronic exposure to inorganic arsenic in drinking water has been associated with diabetes in several cross-sectional studies (2, 3) and in a prospective study from Taiwan (4), although another cross-sectional study from Bangladesh found no association (5). Experimental evidence supports several mechanisms for arsenic-related diabetes (6–8). Few epidemiologic studies, however, have evaluated the association between arsenic and diabetes at low-moderate levels of exposure (6, 9–12). In the US National Health and Nutrition Examination Survey 2003–2004, total arsenic and dimethylarsinate concentrations in urine were associated with prevalent diabetes and with glycated hemoglobin concentrations after adjustment for diabetes risk factors, urine dilution, and markers of seafood intake (9). The National Health and Nutrition Examination Survey was limited by the high contribution of seafood arsenicals to total urine arsenic (13, 14) and by high laboratory detection limits for the quantification of arsenic species that directly reflect inorganic arsenic (10, 15, 16). Additional studies with adequate measures of inorganic arsenic exposure and diabetes outcomes in populations exposed to low-moderate arsenic levels are needed.

Our objective was to evaluate the associations of exposure to inorganic arsenic, as measured in urine, with diabetes prevalence, with the concentration of glycated hemoglobin, and with measures of insulin resistance in American Indians from rural communities in Arizona, Oklahoma, and North and South Dakota who participated in the Strong Heart Study (SHS) in 1989–1991. In this population, seafood intake is very low (17, 18), and total urine arsenic reflects exposure to inorganic arsenic (19). In preliminary analyses, urine arsenic concentrations were stable over a 10-year period, which suggests that urine arsenic is an appropriate surrogate for chronic arsenic exposure in the SHS (18). Although diabetes occurs in epidemic proportions in many American Indian communities (20, 21), and although small rural communities in the United States, including many American Indian communities, are disproportionately exposed to arsenic in drinking water (22, 23), the relation between inorganic arsenic exposure and diabetes prevalence in these communities is unknown.

MATERIALS AND METHODS

Study population

The SHS is a population-based study of cardiovascular disease and diabetes in American Indian communities funded by the National Heart, Lung, and Blood Institute. Persons on tribal rolls in 13 American Indian communities from Arizona, Oklahoma, and North and South Dakota, 45–74 years old, were invited to participate from 1989 to 1991. The goal was to recruit 1,500 participants per region. In Arizona and Oklahoma, all community members were invited. In North and South Dakota, a cluster sampling technique was used (24). A total of 4,549 participants were recruited, with an overall participation rate of 62%. The SHS protocol and consent form were approved by institutional review boards, participating tribes, and the Indian Health Service. All participants provided informed consent.

For this study, we measured urine arsenic in SHS participants who had stored urine samples available ($n = 3,973$). We then excluded 14 participants whose diabetes status was missing and 34 participants who had other missing variables of interest (educational level, body mass index, smoking status, alcohol status, or urine creatinine), leaving 3,925 participants for the main analysis of the association between arsenic and diabetes prevalence ($n = 1,939$ with diabetes, $n = 1,986$ without diabetes). The association between arsenic and glycated hemoglobin was evaluated in analyses stratified by diabetes status. For these analyses, we excluded 223 participants with missing hemoglobin A1c (HbA1c) measurements ($n = 1,845$ with diabetes, $n = 1,857$ without diabetes). The association between arsenic and insulin resistance was evaluated among 1,986 participants without diabetes. For this analysis, we excluded 38 participants with missing values for fasting glucose or insulin, variables needed for the homeostatic model assessment to quantify insulin resistance (HOMA-IR) ($n = 1,948$). Participant characteristics in all analyses were similar to the overall SHS study population cohort (data not shown).

Urine arsenic

As part of the SHS baseline visit (1989–1991), spot urine samples were collected in polypropylene tubes, frozen within 2 hours of collection, shipped on dry ice, and stored at −80°C in the Penn Medical Laboratory, MedStar Health Research Institute (Hyattsville, Maryland, and Washington, DC). In 2009, up to 1.0 mL of urine from each participant was transported on dry ice to the Trace Element Laboratory of the Institute of Chemistry-Analytical Chemistry, Karl Franzens University (Graz, Austria).

The analytical methods used to determine urine arsenic concentrations have been described in detail (25). Total urine arsenic concentrations were measured with inductively coupled plasma-mass spectrometry (Agilent 7700x ICP-MS, Agilent Technologies, Waldbronn, Germany). The limit of quantification for total arsenic was 0.2 μg/L. Total arsenic concentrations were above the limit of quantification in all samples. The interassay coefficient of variation for total arsenic was 4.4%. In a blinded quality control analysis, the intraclass correlation coefficient for total arsenic concentrations in 47 duplicate urine aliquots stored in different vials at the time of collection was 0.99.

Arsenic species concentrations were measured by high-performance liquid chromatography and inductively couple plasma-mass spectrometry (Agilent 1100 HPLC and Agilent 7700x ICP-MS). The percentages of participants with concentrations below the limit of detection were 5.3% for inorganic arsenic, 0.7% for monomethylarsonate, 0.03% for dimethylarsinate, and 2.1% for arsenobetaine plus other cations. For participants with arsenic species below the limits of detection, levels were imputed as the limit of detection divided by the square root of 2. An in-house reference urine and the National Institute for Environmental Studies (Ibaraki, Japan) certified reference material No. 18 *Human urine* were analyzed together with the samples. The interassay coefficients of variation for inorganic arsenic, monomethylarsonate, dimethylarsinate, and arsenobetaine plus other cations in the in-house reference urine were 6.0%, 6.5%, 5.9%, and 6.5%, respectively. The intraclass correlation coefficient for the 47 blinded duplicate urines was 0.99 for all arsenic species.

Diabetes measures

Participants were asked to fast for 12 hours before the clinical examination. Plasma glucose was determined by a hexokinase method at the Penn Medical Laboratory, MedStar Health Research Institute, Washington, DC. A 2-hour, 75-g oral glucose tolerance test was performed (24). The oral glucose tolerance test was not performed if the participant was taking insulin or oral hypoglycemic medication or if the fasting glucose level was greater than 225 mg/dL as determined by Acucek II (Baxter Healthcare, Grand Prairie, Texas) (24). HbA1c was measured by a high-performance liquid chromatography method at the laboratory of the National Institute of Diabetes and Digestive and Kidney Diseases Epidemiology and Clinical Research Branch, Phoenix, Arizona (26). Insulin was measured at the

Penn Medical Laboratory by radioimmunoassay (Linco, St. Louis, Missouri).

Diabetes was defined as a fasting glucose level of 126 mg/dL or higher, a 2-hour post-load plasma glucose level of 200 mg/dL or higher, an HbA1c level of 6.5% or higher, or the use of insulin or an oral hypoglycemic agent (27). HOMA-IR was estimated as a surrogate measure of insulin resistance according to the following equation: [fasting plasma insulin (mU/L) × fasting plasma glucose (mmol/L)] / 22.5 (28).

Other variables

Information on age, sex, educational level, smoking, and alcohol status was collected by certified interviewers using a standardized questionnaire (24). Measured height and weight, percent body fat by bioelectrical impedance, and waist and hip circumferences were collected by centrally trained nurses and medical assistants using a standardized protocol (24). Body mass index was calculated as weight in kilograms divided by the square of height in meters. Urine creatinine levels were measured at the laboratory of the National Institute of Diabetes and Digestive and Kidney Diseases Epidemiology and Clinical Research Branch, Phoenix, Arizona, by an automated alkaline picrate method (29).

Statistical analysis

Statistical analyses were performed in Stata, version 11.2 (StataCorp LP, College Station, Texas). Standard errors for regression analyses were estimated by using 1,000 nonparametric bootstrap samples. Because of the high prevalence of diabetes in the study population, we estimated prevalence ratios of diabetes by urine arsenic with the use of Poisson regression models. We considered total urine arsenic a surrogate for exposure to inorganic arsenic and analyzed it in 3 different ways: (1) approximate quartiles; (2) 75th percentile versus 25th percentile of log-transformed arsenic; and (3) restricted cubic splines of log-transformed arsenic, to evaluate potential nonlinear relations. *P* values for trend were estimated, replacing arsenic concentrations by quartile medians. Models were fitted with progressive degrees of adjustment. First, we adjusted for urine creatinine (log-transformed) to account for urine dilution in spot urine samples (30). Second, we further adjusted for age (<55, 55–64, or ≥65 years), sex, educational level (no high school, some high school, or high school completion or more), drinking status (current, former, never), smoking status (current, former, never), and body mass index (<25, 25–29.9, or ≥30). Replacing body mass index with other measures of adiposity, such as percent body fat or waist circumference, gave similar results (data not shown). Third, we further adjusted for study region (Arizona, Oklahoma, or North and South Dakota). Fourth, to compare models with and without adjustment for urine creatinine, we omitted urine creatinine from the models. To evaluate the consistency of the association between arsenic and diabetes prevalence by participant characteristics, we ran additional analyses stratified by sex, age (<55, 55–64, or ≥65 years), region (Arizona, Oklahoma, North and South Dakota), educational level (no high school, some high school, high school or more), body mass index (<25, 25–29.9, ≥30), smoking status (current, former, or never), and alcohol status (never, former, or current). To evaluate differences by diabetes control, in a post hoc analysis, we considered the association of arsenic with diabetes, with cases of diabetes divided into HbA1c categories (<6.5%, ≥6.5 and <7%, ≥7% and <8%, or ≥8%).

The association between urine arsenic concentrations and HbA1c was analyzed in models stratified by diabetes status because in individuals with diabetes, HbA1c reflects diabetes control (31). We used linear regression models to estimate the difference in the percentage of HbA1c by urine arsenic concentrations with the same adjustment strategy described in the primary diabetes analysis. In post hoc analyses, to evaluate whether the association between arsenic and HbA1c levels in persons with diabetes was related to glucose levels or to treatment type, we evaluated the association stratified by fasting blood glucose levels (<126 mg/dL, ≥126 and <180 mg/dL, ≥180 mg/dL) or by diabetes treatment (no medication, oral hypoglycemic medication, insulin).

The relation between urine arsenic concentrations and log-transformed HOMA-IR was analyzed among participants without diabetes. The geometric mean ratio of HOMA-IR with increasing urine arsenic concentrations was estimated by exponentiating the coefficients from linear regression models of log-transformed HOMA-IR, following the same adjustments described in the primary diabetes analysis. All the analyses were repeated with the sum of inorganic and methylated arsenic concentrations in urine instead of total arsenic.

RESULTS

The prevalence of diabetes was 49.4% (Table 1). The median urine arsenic concentration was 14.1 (interquartile range, 7.9–24.2) μg/L (Web Table 1, available at http://aje.oxfordjournals.org/). Urine arsenic concentrations were higher in men, participants with no high school education, participants from Arizona and North and South Dakota, current smokers, current drinkers, and participants with diabetes (Web Table 1). Arsenobetaine concentrations, reflecting seafood arsenicals, were very low (median = 0.8 μg/L, interquartile range, 0.5–1.7). The Spearman correlation coefficients were 0.93 for total arsenic and the sum of inorganic and methylated species, 0.27 for arsenobetaine and the sum of inorganic and methylated species, and 0.47 for total arsenic and arsenobetaine. Urine creatinine concentrations were lower in participants with diabetes than in participants without diabetes (Table 1). Among participants with diabetes, median (25th–75th percentiles) urine creatinine concentrations were 1.21 (0.77–1.76) and 1.02 (0.69–1.47) g/L for participants with HbA1c <8% and ≥8%, respectively.

After adjustment for diabetes risk factors and urine creatinine, the prevalence ratio of diabetes comparing the highest to the lowest quartile of total urine arsenic was 1.55 (95% confidence interval (CI): 1.39, 1.73) (Table 2, model 2). The positive association between urine arsenic and diabetes prevalence was consistent in models entering arsenic

Table 1. Participant Characteristics, Strong Heart Study, 1989–1991

	No Diabetes ($n = 1,986$, 50.6%)			Diabetes ($n = 1,939$, 49.4%)			*P* Value[a]
	No.	%	Mean (SD)	No.	%	Mean (SD)	
Male			879 (44.3)			721 (37.2)	<0.001
Age, years			55.6 (8.1)			56.9 (7.9)	<0.001
Region							
Arizona	412	20.8		900	46.4		<0.001
Oklahoma	774	39.0		541	27.9		
North and South Dakota	800	40.3		498	25.7		
Educational level							
No high school	361	18.2		507	26.2		<0.001
Some high school	461	23.2		528	27.2		
High school or more	1,164	58.6		904	46.6		
Smoking							
Current	779	39.2		530	27.3		<0.001
Former	622	31.3		715	36.9		
Never	585	29.5		694	35.8		
Alcohol consumption							
Current	942	47.4		704	36.3		<0.001
Former	776	39.1		869	44.8		
Never	268	13.5		366	18.9		
Body mass index[b]			29.6 (5.9)			32.2 (6.4)	<0.001
Urine creatinine, g/L[c]			1.22 (0.79–1.75)			1.10 (0.72–1.62)	<0.001
Fasting glucose, mg/dL			101.4 (10.7)			198.5 (79.4)	<0.001
Hemoglobin A1c, %			5.07 (0.53)			8.30 (2.47)	<0.001

Abbreviation: SD, standard deviation.

[a] Nonparametric Kruskal-Wallis tests for equivalence of populations for continuous data, or Pearson's χ^2 tests for independence for categorical data.

[b] Weight (kg)/height $(m)^2$.

[c] Median (25th–75th percentiles).

as log-transformed (Table 2, model 2) or using restricted cubic splines (Web Figure 1). The association between arsenic and diabetes remained statistically significant but was attenuated after further adjustment for study region (Table 2, model 3) and after removal of urine creatinine from the models (Table 2, model 4). Modeling the sum of inorganic and methylated arsenic species instead of total arsenic slightly increased the association between arsenic and diabetes (Web Figure 1). The prevalence ratio of diabetes comparing the 75th to 25th percentiles of total arsenic concentrations was 1.28 (95% CI: 1.20, 1.36) after adjustment for diabetes risk factors, region, and urine creatinine and was 1.18 (95% CI: 1.12, 1.24) without adjustment for urine creatinine (data not shown). Total urine arsenic concentrations were positively associated with prevalent diabetes in analyses stratified by sex, age group, region, educational level, smoking status, drinking status, and body mass index categories (Web Figure 2).

The association between arsenic and diabetes was observed in participants with uncontrolled diabetes (HbA1c ≥8%) but not in participants with controlled diabetes (Table 3, model 3). Among participants with diabetes, arsenic also was associated with having HbA1c ≥8% (Table 3, model 3). These associations were markedly attenuated but remained statistically significant after removal of urine creatinine from the models (Table 3, model 4).

Total urine arsenic was associated with increasing HbA1c levels among participants with prevalent diabetes after adjustment for urine dilution, sociodemographic characteristics, diabetes risk factors, and region (Table 4, models 1–3). The association was markedly attenuated and was no longer statistically significant when urine creatinine was removed from the model (Table 4, model 4). Total urine arsenic was not associated with HbA1c levels among persons without diabetes (Table 4, models 1–4).

In analyses among participants with diabetes, the differences in HbA1c comparing the 75th versus 25th percentiles of arsenic concentrations were −0.04% (95% CI: −0.33, 0.26), 0.11% (95% CI: −0.08, 0.30), and 0.31% (95% CI: 0.08, 0.55) in participants with fasting glucose <126 mg/dL, ≥126 and <180 mg/dL, and ≥180 mg/dL, respectively (Web Table 2, model 3). The association in the latter group disappeared after removal of urine creatinine from the model (Web Table 2, model 4). By diabetes treatment, the

Table 2. Prevalence Ratios of Diabetes by Urine Arsenic Concentrations, Strong Heart Study, 1989–1991

	No. of Cases	No. of Noncases	Model 1[a]		Model 2[b]		Model 3[c]		Model 4[d]	
			Prevalence Ratio	95% CI	Prevalence Ratio	95% CI	Prevalence Ratio	95% CI	Prevalence Ratio	95% CI
Arsenic quartiles										
1 (<7.9 μg/L)	413	558	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
2 (≥7.9 and <14.1 μg/L)	492	507	1.30	1.17, 1.44	1.26	1.14, 1.39	1.15	1.04, 1.27	1.08	0.98, 1.19
3 (≥14.1 and <24.2 μg/L)	503	467	1.41	1.27, 1.57	1.38	1.25, 1.54	1.21	1.08, 1.34	1.11	1.01, 1.22
4 (≥24.2 μg/L)	531	454	1.55	1.39, 1.74	1.55	1.39, 1.73	1.28	1.14, 1.44	1.14	1.04, 1.26
P for trend (quartile medians)			<0.001		<0.001		<0.001		0.02	
75th vs. 25th arsenic percentiles[e]	1,939	1,986	1.24	1.18, 1.31	1.25	1.19, 1.32	1.14	1.08, 1.20	1.06	1.02, 1.11

Abbreviation: CI, confidence interval.

[a] Adjusted for urine creatinine (log-transformed).

[b] Further adjusted for age group (<55, 55–64,or ≥65 years), sex, educational level (no high school, some high school, or completed high school), alcohol consumption (current, former, or never), smoking (current, former, or never), and body mass index (<25, 25–29.9, or ≥30).

[c] Further adjusted for region (Arizona, Oklahoma, of North and South Dakota).

[d] Model 3 without adjustment for urine creatinine.

[e] Arsenic was log-transformed.

differences in HbA1c comparing the 75th versus 25th percentiles of arsenic concentrations were 0.39% (95% CI: 0.14, 0.64), 0.71% (95% CI: 0.40, 1.02), and 0.22% (95% CI: −0.14, 0.57) in participants with diabetes without treatment, on an oral hypoglycemic agent, and on insulin, respectively (Web Table 2, model 3). These associations also disappeared after adjustment for urine creatinine (Web Table 2, model 4). Total urine arsenic was not associated with levels of HOMA-IR in participants without diabetes after adjustment for sociodemographic characteristics and diabetes risk factors (Web Table 3).

DISCUSSION

Inorganic arsenic exposure, measured as total urine arsenic concentrations in urine, was associated with diabetes prevalence in a sample of rural adults from Arizona, Oklahoma, and North and South Dakota who participated in the SHS in 1989–1991. The association remained after adjustment for diabetes risk factors, and although attenuated, it also remained after adjustment by region and after removal of urine creatinine from the models. The association between arsenic and diabetes, however, was restricted to participants with uncontrolled diabetes (HbA1c ≥8%). Consistent with this finding, the association between arsenic and glycated hemoglobin in participants with diabetes was stronger in participants with higher fasting glucose levels and in participants who were untreated or were taking oral hypoglycemic medications. We found no association between urine arsenic and glycated hemoglobin or insulin resistance among persons without diabetes. These findings suggest that urine arsenic could be associated with poorly controlled diabetes in this population.

A major source of exposure to inorganic arsenic in populations around the world is drinking water contaminated with natural mineral deposits (1). In the United States, arsenic in water is a major concern for many small communities, especially in parts of the Southwest, Midwest, and Northeast (22, 32). Arsenic levels in public water systems measured by the Indian Health Service in the SHS communities during the 1990s and 2000s ranged from less than 10 to 61 μg/L in Arizona and from less than 1 to 21 μg/L in North and South Dakota (18). For the Oklahoma communities, arsenic levels were generally less than 10 μg/L (33). These arsenic measures in drinking water are consistent with urine arsenic levels measured in our study. Also, although concentrations of arsenobetaine, a common seafood arsenical, were lower in the SHS than in the US population (13, 14), total urine arsenic concentrations were markedly higher, especially in Arizona and North and South Dakota, which confirms that seafood intake was low and supports that total arsenic reflects inorganic arsenic exposure in this population. Although our study does not have environmental measurements of arsenic exposure, the US Environmental Protection Agency conducted a detailed study of routes of exposure to arsenic in Arizona (National Human Exposure Assessment Survey Phase I Arizona) in 1995–1998 (34–36). Food, beverages, and water were primary routes of

Table 3. Prevalence Ratio for Cases of Diabetes Divided by Categories of Hemoglobin A1c Comparing the 75th Verus 25th Percentiles of Urine Arsenic Concentrations[a], Strong Heart Study, 1989–1991

	No. of Cases	No. of Noncases	Model 1[b]		Model 2[c]		Model 3[d]		Model 4[e]	
			Prevalence Ratio	95% CI	Prevalence Ratio	95% CI	Prevalence Ratio	95% CI	Prevalence Ratio	95% CI
Comparing cases of diabetes divided by categories of HbA1c to no diabetes										
HbA1c ≥6.5% and <7%	682	1,857	1.12	1.01, 1.24	1.11	1.00, 1.23	1.05	0.94, 1.18	1.07	0.98, 1.17
HbA1c ≥7% and <8%	216	1,857	1.14	0.93, 1.38	1.17	0.96, 1.42	0.93	0.74, 1.17	0.88	0.74, 1.05
HbA1c ≥8%	947	1,857	1.57	1.46, 1.70	1.58	1.47, 1.71	1.36	1.25, 1.48	1.13	1.06, 1.21
Among participants with diabetes										
HbA1c ≥8% vs. <8%	947	898	1.32	1.23, 1.41	1.32	1.23, 1.42	1.24	1.15, 1.34	1.07	1.01, 1.14

Abbreviations: CI, confidence interval; HbA1c, hemoglobin A1c.

[a] Arsenic was log-transformed. These analyses were restricted to participants who were not missing HbA1c values.

[b] Adjusted for urine creatinine (log-transformed).

[c] Further adjusted for age group (<55, 55–64,or ≥65 years), sex, educational level (no high school, some high school, or completed high school), alcohol consumption (current, former, or never), smoking (current, former, or never), and body mass index (<25, 25–29.9, or ≥30).

[d] Further adjusted for region (Arizona, Oklahoma, or North and South Dakota).

[e] Model 3 without adjustment for urine creatinine.

Table 4. Differences in % HbA1c by Urine Arsenic Concentrations, Strong Heart Study, 1989–1991

Quartile	No.	Model 1[a]		Model 2[b]		Model 3[c]		Model 4[d]	
		Differences	95% CI	Differences	95% CI	Differences	95% CI	Differences	95% CI
Diabetes									
1 (<8.0 μg/L)	403	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent
2 (≥8.0 and <14.2 μg/L)	452	0.76	0.44, 1.08	0.76	0.44, 1.08	0.61	0.28, 0.94	0.16	−0.16, 0.47
3 (≥14.2 and <24.5 μg/L)	486	1.35	1.03, 1.67	1.33	1.01, 1.66	1.11	0.77, 1.44	0.48	0.17, 0.79
4 (≥24.5 μg/L)	504	1.52	1.16, 1.88	1.51	1.14, 1.87	1.20	0.82, 1.59	0.28	−0.05, 0.60
P for trend (quartile medians)		<0.001		<0.001		<0.001		0.18	
75th vs. 25th arsenic percentiles[e]	1,845	0.77	0.60, 0.93	0.72	0.55, 0.89	0.59	0.40, 0.78	0.11	−0.04, 0.27
No diabetes									
1 (<8.0 μg/L)	523	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent
2 (≥8.0 and <14.2 μg/L)	468	0.10	0.02, 0.17	0.07	0.00, 0.14	0.07	0.00, 0.15	0.08	0.02, 0.14
3 (≥14.2 and <24.5 μg/L)	443	−0.01	−0.09, 0.07	0.00	−0.08, 0.07	0.00	−0.08, 0.07	0.00	−0.06, 0.07
4 (≥24.5 μg/L)	423	−0.05	−0.13, 0.04	−0.02	−0.10, 0.06	−0.02	−0.10, 0.07	−0.01	−0.08, 0.06
P for trend (quartile medians)		0.01		0.15		0.14		0.24	
75th vs. 25th arsenic percentiles[e]	1,857	−0.05	−0.08, −0.01	−0.02	−0.06, 0.02	−0.03	−0.06, 0.01	−0.01	−0.04, 0.02

Abbreviations: CI, confidence interval; HbA1c, hemoglobin A1c.

[a] Adjusted for urine creatinine (log-transformed).

[b] Further adjusted for age group (<55, 55–64,or ≥65 years), sex, educational level (no high school, some high school, or completed high school), alcohol consumption (current, former, or never), smoking (current, former, or never), and body mass index (<25, 25–29.9, or ≥30).

[c] Further adjusted for region (Arizona, Oklahoma, or North and South Dakota).

[d] Model 3 without adjustment for urine creatinine.

[e] Arsenic was log-transformed.

exposure (37). In addition, there was spatial variation in arsenic exposures related to distance from mines (38). Ambient air concentrations of arsenic were low and unlikely to be a primary route of exposure (1, 37).

Several epidemiologic studies have addressed the association of low-moderate arsenic exposure with diabetes (9–12, 16, 39). The association between urine arsenic and prevalent diabetes in our study is consistent with the association found in a representative sample of the US population (9, 10) and in populations from Northern Mexico (39, 40). Two studies, one in the United States (9) and one in Northern Mexico (39), also reported a positive association between arsenic exposure and glycated hemoglobin, although neither evaluated the association in analyses stratified by diabetes status or medication use. Another cross-sectional study found no association between arsenic exposure and glycated hemoglobin in a population from Bangladesh with a low prevalence of diabetes (5). Finally, one study evaluated the association between arsenic exposure and insulin resistance in individuals with and without diabetes from Northern Mexico (39). In that study, inorganic arsenic exposure was positively associated with both diabetes and glycated hemoglobin but was negatively associated with the HOMA-IR (39). In our study, we found no association between arsenic and HOMA-IR among participants without diabetes.

The association between arsenic and poor diabetes control has not been described previously. Poor diabetes control was a major problem in the SHS (41). Younger participants, women, participants with a high-fat diet, and participants with diabetes who were taking oral medication or insulin had worse diabetes control, although insulin improved diabetes control over time (41, 42). High-fat diet could interact with arsenic to induce glucose intolerance with unaffected plasma insulin (7). Poor diabetes control could be confounded by unmeasured characteristics, such as high-fat diet, that could interact with arsenic to produce diabetes. Our findings are also consistent with arsenic inducing a more severe form of diabetes. In our study, however, we could not determine if arsenic affected diabetes control or if poor diabetes control influenced arsenic metabolism and elimination into urine. Persons with poorly controlled diabetes also could have higher exposure to arsenic, possibly through polydipsia and increased consumption of liquids in areas with arsenic-contaminated drinking water. Interestingly, arsenic and diabetes share associations with several health outcomes, including bladder cancer (43, 44) and peripheral artery disease (45, 46). If poor diabetes control increases arsenic exposure, part of the association between diabetes and these health outcomes could be mediated by arsenic.

Our analyses were robust to adjustment for several sociodemographic and diabetes risk factors. Adjustment for region, however, attenuated the associations. This was related to the fact that arsenic levels were higher in regions with a higher burden of diabetes. Although the possibility of confounding by other environmental, social, or healthcare factors related to region cannot be ruled out, these findings also could indicate that long-term exposure to arsenic might influence population-wide diabetes burden in ways that cannot be captured by single determinations of arsenic in middle-aged participants.

Removing urine creatinine from the models markedly attenuated the associations of arsenic with diabetes and with HbA1c. It is known that persons with diabetes have lower urinary concentrations of creatinine (47), possibly because of hyperfiltration (increased glomerular filtration rate) (48), increased liquid intake due to polidypsia, or lower muscle mass (49). In our study, urine creatinine concentrations were markedly lower among participants with HbA1c $\geq$8%, which suggests that diabetes control rather than diabetes itself was related to lower urine creatinine concentrations.

Our study has several limitations. First, the study was cross sectional, and we cannot separate the direction of the association of arsenic with diabetes and with diabetes control. Prospective studies to evaluate the role of arsenic in diabetes development, the role of arsenic in diabetes control, and the role of diabetes and diabetes control in urine arsenic levels are needed. Second, we used a single urine determination as a biomarker of arsenic exposure. In a pilot study in the SHS, urine arsenic concentrations remained relatively constant over a 10-year period (18). Third, the unexpected association between arsenic and diabetes control was the result of a post hoc analysis and requires replication. Important strengths of this study include the standardized study protocols to determine diabetes, diabetes related-traits, and relevant confounders (27); the rigorous laboratory procedures and the low limit of detection of our assay for urine arsenic (25); the low seafood intake in the population, which simplifies the interpretation of urine arsenic; and the wide range of arsenic exposure at levels relevant to many populations in the United States.

In the SHS, a population from rural communities in the United States with a high burden of diabetes, arsenic was associated with poor diabetes control. Prospective studies to evaluate the direction of the relation between poor diabetes control and arsenic exposure are needed. Furthermore, our findings could provide a potential explanation for some of the observed consequences of diabetes, including cancer (43, 44) and cardiovascular disease (43, 45, 50), which could be related to increased arsenic concentrations in patients with poorly controlled diabetes.

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