Arsenic Exposure and Type 2 Diabetes

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Objectives

- **To review the epidemiologic evidence on the association between arsenic exposure and diabetes**
- **To discuss the implications for populations exposed to arsenic at low-moderate levels through drinking water and food**

Arsenic toxicity

- **Poison: median lethal dose 1-4 mg/kg**
- **Carcinogen for skin, lung, and bladder cancer**
- **Increasing evidence supports arsenic role:**
  - **Cardiovascular disease**
  - **Respiratory disease**
  - **Neurocognitive effects**
  - **Immune effects**
  - **Diabetes**

Drinking water: main source of exposure to inorganic arsenic worldwide

Smedley and Kinninburgh. Applied Geochemistry 2002;17:517-568.

Other sources of inorganic arsenic

- **Food: rice, flour, juice, other**




- **Mineral and herbal supplements**
- **Tobacco**
- **Occupational settings**
- **Air pollution**

Consumer reports analyses

November 2012

Concentrations ranged between 1 and 10 µg arsenic / serving

January 2012

Concentrations ranged between 1 and 25 µg arsenic / L

Review

Evaluation of the Association between Arsenic and Diabetes: A National Toxicology Program Workshop Review

Elizabeth A. Maull,[1] Habibul Ahsan,[2] Joshua Edwards,[3] Matthew P. Longnecker,[4] Ana Navas-Acien,[5,6] Jingbo Pi,[7] Ellen K. Silbergeld,[5] Miroslav Styblo,[8] Chin-Hsiao Tseng,[9,10] Kristina A. Thayer,[11] and Dana Loomis[12]

CONCLUSIONS: Existing human data provide limited to sufficient support for an association between arsenic and diabetes in populations with relatively high exposure levels (≥ 150 µg arsenic/L in drinking water). The evidence is insufficient to conclude that arsenic is associated with diabetes in lower exposure (< 150 µg arsenic/L drinking water), although recent studies with better measures of outcome and exposure support an association. The animal literature as a whole was inconclusive; however, studies using better measures of diabetes-relevant end points support a link between arsenic and diabetes.

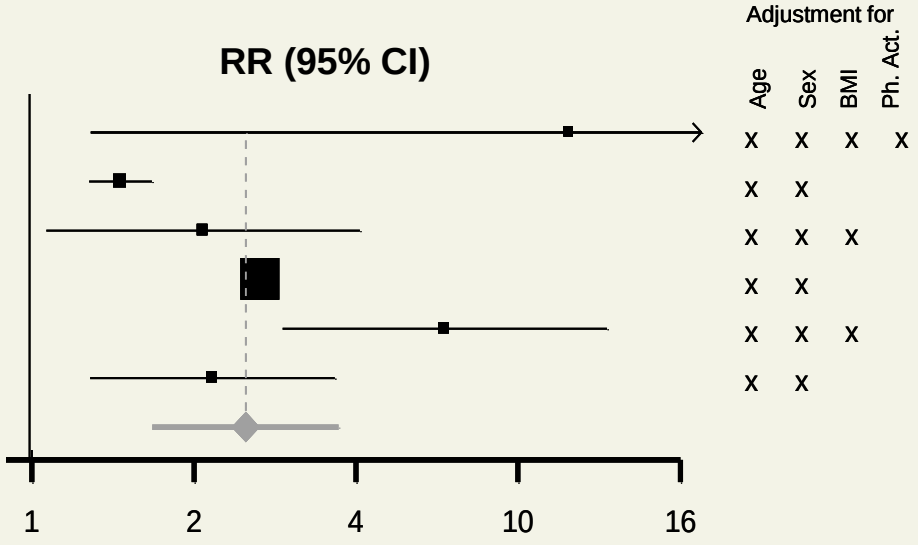
Since the NTP Workshop, a total of 10 studies have been published evaluating the association between arsenic and diabetes, all of them at low-to-moderate levels of exposure

Maull et al. Environ Health Perspect 2012;120:1658-1670

Epidemiologic evidence at high levels of exposure

- **Supportive evidence from Taiwan and Bangladesh**

1st Author, year	Exposed	Reference	RR (95% CI)
Lai, 1994	>15 ppm-y	0 ppm-y	10.1 (1.30, 77.9)
Tsai, 1999	HAA	no HAA	1.46 (1.28, 1.67)
Tseng, 2000	>17 ppm-y	<17ppm-y	2.10 (1.10, 4.20)
Wang, 2003	HAA	no HAA	2.69 (2.65, 2.73)
Rahman, 1998	Keratosis	No Keratosis	5.90 (2.90, 11.6)
Rahman, 1999	> 10 ppm-y	0 ppm-y	2.10 (1.10, 4.20)
		Overall:	**2.52 (1.69, 3.75)**



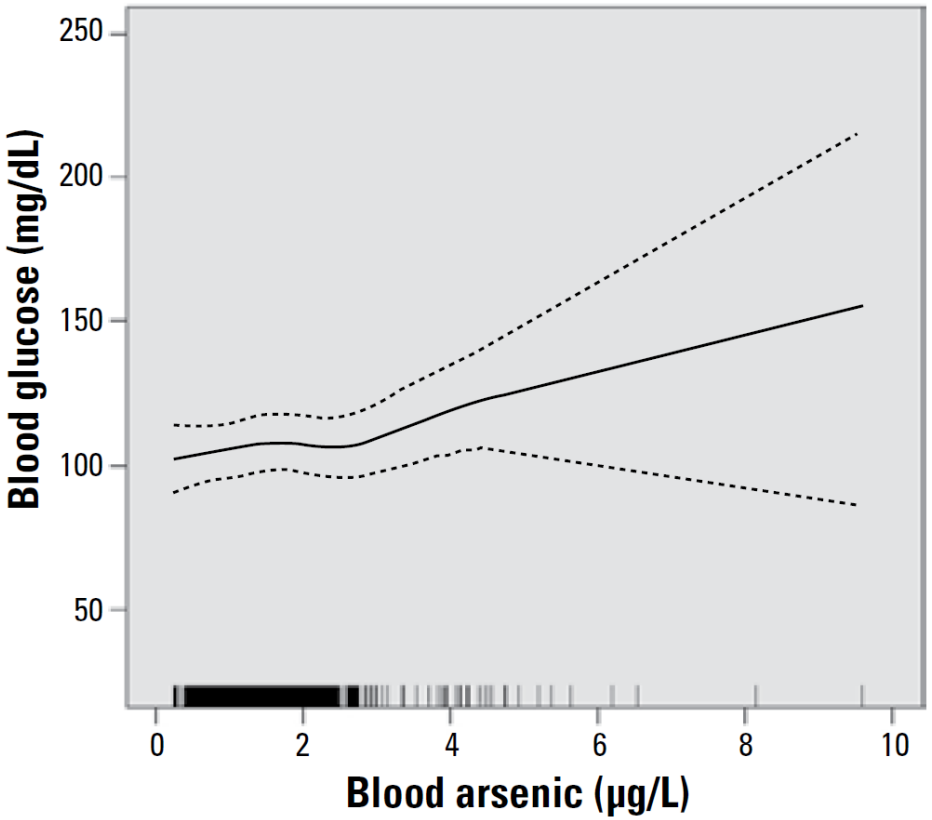
Navas-Acien et al 2006; EHP 113;641-8

- **Mexico (Coronado et al. 2007), OR of diabetes in subjects with total urine arsenic > 104 µg/g vs. <63.5 µg/g = 2.65 (95% CI 1.54, 4.58)**

Evidence from Northern Mexico

- **Coronado et al. Environ Research 2007;104:383-389:**
  - **OR diabetes in subjects with total urine arsenic > 104 µg/g vs. <63.5 µg/g = 2.65 (95% CI 1.54, 4.58)**
- **Del Razo et al. Environ Health 2011;10:73: OR diabetes for a 10 ppb ↑:**
  - **Arsenic in drinking water: 1.13 (95% CI 1.05, 1.22)**
  - **Arsenic in urine: 1.12 (95% CI 0.78, 1.62)**
  - **DMA(III): 1.24 (95% CI 1.00, 1.55)**
  - **Arsenic in drinking water and urine inversely associated with fasting plasma insulin concentrations and HOMA-IR**

Arsenic and gestational diabetes in Oklahoma



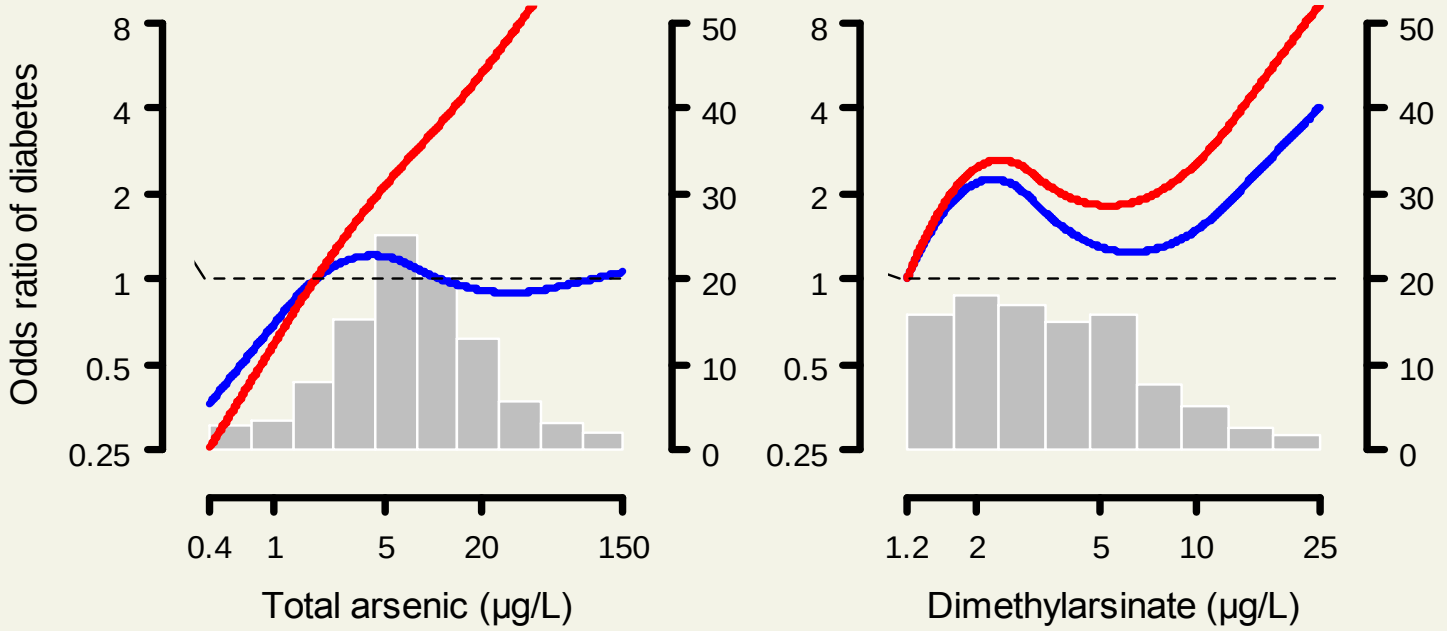
Dose-response adjusted for age, prepregnancy BMI, race, Medicaid, married/partner vs. no partner

Impaired glucose tolerance (>140 mg/dL) at 28 weeks

Blood arsenic (µg/L)	OR[b] (95% CI)
Quartile	
Q1 (0.23–0.92)	1.00 (referent)
Q2 (0.93–1.39)	1.02 (0.39–2.69)
Q3 (1.40–2.08)	2.65 (1.12–6.36)
Q4 (2.09–24.07)	2.79 (1.13–6.87)
p-trend	0.008

Ettinger et al. Environ Health Perspect 2009:117:1059-1064

Arsenic and diabetes in NHANES



Lines represent adjusted odds ratios based on resctricted quadratic splines

Adjusted for sex, age, race and ethnicity, urine creatinine level, education, body mass index, serum cotinine and hypertension medication

Further adjusted for arsenobetaine and blood mercury

Navas-Acien et al. JAMA 2008

Strong Heart Study

A Study of Cardiovascular disease and Diabetes in American Indians funded by the National Heart, Lung and Blood Institute and by the Indian Health Service

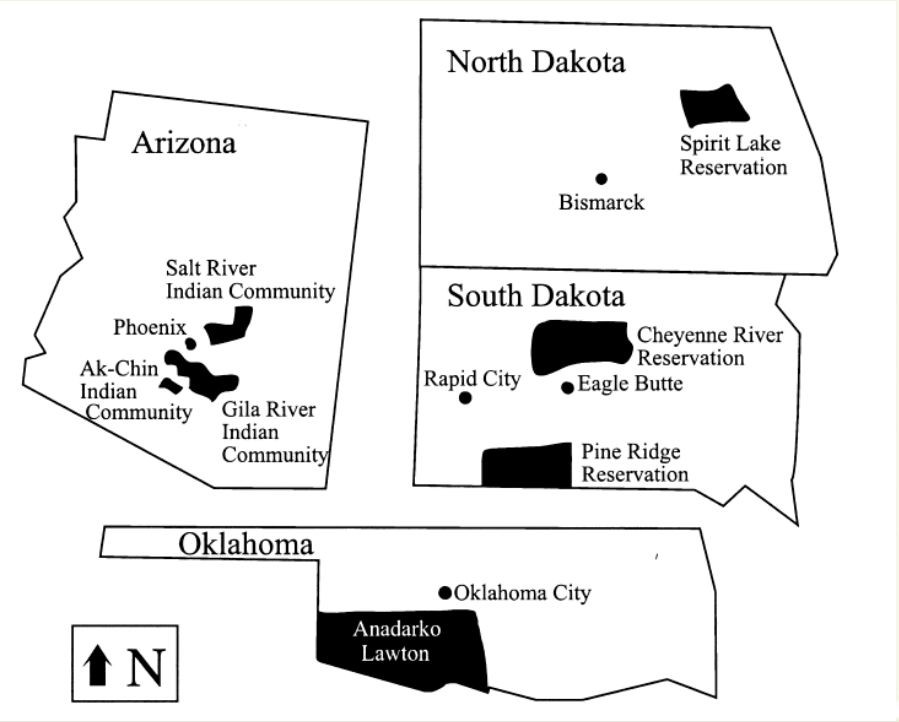
N = 4,549

45 to 74 y in 1989-1991

13 tribes and communities

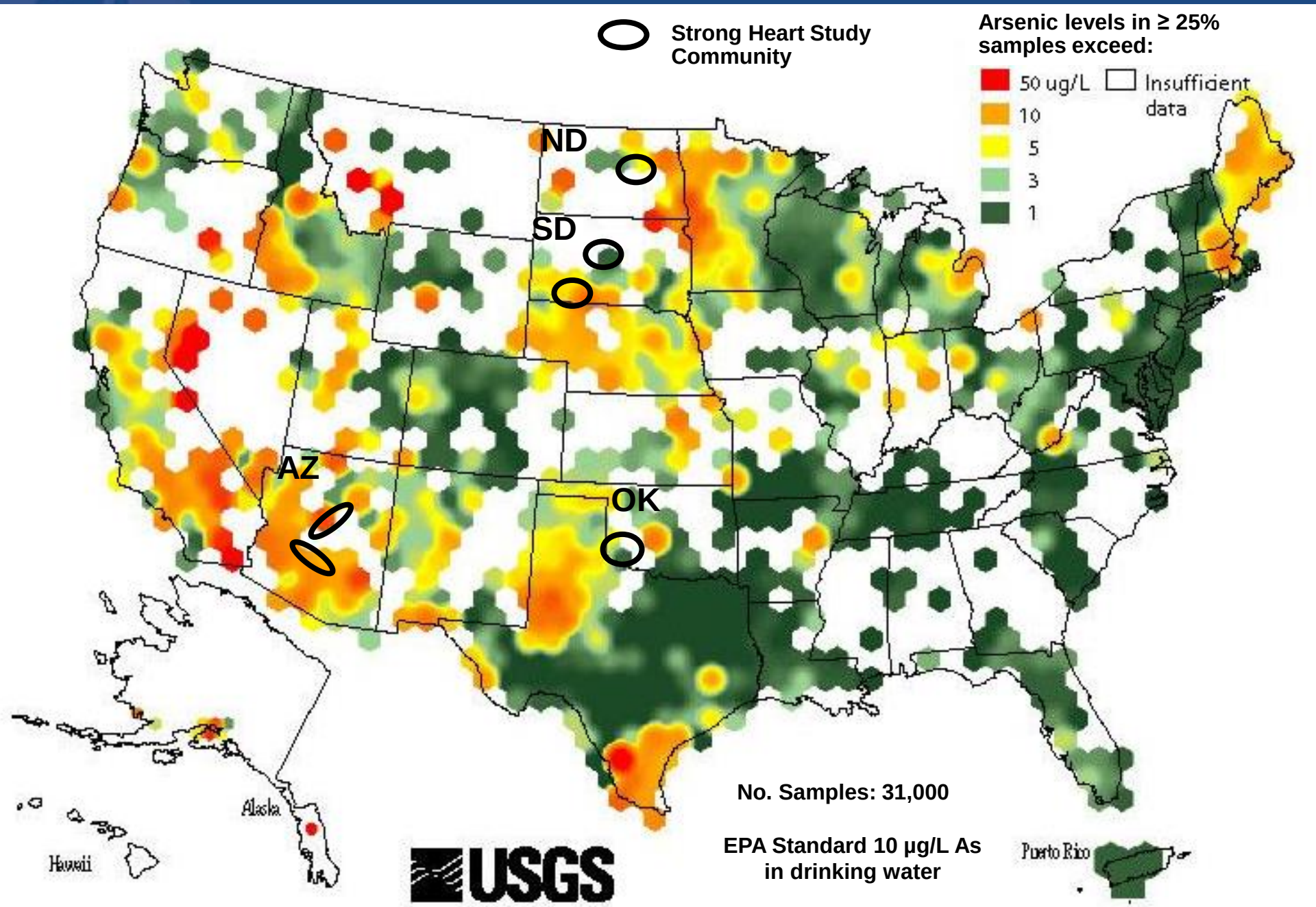
Little seafood

Diabetes prevalence ~50%



http://strongheart.ouhsc.edu

North et al. Am J Epidemiol 2003;157:303–314



Source: Ryker. Geotimes 2001;46:34-36

Prevalence ratio (95% CI) of diabetes by total arsenic levels

	Model 1	Model 2	Model 3	Model 4
Total Arsenic				
Q1 (< 7.92 µg/L)	**1.00 (referent)**	**1.00 (referent)**	**1.00 (referent)**	**1.00 (referent)**
Q2 (7.92 – 14.05 µg/L)	**1.30 (1.17, 1.44)**	**1.26 (1,14, 1.39)**	**1.15 (1.04, 1.27)**	**1.08 (0.99, 1.19)**
Q3 (14.05 – 24.22 µg/L)	**1.41 (1.27, 1.56)**	**1.38 (1.25, 1.52)**	**1.20 (1.08, 1.33)**	**1.10 (1.01, 1.21)**
Q4 (≥ 24.22 µg/L)	**1.55 (1.39, 1.73)**	**1.55 (1.39, 1.72)**	**1.28 (1.15, 1.44)**	**1.14 (1.04, 1.25)**
p for trend	**< 0.001**	**< 0.001**	**< 0.001**	**0.01**
75th to 25th percentile	**1.24 (1.18, 1.31)**	**1.25 (1.19, 1.32)**	**1.14 (1.08, 1.21)**	**1.06 (1.02, 1.11)**

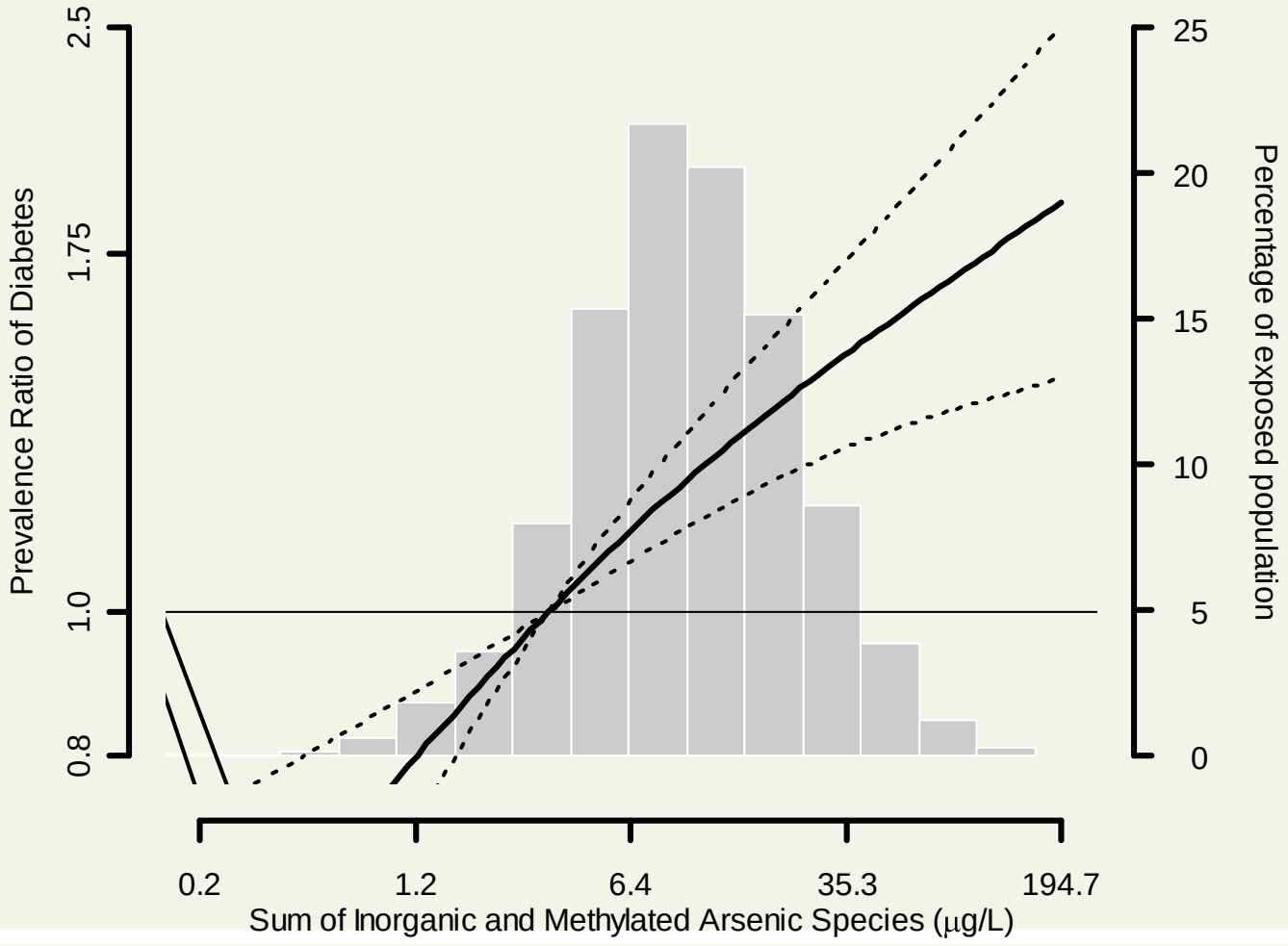
Model 1 adjusted for urine creatinine

Model 2 further adjusted for age group (<55, 55-64, 65+), sex, education (no high school/some high school/completed high school), alcohol (current/former/never), smoking (current/former/never), and body mass index (<25, 24-29, ≥30 kg/m^2)

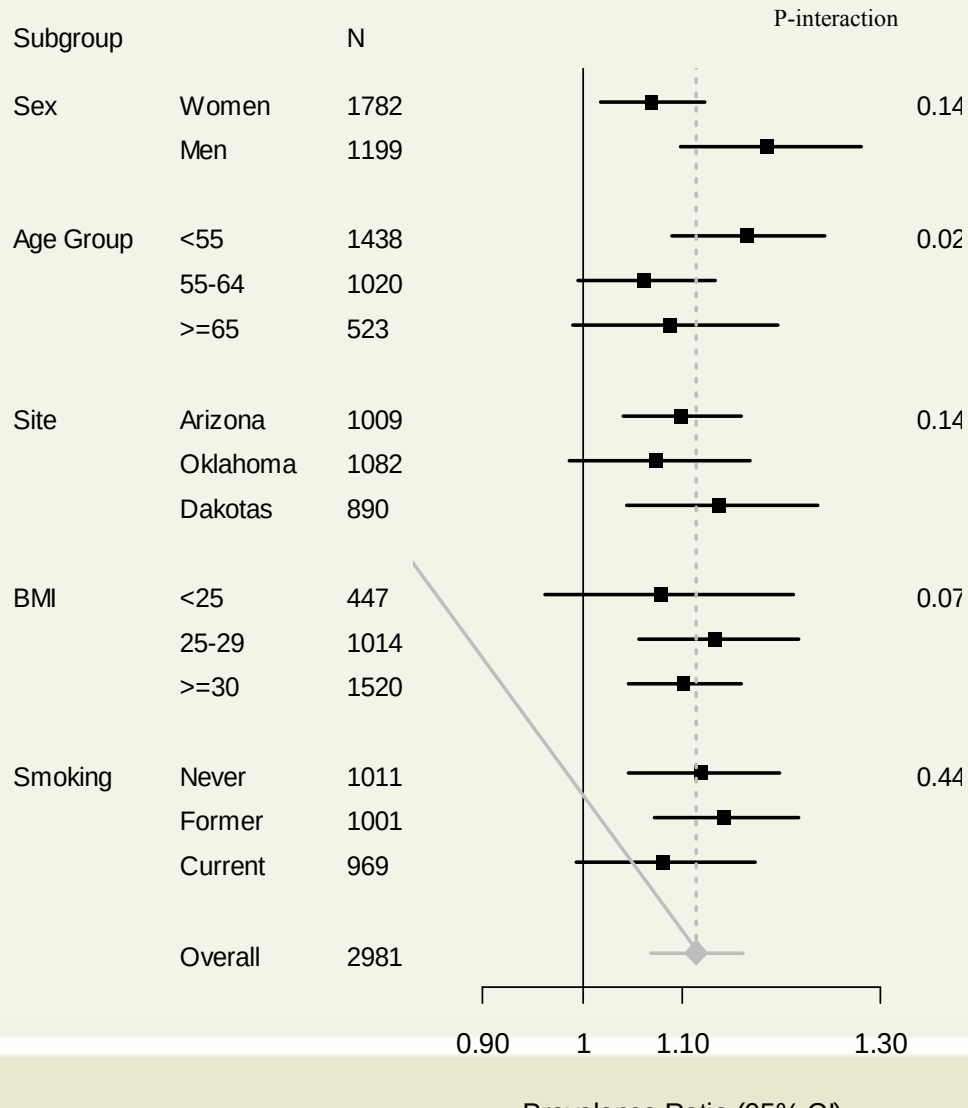
Model 3 further adjusted for region

Model 4 without adjustment for urine creatinine

Dose-response



Prevalence ratio of diabetes for a 2-fold increase in urine arsenic



Ratio (95% CI) of Geometric Mean of HOMA IR by arsenic levels (no diabetes)

	Model 1	Model 2	Model 3	Model 4
Q1 (< 7.30 µg/L)	**1.00 (referent)**	**1.00 (referent)**	**1.00 (referent)**	**1.00 (referent)**
Q2 (7.30 – 12.92 µg/L)	**1.00 (0.90, 1.11)**	**0.97 (0.89, 1.05)**	**0.96 (0.88, 1.05)**	**1.02 (0.94, 1.10)**
Q3 (12.92 – 23.24 µg/L)	**0.99 (0.89, 1.10)**	**0.97 (0.89, 1.06)**	**0.96 (0.87, 1.05)**	**1.03 (0.95, 1.11)**
Q4 (≥ 23.24 µg/L)	**0.87 (0.78, 0.98)**	**0.93 (0.85, 1.02)**	**0.91 (0.83, 1.01)**	**1.01 (0.93, 1.09)**
p for trend*	**0.003**	**0.15**	**0.08**	**0.96**
75^{th} to 25^{th} percentile	**0.92 (0.87, 0.97)**	**0.97 (0.92, 1.01)**	**0.95 (0.91, 1.00)**	**1.01 (0.97, 1.05)**

*Quartile medians

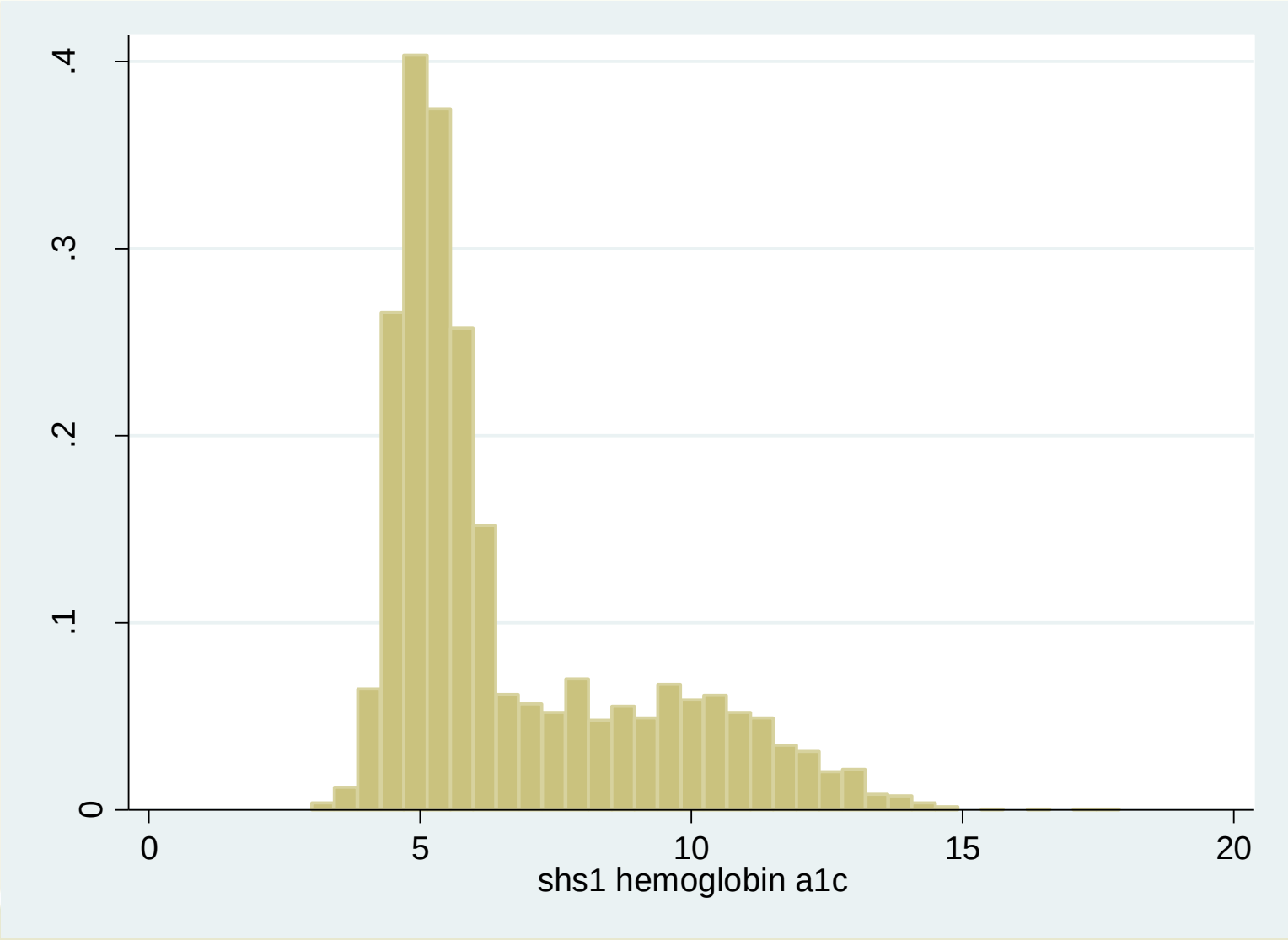
Model 1 adjusted for urine creatinine

Model 2 further adjusted for age (<55, 55-64, 65+), sex, education (no high school/some high school/completed high school), alcohol (current/former/never), smoking (never/former/current), and body mass index (<25, 24-29, ≥30 kg/m^2)

Model 3 further adjusted for region

Model 4 without adjustment for urine creatinine

Distribution of Hba1c in Strong Heart Study participants in 1989-1991



Difference (95% CI) in % HbA1c by total arsenic levels

	Model 1	Model 2	Model 3	Model 4
Diabetes				
Q1 (< 7.92 µg/L)	0.00 (referent)	0.00 (referent)	0.00 (referent)	0.00 (referent)
Q2 (7.92 – 14.05 µg/L)	0.76 (0.43, 1.09)	0.76 (0.43, 1.09)	0.61 (0.27, 0.95)	0.16 (-0.17, 0.48)
Q3 (14.05 – 24.22 µg/L)	1.36 (1.02, 1.69)	1.34 (1.00, 1.68)	1.11 (0.75, 1.47)	0.48 (0.16, 0.81)
Q4 (≥ 24.22 µg/L)	1.52 (1.16, 1.88)	1.50 (1.13, 1.88)	1.20 (0.80, 1.60)	0.28 (-0.06, 0.61)
p for trend	< 0.001	< 0.001	< 0.001	0.20
75^{th} to 25^{th} percentile	0.75 (0.58, 0.92)	0.70 (0.53, 0.87)	0.58 (0.39, 0.77)	0.11 (-0.04, 0.26)
No Diabetes				
Q1 (< 7.92 µg/L)	0.00 (referent)	0.00 (referent)	0.00 (referent)	0.00 (referent)
Q2 (7.92 – 14.05 µg/L)	0.10 (0.03, 0.17)	0.07 (0.01, 0.14)	0.08 (0.01, 0.15)	0.08 (0.02, 0.14)
Q3 (14.05 – 24.22 µg/L)	-0.01 (-0.09, 0.06)	-0.01 (-0.08, 0.07)	-0.01 (-0.08, 0.07)	0.00 (-0.07, 0.07)
Q4 (≥ 24.22 µg/L)	-0.05 (-0.13, 0.03)	-0.02 (-0.10, 0.06)	-0.02 (-0.10, 0.07)	-0.01 (-0.08, 0.06)
p for trend	0.009	0.13	0.12	0.22
75^{th} to 25^{th} percentile	-0.04 (-0.08, -0.01)	-0.02 (-0.06, 0.02)	-0.02 (-0.06, 0.02)	-0.01 (-0.04, 0.02)

Model 1 adjusted for urine creatinine
Model 2 further adjusted for age group (<55, 55-64, 65+), sex, education (no high school/some high school/completed high school), alcohol (current/former/never), smoking (current/former/never), and body mass index (<25, 24-29, ≥30 kg/m^2).
Model 3 further adjusted for site
Model 4 without adjustment for urine creatinine

Conclusions from Strong Heart Study

- **Urine arsenic associated with diabetes prevalence**
- **Urine arsenic associated with glycated hemoglobin among those with diabetes**
- **Urine arsenic not associated with insulin resistance**
- **Prospective evidence needed**

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Original Contribution

Arsenic Exposure and Incidence of Type 2 Diabetes in Southwestern American Indians

Nan Hee Kim, Clinton C. Mason, Robert G. Nelson*, Scott E. Afton, Amal S. Essader, James E. Medlin, Keith E. Levine, Jane A. Hoppin, Cynthia Lin, William C. Knowler, and Dale P. Sandler

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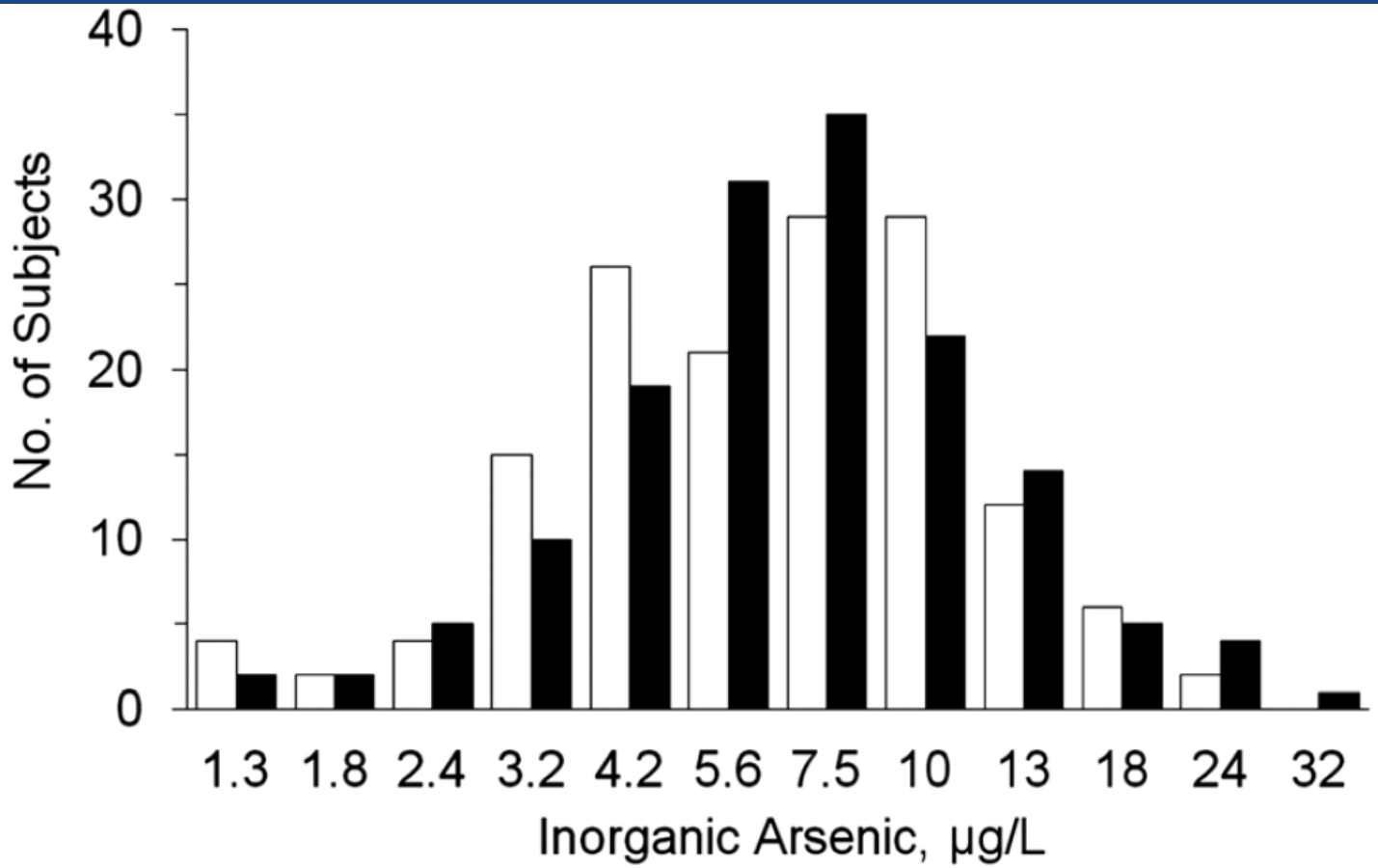

Figure 1. Distributions of total and inorganic urinary arsenic concentrations on a logarithmic scale, adjusted for urinary creatinine concentration and sample date, among southwestern American Indians in Arizona who were screened for diabetes between 1982 and 2007. Black bars, type 2 diabetes cases; white bars, controls.

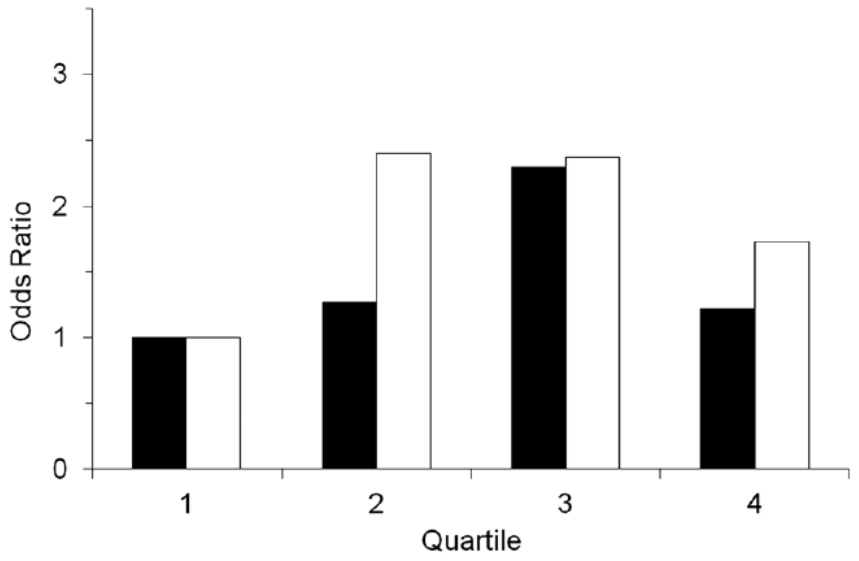

Figure 2. Odds ratios for incident type 2 diabetes among southwestern American Indians in Arizona who were screened for diabetes between 1982 and 2007, by quartiles of total arsenic (black bars) and inorganic arsenic (white bars) concentration, relative to the lowest quartile. Results were obtained from logistic regression models that controlled for age, sex, body mass index, and urinary creatinine concentration. Neither relationship was sta[illegible] but there was a suggestion of higher incidence [illegible] with higher arsenic concentrations, particula[illegible] ($P = 0.12$ for total arsenic; $P = 0.056$ for inc[illegible] values (2-sided) were based on the Wald χ^2 t[illegible]

index, and urinary creatinine concentration. Categorical analyses, however, suggested positive relationships between quartiles of total and inorganic arsenic and incident type 2 diabetes (Figure 2); the stronger relationship was with inorganic arsenic ($P = 0.12$ for total arsenic, $P = 0.056$ for inorganic arsenic). Post-hoc analyses comparing quartiles 2–4 with quartile 1 of inorganic arsenic concentration revealed 2-fold higher odds of diabetes in the upper 3 quartiles (odds ratio = 2.14, 95% confidence interval: 1.19, 3.85).

A case-cohort study examining lifetime exposure to inorganic arsenic in drinking water and diabetes mellitus

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ABSTRACT

Background: Consumption of drinking water with high levels of inorganic arsenic (over 500 μg/L) has been associated with type II diabetes mellitus (DM), but previous studies have been inconclusive about risks at lower levels (< 100 μg/L). We present a case-cohort study based on individual estimates of lifetime arsenic exposure to examine the relationship between chronic low-level arsenic exposure and risk of DM.

Methods: This case-cohort study included 141 cases of DM diagnosed between 1984 and 1998 as part of the prospective San Luis Valley Diabetes Study. A comparison sub-cohort of 488 participants was randomly sampled from 936 eligible participants who were disease free at baseline. Individual lifetime arsenic exposure estimates were determined using a methodology that incorporates the use of a structured interview to determine lifetime residence and employment history, geospatial modeling of arsenic concentrations in drinking water, and urine arsenic concentrations. A Cox proportional hazards model with known DM risk factors as time-dependent covariates was used to assess the association between lifetime exposure to inorganic arsenic in drinking water and incident DM.

Results: Our findings show a significant association between inorganic arsenic exposure and DM risk (hazard ratio [HR]=1.27, 95%=1.01, 1.59 per 15 μg/L) while adjusting for ethnicity and time varying covariates age, body mass index and physical activity level.

Conclusions: Exposure to low-level inorganic arsenic in drinking water is associated with increased risk for type II DM in this population based on a comprehensive lifetime exposure assessment.

Table 3
Cox proportional modeling for the association between inorganic arsenic exposure (standardized by the interquartile range (15 /L) and DM.

Continuous exposure variable	Univariate model HR(95%CI)	Full model HR(95%CI)	Final model HR(95%CI)
Arsenic exposure TWA (per 15 μg/L)*	1.22 (1.03,1.55; p-value=0.03)	1.20 (1.00,1.52; p-value=0.049)	1.27 (1.02,1.64; p-value=0.04)
Female		0.95 (0.66,1.43; p-value=0.34)	
Hispanic		1.59 (1.07,2.31; p-value=0.004)	1.59 (1.19,2.61; p-value=0.002)
Low income		1.17 (0.80,1.82; p-value=0.29)	
BMI (per 5.5 kg/m^2)		1.71 (1.37,2.02; p-value < 0.0001)	1.78 (1.43,1.98; p-value < 0.0001)
Primary family member Diagnosed with DM		1.18 (0.79,1.82; p-value=0.67)	
Sedentary		1.60 (1.01,2.52; p-value=0.03)	1.60 (1.02,2.49; p-value=0.02)
Current/ex smoker		0.77 (0.48,1.24; p-value=0.74)	
High alcohol intake		1.00 (0.43,2.60; p-value=0.83)	
Arsenic exposure TWA 1– < 4 μg/L-yr[a]	1.0	1.0	1.0
≥ 4– < 8 μg/L-yr[b]	1.03 (0.63,1.70; p-value=0.35)	1.10 (0.82,1.92; p-value=0.52)	1.11 (0.82,1.95; p-value=0.52)
≥ 8– < 20 μg/L-yr[c]	1.11 (0.84,1.88; p-value=0.32)	1.42 (0.94,2.48; p-value=0.19)	1.42 (0.94,2.48; p-value=0.19)
≥ 20 μg/L-yr[d]	1.28 (0.99,2.10; p-value=0.05)	1.57 (1.00,2.67; p-value=0.05)	1.55 (1.00,2.51; p-value=0.05)
Female		0.74 (0.50,1.10; p-value=0.14)	
Hispanic		1.74 (1.16,2.58; p-value=0.008)	1.82 (1.25,2.68; p-value=0.002)
Low income		1.22 (0.77,1.93; p-value=0.39)	
BMI (per 5.5 kg/m^2)		1.71 (1.42,2.05; p-value < 0.0001)	1.66 (1.40,1.98; p-value < 0.0001)
Primary family member Diagnosed with DM		1.19 (0.88,1.62; p-value=0.25)	
Sedentary		1.66 (1.06,2.58; p-value=0.03)	1.62 (1.04,2.50; p-value=0.03)
Current/ex smoker		0.87 (0.59,1.24; p-value=0.47)	
High alcohol intake		0.96 (0.37,2.48; p-value=0.94)	

Univariate Model: proportional hazards model with TWA arsenic exposure (main risk factor) as independent variable.
Full Model: proportional hazards model with TWA arsenic exposure (main risk factor) and all listed variables as time dependent independent variables.
Adjusted Model: proportional hazards model with TWA arsenic exposure (main risk factor) and statistically significant covariates (independent variables).
Interaction between gender and BMI was assessed and was not significant (p=0.1410).

* Inter-quartile range of subcohort at baseline.
[a] Person years of follow up=1301.
[b] Person years of follow up=1599.
[c] Person years of follow up=1419.
[d] Person years of follow up=1533.

Summary of the epidemiologic evidence

- **Increasing evidence from populations exposed to low-to-moderate arsenic levels in drinking water in Northern Mexico, Soutwesth US support arsenic is associated with diabetes prevalence**
- **Recent studies also support an association with incident diabetes**
- **Arsenic from food? Rice, grains, juice**
- **Type 1 diabetes?**

Acknowledgments

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