SUPPLEMENTARY DATA

Supplementary Table 1. Standard Reference Material 2669 (SRM 2669)[a].

	iAs (μg/L)	MMA (μg/L)	DMA (μg/L)
Certified values	3880.0	1870.0	3470.0
Measured values			
Average	3506.2	1766.7	2761.7
SD	233.0	258.2	307.2
Recovery (%)	90.4	94.5	79.6
N = 34			

[a]SRM (human urine) was analyzed directly after dilution in deionized water.

Supplementary Table 2. Standard Reference Material 2669 (SRM 2669)[b].

	iAs (μg/L)	MMA (μg/L)	DMA (μg/L)
Certified values	3880.0	1870.0	3470.0
Measured values			
Average	3769.26	1843.69	3087.13
SD	135.15	69.43	102.41
Recovery (%)	97.1	98.6	89.0
N = 12			

[b]SRM was diluted in human plasma (1 : 10) prior to analysis to account for matrix effects.

SUPPLEMENTARY DATA

Supplementary Table 3. Odds ratio (95% confidence interval) for type 1 and type 2 diabetes by plasma arsenic tertiles.

	Type 1 Diabetes				Type 2 Diabetes			
	Cases/ Non Cases	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Cases/ Non Cases	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
ΣAs (ng/L)								
T1: 25.7 - 69.4	137/58	1 (Reference)	1 (Reference)	1 (Reference)	28/58	1 (Reference)	1 (Reference)	1 (Reference)
T2: 69.4 - 103	170/58	1.24 (0.81, 1.91)	1.05 (0.66, 1.66)	0.99 (0.62, 1.61)	40/58	1.43 (0.78, 2.62)	1.58 (0.62, 4.04)	1.78 (0.67, 4.75)
T3: 103 - 1249	122/58	0.89 (0.57, 1.38)	0.87 (0.55, 1.40)	0.83 (0.51, 1.36)	17/58	0.61 (0.30, 1.23)	1.02 (0.36, 2.88)	1.02 (0.35, 2.97)
iAs (ng/L)								
T1: 5.2 - 43.2	177/58	1 (Reference)	1 (Reference)	1 (Reference)	44/58	1 (Reference)	1 (Reference)	1 (Reference)
T2: 43.2 - 58.3	134/58	0.76 (0.49, 1.16)	0.66 (0.42, 1.04)	0.64 (0.39, 1.03)	21/58	0.48 (0.25, 0.90)	0.57 (0.23, 1.39)	0.59 (0.24, 1.45)
T3: 58.3 - 1212	118/58	0.67 (0.43, 1.03)	0.66 (0.42, 1.05)	0.61 (0.37, 1.00)	20/58	0.45 (0.24, 0.87)	0.71 (0.29, 1.72)	0.76 (0.31, 1.86)
MMA (ng/L)								
T1: 0.1 - 5.6	113/58	1 (Reference)	1 (Reference)	1 (Reference)	23/58	1 (Reference)	1 (Reference)	1 (Reference)
T2: 5.6 – 10.9	150/58	1.33 (0.86, 2.06)	1.42 (0.89, 2.27)	1.45 (0.89, 2.37)	22/58	0.96 (0.48, 1.91)	0.46 (0.17, 1.25)	0.39 (0.14, 1.04)
T3: 10.9 - 50.8	166/58	1.47 (0.95, 2.27)	1.53 (0.96, 2.43)	1.58 (0.97, 2.56)	40/58	1.74 (0.92, 3.27)	1.14 (0.47, 2.80)	1.09 (0.46, 2.60)
DMA (ng/L)								
T1: 0.1 - 16.3	112/59	1 (Reference)	1 (Reference)	1 (Reference)	19/59	1 (Reference)	1 (Reference)	1 (Reference)
T2: 16.3 – 26.6	162/57	1.50 (0.97, 2.32)	1.57 (0.98, 2.51)	1.55 (0.95, 2.53)	35/57	1.91 (0.98, 3.73)	1.18 (0.45, 3.08)	1.11 (0.43, 2.90)
T3: 26.6 - 253	155/58	1.41 (0.91, 2.18)	1.48 (0.93, 2.35)	1.47 (0.91, 2.39)	31/58	1.66 (0.84, 3.28)	1.49 (0.57, 3.92)	1.40 (0.54, 3.67)
iAs%								
T1: 7.25 - 55.1	182/58	1 (Reference)	1 (Reference)	1 (Reference)	36/58	1 (Reference)	1 (Reference)	1 (Reference)
T2: 55.1 – 70	147/58	0.81 (0.53, 1.24)	0.78 (0.49, 1.22)	0.77 (0.48, 1.25)	31/58	0.86 (0.47, 1.58)	1.05 (0.42, 2.60)	1.02 (0.41, 2.52)
T3: 70 - 97.5	100/58	0.55 (0.35, 0.85)	0.52 (0.33, 0.84)	0.49 (0.30, 0.81)	18/58	0.50 (0.25, 0.98)	0.89 (0.33, 2.39)	0.94 (0.35, 2.52)
MMA%								
T1: 0.08 - 7.9	122/58	1 (Reference)	1 (Reference)	1 (Reference)	22/58	1 (Reference)	1 (Reference)	1 (Reference)

|		Model 1	Model 2	Model 3		Model 1	Model 2	Model 3
T2: 7.9 - 13.8	142/58	1.16 (0.75, 1.80)	1.13 (0.71, 1.80)	1.16 (0.71 1.89)	28/58	1.27 (0.65, 2.49)	0.90 (0.34, 2.37)	0.84 (0.32, 2.16)
T3: 13.8 - 31.6	165/58	1.35 (0.88, 2.09)	1.39 (0.87, 2.20)	1.48 (0.91 2.42)	35/58	1.59 (0.83, 3.05)	0.95 (0.36, 2.45)	0.93 (0.37, 2.37)
DMA%								
T1: 0.2 – 20.9	107/58	1 (Reference)	1 (Reference)	1 (Reference)	20/58	1 (Reference)	1 (Reference)	1 (Reference)
T2: 20.9 - 30.3	135/58	1.26 (0.81, 1.97)	1.31 (0.82, 2.10)	1.33 (0.81 2.17)	27/58	1.35 (0.68, 2.68)	1.12 (0.42, 2.98)	1.10 (0.42, 2.93)
T3: 30.3 - 81.9	187/58	1.75 (1.13, 2.70)	1.80 (1.13, 2.86)	1.86 (1.14 3.03)	38/58	1.90 (0.99, 3.66)	1.39 (0.55, 3.51)	1.34 (0.53, 3.40)

Cut-points for tertiles categories were obtained based on the corresponding arsenic distributions among control participants.

Model 1 is unadjusted; Model 2 adjusted for age at visit (years), sex, body mass index, parental educational level and race; Model 3 further adjusted for total folate levels and vitamin B12 levels.

Abbreviations: OR, odds ratio; CI, confidence interval; ΣAs, sum of iAs, MMA and DMA; iAs, inorganic arsenic; MMA, monomethylarsonate; DMA, dimethylarsinate; T1, T2 and T3, first tertile, second tertile and third tertile, respectively.
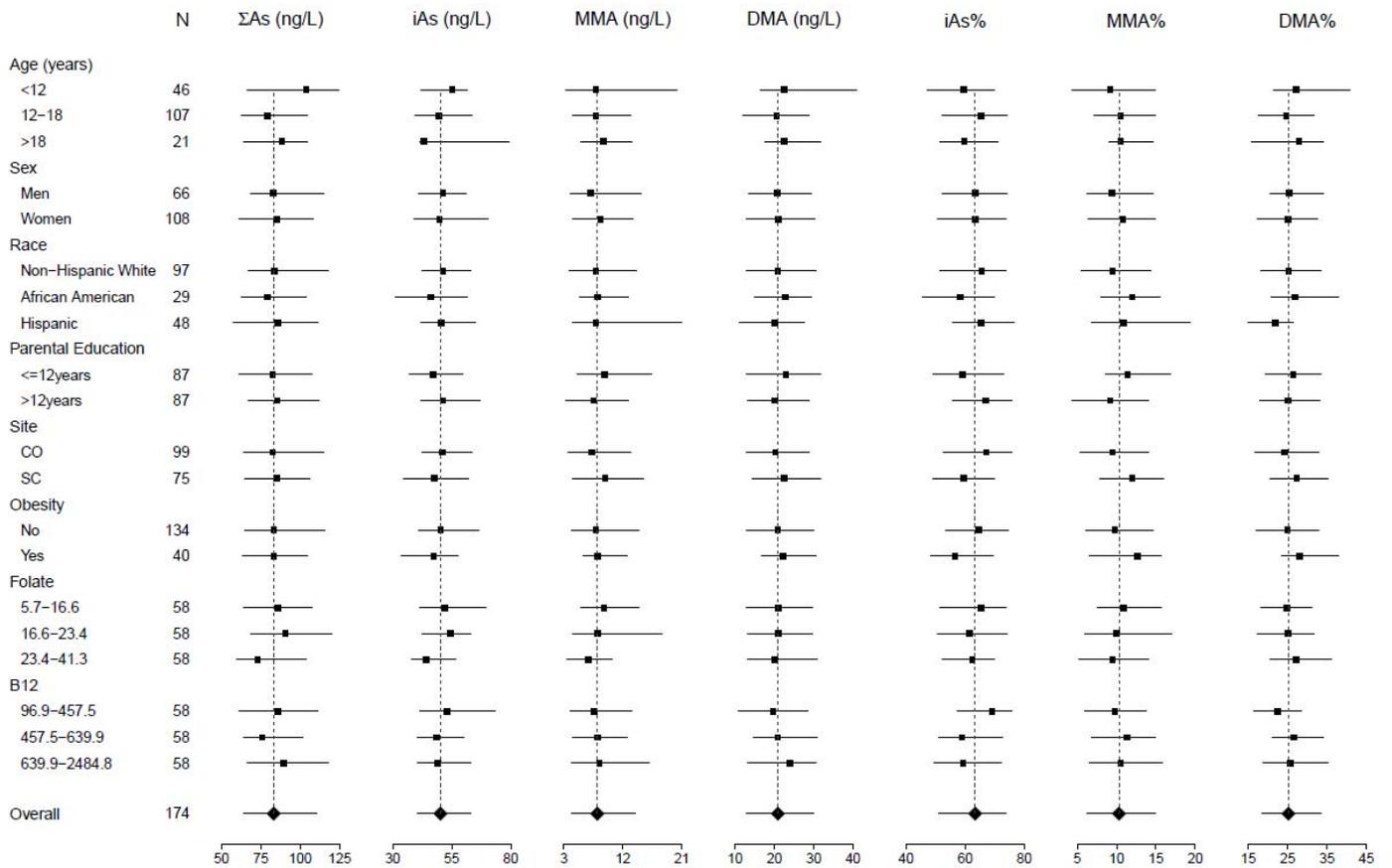
SUPPLEMENTARY DATA

Supplementary Figure 1. Pairwise correlations of total plasma arsenic (ΣAs), arsenic metabolism biomarkers (iAs%, MMA% and DMA%), total folate and vitamin B12. Total plasma arsenic is log-transformed. The diagonal shows the distribution of each variable. The lower panel represents scatterplots for the correlation between each pair of variables and the flexible relationship using locally weighted scatterplot smoothing. The upper panel represents the Spearman pairwise correlation coefficients between variables. The units of the X an Y axes are log(ng/L) for total arsenic percentages for each arsenic metabolism biomarker, and μg/L for total folate and vitamin B12 levels.
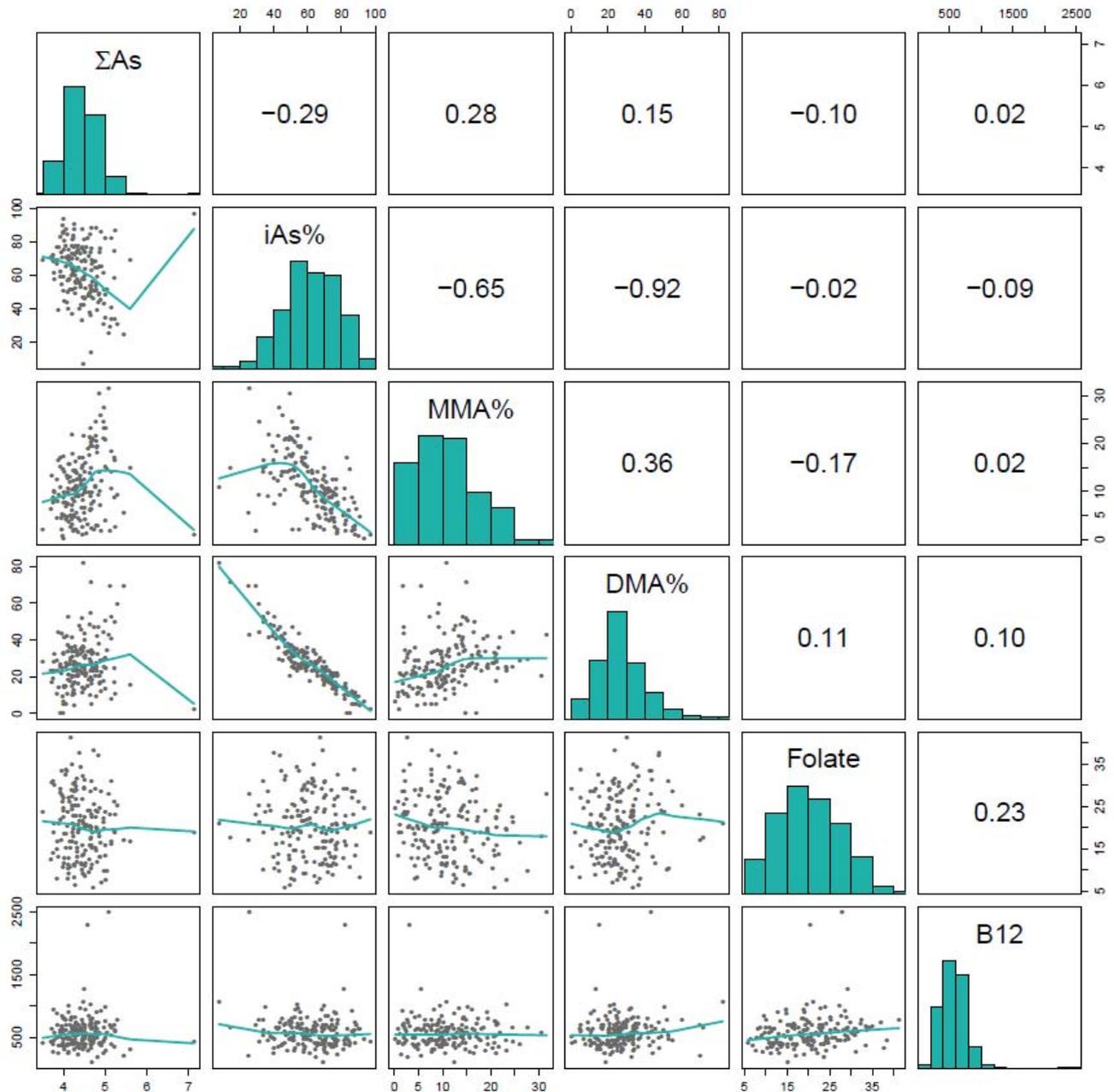
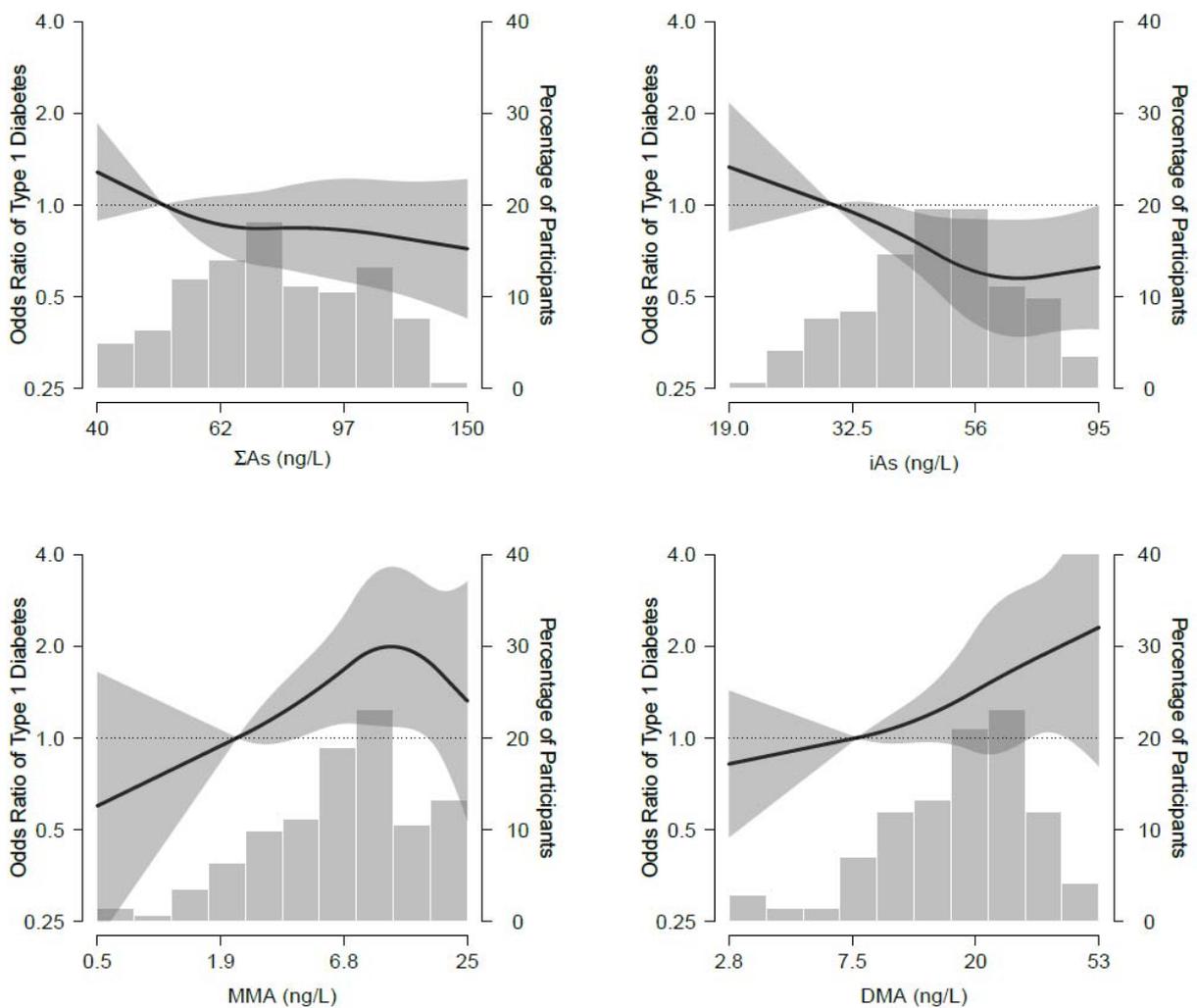**Supplementary Figure 2. Median (interquartile range) of total arsenic (ΣAs), and inorganic arsenic species concentrations (iAs, MMA and DMA) and percentages (iAs%, MMA% and DMA%) by participant characteristics.** Medians and interquartile ranges of arsenic variable concentrations in subgroups were obtained among control participants.
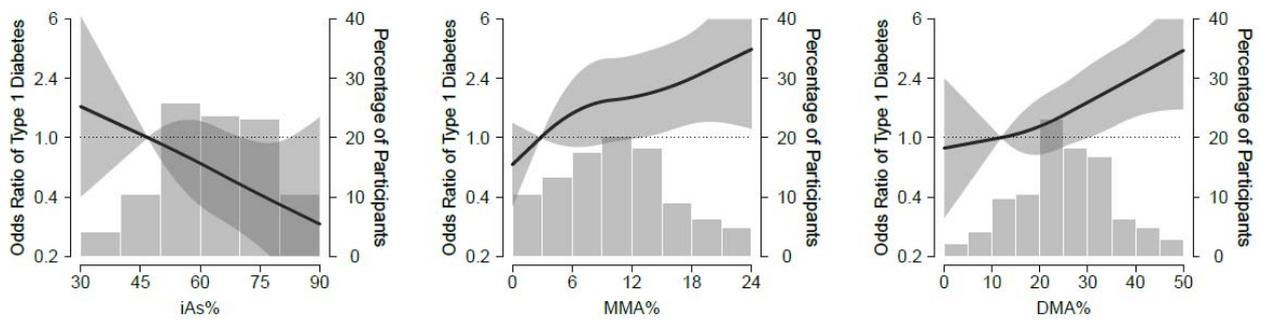
Supplementary Figure 3. Odds ratio (solid line) and 95% confidence interval (shaded area) for type 1 diabetes by plasma concentration of total plasma arsenic (ΣAs=iAs+MMA+DMA) and arsenic species (iAs, MMA and DMA). The lines represent adjusted odds ratios of type 1 diabetes based on restricted quadratic splines for each log-transformed arsenic concentration with knots at the 10th, 50th and 90th percentiles of each arsenic concentration distribution among controls. Shaded areas surrounding the lines represent the 95% confidence intervals. The reference was set at the 10th percentile of each arsenic concentration distribution among controls. Odds ratios were adjusted for age (continuous), sex, body mass index (continuous), parental educational level (≤12, >12 years), race/ethnicity (White/African-American/Hispanic), total folate levels (continuous) and vitamin B12 levels (continuous). Bars represent the distribution of each arsenic concentration within controls. For this figure, we excluded participants with extreme low or high values in the arsenic variables.
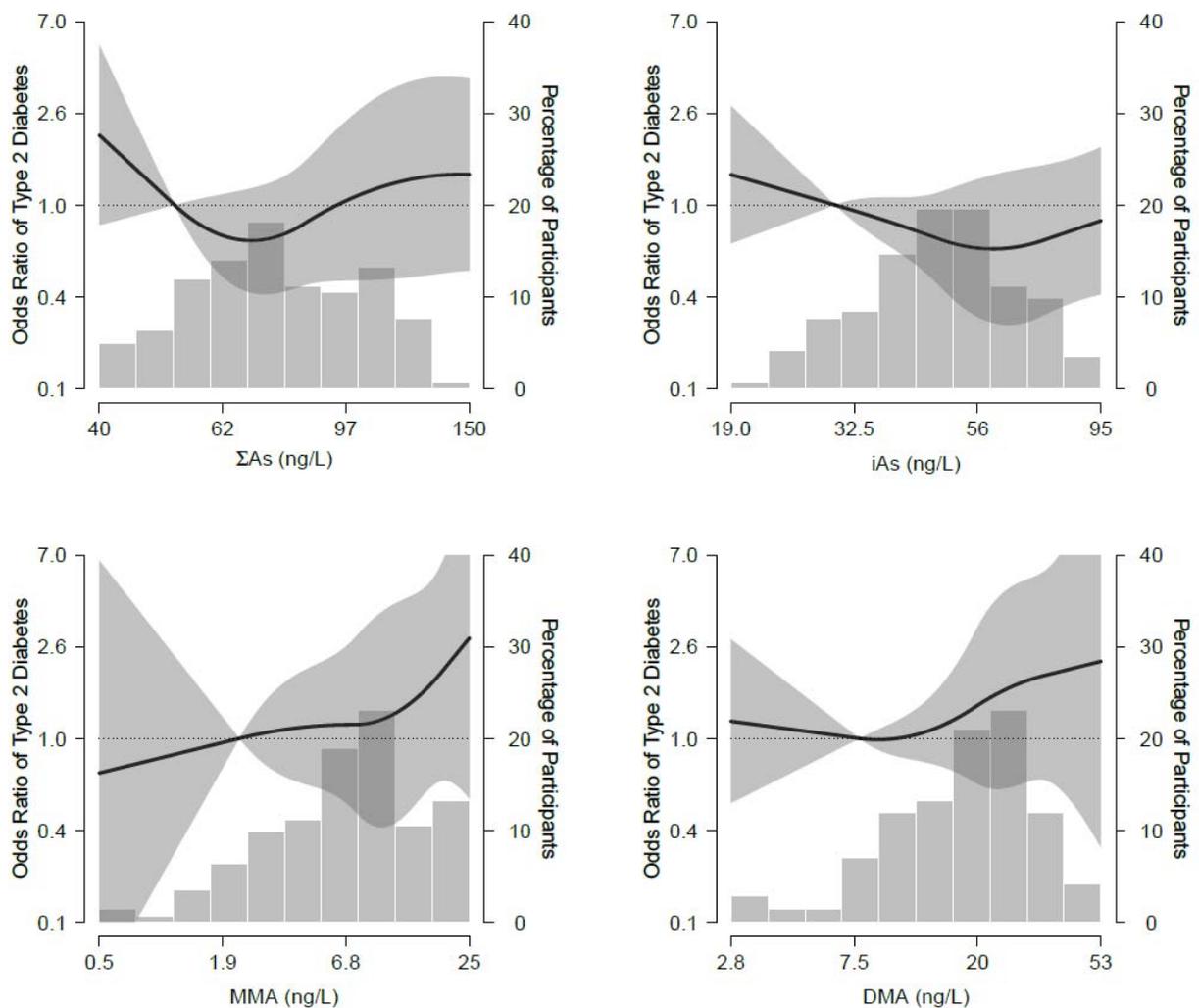
SUPPLEMENTARY DATA

Supplementary Figure 4. Odds ratio (solid line) and 95% confidence interval (shaded area) for diabetes type 1 by arsenic metabolism biomarkers (iAs%, MMA% and DMA%). The lines represent adjusted odds ratios of type 1 diabetes based on restricted quadratic splines for each arsenic percentage with knots at the 10th, 50th and 90th percentiles of each arsenic percentage distribution among controls. Shaded areas surrounding the lines represent the 95% confidence intervals. The reference was set at the 10th percentile of each arsenic percentage distribution among controls. Odds ratios were adjusted for age (continuous), sex, body mass index (continuous), parental educational level (≤12, >12 years), race/ethnicity (Non-Hispanic White/African American/Hispanic), total folate levels (continuous) and vitamin B12 levels (continuous). Bars represent the distribution of each arsenic percentage within controls. For this figure, we excluded participants with extreme low or high values in the arsenic variables.
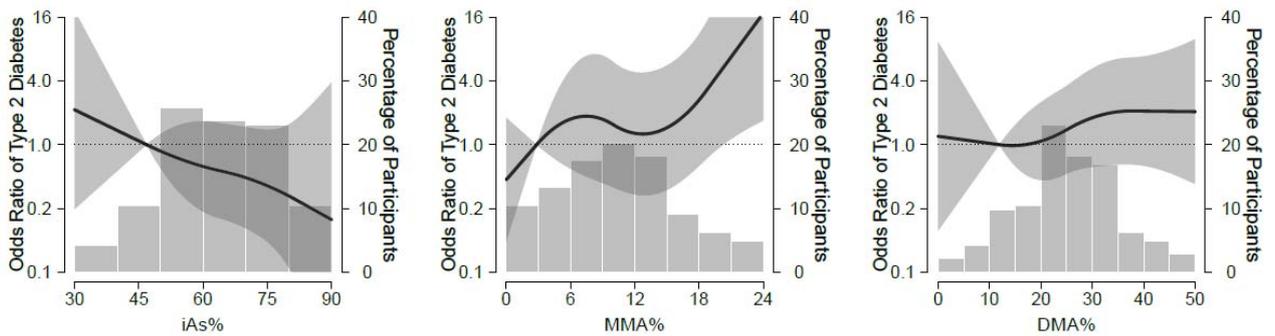
Supplementary Figure 5. Odds ratio (solid line) and 95% confidence interval (shaded area) for type 2 diabetes by plasma total arsenic (ΣAs) and methylated arsenic species (iAs, MMA and DMA) concentrations. The lines represent adjusted odds ratios of type 2 diabetes based on restricted quadratic splines for each log-transformed arsenic concentration with knots at the 10th, 50th and 90th percentiles of each arsenic concentration distribution among controls. Shaded areas surrounding the lines represent the 95% confidence intervals. The reference was set at the 10th percentile of each arsenic concentration distribution among controls. Odds ratios were adjusted for age (continuous), sex, body mass index (continuous), parental educational level (≤12, >12 years), race/ethnicity (White/African-American/Hispanic), total folate levels (continuous) and vitamin B12 levels (continuous). Bars represent the distribution of each arsenic concentration within controls. For this figure, we excluded participants with extreme low or high values in the arsenic variables.

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Supplementary Figure 6. Odds ratio (solid line) and 95% confidence interval (shaded area) for diabetes type 2 by arsenic metabolism biomarkers (iAs%, MMA% and DMA%). The lines represent adjusted odds ratios of type 2 diabetes based on restricted quadratic splines for each arsenic percentage with knots at the 10th, 50th and 90th percentiles of each arsenic percentage distribution among controls. Shaded areas surrounding the lines represent the 95% confidence intervals. The reference was set at the 10th percentile of each arsenic percentage distribution among controls. Odds ratios were adjusted for age (continuous), sex, body mass index (continuous), parental educational level (≤12, >12 years), race/ethnicity (White/African-American/Hispanic), total folate levels (continuous) and vitamin B12 levels (continuous). Bars represent the distribution of each arsenic percentage within controls. For this figure, we excluded participants with extreme low or high values in the arsenic variables.

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Supplementary Table 4. Odds ratio (95% confidence interval) for type 1 and type 2 diabetes comparing interquartile range increase (i.e. participants in the 75th versus the 25th percentiles) in measures of arsenic species in plasma, in models further adjusted by geographical area.

	p75 vs. p25*	Type 1 Diabetes Model 4 OR (95% CI)	Type 2 Diabetes Model 4 OR (95% CI)
Concentrations of Arsenic Species			
ΣAs (ng/L)	110.3 vs 63.8	0.89 (0.71, 1.12)	1.03 (0.65, 1.63)
iAs (ng/L)	63.1 vs 40.7	0.84 (0.71, 0.98)	0.94 (0.69, 1.28)
MMA (ng/L)	13.9 vs 4.2	1.22 (0.94, 1.58)	1.05 (0.63, 1.77)
DMA (ng/L)	30.1 vs 13	1.16 (0.94, 1.43)	1.13 (0.73, 1.74)
Arsenic Metabolism Biomarkers			
iAs%	74 vs 51.2	0.67 (0.51, 0.89)	0.81 (0.48, 1.38)
MMA%	14.9 vs 6.3	1.32 (1.03, 1.69)	1.11 (0.67, 1.86)
DMA%	33.5 vs 18.6	1.30 (1.04, 1.63)	1.17 (0.77, 1.77)

*75th and 25th percentiles of each arsenic variable distribution were among control participants.
Model was adjusted for age at visit (years), sex, body mass index, parental educational level, race, total folate, vitamin B12 levels and geographical area.
Abbreviations: OR, odds ratio; CI, confidence interval; ΣAs, sum of iAs, MMA and DMA; iAs, inorganic arsenic; MMA, monomethylarsonate; DMA, dimethylarsinate; p75, 75th percentile; p25, 25th percentile.

SUPPLEMENTARY DATA

Supplementary Table 5. Odds ratio (95% confidence interval) for type 1 and type 2 diabetes comparing interquartile range increase (i.e. participants in the 75th versus the 25th percentiles) in measures of arsenic species in plasma after excluding participants with extreme arsenic values. (143 controls, 363 type 1 diabetes cases and 71 type 2 diabetes cases)

	p75 vs. p25*	Type 1 Diabetes			Type 2 Diabetes		
		Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Concentrations of Arsenic Species							
ΣAs (ng/L)	110.3 vs 63.8	0.99 (0.72, 1.37)	0.98 (0.69, 1.39)	0.93 (0.65, 1.33)	0.82 (0.49, 1.35)	0.90 (0.45, 1.80)	0.97 (0.48, 1.95)
iAs (ng/L)	63.1 vs 40.7	0.76 (0.60, 0.97)	0.75 (0.58, 0.97)	0.70 (0.54, 0.92)	0.55 (0.38, 0.81)	0.68 (0.41, 1.14)	0.75 (0.45, 1.26)
MMA (ng/L)	13.9 vs 4.2	1.46 (1.09, 1.95)	1.44 (1.05, 1.96)	1.42 (1.03, 1.96)	1.76 (1.11, 2.79)	1.42 (0.75, 2.67)	1.41 (0.74, 2.65)
DMA (ng/L)	30.1 vs 13	1.35 (1.07, 1.70)	1.36 (1.06, 1.74)	1.33 (1.03, 1.72)	1.37 (0.93, 2.03)	1.20 (0.71, 2.02)	1.20 (0.71, 2.02)
Arsenic Metabolism Biomarkers							
iAs%	74 vs 51.2	0.52 (0.37, 0.73)	0.50 (0.34, 0.73)	0.49 (0.33, 0.71)	0.39 (0.23, 0.66)	0.53 (0.26, 1.06)	0.57 (0.28, 1.15)
MMA%	14.9 vs 6.3	1.50 (1.11, 2.03)	1.48 (1.08, 2.04)	1.53 (1.10, 2.13)	2.18 (1.41, 3.37)	1.72 (0.95, 3.10)	1.66 (0.91, 3.02)
DMA%	33.5 vs 18.6	1.59 (1.20, 2.11)	1.65 (1.22, 2.24)	1.67 (1.22, 2.27)	1.76 (1.14, 2.70)	1.43 (0.80, 2.57)	1.35 (0.75, 2.44)

*75th and 25th percentiles of each arsenic variable distribution were among control participants.

Model 1 is unadjusted; Model 2 adjusted for age at visit (years), sex, body mass index, parental educational level and race; Model 3 further adjusted for total folate and vitamin B12 levels.

Abbreviations: OR, odds ratio; CI, confidence interval; ΣAs, sum of iAs, MMA and DMA; iAs, inorganic arsenic; MMA, monomethylarsonate; DMA, dimethylarsinate; p75, 75th percentile; p25, 25th percentile.

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Supplementary Table 6. Odds ratio (95% confidence interval) for type 1 diabetes comparing interquartile range increase (i.e. participants in the 75th versus the 25th percentiles) in measures of arsenic species in plasma based on 1:1 ratio of cases and controls (174 T1D cases randomly selected).

| | Type 1 Diabetes (174 cases vs. 174 controls) | | |
	p75 vs. p25[*]	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Concentrations of Arsenic Species				
ΣAs (ng/L)	110.3 vs 63.8	0.84 (0.64, 1.10)	0.79 (0.59, 1.06)	0.77 (0.57, 1.03)
iAs (ng/L)	63.1 vs 40.7	0.79 (0.65, 0.96)	0.72 (0.58, 0.89)	0.70 (0.56, 0.88)
MMA (ng/L)	13.9 vs 4.2	1.33 (0.99, 1.79)	1.34 (0.98, 1.83)	1.33 (0.97, 1.82)
DMA (ng/L)	30.1 vs 13	1.11 (0.89, 1.39)	1.12 (0.88, 1.41)	1.11 (0.88, 1.42)
Arsenic Metabolism Biomarkers				
iAs%	74 vs 51.2	0.66 (0.48, 0.89)	0.58 (0.42, 0.81)	0.58 (0.41, 0.80)
MMA%	14.9 vs 6.3	1.47 (1.11, 1.95)	1.57 (1.17, 2.12)	1.58 (1.16, 2.14)
DMA%	33.5 vs 18.6	1.28 (1.00, 1.63)	1.40 (1.07, 1.82)	1.42 (1.09, 1.86)

*75th and 25th percentiles of each arsenic variable distribution were among control participants.
Model 1 is unadjusted; Model 2 adjusted for age at visit (years), sex, body mass index, parental educational level and race; Model 3 further adjusted for total folate and vitamin B12 levels.
Abbreviations: OR, odds ratio; CI, confidence interval; ΣAs, sum of iAs, MMA and DMA; iAs, inorganic arsenic; MMA, monomethylarsonate; DMA, dimethylarsinate; p75, 75th percentile; p25, 25th percentile.

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Supplementary Table 7. Odds ratio (95% confidence interval) for typ1 and type 2 diabetes combined comparing interquartile range increase (i.e. participants in the 75th versus the 25th percentiles) in measures of arsenic species in plasma.

	p75 vs. p25*	Diabetes Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Concentrations of Arsenic Species				
ΣAs (ng/L)	110.3 vs 63.8	0.90 (0.73, 1.11)	0.93 (0.75, 1.15)	0.92 (0.74, 1.15)
iAs (ng/L)	63.1 vs 40.7	0.87 (0.75, 1.00)	0.88 (0.76, 1.02)	0.87 (0.75, 1.01)
MMA (ng/L)	13.9 vs 4.2	1.22 (0.96, 1.54)	1.21 (0.95, 1.54)	1.21 (0.95, 1.56)
DMA (ng/L)	30.1 vs 13	1.15 (0.95, 1.39)	1.15 (0.94, 1.40)	1.14 (0.93, 1.40)
Arsenic Metabolism Biomarkers				
iAs%	74 vs 51.2	0.73 (0.56, 0.94)	0.72 (0.56, 0.94)	0.71 (0.54, 0.93)
MMA%	14.9 vs 6.3	1.29 (1.03, 1.63)	1.31 (1.03, 1.65)	1.33 (1.04, 1.70)
DMA%	33.5 vs 18.6	1.22 (0.99, 1.50)	1.22 (0.99, 1.51)	1.23 (0.99, 1.53)

*75th and 25th percentiles of each arsenic variable distribution were among control participants.

Model 1 is unadjusted; Model 2 adjusted for age at visit (years), sex, body mass index, parental educational level and race; Model 3 further adjusted for total folate and vitamin B12 levels.

Abbreviations: OR, odds ratio; CI, confidence interval; ΣAs, sum of iAs, MMA and DMA; iAs, inorganic arsenic; MMA, monomethylarsonate; DMA, dimethylarsinate; p75, 75th percentile; p25, 25th percentile.