Arsenic exposure and type 2 diabetes: results from the 2007–2009 Canadian Health Measures Survey

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Abstract

Introduction: Inorganic arsenic and its metabolites are considered dangerous to human health. Although several studies have reported associations between low-level arsenic exposure and diabetes mellitus in the United States and Mexico, this association has not been studied in the Canadian population. We evaluated the association between arsenic exposure, as measured by total arsenic concentration in urine, and the prevalence of type 2 diabetes (T2D) in 3151 adult participants in Cycle 1 (2007–2009) of the Canadian Health Measures Survey (CHMS).

Methods: All participants were tested to determine blood glucose and glycated hemoglobin. Urine analysis was also performed to measure total arsenic. In addition, participants answered a detailed questionnaire about their lifestyle and medical history. We assessed the association between urinary arsenic levels and T2D and prediabetes using multivariate logistic regression while adjusting for potential confounders.

Results: Total urinary arsenic concentration was positively associated with the prevalence of T2D and prediabetes: adjusted odds ratios were 1.81 (95% CI: 1.12–2.95) and 2.04 (95% CI: 1.03–4.05), respectively, when comparing the highest (fourth) urinary arsenic concentration quartile with the lowest (first) quartile. Total urinary arsenic was also associated with glycated hemoglobin levels in people with untreated diabetes.

Conclusion: We found significant associations between arsenic exposure and the prevalence of T2D and prediabetes in the Canadian population. Causal inference is limited due to the cross-sectional design of the study and the absence of long-term exposure assessment.

Keywords: *urinary arsenic, Canadian Health Measures Survey, type 2 diabetes, population survey*

Key findings

- Our study included 1520 men and 1631 women aged 20 to 79 years with known urine arsenic measures. Diabetes was defined as a fasting glucose level of 126 mg/dL or a hemoglobin A1c (HbA1c) of 6.5% or higher, or diabetes treatment.
- Total urinary arsenic concentration was positively associated with the prevalence of T2D and prediabetes: adjusted odds ratios were 1.81 (95% CI: 1.12–2.95) and 2.04 (95% CI: 1.03–4.05), respectively, when comparing the highest (fourth) urinary arsenic concentration quartile with the lowest (first) quartile.
- Total urinary arsenic was also associated with glycated hemoglobin levels in people with untreated diabetes.

Introduction

The *Canadian Environmental Protection Act* describes inorganic arsenic and its metabolites as toxic enough to ''constitute a danger in Canada to human life or health.''[1] In fact, arsenic is one of the most toxic elements in the environment, where it is present in both organic and inorganic forms, mostly from natural sources. Canadians are exposed to arsenic mainly through food as well as through drinking water, soil and ambient air. Although the concentration of arsenic in drinking water in most municipalities in Canada is less than the Health Canada guideline of 10 µg/L,[2] there are areas in several provinces—particularly those served by private wells—where concentrations exceed this amount.[2]

Seafood is the largest dietary source of organic arsenic.[3,4] The major organic arsenical in most seafood is arsenobetaine, which is considered harmless.[5] Inorganic arsenic, the most toxic form of the metalloid,[6] is metabolized in the liver and transformed into monomethyl and dimethyl species, which are excreted in urine along with unmetabolized inorganic arsenic.[6,7] The toxicity of arsenic may be altered by selenium.[8]

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Low-level inorganic arsenic exposure increases the risk of pre-malignant skin lesions,[9,10] hypertension[11,12] and neurological dysfunctions.[13] Observational studies in humans and experimental studies in animals have found arsenic to be potentially diabetogenic.[14] This effect of arsenic on type 2 diabetes (T2D), a disease which affects approximately 346 million people worldwide[15,16] and 2.4 million people in Canada,[17] is a major public health issue.[14,18]

Early studies were conducted in populations exposed to high levels of arsenic in drinking water in Taiwan and Bangladesh or were occupational studies of copper smelter and glass workers in the United States and Europe. Measures of exposure vary between these studies, from area-wide exposure estimates based on measurement of arsenic in drinking water to individual-level exposure estimates based on detailed water consumption history, work history or actual biomarkers of exposure. A systematic literature review of epidemiological research of arsenic exposure and T2D showed that most of these studies used ecological methods of exposure assessment and did not adjust for potential confounders.[14] Some of the studies that used urinary arsenic levels as a biomarker of exposure did not find any association between arsenic exposure and diabetes[19,20] while others reported a dose-response relationship.[21–27] Moreover, there are no studies evaluating this association in the Canadian population. Therefore, the main objective of this study was to evaluate the association between arsenic exposure, as measured by total arsenic concentration in urine, and the prevalence of T2D in adults who participated in the first cycle of the Canadian Health Measures Survey (CHMS).

Methods

Study population

We used cross-sectional data from the CHMS, Cycle 1, a complex sampling survey designed to collect data on a representative sample of approximately 5600 Canadians aged 6 to 79 years, which took place from 2007 to 2009. The CHMS covers approximately 96.3% of the Canadian population living in private dwellings in all the provinces and territories, but excludes institutional residents and full-time members of the Canadian Forces as well as those living on reserves and certain remote areas. We excluded participants aged less than 20 years. As a result, data from 3517 participants aged 20 to 79 years were available for this study.

Data collection

Data were collected from March 2007 through February 2009 from 16 sites in the Atlantic provinces (Moncton, New Brunswick), Quebec (Québec, Montréal, Monteregie, South Mauricie), Ontario (Charlington, North York, Don Valley, St. Catharines, Kitchener, Northumberland Country), the Prairies (Edmonton and Red Deer, Alberta), and British Columbia (Vancouver, Williams Lake and Quesnel).[28] The survey consisted of a personal household interview followed by a physical examination and biological sampling at a mobile examination centre within 2 days to 6 weeks of the interview. Overall, the combined response rate was 51.7 % for Cycle 1 of CHMS.[29]

Exclusion criteria

For this study, the following exclusion criteria were added: type 1 diabetes ($n = 19$), pregnancy ($n = 11$) and liver problems ($n = 72$). This last criterion was chosen because individuals with elevated liver enzymes, even within the normal range as defined in clinical practice, are at higher risk of diabetes.[30] We also excluded participants who reported high seafood and shellfish consumption ($\geq$ 104 times a year) or high fish consumption ($\geq$ 156 times a year) ($n = 264$) based on the distribution of the sea food consumption in number of meals a week because those participants were likely to have high seafood-derived arsenic levels.

Our final analyses included data from 3151 participants aged 20 to 79 years.

Urine arsenic assessment

Collection of urine samples

Mid-stream spot urine samples (60 ml) were obtained from participants in the mobile examination centres. Urine samples for arsenic analysis were collected in arsenic-free containers, shipped on dry ice and stored at -20°C.

Analysis of urine samples

Total arsenic was measured at the Laboratoire de toxicologie of the Institut national de santé publique du Québec following a standardized protocol accredited under ISO 17025 and using numerous internal and external quality control programs.[31] Urine samples were diluted with an aqueous nitric acid solution (0.5%) and analyzed for total arsenic by inductively coupled plasma-mass spectrometry (ICP-MS) on an Elan DRC II instrument. Matrix-matched calibration was performed using urine from non-exposed individuals.[32] Urinary concentrations were also corrected for creatinine concentrations, to account for urine dilution, which were determined by the Jaffe method.[33] The limit of detection for total urinary arsenic was 0.524 µg/L. The percentage of study participants with total urinary arsenic levels below the limit of detection was 0.35%.

Type 2 diabetes end points

Prevalent T2D was defined as a fasting serum glucose level of 126 mg/dl or more ($\geq$ 7 mmol/L) or a glycated hemoglobin (HbA1c) of 6.5% or more, as recommended by the World Health Organization (WHO) and the American Diabetes Association (ADA).[34,35] A self-reported physician diagnosis of diabetes or the self-reported use of insulin or oral hypoglycemic medication were also used as alternative criteria. Prevalent prediabetes was defined as a fasting serum glucose of between 100 and 125 mg/dl (5.6–6.9 mmol/L) or HbA1c between 5.7% and 6.4% (as recommended by WHO and ADA).[34,35]

Fasting blood glucose

Fasting blood samples were collected from 1714 study participants in the morning, after they had fasted for at least 10 hours. Venous plasma glucose was determined using the clinical chemistry system, VITROS 5.1 FS Ortho-Clinical Diagnostics.[36]

Glycated hemoglobin level

HbA1c concentrations were measured using clinical chemistry system VITROS 5.1 FS Ortho-Clinical Diagnostics.[37]

Other laboratory parameters

Urinary creatinine was determined using the colorimetric end-point Jaffe method to account for urine dilution in spot urine samples. The absorbance was read at 505 nm on a Hitachi 917 chemistry autoanalyzer (C-530).[38]

Urinary selenium concentrations were measured using ICP-MS in the same analysis as arsenic (described above). The limit of detection was 0.08 µmol/L.

Other variables

Blood pressure was measured electronically with an automated oscillometric device (BpTRU™).[39] We used the *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure* definition of hypertension: systolic blood pressure of 140 mmHg or above and diastolic blood pressure of 90 mmHg or above. We also accepted the use of hypertension medications or self-reported medical diagnosis of hypertension as criteria.

Questionnaire

CHMS questionnaire data included self-reported information on sociodemographic variables and an in-depth health questionnaire. The CHMS age groups were 20 to 39, 40 to 59 and 60 to 79 years. Racial background was defined as White and non-White. The level of education was defined as less than secondary, secondary graduation, some postsecondary and postsecondary graduation. Smoking status was divided into three categories: current smoker, former smoker and non-smoker. Alcohol consumption was divided into three categories: current, former and never.

The overall frequency of seafood consumption and of shellfish consumption was categorized into four groups based on the consumption of at least one type of sea fish on the nutrition CHMS survey checklist and of shellfish: less than 12 times per year, 12 to 51 times per year, 52 to 103 times per year and 104 to 155 times per year. The categorization of sea fish and shellfish was based on the distribution of the sea food consumption in terms of number of meals a week, which was then converted into number of meals per year in the study population.

Body mass index (BMI) was calculated by dividing measured weight in kilograms by measured height in metres squared.

Participants were asked if they used municipal treated tap water, private well water, bottled water or other sources of drinking water. We categorized the responses into two: municipal tap water or other.

Statistical analysis

All statistical analyses were performed using the statistical package SAS version 9.3 (SAS Institute Inc., Cary, NC, US), incorporating the CHMS sampling weights. We completed variance estimation (95% confidence intervals [CI]) and significance testing (chi-square) on differences between estimates using the bootstrap weights provided with the data, which account for the complex sampling design.[40] We used descriptive statistics (frequencies, geometric means) to estimate total urinary arsenic concentrations by participant's characteristics. Total urinary arsenic, selenium, fasting plasma glucose and HbA1c were log-transformed for geometric mean analyses. Concentrations below the limit of detection of the analytical method were replaced by a value equal to half of the limit of detection.[42] For each of these laboratory variables, the geometric mean concentrations and 95% CI in participants with prediabetes and diabetes were compared with values in control participants without diabetes or prediabetes, using multivariate regression models. Total urinary arsenic concentration was considered either as a continuous variable or in quartiles.

We used binomial (non-diabetes versus prediabetes or diabetes) and ordinal logistic regression analyses (with the three categories simultaneously) to estimate odds ratios (OR) with their 95% confidence intervals. Our logistic regression models for total urinary arsenic concentrations and diabetes end points were fitted with increasing degrees of adjustment. First, we adjusted for age, sex, educational level, alcohol drinking status, smoking status, BMI, hypertension and for urinary creatinine to account for urine dilution in spot urine samples.[43] Each model was further adjusted for seafood consumption using the categories explained in the questionnaire section.

We analyzed the association between urinary arsenic concentrations and HbA1c in models stratified by diabetes treatment status because HbA1c is an indicator of diabetes control.[44] We used binomial logistic regression models to estimate odds ratios of HbA1c by urinary arsenic concentrations with the same adjustment strategy described in the primary diabetes analysis. We tested the interaction of selenium with arsenic because selenium may be protective against arsenic-induced toxicity.[45]

We also used propensity scores to evaluate the potential selection bias caused by non-respondents by balancing the distribution of covariates on the main risk factor levels.[46] A propensity score–weighted regression model was fitted to compare the outcome of T2D and of prediabetes with urinary arsenic exposure and to study the possible predictors of T2D. A propensity score–weighted regression model was then used to assess the association of urinary arsenic exposure among people with untreated diabetes with biological outcome.

Results

Participant characteristics

Our study included 3151 participants (1520 men and 1631 women). The weighted prevalence of T2D and prediabetes in the study population was 7.1% (95% CI: 6.2%–7.9%) and 26.4% (95% CI: 24.8%–27.9%), respectively. Participants with T2D or prediabetes were significantly older, more frequently non-White, less educated and more likely to have a higher BMI compared with the control participants with neither prediabetes nor T2D (Table 1). The general characteristics of participants

TABLE 1
Diabetes status based on characteristics of study participants, CHMS, Cycle 1, 2007–2009

Characteristics	Diabetes status of participants, % (95% CI)[a]		
	Neither diabetes nor prediabetes n = 2054	Prediabetes[b] n = 831	Type 2 diabetes[c] n = 225
Age, years			
20–39	42.0 (39.8–42.8)	18.7 (17.6–19.8)	8.9 (8.4–10.1)
40–59	35.5 (34.5–36.4)	38.8 (38.1–39.5)	27.6 (26.8–28.7)
60–79	22.5 (21.9–23.6)	42.5 (41.9–43.8)	63.5 (62.0–64.8)
Sex			
Female	46.9 (45.2–47.8)	48.4 (47.9–49.7)	55.1 (54.2–56.5)
Male	53.1 (51.4–54.3)	51.6 (49.2–52.8)	44.9 (44.0–45.8)
Education			
≤ High school	10.7 (10.2–11.8)	18.5 (18.2–18.9)	24.4 (23.9–24.8)
Some post-secondary	25.4 (24.9–25.1)	24.3 (23.1–24.8)	25.3 (24.2–26.2)
≥ University	63.9 (63.7–64.6)	57.2 (56.4–58.1)	50.3 (50.2–51.3)
Ethnicity			
White	88.0 (79.2–88.7)	85.9 (84.8–86.8)	82.7 (81.3–83.1)
Non-White	12.0 (11.2–12.8)	14.1 (13.2–15.4)	17.3 (16.2–17.8)
Smoking status			
Current	21.6 (20.1–21.8)	21.2 (20.9–21.7)	15.5 (14.9–16.1)
Former	29.3 (28.7–30.0)	35.6 (35.2–36.3)	38.7 (38.2–39.4)
Never	49.1 (48.5–49.8)	43.2 (42.6–43.8)	45.8 (45.3–46.2)
Alcohol consumption			
Current	88.2 (87.5–88.9)	79.7 (78.8–80.3)	70.6 (69.2–79.9)
Former	7.4 (6.9–7.8)	14.8 (14.2–16.1)	20.6 (19.9–21.4)
Never	4.4 (4.0–4.8)	5.5 (4.9–5.8)	8.8 (8.1–9.2)
BMI, kg/m^2			
<25	42.1 (41.6–42.7)	26.5 (25.7–27.2)	15.3 (14.4–15.9)
25–29	32.7 (31.8–33.0)	31.5 (31.1–32.4)	26.6 (26.2–27.4)
≥30	25.2 (24.3–25.8)	42.0 (41.2–42.9)	58.1 (57.7–60.2)
Water source			
Municipal tap water	87.2 (86.5–87.8)	85.9 (85.2–86.3)	83.3 (82.9–84.3)
Other	12.8 (12.3–13.6)	14.1 (13.5–14.9)	6.7 (6.2–7.1)

Abbreviations: BMI, body mass index; CHMS, Canadian Health Measures Survey; CI, confidence interval; HbA1c, glycated hemoglobin.

[a] Missing data, n = 41.

[b] Fasting serum glucose = 100–125 mg/dl (5.6–6.9 mmol/L) or HbA1c = 5.7%–6.4%.

[c] Fasting serum glucose ≥ 126 mg/dL (≥ 7 mmol/L) or HbA1c ≥ 6.5% or self-reported medication use or self-reported health care professional diagnosis.

with prediabetes were between those of participants with diabetes and of controls (Table 1). The source of water was the same for all the three groups.

The geometric mean of total urinary arsenic concentrations tended to be higher in female, older and non-White participants and in current alcohol drinkers and former smokers, but the differences were not statistically significant (Table 2).

Arsenic and type 2 diabetes

Geometric means of total urinary arsenic concentrations were greater in participants with diabetes (12.9 µg/L; 95% CI: 9.4–17.7 µg/L) and prediabetes (12.5 µg/L; 95% CI: 10.1–15.4 µg/L) than in controls (11.5 µg/L; 95% CI: 9.4–14.1 µg/L). After correction for urinary creatinine, we observed the same difference for participants with prediabetes and diabetes compared to controls (Table 3). Urinary selenium levels did not differ significantly between the three groups.

Table 4 shows the results for the models derived from the binomial logistic regression analysis of participants with T2D and prediabetes according to urinary arsenic quartiles. Participants in the highest quartile of total urinary arsenic showed a nearly 2-fold higher risk of T2D compared with those in the lowest quartile, after adjustment for sociodemographic characteristics (age and gender), diabetes risk factors, urinary creatinine and seafood consumption (OR = 1.8; 95% CI: 1.1–3.0). Similarly, participants with prediabetes showed a similar association after adjustment for potential confounders (OR = 2.1; 95% CI: 1.0–4.1).

Ordinal logistic regression for T2D, prediabetes and controls together resulted in total urinary arsenic concentrations and diabetes status similar to the previous models for diabetes or prediabetes only. Moreover, there was a general trend of increasing ORs with total urinary arsenic increase and a statistically significant dose response (Table 5).

Finally, total urinary arsenic was not associated with HbA1c among people with treated diabetes (Table 6), but was strongly associated with HbA1c among untreated participants after adjustment for potential confounders.

Selenium did not interact with any arsenic effect in this study (data not shown).

After using the propensity score–inverse probability weight, the results were found to be similar to those found from the initial regression models (data not shown). A regression model conducted to assess the association of urinary arsenic exposure in people with untreated diabetes with biological outcome resulted in similar association (data not shown).

Discussion

We found a positive association between total urinary arsenic concentrations and the prevalence of T2D and prediabetes,

TABLE 2
Levels of urinary arsenic based on participants' characteristics in CHMS, Cycle 1, 2007–2009

Population characteristics	N (%)	Geometric means of urinary arsenic, µg/L (95% CI)	
		Urinary arsenic not corrected for creatinine, µg/L	Urinary arsenic corrected for creatinine, µg/ creatinine
Age, years			
20–39	1059 (33.6)	11.4 (10.0–13.1)	12.8 (9.4–17.4)
40–59	1126 (35.7)	12.0 (10.0–14.3)	15.4 (12.3–19.2)
60–79	966 (30.7)	11.4 (9.3–14.0)	16.0 (11.8–21.6)
Sex			
Female	1520 (48.2)	10.2 (7.6–13.7)	16.4 (12.5–21.5)
Male	1631 (51.8)	13.2 (10.0–17.5)	12.8 (9.6–17.0)
Education			
≤High school	429 (13.6)	11.2 (9.2–13.7)	13.7 (10.6–17.7)
Some post-secondary	780 (24.8)	10.6 (8.4–13.2)	13.5 (10.7–16.9)
≥University	1942 (61.6)	14.1 (10.2–19.7)	17.1 (12.8–22.8)
Ethnicity			
White	2708 (85.9)	11.2 (9.5–13.2)	13.7 (11.1–16.9)
Non-White	443 (14.1)	14.0 (9.6–20.5)	18.4 (12.0–28.3)
Smoking status			
Current	655 (20.8)	10.5 (8.3–13.2)	12.0 (8.1–17.8)
Former	990 (31.4)	12.6 (10.0–15.9)	15.5 (12.0–20.0)
Never	1506 (47.8)	11.7 (10.0–13.6)	15.0 (12.5–18.1)
Alcohol consumption			
Current	2663 (84.5)	11.9 (9.9–14.4)	14.5 (11.5–18.3)
Former	334 (10.6)	9.7 (5.7–16.6)	13.9 (10.9–17.7)
Never	154 (4.9)	11.3 (8.2–15.6)	16.3 (11.3–23.5)
BMI, kg/m^2			
<25	1157 (36.7)	11.7 (10.3–13.3)	16.0 (12.7–20.1)
25–29	989 (31.4)	12.1 (9.9–14.7)	14.1 (11.6–17.0)
≥30	1005 (31.9)	11.2 (9.1–13.8)	13.0 (9.8–17.4)
Water source			
Municipal tap water	2702 (86.0)	12.0 (10.1–14.2)	14.9 (12.0–18.6)
Other	449 (14.0)	10.0 (5.9–16.9)	12.2 (6.8–21.9)

Abbreviations: BMI, body mass index; CHMS, Canadian Health Measures Survey; CI, confidence interval; HbA1c, glycated hemoglobin.

after adjustment for several potential confounders and for seafood consumption, in a representative sample of Canadian adults who participated in the 2007–2009 CHMS. The association between arsenic and HbA1c was significant only in participants with untreated diabetes.

These results are similar to those of several previous studies of lower levels of exposure as well as those with better measures of outcome and exposure.[14,26] The latter estimated exposure to inorganic arsenic and its metabolites[21,22,24] or measured inorganic arsenic as total arsenic with adjustment of results for markers of seafood intake.[23,26] Our findings are also in line with results from a cross-sectional study using data from the National Health Nutrition and Examination Survey (NHANES), suggesting an increased risk for diabetes with urinary arsenic concentrations after adjustment for arsenic contribution from seafood.[23] After adjusting for diabetes risk factors and markers of seafood intake, Navas-Acien et al.[23] found the OR for T2D to be 2.6 (95% CI: 1.1–6.0) when comparing participants in the 80th versus the 20th percentile of total urinary arsenic concentration (7.4 µg/L vs 1.6 µg/L). The researchers also reported a positive association between arsenic concentrations and HbA1c after adjusting for biomarkers of seafood intake (urinary arsenobetaine and mercury), although the association was not statistically significant.[23]

Rhee et al.[26] analyzed data from the Korean KNHANES cross-sectional study (2008–2009) and found that the ORs for diabetes mellitus in all participants were 1.56 (95% CI: 1.03–2.36) within the highest urinary arsenic quartile after adjusting for serum mercury level as an indicator of seafood intake.

The literature on experimental studies on arsenic and diabetes in animals is considered inconclusive, but this has been explained as being due to methodological problems in those studies.[14] In vitro or mechanistic studies suggest several pathways by which arsenic could influence pancreatic β-cell function and insulin sensitivity, including oxidative stress and effects on glucose uptake and transport, gluconeogenesis, adipocyte differentiation, and calcium signalling.[47–50]

Urinary arsenic is generally considered the most reliable indicator of recent exposure to arsenic and is used as the main biomarker of exposure.[51] Arsenic tends not to accumulate in the body but is readily excreted via the kidneys.[52] Urinary profiles of inorganic arsenic metabolites have been used in some epidemiological studies to estimate exposure to inorganic arsenic,[14,53] but such data were not available in CHMS Cycle 1.

By excluding participants who reported high seafood and shellfish consumption and adjusting our models for seafood consumption for other categories of sea fish and seafood consumption, we indirectly controlled the contribution of the low toxicity organic arsenicals of marine origin to total urinary arsenic in order to isolate the influence of inorganic arsenic concentrations. Longnecker,[54] in a commentary entitled ''On confounded fishy results regarding arsenic and diabetes,'' recognized the merit of the measure of total urinary arsenic adjusted for markers of seafood intake as an indicator of inorganic arsenic exposure in a population with low exposure.[23] However, this was challenged by Steinmaus et al.[20] who found no

TABLE 3
Laboratory variables for CHMS participants with prediabetes[a] or diabetes[b] and controls, CHMS cycle 1, 2007–2009

Laboratory analyses	Geometric means (95% CI)		
	Controls (N = 2054)	Prediabetes[a] (N = 831)	Diabetes[b] (N = 225)
Urinary arsenic, μg/L[c]	11.5 (9.4–14.1)	12.5 (10.1–15.4)	12.9 (9.4–17.7)
Urinary arsenic, μg/g creatinine[d,e]	12.3 (9.8–15.4)	15.5 (10.9–22.0)	14.6 (10.5–20.4)
Selenium, μg/L[f]	46.9 (45.1–48.7)	45.8 (43.2–47.9)	49.9 (44.3–54.7)
Fasting glucose, mg/dl[g]	4.7 (4.3–5.2)	5.3 (4.7–5.9)	6.5 (4.2–10.0)
HbA1c, %[h]	5.3 (4.9–5.7)	5.8 (5.3–6.3)	6.9 (4.8–9.8)

Abbreviations: CHMS, Canadian Health Measures Survey; CI, confidence interval; HbA1c, glycated hemoglobin.

[a] Fasting serum glucose = 100–125 mg/dl (5.6–6.9 mmol/L) or HbA1c 5.7%–6.4%.

[b] Fasting serum glucose ≥ 126 mg/dL or HbA1c ≥ 6.5% or self-reported medication use or self-reported health care professional diagnosis.

[c] Urinary arsenic not corrected for urinary creatinine.

[d] Urinary arsenic corrected for urinary creatinine.

[e] Missing data for urinary arsenic corrected for urinary creatinine, n = 39.

[f] Missing data for selenium, n = 76.

[g] Missing data for fasting glucose, n = 1437.

[h] Missing data for HbA1c, n = 106.

association between risk of diabetes and inorganic arsenic exposure based on inorganic and methylated metabolites.

Because drinking water is an important source of arsenic exposure, we assessed the study participants' sources of drinking water and found no association between this and diabetes status. This might be due to our crude classification of exposure or the low level of arsenic in Canadian drinking water. The toxicity of arsenic species can be reduced by selenium through the formation of an arsenic–selenium complex;[45] however, we found no interaction between selenium and arsenic.

Strengths and limitations

One of the strengths of our study is that it was population based and conducted on a large sample of adults assessed as having diabetes or prediabetes based on objective criteria proposed by the ADA and WHO.[34,35] In addition, the HbA1c test

TABLE 4
Binomial logistic regression analysis of participants with prediabetes[a] and type 2 diabetes[b] with controls based on urinary arsenic concentration quartiles, CHMS, Cycle 1, 2007–2009

Urinary arsenic (μg/L)[c]	Number of participants[d]			Crude OR (95% CI)		Adjusted OR (Model 1)[e] (95% CI)		Adjusted OR (Model 2)[f] (95% CI)	
	Controls (n = 2054)	With prediabetes[a] (n = 831)	With diabetes[b] (n = 225)	Prediabetes[a]	Diabetes[b]	Prediabetes[a]	Diabetes[b]	Prediabetes[a]	Diabetes[b]
< 5.71	554	171	46	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
5.71–11.20	520	197	54	1.14 (0.86–1.52)	1.44 (1.08–1.92)	1.38 (0.87–2.21)	1.06 (0.60–1.87)	1.37 (0.88–2.17)	1.20 (0.70–2.05)
11.21–22.98	530	192	64	1.28 (0.92–1.62)	1.65 (1.07–2.54)	1.46 (0.92–2.32)	1.31 (0.63–2.74)	1.46 (0.92–2.35)	1.55 (0.83–2.90)
≥ 22.99	450	271	61	1.48 (1.18– 2.50)	1.92 (1.11–3.33)	2.04 (1.03–4.05)	1.54 (0.74–3.18)	2.14 (1.02–4.07)	1.81 (1.12–2.95)
p for trend				.015	.019	.042	.246	.043	.017

Abbreviations: BMI, body mass index; CHMS, Canadian Health Measures Survey; CI, confidence interval; HbA1c, glycated hemoglobin; OR, odds ratio.

[a] Fasting serum glucose 100–125 mg/dl (5.6–6.9 mmol/L) or HbA1c 5.7%–6.4%.

[b] Fasting serum glucose ≥ 126 mg/dL or HbA1c ≥ 6.5% or self-reported medication use or self-reported health care professional diagnosis.

[c] Urinary arsenic not corrected for urinary creatinine.

[d] Data missing for n = 41 participants.

[e] Model 1 adjusted for urinary creatinine, age, sex, alcohol status, smoking status, educational status, BMI and hypertension.

[f] Model 2 adjusted as for Model 1 plus seafood consumption.

TABLE 5
Multivariable ordinal logistic regression analysis comparing participants with prediabetes[a] and diabetes[b] based on urinary arsenic concentrations quartiles, CHMS, Cycle 1, 2007–2009

Urinary arsenic, μg/L[c]	Number of participants[d]			OR (95% CI)		
	Controls (n = 2054)	With prediabetes[a] (n = 831)	With diabetes[b] (n = 225)	Crude OR	Adjusted OR (Model 1)[e]	Adjusted OR (Model 2)[f]
< 5.71	554	171	46	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
5.71–11.20	520	197	54	1.20 (0.98–1.47)	1.35 (0.95–1.79)	1.35 (0.97–1.82)
11.21–22.98	530	192	64	1.20 (0.88–1.64)	1.39 (1.01–2.00)	1.41 (1.02–2.04)
≥ 22.99	450	271	61	1.56 (1.00–2.44)	1.85 (1.11–3.13)	1.89 (1.12–3.13)
p for trend				.049	.019	.016

Abbreviations: BMI, body mass index; CHMS, Canadian Health Measures Survey; CI, confidence interval; HbA1c, glycated hemoglobin; OR, odds ratio.

[a] Fasting glucose 100–125 mg/dl (5.6–6.9 mmol/L) or HbA1c 5.7%–6.4%.

[b] Fasting glucose ≥ 126 mg/dL or HbA1c ≥ 6.5% or self-reported medication use or self-reported health care professional diagnosis.

[c] Urinary arsenic not corrected for urinary creatinine.

[d] Data missing for n = 41 participants.

[e] Model 1 adjusted for urinary creatinine, age, sex, alcohol status, smoking status, educational status, BMI and hypertension.

[f] Model 2 adjusted as for Model 1 plus for seafood consumption.

was used not only to assess diabetes (when other criteria were not available) but also to evaluate the adequacy of glycemic management. We also considered criteria for prediabetes and used rigorous laboratory procedures with a low limit of detection of assay for urinary arsenic. Moreover, we considered relevant potential confounders (diabetes risk factors and indicators of seafood intake) in our analysis and adjusted for urinary creatinine levels to account for urine dilution.[55]

Our study was cross-sectional and so did not allow us to establish a temporal association between urinary arsenic and type 2 diabetes. Urinary arsenic has a half-life of approximately 3 days, making it a biomarker of short-term exposure only. This makes it difficult to ascertain historical exposures that may be more relevant to the pathogenesis of T2D.[56] Moreover, the exposure assessment in our study was based on urinary arsenic concentration measured in a single spot urine specimen and so reflected exposure at only one point in time. As discussed previously, we did not quantify arsenic species in urine and so could not test based on inorganic or methylated organic arsenic levels. Instead, we adjusted total arsenic concentration for seafood consumption, the main source of organic arsenic, as previously recommend.[23,52] However, seafood consumption was measured using a food frequency questionnaire, and so the information is subject to recall error. Misclassification

TABLE 6
Odds ratio of glycated hemoglobin[a] by urinary arsenic concentrations among participants with treated and untreated diabetes in CHMS, Cycle 1, 2007–2009

Urinary arsenic, (μg/L)[b]	Number of participants, N		OR (95% CI)					
			Crude OR		Adjusted OR (Model 1)[c]		Adjusted OR (Model 2)[d]	
	Treated diabetes[e] (n = 129)	Untreated diabetes[f] (n = 96)	Treated diabetes	Untreated diabetes	Treated diabetes	Untreated diabetes	Treated diabetes	Untreated diabetes
< 5.71	30	22	1 (Referent)	1 (Referent)	1 (Referent)	1 (Referent)	1 (Referent)	1 (Referent)
5.71–11.20	34	26	0.78 (0.41–1.49)	1.22 (0.99–1.48)	0.65 (0.39–1.08)	1.61 (1.47–2.23)	0.66 (0.44–1.04)	1.62 (1.19–2.22)
11.21–22.98	36	27	0.94 (0.58–1.51)	1.21 (0.89–1.65)	0.85 (0.46–1.59)	1.72 (1.13–2.57)	0.80 (0.48–1.34)	1.74 (1.18–2.59)
≥ 22.99	29	21	1.11 (0.59–2.04)	1.74 (1.06–2.89)	0.87 (0.52–1.46)	2.84 (1.62–4.98)	0.85 (0.55–1.32)	2.89 (1.65–5.08)
p for trend			.7444	.005	.6122	.001	.7538	.001

Abbreviations: BMI, body mass index; CHMS, Canadian Health Measures Survey; CI, confidence interval; HbA1c, glycated hemoglobin; OR, odds ratio.

[a] 3 levels of HbA1c: < 5.7%, 5.7%–6.4% and ≥ 6.5%.

[b] Urinary arsenic not corrected for urinary creatinine.

[c] Adjusted for urinary creatinine, age, sex, alcohol intake, smoking, educational status, BMI and hypertension.

[d] Adjusted as for Model 1 plus seafood consumption.

[e] All participants with diabetes who reported use of insulin or oral hypoglycemic medication.

[f] All participants with diabetes who reported no use of insulin or oral hypoglycemic medication.

bias could also occur from inaccuracies in diagnosing T2D; since medical records were not reviewed, errors in self-reported diagnoses or use of insulin or oral hypoglycemic medication may have occurred. However, this issue did not seem to significantly affect the validity of the primary findings because the positive relationship between urinary arsenic exposure and T2D remained after a sensitivity analysis of only biological criteria (HbA1c or fasted blood glucose) in untreated patients. There was also an important non-response rate among eligible participants, which might lead to selection bias. However, our analysis using the propensity score seems to demonstrate that this issue might, at worst, be minor. Nevertheless, we recognize that residual confounding cannot be entirely excluded.

Conclusion

We examined the association between total urinary arsenic concentrations and diabetes status in an adult Canadian population with relatively low to moderate exposure to arsenic via drinking water. Using several accepted approaches to reduce potential misclassification of exposure to organic arsenic, our analysis found an association between total urinary arsenic exposures and T2D in this population study. However, because of the limitations of the cross-sectional design and the absence of long-term assessment of arsenic exposure, we recommend further prospective studies with improved assessment of arsenic exposure. Analysis of recent data from CHMS Cycle 2 with speciated arsenic data in urine might also be useful.

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