Original Contribution

Association of Low to Moderate Levels of Arsenic Exposure With Risk of Type 2 Diabetes in Bangladesh

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Initially submitted July 28, 2012; accepted for publication July 18, 2013.

Chronic exposure to high levels of arsenic in drinking water is associated with increased risk of type 2 diabetes mellitus (T2DM), but the association between lower levels of arsenic and T2DM is more controversial. Therefore, this study evaluated the association between low to moderate arsenic exposure and T2DM. In 2009–2011, we conducted a study of 957 Bangladeshi adults who participated in a case-control study of skin lesions in 2001–2003. The odds ratio of T2DM was evaluated in relationship to arsenic exposure measured in drinking water and in subjects’ toenails (in 2001–2003) prior to the diagnosis of T2DM (in 2009–2011). Compared with those exposed to the lowest quartile of arsenic in water (≤1.7 µg/L), the adjusted odds ratio for T2DM was 1.92 (95% confidence interval (CI): 0.82, 4.35) for those in the second quartile, 3.07 (95% CI: 1.38, 6.85) for those in the third quartile, and 4.51 (95% CI: 2.01, 10.09) for those in the fourth quartile. The relative excess risk of T2DM was 4.78 for individuals who smoked and 8.93 for people who had a body mass index (weight (kg)/height (m)²) greater than 25. These findings suggest that exposure to modest levels of arsenic in drinking water was associated with increased risk of T2DM in Bangladesh. Being overweight or smoking was also associated with increased risk of T2DM.

additive interaction; arsenic; Bangladesh; diabetes; overweight; smoking

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; RERI, relative excess risk due to interaction; RR, relative risk; T2DM, type 2 diabetes mellitus.

Arsenic is a naturally occurring and abundant element in the environment. It is estimated that 140 million people worldwide are exposed to arsenic-contaminated drinking water at levels above the World Health Organization’s recommended guideline value (1). In the United States, approximately 13 million Americans are exposed to arsenic from drinking water that exceeds the Environmental Protection Agency’s current standard of 10 µg/L (2).

Observational studies in Taiwan and Bangladesh show that high levels of arsenic in drinking water are associated with significantly increased risk of type 2 diabetes mellitus (T2DM) (3–6). Experimental studies demonstrate that exposure to high levels of arsenic decreases glucose-stimulated insulin secretion in pancreatic β cells (7), inhibits insulin-dependent glucose uptake in cultured adipocytes (8, 9), and causes insulin insensitivity in animal models (10–12). However, studies examining the association between T2DM and low to moderate levels of arsenic in drinking water have yielded conflicting results (13–18), which could be a function of their cross-sectional design or their diagnosis criteria for T2DM.

As the United States National Research Council has stated, improving our understanding of the dose-response between low to moderate levels of arsenic in drinking water and T2DM has important implications with regard to establishing drinking water standards that protect public health (19, 20). Systematic reviews suggest that future studies should include assessments of known risk factors for diabetes (21, 22).

Hence, we conducted a study that defined T2DM on the basis of hemoglobin A1c levels. We examined the association between arsenic exposure and T2DM in a study of 957 participants...
who had participated in a case-control study in 2001–2003 for arsenic-induced skin lesions in Bangladesh. Additionally, we investigated whether known T2DM risk factors such as cigarette smoking and body mass index (BMI) (calculated as weight (kg)/height (m)\(^2\)) increased susceptibility to this disease.

**MATERIALS AND METHODS**

**Study design and participants**

In 2001–2003, 900 individuals with arsenic-related skin lesions and 900 controls were enrolled in a case-control study in Bangladesh (23). Controls were matched 1-to-1 with cases on the basis of age, sex, and location of residence. In 2009–2011, we were able to contact 1,542 of these participants and successfully recruit 957 individuals to participate in a study investigating metabolic disorders. As such, this study analyzed the secondary phenotype (diabetes) from a case-control study of skin lesions and used the arsenic exposure information that was collected at baseline prior to the diagnosis of diabetes.

In 2001–2003, we used questionnaires to collect information on medical history, cigarette smoking, and other risk factors. Participants also underwent a physical examination and reported their diabetic status. Their heights and weights were recorded, and arsenic exposure was measured in each participant’s drinking water and toenails. No data on hemoglobin A1c levels were collected in 2001–2003. In 2009–2011, hemoglobin A1c levels were measured for each participant. Seventeen individuals reported a diagnosis of T2DM prior to 2001–2003, and 2 individuals did not provide information regarding their diabetic status in 2001–2003. Five individuals were missing hemoglobin A1c data in 2009–2011. These 24 individuals were excluded, which left 933 individuals for our analysis. This study was approved by the institutional review boards of the Harvard School of Public Health and Dhaka Community Hospital. All participants provided written informed consent prior to participation.

**Arsenic exposure**

Sample collection has been described previously (24). Briefly, technicians collected drinking water and toenail samples from each individual. Water was collected from the tube well that participants identified as their primary source of drinking water. Arsenic in water was analyzed by Environmental Laboratory Services (North Syracuse, New York) following the Environmental Protection Agency (Washington, DC) method 200.8 by using inductively coupled plasma mass spectroscopy. For quality control, instrument performance was validated by using repeated measurements of standard reference water (Plasma-Qual Multielement QC Standard 1, SCP Science, Montreal, Canada) with an average recovery of 95%. Ten percent of the samples were randomly selected and analyzed in duplicate to confirm reliability. The average difference between duplicates was 2.5%. The limit of detection is 1 μg/L. Samples below the limit of detection were recorded as 0.5 μg/L.

Toenail samples from each subject were placed in individual sealed envelopes and analyzed at the Harvard School of Public Health by using inductively coupled plasma mass spectrometry following methods described by Chen et al. (25). Toenail arsenic concentrations were corrected for systemic errors by normalizing the sample concentration against the measured average daily National Institute of Standards and Technology 1643d arsenic concentration, and this corrected value was used in all statistical analyses. The average recovery of the National Institute of Standards and Technology standard was 86.5%. The average detection limit was 0.02 μg/g. None of the samples was below the limit of detection.

**Identification of T2DM cases**

In 2009–2010, all participants provided a 2-mL blood sample, which was collected by venipuncture into glass BD Vacutainer Fluoride/EDTA tubes (Becton, Dickson and Company, Franklin Lakes, New Jersey). Samples were analyzed for hemoglobin A1c within 24 hours after collection by the Diabetes Center in Pabna, Bangladesh, by using the NycoCard HbA1c system (Axis-Shield, plc, Dundee, Scotland) following the manufacturer’s instructions. Individuals were defined as T2DM cases if their hemoglobin A1c levels were 6.5% or greater, following the recommendation of the International Expert Committee on Diabetes (26, 27).

**Statistical analysis**

The Fisher’s exact test and Wilcoxon rank sum test with continuity correction were used to compare baseline characteristics between individuals with and without T2DM. Water and toenail arsenic levels were categorized into quartiles. Smoking status was based on data from self-reported questionnaires collected in 2001–2003. The odds ratios and 95% confidence intervals were estimated by logistic regression. The final multiple regression model included age (continuous), sex, BMI (continuous), smoking status (never, past, or current), status of skin lesions (present or absent), and quartiles of water or toenail arsenic. Penalized splines assessed the dose-response relationship between arsenic exposure in natural logarithm scale as a continuous variable and T2DM risks among participants whose arsenic exposure levels in drinking water were below 170 μg/L.

The interaction between arsenic exposure and cigarette smoking and BMI in the additive scale was estimated by 2 indices. The first index was the relative excess risk due to interaction (RERI), which indicates the departure from additivity of effects on a relative risk scale (relative risk (RR\(_{11} \) − RR\(_{01} \) − RR\(_{10} \) + 1]) (28). This approach uses adjusted odds ratios as the approximation of risk ratios in the following equation: RERI ≈ odds ratio (OR\(_{11} \) − OR\(_{10} \) − OR\(_{01} \) + 1). The 95% confidence interval of the RERI was based on 1,000 bootstrap samples as described by Assmann et al. (29). If the RERI between arsenic, smoking, or BMI is greater than 0, then there is evidence of significant excess risk of T2DM from these factors.

The second index was the attributable proportion due to interaction, which indicates the proportion of cases with both arsenic and smoking or arsenic and BMI that was contributed by synergism (attributable proportion due to interaction = RERI/RR\(_{11} \)). We used adjusted odds ratios to approximate the relative risk in the following equation: attributable proportion due to interaction ≈ RERI / OR\(_{11} \).
To address potential selection bias due to loss of 46.8% (843/1,800) of participants from the original case-control study (Web Table 1, available at http://aje.oxfordjournals.org/), we reanalyzed the data by using the inverse probability weighting method. Data on age, educational attainment, and skin lesions were included in logistic regression models to estimate the probability of participating in 2009–2011, because these factors were significantly different between participants and non-participants (Web Table 1). Sensitivity analyses were also conducted to assess the association of hemoglobin A1c in a continuous manner with T2DM, which produced consistent findings compared with those analyzed in a dichotomized fashion (Web Table 2 and Web Figure 1).

All statistical analyses were computed in R statistical software, version 2.13 (R Foundation for Statistical Computing, Vienna, Austria), and P values of 0.05 were considered significant.

RESULTS

Metabolic screening based on blood hemoglobin A1c levels in 2009 to 2011 identified 84 cases of T2DM, yielding a prevalence of 9.0%. Table 1 shows the comparison of characteristics among participants with and without T2DM in 2001–2003. On average, participants with T2DM were older and had higher BMI values compared with participants without T2DM. The median level of arsenic in drinking water was also significantly greater in participants with T2DM compared with participants without T2DM (71.5 vs. 13.9 μg/L; P < 0.001), as were toenail arsenic levels (3.2 vs. 2.0 μg/g; P = 0.007). In this table, values are missing for the following variables: education (1 subject); cigarette smoking (3 subjects); arsenic in drinking water (24 subjects); and toenail arsenic (1 subject).

### Table 1. Distribution of Baseline Demographic, Lifestyle, and Arsenic Exposure Variables by Diabetes Status (n = 933) in Pabna, Bangladesh, 2001–2003

<table>
<thead>
<tr>
<th>Variablea</th>
<th>No (n = 849)</th>
<th>Yes (n = 84)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median (IQR)</td>
<td>No.</td>
</tr>
<tr>
<td>Age, years</td>
<td>33.5 (11.7)</td>
<td>33.0 (18.0)</td>
<td>39.8 (10.7)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>517</td>
<td>60.8</td>
<td>54</td>
</tr>
<tr>
<td>Female</td>
<td>332</td>
<td>39.2</td>
<td>30</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>222</td>
<td>26.2</td>
<td>9</td>
</tr>
<tr>
<td>Married</td>
<td>611</td>
<td>72.0</td>
<td>72</td>
</tr>
<tr>
<td>Widowed or divorced</td>
<td>16</td>
<td>1.9</td>
<td>3</td>
</tr>
<tr>
<td>Educational attainment, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–6</td>
<td>498</td>
<td>58.5</td>
<td>51</td>
</tr>
<tr>
<td>7–12</td>
<td>322</td>
<td>37.6</td>
<td>30</td>
</tr>
<tr>
<td>&gt;12</td>
<td>31</td>
<td>3.6</td>
<td>3</td>
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<tr>
<td>BMIc</td>
<td></td>
<td></td>
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<tr>
<td>&lt;24.9</td>
<td>795</td>
<td>93.7</td>
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<td>5.5</td>
<td>22</td>
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<tr>
<td>&gt;30.0</td>
<td>7</td>
<td>0.8</td>
<td>2</td>
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<tr>
<td>Cigarette smoking</td>
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</tr>
<tr>
<td>Never</td>
<td>607</td>
<td>71.5</td>
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<tr>
<td>Past</td>
<td>13</td>
<td>1.5</td>
<td>6</td>
</tr>
<tr>
<td>Current</td>
<td>229</td>
<td>27.0</td>
<td>29</td>
</tr>
<tr>
<td>Skin lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>490</td>
<td>57.5</td>
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</tr>
<tr>
<td>No</td>
<td>362</td>
<td>42.5</td>
<td>41</td>
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<tr>
<td>Arsenic in drinking water, μg/L</td>
<td>142.0 (278.1)</td>
<td>13.9 (134.2)</td>
<td>202.4 (277.2)</td>
</tr>
<tr>
<td>Toenail arsenic, μg/g</td>
<td>4.8 (7.1)</td>
<td>2.0 (5.0)</td>
<td>5.4 (6.0)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation.

a Data were missing for the following variables: education (1 subject); cigarette smoking (3 subjects); arsenic in drinking water (24 subjects); and toenail arsenic (1 subject).

b P values from Fisher’s exact test for sex, marital status, educational attainment, BMI, cigarette smoking, and skin lesions or from Wilcoxon rank sum test with continuity correction for age, arsenic in drinking water, and toenail arsenic.

c BMI is weight (kg)/height (m)².
population, only men provided information on their smoking history, and the percentage of past and current smokers was greater among men with T2DM compared with men without T2DM (41.6% vs. 28.5%; \( P = 0.005 \)).

Because only 51.8% of the baseline population was included in this analysis, we compared the baseline characteristics of participants \( (n = 933) \) with nonparticipants \( (n = 843) \) and found that the 2 groups were mostly similar except for age, education, and prevalence of skin lesions at baseline (Web Table 1). Additionally, we compared the arsenic exposure in drinking water among participants who were included in both baseline and follow-up periods (Web Table 1). The median arsenic exposure in drinking water was lower at the follow-up period (in 2009–2011) (median levels, 15.2 at baseline vs. 8.73 in the follow-up period; \( P < 0.001 \)). This is likely a result of the water mitigation programs initiated in this population after 2001–2003, which focused on participants whose drinking water contained more than 50 \( \mu \text{g/L} \) of arsenic (30).

Table 2 shows the number of cases of T2DM by sex, cigarette smoking, and skin lesions, as well as by quartiles of arsenic in drinking water and toenails. Univariate analyses indicated that older age, higher BMI, and cigarette smoking were significantly associated with an increased risk of T2DM, whereas skin lesion status and sex were not associated with risk of T2DM. The multivariate-adjusted odds ratios of T2DM were 1.00 (referent), 1.92 (95% confidence interval [CI]: 0.84, 4.35), 3.07 (95% CI: 1.38, 6.85), and 4.51 (95% CI: 2.01, 10.09) for the first, second, third, and fourth quartiles of arsenic in drinking water, respectively. A significant dose-response trend was observed between increasing levels of arsenic in drinking water \( (P < 0.001) \) and in toenails \( (P < 0.001) \) in 2001–2003 with the odds ratios of T2DM in 2009–2011 after adjustment for age, sex, BMI, cigarette smoking, and skin lesion status in 2001–2003.

To test the robustness of the associations between arsenic and T2DM, we performed further restricted analyses. Figure 1 shows the association between arsenic exposure and risk of diabetes in 2 different groups that were restricted on the basis of drinking water arsenic concentrations. For participants with moderate arsenic exposure of less than 170 \( \mu \text{g/L} \) in drinking water, which captured 75% of this population, the dose-response...
The relationship between drinking water arsenic and diabetes was significant ($P < 0.001$) (Figure 1A). Further restriction, which excluded participants with skin lesions at baseline (2001–2003), also showed a consistent relationship between arsenic and T2DM ($P = 0.008$) (Figure 1B). The relationship between toenail arsenic and T2DM was also consistent in these restricted analyses ($P = 0.017$ and $0.043$ for Figures 1C and 1D, respectively).

Among men who smoked, the odds ratio was 8.83 (95% CI: 2.97, 26.2) in the higher category of arsenic exposure ($\geq 15.5 \mu g/L$) compared with those exposed to lower levels ($<15.5 \mu g/L$) (Table 3). Additionally, there was a significant interaction between smoking and arsenic exposure. The RERI between arsenic and smoking was 4.78 (95% CI: 0.04, 28.5) for past or current male smokers exposed to higher levels of arsenic in drinking water ($\geq 15.5 \mu g/L$) compared with non-smokers exposed to lower levels of arsenic in drinking water ($<15.5 \mu g/L$). This indicates a synergistic effect between arsenic and smoking that followed an additive scale. Furthermore, the attributable proportion of T2DM due to this interaction was 0.54, suggesting that 54% of T2DM cases in men were attributable to both arsenic exposure and smoking.

Table 4 shows the effect of the interaction between arsenic and BMI on the odds ratio of T2DM. After the joint effects of arsenic and BMI were combined, participants whose BMI values were greater than 25 and who were exposed to higher levels of arsenic in drinking water ($\geq 15.5 \mu g/L$) had an adjusted odds ratio for T2DM that was 14-fold greater (adjusted OR = 14.4, 95% CI: 6.07, 34.1) compared with participants whose BMI values were less than 25 and who were exposed to lower levels of arsenic in drinking water ($<15.5 \mu g/L$). Furthermore, the RERI between arsenic and BMI was 8.93 (95% CI: 0.14, 32.2) for subjects whose BMI values were greater than 25 and who were exposed to higher levels of arsenic in drinking water compared with participants whose BMI values were less than 25 and who were exposed to lower levels, indicating a synergistic effect between arsenic and BMI on the odds ratio of T2DM. The confidence intervals around these estimates are large, which is likely because of the small sample sizes in some strata.

![Figure 1. Dose-response curve between arsenic exposure and change in risk of type 2 diabetes mellitus among residents exposed to arsenic in drinking water at levels less than 170 $\mu g/L$ in Pabna, Bangladesh, 2001–2011. Associations are shown for A) type 2 diabetes and arsenic in drinking water and C) toenail arsenic. Restricted analyses of dose-response curves on residents without skin lesions at baseline (in 2001–2003) are shown for B) type 2 diabetes and arsenic in drinking water and D) toenail arsenic. The odds ratios were estimated by penalized splines with the reference value set at the lowest exposure levels of arsenic in drinking water (0.5 $\mu g/L$, based on samples whose values were lower than the limit of detection) or toenail arsenic (<0.11 $\mu g/g$). Odds ratios were adjusted for age, sex, body mass index (BMI) (weight (kg)/height (m)$^2$), cigarette smoking, and skin lesions for A and C. Odds ratios were adjusted for age, sex, BMI, and cigarette smoking for B and D. There were 709 subjects whose exposures to arsenic in drinking water were below 170 $\mu g/L$ (A and C) and 354 subjects whose exposures to arsenic in drinking water were below 170 $\mu g/L$ and who were without skin lesions at baseline (B and D). The $P$ values of penalized splines were <0.001, 0.008, 0.017, and 0.043 for A, B, C, and D, respectively. Water and toenail arsenic levels were transformed into a natural logarithm scale. Solid lines denote the estimated odds ratios, and dashed lines denote the 95% confidence intervals of the odds ratios.](Am J Epidemiol. 2013;178(10):1563–1570)
In terms of proportion of losses to follow-up, 46.8% (843/1,800) of the participants who were enrolled in the original case-control study (in 2001–2003) did not participate in 2009–2011, and the distributions of age, educational attainment, and skin lesions were different between participants and nonparticipants (Web Table 1). This may raise the potential for selection bias; therefore, we performed sensitivity analyses by using inverse probability weighting to address this issue. The association between arsenic in drinking water and diabetes was attenuated, on average, by approximately 15% in sensitivity analyses but still reached statistical significance (P for trend < 0.001) (Web Table 3).

**DISCUSSION**

In this report based on a case-control study of arsenic-induced skin lesions, we observed a significant association between low to moderate exposure to arsenic and an increased odds ratio of T2DM. This association remained robust when we excluded participants with skin lesions and drinking water arsenic concentrations greater than 170 μg/L. This suggests that the relationship between arsenic exposure and T2DM was not driven by arsenic-induced skin lesions or highly exposed individuals. Furthermore, the odds ratio of T2DM was dramatically higher in individuals who were exposed to arsenic and who were overweight or who were exposed to arsenic and who had ever smoked.

Other studies also report significant associations between T2DM and arsenic exposure. A systematic review that assessed the associations between high exposure to arsenic in drinking water and T2DM in Taiwan and Bangladesh reported a pooled relative risk of 2.52 (95% CI: 1.69, 3.75) (21), which was slightly lower than we observed in this study. A cross-sectional study conducted in Wisconsin (16) reported adjusted odds ratios for self-reported T2DM of 1.35 (95% CI: 0.78, 2.33) and 1.02 (95% CI: 0.49, 2.15) for arsenic levels in drinking water between 2 and 10 μg/L and greater than 10 μg/L compared with those of people exposed to less than 2 μg/L.

Other cross-sectional studies conducted in similar populations in Bangladesh have reported conflicting associations between arsenic and T2DM. For instance, a large population-based study (n = 1,004), which also reported a 9% prevalence of T2DM based on a fasting blood glucose level of 126 mg/dL or higher or a self-reported physician diagnosis of T2DM, reported a positive association between arsenic exposure and increasing risk of T2DM (31). Specifically, Islam et al. (31)...

<table>
<thead>
<tr>
<th>Smoking Status by Arsenic in Drinking Water, μg/L</th>
<th>No. of T2DM Cases</th>
<th>No. of Subjects</th>
<th>OR</th>
<th>95% CI</th>
<th>RERI</th>
<th>95% CI</th>
<th>Attributable Proportion Due to Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never &lt; 15.5</td>
<td>5</td>
<td>139</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥15.5</td>
<td>15</td>
<td>148</td>
<td>3.74</td>
<td>1.25, 11.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past or current &lt; 15.5</td>
<td>9</td>
<td>149</td>
<td>1.31</td>
<td>0.40, 4.25</td>
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<td>≥15.5</td>
<td>24</td>
<td>119</td>
<td>8.83</td>
<td>2.97, 26.2</td>
<td>4.78</td>
<td>0.04, 28.5</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio; RERI, relative excess risk due to interaction; T2DM, type 2 diabetes mellitus.

a Data adjusted for age, body mass index (weight (kg)/height (m)^2), and skin lesions.
reported an increased risk of T2DM for individuals whose drinking water contained more than 50 µg/L of arsenic. Individuals with the highest levels of arsenic exposure had almost double the risk of T2DM (OR = 1.9, 95% CI: 1.1, 3.5), which is comparable to our observations. However, another large population-based study (n = 11,319), which reported a 2.1% prevalence of T2DM based on self-reported physician diagnosis of diabetes, did not observe any association between self-reported T2DM and time-weighted arsenic exposure in drinking water (adjusted ORs = 1.35 (95% CI: 0.90, 2.02), 1.24 (95% CI: 0.82, 1.87), 0.96 (95% CI: 0.62, 1.49), and 1.11 (95% CI: 0.73, 1.69) for the second, third, fourth, and fifth quintiles of time-weighted arsenic in drinking water compared with the first quintile, respectively) (18). Chen et al. (18) also measured hemoglobin A1c in a subset of 2,100 participants and did not observe any relationship between arsenic exposure and hemoglobin A1c levels. The different results among these studies could be due to the cross-sectional study design or the reliance on self-reported physician diagnosis of T2DM, which could lead to disease misclassification. Interestingly, none of these studies reported an association between the presence of skin lesions and T2DM. Additional studies using National Health and Nutrition Examination Survey (17) data found conflicting results, with 1 study reporting an increased risk of T2DM of 3.58 (95% CI: 1.18, 10.83) when comparing participants in the 80th versus the 20th percentile of total urinary arsenic exposure after adjustment for markers of seafood intake. Another group that analyzed the same National Health and Nutrition Examination Survey data excluding seafood-related arsenic species from total urinary arsenic exposure found a null finding (14).

It is important to consider the limitations of this study. First, this population originated from a case-control study of arsenic-related skin lesions, which might limit the generalizability of our findings to different populations. However, the restricted analysis of participants without skin lesions showed a similar association between arsenic exposure and risk of T2DM. Additionally, there is no evidence that skin lesions are an independent risk factor for T2DM, even though they are associated with chronic arsenic exposure. Second, the results of sensitivity analysis may suggest some degree of selection bias because the association between arsenic exposure and diabetes was attenuated. This may result from the overall healthier weighted population (younger, more educated, with smaller proportion of skin lesions) compared with the unweighted participants. However, this issue did not significantly affect the validity and robustness of the primary findings because the positive relationship between arsenic exposure and diabetes remained after correcting for the influence of loss to follow-up by using inverse probability weighting.

Third, this study did not collect information on physical activity levels or caloric intakes, which are both risk factors for T2DM. Nevertheless, the adjustment of BMI in the analysis would partially account for confounding effects by physical activity and caloric intake because BMI is used as a surrogate for both. We would therefore expect the influence of unmeasured confounding due to these factors to be relatively minor. Fourth, although we excluded from our analysis subjects who reported a physician diagnosis of T2DM in 2001–2003, we did not measure hemoglobin A1c in 2001–2003. Therefore, we cannot be certain that we excluded all prevalent cases of T2DM. This may bias the observed association between arsenic exposure and T2DM. Fifth, we had small sample sizes when examining the interactions between arsenic exposure and being overweight or smoking. Although we believe that the results from these analyses help to place in perspective the relative excess risk of T2DM from arsenic exposure by comparing it with more well-recognized risk factors for T2DM, we recognize that the estimates may be unstable, as indicated by the large confidence intervals. Finally, this study population might be experiencing other nutritional deficiencies, which might affect arsenic toxicity or the development of T2DM.

Our study has several strengths, including the diagnosis of T2DM by using hemoglobin A1c and the measurement of arsenic exposure prior to the diagnosis of T2DM. It is also noteworthy that we found similar associations whether we measured arsenic in the participants’ drinking water, reflecting their environmental exposure, or in their toenails, reflecting their internal dose. This population was also subject to a wide range of arsenic exposures (from undetectable to 1,480 µg/L), which allowed us to characterize the dose-response relationship.

We also observed that known risk factors of T2DM interacted with arsenic exposure to increase the odds ratio of T2DM. Whereas the odds ratio of T2DM was much greater in participants who were overweight or obese or in men who smoked, a significant increase in T2DM was still observed in those individuals with normal BMI values and in those who had never smoked, indicating that arsenic acts independently from these known risk factors for T2DM. It is particularly striking that this population had a mean BMI value of 20.3, which is considerably lower than that of the US population, whose age-adjusted BMI values were 28.5 and 26.1 among men and women in 2008, respectively (32). This suggests that chronic arsenic exposure might contribute to T2DM through different biological pathways than obesity.

In this study, we found a strong association between low to moderate levels of arsenic exposure and increased odds ratios of T2DM. There appeared to be a synergistic effect between arsenic exposure, smoking, and BMI, which substantially increased the risk of T2DM. Considering that the prevalence of T2DM is increasing in rural Bangladesh, it is critical that drinking water remediation programs continue to effectively reduce arsenic exposure. Also, efforts to reduce smoking and maintain normal BMI may help reduce the risk of T2DM in Bangladesh.

ACKNOWLEDGMENTS

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