Arsenic and Fasting Blood Glucose in the Context of Other Drinking Water Chemicals: A Cross-Sectional Study in Bangladesh

Citation:

Arsenic and fasting blood glucose in the context of other drinking water chemicals: a cross-sectional study in Bangladesh

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Abstract

Goal: The goal of this study was to evaluate the association between groundwater arsenic and fasting blood glucose in the context of other groundwater chemicals, in Bangladesh.

Methods: Fasting blood glucose, gender, body mass index, sociodemographic variables, and diabetes medication use were measured among adults $\geq$ 35 years of age (n=6,587) participating in the Bangladesh Demographic and Health Survey (BDHS) 2011. Groundwater chemicals in 3,534 well water samples were measured in the British Geological Survey (BGS) and Department of Public Health Engineering (DPHE) 1998-99 survey. We assigned the nearest BGS-DPHE well's chemical exposure to each BDHS participant. We used survey-estimation linear regression methods to model log-transformed fasting blood glucose, among those using groundwater as their primary drinking-water source, as a function of groundwater arsenic. We considered possible interactions between categorical arsenic exposure and each of 14 other groundwater chemicals dichotomized at their medians. The chemicals considered as possible effect modifiers included: aluminum, barium, calcium, iron, potassium, lithium, magnesium, manganese, sodium, phosphorous, silicon, sulfate, strontium, and zinc.

Results: Compared to persons exposed to groundwater arsenic $\leq$ 10 µg/L, the adjusted geometric mean ratio (GMR) of fasting blood glucose was 1.01 (95% confidence interval: 0.98, 1.04) for individuals exposed to groundwater arsenic concentrations >10 µg/L and $\leq$50 µg/L, and was 1.01 (0.97, 1.03) for those with > 50 µg/L arsenic. There were no Bonferroni-significant interactions with other chemicals, after accounting for the large number of chemicals tested as modifiers.

Conclusions: In our analysis of groundwater chemistry data from 1998/99 and fasting blood glucose outcomes measured in nearby populations approximately a decade later, there was no overall association of fasting blood glucose with nearby historical groundwater arsenic. This null association was not significantly modified by the historical levels of other groundwater chemicals. These null results are inconclusive regarding shorter-term potential toxicity of arsenic for glucose regulation, if there are differences between the historical concentrations measured in nearby groundwater and the actual drinking water chemical exposures in the population during the etiologically relevant period for more acute phenotypes like fasting blood glucose. Individual, longitudinal exposure assessment with less measurement error is needed to more precisely evaluate the joint impacts of drinking water chemicals and establish if there is a sensitive time window for glycemic outcomes.

Keywords: cumulative risk assessment; exposure mixtures; medical geology; epidemiology; diabetes; Exposome

1. Introduction

Efforts to reduce water-borne infectious diseases caused by drinking contaminated surface water led to millions of shallow wells to be built in Bangladesh during the last 30 years, triggering mass population exposures to geogenic arsenic [1]. This has caused nearly 35 million people to be exposed to arsenic exceeding Bangladesh's 50 µg/L standard, and 57 million people exposed to a concentrations exceeding the World Health Organizations standard of 10 µg/L [2], and has led to considerable arsenic poisoning and related diseases [1].

There have been several studies reporting positive associations between exposure to high levels of arsenic and diabetes in Bangladesh and Taiwan [3-7]. Additionally, low levels of exposure to inorganic arsenic via drinking water may be a factor in diabetes prevalence [8]. A study in western Bangladesh examined arsenic exposure and prevalent diabetes mellitus among people who were drinking tube-well water. The investigators found that the prevalence ratio of diabetes mellitus among 163 subjects with keratosis as a proxy for arsenic exposure, compared to 854 unexposed individuals without, was 5.2 (2.5 – 10.5) adjusting for age, sex and BMI [9]. However, the authors noted that other confounders than age, sex, and BMI were not included in that study, as well as the possibility of a selection bias that favored the participation of individuals with diabetes. A case-control study of arsenicosis patients and biochemical changes in Bangladesh, while not targeted to investigate arsenic exposure and diabetes, estimated that the prevalence of diabetes mellitus among arsenicosis patients was 2.8 times higher than controls [10]. A cohort study, in regions of Taiwan similarly contaminated with high arsenic, found that the incidence rate ratio of diabetes comparing villages exposed to high arsenic versus low arsenic within specific age groups were: 3.6 (3.5–3.6) among adults age 35-44; 2.3 (1.1–4.9) among adults age 45-54 years old; 4.3 (2.4–7.7) among adults age 55-64 years old; and 5.5 (2.2–13.5) among adults age 65-74 years old [4, 5].

Arsenic toxicokinetics is known to be affected by many environmental factors [11] but drinking water co-exposures have not been extensively studied as effect modifiers. For specific health outcomes (e.g., glucose regulation) it is possible that there also could be toxicodynamic interactions of arsenic with other drinking water chemicals if the co-exposures act on similar pathways, which has not been extensively studied, although it is possible to speculate about possible toxicodynamic mechanisms based on previous toxicological studies. There are a large number of possible pairwise chemical interactions that might be investigated through toxicological experiments, so an agnostic screen for interactions using existing epidemiological data might help prioritize specific targets for future toxicological experimental studies.

The goal of this hypothesis-generating study is to assess the cross-sectional association of groundwater arsenic with fasting blood glucose among individuals 35 or older near wells with moderate (As ≤ 10 µg/L), high (10 < As ≤ 50 µg/L), or very high (As > 50 µg/L) elevated environmental groundwater arsenic and other groundwater chemicals for glycemic outcomes in a sample representative of Bangladesh.

2. Methods

2.1 *Source Population*

The Demographic and Health Surveys (DHS) are nationally-representative household surveys that collect data on a wide range of indicators pertaining to population demographics, health status, and nutrition [12]. The Bangladesh Demographic Health Survey (BDHS) sampled individuals from 600 clusters in a survey conducted in 2011. Sampling was stratified by rural and urban areas that comprise the seven administrative divisions of Bangladesh. Each cluster was made up of 30 households [12]. To protect household identity, one randomly selected GPS location was taken per cluster.

2.2 *Clinical and Demographic Data*

Data collection for the BDHS began July 2011 and finished in December 2011 [12]. The survey was conducted by 16 interviewing teams, each with one supervisor, one field editor, and female and male interviewers [12]. Information on clinical and demographic factors relevant to fasting blood glucose were collected by the BDHS from 18,000 residential households, and included: age, sex, educational level, current smoking status, rural or urban residence, geographical region, household wealth, drinking water sources, and whether individuals were taking medications to treat diabetes. A subsample of one-third of the households were surveyed, and eligible members were selected to participate in the biomarker testing components, blood glucose testing, height and weight measurements. Body mass index (BMI) was calculated from measured weight and height as kg/m^2 [12].

The wealth index has been used in several DHS and other country-level surveys to measure disparities. It serves as an indicator of household level wealth that is consistent with expenditure and income measures. The wealth score is constructed in three steps by inventorying household assets and summarizing by principal components analysis [12]. In the first step, principal components are calculated among a subset of household assets commonly seen in households across the country. In the second step, separate principal component scores were calculated for urban or rural households based on assets specific to urban, or to rural settings. In the third step, a wealth index was produced by regressing the area-specific asset scores on the general asset scores [12].

To gauge food security, the BDHS collected data from eligible participants using the Woman's Questionnaire. These questions were developed from the 2011 Nepal DHS food insecurity module and the Household Food Insecurity Access Scale indicators established by USAID's Food and Nutrition Technical Assistance project, and were modified to be specific to Bangladesh [12]. The kinds of questions asked included, "How often did you eat three `square meals' (full stomach meals) a day in the past 12 months (not a festival day)?", and "In the last 12 months, how often did you or any of your family have to eat wheat (or another grain) although you wanted to eat rice (not including when you were sick)?" Based on the responses to questions, four categories of food security were created, all the responses were then summed to create a food security indicator score. A score of 0 was considered as food secure, all the way to a maximum score of 15, being severe insecurity [12]. For our analyses and using BDHS descriptive scores, we dichotomized this indicator into either "food secure" or "food insecure"

and assumed that individuals coming from the same household had similar food availability and security.

2.3 Fasting Blood Glucose Outcomes

Women and men who were age 35 or older in selected households were eligible to have their blood glucose tested [12]. BDHS 2011 indicated that 4,311 women and 4,524 men age 35 and older were eligible for blood glucose testing. Among these individuals, 89% of women and 83% of men participated in the blood glucose measurement [12].

The protocol for measuring fasting blood glucose in the BDHS 2011 survey has been previously described [12]. Briefly, participants in the biomarker sub-study were asked if they had eaten or had anything to drink (except water) before the glucose test. If the participant had not been fasting, an appointment was scheduled for the next morning [12]. Blood was obtained from the middle or ring finger of eligible participants who had fasted overnight. Before being pricked with a non-reusable lancet, the participants' finger was swabbed with 70% isopropyl alcohol and allowed to dry. The first two drops of blood were wiped away, and the third drop was used to perform the field test. Blood glucose was measured using a HemoCue 201+ blood glucose analyzer (HemoCue America, Brea, California).

Within the subsample, there were three observations with fasting blood glucose measurements greater than 400 mg/dL. This is biologically possible, but unlikely. These observations were included in the main analysis and excluded in sensitivity analyses.

We considered fasting blood glucose to be in the impaired fasting glucose or diabetes ranges using cut-points from the World Health Organization [13]. Fasting blood glucose ≤ 110 mg/dL was considered the reference category, and this category included 499 individuals in our sample with hypoglycemic status as defined by low fasting blood glucose (< 70 mg/dL). We defined fasting glucose in the impaired fasting glucose range as a fasting blood glucose measurement between 110 and 126 mg/dL. We defined fasting blood glucose in the diabetes range as a fasting blood glucose ≥ 126 mg/dL.

2.4 Groundwater Chemistry Data

Chemical concentrations in wells across Bangladesh were measured by the British Geological Survey (BGS), which collects groundwater information within the United Kingdom and internationally [14]. In 1998-99, BGS staff in close collaboration with the Department of Public Health Engineering (DPHE) of Bangladesh carried out a groundwater chemical survey to develop maps showing the regional distribution elements in Bangladesh groundwater [2]. The survey employed a stratified random sampling in which stratification was by units of area (km^2) to ensure a uniform distribution of sites [2, 14]. Water samples were collected from 3,534 well water samples across Bangladesh (excluding the Chittagong Hill Tracts), covering one sample for 37 km^2 area [2]. All samples were collected from drinking water wells, which ranged in depth from 7-362 meters deep [15]. The GPS coordinates of each well were recorded. Arsenic was measured using hydride generation-atomic fluorescence spectrometry (HG-AFS) with a detection limit of 0.25 or 0.5 $\mu g \ L^{-1}$ [2]. Other chemicals were measured by inductively-coupled

plasma-atomic emission spectrometry (ICP-AES), and in a few cases by inductively-coupled plasma-mass spectrometry (ICP-MS) [2]. All analyses were carried out in BGS laboratories using filtered (0.22 μm) samples; results from both ICP-AES and ICP-MS methods were in good agreement [14].

Arsenic was categorized based off well concentrations with moderate being As ≤ 10 μg/L, high 10 < As ≤ 50 μg/L, and very high As > 50 μg/L. Other groundwater chemicals were dichotomized at their medians to create low and high strata of each chemical. Dichotomized chemicals included: aluminum, barium, calcium, iron, potassium, lithium, magnesium, manganese, sodium, phosphorous, silicon, sulfate, strontium, and zinc. We excluded boron, cobalt, chromium, copper, and vanadium from our analysis as a significant proportion (over 50%) of the samples were below the limit of detection (Table 2).

2.5 Exposure Assignment

BDHS participants were assigned arsenic and other groundwater chemical exposures based on data from their cluster's nearest BGS well. Only one well (the nearest) was assigned to each cluster. The mean distance between the randomly selected point of the cluster and the nearest well was 2.3 (95% CI: 1.3 — 3.6) kilometers.

To do the spatial data merge and exposure assignment, we used administrative shapefiles for Bangladesh from DIVA-GIS [16]. We extracted the GPS locations of the BDHS clusters and BGS-DPHE wells, then imported and projected these in ArcGIS 10.4.1 using the UTM 1984 45 N projection system. We determined the nearest BGS-DPHE wells for each BDHS 2011 clusters using spatial joining in ArcGIS to calculate the distances in kilometers from clusters to wells.

2.6 Statistical Analysis

Our analysis is focused on men and women in Bangladesh who were at least 35 years and who indicated using groundwater as their primary drinking water source. Therefore, we used survey estimation methods [17] to draw inferences for that subpopulation. **Supplemental Figure 1** illustrates the process used for their selection.

Missing data were handled using multiple imputation by chained equations [18]. Four variables (current smoker, BMI, taking diabetes medications, and food security) were imputed. Smoking status had 7,527 complete observations (38 imputed), BMI had 7,329 complete observations (236 imputed), diabetes medication use had 7,018 complete observations (547 imputed), and food security had 5,191 complete observations (2,374 imputed). The analytic sample size, after weighting, was 6,587.

We estimated the population proportions for categorical variables (current smoker, taking diabetes medications, urban residence, household wealth, and regional distributions), the population arithmetic means of approximately normally distributed continuous variables (age, BMI, and years of education) and the population geometric means of skewed continuous variables (arsenic, other groundwater chemicals, and fasting blood glucose). The fasting blood glucose distribution was approximately log-normal.

Survey estimation linear regression methods [17] were used to assess the association of groundwater arsenic with natural log-transformed fasting blood glucose. Models were sequentially adjusted: Model 1 was the unadjusted association; Model 2 further adjusted for age, sex and BMI; Model 3 further adjusted for current smoking status, education, household wealth, and whether an individual was currently taking medications for diabetes, and Model 4 further adjusted for food security. Survey estimation multinomial logistic regression methods were used to assess the relative odds of prevalent high fasting blood glucose (i.e., odds ratio of having fasting blood glucose in the range of impaired fasting glucose vs. range of normal glycemia or hypoglycemia, and having fasting blood glucose in the diabetes range vs. having fasting blood glucose in the range of normal glycemia or hypoglycemia) with increasing well water arsenic.

Because sex [19-24] and BMI [24-27] have been associated in several studies with arsenic toxicokinetics and the related one-carbon metabolism pathway, we considered possible effect modification of the hypothesized arsenic toxicity, by sex and by BMI categories, using models with interaction terms between BMI category and arsenic category, or sex and arsenic category, and adjustment for the same suite of confounders as in our fully adjusted main analyses (Model 4).

To examine potential effect modification by other water well chemicals, we fit separate models with interaction terms between arsenic categories and each of the 14 other groundwater chemicals dichotomized at their medians. We used Bonferroni correction to account for the 14 well water chemicals considered in F test hypothesis tests ($\alpha = 0.05/14$) [28]. We applied this same standard to the unadjusted and the adjusted models separately, under the assumption that analyses of the same chemical were dependent hypotheses.

To assess whether associations were dominated by urban populations, in a sensitivity analyses we excluded urban and Dhaka residents. We also conducted another sensitivity analysis considering the impact of diabetes status in a sensitivity analysis stratifying by blood glucose and diabetes medications.

All statistical analyses were performed in Stata/SE, version 15.1.

2.7 Ethics Approval

This secondary data analysis protocol was approved by Emory University IRB (IRB00088075). The DHS Program provided the survey and GPS data after examining the project goal and all DHS survey participants provided informed consent. Permission was attained from the copyright section of the British Geological Survey Environmental Science Centre to use the publicly available BGS-DPHE dataset.

3. Results

The characteristics of the adult sample age ≥ 35 drinking groundwater in Bangladesh are described in **Table 1**. There were 6,281 participants with fasting glucose < 126 mg/dL: 3,090 men and 3,191 women. There were 306 participants with fasting blood glucose $\geq$ 126 mg/dL: 146 men and 160 women. The higher and lower blood glucose populations had similar mean

ages, but the population with fasting blood glucose $\geq$ 126 mg/dL had a mean BMI of 22.6 (22.1, 23.2) kg/m^2 compared to a mean BMI of 20.5 (20.3, 20.6) kg/m^2 among persons fasting blood glucose < 126 mg/dL. The wealth distributions were dissimilar between these populations, with a greater proportion of persons with fasting blood glucose $\geq$ 126 mg/dL belonging to the highest two household wealth quintiles. There were more years of education among men with fasting blood glucose < 126 mg/dL [mean 3.9 (95 CI: 3.7, 4.2)] than among women with fasting blood glucose < 126 mg/dL [mean 1.9 (1.7, 2.1)], but these sex differences in educational attainment were eclipsed by the differences in by blood sugar categories: the mean education attained by men with fasting blood glucose $\geq$ 126 mg/dL was 6.1 (95% CI: 5.1, 7.1) years, while among women with fasting blood glucose $\geq$ 126 mg/dL the mean educational attainment was 4.8 (95% CI: 4.1, 5.4) years. Smoking was more common among persons with fasting blood glucose < 126 mg/dL than among persons with fasting blood glucose $\geq$ 126 mg/dL. Among persons with fasting glucose < 126 mg/dL, 1.6% (1.3, 2.0) reported taking diabetes related medications, indicating that this group also included some persons with well-controlled diabetes. Among persons with fasting glucose $\geq$ 126 mg/dL, the proportion reporting use of diabetes-related medication was 35.3% (28.6, 42.0). More of the population with fasting blood glucose $\geq$ 126 mg/dL lived in urban environments, compared to persons with lower fasting blood glucose.

Water chemistry measurements are described in **Supplemental Table 1**. The most common chemicals were sodium with a geometric mean of 40.22 mg/L, calcium with a geometric mean of 26.21 mg/L, and silicon with a geometric mean of 18.82 mg/L. The geometric mean of arsenic was 4.14 µg/L. Groundwater arsenic levels varied geographically across regions (**Supplemental Table 2**). The region with the highest geometric mean arsenic concentration was Chittagong (16.7 µg/L), followed by Khulna (8.4 µg/L), and Sylhet (5.8 µg/L). The lowest geometric mean arsenic was in the Rangpur region (1.1 µg/L).

Table 2 presents the association of arsenic with the geometric means of fasting blood glucose. In unadjusted models, persons with groundwater arsenic in the 10 to 50 µg/L range had a geometric mean ratio of 1.02 (0.99, 1.05) compared to individuals in the $\leq$10 µg/L range, and persons with groundwater arsenic >50 µg/L had a geometric mean ratio of 1.02 (0.99, 1.05) compared to persons with groundwater arsenic $\leq$10 µg/L. However, these associations were not statistically significant. The ratio of geometric means of fasting blood glucose adjusting for age, sex, BMI, and region was 1.01 (0.98, 1.04) among participants in the 10 to 50 µg/L arsenic exposure category compared to the $\leq$ 10 µg/L category. The fully adjusted models had similar associations, with a geometric mean ratio of 1.01 (0.98, 1.04) for fasting glucose comparing persons with arsenic in the 10 – 50 µg/L range compared to persons in the $\leq$ 10 µg/L category, and 1.00 (0.97, 1.03) increase for > 50 µg/L arsenic concentration category compared to the $\leq$ 10 µg/L category. None of these associations of fasting blood glucose with groundwater arsenic category were statistically significant. Restriction to persons outside Dhaka and urban areas did not change these from null associations (**Supplemental Table 3**). Considering a possible linear relationship of the geometric mean of fasting blood glucose with arsenic as a continuous predictor, the association remained null (**Supplemental Table 4**). There were no significant linear associations of continuous arsenic with fasting blood glucose after stratifying by range of fasting blood glucose and diabetes medication use (**Supplemental Table 5**).

Table 3 reports the odds ratios from multinomial logistic regressions of a person having fasting glucose in the impaired fasting glucose (fasting blood glucose ≥ 110 mg/dL and <126 mg/dL) or diabetes (≥126 mg/dL) ranges, relative to fasting blood glucose < 110 mg/dL, as groundwater arsenic increases. The unadjusted odds ratio comparing persons in the 10 – 50 µg/L arsenic range to those in the ≤ 10 µg/L arsenic for impaired fasting glucose range fasting glucose was 0.89 (0.62, 1.28), and among persons with arsenic > 50 µg/L vs. arsenic ≤ 10 µg/L, the odds ratio of impaired fasting glucose range glucose was 1.21 (0.84, 1.74). The fully adjusted odds ratio for impaired fasting glucose-range fasting glucose among participants in the > 50 µg/L vs. ≤ 10 µg/L arsenic category was 0.88 (0.62, 1.27), and for persons with arsenic > 50 µg/L vs. ≤10 arsenic category was 1.14 (0.79, 1.66). The unadjusted odds ratios for having fasting blood glucose in the diabetes range for persons in the 10 – 50 µg/L arsenic category vs. ≤ 10 µg/L arsenic category was 1.15 (0.78, 1.69), and the odds ratio for having fasting glucose in the diabetes range among persons in the > 50 µg/L arsenic category vs. ≤ 10 arsenic category was 1.33 (0.97, 1.82). The fully adjusted odds ratio for diabetes-range fasting glucose among participants in the > 50 µg/L compared with the ≤ 10 µg/L arsenic category was 1.19 (0.80, 1.78), and the adjusted odds ratio for persons in the > 50 µg/L arsenic category vs. ≤10 arsenic category was 1.40 (0.96, 2.04). In sensitivity analysis excluding urban populations and the Dhaka region (**Supplemental Table 6**), there were no significant odds ratios.

We considered the possible role of BMI or sex as possible effect modifiers in the fully adjusted arsenic - fasting blood glucose associations, by examining the ratios of geometric mean ratios (GMRR) to contrast the magnitude of associations of arsenic with fasting blood glucose, comparing persons in the normal weight range (18.5 ≤ BMI < 25), in overweight persons (25 ≤ BMI < 30), or in obese persons (30 ≤ BMI < 60) compared to the reference associations for arsenic with fasting blood glucose among underweight (BMI < 18.5) persons. The normal weight vs. underweight GMRR for the fasting blood glucose contrast between persons with arsenic concentrations 10 – 50 µg/L relative to the ≤ 10 µg/L arsenic category was 1.03 (0.99, 1.07), and the normal weight vs. underweight GMRR for the contrast between persons in the > 50 µg/L vs. ≤ 10 µg/L arsenic category was 1.06 (1.02, 1.10). The GMRR for overweight participants vs. underweight participants for the contrast in blood glucose between persons in the 10 – 50 µg/L relative to the ≤ 10 µg/L arsenic category was 1.02 (0.96, 1.07), and the GMRR for the contrast between the > 50 µg/L vs. ≤ 10 µg/L arsenic category was 1.04 (0.99, 1.10). The GMRR for obese persons versus underweight persons for the contrast between persons with groundwater arsenic in the 10 – 50 µg/L range vs. ≤ 10 µg/L arsenic category was 1.09 (0.98, 1.22), and the GMRR for the contrast between persons in the > 50 µg/L category vs. the ≤ 10 µg/L arsenic category was 1.10 (0.99, 1.22). There was no significant effect modification by sex. The adjusted GMRR for men vs. women in the contrast in fasting blood glucose between persons with arsenic in the 10 – 50 µg/L category vs. the ≤ 10 µg/L arsenic category was 1.00 (0.98, 1.03), and the GMRR for the contrast in fasting blood glucose between the > 50 µg/L arsenic category vs. the ≤ 10 µg/L arsenic category was 1.02 (0.99, 1.04).

Table 4 considers potential interactions of categorical arsenic exposure with 14 other groundwater chemicals dichotomized at their median concentrations; the presence of a significant effect of any arsenic category in any chemical stratum was assessed by a separate F test per chemical. There were no Bonferroni-significant interactions, after accounting for the

multiple F tests. In fully adjusted models, among persons with low drinking-water calcium (≤ 25.5 mg/L), arsenic exposure in the 10 to 50 µg/L range had a fasting blood glucose geometric mean ratio of 1.03 (1.00, 1.06) compared to the referent group of ≤ 10 µg/L water arsenic. Among persons with low drinking-water iron (≤ 0.69 mg/L), the geometric mean ratio of fasting blood glucose for persons in the > 10 and ≤ 50 µg/L arsenic range vs. the ≤ 10 µg/L arsenic range was 1.03 (0.98, 1.08), and for persons with arsenic in the > 50 µg/L range vs. arsenic ≤ 10 µg/L was 1.06 (1.01, 1.11). Low potassium (≤ 3.0 mg/L) may have potentiated arsenic toxicity, as in that stratum the geometric mean ratio of fasting blood glucose contrasting persons in the > 10 and ≤ 50 µg/L arsenic range vs. ≤10 µg/L arsenic range was 1.03 (1.00, 1.07), and contrasting persons in the > 50 µg/L arsenic range vs. ≤ 10 µg/L arsenic range was 1.06 (1.02, 1.11). Among persons with low water magnesium (≤ 12.1 mg/L), persons with arsenic concentrations in the 10 to 50 µg/L range compared to the participants with ≤ 10 µg/L arsenic had a fasting blood glucose geometric mean ratio of 1.05 (1.02, 1.07). Among persons with high-zinc water (> 0.014 mg/L), persons in the 10 - 50 µg/L arsenic concentration group, compared to persons with arsenic < 10 µg/L, had a fasting blood glucose geometric mean ratio of 1.06 (1.01, 1.11), but among persons exposed to high zinc the contrast in fasting blood glucose between the >50 µg/L and ≤ 10 µg/L was a null association of 0.98 (0.93, 1.03). There were no significant associations detected in other groups. A sensitivity analysis using stratified analyses rather than interaction-term models did not have Bonferroni-significant adjusted associations in any water chemistry stratum after accounting for the number of stratified models (**Supplemental Table 7**).

4. Discussion

We did not detect an overall association between arsenic, measured a decade prior at proxy locations, with fasting blood glucose, or with the prevalence of having elevated fasting blood glucose in the range of impaired fasting blood glucose or diabetes, among adults age ≥ 35 in Bangladesh in 2011. Results were similar when treating arsenic as a categorical or continuous exposure (Table 3, 4). Arsenic levels in urban areas and in Dhaka were low as measured in the British Geologic Survey, but there are other risk factors in these communities that could influence the development of diabetes. However, the association remained similar in sensitivity analyses excluding urban and Dhaka participants (**Supplemental Table 2**).

There were a small number of persons with fasting blood glucose in the diabetes range in our sample. This could be important if the effects of arsenic on fasting blood glucose differ across quantiles of the glycemia distribution - in particular, if arsenic has impacts primarily at high levels of fasting blood glucose (e.g., among persons with uncontrolled diabetes). In a few previous studies of arsenic and glycemia, the association of arsenic with glycemic biomarkers was primarily among persons very poorly controlled diabetes; this pattern was reported both in an American Indian sample [29] and in a nationally representative sample of Canadians [30], although in both of those North American cross-sectional studies the exposure metric was a urine arsenic biomarker rather than groundwater arsenic. In this study, although the associations had wide confidence intervals and were not significant, there was a monotonic increase in the odds ratio of having fasting blood glucose ≥ 126 mg/dL versus fasting glucose < 110 mg/dL with increasing arsenic categorical exposure (**Table 3**), and these odds ratios were robust to adjustment for confounders. Whether our finding is another replication of an arsenic association

peculiar to the tail of the glycemia distribution, but not significant in our analysis because of the small number of persons with poorly controlled diabetes in this study, is ambiguous.

Arsenic toxicity in the context of other water chemicals has only recently begun to be studied, but mixtures including arsenic are common in areas such as the Bengal delta. Hoque *et al.* investigated the status of several groundwater toxicants and nutrients relevant to human health in Asian deltas [31], compiling data on 5,256 tube-wells from published literature for Bengal, Mekong, and Red River deltas. Most of the high calcium and magnesium wells are located in the south-west and southern parts of the Bengal delta, and contained between 25-50% of the recommended daily intake for magnesium. Northeastern regions of Bangladesh had much lower magnesium concentrations, with wells containing < 10% of the recommended daily intake.

That we did not see strong evidence for effect modification of the hypothesized arsenic toxicity by strong correlates of arsenic toxicokinetic differences between people (i.e., no significant interactions by sex, and no monotonic trend of interactions with increasing categories of BMI) could suggest that our local, historical groundwater arsenic exposure measure may have limited construct validity as a surrogate for people's drinking water arsenic exposures at the etiologically relevant time for impacting fasting blood glucose measures [32]. However, it is also possible that there exists an arsenic toxicity for glucose regulation that is not modified by sex nor by BMI. A United States-based cohort study that found a positive association between drinking water supply arsenic and incident diabetes did not show significant interactions by sex, nor by waist circumference [33].

Our study has several key limitations. We think the most important limitation is that groundwater arsenic and other chemical concentrations were measured in the BGS survey conducted in 1998/99, not concurrently with the glucose measurements, and in nearby areas, not in household water supplies. The appropriateness of these measures as a proxy for drinking water chemicals encountered by groundwater-consuming BDHS participants in the etiologically relevant time for glycemic outcomes in 2011 depends on the extent of water chemistry differences between the measured BGS survey wells and the unmeasured BDHS household water supply wells. Deeper aquifers (> 30m) likely have arsenic concentrations that have less temporal measurement error and are lower overall than in the shallow aquifers [34, 35]. In addition to random error differing by well depth, in an Araihazar, Bangladesh temporal variability study there were systematic changes in arsenic concentration for 11 of their 26 monitoring wells observed over a period of 2-3 years, with trends that differed in direction across wells [35]. The water samples from the BGS-DPHE were collected from drinking water wells that ranged from seven to 362 meters deep, the median depth was 35 m (25%ile: 22 m, 75%ile: 56 m) [2]. In addition to these hydrological sources of temporal error in the same well over time, since the time of the BGS-DPHE survey, millions of pumps have been implemented to improve access to safe drinking water, potentially leading to major and systematic changes in exposures if the BGS well and BDHS water supply wells are at systematically different depths [36]. We lack data on the well depth distribution for the BDHS household water supplies, but if the discrepancy in well depths between the two populations is spatially patterned similarly to the distribution of diabetes across our study participants, this could introduce differential measurement error, dependent measurement error, or both, of exposure by outcome, contributing to information bias that could be in any direction.

Another concern for potential information bias is that fasting blood glucose has temporal variability as well as other sources of measurement error, and this study is based on a single glucose measurement. Past research by Selvin *et al*, suggests that studies using only a single measurement could arrive at considerably different prevalence estimates for diabetes compared to using two glucose measurements [37].

Lastly, our modeling approach has a possible limitation: the distributional assumption of fasting blood glucose being lognormal is a strong assumption, and our P values may be sensitive to departures of the empirical distribution from a lognormal distribution. This could bias standard errors of our estimates and therefore our claims of significance or lack thereof; but the point estimates of associations are likely reasonable. This may be important for interpreting the odds ratios of high blood sugar with low arsenic, as these point estimates were substantial even if not statistically significant, and showed a monotonic dose-response.

To better understand the relationship between arsenic and fasting blood glucose in Bangladesh, prospective epidemiological studies with more participant-relevant, longitudinal arsenic exposure measures could reduce exposure measurement error and allow assessment of the potential timing of an arsenic exposure-glycemic trait association. We did not identify groundwater chemicals that were Bonferroni-significant modifiers of groundwater arsenic's association with fasting blood glucose outcomes; but these putative modifiers may have shared many of the same sources of measurement error as our arsenic exposure measure. More precise measurements of drinking water chemistry joint exposures could improve ability to detect interactions where present.

5. Conclusions

We did not detect a strong relationship between our surrogate measure of arsenic exposure and fasting blood glucose in Bangladesh in 2011. This could be due to measurement error but also due to a limited number of persons with diabetes, if the association of arsenic with higher blood sugar is specific to very poorly controlled diabetes. We were unable to detect Bonferroni-significant interactions of arsenic with other groundwater chemicals, but this does not preclude the existence of interactions that could be observed in studies with less measurement error, a greater number of persons affected by diabetes, or both.

Table 1: Characteristics of BDHS 2011 sample who were eligible for fasting blood glucose tests (age ≥ 35) and who reported their primary source of drinking water was groundwater. Given in parentheses is the 95% confidence interval.

Participant Characteristics	Participants with fasting blood glucose < 126 mg/dL (n=6,281)	Participants with fasting blood glucose ≥ 126 mg/dL (n=306)
Age (in years)	51.8 (51.4, 52.2)	52.9 (51.2, 54.6)
Sex (male)	49.2% (48.0, 50.4)	47.7% (42.1%, 53.3%)
BMI (kg/m2)	20.5 (20.3, 20.6)	22.6 (22.1, 23.2)
Years of education	2.9 (2.7, 3.1)	4.8 (4.1, 5.4)
Fasting blood glucose (mg/dL)	91.6 (90.8, 92.5)	165.1 (158.9, 171.4)
Current Smoker	14.0% (12.4, 15.6)	9.0% (5.5, 12.6)
Taking diabetes medication	1.6% (1.3, 2.0)	35.3% (28.6, 42.0)
Household characteristics		
Urban residence	15.5% (13.8, 17.1)	23.0% (18.4, 27.6)
Household wealth index		
Quintile 1	21.7% (19.6, 23.8)	11.8% (6.9, 16.6)
Quintile 2	21.7% (20.0, 23.4)	12.4% (7.4, 17.3)
Quintile 3	21.9% (20.3, 23.6)	19.6% (14.4, 24.8)
Quintile 4	21.6% (19.8, 23.3)	24.5% (18.7, 30.2)
Quintile 5	13.1% (11.4, 14.7)	31.8% (25.8, 37.8)
Regional distribution		
Barisal	6.1% (5.5, 6.6)	8.0% (5.4, 10.7)
Chittagong	16.8% (15.7, 17.9)	23.7% (18.3, 29.1)
Dhaka	29.4% (27.7, 31.2)	19.0% (13.2, 24.9)
Khulna	13.4% (12.3, 14.5)	12.2% (8.5, 15.9)
Rajshahi	15.2% (14.1, 16.3)	20.6% (15.5, 25.8)
Rangpur	13.4% (12.6, 14.2)	11.4% (7.7, 15.1)
Sylhet	5.7% (5.1, 6.2)	5.0% (2.9, 7.1)

* There were three observations that had fasting blood glucose measurements above 400 mg/dL that slightly skew the mean fasting glucose.

Table 2. Geometric mean ratios of fasting blood glucose across three categories of arsenic exposure.

	Model 1	Model 2	Model 3	Model 4
Arsenic (µg/L)				
As ≤ 10	Referent	Referent	Referent	Referent
10 < As ≤ 50	1.02 (0.99, 1.05)	1.01 (0.98, 1.04)	1.01 (0.98, 1.04)	1.01 (0.98, 1.04)
50 < As ≤667	1.02 (0.99, 1.05)	1.00 (0.97, 1.03)	1.00 (0.97, 1.03)	1.00 (0.97, 1.03)

Model 1. Unadjusted.
Model 2. Adjusted for age, sex, BMI, and region.
Model 3. Further adjusted for smoking status, educational attainment, urban vs rural residence, household wealth, and diabetes medication use.
Model 4. Further adjusted for food security.

Table 3. Odds ratios of fasting blood glucose in the ranges of impaired fasting glucose (fasting blood glucose ≥ 110 mg/dL and <126 mg/dL) or diabetes (fasting blood glucose ≥126 mg/dL) relative to a reference category of fasting blood glucose < 110 mg/dL across three categories of arsenic exposure.

	Fasting blood glucose in impaired fasting glucose range	Fasting blood glucose in diabetes range
Model 1		
Arsenic (µg/L)		
As ≤ 10	Referent	Referent
10 < As ≤ 50	0.89 (0.62, 1.28)	1.15 (0.78, 1.69)
50 < As ≤667	1.21 (0.84, 1.74)	1.33 (0.97, 1.82)
Model 2		
Arsenic (µg/L)		
As ≤ 10	Referent	Referent
10 < As ≤ 50	0.87 (0.61, 1.25)	1.14 (0.80, 1.64)
50 < As ≤667	1.11 (0.76, 1.62)	1.35 (0.97, 1.88)
Model 3		
Arsenic (µg/L)		
As ≤ 10	Referent	Referent
10 < As ≤ 50	0.89 (0.62, 1.27)	1.19 (0.80, 1.78)
50 < As ≤667	1.14 (0.79, 1.67)	1.40 (0.97, 2.04)
Model 4		
Arsenic (µg/L)		
As ≤ 10	Referent	Referent
10 < As ≤ 50	0.88 (0.62, 1.27)	1.19 (0.80, 1.78)
50 < As ≤667	1.14 (0.79, 1.66)	1.40 (0.96, 2.04)

Model 1. Unadjusted.
Model 2. Adjusted for age, sex, BMI, and region.
Model 3. Further adjusted for smoking status, educational attainment, urban vs rural residence, household wealth, and diabetes medication use.
Model 4. Further adjusted for food security.

Table 4. Associations of arsenic with fasting blood glucose (geometric mean ratios, GMR) assessing for interaction by other groundwater chemicals dichotomized at their median concentration, considered separately. P values are from F test. The Bonferroni-adjusted significance threshold considering these 14 chemicals' hypothesis tests is α=0.0036. Adjusted models controlled for age, sex, BMI, region, smoking status, educational attainment, urban vs rural residence, household wealth, diabetes medication use, and food security.

	Unadjusted GMR	F-test P Value	Adjusted GMR	F-test P Value
Aluminum: Low (≤ 0.04 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	1.01 (0.98, 1.04)		1.00 (0.97, 1.03)	
50 < As ≤667	1.01 (0.98, 1.05)		1.00 (0.97, 1.03)	
Aluminum: High (> 0.04 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	1.03 (0.98, 1.09)	0.5350	1.02 (0.96, 1.08)	0.7645
50 < As ≤667	0.99 (0.93, 1.05)		0.99 (0.93, 1.05)	
Barium: Low (≤ 0.05 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	1.03 (0.99, 1.08)		1.02 (0.98, 1.06)	
50 < As ≤667	1.03 (0.98, 1.08)		0.98 (0.93, 1.03)	
Barium: High (> 0.05 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	0.98 (0.93, 1.03)	0.6870	0.98 (0.94, 1.03)	0.4915
50 < As ≤667	0.99 (0.94, 1.05)		1.03 (0.97, 1.10)	
Calcium: Low (≤ 25.5 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	1.03 (1.00, 1.07)		1.03 (1.00, 1.06)	
50 < As ≤667	1.02 (0.97, 1.06)		0.99 (0.94, 1.04)	
Calcium: High (> 25.5 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	0.95 (0.91, 0.99)	0.0635	0.94 (0.90. 0.98)	0.0194
50 < As ≤667	0.98 (0.93, 1.04)		0.99 (0.93, 1.04)	
Iron: Low (≤ 0.69 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	1.04 (1.00, 1.08)		1.03 (0.98, 1.08)	
50 < As ≤667	1.09 (1.05, 1.14)		1.06 (1.01, 1.11)	
Iron: High (> 0.69 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	0.98 (0.93, 1.03)	0.0018	0.98 (0.93, 1.03)	0.0538
50 < As ≤667	0.92 (0.88, 0.97)		0.94 (0.90, 0.99)	
Potassium: Low (≤ 3.0 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	1.04 (1.00, 1.08)		1.03 (1.00, 1.07)	

50 < As ≤667	1.06 (1.02, 1.11)		1.06 (1.02, 1.11)	
Potassium: High (> 3.0 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	0.98 (0.93, 1.03)	0.1367	0.97 (0.93, 1.02)	0.0180
50 < As ≤667	0.96 (0.91, 1.00)		0.94 (0.89, 0.98)	
Lithium: Low (≤ 0.004 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	1.01 (0.98, 1.05)		1.00 (0.97, 1.04)	
50 < As ≤667	1.00 (0.96, 1.04)		0.99 (0.95, 1.02)	
Lithium: High (> 0.004 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	1.04 (0.99, 1.09)	0.0076	1.04 (0.99, 1.09)	0.0298
50 < As ≤667	1.07 (1.02, 1.12)		1.05 (1.01, 1.10)	
Magnesium: Low (≤ 12.1 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	1.05 (1.02, 1.08)		1.05 (1.02, 1.07)	
50 < As ≤667	1.04 (0.99, 1.10)		1.04 (0.99, 1.09)	
Magnesium: High (> 12.1 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	0.94 (0.90, 0.99)	0.0309	0.93 (0.89, 0.98)	0.0045
50 < As ≤667	0.97 (0.92, 1.03)		0.96 (0.90, 1.01)	
Manganese: Low (≤ 0.26 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	1.02 (0.99, 1.06)		1.01 (0.98, 1.05)	
50 < As ≤667	1.05 (1.01, 1.09)		1.03 (0.99, 1.07)	
Manganese: High (> 0.26 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	0.99 (0.94, 1.03)	0.0552	1.00 (0.95, 1.04)	0.0903
50 < As ≤667	0.94 (0.90, 0.99)		0.95 (0.91, 0.99)	
Sodium: Low (≤ 34.6 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	1.01 (0.97, 1.05)		1.01 (0.97, 1.04)	
50 < As ≤667	0.99 (0.95, 1.04)		0.98 (0.93, 1.03)	
Sodium: High (> 34.6 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	1.04 (0.99, 1.09)	0.0652	1.01 (0.96, 1.06)	0.3598
50 < As ≤667	1.05 (0.99, 1.10)		1.04 (0.98, 1.09)	
Phosphorous: Low (≤ 0.3 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	1.00 (0.96, 1.05)		1.00 (0.96, 1.05)	
50 < As ≤667	0.92 (0.81, 1.04)		0.91 (0.81, 1.03)	
Phosphorous: High (> 0.3 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	1.03 (0.98, 1.08)	0.1037	1.01 (0.97, 1.07)	0.2368

50 < As ≤667	1.12 (0.99, 1.27)		1.11 (0.98, 1.25)	
Silicon: Low (≤ 19.6 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	1.01 (0.98, 1.05)		1.00 (0.97, 1.04)	
50 < As ≤667	1.02 (0.99, 1.06)		1.01 (0.97, 1.04)	
Silicon: High (> 19.6 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	1.02 (0.97, 1.07)	0.7335	1.02 (0.97, 1.07)	0.7962
50 < As ≤667	0.99 (0.94, 1.04)		1.00 (0.95, 1.05)	
Sulfate: Low (≤ 0.8 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	1.01 (0.97, 1.05)		1.00 (0.97, 1.04)	
50 < As ≤667	1.02 (0.99, 1.05)		1.01 (0.99, 1.05)	
Sulfate: High (> 0.8 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	1.00 (0.95, 1.05)	0.5273	1.01 (0.96, 1.06)	0.2199
50 < As ≤667	0.97 (0.91, 1.03)		0.95 (0.90, 1.01)	
Strontium: Low (≤ 0.16 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	1.02 (0.99, 1.06)		1.02 (0.99, 1.05)	
50 < As ≤667	1.02 (0.97, 1.07)		1.01 (0.96, 1.06)	
Strontium: High (> 0.16 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	0.97 (0.92, 1.02)	0.4682	0.95 (0.91, 1.00)	0.1352
50 < As ≤667	0.98 (0.93, 1.04)		0.97 (0.92, 1.03)	
Zinc: Low (≤ 0.014 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	0.99 (0.95, 1.03)		0.98 (0.94, 1.02)	
50 < As ≤667	1.03 (0.99, 1.06)		1.02 (0.99, 1.05)	
Zinc: High (> 0.014 mg/L)				
As ≤ 10	referent		referent	
10 < As ≤ 50	1.06 (1.01, 1.11)	0.0392	1.06 (1.01, 1.11)	0.0241
50 < As ≤667	0.98 (0.93, 1.03)		0.98 (0.93, 1.03)	

*Fully adjusted for age, sex, BMI, region, smoking status, education, urban vs rural residence, wealth, if individuals were taking diabetes medications, and food security.

Acknowledgements

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Supplemental Table 1. Chemicals measured in the 1998/99 BGS-DPHE survey: geometric mean, 25th and 75th percentile, and whether included or excluded in subsequent statistical analyses.

Chemical name	Geometric Mean	75th and 25th percentiles	Inclusion/Exclusion in Analysis	Reason for Exclusion
Aluminum (mg/L)	0.031	0.04 – 0.02	Included	-----
Arsenic (µg/L)	4.137	35 – .04	Included	-----
Boron (mg/L)	0.019	0.1 – 0.005	Excluded	56% values < LOD
Barium (mg/L)	0.046	0.085 – 0.024	Included	-----
Calcium (mg/L)	26.209	60.1 – 12	Included	-----
Cobalt (mg/L)	0.003	0.007 – 0.002	Excluded	97% values < LOD
Chromium (mg/L)	0.003	0.01 – 0.076	Excluded	97% values < LOD
Copper (mg/L)	0.007	0.007 – 0.007	Excluded	95% values < LOD
Iron (mg/L)	0.650	4.25 – 0.122	Included	-----
Potassium (mg/L)	3.222	5.2 – 1.8	Included	-----
Lithium (mg/L)	0.005	0.007 – 0.003	Included	-----
Magnesium (mg/L)	11.878	26.3 – 5.97	Included	-----
Manganese (mg/L)	0.214	0.67 – 0.076	Included	-----
Sodium (mg/L)	40.217	89.6 – 15.9	Included	-----
Phosphorus (mg/L)	0.294	0.9 – 0.1	Included	-----
Silicon (mg/L)	18.824	24 – 15.2	Included	-----
Sulfate (mg/L)	1.158	4 – 0.2	Included	-----
Strontium (mg/L)	0.154	0.296 – 0.0859	Included	-----
Vanadium (mg/L)	0.003	0.0042 – 0 .0014	Excluded	88% values < LOD
Zinc (mg/L)	0.017	0.027 – 0.008	Included	-----

Supplemental Table 2. Geometric mean, 25%ile, 75%ile of groundwater arsenic concentrations in the seven administrative regions of Bangladesh. Units are µg/L. The limit of detection for arsenic was 0.4 µg/L.

Arsenic (µg/L)	Geometric Mean	25%ile	75%ile
Barisal	2.3	≤ 0.4	5
Chittagong	16.7	2.7	148
Dhaka	3.3	≤ 0.4	42.2
Khulna	8.4	≤ 0.4	73
Rajshahi	2.1	≤ 0.4	12.6
Rangpur	1.1	≤ 0.4	3.2
Sylhet	5.8	≤ 0.4	35.8

Supplemental Table 3. Geometric mean ratios of fasting blood glucose across three categories of arsenic exposure, excluding urban and Dhaka region populations.

	Model 1	Model 2	Model 3	Model 4
Arsenic (μg/L)				
As ≤ 10	Referent	Referent	Referent	Referent
10 < As ≤ 50	1.03 (0.99, 1.06)	1.02 (0.98, 1.06)	1.01 (0.98, 1.05)	1.01 (0.98, 1.05)
50 < As ≤667	1.02 (0.98, 1.06)	0.99 (0.96, 1.03)	0.99 (0.96, 1.03)	0.99 (0.96, 1.02)

Model 1. Unadjusted.

Model 2. Adjusted for age, sex, body mass index, and region.

Model 3. Further adjusted for smoking status, educational attainment, urban vs rural residence, household wealth, and diabetes medication use.

Model 4. Further adjusted for food security.

Supplemental Table 4. Geometric mean ratios of fasting blood glucose per 1 μg/L groundwater arsenic.

	Model 1	Model 2	Model 3	Model 4
Arsenic (μg/L)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)

Model 1. Unadjusted.
Model 2. Adjusted for age, sex, body mass index, and region.
Model 3. Further adjusted for smoking status, educational attainment, urban vs rural residence, household wealth, and diabetes medication use.
Model 4. Further adjusted for food security.

Supplemental Table 5. Geometric mean ratios of fasting blood glucose per 1 μg/L increase in arsenic exposure, stratified by diabetes status.

	Model 1	Model 2	Model 3	Model 4
Normal blood sugar or hypoglycemic (< 110 mg/dL and no diabetes medication use)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)
Untreated Impaired Fasting Glucose (glucose ≥ 110 mg/DL and < 126 mg/dL; and no diabetes medication use)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)
Untreated Diabetes (glucose ≥ 126 mg/dL; and no diabetes medication use)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)
Treated Diabetes (diabetes medication use)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)

Model 1. Unadjusted.

Model 2. Adjusted for age, sex, body mass index, and region.

Model 3. Further adjusted for smoking status, educational attainment, urban vs rural residence, household wealth, and diabetes medication use.

Model 4. Further adjusted for food security.

Supplemental Table 6. Odds ratios of having fasting blood glucose in the impaired fasting glucose range (≥ 110 and < 126 mg/dL) or diabetes range (≥126 mg/L), relative to fasting glucose < 110 mg/dL, with increasing categories of arsenic exposure, excluding urban and Dhaka region populations.

	Impaired Fasting Glucose Range (≥ 110 and < 126 mg/dL)	Diabetes Range (≥126 mg/L)
Model 1		
Arsenic (µg/L)		
As ≤ 10	Referent	Referent
10 < As ≤ 50	1.02 (0.66, 1.59)	1.19 (0.73, 1.94)
50 < As ≤667	0.99 (0.63, 1.56)	1.16 (0.77, 1.76)
Model 2		
Arsenic (µg/L)		
As ≤ 10	Referent	Referent
10 < As ≤ 50	1.04 (0.68, 1.58)	1.22 (0.77, 1.93)
50 < As ≤667	0.78 (0.50, 1.21)	0.99 (0.63, 1.58)
Model 3		
Arsenic (µg/L)		
As ≤ 10	Referent	Referent
10 < As ≤ 50	1.02 (0.66, 1.59)	1.28 (0.76, 2.15)
50 < As ≤667	0.77 (0.50, 1.19)	0.93 (0.54, 1.60)
Model 4		
Arsenic (µg/L)		
As ≤ 10	Referent	Referent
10 < As ≤ 50	1.02 (0.66, 1.59)	1.28 (0.76, 2.15)
50 < As ≤667	0.77 (0.50, 1.19)	0.93 (0.54, 1.60)

Model 1. Unadjusted.
Model 2. Adjusted for age, sex, body mass index, and region.
Model 3. Further adjusted for smoking status, educational attainment, urban vs rural residence, household wealth, and diabetes medication use.
Model 4. Further adjusted for food security.

Supplemental Table 7. Associations of arsenic with fasting blood glucose (geometric mean ratios) within strata of other well water chemicals dichotomized at their median concentration, considered separately. P values for any significant arsenic effects within a stratum (low or high concentrations of the other chemical) are from F test.

	Unadjusted Association	F-test P Value	Fully Adjusted Association*	F-test P Value
Aluminum: Low (≤ 0.04 mg/L)				
As ≤ 10 (N=3570)	referent		referent	
10 < As ≤ 50 (N=836)	1.01 (0.98, 1.04)	0.6137	1.00 (0.97, 1.03)	0.8900
50 < As ≤667 (N=989)	1.01 (0.98, 1.05)		0.99 (0.96, 1.02)	
Aluminum: High (> 0.04 mg/L)				
As ≤ 10 (N=718)	referent		referent	
10 < As ≤ 50 (N=163)	1.06 (1.00, 1.12)	0.1174	1.06 (0.99, 1.14)	0.1742
50 < As ≤667 (N=311)	1.03 (0.96, 1.09)		1.05 (0.98, 1.12)	
Barium: Low (≤ 0.05 mg/L)				
As ≤ 10 (N=2473)	referent		referent	
10 < As ≤ 50 (N=325)	1.03 (0.99, 1.08)	0.2009	1.02 (0.98, 1.07)	0.4404
50 < As ≤667 (N=411)	1.03 (0.98, 1.08)		0.98 (0.93, 1.04)	
Barium: High (> 0.05 mg/L)				
As ≤ 10 (N=1815)	referent		referent	
10 < As ≤ 50 (N=674)	1.01 (0.97, 1.04)	0.9107	1.00 (0.97, 1.04)	0.8250
50 < As ≤667 (N=411)	1.01 (0.97, 1.04)		1.01 (0.98, 1.05)	
Calcium: Low (≤ 25.5 mg/L)				
As ≤ 10 (N=2320)	referent		referent	
10 < As ≤ 50 (N=488)	1.03 (1.00, 1.07)	0.1116	1.03 (1.00, 1.06)	0.0979
50 < As ≤667 (N=318)	1.02 (0.97, 1.06)		0.99 (0.94, 1.03)	
Calcium: High (> 25.5 mg/L)				
As ≤ 10 (N=1968)	referent		referent	
10 < As ≤ 50 (N=511)	1.01 (0.97, 1.05)	0.3951	1.01 (0.97, 1.05)	0.407
50 < As ≤667 (N=982)	1.03 (0.99, 1.06)		1.03 (0.99, 1.06)	
Iron: Low (≤ 0.69 mg/L)				
As ≤ 10 (N=2897)	referent		referent	
10 < As ≤ 50 (N=164)	1.04 (1.00, 1.08)	< 0.0001	1.03 (0.98, 1.08)	0.0919
50 < As ≤667 (N=168)	1.09 (1.05, 1.14)		1.06 (1.01, 1.12)	
Iron: High (> 0.69 mg/L)				
As ≤ 10 (N=1391)	referent		referent	
10 < As ≤ 50 (N=835)	1.01 (0.97, 1.04)	0.9291	1.01 (0.97, 1.04)	0.8735
50 < As ≤667 (N=1132)	1.00 (0.96, 1.04)		1.00 (0.96, 1.03)	
Potassium: Low (≤ 3.0 mg/L)				
As ≤ 10 (N=2555)	referent		referent	
10 < As ≤ 50 (N=505)	1.04 (1.00, 1.08)	0.004	1.03 (1.00, 1.07)	0.0123
50 < As ≤667 (N=226)	1.06 (1.02, 1.11)		1.06 (1.01, 1.11)	

Potassium: High (> 3.0 mg/L)				
As ≤ 10 (N=1733)	referent		referent	
10 < As ≤ 50 (N=494)	0.99 (0.95, 1.03)		0.98 (0.94, 1.02)	
50 < As ≤667 (N=1074)	0.99 (0.95, 1.03)	0.8633	0.98 (0.94, 1.01)	0.3609
Lithium: Low (≤ 0.004 mg/L)				
As ≤ 10 (N=2427)	referent		referent	
10 < As ≤ 50 (N=685)	1.01 (0.98, 1.05)	0.7661	1.00 (0.97, 1.03)	0.9520
50 < As ≤667 (N=844)	1.00 (0.96, 1.04)		0.99 (0.96, 1.03)	
Lithium: High (> 0.004 mg/L)				
As ≤ 10 (N=1861)	referent		referent	
10 < As ≤ 50 (N=314)	1.03 (0.99, 1.08)	0.0258	1.02 (0.98, 1.06)	0.3229
50 < As ≤667 (N=456)	1.05 (1.01, 1.10)		1.03 (0.99, 1.07)	
Magnesium: Low (≤ 12.1 mg/L)				
As ≤ 10 (N=2521)	referent		referent	
10 < As ≤ 50 (N=485)	1.05 (0.98, 1.06)	0.0033	1.05 (1.02, 1.08)	0.0032
50 < As ≤667 (N=214)	1.04 (0.99, 1.10)		1.04 (0.99, 1.10)	
Magnesium: High (> 12.1 mg/L)				
As ≤ 10 (N=1767)	referent		referent	
As 10 - 50 (N=514)	0.99 (0.95, 1.04)	0.7047	0.98 (0.94, 1.03)	0.6983
50 < As ≤667 (N=1086)	1.01 (0.98, 1.05)		1.01 (0.97, 1.05)	
Manganese: Low (≤ 0.26 mg/L)				
As ≤ 10 (N=2061)	referent		referent	
10 < As ≤ 50 (N=439)	1.02 (0.99, 1.06)	0.0498	1.01 (0.98, 1.05)	0.3546
50 < As ≤667 (645)	1.05 (1.01, 1.09)		1.03 (0.99, 1.07)	
Manganese: High (> 0.26 mg/L)				
As ≤ 10 (N=2227)	referent		referent	
10 < As ≤ 50 (N=560)	1.02 (0.99, 1.06)	0.6847	1.01 (0.97, 1.05)	0.6109
50 < As ≤667 (N=655)	0.99 (0.95, 1.03)		0.99 (0.95, 1.03)	
Sodium: Low (≤ 34.6 mg/L)				
As ≤ 10 (N=2330)	referent		referent	
10 < As ≤ 50 (N=529)	1.01 (0.97, 1.05)	0.8537	1.01 (0.97, 1.05)	0.6186
50 < As ≤667 (N=645)	0.99 (0.95, 1.04)		0.98 (0.94, 1.03)	
Sodium: High (> 34.6 mg/L)				
As ≤ 10 (N=1958)	referent		referent	
10 < As ≤ 50 (N=470)	1.03 (0.99, 1.07)	0.1678	1.01 (0.98, 1.05)	0.7573
50 < As ≤667 (N=780)	1.03 (0.99, 1.06)		1.00 (0.97, 1.04)	
Phosphorous: Low (≤ 0.3 mg/L)				
As ≤ 10 (N=3050)	referent		referent	
10 < As ≤ 50 (N=293)	1.00 (0.96, 1.05)	0.3678	1.00 (0.96, 1.05)	0.3600
50 < As ≤667 (N=84)	0.92 (0.81, 1.04)		0.92 (0.81, 1.04)	
Phosphorous: High (> 0.3 mg/L)				
As ≤ 10 (N=1238)	referent		referent	
10 < As ≤ 50 (N=706)	1.01 (0.97, 1.05)	0.8840	1.00 (0.97, 1.04)	0.9234

50 < As ≤667 (N=1216)	1.01 (0.97, 1.04)		1.00 (0.96, 1.03)	
Silicon: Low (≤ 19.6 mg/L)				
As ≤ 10 (N=2135)	referent		referent	
10 < As ≤ 50 (N=492)	1.01 (0.98, 1.05)	0.3958	1.00 (0.96, 1.07)	0.9895
50 < As ≤667 (N=794)	1.03 (0.99, 1.06)		1.00 (0.97, 1.04)	
Silicon: High (> 19.6 mg/L)				
As ≤ 10 (N=2153)	referent		referent	
10 < As ≤ 50 (N=507)	1.02 (0.98, 1.07)	0.5969	1.01 (0.97, 1.06)	0.7469
50 < As ≤667 (N=506)	1.01 (0.96, 1.06)		0.99 (0.95, 1.04)	
Sulfate: Low (≤ 0.8 mg/L)				
As ≤ 10 (N=2034)	referent		referent	
10 < As ≤ 50 (N=628)	1.01 (0.97, 1.05)	0.4612	1.00 (0.97, 1.04)	0.8073
50 < As ≤667 (N=896)	1.02 (0.99, 1.05)		1.01 (0.98, 1.04)	
Sulfate: High (> 0.8 mg/L)				
As ≤ 10 (N=2254)	referent		referent	
10 < As ≤ 50 (N=371)	1.02 (0.98, 1.07)	0.5689	1.02 (0.98, 1.06)	0.3292
50 < As ≤667 (N=404)	1.00 (0.94, 1.06)		0.98 (0.93, 1.04)	
Strontium: Low (≤ 0.16 mg/L)				
As ≤ 10 (N=2492)	referent		referent	
10 < As ≤ 50 (N=561)	1.02 (0.99, 1.06)	0.2839	1.02 (0.99, 1.05)	0.3821
50 < As ≤667 (N=219)	1.02 (0.97, 1.07)		1.01 (0.96, 1.06)	
Strontium: High (> 0.16 mg/L)				
As ≤ 10 (N=1796)	referent		referent	
10 < As ≤ 50 (N=438)	1.01 (0.96, 1.06)		1.01 (0.96, 1.06)	
50 < As ≤667 (N=1081)	1.02 (0.99, 1.06)	0.4707	1.02 (0.99, 1.06)	0.5057
Zinc: Low (≤ 0.014 mg/L)				
As ≤ 10 (N=2174)	referent		referent	
10 < As ≤ 50 (N=477)	0.99 (0.95, 1.03)	0.1477	0.97 (0.93, 1.00)	0.1403
50 < As ≤667 (N=745)	1.03 (0.99, 1.07)		1.00 (0.97, 1.04)	
Zinc: High (> 0.014 mg/L)				
As ≤ 10 (N=2114)	referent		referent	
10 < As ≤ 50 (N=477)	1.04 (1.00, 1.08)	0.0979	1.04 (1.00, 1.08)	0.1174
50 < As ≤667 (N=745)	1.00 (0.96, 1.05)		1.00 (0.95, 1.04)	

*Adjusted for age, sex, body mass index, region, smoking status, education, urban vs rural residence, wealth, food security, and diabetes medication use.

Supplemental Figure 1. Diagram demonstrating 2011 BDHS and BGS-DPHE 1998-98 sample selection process. BDHS included a total sample of 83,731 participants from household surveys that were carried out in 600 clusters. Groundwater chemical data were merged from 3,534 tested wells tested in the BGS-DPHE. Our inclusion criteria were: age ≥ 35, fasting blood glucose measure available, and self-report of groundwater as primary drinking source.