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Shadassa Ourshalimian Date

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

By

Shadassa Ourshalimian
Master of Public Health

Environmental Health

_____
Matthew Gribble, Ph.D.
Committee Chair

_____
Paige Tolbert, Ph.D.
Committee Member

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By

Shadassa Ourshalimian

Bachelor of Science
Southern Oregon University
2012

Thesis Committee Chair: Matthew Gribble, Ph.D.

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Abstract

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

By Shadassa Ourshalimian

Goal: To evaluate the association between groundwater arsenic and fasting blood glucose (FBG), in the context of other groundwater chemicals, in Bangladesh.

Methods: Fasting blood glucose, body mass index, sociodemographic variables, and diabetes medication use were measured among adults ≥ 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. Survey-estimation linear regression methods were used to model FBG, among those using groundwater as primary drinking-water source, as a function of groundwater arsenic. We considered possibly context-dependent arsenic effects within strata of the 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, and used 2 df F-tests to evaluate any arsenic-FBG association.

Results: Compared to persons exposed to groundwater arsenic ≤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 ≤50 μg/L, and was 1.01 (0.97, 1.03) for those with >50 μg/L arsenic. In adjusted models, arsenic was nominally associated ($p<0.05$) with fasting blood glucose within strata of other chemicals: high zinc, as well as low calcium, iron, magnesium, and potassium. No chemical-stratified, confounder-adjusted models had Bonferroni-significant arsenic associations, but among persons with low-iron water, arsenic's unadjusted association with fasting blood glucose was Bonferroni-significant ($p<0.0018$).

Conclusions: In our exploratory analysis, no overall association between arsenic and fasting blood glucose was detected. This may be due to exposure misclassification. We did detect associations of arsenic with fasting blood glucose conditional on other groundwater chemicals, but these associations may be false positives from multiple testing. Future research might consider these drinking water chemicals as potential effect modifiers of arsenic's associations with glycemia.

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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 caused nearly 45% of Bangladesh's population to be exposed to arsenic concentrations above the World Health Organizations arsenic standard of 10 micrograms per liter for drinking water [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]. 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, was 5.2 (2.5 – 10.5) adjusting for age, sex and BMI [4]. 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, noted that the prevalence of diabetes mellitus among arsenicosis patients was 2.8 times higher than controls [5]. 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 and 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 [6, 7].

An exposure-stratified sample of 11,319 men and women from Bangladesh participating in the Health Effects of Arsenic Longitudinal Study (HEALS) did not find any cross-sectional associations of urinary arsenic or time-weight arsenic (a function of drinking durations and well arsenic concentrations) quintiles with self-reported prevalent diabetes, prevalent glucosuria, or hemoglobin A1c (HbA1c) levels at the HEALS baseline visit [8]. There was potential for diabetes misclassification through self-report of a physician's prior diagnosis. They used total urinary arsenic concentration as a measure of recent arsenic exposure that integrates across multiple routes of exposure [9]. However, diabetes is a complex metabolic disorder and individuals with diabetes could have altered metabolism and excretion, complicating the interpretation of urine arsenic biomarker measures in the context of diabetes [10-12]. Thus, although some studies have suggested a strong association and the United States National Toxicology Program concluded there is likely a causal relationship between high arsenic exposures and diabetes [13], the evidence from Bangladesh is mixed. There is a continued need for additional investigation into the relationship of arsenic and diabetes given different risk factors that may influence the effect of arsenic exposure and lead to locally heterogeneous effects.

There are several toxicological mechanisms for arsenic that have been highlighted by the National Toxicology Program Workshop Review. Relevant to diabetes pathophysiology, *in vitro* toxicology studies suggest that arsenic can impact a variety of processes related to glucose

uptake and insulin secretion [13]. Arsenite and/or its methylated trivalent metabolites can cause insulin resistance in adipocytes by inhibiting insulin signaling and insulin-activated glucose uptake [13, 14]. This mechanism could be responsible for the development of type-2 diabetes when chronically exposed to inorganic arsenic [14]. Insulin resistance is a trademark of diabetes and the role of adipocytes in arbitrating insulin resistance is an area that is under research [13]. Wauson *et al.* found that arsenite inhibits and reverses differentiation of adipocytes by disrupting the expression of the genes involved in adipogenesis [15]. Additionally, there is growing evidence that supports other pathways by which arsenic can effect pancreatic β-cell function and insulin sensitivity, including oxidative stress, glucose uptake and transport, gluconeogenesis, adipocyte differentiation, and calcium signaling [13]. To summarize the review, these *in vitro* studies have used high concentrations of arsenic (≥ 1 mM) to evaluate stress response in different cell types. At such high doses, interpretations are not always considered to by human relevant but allow for the study of cytotoxicity. The authors note several studies that have used lower arsenic concentrations (< 100 μM) to examine processes of insulin signaling, glucose uptake [14, 16]. Cell line or isolated pancreatic islet studies have suggested mechanisms by which arsenic affects β-cells to hinder insulin expression and/or secretion are concentration dependent [13, 17]. Low concentration of arsenic can induce oxidative stress resulting initiating antioxidant enzymes and reduced reactive oxygen species that may impair of glucose-stimulated insulin secretion [17]. High concentrations result in irreversible damage and ultimately lead to apoptosis or necrosis. Oxidative stress is also connected in various aspects of arsenic toxicity, a recent *in vitro* study suggests that transcription factor (Nrf2) can mediate antioxidant response may influence impairment of glucose-stimulated insulin secretion in β-cells at low arsenic concentrations [17]. The transcription factor Nrf2 is implicated a key defense against cellular insults, and assists in regulating many antioxidant/detoxification enzymes [13]. Antioxidants are often protective for a cell, they may decrease insulin secretion by reducing the accessibility of reactive oxygen species. During glucose metabolism, reactive oxygen species have been identified as intracellular governors of insulin secretion [13].

Although exposure to arsenic is often through drinking water, little is known about the role that other groundwater chemicals may have as possible effect modifiers of the association between high arsenic and diabetes. 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 (≤ 10 μg/L), high (10 < As ≤ 50 μg/L), or very high (As > 50 μg/L) environmental arsenic levels in the context of 14 other groundwater chemicals in Bangladesh.

Methods:

Source Population

The Demographic and Health Surveys (DHS) are nationally-representative household surveys that collect data on a wide range indicators pertaining to population demographics, health status, and nutrition [18]. 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 [18]. To protect household identity, one randomly selected GPS location was taken per cluster.

Clinical and Demographic Data

Data collection for the BDHS began July 2011 and finished in December 2011 [18]. The survey was conducted by 16 interviewing teams, each with one supervisor, one field editor, and female and male interviewers [18]. 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 [18].

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 [18]. 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 [18].

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 [18]. 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 [18]. 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.

Fasting Blood Glucose & Diabetes Status

Women and men who were age 35 or older in selected households were eligible to have their blood glucose tested [18]. 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 [18].

The protocol for measuring fasting blood glucose (FBG) in the BDHS 2011 survey has been previously described [18]. 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 [18]. 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.

Diabetes was defined using glycemic cut-points from the World Health Organization [19]. Fasting blood glucose ≤ 100 mg/dL was considered normal, and this category included 499 individuals with hypoglycemic status as defined by low fasting blood glucose (< 70 mg/dL). Having pre-diabetes was defined as a fasting blood glucose measurement between 100 and 126 mg/dL. Having diabetes was defined as a fasting blood glucose ≥ 126 mg/dL.

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 [20]. 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, 20]. 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 [21]. 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 [20].

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).

Exposure Assignment

DHS participants were assigned arsenic and other groundwater chemical exposures based on data from their cluster's nearest BGS well.

To do the spatial data merge and exposure assignment, we used administrative shapefiles for Bangladesh from DIVA-GIS [22]. We extracted the GPS locations of the BDHS clusters and BGS-DPHE wells, and imported and projected 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.

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 [23] to draw inferences for that subpopulation. **Figure 1** demonstrates, at a glance, the process used for subpopulation selection.

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, body mass index, 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 measure of study sample were skewed but approximated a log-normal distribution (Figure 2, Supplemental).

Survey estimation linear regression methods [23] were used to assess the association of groundwater arsenic with 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 pre-diabetes vs. normal glycemia or hypoglycemia, and diabetes vs. normal glycemia or hypoglycemia) with increasing well water arsenic.

Stratified analyses were used to examine potential effect modification by other water well chemicals, by fitting separate models within the low and high strata of each of the 14 other groundwater chemicals dichotomized at their medians. The chemicals considered as potential effect modifiers included: aluminum, barium, calcium, iron, potassium, lithium, magnesium, manganese, sodium, phosphorous, silicon, sulfate, strontium, and zinc. We used Bonferroni correction to account for the probability of detecting an arsenic effect within a stratum given the large number of strata, 14 well water chemicals classified as low or high ($\alpha = 0.05/28$) [24]. 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.

Missing data were handled using multiple imputation by chained equations [25]. 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).

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

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 [26]. Permission was attained from the copyright section of the British Geological Survey Environmental Science Centre to use the publicly available BGS-DPHE dataset.

Results:

The characteristics of the adult sample age ≥ 35 drinking groundwater in Bangladesh are described in **Table 1**.

There were 6,281 participants living without diabetes: 3,090 men and 3,191 women. Mean age and BMI was 51.8 (51.4, 52.2) years, and 20.5 (20.3, 20.6) kg/m^2. Average years of education for men was 3.9 (3.7, 4.2), among women without diabetes it was 1.9 (1.7, 2.1), and the total average years of education among individuals without diabetes was 2.9 (2.7, 3.1). Mean fasting blood glucose was 91.6 (90.8, 92.5). The proportion of current smokers for men was 17.6% (15.5, 19.6) compared to women 10.6% (8.7, 12.4) who smoked, the total proportion of current smokers was 14.0% (12.4, 15.6). Among persons without diabetes, 1.6% (1.3, 2.0) indicated taking diabetes related medications. The proportion of the sample living in urban environments was 15.5% (13.8, 17.1). Household wealth was broken into quintiles: the proportion of households falling within each of the first to fourth quintiles were ~21%, while the fifth (wealthiest) quintile was 13.1% (11.4, 14.7).

There was a total of 306 participants living with diabetes (fasting blood glucose ≥ 126 mg/dL), 146 men and 160 women. Mean age was 52.9 (51.2, 54.6) years, and BMI was 22.6 (22.1, 23.2) kg/m^2. Average years of education for men was 6.1 (5.1, 7.1) while women had 4.8 (4.1, 5.4) the total years of education was 4.8 (4.1, 5.4). Mean fasting blood glucose was similar between men and women, the total was 165.1 (158.9, 171.4). The proportion of current smokers for men was 10.6% (4.4, 14.9) compared to women 8.5% (3.3, 13.6) who smoked, the total proportion of current smokers was 9.0% (5.5, 12.6). The proportion of men and women who indicated taking related medications was similar, the total proportion was 35.3% (28.6, 42.0). The proportion of men living in urban environments was 27.4% (20.1, 17.1) compared to women 19.0% (13.3, 24.8). Of the household's 11.8% (6.9, 16.6) were in the lowest wealth quintile, while 31.8% (25.8, 37.8) were in the highest quintile.

Chemical information can be found in **Table 2**. Geometric mean concentrations for groundwater chemicals were varied, with the highest values seen for sodium 40.22 mg/L, calcium 26.21 mg/L, silicon 18.82 mg/L, and arsenic 4.14 (μg/L). Additionally, arsenic concentrations varied across the seven regions of Bangladesh (**Table 3**). 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 was seen in the Rangpur region (1.1 μg/L).

Table 4 presents the association of arsenic with fasting blood glucose. Model 1, the crude model, indicates for individuals with an arsenic concentration of 10 to 50 μg/L will have a geometric mean ratio (GMR) fasting blood glucose measure of 1.02 (0.99, 1.05) higher than individuals attached to groundwater supplies with ≤10 μg/L; the GMR among those in the >50 μg/L arsenic concentration category vs. ≤10 μg/L was 1.02 (0.99, 1.05). However, these associations were not statistically significant. The ratio of geometric mean fasting blood glucose for Model 2 was 1.01 (0.98, 1.04) among participants in the 10 to 50 μg/L arsenic exposure category compared to the ≤ 10 μg/L category, GMR fasting blood glucose for arsenic concentrations > 50 μg/L was 1.00 (0.97, 1.03). For Model 3, arsenic category 10 – 50 μg/L vs. ≤ 10 μg/L, the GMR of fasting blood glucose was 1.01 (0.98, 1.04), and the GMR was 1.02 (0.97, 1.03) for arsenic category >50 vs ≤ 10 μg/L. Model 4 indicated similar GMRs for fasting blood glucose with a 1.01 (0.98, 1.04) increase in the 10 – 50 μg/L category, and 1.01 to 1.02 (0.97, 1.03) increase for > 50 μg/L arsenic concentration category. However, none of these associations were statistically significant.

Table 5 gives the odds ratios from multinomial logistic regressions of arsenic concentrations for pre-diabetes and diabetes relative to normal. Crude (Model 1) indicates for participants in the 10 – 50 μg/L vs. ≤ 10 μg/L arsenic category, the odds ratio of having pre-diabetes (vs. normal glycemia or hypoglycemia) was 0.95 (0.70, 1.28). However, for participants in the > 50 μg/L vs. ≤ 10 μg/L arsenic category, the odds ratio of having pre-diabetes (vs. glycemia or hypoglycemia) was 1.15 (0.87, 1.51). The fully adjusted (Model 4), for participants in the > 50 μg/L vs. ≤ 10 μg/L arsenic category, the odds ratio of having pre-diabetes (vs. normal glycemia or hypoglycemia) was 0.92 (0.68, 1.23), and odds ratios for > 50 μg/L vs. ≤10 arsenic category was 1.08 (0.81, 1.45). Crude (Model 1) indicates for participants in the 10 – 50 μg/L vs. ≤ 10 μg/L arsenic category, the odds ratio of having diabetes (vs. normal glycemia or hypoglycemia) was 1.15 (0.70, 1.28), and odds ratio for participants with diabetes in > 50 μg/L vs. ≤10 arsenic category was 1.35 (0.97, 1.89). The fully adjusted (Model 4), for participants in the > 50 μg/L vs. ≤ 10 μg/L arsenic category, the odds ratio of having diabetes (vs. normal glycemia or hypoglycemia) was 1.17 (0.77, 1.79), and odds ratios for > 50 μg/L vs. ≤10 arsenic category was 1.42 (0.96, 2.09).

Table 6 presents the associations of arsenic concentration categories and fasting blood glucose stratified on median cut-points of 14 separate drinking water chemicals. 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 the geometric mean ratio for the > 50 μg/L group vs. ≤ 10 μg/L was 1.06 (1.01, 1.12). Low potassium (≤ 3.0 mg/L) may have potentiated arsenic toxicity, as in that stratum the geometric mean ratio of fasting blood glucose for the > 10 and ≤ 50 μg/L arsenic range vs. ≤10 μg/L arsenic range was 1.03 (1.00, 1.07), and for the > 50 μg/L arsenic vs. ≤ 10 μg/L arsenic was 1.06 (1.01, 1.11). Among persons with low water magnesium (≤ 12.1 mg/L), arsenic concentration in the 10 to 50 μg/L range had a fasting blood glucose geometric mean ratio of 1.05 (1.02, 1.08) compared to the participants with ≤ 10 μg/L water arsenic. There was also an association of arsenic with fasting blood glucose among persons with high water aluminum (> 0.04 mg/L): in the 10 to 50 μg/L arsenic concentration group, the fasting blood glucose geometric mean ratio was 1.06 (0.99, 1.14); and in the > 50 μg/L vs. 10 μg/L arsenic comparison, the fasting blood glucose geometric mean ratio was 1.05 (0.98, 1.09). Among persons with high-zinc water (> 0.014 mg/L), persons in the 10 to 50 μg/L arsenic concentration group, compared to 10 μg/L, had a fasting blood glucose geometric mean ratio of 1.04 (1.00, 1.08), and in the > 50 μg/L vs. ≤10 arsenic comparison, a blood glucose geometric mean ratio of 1.00 (0.95, 1.04). There were no significant association detected in other groups.

Discussion

We did not detect an overall association between arsenic, measured a decade prior at proxy locations, with fasting blood glucose, prevalent pre-diabetes, or prevalent diabetes among adults age ≥ 35 in Bangladesh in 2011. However, there was nominally significant evidence for an association of arsenic with fasting blood glucose within specific strata of several other drinking water chemicals. Among the participants with low groundwater iron, the unadjusted arsenic association with fasting blood glucose was Bonferroni-significant ($p < 0.0018$), but the adjusted association was not significant. These stratum-specific nominally significant associations may be false positives, or they could be reflecting biologically relevant interactions. Additional research may clarify the role of these candidate effect modifiers in future studies.

There is emerging toxicological evidence to support the biological plausibility of an arsenic-iron interaction. Yu *et al.* published a 2015 review paper on several influencing factors on arsenic metabolism and toxicity, which encompassed a review on trace elements including iron. They highlighted a potential beneficial effect that iron has in improving the altered heme biosynthesis pathway and depletion of blood arsenic with monoisoamyl-2, 3-dimercaptosuccinic acid (MiDMSA). However, they did note that both acute (hepatic oxidative damage in rats) and sub-chronic (toxicity in HepG2 mice cell line) exposures of arsenic and iron have negative effects by either increasing bioaccessibility of arsenic or by elevating reactive oxygen species leading to oxidative stress [27]. A study Yu *et al.* published in 2016 has continued the investigation of arsenic metabolism and toxicity and ferric iron. Briefly, the authors used relevant drinking water concentrations of iron (0.1, 0.3, and 3 mg/L) on arsenic (100 and 600 μg/L) to test metabolism and toxicity, and the role of gut microbiota by using *in vitro* Simulator of the Human Intestinal Microbial Ecosystem (SHIME). The SHIME was sequentially exposed to nutritional medium (CK), CK +100 μg/L As, CK +600 μg/L As, CK +600 μg/L As + 0.1 mg/L Fe, CK +600 μg/L As+0.3 mg/L Fe, and CK +600 μg/L As+3 mg/L Fe. The results of the Yu *et al* study demonstrated that low-level iron could change the bioaccessibility, metabolism and

toxicity of arsenic in simulated human gastrointestinal tract, and that gut microbiota were important in the process. Iron decreased arsenic bioaccessibility in the small intestine, disturbed gut microbial community in colon, and thus caused changes in arsenic methylation and toxicity. The 0.1 and 0.3 mg/L iron significantly increased arsenic methylation. However, their findings suggested that 0.3 and 3 mg/L iron decreased arsenic toxicity[28]. Our results support that when conducting research on arsenic in drinking water, it is important to consider the health risk of residual iron that can potentially exacerbate certain mechanisms of arsenic toxicity.

Arsenic toxicity with other water constituents has only recently begun to be studied. Hoque *et al.* investigated the status of groundwater toxicants and nutrients relevant to human health in Asian deltas [29]. They used a compiled dataset of 5,256 tube-wells from published literature for Bengal, Mekong, and Red River deltas. Most wells had available chemical composition and trace elements, including calcium, iron, magnesium, and zinc. Most of these high calcium and magnesium wells are located in the south-west and southern parts of the Bengal delta, and contain between 25-50% of the recommended daily intake for magnesium. North eastern regions of Bangladesh demonstrated much lower magnesium concentration with wells containing < 10% recommended daily intake. The authors noted, there was no clear depth-wise trend for these concentrations. Additionally, they implicated two potential public health concerns linked to magnesium, low birth-weight and diabetes. One, an association between magnesium deficiency during pregnancy and low birth weight [30] and second, that magnesium during pregnancy, as well as in adulthood has been associated with glucose intolerance potentially leading to type 2 diabetes [31]. Epidemiological studies have suggested an inverse association between the ingestion of food high in magnesium and the risk of diabetes [32]. Sales *et al.* concluded that diabetes interferes in the maintenance of the normal body magnesium concentration, and is able spark metabolic control of magnesium thus leading to increased chronic complications associated with diabetes. They suggest that hypomagnesemia might be able to develop diabetes mellitus, particularly when considered with other risk factors [31]. In Bangladesh spatial differences in tube-well magnesium concentrations are also significant. However, the influence of this spatial magnesium variation on the spatial pattern of prevalence of diabetic and pre-diabetic conditions has yet to be established [29].

There is some evidence for toxicological interactions between arsenic and calcium. A 2010 study reported potential protective effects of calcium and magnesium on hematological and biochemical parameters in male rats [33]. Briefly, animals were assigned to one of five treatment groups and received the following exposures for 3 weeks: Group 1: drinking water; Group 2: 50 mgL^{-1} of sodium arsenite dissolved in drinking water; Group 3: 50 mg/L of sodium arsenite + 6.3 μmol/L of sodium selenite by gavage (2 mL/kg) once a day; Group 4: 50 mg/L of sodium arsenite + 20 mmol/L of magnesium sulphate by gavage (2 mL/kg) once a day; and Group 5: 50 mg/L of sodium arsenite + 20 mmol/L of calcium sulphate by gavage (2 mL/kg) once a day. Their results suggested that trace metals (calcium and magnesium) had marginal effects on increased liver and kidney glutathione and may act as a potential antioxidant. Additionally, results suggested that calcium or magnesium prevented aminotransferase and alanine aminotransferase serum increase when co-administered with arsenic. The authors noted though that the mechanism by which calcium interferes with arsenic absorption is not clear [33]. Calcium appears to partly inhibit metal absorption via competition for common binding sites on

intestinal binding proteins [34]. Our calcium results, while not significant when fully adjusted, are suggestive of a high-dose arsenic effect in the low-calcium range.

Aluminum has been studied as an exposure from drinking water as it relates to the development of neurological disorders [35]. Aluminum and diabetes has not been extensively studied, nor has it been routinely considered as a potential effect modifier of arsenic toxicity has not been extensively studied, but has been purposed as a method for arsenic removal via coagulation so it is possible, although this is speculative, that aluminum might have implications for toxicokinetics [36]. In one drinking water quality study, three aluminum based coagulants (aluminum chloride and two types of poly aluminum chlorides) were found to reduce the concentration of arsenic in drinking water [37].

Our study had several limitations. The distributional assumption of fasting blood glucose being lognormal is a strong assumption, and our P values may be sensitive to departures from the empirical distribution from a lognormal distribution. Thus there is potential for both Type I and II errors regarding which other groundwater chemicals are effect modifiers: however, point estimates of associations of arsenic with fasting blood glucose are likely valid. Another important consideration is groundwater arsenic and other chemical concentrations, were obtained from data from the BGS survey conducted in 1998/99. These groundwater chemical concentrations are being used as a proxy for well water chemicals encountered by BDHS participants in 2011. Furthermore, well depth is an important consideration, due to differential temporal measurement error of the chemical exposures by well depth. A study investigating temporal variability of groundwater in Bangladesh found that for shallow wells (< 30 m), arsenic concentrations generally increased with depth starting from the shallowest monitoring well, peaks around 15 meters and then declines again towards the deeper part of shallow aquifers [38]. Comparatively deep (> 30m) aquifers, in terms of arsenic, were found to be reasonably stable. The well 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 (IQR: 22, 56) [2]. Our analyses assume that arsenic concentrations have not changed over the decade between the BGS and BDHS surveys. This is supported for deeper wells but not for shallow wells.

Since the BGS-DPHE survey, millions of pumps have been implemented to improve access to safe drinking water [39]. Therefore, participants who reported groundwater as their primary drinking water in 2011 may actually have had much lower arsenic exposures in 2011 than estimated from the 1998-1999 BGS-DPHE survey data.

In Bangladesh, wells are being built rapidly and sources of drinking water have diversified in the last decade; it follows that the 1998-99 BGS-DPHE well concentrations may be a limited reflection of arsenic exposure in 2011. Additionally, while new wells increase water coverage throughout the country, the supply is largely decentralized. Private wells are often installed without regulation or testing leading to increasing proportions of the country's water sources having unknown arsenic levels [39]. The majority of rural residents get their drinking water from hand pumps, or tube-wells [40], therefore we expect that chemical concentration are potentially higher or lower. This hypothesis is supported by spatial variation of water chemistry in Bangladesh [41, 42]. Nonetheless, we treated all households in a cluster to the same arsenic exposure as the closest BGS-DPHE well.

To better understand the relationship between arsenic and fasting blood glucose in Bangladesh, prospective epidemiological studies with more precise groundwater arsenic measurement and a connected biomarker of arsenic exposure would reduce exposure misclassification and establish temporality of an exposure-outcome relationship. Follow-up toxicology studies of possible interactions between the water chemicals identified as possible effect modifiers in this study, in the context of arsenic and diabetes, would also be interesting.

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 misclassification of true arsenic exposure. However, it is possible that the particular concentrations of some other groundwater chemicals (i.e., aluminum, calcium, magnesium, potassium, iron, and zinc) may have modified arsenic toxicity to be detectible despite arsenic exposure misclassification. Prospective studies with less exposure measurement error should further explore these potential sources of effect modification.

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	Persons without Diabetes as Defined by FBG < 126			Persons with Diabetes		
	Male (n=3,090)	Female (n=3,191)	Total (n=6,281)	Male (n=146)	Female (n=160)	Total (n=306)
Age (in years)	52.3 (51.8, 52.8)	51.3 (50.7, 51.8)	51.8 (51.4, 52.2)	54.8 (52.4, 57.1)	51.3 (48.9, 53.6)	52.9 (51.2, 54.6)
BMI (kg/m2)	20.2 (20.0, 20.3)	20.8 (20.6, 20.9)	20.5 (20.3, 20.6)	21.8 (21.1, 22.5)	23.4 (22.7, 24.2)	22.6 (22.1, 23.2)
Years of education	3.9 (3.7, 4.2)	1.9 (1.7, 2.1)	2.9 (2.7, 3.1)	6.1 (5.1, 7.1)	3.5 (2.8, 4.2)	4.8 (4.1, 5.4)
Fasting blood glucose (mg/dL)	91.8 (90.9, 92.7)	91.5 (90.5, 92.5)	91.6 (90.8, 92.5)	169.3 (158.7, 179.8)	161.4 (154.2, 168.6)	165.1 (158.9, 171.4)
Current Smoker	17.6% (15.5, 19.6)	10.6% (8.7, 12.4)	14.0% (12.4, 15.6)	10.6% (4.4, 14.9)	8.5% (3.3, 13.6)	9.0% (5.5, 12.6)
Taking diabetes medication	1.4% (1.0, 1.9)	1.8% (1.3, 2.4)	1.6% (1.3, 2.0)	33.8% (24.6, 42.9)	36.7% (27.7, 45.7)	35.3% (28.6, 42.0)
Household characteristics						
Urban residence	15.6% (13.8, 17.4)	15.4% (13.7, 17.0)	15.5% (13.8, 17.1)	27.4% (20.1, 34.7)	19.0% (13.3, 24.8)	23.0% (18.4, 27.6)
Household's wealth index (i.e. wealth)*						
Quintile 1	22.2% (19.9, 24.5)	21.1% (18.9, 23.4)	21.7% (19.6, 23.8)	12.2% (5.8, 18.6)	11.3% (5.4, 17.3)	11.8% (6.9, 16.6)
Quintile 2	21.9% (20.2, 23.7)	21.5% (19.6, 23.4)	21.7% (20.0, 23.4)	18.3% (9.9, 26.6)	7.0% (2.1, 12.0)	12.4% (7.4, 17.3)
Quintile 3	21.6% (19.8, 23.4)	22.3% (20.4, 24.2)	21.9% (20.3, 23.6)	16.7% (9.7, 23.8)	22.2% (14.8, 29.5)	19.6% (14.4, 24.8)
Quintile 4	21.4% (19.5, 23.3)	21.7% (19.8, 23.7)	21.6% (19.8, 23.3)	19.4% (12.6, 26.1)	29.1% (21.0, 37.2)	24.5% (18.7, 30.2)
Quintile 5	12.8% (11.1, 14.5)	13.3% (11.5, 15.1)	13.1% (11.4, 14.7)	33.4% (24.8, 42.0)	30.3% (22.6, 38.1)	31.8% (25.8, 37.8)
Regional distribution						
Barisal	6.0% (5.4, 6.6)	6.1% (5.5, 6.8)	6.1% (5.5, 6.6)	7.6% (4.4, 10.8)	8.4% (4.8, 12.1)	8.0% (5.4, 10.7)
Chittagong	15.4%, (14.2, 16.7)	18.1% (16.9, 19.4)	16.8% (15.7, 17.9)	22.5% (15.2, 29.7)	24.8% (16.8, 32.8)	23.7% (18.3, 29.1)
Dhaka	29.6% (27.6, 31.5)	29.3% (27.3, 31.3)	29.4% (27.7, 31.2)	19.1% (10.0, 28.2)	19.0% (11.1, 26.9)	19.0% (13.2, 24.9)
Khulna	13.6% (12.3, 14.8)	13.2% (12.0, 14.4)	13.4% (12.3, 14.5)	14.3 (8.7, 19.9)	10.3% (5.8, 14.8)	12.2% (8.5, 15.9)
Rajshahi	15.6% (14.2, 17.0)	14.9% (13.7, 16.1)	15.2% (14.1, 16.3)	18.0% (10.4, 25.6)	23.0% (16.0, 30.0)	20.6% (15.5, 25.8)
Rangpur	14.3% (13.3, 15.3)	12.5% (11.5, 13.6)	13.4% (12.6, 14.2)	14.1% (7.8, 20.3)	9.0% (4.5, 13.5)	11.4% (7.7, 15.1)
Sylhet	5.5% (4.9, 6.1)	5.8% (5.2, 6.4)	5.7% (5.1, 6.2)	4.5% (2.2, 6.9)	5.5% (2.6, 8.4)	5.0% (2.9, 7.1)

* Household wealth index is a composite measure from DHS that estimates cumulative living standard based off selected assets such as televisions, and bicycles, materials used for housing construction as well as facilities. DHS separates households into five wealth quintiles, 1 being the lowest and 5 being the highest.

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

Table 2: Chemicals measured in the 1998/99 BGS-DPHE survey, geometric mean and interquartile range (IQR), as well as inclusion/exclusion criteria.

Chemical name	Geometric Mean	IQR	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	-----

Table 3. Geometric mean, and interquartile range for arsenic concentrations by administrative regions of Bangladesh.

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

Table 4. Geometric mean ratios of fasting blood glucose across three categories of arsenic exposure.

	Model 1	Model 2	Model 3	Model 4
Arsenic (μg/L)				
≤ 10	Referent	Referent	Referent	Referent
10 - 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	1.02 (0.99, 1.05)	1.00 (0.97, 1.03)	1.02 (0.97, 1.03)	1.01 (0.97, 1.03)

Model 1, crude association for arsenic and fasting blood glucose.
Model 2, included adjustment for age, sex, body mass index, and region.
Model 3, controlled for smoking status, education, urban vs rural residence, wealth, and if individuals were taking diabetes medications.
Model 4, additionally controlled for food security.

Table 5. Multinomial logistic estimates investigating odds ratios of pre-diabetes and diabetes relative to normal glycemia or hypoglycemia across three categories of arsenic exposure.

Parameters	Pre-diabetes (100 < FBG < 126)	Diabetes (FBG ≥ 126)
	Model 1	
Arsenic (μg/L)		
≤ 10	Referent	Referent
10 - 50	0.95 (0.70, 1.28)	1.15 (0.70, 1.28)
> 50	1.15 (0.87, 1.51)	1.35 (0.97, 1.89)
	Model 2	
Arsenic (μg/L)		
≤ 10	Referent	Referent
10 - 50	0.92 (0.68, 1.23)	1.13 (0.76, 1.66)
> 50	1.08 (0.81, 1.45)	1.36 (0.96, 1.92)
	Model 3	
Arsenic (μg/L)		
≤ 10	Referent	Referent
10 - 50	0.92 (0.69, 1.23)	1.18 (0.77, 1.79)
> 50	1.09 (0.81, 1.45)	1.42 (0.96, 2.09)
	Model 4	
Arsenic (μg/L)		
≤ 10	Referent	Referent
10 - 50	0.92 (0.68, 1.23)	1.17 (0.77, 1.79)
> 50	1.08 (0.81, 1.45)	1.42 (0.96, 2.09)

Model 1, crude association for arsenic and fasting blood glucose.
Model 2, included adjustment for age, sex, body mass index, and region.
Model 3, controlled for smoking status, education, urban vs rural residence, wealth, and if individuals were taking diabetes medications.
Model 4, additionally controlled for food security.

Table 6. 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 are from F test. The Bonferroni-adjusted significance threshold is α=0.0018.

	Crude Association	F-test P Value	Fully Adjusted Association*	F-test P Value
Aluminum: Low (≤ 0.04 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.01 (0.98, 1.04)	0.6137	1.00 (0.97, 1.03)	0.8900
As > 50	1.01 (0.98, 1.05)		0.99 (0.96, 1.02)	
Aluminum: High (> 0.04 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.06 (1.00, 1.12)	0.1174	1.06 (0.99, 1.14)	0.1742
As > 50	1.03 (0.96, 1.09)		1.05 (0.98, 1.12)	
Barium: Low (≤ 0.05 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.03 (0.99, 1.08)	0.2009	1.02 (0.98, 1.07)	0.4404
As > 50	1.03 (0.98, 1.08)		0.98 (0.93, 1.04)	
Barium: High (> 0.05 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.01 (0.97, 1.04)	0.9107	1.00 (0.97, 1.04)	0.8250
As > 50	1.01 (0.97, 1.04)		1.01 (0.98, 1.05)	
Calcium: Low (≤ 25.5 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.03 (1.00, 1.07)	0.1116	1.03 (1.00, 1.06)	0.0979
As > 50	1.02 (0.97, 1.06)		0.99 (0.94, 1.03)	
Calcium: High (> 25.5 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.01 (0.97, 1.05)	0.3951	1.01 (0.97, 1.05)	0.407
As > 50	1.03 (0.99, 1.06)		1.03 (0.99, 1.06)	
Iron: Low (≤ 0.69 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.04 (1.00, 1.08)	< 0.0001	1.03 (0.98, 1.08)	0.0919
As > 50	1.09 (1.05, 1.14)		1.06 (1.01, 1.12)	
Iron: High (> 0.69 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.01 (0.97, 1.04)	0.9291	1.01 (0.97, 1.04)	0.8735
As > 50	1.00 (0.96, 1.04)		1.00 (0.96, 1.03)	
Potassium: Low (≤ 3.0 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.04 (1.00, 1.08)	0.004	1.03 (1.00, 1.07)	0.0123
As > 50	1.06 (1.02, 1.11)		1.06 (1.01, 1.11)	
Potassium: High (> 3.0 mg/L)				
As ≤ 10 (referent)	0.00		0.00	

As 10 - 50	0.99 (0.95, 1.03)	0.8633	0.98 (0.94, 1.02)	0.3609
As > 50	0.99 (0.95, 1.03)		0.98 (0.94, 1.01)	
Lithium: Low (≤ 0.004 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.01 (0.98, 1.05)	0.7661	1.00 (0.97, 1.03)	0.9520
As > 50	1.00 (0.96, 1.04)		0.99 (0.96, 1.03)	
Lithium: High (> 0.004 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.03 (0.99, 1.08)	0.0258	1.02 (0.98, 1.06)	0.3229
As > 50	1.05 (1.01, 1.10)		1.03 (0.99, 1.07)	
Magnesium: Low (≤ 12.1 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.05 (0.98, 1.06)	0.0033	1.05 (1.02, 1.08)	0.0032
As > 50	1.04 (0.99, 1.10)		1.04 (0.99, 1.10)	
Magnesium: High (> 12.1 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	0.99 (0.95, 1.04)	0.7047	0.98 (0.94, 1.03)	0.6983
As > 50	1.01 (0.98, 1.05)		1.01 (0.97, 1.05)	
Manganese: Low (≤ 0.26 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.02 (0.99, 1.06)	0.0498	1.01 (0.98, 1.05)	0.3546
As > 50	1.05 (1.01, 1.09)		1.03 (0.99, 1.07)	
Manganese: High (> 0.26 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.02 (0.99, 1.06)	0.6847	1.01 (0.97, 1.05)	0.6109
As > 50	0.99 (0.95, 1.03)		0.99 (0.95, 1.03)	
Sodium: Low (≤ 34.6 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.01 (0.97, 1.05)	0.8537	1.01 (0.97, 1.05)	0.6186
As > 50	0.99 (0.95, 1.04)		0.98 (0.94, 1.03)	
Sodium: High (> 34.6 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.03 (0.99, 1.07)	0.1678	1.01 (0.98, 1.05)	0.7573
As > 50	1.03 (0.99, 1.06)		1.00 (0.97, 1.04)	
Phosphorous: Low (≤ 0.3 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.00 (0.96, 1.05)	0.3678	1.00 (0.96, 1.05)	0.3600
As > 50	0.92 (0.81, 1.04)		0.92 (0.81, 1.04)	
Phosphorous: High (> 0.3 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.01 (0.97, 1.05)	0.8840	1.00 (0.97, 1.04)	0.9234
As > 50	1.01 (0.97, 1.04)		1.00 (0.96, 1.03)	
Silicon: Low (≤ 19.6 mg/L)				
As ≤ 10 (referent)	0.00		0.00	

As 10 - 50	1.01 (0.98, 1.05)	0.3958	1.00 (0.96, 1.07)	0.9895
As > 50	1.03 (0.99, 1.06)		1.00 (0.97, 1.04)	
Silicon: High (> 19.6 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.02 (0.98, 1.07)	0.5969	1.01 (0.97, 1.06)	0.7469
As > 50	1.01 (0.96, 1.06)		0.99 (0.95, 1.04)	
Sulfate: Low (≤ 0.8 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.01 (0.97, 1.05)	0.4612	1.00 (0.97, 1.04)	0.8073
As > 50	1.02 (0.99, 1.05)		1.01 (0.98, 1.04)	
Sulfate: High (> 0.8 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.02 (0.98, 1.07)	0.5689	1.02 (0.98, 1.06)	0.3292
As > 50	1.00 (0.94, 1.06)		0.98 (0.93, 1.04)	
Strontium: Low (≤ 0.16 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.02 (0.99, 1.06)	0.2839	1.02 (0.99, 1.05)	0.3821
As > 50	1.02 (0.97, 1.07)		1.01 (0.96, 1.06)	
Strontium: High (> 0.16 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.01 (0.96, 1.06)	0.4707	1.01 (0.96, 1.06)	0.5057
As > 50	1.02 (0.99, 1.06)		1.02 (0.99, 1.06)	
Zinc: Low (≤ 0.014 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	0.99 (0.95, 1.03)	0.1477	0.97 (0.93, 1.00)	0.1403
As > 50	1.03 (0.99, 1.07)		1.00 (0.97, 1.04)	
Zinc: High (> 0.014 mg/L)				
As ≤ 10 (referent)	0.00		0.00	
As 10 - 50	1.04 (1.00, 1.08)	0.0979	1.04 (1.00, 1.08)	0.1174
As > 50	1.00 (0.96, 1.05)		1.00 (0.95, 1.04)	

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

BDHS 2011 Sample Selection Diagram

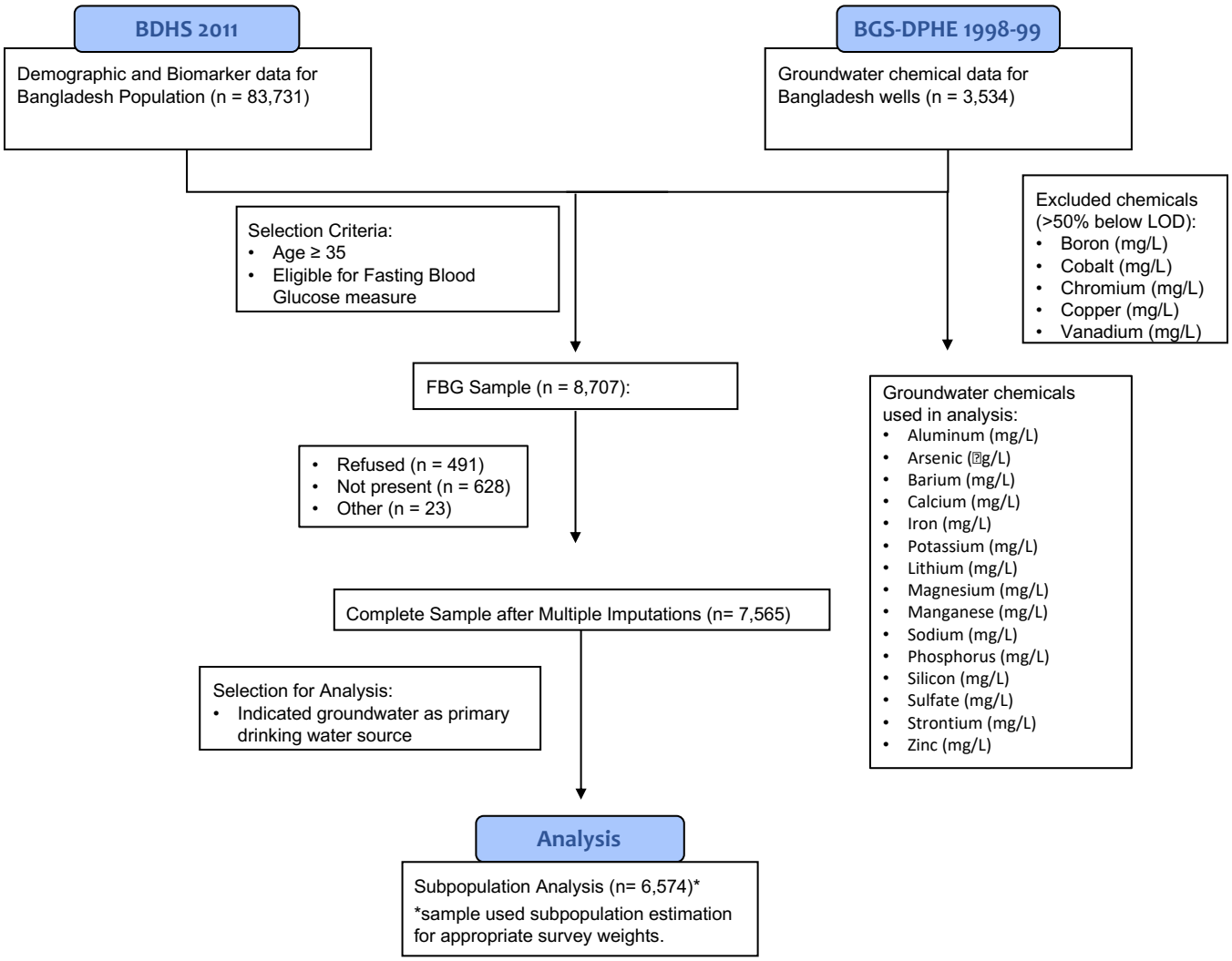

Figure 1. Diagram demonstrating 2011 BDHS and BGS-DPHE 1998-98 sample selection process. BDHS included a total sample of 83,731 participants from household surveys carried out in 600 clusters. Groundwater chemical data was merged from 3,534 tested wells in the BGS-DPHE dataset. To arrive at the subpopulation analysis sample, the selection criteria was age ≥ 35, fasting blood glucose measure present, and Indicated groundwater as primary drinking source. For appropriate survey weights, no participants were dropped from subanalyses.

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Supplemental

Table 7. Imputation variance information. Presented is imputation variance within and between the 40 imputed datasets, Relative Increase in Variance (RVI), Fraction of Missing Information (FMI), and Relative Efficiency (RE). The highest FMI is seen when imputing food security (2.57E-01), which indicates that approximately 25% of the total sample variance is explained by the missing data. None the less, we are well within recommendations with 40 imputations [43].

	Imputation Variance					
	Within	**Between**	**Total**	**RVI**	**FMI**	**RE**
Intercept	3.25E-04	1.00E-05	3.36E-04	3.24E-02	3.15E-02	9.99E-01
Arsenic (μg/L)						
≤ 10	Referent	Referent	Referent	Referent	Referent	Referent
10 - 50	1.92E-04	2.50E-07	1.92E-04	1.31E-03	1.32E-03	1.00E+00
≥ 50	2.14E-04	2.00E-07	2.14E-04	9.41E-04	9.55E-04	1.00E+00
Age	4.90E-08	3.90E-10	4.90E-08	8.20E-03	8.18E-03	1.00E+00
Sex	2.80E-05	9.00E-08	2.90E-05	3.25E-03	3.26E-03	1.00E+00
BMI Centered	8.20E-07	3.90E-08	8.60E-07	4.85E-02	4.65E-02	9.99E-01
BMI^2	3.20E-10	4.90E-11	3.70E-10	1.60E-01	1.39E-01	9.97E-01
Region						
Barisal	Referent	Referent	Referent	Referent	Referent	Referent
Chittagong	4.19E-04	4.70E-07	4.20E-04	1.15E-03	1.17E-03	1.00E+00
Dhaka	3.72E-04	4.40E-07	3.73E-04	1.21E-03	1.23E-03	1.00E+00
Khulna	3.62E-04	4.40E-07	3.63E-04	1.26E-03	1.27E-03	1.00E+00
Rajshahi	4.22E-04	4.30E-07	4.23E-04	1.04E-03	1.05E-03	1.00E+00
Rangpur	5.34E-04	5.50E-07	5.35E-04	1.07E-03	1.08E-03	1.00E+00
Sylhet	4.83E-04	6.40E-07	4.84E-04	1.36E-03	1.38E-03	1.00E+00
Current Smoker	8.00E-05	6.80E-07	8.10E-05	8.68E-03	8.65E-03	1.00E+00
Education Levels						
No education	Referent	Referent	Referent	Referent	Referent	Referent
Primary level	5.70E-05	1.70E-07	5.70E-05	3.07E-03	3.09E-03	1.00E+00
Secondary level	1.14E-04	3.20E-07	1.14E-04	2.85E-03	2.87E-03	1.00E+00
Tertiary level	1.25E-04	6.70E-07	1.25E-04	5.55E-03	5.55E-03	1.00E+00
Urban vs Rural	1.60E-04	1.90E-07	1.60E-04	1.21E-03	1.22E-03	1.00E+00
Wealth status	9.60E-06	2.80E-07	9.80E-06	3.04E-02	2.97E-02	9.99E-01
On diabetes medications	7.87E-04	1.50E-05	8.02E-04	1.91E-02	1.89E-02	1.00E+00
Food Security	4.40E-05	1.50E-05	5.90E-05	3.39E-01	2.57E-01	9.94E-01

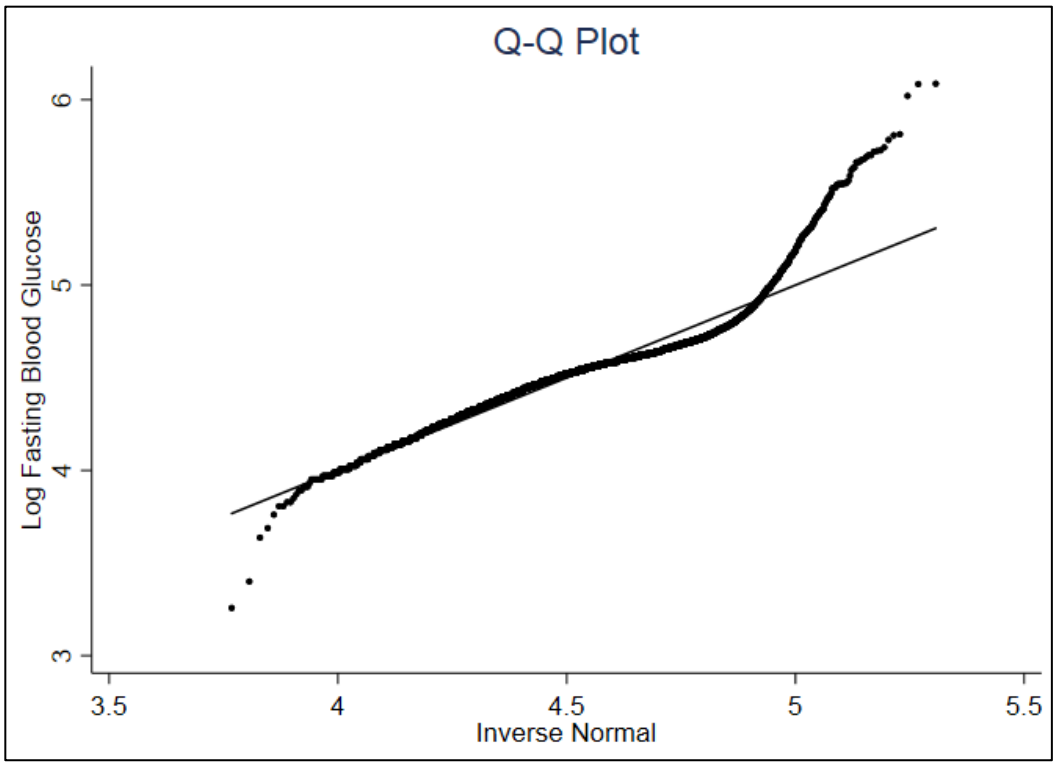

Figure 2. Q-Q plot demonstrating an approximated log-normal distribution for fasting blood glucose.