A case-cohort study examining lifetime exposure to inorganic arsenic in drinking water and diabetes mellitus

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A B S T R A C T

Background: Consumption of drinking water with high levels of inorganic arsenic (over 500 μg/L) has been associated with type II diabetes mellitus (DM), but previous studies have been inconclusive about risks at lower levels (< 100 μg/L). We present a case-cohort study based on individual estimates of lifetime arsenic exposure to examine the relationship between chronic low-level arsenic exposure and risk of DM.

Methods: This case-cohort study included 141 cases of DM diagnosed between 1984 and 1998 as part of the prospective San Luis Valley Diabetes Study. A comparison sub-cohort of 488 participants was randomly sampled from 936 eligible participants who were disease free at baseline. Individual lifetime arsenic exposure estimates were determined using a methodology that incorporates the use of a structured interview to determine lifetime residence and employment history, geospatial modeling of arsenic concentrations in drinking water, and urine arsenic concentrations. A Cox proportional hazards model with known DM risk factors as time-dependent covariates was used to assess the association between lifetime exposure to inorganic arsenic in drinking water and incident DM.

Results: Our findings show a significant association between inorganic arsenic exposure and DM risk (hazard ratio [HR] = 1.27, 95%CI = 1.01, 1.59 per 15 μg/L) while adjusting for ethnicity and time varying covariates age, body mass index and physical activity level.

Conclusions: Exposure to low-level inorganic arsenic in drinking water is associated with increased risk for type II DM in this population based on a comprehensive lifetime exposure assessment.

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1. Background

Human exposure to arsenic can occur from many sources including the occupational setting (smelting and wood preservation), ingestion of contaminated food, and smoking; however, the majority of exposure is through drinking contaminated water (US EPA, 1988). Previous research has documented a relationship between exposure to high concentrations of inorganic arsenic in drinking water and the risk of type 2 diabetes mellitus (DM) (Lai et al., 1994; Tseng et al., 2000; Rahman et al., 2003; Wang et al., 2003; Chen et al., 2007; Navas-Acien et al., 2008; Del Razo et al., 2011; Jovanovic et al., 2012), but the risk at lower levels is unclear (Chen et al., 2010; Huang et al., 2011). Studies from Asia, where water concentrations of inorganic arsenic can be over 500 μg/L, found consumption of inorganic arsenic in drinking water to be associated with increased risk for DM; however in a recent study by Chen et al., 2010, at levels below 300 μg/L there was no association. Research conducted here in the United States (US), where water arsenic concentrations are typically between 1 and 100 μg/L, have found inconclusive associations between inorganic arsenic exposure and risk for DM (Lewis et al., 1999; Meliker et al., 2007; Zierold et al., 2007). A more recent cross-sectional study using the National Health and Nutrition Examination Survey (NHANES), a nationally representative sample, suggested an increased risk for diabetes with higher arsenic concentrations in urine after adjustment for arsenic contribution from seafood (Navas-Acien et al., 2008). However, Steinmaus et al., 2009 replicated the analysis removing arsenobetaine (arsenic contribution from food) from the arsenic metric and...
found no association with diabetes mellitus. These two sets of findings in the same cohort show how the association between diabetes and inorganic arsenic exposure centers on the exposure definition and assessment lending weight to the need for studies involving comprehensive lifetime exposure assessments.

Potential diabetogenic effects of inorganic arsenic exposure have been described (Tseng, 2004; Izquierdo-Vega et al., 2006; Navas-Acién et al., 2006; Díaz-Villalobos et al., 2007a, 2007b; Paul et al., 2007a; Chen et al., 2009; Lu et al., 2011; Escobar-García et al., 2012), but inconsistency in human studies limits conclusions on the causal association. A systematic literature review examined epidemiologic research relating arsenic exposure and DM in several types of populations (high exposure, general population, and occupational setting) and concluded weaknesses in human studies are due to exposure assessment methods, disease diagnostic criteria, population demographics, study design, and insufficient consideration of other DM risk factors (Navas-Acién et al., 2006). Recently, findings from a workshop established to review the toxicology of arsenic relative to diabetes determined that evidence supporting an association between arsenic exposure < 150 μg/L and diabetes is insufficient (Maull et al., 2012). Research such as this study, which is prospective in design, has standard criteria for case definition, and detailed lifetime estimates of individual-level exposure to inorganic arsenic, could help clarify the possibility of an association between arsenic and diabetes at levels < 150 μg/L.

2. Methods

2.1. Study sample

The relationship between inorganic arsenic exposures over time and the risk of incident DM was studied using a case-cohort design within the San Luis Valley Diabetes Study (SLVDS). The SLVDS is a population-based prospective study of risk factors for diabetes mellitus (DM) and other related chronic diseases among Hispanic and non-Hispanic white residents of Alamosa and Conejos Counties in south-central Colorado who were 20 to 74 years of age at their initial study visit. Participant recruitment and data collection methods have been previously described (Hamman et al., 1989). In brief, between 1984 and 1988, participants provided clinical, behavioral, and demographic data, and diagnostic assessments including the diagnosis of DM (Hamman et al., 1990). All participants were invited to attend two follow up visits, once between 1988 and 1992 and once between 1997 and 1998 where behavioral, demographic, and clinical assessments were updated with a retention rate of 86 percent. In addition, participants with impaired glucose tolerance at baseline were invited for two additional visits for an abbreviated set of assessments. All participants were followed between clinic visits through 1998 with telephone interviews and searches of vital statistics records to track vital status and underlying cause of death (Hokanson et al., 2002).

SLVDS participants without a history of DM and who tested normal or with impaired glucose tolerance but not with diabetes at baseline (n=1297) were eligible for this study. Participants with a documented permanent refusal or lost to follow up (n=361) were excluded from selection. The remaining 936 participants were eligible for random selection into the study subcohort (n=488) which was disease free at the time of initial enrollment. Cases of DM (n=141) included all eligible SLVDS participants with a documented DM diagnosis between their baseline visit and 1998. A DM diagnosis was determined either through self-report on yearly follow-up phone calls (with medical record verification) or during a baseline or follow up clinic visit by an 8-h fasting 75 g oral glucose test using the 1985 World Health Organization criteria for DM (WHO required either a fasting venous plasma glucose greater than or equal to 140 mg/dL or a two-hour glucose level greater than or equal to 200 mg/dL) (Hamman et al., 1989). The total study cohort in this case-cohort design, included 548 subjects including 488 randomly selected subjects, of which 81 developed diabetes, and 60 diabetes cases not initially selected, but included as part of the case-cohort design.

This study was reviewed and approved by the Colorado Multiple Institutional Review Board (COMIRB) prior to participant contact or initiating data collection.

2.2. Estimating arsenic exposure

The exposure assessment for this study included a lifetime reconstruction of exposure through a structured interview and geospatial modeling of groundwater inorganic arsenic concentrations which was validated by urinary inorganic arsenic species concentrations.

Study subjects (n=548) or designated next of kin of deceased subjects were contacted during the 2007–2009 data collection period by mail with information on the study followed by a call to set up an appointment for an interview and water sample collection at their residence. Data collected during the interview (n=334 (males: n=115; females: n=219)) included addresses for past residences and workplace/school locations, and history of drinking water consumption at each location. For subjects who were not interviewed (n=203, 37%), their residential histories were re-constructed from public assessor records at the county clerk office; however past schooling and employment locations are missing for those subjects. There were 11 (3%) subjects who refused participation in this current study.

Residential water samples (both private well and public water) were collected at time of interview (n=334) and analyzed by the chemistry laboratory of the Colorado Department of Public Health and Environment using standard Ion Chromatography (IC) and Inductively Coupled Plasma Mass Spectrometry (ICP–MS) with a detection limit of 1 μg/L. Geographical coordinates were determined with a global positioning system (GPS) unit for all water samples collected at houses supplied by private wells.

In other work we detail our methods and findings specific to the temporal and spatial characterization of groundwater inorganic arsenic concentrations in the SLV (James, 2010). In brief, findings indicate that naturally occurring inorganic arsenic concentrations in 175 groundwater wells monitored from 1982 to 2005 (n=3759 samples) by the Bureau of Reclamation are stable over long periods of time (samples collected 1 to 5 years apart: r=0.87; 5 to 10 years apart: r=0.89; 10 to 15 years apart: r=0.89; 15 to 25 years apart: r=0.88) which justifies the use of re-constructed inorganic arsenic water concentrations in spatial models to predict historical exposures through drinking water. In brief, there are two aquifers in the SLV (confined and unconfined). Wells drawing water from the unconfined aquifer are used primarily for irrigation whereas wells drawing from the confined aquifer are mostly for domestic use or pasture irrigation (Emery, 1979). Inorganic arsenic concentrations in the San Luis Valley ranged from non-detectable to 752 μg/L with a mean concentration of 39 μg/L in domestic wells drawing from the confined aquifer.

We collected characteristics on each of the 595 wells in our dataset including, land use, soil type, well depth, use of an irrigation system, land cover, aquifer depth, and distance to the outer edge of the aquifer, the outer edge boundary of the aquifer, and determination analysis identified well depth as the only factor significantly associated with arsenic concentration within the well. The spatial variability of inorganic arsenic concentrations in ground water was characterized by testing five separate geostatistical models including Kriging with external drift and indicator kriging which both account for well weighted. A geostatistical analysis were determined validation sample of observed and predicted values (ρ=0.715; 95%CI=0.67, 0.75 (James, 2010)) ordinary kriging was found to be the most accurate model for predicting inorganic arsenic in groundwater at residential locations for each participant.

The exposure matrix characterized each participant’s annual exposure to arsenic in drinking water. Each participant had one record per year of life starting at birth through year of diagnosis or 1998, whichever came first. Each year’s data included residential, employment, and school location and for each location the number of cups of water and arsenic concentration (either observed, if available, or predicted). A time-weighted average (TWA) was calculated by dividing the cumulative arsenic exposure by the number of years in the subject’s lifetime to get an annuitized exposure per year (James, 2010).

We validated the method for estimating past arsenic exposure by regressing spatially arsenic concentration on 642 historical monitored groundwater wells (collected 1984–1991) on residential arsenic concentrations, residential dose, and total dose estimated at time of urine collection, adjusting for gender and creatinine (James et al., in press) (James, 2010). In brief, the sum of the toxic urine arsenic species (AsIII, AsV, dimethylarsinic acid, monomethylarsinic acid) (geometric mean: 16.9 μg/dL; range: non-detectable to 123.0 μg/dL) was most strongly correlated with estimates of residential arsenic concentration (ρ=0.55 as opposed to other estimates (residential dose: ρ=0.37 and total dose: ρ=0.39) for residential drinking water arsenic was used for the TWA arsenic exposure measure.

2.3. Statistical analyses

A Cox proportional hazards model incorporating a robust variance estimator specific for case-cohort study designs (Barlow et al., 1999) was utilized to examine the association between the TWA residential inorganic arsenic exposure and development of DM. The arsenic exposure estimate was scaled to the inter-quartile range (IQR) (15 μg/L). Other continuous covariates were also scaled to the IQR (Lin and Huang, 1995). Longitudinal data from two to five study visits including information on known risk factors for DM were included for each subject. Variables hypothesized as DM risk factors independent of the mechanistic pathways proposed for arsenic were included in the proportional hazards multivariate model as time-dependent covariates. These variables included: ethnicity (white non-Hispanic, Hispanic), gender (male-female), and socioeconomic status (high > $20,000: low < $20,000), first degree family history (noyes), body mass index (BMI: interquartile rage scaled, median=26.7, IQR=23.8, 29.3), smoker status (noyes), alcohol consumption

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(low < = 168 g/week; high > = 168 g/week), and physical activity level (active:sedentary). Lastly, gender and BMI have been suggested as potential modifiers (Paul et al., 2007; Davey et al., 2008) and therefore were included in the model as an interaction term and also modeled the data stratified separately by gender and BMI.

An analysis was also completed to assess the linearity of the hazard ratio for DM across categories of arsenic exposure (TWA concentration 1 to 4 μg/L, 4 to 8 μg/L, 8 to 20 μg/L, and greater than 20 μg/L). Lastly, we ran Cox proportional hazards models stratified separately by gender and BMI (≤ 25 kg/m² and > = 25 kg/m²) to evaluate the stability of the findings across groups. Statistical Analysis System 9.2 (PROC PHREG, SAS, version 9.2, SAS Institute, Inc., Cary, North Carolina) was used for the statistical analyses. The sample size of the subcohort (n=488) was determined in PASS® software based on preliminary data collected to estimate effect size (approximately 1.4) with alpha=0.05 and power of 80 percent.

3. Results

This study included a cohort of 548 participants in which there were 141 cases and 6956 person years of follow-up. The study cohort (n=488) was similar to the original cohort (n=936) in demographic, behavioral, and clinical characteristics. On average, cases were similar to non-cases in age and distribution of gender, income group, smokers, and intake of alcohol (Table 1). Cases had a higher percentage of Hispanics and participants with a family history of DM than non-cases. At baseline, participants who later became cases were slightly less active than non-cases and had a higher BMI.

Across exposure groups, Hispanics (p=0.001) and participants in the lower income group (p<0.0001) had higher percentages in lower arsenic exposure groups whereas non-Hispanic whites and the higher income group had higher percentages in the higher exposure groups. Other risk factors for DM were not statistically different across arsenic exposure groups (Table 2).

The association between inorganic arsenic exposure and DM was examined with a modified Cox proportional hazards model (Table 3). The univariate model estimated the unadjusted hazard ratio which shows that for every 15 μg/L increase in the time weighted residential inorganic arsenic water concentration, the risk for DM increases 22 percent (HR=1.22; 95%CI=1.03, 1.55). After adjusting for known risk factors for DM (Final Model, Table 3) there was an increased risk for DM in people exposed to inorganic arsenic (HR=1.27; 95%CI=1.02, 1.64 per 15 μg/L). When inorganic arsenic exposure was categorized, the hazard ratios across exposure groups increased with increasing level of exposure however the trend was borderline statistically significant (p=0.07).

In the stratified analysis, the association was stronger in females than males (Females: HR=1.25, 95%CI: 1.03, 4.96; Males: HR=1.16, 95%CI: 0.88, 1.7) and in those overweight (normal weight: HR=1.05, 95%CI: 0.78, 1.78; overweight: HR=1.30, 95%CI:1.10, 1.68), however the interaction between BMI and gender was not significant in the final model (p=0.1410).

4. Discussion

In this case-cohort study we found a modest association between DM risk and lifetime exposure to low levels of inorganic arsenic in drinking water (<100 μg/L). Specifically, we found that for every 15 μg/L increase in arsenic concentration in the drinking water, risk for DM increased by 27 percent (95% CI 1% to 59%) after adjusting for ethnicity, and time varying measures of BMI and physical activity.

The cohort used for this study allowed for a strong study design because of the ongoing longitudinal health studies in the San Luis Valley of Colorado, the low rate of out-migration, and the well-characterized spatial variability and temporal stability in water arsenic concentrations. Arsenic contamination in this region is natural, from weathering and erosion of rock formations in the mountains (IDEQ, 2002), with spatial variation being caused by long-term patterns of rainfall and physio-chemical conditions (Abernathy et al., 2003; Hinwood et al., 2003). The temporal stability of inorganic arsenic in the SLV and accuracy of the spatial prediction model supports the use of more recently collected inorganic arsenic water concentrations in spatial models to predict historical exposures. The major strength of this study is the prospective design, a first in the United States or any other low to moderate arsenic exposure area. Also, in comparison to prior studies, the use of residential histories to reconstruct drinking water arsenic exposure estimates over a lifetime is a strength.

Our study employs a thorough residential history and a comprehensive spatial prediction model of inorganic arsenic concentrations in ground water to characterize a life course

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Descriptive information on risk factors for subject cohort.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total subcohort</td>
</tr>
<tr>
<td></td>
<td>N=488</td>
</tr>
<tr>
<td>Age (baseline) (median, IQR)</td>
<td>56 (46.0, 63.0)</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>Female</td>
</tr>
<tr>
<td>Income</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>High</td>
</tr>
<tr>
<td>First degree family History</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>BMI (median, IQR)</td>
<td>26.4 (23.5, 29.9)</td>
</tr>
<tr>
<td>Smoke</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Average</td>
</tr>
<tr>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Water consumption</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Sedentary</td>
</tr>
<tr>
<td></td>
<td>active</td>
</tr>
</tbody>
</table>
time-weighted arsenic exposure at the individual level. The components of the inorganic arsenic exposure estimation were selected based on a correlation analysis with arsenic concentrations in repeated urine samples historically collected from a subset of this same cohort. This arsenic study is one of the first to examine such a detailed and multifaceted exposure estimate as related to risk for DM.

The modest size of the association between inorganic arsenic exposure and DM can be due to several factors. First, it is unknown what concentration of arsenic exposure is needed to induce diabetogenic effects. The cohort in this study had a relatively small number of subjects (n=235) with time-weighted arsenic exposure concentration above 10 µg/L, which may not be elevated enough to see adverse effects associated with DM. This is evident in our results that show an increase in risk with exposure even below 10 µg/L. Second, DM is a complex disease with multiple causal pathways and arsenic is probably not involved in all of these pathways, thereby, reducing the strength of the association seen with arsenic.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Distribution of risk factors for DM by arsenic exposure group (time weighted average).</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Arsenic exposure groups</td>
</tr>
<tr>
<td></td>
<td>≤ 4 µg/L-yr</td>
</tr>
<tr>
<td>Age (baseline)</td>
<td>120 (56%)</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
</tr>
<tr>
<td></td>
<td>33 (33%)</td>
</tr>
<tr>
<td>Income</td>
<td>80 (67%)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>54 (44%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
</tr>
<tr>
<td>First degree family History</td>
<td>No 117 (95%)</td>
</tr>
<tr>
<td>BMI (median, IQR)</td>
<td>27.4 (24.3,30.6)</td>
</tr>
<tr>
<td>Smoke</td>
<td>Yes 56 (47%)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Average 119 (99%)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>sedentary 80 (67%)</td>
</tr>
</tbody>
</table>

Table 3
Cox proportional modeling for the association between inorganic arsenic exposure (standardized by the interquartile range (15 µL) and DM.

<table>
<thead>
<tr>
<th>Continuous exposure variable</th>
<th>Univariate model HR(95%CI)</th>
<th>Full model HR(95%CI)</th>
<th>Final model HR(95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic exposure TWA (per 15 µg/L)*</td>
<td>1.22 (1.03,1.55; p-value=0.03)</td>
<td>1.20 (1.00,1.52; p-value=0.049)</td>
<td>1.27 (1.02,1.64; p-value=0.04)</td>
</tr>
<tr>
<td>Female</td>
<td>0.95 (0.66,1.43; p-value=0.34)</td>
<td>1.19 (0.82,1.72; p-value=0.04)</td>
<td>1.53 (1.17,2.02; p-value=0.000)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.59 (1.07,2.31; p-value=0.004)</td>
<td>1.71 (1.27,2.26; p-value=0.000)</td>
<td>1.83 (1.34,2.52; p-value=0.000)</td>
</tr>
<tr>
<td>BMI (per 5.5 kg/m²)</td>
<td>1.17 (0.80,1.38; p-value=0.29)</td>
<td>1.71 (1.27,2.02; p-value=0.000)</td>
<td>1.81 (1.34,2.52; p-value=0.000)</td>
</tr>
<tr>
<td>Primary family member Diagnosed with DM</td>
<td>1.18 (0.79,1.82; p-value=0.067)</td>
<td>1.60 (1.01,2.52; p-value=0.03)</td>
<td>1.56 (1.01,2.52; p-value=0.03)</td>
</tr>
<tr>
<td>Sedentary</td>
<td>1.60 (1.01,2.52; p-value=0.03)</td>
<td>1.60 (1.01,2.52; p-value=0.03)</td>
<td>1.56 (1.01,2.52; p-value=0.03)</td>
</tr>
<tr>
<td>Current/ex smoker</td>
<td>0.77 (0.48,1.24; p-value=0.74)</td>
<td>0.77 (0.48,1.24; p-value=0.74)</td>
<td>0.77 (0.48,1.24; p-value=0.74)</td>
</tr>
<tr>
<td>High alcohol intake</td>
<td>1.00 (0.43,2.60; p-value=0.83)</td>
<td>1.00 (0.43,2.60; p-value=0.83)</td>
<td>1.00 (0.43,2.60; p-value=0.83)</td>
</tr>
</tbody>
</table>

Univariate Model: proportional hazards model with TWA arsenic exposure (main risk factor) as independent variable.
Full Model: proportional hazards model with TWA arsenic exposure (main risk factor) and all listed variables as time dependent independent variables.
Adjusted Model: proportional hazards model with TWA arsenic exposure (main risk factor) and statistically significant covariates (independent variables).
Interaction between gender and BMI was assessed and was not significant (p=0.1410).

* Inter-quartile range of subcohort at baseline.
* Person years of follow up = 1301.
* Person years of follow up = 1599.
* Person years of follow up = 1419.
* Person years of follow up = 1533.
One plausible mechanism for inorganic arsenic diabetotoxicity is modification of the expression of genes involved in both insulin resistance in peripheral muscle and adipose tissue cells leading to insulin sensitivity and gluconeogenesis in the liver leading to abnormal sugar production (Tseng, 2004; Paul et al., 2007b; Lu et al., 2011). Inorganic arsenic exposure can lead to reactive oxygen species production inducing oxidative damage to pancreatic cells decreasing the synthesis and secretion of insulin (Tseng, 2004; Izquierdo-Vega et al., 2006; Diaz-Villasenor et al., 2007a, 2007b; Chen et al., 2009; Lu et al., 2011).

In the final model, the interaction between gender and BMI was not statistically significant \((p=0.1410)\) indicating that even though our stratified analysis implies that the risk for diabetes due to exposure to inorganic arsenic in drinking water is higher in women and those that are overweight \((\text{BMI} \geq 25 \text{ mg/dL})\) the potential effect modification is not statistically significant in our cohort.

Our findings support research of arsenic association with DM from Taiwan and Bangladesh where arsenic concentrations can be up to 100 times greater (Lai et al., 1994; Tseng et al., 2000; Rahman et al., 2003; Wang et al., 2003; Chen et al., 2007) and also recent research in areas with low to moderate exposure (Navas-Acien et al., 2008; Del Razo et al., 2011; Jovanovic et al., 2012). Research from high arsenic areas report relative risk estimates for DM between 1.5 and 10.1 for exposure levels between 100 and 2000 \(\mu g/L\) while controlling for known risk factors (Navas-Acien et al., 2006). Our study found consistent results at lower levels with a hazards ratio of 1.55 for exposure levels greater than 20 \(\mu g/L\). These findings suggest that the dose–response relationship between arsenic and DM may exist at levels of arsenic found in many areas of the U.S.

Although the other studies in Taiwan and Bangladesh have the advantage of populations with high concentrations of arsenic exposure resulting in greater effect size and more favorable statistical power, most were unable to estimate individual level arsenic exposure as completely as in this study. Most have employed an ecologic design, with exposures estimated by assigning the same arsenic concentration to large groups of subjects based only on a single residence location without sufficient resolution (zip code or county). This type of estimation can lead to considerable exposure misclassification and hence an error in risk estimates, more critical in studies of low-level exposure such as this one.

Prevalence studies which assess arsenic at the population-level have produced mixed results. Chen et al. (2010) found no association between an increased prevalence of diabetes and inorganic arsenic in drinking water in Bangladesh; however in the United States, Meliker et al. (2007) found an increased risk for mortality due to diabetes mellitus with inorganic arsenic exposure in drinking water (Male standardized mortality ratio (SMR): 1.28; CI, 1.18–1.37; Female SMR: 1.27; CI, 1.19–1.35). These studies employed a cross-sectional design and defined chronic exposure based on water consumption data and arsenic concentrations at the time of the study.

One limitation to our study was that the case definition for diabetes was based on the WHO standards during the time the SLVDS study was conducted (1984 to 1998) and not based on the current standard of oral fasting glucose \(\geq 126 \text{ mg/dL}\). We used the older case definition (oral fasting glucose \(\geq 140 \text{ mg/dL}\)) because diabetes cases diagnosed during SLVDS were adjudicated by study investigators and clinicians using a strict protocol, a process that could not be duplicated by employing the current definition on the cohort. However, to confirm that the case definition did not affect the association, we replicated the analysis using fasting oral glucose levels collected at every clinic visit. This change in case definition removed 15 subjects with glucose levels \(\geq 126 \text{ mg/dL}\) at the baseline visit and identified 3 cases three years earlier than by the old standard (\(> 140 \text{ mg/dL}\)) and reduced the person-years of follow-up to 6957 years. In a univariate Cox proportional regression model the association remained significant \((\text{HR} = 1.26; 95\% \text{CI}: 1.02, 1.51)\). Therefore, we do not believe that use of the older case definition affected the association observed in this population.

We standardized arsenic to the inter-quartile range for easier interpretation and translation into water quality standards however, there is potential that the association identified could be influenced by outliers of arsenic exposure. Therefore, we re-ran the analysis using log-transformed arsenic exposure to investigate sensitivity of the results. The analysis yielded a slightly decreased but still significant association in a univariate Cox proportional hazard model \((\text{HR} = 1.17; 95\% \text{CI}: 1.01, 1.35)\) suggesting that any potential outliers might mildly influence the strength of the association.

Our study employs a complex assessment of inorganic arsenic through drinking water; however, the assessment does not include exposure that may result from food, inhalation of dust or soil, or tobacco products. Based on numerous studies that have shown that arsenic in drinking water is by far the major determinant of overall inorganic arsenic exposure (ATSDR, 2000; Roychowdhury et al., 2002; Tao and Bolger, 1999) any potential misclassification bias would be expected to be minimal and non-differential with respect to case status.

Our study employs a thorough residential history and a comprehensive spatial prediction model of inorganic arsenic concentrations in ground water to characterize a lifetime time-weighted arsenic exposure at the individual level. Supporting our findings, a recent study by Del Razo et al. (2011), found that estimated lifetime inorganic arsenic exposure at the individual level was associated with an increased risk for incident diabetes \((\text{OR} = 1.13; 95\% \text{CI}: 1.05, 1.22)\) for every 10 \(\mu g/L\) increase in inorganic arsenic in drinking water in Mexico, a finding similar to this study.

5. Conclusion

Our study presents an association between chronic low-level inorganic arsenic exposure and DM while adjusting for known risk factors over time: age, BMI, ethnicity, and physical activity. Given the complexity of DM, future research relating arsenic exposure to intermediate endpoints is recommended. Investigating the association between inorganic arsenic and outcomes such as impaired glucose tolerance or insulin resistance can shed light on the mechanistic pathway for disease. Lastly, the clinically relevant exposure period for inorganic arsenic is unknown and its characterization would provide a time relevant to the natural history of the disease in epidemiology studies. Arsenic in drinking water is still a common exposure in the United States and further research on these topics is crucial to elucidate the pathobiology linking arsenic exposure to the risk of type 2 diabetes.

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Disclosure

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References


