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Socioeconomic status and the association between arsenic exposure and type 2 diabetes

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ABSTRACT

Objective: Evaluate whether arsenic-related diabetes risks differ between people of low and high socioeconomic status (SES).

Methods: We used data collected between October 2007-December 2010 from a population-based cancer case-control study (N = 1301) in Northern Chile, an area with high arsenic water concentrations (> 800 μg/L) and comprehensive records of past exposure. Information on lifetime exposure and potential confounders were obtained using structured interviews, questionnaires, and residential histories. Type 2 diabetes was defined as physician-diagnosed diabetes or oral hypoglycemic medication use. SES was measured using a 14-point scale based on ownership of household appliances, cars, internet access, or use of domestic help. Logistic regression was used to assess the relationship between arsenic and diabetes within strata of SES.

Results: Among those with low SES, the odds ratio (OR) for diabetes comparing individuals in the highest to lowest tertile of lifetime average arsenic exposure was 2.12 (95% confidence interval (CI) 1.29–3.49, p = 0.004). However, those in the high SES group were not at increased risk (OR = 1.12 [95% CI = 0.72–1.73]).

Conclusions: Our findings provide evidence that risks of arsenic-related diabetes may be higher in Chile in people with low versus high SES.

1. Introduction

The global prevalence of type 2 diabetes (T2D) has increased from 108 million in 1980 to 422 million in 2014, and continues to increase (World Health Organization, 2018). This metabolic disorder is characterized by insulin resistance, and compromises most diabetes cases worldwide (Olokoba et al., 2012). Known risk factors include increasing age, obesity, and lack of physical activity (Olokoba et al., 2012). In addition to these well-known factors, there is increasing interest in identifying environmental agents and chemical exposures that may also influence diabetes risk (Ruiz et al., 2018).

Millions of people are exposed to arsenic through contaminated drinking water, food and soil (Chung et al., 2014). Although the World Health Organization recommends drinking water arsenic levels be below 10 μg/L, over 100 million people worldwide may be consuming drinking water with arsenic concentrations greater than 50 μg/L (Van Halem et al., 2009). Arsenic has been long recognized as a human carcinogen and has been linked to cardiovascular and lung disease, skin lesions, and reproductive and developmental defects (Hall et al., 2017; Kwok et al., 2006; Tyler and Allan, 2014). Furthermore, studies have linked high exposures of arsenic to increased prevalence of diabetes (Chen et al., 2007; Steinmaus et al., 2009). Although the exact mechanism is unknown, arsenic exposure can cause increased oxidative stress and upregulation of inflammatory markers, factors associated with insulin resistance and decreased glucose metabolism (Tseng, 2004).

T2D is generally more prevalent among those with low socioeconomic status (SES) (Agardh et al., 2011). SES may contribute to diabetes risk largely via obesity, smoking, and sedentary lifestyle (Bertoglia et al., 2017). However, the causes responsible for the SES-diabetes association are incompletely understood. Additionally, SES has been identified as an important contributor to a range of health

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outcomes, including those linked to environmental exposures (Hajat et al., 2013). For example, individuals with a high family income and individuals with a college degree or greater have a mean $PM_{2.5}$ concentration lower than their lower SES counterparts (Hajat et al., 2013). Similarly, an increased risk of arsenic-related skin lesions was observed among lower SES individuals in Bangladesh (Argos et al., 2007). Since SES has been shown to influence risks of environmentally-related disease, we used data from an epidemiologic study in Northern Chile to evaluate whether low SES individuals might be susceptible to developing arsenic-related diabetes. To the best of our knowledge, no studies have examined the combined role of SES and arsenic on diabetes risk.

Northern Chile provides a unique scenario for examining the chronic health effects of arsenic. This area is the driest inhabited place on earth. Essentially everyone in the area lives in one of the cities or towns and gets their drinking water from municipal sources. Arsenic concentrations have been measured in these municipal water sources dating back many decades, with levels ranging from < 5 to > 800 μg/L (Ferreccio et al., 2000). Thus, comprehensive estimates of lifetime arsenic exposure can be made by knowing which cities people lived in throughout their lives. Previously, using study data from Northern Chile we identified an association between increasing arsenic exposure and an increased prevalence of diabetes (odds ratio [OR] = 1.50, 95% confidence interval [CI] = 1.03–2.19 for cumulative exposure ≥8665 μg/L-years) (Castriota et al., 2018). In this paper, we build upon this work to examine the association between arsenic exposure and T2D within strata of SES under the *a priori* hypothesis that low SES individuals might be at increased risk of diabetes.

2. Methods

2.1. Study population

A detailed description of this study population is provided elsewhere (Ferreccio et al., 2013; Steinmaus et al., 2013). Briefly, study subjects were participants in a population-based arsenic-cancer case-control study in Regions I and II in Northern Chile. A rapid case ascertainment system involving all pathologists, radiologists, and hospitals in these Regions was used to identify all incident cases of lung, bladder, and kidney cancer between October 2007 and December 2010. Individuals with cancer were eligible for inclusion if they were ≥ 25 years of age, lived in these Regions at the time of cancer diagnosis, and were available for interview or had a close family member available. Individuals without cancer were selected randomly from those matched participants with cancer on sex and 5-year age groups, and were selected from the Chilean Electoral Registry, which includes > 90% of adults ages ≥40 in these Regions. Institutional Review Board approval was obtained in the U.S. and Chile.

2.2. Exposure and outcome assessment

Standardized questionnaires were used to interview all study participants in-person (non-proxies). Next-of-kin (proxies) were interviewed for deceased participants. Participants were asked about all medications taken within the last year and if they had ever been diagnosed with T2D. Individuals were considered to have diabetes if they reported being told they had diabetes or reported oral hypoglycemic medication usage. Individuals who reported taking insulin since childhood were excluded.

Participants were also asked to provide all residences they lived at for at least six months. Each city or town subjects lived in was linked to an arsenic water concentration measurement for that city or town and for the time period the participant lived there so that an arsenic concentration could be assigned to each year of each subject's life. Records of historical arsenic water concentrations were ascertained from municipal water companies, government agencies, research studies and other sources and were available for all major water sources in Regions I and II. Arsenic water concentrations were available for > 95% of all participants' residences. Residences for which water records were unavailable were in areas not known to have high arsenic levels so were assigned a value of zero. Bottled and water filtered with reverse osmosis were also assigned a value of zero, although were rarely used until recently. The annual water concentrations assigned to each year of each subject's life were used to calculate arsenic exposure metrics. The highest single year exposure was estimated using the highest arsenic concentration recorded for any year of the subject's life. Cumulative exposure in μg/L-years was calculated by summing the annual arsenic concentrations for each year of the subject's life. The mean of the annual arsenic concentrations estimated for each year of the subject's life was used to estimate lifetime average exposure. Each exposure metric was classified into tertiles for analysis.

2.3. Socioeconomic status

SES scores were based on self-reported ownership or use of 12 items and information on SES was obtained at the same time as self-reported diabetes. These included ownership of household appliances (television, kitchen, microwave, refrigerator, washing machine), electronics (computer, DVD player, cellular telephone), automobile, internet access at home, or use of domestic help. A 14-point SES scale was developed for this study by assigning one point for each item except for car ownership, internet access, and domestic help, which were assigned two points. Higher scores on the SES scale indicate higher SES. This scale was created based on the advice of researchers in Chile and was adapted from the National Health Surveys in Chile (Ministerio de Salud, 2003). This scale has not been validated in other populations. However, other global health studies have used similar indices of tangible household items as indicators of SES (Bofah and Hannula, 2017; Bangdiwala et al., 2004; Belo et al., 2006). Subjects were also asked their highest education or grade achieved.

2.4. Covariate information

Diet information was collected using the Diet History Questionnaire (DHQ) at the same time as self-reported diabetes and asked about the participants typical diet in the year before they were interviewed (or the year before they became ill if they have cancer). Diet*Calc software was used to convert food intakes into estimated nutrient levels (National Cancer Institute Division of Cancer Control and Population Sciences, 2018). Validation surveys have shown that the DHQ provides a good estimate of nutrient intakes (Subar et al., 2001). To help evaluate whether nutrition might be responsible for any impacts we identified for SES, associations between nutrient intakes and SES were assessed using *t*-tests and logistic regression.

Subjects with physician-diagnosed hypertension or who reported using anti-hypertensive medication were considered to have hypertension. Subjects without cancer were asked to provide their current height and weight. Subjects with cancer were asked to provide their typical weight over the ten years preceding their cancer diagnosis. Information about smoking included number of years smoked and average number of cigarettes smoked per day.

2.5. Statistical analysis

Unconditional logistic regression was used to calculate crude and adjusted ORs and 95% CIs for the associations between various arsenic exposure metrics and T2D. Linear trend tests were conducted using the Cochrane-Armitage test. Covariates initially included in logistic regression models were sex (male, female), age (< 55, 55–65, 66–75, > 75 years), race (European, Indigenous, other), obesity (body mass index < 30 kg/m^2, ≥30 kg/m^2), hypertension (yes, no), cancer (yes, no), typical fruit and vegetable servings (0–2/day, > 2/day), smoking status (ever, never), and average number of cigarettes per day

(never smoker, > 0–20, > 20). Variables were selected as potential confounders based on the current knowledge of diabetes and arsenic effects and then entered into logistic regression models to determine which covariates changed the arsenic-diabetes OR by > 10%. Thus, age, obesity, and smoking were entered into final models *a priori* since they are known risk factors for diabetes and were either associated with arsenic exposure or modified the effect of arsenic. Sex was not included in the final models because it had little impact on arsenic-diabetes ORs and was not associated with arsenic exposure in our study.

We examined the relationship between arsenic exposure and diabetes stratified by SES. Here, we dichotomized SES at the median into low (< 9) and high (≥9) SES for analysis, where 9 was the exact median in this population. Other cut points, such as dichotomizing at 7 or 8, were also assessed.

We then examined the arsenic-diabetes and SES relationships within strata of sex and cancer status. Minimal differences in OR estimates were observed, so we combined both sexes and those with and without cancer into our main analyses to increase study power. Additionally, we examined whether effect sizes might differ between those with low and high SES (i.e. effect modification) using the methods presented by Altman and Bland (Altman and Bland, 2003). Based on previous research linking low SES to increased diabetes we had a clear one directional hypothesis that effect sizes would be greater, not less, in low SES participants. As such, we present a one-sided p-value for our test of effect modification.

We performed numerous analyses to identify specific risk factors and potential confounders that might account of any impacts of SES we identified. Diet was assessed by examining arsenic-diabetes relationships stratified by SES and by high and low macro- or micronutrient levels. Nutrient levels were dichotomized into high and low based on medians. Adjusted means and standard deviations were calculated using the SAS procedure PROC GLM. The focus of these analyses was on folate, selenium, and protein since these have previously been linked to arsenic-related disease (Chen et al. 2007; Gamble et al., 2006). We adjusted nutrient levels for total caloric intake by dividing them by total energy intake in kilocalories (Willett and Stampfer, 1986). Potential confounding by obesity was also assessed in stratified analyses. All analyses were conducted in SAS 9.4 (Cary, NC).

3. Results

Individuals with diabetes were more likely to be older, obese, hypertensive and consume > 2 servings of fruit or vegetables per day compared to those without diabetes (Table 1).

Compared to those in the lowest exposure tertiles, those in the highest tertile of lifetime average (> 155.2 μg/L) and cumulative (> 10,118.2 μg/L-years) arsenic exposure had increased odds of diabetes (adjusted OR = 1.50 [95% CI = 1.08–2.09] and OR = 1.52 [95% = CI 1.09–2.11], respectively) (Table 2). Arsenic water concentrations for those in the highest category of cumulative exposure (> 10,118.2) ranged from 250 to 860 μg/L with 85% exposed at 860 μg/L for at least one year in their lives. In analyses confined to low SES individuals, those in the highest tertile of arsenic exposure had increased odds of diabetes across all exposure metrics. The strongest relationship was observed for cumulative arsenic exposure, where those in the highest tertile had 2.18 greater odds of diabetes versus those in the lowest tertile (95% CI = 1.31–3.62, p-trend = 0.01). For high SES participants, arsenic-diabetes ORs were near 1.0. For example, among high SES individuals the diabetes OR comparing those in the highest versus lowest tertile of cumulative arsenic exposure was 1.12 (95% CI = 0.72–1.73) (Table 2). Additionally, we examined whether effect sizes might differ between those with low and high SES (i.e. effect modification). The one-sided p-value for interaction comparing the odds ratios in the highest tertile of cumulative arsenic exposure in the low (OR = 2.18 (95% CI, 1.31–3.62)) and high SES (OR = 1.12 (95% CI, 0.72–1.73)) groups was 0.03. Categorizing SES at cut-points other than the median gave similar results (data not shown).

Table 1
Demographics of study population among those with and without diabetes.

	With diabetes N (%)	Without diabetes N (%)	Odds ratio (95% CI)
Sex			
Female	172 (57.0)	554 (55.5)	1.00 (Ref)
Male	130 (43.0)	445 (44.5)	0.94 (0.73–1.22)
Age (years)			
< 55	38 (12.6)	207 (20.7)	1.00 (Ref)
55–65	76 (25.2)	301 (30.1)	1.38 (0.90–2.11)
66–75	105 (34.8)	285 (28.5)	2.01 (1.33–3.03)
> 75	83 (27.5)	206 (20.6)	2.19 (1.43–3.37)
Race			
European descent	229 (75.8)	743 (74.4)	1.00 (Ref)
Indigenous[a]	19 (6.29)	78 (7.8)	0.79 (0.47–1.33)
Other	54 (17.9)	178 (17.8)	0.98 (0.70–1.38)
Obese[b,c]			
No	223 (74.3)	829 (84.2)	1.00 (Ref)
Yes	77 (25.7)	156 (15.8)	1.83 (1.35–2.50)
Hypertension[c]			
No	89 (30.2)	563 (58.1)	1.00 (Ref)
Yes	206 (69.8)	406 (41.9)	3.21 (2.43–4.24)
Cancer			
No cancer	145 (48.0)	495 (49.5)	1.00 (Ref)
Lung	68 (22.5)	238 (23.8)	0.98 (0.70–1.35)
Bladder	66 (21.9)	167 (16.7)	1.35 (0.96–1.90)
Kidney	23 (7.6)	99 (9.9)	0.79 (0.49–1.30)
Socioeconomic status[d]			
> 50th percentile	163 (54.0)	533 (53.4)	1.00 (Ref)
< 50th percentile	139 (46.0)	466 (46.6)	0.89 (0.68–1.17)
Fruit/vegetable servings[c]			
0–2/day	75 (32.1)	324 (43.1)	1.00 (Ref)
> 2/day	159 (67.9)	428 (56.9)	1.60 (1.18–2.19)
Smoking status			
Never	103 (34.1)	307 (30.7)	1.00 (Ref)
Ever	199 (65.9)	692 (69.3)	0.86 (0.65–1.13)
Average cigarettes/day[c]			
Never	103 (34.2)	307 (30.9)	1.00 (Ref)
> 0–20	171 (56.8)	607 (61.1)	0.84 (0.63–1.11)
> 20	27 (9.0)	80 (8.0)	1.01 (0.62–1.64)
Proxy[e]			
No	242 (80.1)	794 (79.5)	1.00 (Ref)
Yes	60 (19.9)	205 (20.5)	0.96 (0.70–1.33)

Abbreviations: OR, odds ratio; CI, confidence interval; Ref, reference.
Note: percentages may not sum to 100 due to rounding.
[a] Indigious includes Aymara and Atacameño ethnicity.
[b] Obese defined as body mass index ≥30 kg/m^2.
[c] Data on BMI (obesity), hypertension, diet, and average number of cigarettes per day not available in all subjects.
[d] Odds ratio adjusted for obesity, age, and smoking status. The unadjusted odds ratio is 0.98 (95% CI = 0.75–1.26).
[e] Proxy defined as next-of-kin interviewed for deceased patients.

Arsenic-diabetes ORs were also higher among low SES compared to high SES individuals in analyses excluding cancer cases, although findings were less precise (Table 3). For example, among low SES individuals, those in the highest tertile of cumulative exposure had greater odds of diabetes versus those in the lowest tertile (adjusted OR = 2.69 [95% CI = 1.33–5.45]). P-values were below 0.05 for linear tests for trend. No associations were observed between arsenic and diabetes among those with high SES in analyses excluding cancer cases.

Several analyses were performed to evaluate whether certain factors might account for the stronger arsenic-diabetes associations we identified in lower SES individuals. For obesity and hypertension, the prevalence of these conditions were similar among low and high SES individuals (Table S1). Low SES individuals were more likely to be male, older, of indigenous descent, have lung cancer, be never smokers, and have proxy respondents, compared to high SES individuals (Table S1).

In order to evaluate whether these particular factors may have

Table 2
Associations between selected arsenic exposure metrics and diabetes within strata of socioeconomic status.

All Subjects					
Exposure	Exposure level	With diabetes	Without diabetes	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
Highest single year exposure (μg/L)	< 60	48	183	1.00 (Ref)	1.00 (Ref)
	60–859	134	475	1.08 (0.74–1.56)	1.15 (0.79–1.70)
	> 859	120	341	1.34 (0.92–1.96)	1.53 (1.03–2.27)
	p trend			0.07	0.02
Lifetime average (μg/L)	< 42.9	92	338	1.00 (Ref)	1.00 (Ref)
	42.9–155.2	94	348	0.99 (0.72–1.37)	1.04 (0.74–1.44)
	> 155.2	116	313	1.36 (0.99–1.86)	1.50 (1.08–2.09)
	p trend			0.03	0.01
Cumulative exposure ([μg/L]-years)	< 2780	90	339	1.00 (Ref)	1.00 (Ref)
	2780–10,118.2	92	352	0.98 (0.71–1.36)	1.03 (0.73–1.43)
	> 10,118.2	120	308	1.47 (1.07–2.01)	1.52 (1.09–2.11)
	p trend			0.01	0.01
	Low socioeconomic status				
		With Diabetes	Without Diabetes	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
Highest single year exposure (μg/L)	< 60	20	96	1.00 (Ref)	1.00 (Ref)
	60–859	67	224	1.44 (0.83–2.50)	1.58 (0.88–2.82)
	> 859	52	146	1.71 (0.96–3.04)	2.08 (1.13–3.83)
	p trend			0.13	0.04
Lifetime average (μg/L)	< 42.9	38	174	1.00 (Ref)	1.00 (Ref)
	42.9–155.2	48	157	1.40 (0.87–2.26)	1.48 (0.90–2.43)
	> 155.2	53	135	1.80 (1.12–2.89)	2.12 (1.29–3.49)
	p trend			0.02	0.004
Cumulative exposure ([μg/L]-years)	< 2780	35	170	1.00 (Ref)	1.00 (Ref)
	2780–10,118.2	51	161	1.54 (0.95–2.49)	1.68 (1.02–2.78)
	> 10,118.2	53	135	1.91 (1.18–3.09)	2.18 (1.31–3.62)
	p trend			0.01	0.01
	High socioeconomic status				
		With Diabetes	Without Diabetes	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
Highest single year exposure (μg/L)	< 60	28	87	1.00 (Ref)	1.00 (Ref)
	60–859	67	251	0.83 (0.50–1.37)	0.88 (0.52–1.48)
	> 859	68	195	1.08 (0.65–1.80)	1.16 (0.69–1.97)
	p trend			0.28	0.22
Lifetime average (μg/L)	< 42.9	54	164	1.00 (Ref)	1.00 (Ref)
	42.9–155.2	46	191	0.73 (0.47–1.14)	0.78 (0.49–1.22)
	> 155.2	63	178	1.07 (0.71–1.64)	1.12 (0.72–1.73)
	p trend			0.46	0.40
Cumulative exposure ([μg/L]-years)	< 2780	55	169	1.00 (Ref)	1.00 (Ref)
	2780–10,118.2	41	191	0.66 (0.42–1.04)	0.67 (0.42–1.07)
	> 10,118.2	67	173	1.19 (0.79–1.80)	1.12 (0.72–1.73)
	p trend			0.16	0.30

Abbreviations: OR, odds ratio; CI, confidence interval; Ref, reference.
[a] Models adjusted for obesity, age, and smoking status.

played some role in the associations we identified above, we calculated arsenic-diabetes ORs by strata of low and high SES in analyses further stratified by these other factors (Table 4). Here, participants in the highest tertile of cumulative exposure were compared to those in the lowest tertile. In analyses confined by sex, those above and below the median age of 66, smokers, non-indigenous subjects, and non-proxy subjects, the odds of arsenic-related diabetes was higher among individuals with low SES than in those with high SES (Table 4). For example, among females, the arsenic-diabetes OR was 2.38 (95% CI = 1.14–4.97) in the low SES group compared to 0.93 (95% CI = 0.54–1.62) in the high SES group. Among never smokers, arsenic-diabetes ORs were above 1.0 in both those with low and high SES, although somewhat higher in the high SES group (ORs of 1.83 (95% CI = 0.79–4.23) vs. 2.49 (95% CI = 1.04–5.98)), respectively.

We also examined the potential role of folate, selenium, protein, and other dietary variables. We found that estimates of absolute (not energy adjusted) intakes of folate, selenium, protein, and total energy (i.e., total caloric) intake were lower among those in the low compared to high SES group (Table S2). However, when we adjusted for total energy intake, clear differences were not observed between low and high SES individuals. Further, when participants with unadjusted selenium, folate, and protein levels below the median were excluded, low SES individuals continued to have higher odds of arsenic-related diabetes compared to high SES individuals (Table 4), although with markedly smaller sample sizes and wider confidence intervals compared our analyses including all subjects. Additionally, adjusting for folate, selenium, and protein had little impact on our results. Similar results were seen for other dietary variables including total fat, beta-carotene, vitamin E, methionine, total energy, and typical vegetable, fruit, dairy, or meat intake (data not shown).

Lastly, we examined the arsenic-related diabetes ORs within subcategories of education (< 9th grade, grades 9–12, and > 12th grade) and found no evidence of effect modification by education (Table S3). In stratified analyses low SES individuals continued to have increased odds of arsenic-related diabetes across all education categories (data not shown).

4. Discussion

This is one of few studies examining the combined role of SES and environmental exposure on diabetes risk. We found that odds ratios for arsenic-related diabetes were elevated in people with low SES but not in people with higher SES. P-values for linear tests for trend in low SES individuals provided evidence that our findings in this group are unlikely due to chance (p = 0.04, 0.004 and 0.01, depending on the arsenic exposure metric used). In addition, these findings persisted after

Table 3
Associations between selected arsenic exposure metrics and diabetes within strata of socioeconomic status excluding cancer cases.

		Low socioeconomic status				High socioeconomic status			
Exposure	Exposure Level	With diabetes	Without diabetes	Crude OR (95% CI)	Adjusted[a] OR (95% CI)	With diabetes	Without diabetes	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
Highest single year exposure (μg/L)	< 60	11	50	1.00 (Ref)	1.00 (Ref)	16	61	1.00 (Ref)	1.00 (Ref)
	60–859	37	123	1.37 (0.65–2.89)	1.35 (0.61–2.97)	40	137	1.11(0.58–2.14)	1.35 (0.68–2.71)
	> 859	23	54	1.94 (0.86–4.37)	2.01 (0.86–4.70)	18	70	0.98 (0.46–2.09)	1.06 (0.48–2.35)
	p trend			0.12	0.10			0.80	0.73
Lifetime average (μg/L)	< 42.9	23	101	1.00 (Ref)	1.00 (Ref)	34	108	1.00 (Ref)	1.00 (Ref)
	42.9–155.2	24	80	1.32 (0.69–2.51)	1.32 (0.67–2.59)	22	99	0.71 (0.39–1.29)	0.78 (0.42–1.45)
	> 155.2	24	46	2.29 (1.17–4.48)	2.51 (1.24–5.08)	18	61	0.94 (0.49–1.80)	0.89 (0.45–1.78)
	p trend			0.01	0.01			0.88	0.77
Cumulative exposure ([μg/L]-years)	< 2780	21	98	1.00 (Ref)	1.00 (Ref)	33	109	1.00 (Ref)	1.00 (Ref)
	2780–10,118.2	23	80	1.34 (0.69–2.60)	1.37 (0.68–2.74)	23	99	0.77 (0.42–1.40)	0.79 (0.42–1.46)
	> 10,118.2	27	49	2.57 (1.32–5.00)	2.69 (1.33–5.45)	18	60	0.99 (0.51–1.91)	0.83 (0.41–1.69)
	p trend			0.004	0.01			0.98	0.64

Abbreviations: OR, odds ratio; CI, confidence interval; Ref, reference.
[a] Models adjusted for obesity, age, and smoking status.

adjusting for potential confounders, after removing individuals with cancer (i.e. after accounting for the original cancer case-control design), and in numerous other sensitivity analyses. Overall, our findings raise the possibility that low SES individuals are more vulnerable to at least some of the harmful effects of arsenic.

The exposure levels in our study were high, with many subjects exposed to arsenic water concentrations > 800 μg/L. This is > 80-times higher than the current US regulatory standard of 10 μg/L. As we previously reported (Castriota et al., 2018), our finding that arsenic may be a risk factor for T2D in Northern Chile is supported by prior findings in other communities with high arsenic exposures. In an arsenic endemic area in Taiwan, the adjusted relative risk (RR) for diabetes for cumulative arsenic exposures ≥ 17,000 μg/L-years was 2.1 (95% CI = 1.1–4.2) (Tseng et al., 2000). In Bangladesh, patients with arsenic-caused skin lesions (average arsenic water concentrations of 218.1 μg/L) had a prevalence of diabetes that was 2.8-times that of controls subjects without these lesions (Nabi et al., 2005).

A unique aspect of our study is that we assessed arsenic-related diabetes risk by SES. Although diabetes prevalence was not clearly linked to SES in our study, a number of other studies have found that diabetes was more common among those with low SES compared to high SES (RRs between 1.28 and 1.41) (Agardh et al., 2011). Although the exact biologic pathway remains unknown, research has suggested that the link between SES and diabetes could be due to smoking, obesity, or sedentary lifestyle (Bertoglia et al., 2017). Currently however, the mechanism through which SES may influence diabetes risk is unclear or inconsistent across studies. We conducted sensitivity analyses in an attempt to better understand what might be driving the associations identified. Previously, we observed evidence that arsenic-related diabetes risks were especially high in obese people (Castriota et al., 2018). However, obesity is an unlikely explanation for our SES results since obesity was less prevalent in our low SES group (Table S1). More recent data from the Chilean National Health Surveys has shown that a greater percentage of low compared to high SES individuals were obese and this data suggests that the obesity epidemic is relatively new (Ministerio de Salud, 2010). Previous studies have also identified evidence of synergy between smoking and arsenic on cancer risk (Chen et al., 2004). However, just like obesity, smoking was also less prevalent among our low SES participants (Table S1). Interestingly, although arsenic-diabetes ORs were higher in low SES vs. high SES participants in our analyses confined to smokers, this was not the case in non-smokers (Table 4). The reason for this is unknown, although the wide confidence intervals in these analyses suggest these findings could be due to chance. We also explored whether our inclusion of cancer cases may have impacted our results. Lung cancer, but not kidney or bladder cancer was higher among our low SES participants (Table S1). Importantly though, the fairly strong impact SES remained after cancer cases were excluded, providing very strong evidence that their inclusion did not cause important bias.

We also explored whether dietary differences may explain the link we identified between low SES and arsenic-related diabetes. Arsenic metabolism varies from person to person and more effective arsenic metabolism has been linked to reduced risks of arsenic-related diseases (Smith and Steinmaus, 2009). Numerous studies have shown that decreased intake of folic acid and selenium may lead to less effective arsenic metabolism (Chen et al., 2007; Gamble et al., 2006), and potentially to increased risk of arsenic-related disease. Although we found that low SES individuals in our study did have decreased estimated absolute intakes of folate, selenium, and protein than high SES individuals, no differences were seen when these variables were adjusted for total caloric intake. Furthermore, we repeated our analyses after removing participants with lower folate, selenium, and protein levels. Although these analyses have small numbers and confidence intervals were wide, our finding that arsenic-diabetes ORs remained markedly higher in low vs. high SES participants when these subjects were removed suggests that these nutrients were not responsible for the

Table 4
Subgroup analyses for the associations between highest versus lowest tertile of cumulative arsenic exposure and diabetes within strata of socioeconomic status.

		Low socioeconomic status			High socioeconomic status		
Exposure	Exposure level	With diabetes	Without diabetes	Adjusted OR[a] (95% CI)	With diabetes	Without diabetes	Adjusted OR[a] (95% CI)
All subjects							
	< 2780	35	170	1.00 (Ref)	55	169	1.00 (Ref)
	> 10,118.2	53	135	2.18 (1.31–3.62)	67	173	1.12 (0.72–1.73)
Smokers							
	< 2780	20	95	1.00 (Ref)	42	119	1.00 (Ref)
	> 10,118.2	37	94	2.37 (1.24–4.54)	43	130	0.83 (0.50–1.40)
Never smokers							
	< 2780	15	75	1.00 (Ref)	13	50	1.00 (Ref)
	> 10,118.2	16	41	1.83 (0.79–4.23)	24	43	2.49 (1.04–5.98)
Male							
	< 2780	18	78	1.00 (Ref)	18	71	1.00 (Ref)
	> 10,118.2	27	65	2.05 (1.00–4.17)	25	71	1.49 (0.72–3.11)
Female							
	< 2780	17	92	1.00 (Ref)	37	98	1.00 (Ref)
	> 10,118.2	26	70	2.38 (1.14–4.97)	42	102	0.93 (0.54–1.62)
Age < 66 years							
	< 2780	12	76	1.00 (Ref)	27	117	1.00 (Ref)
	> 10,118.2	15	47	2.16 (0.91–5.14)	22	84	1.31 (0.68–2.53)
Age ≥ 66 years							
	< 2780	23	94	1.00 (Ref)	28	52	1.00 (Ref)
	> 10,118.2	38	88	2.18 (1.15–4.10)	45	89	0.96 (0.53–1.63)
Non-indigenous[b]							
	< 2780	27	132	1.00 (Ref)	52	151	1.00 (Ref)
	> 10,118.2	52	130	2.13 (1.24–3.68)	66	172	1.04 (0.66–1.63)
No proxy[c]							
	< 2780	27	139	1.00 (Ref)	47	148	1.00 (Ref)
	> 10,118.2	42	93	2.64 (1.47–4.73)	56	139	1.15 (0.71–1.85)
High folate							
	< 2780	7	58	1.00 (Ref)	18	74	1.00 (Ref)
	> 10,118.2	13	29	3.83 (1.29–11.38)	25	56	1.84 (0.87–3.87)
High selenium							
	< 2780	8	58	1.00 (Ref)	16	78	1.00 (Ref)
	> 10,118.2	11	29	2.51 (0.88–7.20)	21	63	1.55 (0.71–3.39)
High protein							
	< 2780	9	56	1.00 (Ref)	19	78	1.00 (Ref)
	> 10,118.2	13	26	3.09 (1.11–8.63)	20	56	1.33 (0.63–2.84)

Abbreviations: OR, odds ratio; CI, confidence interval; Ref, reference.
[a] Models adjusted for age, obesity, and smoking status with the exception of the smokers and non-smokers subgroups, which are not adjusted for smoking status.
[b] Indigious includes Aymara and Atacameño ethnicity.
[c] Proxy defined as next-of-kin interviewed for deceased patients.

impacts of SES identified. Similar results were seen with all other dietary variables explored. Errors in the recall of dietary information or the fact that food-nutrient tables specific to Northern Chile were unavailable could have limited our ability to evaluate the true impact of diet. Furthermore, individuals may have changed their diet as a result of diabetes diagnosis, thus limiting our ability to evaluate whether diet is responsible for some of the SES effects we saw. Further research assessing diet prior to diabetes onset and including more specific food-nutrient tables, serum levels of some nutrients, or that examines additional nutritional factors may add further insight into the possible role of diet on our results.

The underlying mechanism that may explain why we saw increased arsenic-related risks in people with low SES is unknown but several possibilities exist. Arsenic has been shown to alter glucocorticoid levels and programming of the glucocorticoid signaling system in rodents (Caldwell et al., 2015), a pathway which has been linked with susceptibility to metabolic diseases (Spencer, 2012). Low SES individuals experience chronic stress through impaired glucocorticoid signaling, which could make them more susceptible to diseases like diabetes (Cohen et al., 2012). Thus, the combination of early life arsenic exposure and chronic stress may synergistically impact the responsiveness of the glucocorticoid signaling system and the ability of the body to maintain metabolic homeostasis. Chronic inflammation is another mechanism by which SES could impact the arsenic-diabetes relationship. SES is inversely associated with biomarkers of inflammation (Gruenewald et al., 2009), which are elevated among arsenic-exposed individuals (Das et al., 2012).

Misclassification of arsenic exposure may have occurred in our study from inaccurate recall of residential history, missing exposure data, or non-water sources of arsenic. However, since arsenic exposure was assessed similarly for individuals with and without diabetes, these errors would likely be non-differential and bias results towards the null. Additionally, inaccurate recall of residential history is likely minimal as it is unlikely that individuals would forget where they lived. Arsenic exposure may also occur through food or air. However, because the climate in the study area is so dry, most food is imported from outside the study regions from areas with low arsenic water levels; the main local foods are fish and seafood, which contains mostly organic arsenic. Air and food samples tested for arsenic revealed relatively low arsenic concentrations, with similar levels in the parts of our study area with and without high arsenic water concentrations, and generally accounted for inorganic arsenic intakes of roughly < 1–13 μg/day (Ferreccio and Sancha, 2006). In contrast, intakes from water would be about 1720 μg/day in those drinking 2 L/day of water with arsenic concentrations of 860 μg/L, the historical level in Antofagasta, the largest city in our study area.

Misclassification of diabetes may have occurred. An estimated 22.5% of diabetes cases in Chile are undiagnosed (Ministerio de Salud, 2009). However, Chile has a good health care system with essentially universal coverage, meaning most diagnosed diabetes patients would

be linked to care regardless of SES. Previously we showed that correcting for this level of under-diagnosis would only have small impacts on arsenic-diabetes ORs in our study (Castriota et al., 2018).

Despite these limitations, our study has many strengths. Our estimate of SES was robust in that we did not rely solely on income or education as SES indicators. However, our SES indicators may not be applicable to other populations and other indicators of SES may produce different results in other contexts. We also had robust exposure estimates based on hundreds of historical arsenic water measurements, which allowed us to assess participants lifetime arsenic exposure. Lastly, this study was conducted in an area with a good range in arsenic water concentrations and in area where exposure from water outweighs that from other sources.

5. Conclusions

Our findings contribute to the growing literature suggesting that low SES is an important risk factor for environmentally-induced diseases. This literature highlights the potential benefits of interventions aimed at reducing toxic exposures in low SES populations. Future research is needed to understand the set of specific factors like stress, multiple co-exposures, or nutrition that could underlie the higher risks in low SES populations. This research could help identify other specific interventions that may help reduce risks in these susceptible populations.

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Contributions

SME contributed to the analysis, interpretation of the data, drafting and revision of the manuscript. CF contributed to study implementation, study design and analysis and revision of the manuscript. JA contributed to study design, study implementation, data collection and analysis, and revision of the manuscript. FC contributed to data collection and analysis and revision of the manuscript. JFC contributed to revision of the manuscript. TR contributed to revision of the manuscript. AHS contributed to study design, interpretation of the data, and revision of the manuscript. MTS contributed to revision of the manuscript. CS was the Principal Investigator, and contributed to study design, interpretation of the data, and revision of the manuscript. All authors approved the final version of the manuscript.

Conflicts of interest

The authors report no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envres.2019.03.013.

References

Agardh, E., Allebeck, P., Hallqvist, J., Moradi, T., Sidorchuk, A., 2011. Type 2 diabetes incidence and socio-economic position: a systematic review and meta-analysis. Int. J. Epidemiol. 40 (3), 804–818.

Altman, D.G., Bland, J.M., 2003. Interaction revisited: the difference between two estimates. Bmj 326 (7382), 219.

Argos, M., Parvez, F., Chen, Y., et al., 2007. Socioeconomic status and risk for arsenic-related skin lesions in Bangladesh. Am. J. Public Health 97 (5), 825–831.

Bangdiwala, S.I., Ramiro, L., Sadowski, L.S., Bordin, I.A., Hunter, W., Shankar, V., 2004. Intimate partner violence and the role of socioeconomic indicators in WorldSAFE communities in Chile, Egypt, India and the Philippines. Inj. Control Saf. Promot. 11 (2), 101–109.

Belo, M.T., Selig, L., Luiz, R.R., et al., 2006. Choosing incentives to stimulate tuberculosis treatment compliance in a poor county in Rio de Janeiro state, Brazil. Med. Sci. Monit.: Int. Med. J. Exp. Clin. Res. 12 (5) (Ph1-5).

Bertoglia, M.P., Gormaz, J.G., Libuy, M., et al., 2017. The population impact of obesity, sedentary lifestyle, and tobacco and alcohol consumption on the prevalence of type 2 diabetes: analysis of a health population survey in Chile, 2010. PloS One 12 (5).

Bofah, EA-t, Hannula, M.S., 2017. Home resources as a measure of socio-economic status in Ghana. Large-Scale Assess. Educ. 5 (1), 1.

Caldwell, K.E., Labrecque, M.T., Solomon, B.R., Ali, A., Allan, A.M., 2015. Prenatal arsenic exposure alters the programming of the glucocorticoid signaling system during embryonic development. Neurotoxicol. Teratol. 47, 66–79.

Castriota, F., Acevedo, J., Ferreccio, C., et al., 2018. Obesity and increased susceptibility to arsenic-related type 2 diabetes in Northern Chile. Environ. Res.

Chen, C.J., Wang, S.L., Chiou, J.M., et al., 2007. Arsenic and diabetes and hypertension in human populations: a review. Toxicol. Appl. Pharmacol. 222 (3), 298–304.

Chen, C.L., Hsu, L.I., Chiou, H.Y., et al., 2004. Ingested arsenic, cigarette smoking, and lung cancer risk: a follow-up study in arseniasis-endemic areas in Taiwan. Jama 292 (24), 2984–2990.

Chen, Y., Hall, M., Graziano, J.H., et al., 2007. A prospective study of blood selenium levels and the risk of arsenic-related premalignant skin lesions. Cancer Epidemiol. Biomark. Prev. 16 (2), 207–213.

Chung, J.Y., Yu, S.D., Hong, Y.S., 2014. Environmental source of arsenic exposure. J. Prev. Med. Public Health 47 (5), 253–257.

Cohen, S., Janicki-Deverts, D., Doyle, W.J., et al., 2012. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. Proc. Natl. Acad. Sci. USA 109 (16), 5995–5999.

Das, N., Paul, S., Chatterjee, D., et al., 2012. Arsenic exposure through drinking water increases the risk of liver and cardiovascular diseases in the population of West Bengal, India. BMC Public Health 12, 639.

Ferreccio, C., Sancha, A.M., 2006. Arsenic exposure and its impact on health in Chile. J. Health Popul. Nutr. 24 (2), 164–175.

Ferreccio, C., Gonzalez, C., Milosavjlevic, V., Marshall, G., Sancha, A.M., Smith, A.H., 2000. Lung cancer and arsenic concentrations in drinking water in Chile. Epidemiology 11 (6), 673–679.

Ferreccio, C., Smith, A.H., Duran, V., et al., 2013. Case-control study of arsenic in drinking water and kidney cancer in uniquely exposed Northern Chile. Am. J. Epidemiol. 178 (5), 813–818.

Gamble, M.V., Liu, X., Ahsan, H., et al., 2006. Folate and arsenic metabolism: a double-blind, placebo-controlled folic acid–supplementation trial in Bangladesh. Am. J. Clin. Nutr. 84 (5), 1093–1101.

Gruenewald, T.L., Cohen, S., Matthews, K.A., Tracy, R., Seeman, T.E., 2009. Association of socioeconomic status with inflammation markers in black and white men and women in the Coronary Artery Risk Development in Young Adults (CARDIA) study. Soc. Sci. Med. 69 (3), 451–459.

Hajat, A., Diez-Roux, A.V., Adar, S.D., et al., 2013. Air pollution and individual and neighborhood socioeconomic status: evidence from the Multi-Ethnic Study of Atherosclerosis (MESA). Environ. Health Perspect. 121 (11–12), 1325–1333.

Hall, E.M., Acevedo, J., Lopez, F.G., et al., 2017. Hypertension among adults exposed to drinking water arsenic in Northern Chile. Environ. Res. 153, 99–105.

Kwok, R.K., Kaufmann, R.B., Jakariya, M., 2006. Arsenic in drinking-water and reproductive health outcomes: a study of participants in the Bangladesh Integrated Nutrition Programme. J. Health Popul. Nutr. 24 (2), 190–205.

Ministerio de Salud, 2003. Encuesta Nacional de Salud 2003. ⟨http://epi.minsal.cl/wp-content/uploads/2016/03/ENS2003.f1.pdf⟩.. (Accessed 13 February 2019).

Ministerio de Salud, 2009. Implementación del enfoque de riesgo en el Programa de Salud Cardiovascular; ⟨http://buenaspracticasaps.cl/wp-content/uploads/2014/07/MINSAL-2009-enfoque-riesgo-CV.pdf2009⟩. (Accessed 5 April 2018).

Ministerio de Salud, 2010. Encuesta Nacional de Salud ENS Chile 2009–2010. ⟨http://epi.minsal.cl/wp-content/uploads/2016/06/InformeENS_2009-2010_CAP1.pdf⟩. (Accessed 14 February 2019).

Nabi, A.H., Rahman, M.M., Islam, L.N., 2005. Evaluation of biochemical changes in chronic arsenic poisoning among Bangladeshi patients. Int. J. Environ. Res. Public Health 2 (3–4), 385–393.

National Cancer Institute Division of Cancer Control and Population Sciences, 2018. Diet History Questionnaire II (DHQ II) for U.S. & Canada; ⟨https://epi.grants.cancer.gov/dhq2/⟩. (Accessed 5 August 2018).

Olokoba, A.B., Obateru, O.A., Olokoba, L.B., 2012. Type 2 diabetes mellitus: a review of current trends. Oman Med. J. 27 (4), 269–273.

Ruiz, D., Becerra, M., Jagai, J.S., Ard, K., Sargis, R.M., 2018. Disparities in environmental exposures to endocrine-disrupting chemicals and diabetes risk in vulnerable populations. Diabetes Care 41 (1), 193–205.

Smith, A.H., Steinmaus, C.M., 2009. Health effects of arsenic and chromium in drinking water: recent human findings. Annu. Rev. Public Health 30, 107–122.

Spencer, S.J., 2012. Early life programming of obesity: the impact of the perinatal environment on the development of obesity and metabolic dysfunction in the offspring. Curr. Diabetes Rev. 8 (1), 55–68.

Steinmaus, C., Yuan, Y., Liaw, J., Smith, A.H., 2009. Low-level population exposure to inorganic arsenic in the United States and diabetes mellitus: a reanalysis. Epidemiology 20 (6), 807–815.

Steinmaus, C.M., Ferreccio, C., Romo, J.A., et al., 2013. Drinking water arsenic in northern chile: high cancer risks 40 years after exposure cessation. Cancer Epidemiol. Biomark. Prev. 22 (4), 623–630.

Subar, A.F., Thompson, F.E., Kipnis, V., et al., 2001. Comparative validation of the block, Willett, and National Cancer Institute food frequency questionnaires: the Eating at America's Table Study. Am. J. Epidemiol. 154 (12), 1089–1099.

Tseng, C.H., 2004. The potential biological mechanisms of arsenic-induced diabetes mellitus. Toxicol. Appl. Pharmacol. 197 (2), 67–83.
Tseng, C.H., Tai, T.Y., Chong, C.K., et al., 2000. Long-term arsenic exposure and incidence of non-insulin-dependent diabetes mellitus: a cohort study in arseniasis-hyperendemic villages in Taiwan. Environ. Health Perspect. 108 (9), 847–851.
Tyler, C.R., Allan, A.M., 2014. The effects of arsenic exposure on neurological and cognitive dysfunction in human and rodent studies: a review. Curr. Environ. Health Rep. 1 (2), 132–147.
Van Halem, D., Bakker, S.A., Amy, G.L., Van Dijk, J.C., 2009. Arsenic in drinking water: a worldwide water quality concern for water supply companies. Drink. Water Eng. Sci. 2.
Willett, W., Stampfer, M.J., 1986. Total energy intake: implications for epidemiologic analyses. Am. J. Epidemiol. 124 (1), 17–27.
World Health Organization, 2018. Diabetes Key Facts. Fact Sheets 2017; 〈http://www.who.int/news-room/fact-sheets/detail/diabetes〉 (Accessed 6 July 2018).