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Hypertension among adults exposed to drinking water arsenic in Northern Chile

Emily M. Hall[a], Johanna Acevedo[b,c], Francisca González López[b], Sandra Cortés[b,c], Catterina Ferreccio[b,c], Allan H. Smith[d], Craig M. Steinmaus[d,e,*]

[a] Texas Department of State Health Services, Austin, Texas, USA
[b] Pontificia Universidad Católica de Chile, Santiago, Chile
[c] Advanced Center for Chronic Diseases (ACCDIS), Chile
[d] Arsenic Health Effects Research Group, School of Public Health, University of California, Berkeley, USA
[e] Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, California, USA

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ABSTRACT

Background: A growing number of studies have identified an association between exposure to inorganic arsenic and hypertension. However, results have not been consistent across studies. Additional studies are warranted, given the global prevalence of both arsenic exposure and morbidity attributable to hypertension.
Methods: We analyzed data collected from October 2007-December 2010 for a population-based cancer case-control study in northern Chile. Data included lifetime individual arsenic exposure estimates and information on potential confounders for a total of 1266 subjects. Those self-reporting either a physician diagnosis of hypertension or use of an anti-hypertensive medication were classified as having hypertension (n=612). The association between hypertension and drinking water arsenic exposure was analyzed using logistic regression models.
Results: Compared to those in the lowest category for lifetime highest 5-year average arsenic exposure (< 60 μg/L), those in the middle (60–623 μg/L) and upper (> 623 μg/L) exposure categories had adjusted hypertension ORs of 1.49 (95% CI: 1.09, 2.05) and 1.65 (95% CI: 1.18, 2.32), respectively. Similar results were observed in analyses of lifetime cumulative exposures and analyses restricted to exposures from the distant past.
Conclusions: We identified evidence of increased odds of hypertension with exposure to arsenic in drinking water among study participants. Our findings add to the growing body of research supporting this association, which could have important public health implications.

1. Introduction

Hypertension, or elevated blood pressure, is a well-known risk factor for cardiovascular disease (CVD), the leading cause of morbidity and mortality worldwide (World Health Organization, 2009). With a global prevalence of approximately 40%, the World Health Organization (WHO) estimates that 12.8% (7.5 million) of all deaths are attributable to hypertension each year (Alwan, 2011). There is growing evidence that drinking water arsenic exposure is associated with hypertension and a number of cardiovascular diseases (National Research Council, 2014).

Arsenic-induced damage to the vascular system is hypothesized to be associated with oxidative stress and inflammation, but is not fully understood (Lantz and Hays, 2006).

A small number of epidemiologic studies have assessed the relationship between arsenic exposure and hypertension, and several, though not all, have identified positive associations (Chen et al., 1995; Rahman et al., 1999; Huang et al., 2007; Abhyankar et al., 2012; Wang et al., 2011, 2007; Guo et al., 2007; Kwok et al., 2007). One recent prospective study found significantly greater year-to-year increases in blood pressure (BP) among participants with higher drinking water arsenic exposure compared to those in the lowest exposure group (Jiang et al., 2015).

While several studies have identified associations between drinking water arsenic exposure and hypertension, study limitations impede characterization of the dose-response relationship (Abhyankar et al., 2012; Navas-Acien et al., 2005). The majority have been cross-sectional. Individual lifetime arsenic exposure data have not been available, and some have depended on ecological estimates of exposure. Furthermore, many studies have taken place in Taiwan, Bangladesh

* Correspondence to: University of California, Berkeley, School of Public Health, 50 University Hall, MC7360, Berkeley, CA 94720-7360, USA.
E-mail address: craigs@berkeley.edu (C.M. Steinmaus).

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and the United States (Abhyankar et al., 2012); results may not be generalizable to all potentially-exposed populations due to possible differences in nutrition, genetics, baseline hypertension rates, co-exposures, or other susceptibility factors (Chen et al., 1996; Lan et al., 2011).

Each year, millions are at risk of drinking water arsenic exposure in excess of the WHO-recommended limit of 10 μg/L, and it is estimated that over 100 million individuals might consume water containing arsenic concentrations greater than 50 μg/L (Alwan, 2011; van Halem et al., 2009). Considering the sizable population exposed to arsenic, and the high global prevalence of morbidity and mortality attributable to high blood pressure, any arsenic-associated increase in hypertension could result in hundreds of thousands of additional deaths (Alwan, 2011). Therefore, further investigation is needed to confirm and further elucidate the characteristics of this association.

The cities and towns in Regions I and II in northern Chile have had a wide range of arsenic concentrations in their drinking water sources (Ferreccio et al., 2000). In the largest city in the area, Antofagasta, hundreds of thousands of residents were exposed to high levels of drinking water arsenic beginning in 1958, when arsenic-contaminated rivers were diverted to supply water to the area's growing population. Residents of Antofagasta and neighboring Mejillones ingested water containing 860 μg/L or greater of arsenic until these concentrations were drastically decreased between 1970 and 1978 with the installation and improvement of a new water treatment plant (Yuan et al., 2007; Steinmaus et al., 2013; Ferreccio et al., 2013; Ferreccio and Sancha, 2006). Other cities in Regions I and II, which are demographically comparable to Antofagasta, vary widely in drinking water arsenic concentrations, from 1 μg/L to >600 μg/L (Ferreccio et al., 2013).

Northern Chile is the driest habitable place on earth, and there are relatively few individual water sources. Almost all inhabitants receive water from one of a limited number of public water utilities, which have robust historical records of water arsenic concentrations over a period of many decades in the past. Until recently, consumption of bottled water was uncommon. Because of the limited water sources and availability of good historical arsenic records, individual lifetime drinking water arsenic exposure can be estimated with a high level of accuracy (Steinmaus et al., 2013; Ferreccio et al., 2013).

Previous studies conducted in northern Chile have found increased lung, bladder, skin, and kidney cancer risk, as well as cardiovascular disease mortality among exposed populations (Yuan et al., 2007; Steinmaus et al., 2013; Smith et al., 2012). This is the first study of the relationship between drinking water arsenic and hypertension in this population.

2. Methods

2.1. Study setting

To assess the relationship between historical drinking water arsenic exposure and hypertension later in life among adults in northern Chile, we conducted a secondary analysis of data collected from a cancer case-control study in this area. Details of the original case-control study are described elsewhere (Steinmaus et al., 2013; Ferreccio et al., 2013). In summary, participants were selected from Regions I and II in northern Chile. Lung, bladder, and kidney cases newly diagnosed between October 2007 and December 2010 were identified from all local pathologists, radiologists, and hospitals in the Regions. Cancer cases over 25 years of age, residing in the study area at diagnosis, and who were available for interview or had a close relative who was, were included in the study. Lung, bladder, and kidney cancer-free controls residing in the study area from 2007 to 2009 were randomly selected from the Chilean Voter Registry, and frequency matched to cases by sex and 5-year age range. Because of this matching, the study participants represent the age and sex distribution of bladder, lung, and kidney cancer cases in the study area. The registry is estimated to include over 90% of Chilean adults ages 40 years and older. A total of 665 cancer cases and 640 cancer-free controls (or their proxy respondents) were eligible, gave informed consent, and participated in standardized interviews. Proxies responded for 121 (19.8%) of those with hypertension and 130 (19.9%) of those without hypertension.

2.2. Outcome assessment

All participants were interviewed using a standard structured questionnaire by trained personnel during a single study visit. During interviews, all participants were asked if they had ever been told by a physician that they had high blood pressure or hypertension. Additionally, they were asked to report all medications taken in the calendar year prior to the time of interview. All study participants who answered either of these questions were eligible for inclusion in the current analysis. Those self-reporting either a physician diagnosis of hypertension or use of an anti-hypertensive medication were classified as hypertension cases (n=612), while the remainder (n=654) comprised the hypertension-free controls. Among those with hypertension, 224 (36.6%) reported physician diagnosis alone, 20 (3.3%) reported anti-hypertensive medication use alone, and the remaining 368 (60.1%) reported both. Because analyses showed no major effect modification by cancer status, cancer cases and non-cancer controls were combined in some analyses. Thirty-nine individuals with missing outcome or predictor variable data were excluded. The remaining 1266 participants ranged in age from 32 to 98 years.

Subjects who reported physician-diagnosed diabetes or use of an oral hypoglycemic medication were defined as having diabetes. Current height and weight were also measured in all subjects by study nurses using standard study protocols. Information on diet was collected using a food frequency questionnaire that asked about intake of all foods within the year preceding interview and any major changes from 20 years previously. Socioeconomic status (SES) scores were calculated on a 12-point scale based on self-reported ownership of several household appliances, electronics (e.g. computer, television), car, or employment of domestic help.

2.3. Exposure estimation

A detailed lifetime residential history was collected for each participant during interview. Annual drinking water arsenic concentrations for each year of every participant's life were then estimated by linking each residence with arsenic water records for that residence. Arsenic water concentration records were available for approximately 95% of municipal water sources in the study area and for all larger Chilean cities outside of the study area (Ferreccio et al., 2000). These annual estimates were then used to calculate arsenic exposure metrics. Because it is unknown whether exposure intensity or cumulative exposure has a greater impact on the risk of arsenic-associated hypertension, results for several different metrics are reported. Cumulative arsenic exposure was calculated by summing the annual arsenic concentrations estimated for each year of each subject's life. Each subject's peak exposure was defined as the highest arsenic concentration estimated for any single year, while the highest 5-year average exposure was calculated as the highest annual concentration averaged over any contiguous 5-year period. Because high exposures in Antofagasta ended in 1970, and to evaluate possible latency effects, some analyses were limited to exposures before 1971 and excluded 11 individuals born in 1971 or later. For 23 individuals born between 1966 and 1970, highest average exposures prior to 1971 were calculated for time periods less than 5 years. These individuals were included in analyses, as their exclusion did not impact results.

Participants were categorized by tertile values for each metric among all participants. For several exposure metrics, the value dividing the lowest and middle tertiles was 60 μg/L, which corresponded to water arsenic concentrations in Iquique, one of the largest cities in the

study area. Because of this, all individuals with exposures of 60 μg/L were assigned to the middle tertile group. Therefore, the number of participants in each exposure category was unequal for these exposure metrics.

2.4. Statistical analysis

Unconditional logistic regression was used to calculate crude and adjusted hypertension odds ratios (ORs) and 95% confidence intervals (CIs). Potential confounders initially entered into logistic regression models included age (continuous); sex; race/ethnicity (Hispanic, European, Indigenous, or other); cigarette smoking (ever vs. never); cancer status; body mass index (BMI) calculated as (weight in kg)/(height in m^2) and categorized as underweight (< 18.5), normal weight (18.5–24.9), overweight (25–29.9), and obese (30+); employment in mining (ever vs. never); diabetes (self-reported physician diagnosed or medication use); SES score tertile; self-reported daily fruit and vegetable intake; and high-school graduation, given the higher prevalence of hypertension among Chileans with low educational attainment (Ministry of Health, 2010). Tests for linear trend were performed using the Cochrane-Armitage test.

For each exposure metric, final logistic regression models adjusted for age, BMI category, cigarette smoking, and sex. Smoking and sex did not appreciably alter estimates, but were included in the models, as they are known risk factors for hypertension. Adjusting for daily average or maximum cigarettes smoked had little effect on ORs. The remaining potential confounders were not statistically significant in the final models and had little or no effect on model fit or ORs. Although cancer status was not statistically significant in logistic regression models, we calculated crude and adjusted ORs stratified by cancer case-control status to ensure that original enrollment status (cancer case vs. cancer control) did not mediate or modify the association between arsenic exposure and hypertension.

All p-values are two-sided and considered significant at the p=0.05 level. Analyses were completed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

3. Results

Individuals with hypertension were older and more likely to have diabetes, higher BMIs, and to be female compared to those without hypertension (Table 1). They also had greater median arsenic exposures, with median lifetime cumulative exposures of 3789 (ug/L)-years among those without hypertension and 4638 (ug/L)-years among those with hypertension (p=0.002). There was no difference in race, socioeconomic status, history of mining work, daily fruit and vegetable intake, or original cancer case-control status between those with hypertension and those without. The unadjusted and adjusted (for age, sex, BMI, smoking, and lifetime highest 5-year average arsenic exposure) ORs between cancer status and hypertension were 1.01 (95% CI: 0.81, 1.26) and 1.11 (95% CI: 0.87, 1.42), respectively.

Compared to those in the lowest exposure category, adjusted hypertension ORs were 1.49 (95% CI: 1.09, 2.05) and 1.65 (95% CI: 1.18, 2.32) for those with a lifetime highest 5-year average exposure of 60–623 μg/L and > 623 μg/L, respectively (Table 2). The median arsenic water concentrations in these three groups were 10 μg/L, 178 μg/L, and 860 μg/L. Similar results were observed for highest 5-year average and peak exposures prior to 1971.

Hypertension ORs were 1.12 (95% CI: 0.84, 1.49) and 1.60 (95% CI: 1.20, 2.13) respectively for those with lifetime cumulative arsenic exposures of 2,188-7,025 and > 7,025 (μg/L)-years, compared to the lowest exposure group (Table 2). For each of these three groups, the median cumulative arsenic exposures were 764 (μg/L)-years, 4,091 (μg/L)-years, and 13,028 (μg/L)-years. Similarly, hypertension ORs for cumulative exposures prior to 1971 were 1.31 (95% CI: 0.98, 1.75) and 1.57 (95% CI: 1.18, 2.10) for those in the middle and highest exposure categories, compared to those with exposures < 720 (μg/L)-years (Supplemental Table). Median arsenic exposures were 142 (μg/L)-years, 1982 (μg/L)-years, and 11,450 (μg/L)-years among these three groups, respectively.

When analyses were stratified by original cancer case-control status, ORs greater than 1.0 were observed among both cancer cases and controls, though not all elevated ORs were statistically significant (Table 3). Adjusting for diabetes status led to small changes in the magnitude of some ORs. For example, the OR for subjects with lifetime highest 5-year average arsenic exposures > 623 μg/L changed from 1.65 (95% CI: 1.18, 2.32) to 1.55 (95% CI: 1.10, 2.19) after adjustment for diabetes. Stratification by sex led to similar ORs as non-stratified analyses, though with wider confidence intervals.

4. Discussion

This is one of few studies to utilize individual exposure estimates to assess associations between drinking water arsenic exposure and hypertension. We addressed several methodological limitations of previous studies by controlling for several potential sources of confounding in our analyses and using robust estimates of lifetime individual exposures. Overall, we found a positive association between drinking water arsenic concentration and hypertension. Adjusted ORs were statistically significant for the highest exposure tertile for all exposure metrics, as well as for the second-highest exposure tertiles for both highest five-year average metrics (Table 2). In analyses both non-stratified and stratified by cancer status, linear trends for all exposure metrics were statistically significant.

Analyses stratified by original cancer case-control status were still suggestive of a positive association between arsenic exposure and hypertension for all exposure metrics (Table 3). In each strata, ORs varied somewhat from those for the entire sample, although ORs for the upper tertiles of each exposure metric for both cancer cases and non-cancer controls subjects were greater than 1.0. There were some differences in the magnitude of the hypertension ORs between cancer cases and non-cancer controls, but these differences were not consistent across the different exposure metrics. The wide confidence intervals suggest that these differences could be due to chance. We considered the possibility that our inclusion of cancer cases in our main analyses, and the possibility that having cancer or pre-cancer illness, may have mediated some of the arsenic-hypertension association we identified. However, this seems unlikely given that cancer cases did not have a greater prevalence of hypertension than the non-cancer controls (Table 1). In addition, adjusting for cancer status had little impact on results of the main analyses, and some evidence of an association between arsenic and hypertension is seen in the analyses confined to non-cancer controls. Overall, these findings suggest that the positive associations we identified here are not due the inclusion of cancer cases.

The results of previously-published studies on arsenic and hypertension have been mixed. For example, a 2012 meta-analysis of arsenic and hypertension studies in areas with known high arsenic water concentrations reported a pooled OR of 1.15 (95% CI: 0.96, 1.37) (Abhyankar et al., 2012). Interestingly, three of the five studies included in the analysis reported statistically significantly increased odds of hypertension associated with arsenic exposure (Chen et al., 1995; Rahman et al., 1999; Guo et al., 2007; Wang et al., 2007; Zierold et al., 2004). However, the degree of heterogeneity across individual study results was high (Higgins I^2=76.6%), with individual ORs ranging from 0.71 to 16.54 (Abhyankar et al., 2012). The exact reasons for the inconsistency in results across studies is unknown, although most studies in areas with high arsenic exposure have had limited exposure data or have been conducted among populations in Bangladesh or Taiwan, where rates of hypertension and related risk factors may be relatively low. In these populations, arsenic may be associated with elevations in blood pressure, but not overt clinical

Table 1
Demographic characteristics of study participants with and without hypertension.

	Without hypertension	With hypertension	
	***n* (%)**	***n* (%)**	**OR (95% CI)**
Total	654 (100)	612 (100)	
Sex			
Female	194 (29.7)	216 (35.3)	1.00
Male	460 (70.3)	396 (64.7)	0.77 (0.61, 0.98)
Cancer Case-Control Status			
Control	324 (49.5)	302 (49.4)	1.00
Case	330 (50.5)	310 (50.7)	1.01 (0.81, 1.26)
BMI Category			
Low	29 (4.4)	16 (2.6)	0.71 (0.38, 1.35)
Normal	258 (39.5)	200 (32.7)	1.00
Overweight	276 (42.2)	257 (42.0)	1.20 (0.94, 1.54)
Obese	91 (13.9)	139 (22.7)	1.97 (1.43, 2.72)
Mining Work			
No	487 (74.5)	468 (76.5)	1.00
Yes	167 (25.5)	144 (23.5)	0.90 (0.69, 1.16)
Cigarette Smoking			
Never	164 (25.1)	185 (30.2)	1.00
Ever	469 (71.7)	404 (66.0)	0.76 (0.60, 0.98)
Unknown	21 (3.2)	23 (3.8)	0.97 (0.52, 1.82)
Diabetes			
No	565 (86.4)	412 (66.3)	1.00
Yes	89 (13.6)	200 (33.7)	3.22 (2.44, 4.26)
Daily Fruit and Vegetable Intake			
< =1/day	223 (34.1)	198 (32.4)	1.00
1–2/day	160 (24.5)	138 (22.6)	0.97 (0.72, 1.31)
> 2/day	138 (21.1)	151 (24.7)	1.23 (0.91, 1.66)
Unknown	133 (20.3)	125 (20.4)	1.06 (0.78, 1.44)
High School Graduation			
No	401 (61.3)	411 (67.2)	1.31 (1.04, 1.66)
Yes	247 (37.8)	193 (31.5)	1.00
Doesn't know	6 (0.92)	8 (1.3)	1.71 (0.58, 5.00)
Race			
European	27 (4.2)	28 (4.7)	1.07 (0.62, 1.84)
Hispanic	485 (75.6)	471 (78.4)	1.00
Indigenous	69 (10.8)	49 (8.2)	0.73 (0.50, 1.08)
Other	61 (9.5)	53 (8.8)	0.90 (0.60, 1.32)
	Mean (SD)	**Mean (SD)**	***p*-value**
Age	63.0 (11.8)	68.7 (9.9)	< 0.0001
Arsenic exposure metric	**Median (Min-Max)**	**Median (Min-Max)**	***p*-value***
Cumulative lifetime exposure ([μg/L]-years)	3,789 (0–18,330)	4,638 (82–32,243)	0.002
Peak exposure prior to 1971 (μg/L)	203 (0–860)	250 (0–860)	0.09
Highest 5-year average prior to 1971 (μg/L)	150 (0–860)	250 (0–860)	0.07
Lifetime highest 5-year average (μg/L)	250 (0–860)	287 (0–860)	0.05

* *p*-values calculated using Wilcoxon rank-sum tests.

hypertension. This is in contrast to our study, which involved lifetime exposure data and a population with obesity rates and dietary patterns that are more similar to those in the U.S. Several studies of lower arsenic water concentrations have also reported some evidence of an association with hypertension, but these have been limited by cross-sectional or ecologic study designs or a lack of data on potential confounders (Wang et al., 2007; Zierold et al., 2004; Jones et al., 2011).

The mechanism through which inorganic arsenic may damage the human vascular system is not fully understood. However, a number of studies, in both humans and animals, have linked arsenic exposure to oxidative stress and inflammation (Chen et al., 2011, 2009; Kitchin and Ahmad, 2003; Simeonova and Luster, 2004; Balakumar et al., 2008; Chobanian and Alexander, 1996; Hwang et al., 1997). These processes are known to lead to endothelial cell damage, increased platelet adhesion, and reduced vasodilation, effects that could be the primary mechanism of arsenic-related hypertension. In addition, a number of studies, including our studies in northern Chile, have linked arsenic to non-malignant kidney disease and dysfunction so altered kidney function might also mediate arsenic-hypertension associations (Smith et al., 2012; Hsueh et al., 2009; Huang et al., 2011). Overall, the fact that arsenic has been shown to impact several physiologic processes that have been linked to hypertension supports the biologic plausibility of our findings.

Self-report of physician diagnosis of disease or use of anti-hypertensive medication was used to determine disease status in our study, which could lead to some misclassification of true hypertension status. However, in other populations, studies have found high concordance

Table 2
Adjusted hypertension ORs for selected arsenic exposure metrics.

Arsenic exposure metric	Without hypertension (n)	With hypertension (n)	Adjusted ORs[a] (95% CI)	*p*-value
Lifetime cumulative exposure ([μg/L]-years)				
< 2,188	233	188	1.00	*Ref*
2,188–7,025	230	192	1.12 (0.84, 1.49)	0.45
> 7,025	191	232	1.60 (1.20, 2.13)	0.002
Trend				< 0.0001
Peak exposure prior to 1971 (μg/L)				
< 60	183	140	1.00	*Ref*
60–859	236	246	1.33 (0.98, 1.79)	0.06
> 859	225	225	1.42 (1.04, 1.92)	0.03
Trend				< 0.0001
Highest 5-year average prior to 1971 (μg/L)				
< 60	201	149	1.00	*Ref*
60–559	234	252	1.42 (1.06, 1.90)	0.02
> 559	209	210	1.50 (1.10, 2.03)	0.01
Trend				< 0.0001
Lifetime highest 5-year average (μg/L)				
< 60	148	105	1.00	*Ref*
60–623	297	293	1.49 (1.09, 2.05)	0.01
> 623	209	214	1.65 (1.18, 2.32)	0.003
Trend				< 0.0001

[a] ORs adjusted for age, BMI, sex, and smoking.

(up to 91%) between self-report and clinical diagnosis of hypertension (Martin et al., 2000; Kehoe et al., 1994; Giles et al., 1995). Chile has a popular public health care system and has achieved universal health care coverage. As such, the number of people with undiagnosed hypertension is probably relatively low. In addition, access to free medical care is readily available throughout Regions I and II, including areas with higher and lower arsenic water concentrations. Additionally, the relatively high hypertension prevalence among study participants (48.3%) is similar to that found among the Chilean population of a similar age distribution, which was estimated to be 44% among those ages 45-64 and 75% among those 65 and older, according to the 2009–2010 Chilean National Health Survey (Ministry of Health, 2010; Ministerio de Salud, 2010). Thus among our study population, any misclassification of disease would most likely have been non-differential by exposure status, which would tend to bias ORs towards the null.

Misclassification of arsenic exposure is possible, but is unlikely to have caused the positive associations we identified in this study. We did not account for dietary intake of arsenic. However, given the dry conditions of the study area, agricultural activities are minimal, and most food is imported from other regions where arsenic water concentrations are low. As such, any dietary contribution to total arsenic exposure is likely small and misclassification of exposure most likely non-differential. Misclassification of drinking water arsenic concentrations is also possible, but unlikely since exposure estimates were primarily based on subject's recall of past residences, data that can be reliably recalled from the distant past. In addition, since exposure was ascertained in the same way for both people with and without hypertension, and since arsenic water concentrations were assigned blinded to hypertension status, any misclassification of arsenic exposure from water would most likely be non-differential. Non-differential misclassification from either potential source (water or food) would most likely bias ORs towards the null. Arsenic exposure can also occur through air or from work, although arsenic air concentrations in these regions have been relatively low (0.025–0.129 μg/m^3) (Ferreccio and Sancha, 2006) and adjustments for mining work, the major source of occupational arsenic exposures, had little impact on results.

While we did not adjust for physical activity or dietary salt intake, both known risk factors for hypertension, the 2003 and 2009–2010 Chilean National Health Surveys found that daily activity levels, prevalence of sedentary lifestyle, and sodium intake were similar among the higher and lower arsenic exposure regions in our study (Ministry of Health, 2010, 2003). We did not adjust for drinking water sodium intake. However, while moderately elevated sodium levels have been documented in several surface water sources in our study area, this has occurred independently of water arsenic concentrations (Margaritz et al., 1989; Torres, 2008; Romero et al., 2003). Additionally, drinking water monitoring data for January 2012-August 2016 show that the three largest cities in Regions I and II (Antofagasta, Arica, and Iquique) have consistently been in compliance with Chilean regulations for total dissolved solids (Superintendencia de Servicios Sanitarios, 2016). Because salinity is unrelated to arsenic concentrations it is unlikely to have caused important confounding in our study.

It is possible that some confounding factor may have caused the associations we have identified here. However, the major risk factors associated with hypertension including age, gender, diet, smoking, and obesity were similar amongst our subjects with higher and lower arsenic exposures. In addition, adjusting for each of these factors had little impact on results. Overall, while confounding by some unknown factor cannot be ruled out, it seems an unlikely cause of the associations we report here.

5. Conclusions

Many past studies on the association between ingested arsenic and hypertension have been cross-sectional and some relied on population-level arsenic exposure estimates. The current study utilized individual arsenic exposure estimates over subjects' lifetimes to explore this association. We identified statistically significant associations between drinking water arsenic exposure and hypertension among study participants, and our findings add to the growing body of research supporting this association. The magnitude of the association is important considering the high prevalence of hypertension globally, as a 50% increase in hypertension odds could signify a large number of additional cases. Our main analyses included both cancer cases and subjects without cancer. While some differences in ORs were seen between these groups, evidence for bias resulting from inclusion of cancer cases was not seen, and arsenic-hypertension ORs were elevated

Table 3
Adjusted hypertension ORs for selected arsenic exposure metrics, stratified by cancer status.

	Cancer Cases (n=640)				**Non-Cancer Controls** (n=626)			
Arsenic exposure metric	**Without hypertension (n)**	**With hypertension (n)**	**OR (95% CI)**[a]	***p*-value**	**Without hypertension (n)**	**With hypertension (n)**	**OR (95% CI)**[a]	***p*-value**
Lifetime cumulative exposure ([μg/L]-years)								
< 2,188	102	81	1.00	*Ref*	131	107	1.00	*Ref*
2,188–7,025	117	94	1.12 (0.73, 1.70)	0.61	113	98	1.13 (0.76, 1.69)	0.55
> 7,025	111	135	1.74 (1.16, 2.61)	0.01	80	97	1.32 (0.86, 2.01)	0.20
Trend				< 0.0001				< 0.0001
Peak exposure prior to 1971 (μg/L)								
< 60	65	54	1.00	*Ref*	118	86	1.00	*Ref*
60–859	113	115	1.23 (0.77, 1.97)	0.38	123	131	1.38 (0.92, 2.05)	0.12
> 859	146	141	1.33 (0.84, 2.09)	0.22	79	84	1.36 (0.86, 2.12)	0.18
Trend				< 0.0001				< 0.0001
Highest 5-year average prior to 1971 (μg/L)								
< 60	72	57	1.00	*Ref*	129	92	1.00	*Ref*
60–559	112	121	1.36 (0.86, 2.14)	0.18	123	131	1.43 (0.97, 2.12)	0.07
> 559	140	132	1.36 (0.88, 2.13)	0.17	69	78	1.51 (0.96, 2.38)	0.07
Trend				< 0.0001				< 0.0001
Lifetime highest 5-year average (μg/L)								
< 60	55	44	1.00	*Ref*	93	61	1.00	*Ref*
60–623	136	131	1.28 (0.79, 2.09)	0.32	161	162	1.69 (1.11, 2.58)	0.02
> 623	139	135	1.43 (0.88, 2.33)	0.15	70	79	1.71 (1.05, 2.81)	0.03
Trend				< 0.0001				< 0.0001

[a] ORs adjusted for age, BMI, sex, and smoking.

above 1.0 in both groups. Although this study provides new evidence that arsenic in drinking water is associated with hypertension, detailed analyses of dose-response patterns (e.g. threshold effects) could not be done due to the relatively small sample size and limited statistical power. Larger studies, especially in areas with good data on lifetime exposure, could help elucidate more specific dose-response relationships.

Disclaimer

The views expressed are those of the authors and do not necessarily represent those of the Office of Environmental Health Hazard Assessment, the California Environmental Protection Agency, the State of California, the Texas Department of State Health Services, or the State of Texas.

Disclosure of Potential Conflicts of Interest

Dr. Craig Steinmaus has done consulting work on the toxic effects of arsenic for both industry and environmental groups.

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Human subjects research approval

Institutional review board approval was granted by the Committee for the Protection of Human Subjects at the University of California Berkeley and the ethics committee of the School of Medicine at the Pontificia Universidad Católica de Chile.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envres.2016.11.016.

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