Original Contribution

Age at Exposure to Arsenic in Water and Mortality 30–40 Years After Exposure Cessation

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Arsenic in drinking water is known to cause cancer and noncancer diseases, but little is known about its association with age at exposure. Here, we investigated age at arsenic exposure and mortality in Antofagasta, Chile, 30–40 years after a distinct period of very high water arsenic concentrations (1958–1970). We calculated standardized mortality ratios (SMRs) comparing Antofagasta with the rest of Chile for 2001–2010 by sex and age at potential first exposure. A remarkable relationship with age at first exposure was found for bronchiectasis, with increased risk in adults 30–40 years after exposure being confined to those who were in utero (SMR = 11.7, 95% confidence interval (CI): 4.3, 25.4) or aged 1–10 years (SMR = 5.4, 95% CI: 1.1, 15.8) during the high-exposure period. Increased SMRs for lung, bladder, and laryngeal cancer were evident for exposures starting at all ages, but the highest SMRs were for exposures beginning at birth (for bladder cancer, SMR = 16.0 (95% CI: 10.3, 23.8); for laryngeal cancer, SMR = 6.8 (95% CI: 2.2, 15.8); for lung cancer, SMR = 3.8 (95% CI: 2.9, 4.9)). These findings suggest that interventions targeting early-life arsenic exposure could have major impacts in reducing long-term mortality due to arsenic 30–40 years after exposure ends.

age at first exposure; arsenic; Chile; drinking water

Abbreviations: CI, confidence interval; ICD-9, *International Classification of Diseases, Ninth Revision*; SMR, standardized mortality ratio.

Arsenic is a naturally occurring element in the earth's crust and is frequently detected in drinking water. Millions of people around the world are exposed to arsenic through drinking water (1). Arsenic is classified by the International Agency for Research on Cancer as a human carcinogen, and there is sufficient evidence that it can cause cancer of the lung, urinary bladder, and skin (2). Many noncancer diseases have been found to be associated with arsenic exposure, including reproductive, cardiovascular, pulmonary, neurological, and dermal effects (3).

Northern Chile is the driest habitable place on earth, and almost all of the population there relies exclusively on public water systems, with no other significant water sources such as bottled water or private wells (4). Antofagasta (Figure 1) is the largest city in northern Chile (population 378,244 in 2015 (5)). Before 1958, the arsenic concentration in its water supply was 90 μg/L (6). In 1958, because of population growth, the city's water source was changed to the Toconce and Hojalar rivers, which emanate as geothermal water (a type of groundwater)

from the Andes mountains. This water contains high levels of arsenic, resulting in city water arsenic concentrations of approximately 860 μg/L (6–8). In 1970 a treatment plant was installed, and water arsenic levels decreased dramatically to about 100 μg/L. Current concentrations are less than 10 μg/L, following improvements to the arsenic removal plant.

Relatively few people in other studies have been exposed to arsenic concentrations over 500 μg/L. For example, in a study carried out in southwestern Taiwan, 8,251 participants were exposed to water arsenic levels over 600 μg/L (9). In a study in northeastern Taiwan, 698 people were exposed to water arsenic levels over 300 μg/L (10). In a study conducted in the South 24 Parganas district of West Bengal, India, 902 people drank well water with arsenic concentrations over 500 μg/L (11). In Matlab, a rural area in Bangladesh, 10,430 participants were exposed to arsenic levels over 300 μg/L from drinking water (12). However, in Antofagasta, approximately 125,000 residents were exposed to arsenic at concentrations of 860 μg/L

Figure 1. Map of Chile showing the locations of the study cities, Antofagasta and Mejillones, in region II.
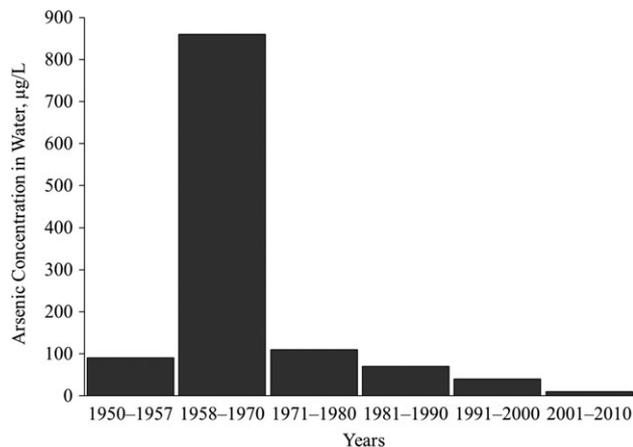

Figure 2. Concentrations of drinking water arsenic in Antofagasta, Chile, 1950–2010. New water sources with high levels of arsenic were used from 1958 onward, and a water treatment plant for arsenic removal was installed in 1970, with improved removal efficiency thereafter. The current concentration of arsenic in drinking water in Antofagasta is below the World Health Organization standard of 10 μg/L (21).

from the city's only water source until 1970, with over 10 times more people being exposed to high arsenic concentrations than in any other study. Since there was no other water source, all residents were exposed to the same high level of arsenic. This scenario, with its distinct high-exposure period (1958–1970), large population, good exposure records, and appropriate latency period, provided us with a unique opportunity to investigate the long-term consequences of arsenic exposure (13).

In previous studies, we found that mortality from lung, bladder, laryngeal, and kidney cancers and from noncancer diseases such as acute myocardial infarction had increased after the high arsenic exposure period of 1958–1970 in Chile's region II (14–17). In several analyses, we examined mortality among adults who were in utero or were young children at the time of the high-exposure period in Antofagasta (1958–1970) and found especially high mortality ratios for lung, bladder, liver, and laryngeal cancers, chronic renal disease, and bronchiectasis in adulthood, even before age 50 years (13, 18–20). These previous early-life arsenic exposure mortality findings involved the years 1989–2000 (14–20), and in the present study, which involved mortality during the years 2001–2010, we were able to again assess the impact of early-life arsenic exposure with nonoverlapping mortality data. In addition, only limited information concerning the impact of age at first exposure has been published so far. Here we present evidence concerning age at potential first arsenic exposure and mortality from arsenic-related causes of death 30–40 years later in the largest population in the world with a distinct period of high exposure to arsenic in drinking water.

METHODS

Exposure data

Historical data on water arsenic levels in Chile have been provided in previous studies (4, 6) (Figure 2). After the water

source change in the city of Antofagasta, the average arsenic concentration in the public water supply increased greatly, up to 860 μg/L, between 1958 and 1970, until a water treatment plant commenced operations in 1970. Now arsenic concentrations in Antofagasta are below 10 μg/L, the World Health Organization guideline for arsenic in drinking water (21). Antofagasta and Mejillones are neighboring cities that share the same water system, so in this article, "Antofagasta" refers to both cities together, accounting for more than 65% of the population of region II in Chile. Although the rest of region II also had arsenic in drinking water, the degree of contamination was less than that in Antofagasta. The "rest of Chile" in this paper is defined as any part of Chile outside of region II, which had low arsenic concentrations of generally less than 10 μg/L.

Exposure data in this paper were based on the locations where subjects died, without detailed histories of residential location over the years. Since some people will have migrated into Antofagasta later in life, when we identify "early-life exposure" it means that there was potential for early-life exposure if the person was living in Antofagasta at that time. The impact of migration into Antofagasta from elsewhere in Chile would have the effect of biasing estimates of association towards the null, which is not of concern given the major increases in risk we report.

Mortality data

Mortality data were computerized and provided by the Chilean Ministry of Health for all regions of Chile for the years 2001–2010 (T.R., Ministry of Health of Chile, unpublished data, 2015). The causes of death were based on death certificates signed by physicians, and trained nosologists coded them according to the *International Classification of Diseases, Tenth Revision*. Nosologists were blinded to the place of death of subjects to prevent bias. We converted *International Classification*

of Diseases, Tenth Revision, codes to *International Classification of Diseases, Ninth Revision* (ICD-9) codes for our analysis in order to compare results obtained over the years with previous findings. In this study, we focused on lung cancer (ICD-9 code 162), bladder cancer (ICD-9 code 188), kidney cancer (ICD-9 code 189), laryngeal cancer (ICD-9 code 161), and the noncancer diseases of bronchiectasis (ICD-9 code 494), acute myocardial infarction (ICD-9 code 410), and chronic renal failure (ICD-9 codes 582, 585, 586, and 587), all of which are reported to be associated with arsenic exposure. ICD-9 code 189 includes both renal cell carcinoma and transitional cell carcinoma, so those conditions could not be separated for this analysis. "Chronic renal disease" combines related diseases such as chronic renal failure, unspecified renal failure, chronic glomerulonephritis, and renal sclerosis (18).

Statistical analysis

We estimated standardized mortality ratios (SMRs) for deaths occurring over the age of 30 years in Antofagasta by dividing the observed number of deaths by the expected number of deaths for each age group at potential first exposure: birth, 1–10 years, 11–20 years, 21–30 years, 31–40 years, and ≥41 years. Age at potential first exposure was identified on the basis of birth cohort: births occurring during 1958–1970 (the high-exposure period in Antofagasta), 1948–1957, 1938–1947, 1928–1937, 1918–1927, and before 1918. The expected number of deaths in Antofagasta was calculated on the basis of the population of the rest of Chile using indirect age standardization. Population data by age (in 10-year age groups) and sex were obtained from Chilean census data for 1992, 2002, and 2012 (T.R., National Statistics Institute of Chile, unpublished data, 2015) and were interpolated linearly to estimate person-years for Antofagasta and the rest of Chile in 2001–2010. Exact 95% confidence intervals and *P* values for the SMRs were calculated on the basis of the Poisson distribution. Average percent changes for trends in SMRs by age group at first exposure were evaluated using the linear Poisson regression model (22, 23). One-sided statistical tests were used because there is a clear direction in the hypothesis that arsenic increases mortality from the selected diseases. All statistical analyses were conducted with SAS software (version 9.4; SAS Institute, Inc., Cary, North Carolina).

RESULTS

Table 1 shows the SMRs for lung, bladder, kidney, and laryngeal cancers by age at potential first exposure and sex for 2001–2010, comparing Antofagasta with the rest of Chile. The highest lung cancer SMR among males was 5.0 (95% confidence interval (CI): 4.3, 5.8) for persons likely to have been first exposed to arsenic at ages 1–10 years. In women, the SMR for lung cancer was 5.1 (95% CI: 3.4, 7.3) when they had probably been exposed to arsenic at birth, and the risk remained elevated over all age groups, even when they were first exposed at age 41 years or older (SMR = 2.7, 95% CI: 1.6, 4.2). For men and women combined, the lung cancer SMRs gradually decreased with likely age of exposure, with an 11% reduction for each 10-year increase in age (*P* for trend < 0.001) (Figure 3).

Bladder cancer SMRs for men and women who were probably exposed very early in their lives were extremely high. For

people exposed at birth, the SMR was 16.8 (95% CI: 9.8, 27.0) in men and 13.6 (95% CI: 5.5, 27.9) in women. For men and women combined, the SMRs dropped at a rate of 17% for each 10-year increase in age (*P* for trend < 0.001) (Figure 3) but remained elevated in all groups of age at first exposure, within a range of 4–10. Laryngeal cancer showed a similar trend as bladder cancer when subjects were probably exposed starting in early life. Among cancer causes of death, laryngeal cancer showed the strongest relationship with age at first exposure, with a 23% reduction in SMRs for each 10-year increase in age at exposure (*P* for trend = 0.03) (Figure 3). SMRs for all of the cancers above combined were increased in all age groups at first exposure (Table 1).

Table 2 presents the SMRs for arsenic-related noncancer deaths in Antofagasta from bronchiectasis, acute myocardial infarction, and chronic renal disease. The SMRs for all of these diseases were elevated only when subjects had been exposed starting at younger ages. For bronchiectasis, mortality was greatly increased in the group probably exposed to arsenic in early life (at birth and ages 1–10 years). In fact, the SMR for bronchiectasis was not elevated for persons who were probably exposed to arsenic only at age 11 years or more. Mortality from acute myocardial infarction was increased in those exposed to high levels of arsenic before age 21 years. The SMR for chronic renal disease was highest in those exposed to arsenic before age 31 years. The SMRs for acute myocardial infarction and chronic renal failure decreased by 17% and 18%, respectively, for each 10-year increase in age at first exposure (*P* for trend < 0.001) (Figure 3). Mortality from all of these noncancer diseases combined was increased with exposure starting early in life. Mortality from all other noncancer diseases not associated with arsenic did not differ between Antofagasta and the rest of Chile in any age group at first exposure (Table 2).

DISCUSSION

We found especially strong relationships with age at first exposure for bladder cancer, laryngeal cancer, bronchiectasis, myocardial infarction, and chronic renal disease. Persons born during the high-exposure period (1958–1970) had a nearly 12-fold increase in mortality from bronchiectasis in 2001–2010 (SMR = 11.7, 95% CI: 4.3, 25.4), 30–40 years after the high exposure ceased. We previously reported that in the years 1989–2000, this same birth cohort had a bronchiectasis SMR of 46.2 (95% CI: 21.1, 87.7; *P* < 0.001) (19). Thus, 2 nonoverlapping studies with nonoverlapping mortality data both demonstrated an astonishingly increased risk of death from bronchiectasis following early-life arsenic exposure. Persons first exposed at ages 1–10 years had a 5-fold increased risk of mortality, but if exposure to arsenic did not start until after age 10 years, there was no meaningful increase in mortality from bronchiectasis (although the numbers were small and confidence intervals wide). In our previous study, we did not assess children with first exposure after age 10 years, and we are not aware of any other studies with data on age at first exposure that separated out persons first exposed only after age 10 years. The findings we report here suggest that arsenic may affect the growing lung, making it particularly susceptible to bronchiectasis in later years.

Table 1. Observed and Expected Numbers of Deaths and Standardized Mortality Ratios for Cancer According to Age at Potential First Exposure to High Levels of Arsenic in Drinking Water, Antofagasta[a], Chile, 2001–2010

Disease and Age at First Exposure, years	Total					Men					Women				
	Obs	Exp	SMR	95% CI	P Value[b]	Obs	Exp	SMR	95% CI	P Value	Obs	Exp	SMR	95% CI	P Value
Lung cancer															
Birth	57	15.1	3.8	2.9, 4.9	<0.001	27	9.3	2.9	1.9, 4.2	<0.001	30	5.9	5.1	3.4, 7.3	<0.001
1–10	237	52.4	4.5	4.0, 5.1	<0.001	178	35.8	5.0	4.3, 5.8	<0.001	59	17.4	3.4	2.6, 4.4	<0.001
11–20	417	101.6	4.1	3.7, 4.5	<0.001	328	69.2	4.7	4.2, 5.3	<0.001	89	32.9	2.7	2.2, 3.3	<0.001
21–30	457	122.1	3.7	3.4, 4.1	<0.001	322	77.7	4.1	3.7, 4.6	<0.001	135	43.1	3.1	2.6, 3.7	<0.001
31–40	176	62.6	2.8	2.4, 3.3	<0.001	112	33.8	3.3	2.7, 4.0	<0.001	64	27.6	2.3	1.8, 3.0	<0.001
≥41	28	13.6	2.1	1.4, 3.0	<0.001	9	5.6	1.6	0.7, 3.0	0.12	19	7.1	2.7	1.6, 4.2	<0.001
P for trend[c]			<0.001					0.001					0.006		
Bladder cancer															
Birth	24	1.5	16.0	10.3, 23.8	<0.001	17	1.0	16.8	9.8, 27.0	<0.001	7	0.5	13.6	5.5, 27.9	<0.001
1–10	35	4.8	7.4	5.1, 10.3	<0.001	28	3.5	7.9	5.3, 11.5	<0.001	7	1.3	5.3	2.2, 11.0	<0.001
11–20	59	9.3	6.3	4.8, 8.1	<0.001	32	6.7	4.8	3.3, 6.8	<0.001	27	2.7	9.9	6.5, 14.5	<0.001
21–30	112	16.6	6.7	5.5, 8.1	<0.001	65	11.1	5.9	4.5, 7.5	<0.001	47	5.3	8.8	6.5, 11.7	<0.001
31–40	80	15.6	5.1	4.1, 6.4	<0.001	39	8.8	4.4	3.1, 6.0	<0.001	41	6.4	6.4	4.6, 8.7	<0.001
≥41	22	5.3	4.2	2.6, 6.3	<0.001	13	2.6	4.9	2.6, 8.4	<0.001	9	2.5	3.6	1.6, 6.8	0.001
P for trend			<0.001					<0.001					0.01		
Kidney cancer															
Birth	8	6.2	1.3	0.6, 2.5	0.28	4	4.5	0.9	0.2, 2.3	0.50	4	1.8	2.2	0.6, 5.6	0.11
1–10	25	14.4	1.7	1.1, 2.6	0.007	18	10.8	1.7	1.0, 2.6	0.03	7	3.9	1.8	0.7, 3.7	0.10
11–20	49	21.5	2.3	1.7, 3.0	<0.001	32	15.3	2.1	1.4, 3.0	<0.001	17	6.4	2.6	1.5, 4.2	<0.001
21–30	46	26.1	1.8	1.3, 2.4	<0.001	29	16.7	1.7	1.2, 2.5	0.009	17	9.0	1.9	1.1, 3.0	0.01
31–40	38	14.1	2.7	1.9, 3.7	<0.001	16	7.4	2.2	1.2, 3.5	0.004	22	6.5	3.4	2.1, 5.1	<0.001
≥41	7	3.4	2.0	0.8, 4.2	0.06	3	1.5	2.0	0.4, 5.9	0.19	4	1.9	2.1	0.6, 5.4	0.12
P for trend			0.12					0.24					0.39		
Laryngeal cancer															
Birth	5	0.7	6.8	2.2, 15.8	0.001	3	0.6	4.8	1.0, 14.1	0.03	2	0.1	14.4	1.3, 51.9	0.009
1–10	6	2.6	2.3	0.8, 4.9	0.05	5	2.4	2.1	0.7, 4.8	0.10	1	0.3	3.3	0.1, 18.3	0.26
11–20	17	5.3	3.2	1.9, 5.1	<0.001	15	4.8	3.1	1.7, 5.1	<0.001	2	0.5	3.7	0.4, 13.2	0.10
21–30	12	7.6	1.6	0.8, 2.7	0.09	10	6.5	1.5	0.7, 2.8	0.12	2	1.0	2.1	0.3, 7.5	0.25
31–40	8	3.9	2.1	0.9, 4.1	0.04	6	3.0	2.0	0.7, 4.3	0.09	2	0.7	2.9	0.4, 10.6	0.15
≥41	1	0.8	1.3	0.1, 7.1	0.50	1	0.5	1.9	0.1, 10.3	0.42	0	0.2	0		
P for trend			0.03					0.18					0.06		
All cancers															
Birth	94	23.5	4.0	3.2, 4.9	<0.001	51	15.5	3.3	2.4, 4.3	<0.001	43	8.4	5.1	3.7, 6.9	<0.001
1–10	303	74.2	4.1	3.6, 4.6	<0.001	229	52.5	4.4	3.8, 5.0	<0.001	74	22.9	3.2	2.5, 4.1	<0.001
11–20	542	137.8	3.9	3.6, 4.3	<0.001	407	95.9	4.2	3.8, 4.7	<0.001	135	42.6	3.2	2.7, 3.8	<0.001
21–30	627	172.5	3.6	3.4, 3.9	<0.001	426	112.0	3.8	3.4, 4.2	<0.001	201	58.4	3.4	3.0, 4.0	<0.001
31–40	302	96.1	3.1	2.8, 3.5	<0.001	173	53.1	3.3	2.8, 3.8	<0.001	129	41.2	3.1	2.6, 3.7	<0.001
≥41	58	23.0	2.5	1.9, 3.3	<0.001	26	10.9	2.4	1.6, 3.5	<0.001	32	11.7	2.7	1.9, 3.9	<0.001
P for trend			<0.001					0.002					0.06		

Table continues

Bladder cancer also had a remarkably strong relationship to early-life exposure (for persons exposed from birth, SMR = 16.0, 95% CI: 10.3, 23.8). This finding is also consistent with our previously published findings for bladder cancer mortality in 1989–2000 (SMR = 18.1, 95% CI: 11.3, 27.4) (18). However, unlike bronchiectasis, bladder cancer mortality continued

Table 1. Continued

Disease and Age at First Exposure, years	Total					Men					Women				
	Obs	Exp	SMR	95% CI	*P* Value[b]	Obs	Exp	SMR	95% CI	*P* Value	Obs	Exp	SMR	95% CI	*P* Value
All other cancers															
Birth	278	238.8	1.2	1.0, 1.3	0.007	133	97.3	1.4	1.1, 1.6	<0.001	145	138.2	1.0	0.9, 1.2	0.29
1–10	454	389.2	1.2	1.1, 1.3	<0.001	239	170.0	1.4	1.2, 1.6	<0.001	215	216.9	1.0	0.9, 1.1	0.53
11–20	652	614.7	1.1	1.0, 1.1	0.07	353	308.8	1.1	1.0, 1.3	0.007	299	305.7	1.0	0.9, 1.1	0.64
21–30	833	803.2	1.0	1.0, 1.1	0.15	453	420.0	1.1	1.0, 1.2	0.06	380	378.5	1.0	0.9, 1.1	0.48
31–40	604	582.6	1.0	1.0, 1.1	0.19	305	274.9	1.1	1.0, 1.3	0.04	299	301.0	1.0	0.9, 1.1	0.53
≥41	166	189.5	0.9	0.7, 1.0	0.95	68	75.7	0.9	0.7, 1.1		98	112.3	0.9	0.7, 1.1	0.91
P for trend		0.001					<0.001					0.37			

Abbreviations: CI, confidence interval; Exp, expected number; Obs, observed number; SMR, standardized mortality ratio.

[a] All data presented for Antofagasta include neighboring Mejillones, which had the same water sources.

[b] One-sided *P* value for mortality being increased in Antofagasta as compared with the rest of Chile.

[c] Two-sided *P* value for linear trend in the SMRs for each 10-year increase in age at first exposure in Antofagasta.

to be increased for older ages at first exposure, even for first exposures after age 40 years (Table 1). The finding for laryngeal cancer was rather similar (for exposure from birth, SMR = 6.8, 95% CI: 2.2, 15.8), although increased risks were evident only if exposure started before age 41 years. Once again, we confirmed the earlier finding for mortality in 1989–2000 following exposure from birth (SMR = 8.1, 95% CI: 3.5, 16.0) (18).

Lung cancer SMRs were increased with all ages at first exposure, with a small trend downward by age, but kidney cancer showed an upward trend with age at first exposure (*P* for trend = 0.12). This finding could have been due to chance, but it was surprising since in 1989–2000 we reported a kidney cancer SMR of 3.5 (95% CI: 2.1, 5.4) for potential exposure from birth (18). Mortality from myocardial infarction and chronic renal disease both

Figure 3. Change in the standardized mortality ratio (SMR) for selected diseases per 10-year increase in age at first exposure to drinking water arsenic, Antofagasta, Chile, 2001–2010. Among cancers, the strongest relationship with age at first exposure was for cancer of the larynx, with a 23% reduction in the SMR for each 10-year increase in age (*P* for trend = 0.03). Among noncancer diseases, the strongest age relationship was for bronchiectasis, with a 49% reduction for each 10-year increase in age at first exposure (*P* for trend < 0.001). *P* values for trends are provided in Table 2. Bars, 95% confidence intervals. AMI, acute myocardial infarction; CRD, chronic renal disease.

trended downward with increasing age. Increased numbers of myocardial infarction deaths were only evident if exposure started before age 21 years, but some increase in chronic renal disease persisted with exposure starting at older ages.

The observed trends by age group at first exposure for bladder cancer, laryngeal cancer, bronchiectasis, myocardial infarction, and chronic renal disease were very strong and were beyond what could be attributed to unaccounted potential bias.

Our findings on lung and bladder cancer are consistent with the results of a previous case-control study of incident cancer we conducted in the same area (13). In a case-control study of 221 lung cancer patients and 160 bladder cancer patients with 508 matched controls from northern Chile for the years 2007–2010, we observed that the risks of lung and bladder cancer were elevated with early-life arsenic exposure in a dose-response manner (13). The trends with age of exposure in the case-control study were similar to those we report for cancer mortality here. For lung cancer, high odds ratios for males and females combined were seen in the case-control study for arsenic exposures incurred at birth and up to approximately age 20 years, with a gradual decline in odds ratios for exposures incurred at age 21 years and beyond. In this paper, for males and females combined, the highest SMRs were seen for ages 1–20 years, also with a decline in relative risk for exposure after these ages. For bladder cancer, the highest odds ratios in the case-control study were seen for exposure at birth, with a marked decrease in relative risk for exposure at older ages. A similar pattern was seen for mortality here, with the highest SMRs by far being seen for likely exposure at birth and markedly lower SMRs being seen for first exposure at older ages.

In this study, we considered the subjects exposed if they died in Antofagasta or Mejillones during 2000–2010 and were of ages at which they would have been born or lived in Antofagasta during the high-exposure period (1958–1970). Because our study design was ecological, we considered the possibility that exposure misclassification might have affected our results. As we mentioned above, the region of Chile containing Antofagasta (region II) receives very little rainfall, and there are very few water sources in the area. Because of this, essentially everyone
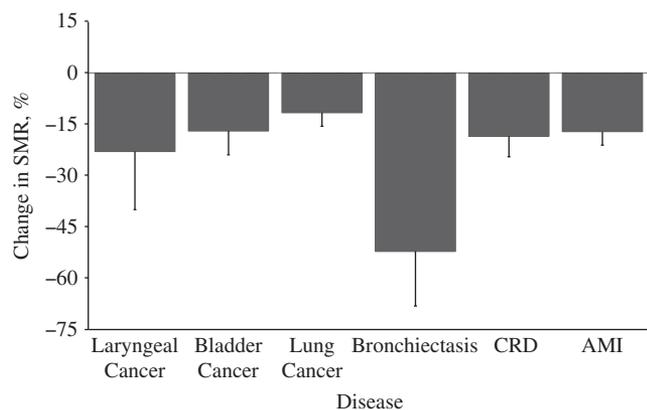
Table 2. Observed and Expected Numbers of Deaths and Standardized Mortality Ratios for Noncancer Diseases According to Age at Potential First Exposure to High Levels of Arsenic in Drinking Water, Antofagasta[a], Chile, 2001–2010

Disease and Age at First Exposure, years	Total					Men					Women				
	Obs	Exp	SMR	95% CI	P Value[b]	Obs	Exp	SMR	95% CI	P Value	Obs	Exp	SMR	95% CI	P Value
Bronchiectasis															
Birth	6	0.5	11.7	4.3, 25.4	<0.001	4	0.2	24.9	6.8, 63.7	<0.001	2	0.3	5.9	0.7, 21.3	0.05
1–10	3	0.6	5.4	1.1, 15.8	0.02	1	0.4	2.4	0.1, 13.5	0.34	2	0.2	13.2	1.6, 47.7	0.01
11–20	1	0.7	1.3	0.1, 7.5	0.50	1	0.4	2.6	0.1, 14.6	0.32	0	0.4	0		
21–30	2	1.7	1.2	0.1, 4.3	0.50	0	0.9	0			2	0.8	2.4	0.3, 8.8	0.20
31–40	0	2.0	0			0	0.8	0			0	1.2	0		
≥41	1	1.1	0.9	0.1, 5.1	0.50	1	0.4	2.6	0.1, 14.2	0.32	0	0.7	0		
P for trend[c]			<0.001					0.004					0.006		
Myocardial infarction															
Birth	94	51.5	1.8	1.5, 2.2	<0.001	74	44.4	1.7	1.3, 2.1	<0.001	20	9.2	2.2	1.3, 3.4	0.001
1–10	171	107.3	1.6	1.4, 1.9	<0.001	139	86.5	1.6	1.4, 1.9	<0.001	32	23.3	1.4	0.9, 1.9	0.05
11–20	231	188.2	1.2	1.1, 1.4	0.001	162	137.7	1.2	1.0, 1.4	0.02	69	51.9	1.3	1.0, 1.7	0.01
21–30	275	260.3	1.1	0.9, 1.2	0.19	181	158.9	1.1	1.0, 1.3	0.05	94	98.9	1.0	0.8, 1.2	0.33
31–40	220	228.6	1.0	0.8, 1.1	0.70	113	108.5	1.0	0.9, 1.3	0.34	107	117.5	0.9	0.7, 1.1	0.82
≥41	69	112.1	0.6	0.5, 0.8	0.99	27	36.7	0.7	0.5, 1.1	0.94	42	75.6	0.6	0.4, 0.8	0.99
P for trend			<0.001					<0.001					<0.001		
Chronic renal disease															
Birth	23	9.4	2.5	1.6, 3.7	<0.001	13	5.9	2.2	1.2, 3.8	0.008	10	3.6	2.8	1.3, 5.2	0.004
1–10	39	16.6	2.3	1.7, 3.2	<0.001	19	10.1	1.9	1.1, 2.9	0.008	20	6.7	3.0	1.8, 4.6	<0.001
11–20	60	34.1	1.8	1.3, 2.3	<0.001	33	19.2	1.7	1.2, 2.4	0.003	27	15.0	1.8	1.2, 2.6	0.003
21–30	106	61.5	1.7	1.4, 2.1	<0.001	54	32.2	1.7	1.3, 2.2	<0.001	52	28.8	1.8	1.3, 2.4	<0.001
31–40	77	61.0	1.3	1.0, 1.6	0.03	38	28.4	1.3	0.9, 1.8	0.05	39	31.9	1.2	0.9, 1.7	0.12
≥41	24	29.8	0.8	0.5, 1.2	0.83	10	10.9	0.9	0.4, 1.7	0.53	14	18.7	0.7	0.4, 1.3	0.84
P for trend			<0.001					0.02					<0.001		
All noncancer diseases															
Birth	123	61.3	2.0	1.7, 2.4	<0.001	91	50.5	1.8	1.5, 2.2	<0.001	32	13.1	2.4	1.7, 3.4	<0.001
1–10	213	124.5	1.7	1.5, 2.0	<0.001	159	97.0	1.6	1.4, 1.9	<0.001	54	30.2	1.8	1.3, 2.3	<0.001
11–20	292	223.1	1.3	1.2, 1.5	<0.001	196	157.2	1.2	1.1, 1.4	0.002	96	67.2	1.4	1.2, 1.7	<0.001
21–30	383	323.4	1.2	1.1, 1.3	<0.001	235	192.0	1.2	1.1, 1.4	0.001	148	128.5	1.2	1.0, 1.4	0.05
31–40	297	291.6	1.0	0.9, 1.1	0.38	151	137.7	1.1	0.9, 1.3	0.13	146	150.7	1.0	0.8, 1.1	0.63
≥41	94	143.0	0.7	0.5, 0.8	0.99	38	48.0	0.8	0.6, 1.1	0.92	56	95.0	0.6	0.4, 0.8	0.99
P for trend			<0.001					<0.001					<0.001		

Table continues

Table 2. Continued

Disease and Age at First Exposure, years	Total					Men					Women				
	Obs	Exp	SMR	95% CI	P Value[b]	Obs	Exp	SMR	95% CI	P Value	Obs	Exp	SMR	95% CI	P Value
All other noncancer diseases															
Birth	773	872.6	0.9	0.8, 1.0	0.99	546	710.1	0.8	0.7, 0.8	0.99	227	195.2	1.2	1.0, 1.3	0.01
1–10	957	911.6	1.0	1.0, 1.1	0.07	647	669.2	1.0	0.9, 1.0	0.80	320	260.0	1.2	1.1, 1.4	<0.001
11–20	1,412	1,284.7	1.1	1.0, 12	<0.001	888	839.9	1.1	1.0, 1.1	0.05	524	451.3	1.2	1.1, 1.3	<0.001
21–30	2,306	1,978.5	1.2	1.1, 1.2	<0.001	1,250	1,080.3	1.2	1.1, 1.2	<0.001	1,056	885.5	1.2	1.1, 1.3	<0.001
31–40	2,434	2,219.8	1.1	1.1, 1.1	<0.001	1,053	947.7	1.1	1.0, 1.2	<0.001	1,381	1,256.3	1.1	1.0, 1.2	<0.001
≥41	1,289	1,399.7	0.9	0.9, 1.0	0.99	353	417.3	0.8	0.8, 0.9	0.99	936	989.6	0.9	0.9, 1.0	0.96
P for trend			0.44					<0.001					<0.001		

Abbreviations: CI, confidence interval; Exp, expected number; Obs, observed number; SMR, standardized mortality ratio.

[a] All data presented for Antofagasta include neighboring Mejillones, which had the same water sources.

[b] One-sided *P* value for mortality being increased in Antofagasta as compared with the rest of Chile.

[c] Two-sided *P* value for linear trend in the SMRs for each 10-year increase in age at first exposure in Antofagasta.

who lived in Antofagasta during the high-exposure period received their drinking water from the single public water source supplying the city. Detailed records of historical arsenic water concentrations are available, including those from the high-exposure period, and until recently bottled water use was minimal (4). In a case-control study we are currently conducting among 296 participants who were living in region II before 1970, only 1 person reported using bottled water while residing in region II (17).

Consequently, if a person resided in Antofagasta during the high-exposure period, we can be assured that he or she was highly exposed to arsenic. A few other areas in the rest of Chile, the site of our comparison population, had measurable arsenic levels in drinking water, but these areas were relatively few, and none of the arsenic levels approached anything near those seen in Antofagasta. Because of this unique situation, operation of the ecological fallacy in our study is virtually inconceivable.

Migration is another issue we considered. Because we did not have people's full residential history, we could not account for people moving in and out of Antofagasta. However, both migration into and out of Antofagasta during our study period would most likely have biased our results towards the null, not towards the large SMRs we identified. In addition, the migration rate in Chile was low (only 0.6% per year) during the study period (18, 24).

Another potential concern is that the associations we identified might have been affected by confounding. For example, smoking is the main risk factor for bladder cancer, but it is not possible that our results for this cancer could have been due to confounding by smoking. In a meta-analysis based on 83 studies carried out in many different countries (25), the pooled relative risk of bladder cancer mortality for smokers versus nonsmokers was approximately 1.5. Given this, even if all subjects in Antofagasta were smokers and all subjects in the rest of Chile were nonsmokers (a highly improbable exaggerated scenario), the SMR due to confounding by smoking would only be around 1.5. However, our results showed that SMRs for bladder cancer were much higher (e.g., SMR = 16.0 in people potentially first exposed at birth). In fact, data from the Chile National Health Survey (26) and elsewhere show that smoking rates do not differ between region II and the rest of Chile (Table 3). In our previous paper, we also reported similar smoking patterns in region II and all of Chile, even showing lower smoking rates in region II in some years between 1990 and 2014 (17).

Overall, given the very high SMRs we identified and the fact that no major differences in smoking rates were observed between Antofagasta and the rest of Chile, we can conclude that the associations we identified here were not due to confounding by smoking. Relatively small differences in other demographic and risk factors were seen between region II and the rest of Chile (Table 3). In addition, there is no notable occupational or environmental exposure that is sufficiently prevalent or sufficiently strongly related to the outcomes we assessed to cause the very high SMRs we identified. Our previous lung and bladder cancer case-control study in this same area showed that age, sex, smoking, diet, occupational exposure, socioeconomic status, and obesity had little influence on the arsenic-cancer associations identified (13).

Some outcomes appeared to show differences in SMRs by sex. For example, the SMRs for laryngeal cancer in men were lower than those for women. However, there was considerable overlap in the confidence intervals. Additionally, the relative risks for men were lower because they had a much higher

Table 3. Distribution (%) of Demographic, Lifestyle-Related, and Medical Risk Factors for Mortality in Region II[a] and All of Chile, 2003–2010

Characteristic[b]	Region II	All of Chile
Demographic risk factors		
Female sex	48.1	51.1
Urban residence	97.7	91.6
Higher education (university/ professional)	17.0	14.0
Poverty-level SES	11.4	18.8
Lifestyle-related risk factors		
Current smoking	42.8	40.5
Passive tobacco smoke exposure	7.1	9.6
Tobacco smoking, cigarettes/day	7.7	10.4
Alcohol consumption, g/day	41.5	55.6
Fruit/vegetable consumption, g/day	174.0	186.0
Salt consumption, g/day	9.6	9.8
Regular physical activity[c]	13.8	10.6
Medical risk factors		
Average BMI[d]	27.2	27.4
Obesity (BMI ≥30)	24.7	25.1
Hypertension (BP ≥140/90 mm Hg)	21.1	26.9
Diabetes mellitus	9.3	9.4

Abbreviations: BMI, body mass index; BP, blood pressure; SES, socioeconomic status.

[a] Antofagasta is the second-largest city in Chile, and combined with Mejillones, its population accounts for more than 65% of the population of region II.

[b] Data were obtained from the Ministry of Health (2010) (26), the National Statistics Institute (2003) (30), the Ministry of Health (2003) (31), and the Ministry of Planning and Cooperation (2004) (32).

[c] Engaging in physical activity for at least 30 minutes 3 or more times per week.

[d] Weight (kg)/height (m)^2.

background rate of laryngeal cancer (2.86 deaths per 100,000 in men and 0.41 deaths per 100,000 in women for the rest of Chile) due to smoking and alcohol drinking, which are major risk factors for laryngeal cancer.

In this study, for most outcomes we found higher relative risks for exposures occurring in early life, and there are several plausible mechanisms that may explain this finding. The fetus and young children may have undeveloped immune systems and may undergo metabolic, excretory, and other pharmacokinetic processes that decrease their ability to counteract early toxic effects (27). They have greater exposure per body weight for a given level of toxicant in water, and rapid organ growth also makes them more vulnerable to toxicants (27). In addition, molecular changes, including epigenetic modification, may result in increased risk of diseases in later life (28, 29). We found that age was an effect modifier in diseases associated with arsenic exposure 30–40 years after cessation. Cancer mortality remained elevated with exposure commencing at older ages, although mortality from most noncancer diseases was increased during this

period only in people who had early-life arsenic exposure. For bronchiectasis, bladder cancer, and laryngeal cancer, young age at first exposure was associated with major increases in mortality in adults.

Overall, the findings we present here for the 2001–2010 period, combined with the very high SMRs associated with early-life exposure we previously published for the 1989–2000 period (14–20), provide strong evidence that the fetus and young children are particularly susceptible to arsenic exposure. Millions of people worldwide are exposed to high concentrations of arsenic in drinking water. Although attempts should be made to decrease these exposures in all population groups, our results suggest that reducing exposures in pregnant women and young children could have major impacts on reducing the long-term mortality risks from arsenic, even 30–40 years after exposure.

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