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Original Contribution

Acute Myocardial Infarction Mortality in Comparison with Lung and Bladder Cancer Mortality in Arsenic-exposed Region II of Chile from 1950 to 2000

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Arsenic in drinking water is known to be a cause of lung, bladder, and skin cancer, and some studies report cardiovascular disease effects. The authors investigated mortality from 1950 to 2000 in the arsenic-exposed region II of Chile (population: 477,000 in 2000) in comparison with the unexposed region V. Increased risks were found for acute myocardial infarction (AMI), with mortality rate ratios of 1.48 for men (95% confidence interval (CI): 1.37, 1.59; $p < 0.001$) and 1.26 for women (95% CI: 1.14, 1.40; $p < 0.001$) during the high-exposure period in region II from 1958 to 1970. The highest rate ratios were for young adult men aged 30–49 years who were born during the high-exposure period with probable exposure in utero and in early childhood (rate ratio = 3.23, 95% CI: 2.79, 3.75; $p < 0.001$). Compared with lung and bladder cancer, AMI mortality was the predominant cause of excess deaths during and immediately after the high-exposure period. Ten years after reduction of exposures, AMI mortality had decreased, and longer latency excess deaths from lung and bladder cancer predominated. With these three causes of death combined, increased mortality peaked in 1991–1995, with estimated excess deaths related to arsenic exposure constituting 10.9% of all deaths among men and 4.0% among women.

arsenic; Chile; lung neoplasms; mortality; myocardial infarction; urinary bladder neoplasms; water

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; ICD-9, *International Classification of Diseases,* Ninth Revision; ICD-10, *International Classification of Diseases,* Tenth Revision; RR, rate ratio.

Arsenic in drinking water is classified as carcinogenic to humans by the International Agency for Research on Cancer on the basis of evidence that it causes skin, lung, and bladder cancer (1). Chronic exposure to arsenic in drinking water is also linked to an increased risk of various noncancer health outcomes including dermal, reproductive, pulmonary, and neurologic effects (2, 3). The first evidence of cardiovascular disease associated with arsenic in drinking water came from Antofagasta in region II of Chile, with a case series of 17 deaths from myocardial infarction reported in subjects under the age of 40 years (4). Later evidence mainly from Taiwan suggested that long-term arsenic ingestion may be associated with increased risk of circulatory disease mortality, including cardiovascular disease (5, 6), ischemic heart disease (7–12), cerebrovascular disease (10, 13), and diseases of the arteries, arterioles, and capillaries (14).

Region II of Chile, which had a population of 477,000 in 2000, is unique in the world for investigating the long-term health effects of arsenic in drinking water. One reason is that almost all drinking water in this region is supplied by a few

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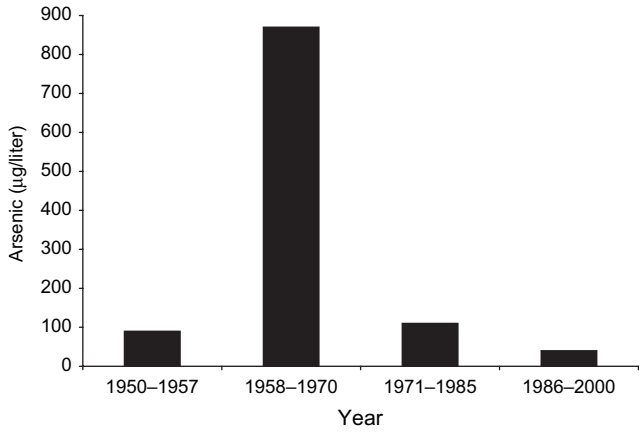

FIGURE 1. Arsenic concentrations (μg/liter) in drinking water before and after an arsenic removal plant was installed in 1971 for Antofagasta and Mejillones (region II), Chile, 1950–2000.

large municipal water sources, with known arsenic concentrations for the past 50 years. This is in contrast to other countries with high arsenic exposures, such as Argentina, Bangladesh, China, India, Taiwan, and the United States, where high arsenic exposures come primarily from wells. Assessing exposure in these areas is extremely difficult because of the large number of wells, the high variability in arsenic concentrations from well to well, and the general lack of historical arsenic measurements.

The second unique aspect of arsenic exposure in region II is that it involves a large population with a rapid onset of very high arsenic exposure when rivers contaminated with arsenic began to be used. Exposure was later sharply reduced around 1971 when installation of water treatment plants began. This situation has not been seen before, will probably never recur, and offers an important opportunity to study the health impacts of arsenic. More than half of region II's population live in Antofagasta and Mejillones (current population: 318,000) and were exposed to levels of arsenic greater than 850 μg/liter for a 13-year period (1958–1970) (figure 1).

We recently reported on lung and bladder cancer mortality in region II from 1950 to 2000 (15). We showed that mortality rates from these cancers started to increase about 10 years after the high exposures commenced and did not peak until about 20 years after the start of reductions in exposure. The purpose of this study was to investigate circulatory disease mortality in region II before, during, and after the period of very high arsenic exposure and to compare this mortality with that from lung and bladder cancer, the two major established causes of mortality from arsenic in drinking water. The a priori hypothesis was that circulatory disease mortality might be increased with arsenic exposure, in particular, mortality from acute myocardial infarction (AMI). Our aim was to investigate the latency patterns between onset and decline of exposure and increased circulatory disease mortality. We also planned to assess separately those with in utero and early childhood exposure and those exposed only as adults.

MATERIALS AND METHODS

Exposure data

Details concerning the arsenic concentrations in water in region II have been reported previously (16–18). As shown in figure 1, prior to 1958, the drinking water supply in the major city of Antofagasta had an arsenic concentration of about 90 μg/liter. A growing population and increased need for water led to supplementation of Antofagasta's water supply with water from the Toconce and the Holajar rivers that had arsenic concentrations of 800 μg/liter and 1,300 μg/liter, respectively. The concentration of arsenic in Antofagasta's drinking water, along with that of Mejillones which shared the same supply, increased in 1958 to an average of 870 μg/liter. About 90 percent of the population of region II lives in cities and towns. The other towns in the region, with the exception of Taltal, also had high concentrations of arsenic in their drinking water for various overlapping periods. The population-weighted average arsenic concentration in drinking water for the entire region was about 580 μg/liter for about 13 years from 1958 to 1970 (16). With the introduction in 1971 of a water treatment plant, Antofagasta's water arsenic concentration dropped to about 110 μg/liter, and further reductions occurred as a result of treatment plant improvements. In recent years, Antofagasta's water contained about 40 μg of arsenic per liter (16, 17), and the concentration is now below 10 μg/liter, which is the World Health Organization guideline for arsenic in drinking water. Other cities and towns also implemented water treatment strategies or used alternative sources to reduce arsenic levels. By the late 1980s, almost all of the towns with populations over 1,000 had water arsenic concentrations of less than 100 μg/liter. The exception was San Pedro de Atacama (population: 3,700), which has only recently had an arsenic removal plant installed. In contrast, water sources in the rest of Chile have had low levels of arsenic, generally less than 10 μg/liter. The major city of the comparison region V population, Valparaíso, has water concentrations close to 1 μg/liter (18).

Selection of the comparison population

Electronically stored mortality data were not available for Chile from 1950 to 1970. It was impractical and prohibitively expensive for the study team to nosologize all of the death certificates for Chile for these years. Because of this, it was necessary to select an alternative referent population to span the whole study period, 1950–2000. It was desirable that the referent population be significantly larger than that of region II, in order to maximize statistical precision. After careful consideration, region V, with a population about four times that of region II, was selected. In 1980, the population of region II was 314,807, while the population of region V was 1,230,498. This ratio has been similar throughout the study period of 1950–2000.

TABLE 1. Numbers of circulatory disease deaths and person-years at risk for adults aged 20 years or above in region II (exposed) and region V (unexposed), Chile, 1950–2000

	Mortality, 1950–1957		Mortality, 1958–1970		Mortality, 1971–1985		Mortality, 1986–2000	
	Region II	Region V	Region II	Region V	Region II	Region V	Region II	Region V
Male person-years	472,234	1,379,972	824,258	2,760,739	1,218,962	4,253,502	1,938,205	6,297,084
Male deaths								
All circulatory diseases	1,803	7,052	3,656	13,467	4,362	18,338	4,604	21,425
Hypertensive disease	243	760	295	963	171	717	230	1,384
Ischemic heart disease	442	1,638	1,496	4,459	2,090	7,228	2,360	9,361
Acute myocardial infarction	321	1,253	1,352	3,618	1,592	5,204	1,736	6,686
Cerebrovascular disease	372	1,589	897	3,805	1,121	5,720	1,153	6,386
Cerebral hemorrhage	274	1,242	409	1,714	300	1,391	381	1,812
Cerebral infarction	67	250	445	1,796	658	3,443	599	3,520
Diseases of arteries, arterioles, and capillaries	208	865	461	1,703	372	1,466	268	965
Female person-years	383,571	1,524,899	755,882	3,106,392	1,201,699	4,805,893	1,892,032	7,034,334
Female deaths								
All circulatory diseases	1,375	6,947	2,508	13,673	3,540	19,003	4,082	21,762
Hypertensive disease	260	898	312	1,311	182	948	287	1,859
Ischemic heart disease	205	1,037	700	3,268	1,304	6,079	1,597	8,228
Acute myocardial infarction	141	770	576	2,332	804	3,608	862	5,185
Cerebrovascular disease	255	1,830	727	4,415	1,132	7,061	1,298	7,369
Cerebral hemorrhage	181	1,424	324	1,967	238	1,688	376	1,876
Cerebral infarction	61	304	373	2,082	744	4,151	702	4,244
Diseases of arteries, arterioles, and capillaries	168	930	329	1,882	363	1,863	260	1,021

To ensure that region V was an appropriate choice, preliminary investigations were conducted to compare per capita income, smoking rates, and death certification among region II, region V, and national data for the whole of Chile. Per capita income in region V in 1990 was similar to that of the rest of the country (US $2,053 vs. US $2,011). Region II had higher per capita income (US $3,853), but this was the result of exports generated by the mining industry rather than signifying higher personal income. Smoking surveys were carried out on random population samples in 1990 and 1992, both years giving similar data. In 1990, 26.6 percent of men and 19.3 percent of women in Chile said they smoked. The corresponding percentages from regions II and V were similar: 27.4 percent and 28.5 percent for men and 16.6 percent and 20.2 percent for women, respectively (19). We also obtained information concerning death certification by health services regions in the country from a study conducted in 1983 (20). For the whole country, 85.6 percent of the death certificates in that year were certified by a physician. The corresponding percentages in regions II and V were 89.8 percent and 94.5 percent. Thus, the large majority of death certificates were completed by physicians, with both region II and region V having a higher percentage than the national average. The information above gave assurance that region V was a suitable referent population for two major determinants of cardiovascular morality, socioeconomic status and cigarette smoking, and that it was also a suitable referent population based on quality of death certification.

Mortality data collection

For the years 1950–1970, all the death certificates for region II and region V were photographed, displayed on computer monitors, and coded by trained nosologists according to the *International Classification of Diseases*, Ninth Revision (ICD-9). Death certificates from both regions were intermingled, and nosologists were kept blind as to the region from which each death certificate originated. Computerized mortality data first became available in Chile in 1971. These data, already coded to ICD-9 for all regions of Chile for the years 1971–1979 (excluding 1976), were obtained from the Chilean National Institute of Statistics (Instituto Nacional Estadisticas). For 1976, the information that is normally stored on computer disk at the Institute was never completed because of political unrest in the country. Mortality data for all regions of Chile for the years 1980–2000 were obtained from the Ministry of Health. ICD-9 codes had been used for 1980–1998, and *International Classification of Diseases*, Tenth Revision (ICD-10), codes had been used for 1999 and 2000. These codes were used to group cause-specific mortality into diseases of the circulatory system (ICD-9 codes 390–459; ICD-10 codes I00–I99); hypertensive disease (ICD-9 codes 401–405; ICD-10 codes

TABLE 2. Age-adjusted rate ratios for circulatory disease mortality for region II (exposed) compared with region V (unexposed), Chile, for 1950–1957 (before the peak exposures in region II), 1958–1970 (the peak exposure period), 1971–1985 (after an arsenic removal plant was installed in the major city of Antofagasta), and 1986–2000

	Mortality, 1950–1957			Mortality, 1958–1970			Mortality, 1971–1985			Mortality, 1986–2000		
	Rate ratio	95% confidence interval	*p* value	Rate ratio	95% confidence interval	*p* value	Rate ratio	95% confidence interval	*p* value	Rate ratio	95% confidence interval	*p* value
Males												
All circulatory diseases	0.90	0.82, 0.99	0.03	1.09	1.06, 1.12	<0.001	1.11	1.06, 1.16	<0.001	1.03	0.98, 1.08	0.28
Hypertensive disease	1.15	0.98, 1.35	0.08	1.25	1.06, 1.46	<0.01	1.12	0.98, 1.28	0.08	0.84	0.70, 1.00	0.06
Ischemic heart disease	0.93	0.81, 1.07	0.31	1.34	1.22, 1.47	<0.001	1.35	1.24, 1.48	<0.001	1.21	1.05, 1.39	<0.01
Acute myocardial infarction	0.88	0.74, 1.03	0.11	1.48	1.37, 1.59	<0.001	1.41	1.27, 1.56	<0.001	1.21	1.00, 1.47	0.05
Cerebrovascular disease	0.81	0.68, 0.97	0.02	0.95	0.87, 1.03	0.22	0.91	0.81, 1.03	0.13	0.86	0.81, 0.92	<0.001
Cerebral hemorrhage	0.75	0.65, 0.88	<0.001	0.94	0.84, 1.05	0.25	0.94	0.84, 1.05	0.28	0.90	0.78, 1.04	0.16
Cerebral infarction	0.97	0.73, 1.30	0.86	1.01	0.90, 1.13	0.87	0.91	0.76, 1.07	0.25	0.85	0.78, 0.91	<0.001
Diseases of arteries, arterioles, and capillaries	0.94	0.73, 1.21	0.64	1.14	0.96, 1.36	0.14	1.25	1.04, 1.49	0.02	1.40	1.07, 1.83	0.01
Females												
All circulatory diseases	0.96	0.86, 1.07	0.50	0.94	0.90, 0.99	0.02	1.01	0.97, 1.05	0.61	1.01	0.95, 1.08	0.73
Hypertensive disease	1.42	1.27, 1.59	<0.001	1.24	1.15, 1.33	<0.001	1.05	0.93, 1.20	0.42	0.85	0.69, 1.03	0.10
Ischemic heart disease	0.96	0.73, 1.25	0.75	1.11	0.99, 1.24	0.08	1.18	1.12, 1.24	<0.001	1.06	0.93, 1.22	0.37
Acute myocardial infarction	0.88	0.67, 1.14	0.33	1.26	1.14, 1.40	<0.001	1.21	1.11, 1.31	<0.001	0.90	0.71, 1.14	0.37
Cerebrovascular disease	0.67	0.61, 0.73	<0.001	0.84	0.79, 0.90	<0.001	0.86	0.81, 0.92	<0.001	0.94	0.86, 1.03	0.16
Cerebral hemorrhage	0.60	0.55, 0.66	<0.001	0.82	0.74, 0.92	<0.01	0.72	0.64, 0.81	<0.001	0.98	0.89, 1.08	0.72
Cerebral infarction	0.99	0.78, 1.27	0.95	0.93	0.86, 1.01	0.10	0.97	0.91, 1.04	0.46	0.90	0.80, 1.02	0.10
Diseases of arteries, arterioles, and capillaries	0.95	0.80, 1.14	0.59	0.95	0.84, 1.07	0.36	1.10	0.91, 1.33	0.33	1.42	1.19, 1.69	<0.001

I10–I15); ischemic heart disease (ICD-9 codes 410–414; ICD-10 codes I20–I25); AMI (ICD-9 code 410; ICD-10 codes I21–I22); cerebrovascular disease (ICD-9 codes 430–438; ICD-10 codes I60–I69); subarachnoid and intracerebral hemorrhage (ICD-9 codes 430–432; ICD-10 codes I60–I62); cerebral infarction (ICD-9 codes 434 and 436; ICD-10 code I63); and diseases of the arteries, arterioles, and capillaries (ICD-9 codes 440–448; ICD-10 codes I70–I78).

Annual estimates of the population living in regions II and V stratified by age and gender for the period 1950–2000 were obtained from the National Institute of Statistics. The estimates were obtained by linear interpolation between census data collected approximately every 10 years.

Statistical analysis

To investigate the temporal relation of mortality to changes in the concentration of arsenic, we categorized calendar years into four time periods on the basis of period of high exposure in region II: 1950–1957 (preexposure), 1958–1970 (high exposure), 1971–1985 (intermediate exposure), and 1986–2000 (low exposure). We estimated mortality rate ratios using Poisson regression analysis for each cause of death, comparing region II with region V in each exposure time period for men and women separately and age adjusted in 10-year age strata from 20 to greater than 80 years.

Poisson regression analysis was performed using the PROC GENMOD procedure provided in SAS, version 8.2, software (SAS Institute, Inc., Cary, North Carolina). Analyses were conducted with the link function as the log and the offset as the log of the total population in each region, sex, and age stratum. To further help identify the trends in mortality rate ratios, we calculated and plotted 5-year Poisson regression rate ratios for the entire study period, 1950–2000.

A separate analysis was done to evaluate the impacts of early life arsenic exposure on the risks of AMI mortality later in life. To do this, we defined two birth cohorts based on the high-exposure period in region II (1958–1970): those born during the high-exposure period and those born in 1950–1957, just before the high-exposure period. Those born during the high-exposure period would have experienced exposure in utero, as well as early childhood, while those born just before 1958 would have experienced high exposure during childhood but not in utero. In this analysis, we focused on the age group 30–49 years, since all of these subjects would be aged 50 years or younger by the end of our study period (the year 2000). For the years 1989–2000, deaths and population estimates were available for two major cities in region II, Antofagasta and Mejillones, which had the highest arsenic exposure. We therefore were able to compare mortality rates in Antofagasta and Mejillones with those of region V, using Poisson regression estimation of rate ratios, and also with the rest of Chile using standardized

mortality ratios, since computerized mortality data were available for the whole county for these years.

The numbers of excess deaths due to AMI, lung cancer, and bladder cancer in region II for the years 1950–2000 were estimated. We grouped 1950–1957 because it was the preexposure period. The high-exposure period 1958–1970 was divided roughly in half into two periods, 1958–1964 and 1965–1970. We first estimated rate ratios for AMI, lung cancer, and bladder cancer, comparing region II with region V in each grouped time period for men and women separately, and age adjusted in 10-year age strata from age 20 to age 80 years or more using Poisson regression analysis. Then, the estimated numbers of excess deaths for each cause of death were calculated for each grouped time period: ((rate ratio (RR) − 1)/RR) × N, where N is the total number of deaths from the cause of death in that time period in region II.

RESULTS

Table 1 presents the numbers of the circulatory disease deaths and person-years at risk. The age-adjusted mortality rate ratios comparing region II with region V are shown in table 2 for men and women separately. The mortality rates for AMI in region II were increased during the high-exposure period 1958–1970 (men: RR = 1.48, 95 percent confidence interval (CI): 1.37, 1.59 ($p < 0.001$); women: RR = 1.26, 95 percent CI: 1.14, 1.40 ($p < 0.001$)). Region II rates remained elevated during the immediate postexposure period 1971–1985 (men: RR = 1.41, 95 percent CI: 1.27, 1.56 ($p < 0.001$); women: RR = 1.21, 95 percent CI: 1.11, 1.31 ($p < 0.001$)) and then gradually decreased during the final study period 1986–2000 (men: RR = 1.21, 95 percent CI: 1.00, 1.47 ($p = 0.05$); women: RR = 0.90, 95 percent CI: 0.71, 1.14 ($p = 0.37$)). Figure 2 presents the time pattern using 5-year mortality rate ratio estimates.

Hypertensive disease mortality in men increased during the high-exposure period 1958–1970 (RR = 1.25, 95 percent CI: 1.06, 1.46 ($p < 0.01$)) and then gradually decreased during the intermediate-exposure period 1971–1985 (RR = 1.12, 95 percent CI: 0.98, 1.28 ($p = 0.08$)) (table 2). The temporal relation between arsenic exposure and hypertensive disease mortality was not evident in women. Rate ratios for cerebrovascular disease mortality were not increased in region II for any time period. Indeed, the rate ratios for cerebral hemorrhage in region II were reduced in all study periods, especially among women, without evidence of a temporal pattern related to arsenic exposure. Increases in mortality from diseases of the arteries, arterioles, and capillaries—which includes peripheral vascular disease—can be seen among men and women, especially in the final period 1986–2000.

Table 3 presents AMI rate ratios by age group. Leaving aside the age group 20–29 years that involves small numbers, there was a general pattern of an inverse relation of rate ratios with age in the high-exposure and following time periods. The highest rate ratios among both men and women were for the age group 30–39 years.

We next estimated rate ratios comparing Antofagasta and Mejillones with region V for AMI mortality in two birth cohorts, those born in 1950–1957 just before the high-exposure period and those born in 1958–1970 during the high-exposure period, for ages at death of 30–39 and 40–49 years separately and combined and for men and women separately (table 4). Compared with those for region V, the rate ratios for Antofagasta and Mejillones men aged 30–49 years were increased for those born in the period 1950–1957 (RR = 2.56, 95 percent CI: 1.26, 5.18 ($p < 0.001$)) and those born in the period 1958–1970 (RR = 3.23, 95 percent CI: 2.79, 3.75 ($p < 0.001$)). Table 4 also shows standardized mortality ratios comparing Antofagasta and Mejillones with the rest of Chile, with findings similar to the comparisons with region V. For men born in 1950–1957, the standardized mortality ratio for those aged 30–49 years was 2.51 compared with a rate ratio of 2.56 for the comparison with region V. For men born in 1958–1970, the standardized mortality ratio was 2.72 compared with a rate ratio of 3.23 for the comparison with region V. The relative risk estimates for females are generally lower than the estimates for men,

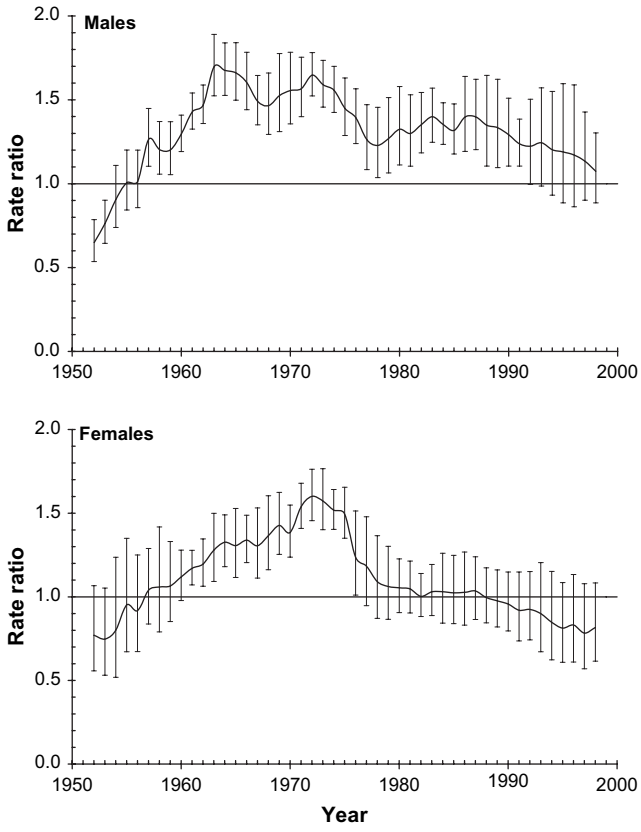

FIGURE 2. Age-adjusted mortality rate ratios and 95% confidence intervals for acute myocardial infarction for males and females, region II (exposed) compared with region V (unexposed), Chile, 1950–2000. Each point represents an estimate for 5 years and is plotted at the midpoint of the 5-year period, starting with the estimate for 1950–1954, which is plotted at the year 1952. (Note: The years 1950–1957 were prior to exposure, followed by high exposure from 1958 to 1970. During 1971–1985, there was intermediate exposure, and in 1986–2000, low exposure.)

TABLE 3. Numbers of deaths from acute myocardial infarction and rate ratios according to sex and age for region II (exposed) compared with region V (unexposed), Chile, for 1950–1957 (before the peak exposures in region II), 1958–1970 (the peak exposure period), 1971–1985 (after an arsenic removal plant was installed in the major city of Antofagasta), and 1986–2000

	Mortality, 1950–1957					Mortality, 1958–1970					Mortality, 1971–1985					Mortality, 1986–2000				
	Region II deaths	Region V deaths	Rate ratio	95% confidence interval	*p* value	Region II deaths	Region V deaths	Rate ratio	95% confidence interval	*p* value	Region II deaths	Region V deaths	Rate ratio	95% confidence interval	*p* value	Region II deaths	Region V deaths	Rate ratio	95% confidence interval	*p* value
Males (years)																				
20–29	6	11	1.43	0.53, 3.86	0.48	10	22	1.41	0.67, 2.98	0.36	10	16	1.98	0.90, 4.35	0.09	8	17	1.42	0.61, 3.30	0.41
30–39	14	50	0.80	0.44, 1.44	0.46	57	77	2.27	1.61, 3.20	<0.001	43	65	2.08	1.42, 3.06	<0.001	49	65	2.14	1.48, 3.10	<0.001
40–49	59	162	1.13	0.84, 1.52	0.42	151	313	1.65	1.36, 2.00	<0.001	139	297	1.61	1.31, 1.97	<0.001	157	229	2.07	1.69, 2.54	<0.001
50–59	80	282	0.89	0.70, 1.15	0.37	297	758	1.47	1.29, 1.68	<0.001	337	804	1.66	1.46, 1.89	<0.001	339	839	1.46	1.29, 1.66	<0.001
60–69	91	399	0.74	0.59, 0.93	0.01	406	1,150	1.41	1.26, 1.58	<0.001	435	1,455	1.37	1.24, 1.53	<0.001	497	1,735	1.27	1.15, 1.41	<0.001
70–79	64	256	1.01	0.77, 1.33	0.93	328	934	1.47	1.30, 1.67	<0.001	398	1,666	1.24	1.11, 1.39	<0.001	465	2,177	1.12	1.02, 1.24	0.02
≥80	7	93	0.43	0.20, 0.92	0.03	103	364	1.35	1.09, 1.69	<0.01	230	901	1.31	1.14, 1.52	<0.001	221	1,624	0.80	0.70, 0.92	<0.01
Females (years)																				
20–29	5	10	1.77	0.60, 5.17	0.30	6	16	1.37	0.53, 3.49	0.52	1	6	0.58	0.07, 4.80	0.61	4	0			
30–39	7	33	0.81	0.36, 1.84	0.62	20	30	2.51	1.43, 4.42	<0.01	12	24	1.80	0.90, 3.59	0.10	5	12	1.36	0.48, 3.87	0.56
40–49	8	67	0.50	0.24, 1.03	0.06	38	135	1.20	0.84, 1.72	0.32	31	117	1.07	0.72, 1.60	0.72	34	89	1.37	0.92, 2.03	0.12
50–59	37	130	1.27	0.88, 1.84	0.19	98	339	1.38	1.10, 1.72	<0.01	81	316	1.19	0.93, 1.52	0.16	79	285	1.16	0.90, 1.49	0.25
60–69	31	223	0.65	0.45, 0.95	0.02	142	631	1.15	0.96, 1.38	0.14	196	772	1.36	1.17, 1.60	<0.001	223	846	1.30	1.12, 1.50	<0.001
70–79	33	213	0.81	0.56, 1.17	0.26	162	693	1.22	1.03, 1.44	0.03	262	1,177	1.24	1.09, 1.42	<0.01	247	1,656	0.83	0.73, 0.95	<0.01
≥80	20	94	1.26	0.78, 2.04	0.36	110	488	1.32	1.07, 1.63	<0.01	221	1,196	1.08	0.93, 1.24	0.31	270	2,297	0.69	0.61, 0.79	<0.001

TABLE 4. Rate ratios* and standardized mortality ratios† for acute myocardial infarction mortality in the years 1989–2000 for children born in 1950–1957 and in 1958–1970, the peak exposure periods in Antofagasta and Mejillones, Chile

	Born in 1950–1957					Born in 1958–1970				
	Region II deaths	Region V deaths	Rate ratio	95% confidence interval	*p* value	Region II deaths	Region V deaths	Rate ratio	95% confidence interval	*p* value
Antofagasta and Mejillones (region II) vs. region V										
Males (years)										
30–39	6	28	1.11	0.46, 2.68	0.82	18	28	3.32	1.84, 6.01	<0.001
40–49	47	81	3.06	2.14, 4.39	<0.001	2	4	2.61	0.48, 14.2	0.27
Pooled	53	109	2.56	1.26, 5.18	<0.001	20	32	3.23	2.79, 3.75	<0.001
Females (years)										
30–39	0	5	0			2	6	1.95	0.39, 9.68	0.41
40–49	8	33	1.47	0.68, 3.18	0.33	0	0			
Pooled	8	38	1.27	0.55, 2.94	0.57	2	6	1.95	0.39, 9.68	0.41
	Born in 1950–1957					Born in 1958–1970				
	Observed deaths	Expected deaths	Standardized mortality ratio	95% confidence interval	*p* value	Observed deaths	Expected deaths	Standardized mortality ratio	95% confidence interval	*p* value
Antofagasta and Mejillones vs. the rest of Chile										
Males (years)										
30–39	6	3.73	1.61	0.59, 3.50	0.17	18	6.11	2.94	1.74, 4.65	<0.001
40–49	47	16.7	2.81	2.06, 3.73	<0.001	2	1.24	1.62	0.20, 5.84	0.35
Pooled	53	21.1	2.51	1.88, 3.29	<0.001	20	7.35	2.72	1.66, 4.20	<0.001
Females (years)										
30–39	0	0.86	0			2	1.34	1.49	0.18, 5.38	0.39
40–49	8	4.59	1.74	0.75, 3.43	0.09	0	0.16	0		
Pooled	8	5.58	1.43	0.62, 2.83	0.20	2	1.51	1.33	0.16, 4.80	0.44

* Rate ratios for Antofagasta and Mejillones compared with region V.
† Standardized mortality ratios for Antofagasta and Mejillones compared with the rest of Chile.

but it should be noted that the upper limits of the confidence intervals of the estimates for women are very high.

Table 5 shows the estimated numbers of excess deaths from AMI, lung cancer, and bladder cancer in region II for the years 1950–2000. During the study period, 38 percent of the excess deaths in men and 32 percent in women were from AMI. Figure 3 shows the number of those excess deaths divided by all deaths. From 1958 to 1979, the majority of excess deaths among both men and women were from AMI. After 1979, the excess deaths associated with AMI decreased, while those associated with lung cancer and bladder cancer continued to increase and remained elevated up to the year 2000. Table 5 also presents the percentage of all deaths estimated to be excess deaths attributable to arsenic. For both men and women, the peaks were in the period 1991–1995, more than 30 years after the high exposures commenced and about 20 years after the installation of an arsenic removal plant for Antofagasta and Mejillones. The peak for men was 10.9 percent, which means that just over one of 10 deaths among men in the period 1991–1995 is attributable to arsenic in drinking water, assuming a causal relation and no bias. The peak for women was lower, reaching 4 percent of all deaths in 1991–1995, suggesting that one of 25 deaths among women might be attributable to arsenic.

DISCUSSION

This 50-year mortality study has demonstrated a clear increase in deaths from AMI, with increased risks at the same time that high exposures to arsenic in drinking water started and declining risks about 10 years after exposures were reduced (figure 2). We believe this is an important addition to the body of evidence linking increased mortality from AMI with arsenic in drinking water (4, 7–12), and it is the first study to map out latency from onset of exposure. The study is by far the largest to date on circulatory disease mortality, with more than 8,000 AMI deaths in the exposed population, over 10 times more than those in the largest study in Taiwan. This is also the first study to show that excess AMI deaths predominated during the high-exposure period and for about 10 years thereafter (figure 3). Later,

TABLE 5. Excess deaths due to acute myocardial infarction, lung cancer, and bladder cancer for males and females, region II (exposed) compared with region V (unexposed), Chile, for the preexposure period 1950–1957, high-exposure period 1958–1970, intermediate-exposure period 1971–1985, and low-exposure period 1986–2000

Years	Total deaths	Excess deaths due to acute myocardial infarction	Excess deaths due to lung cancer	Excess deaths due to bladder cancer	Total excess deaths	Excess deaths as a percentage of total deaths (%)
Males						
1950–1957	5,604	29	17	10	56	1.00
1958–1964	5,650	222	9	6	237	4.19
1965–1970	5,025	230	62	11	303	6.03
1971–1979*	7,966	267	229	20	516	6.48
1980–1985	6,285	195	303	64	562	8.94
1986–1990	5,152	154	305	60	519	10.07
1991–1995	5,639	115	412	86	613	10.87
1996–2000	5,944	40	358	73	471	7.92
Total	47,265	1,252	1,695	330	3,277	6.93
Females						
1950–1957	3,722	9	4	5	18	0.48
1958–1964	3,596	45	7	5	57	1.59
1965–1970	3,251	84	12	5	101	3.11
1971–1979*	5,158	137	41	17	195	3.78
1980–1985	3,998	12	39	39	90	2.75
1986–1990	3,793	8	84	50	142	3.85
1991–1995	4,079	5	92	65	162	4.00
1996–2000	4,568	0	113	69	182	3.36
Total	32,165	300	392	255	947	2.94

* Excluding 1976 data that were not available.

lung cancer and bladder cancer became the predominant contributors to excess deaths. Interestingly, smoking causes both lung and bladder cancer with long latencies, but the risk of AMI associated with smoking increases rapidly (as evidenced by high relative risks in young adults) and also declines rapidly following cessation of smoking (21). However, we have no explanation for the longer continuation of increased risks among men than among women following reduction in arsenic exposure (figure 2).

The main potential limitation of this study is the ecologic design. Potential biases that can result from the lack of individual data on exposure and confounding factors are well known (22). However, we do not believe that ecologic bias is a problem in our study. The first reason for this confidence in our results relates to exposure, since essentially everyone living in region II was exposed to arsenic at high concentrations while those in region V and the rest of Chile were not. This exposure contrast is markedly different from that of most ecologic studies in which it is unclear if the individuals who get disease are those who were actually exposed or not. In our study in Chile, we can state that there were increased rates of AMI in region II (where virtually everyone was exposed to high concentrations of arsenic in drinking water) compared with region V (where all drinking water sources contained low arsenic concentrations). Some people who died in region II would have recently migrated from another part of Chile where they were not exposed, and some from region II may have migrated in the opposite direction. However, the effect of such migration would be to dilute exposure contrasts and would, therefore, reduce, rather than cause, the positive associations we identified. From 1965 to 2000, annual internal migration among regions was only 0.6 percent, compared with 1.2 percent in Argentina, 3.1 percent in the United Kingdom, and 6.6 percent in United States (23). To conclude, although our ecologic study lacks individual data on exposure, the only likely ecologic bias would be a small bias toward the null from migration.

Our study also did not have individual data on confounding factors, but for two reasons it is very unlikely that our findings could be due to confounding. The first reason relates to timing. For confounding factors to explain the rise and fall in AMI mortality that we saw, they would have to have a similar relation in time to the rise and fall in arsenic concentrations. For example, if smoking were to explain the increasing and then decreasing mortality rate ratios between regions II and V, there would have to be a sudden rise in smoking rates in region II compared with region V in the 1950s, followed by a return to similar smoking rates in the 1970s.

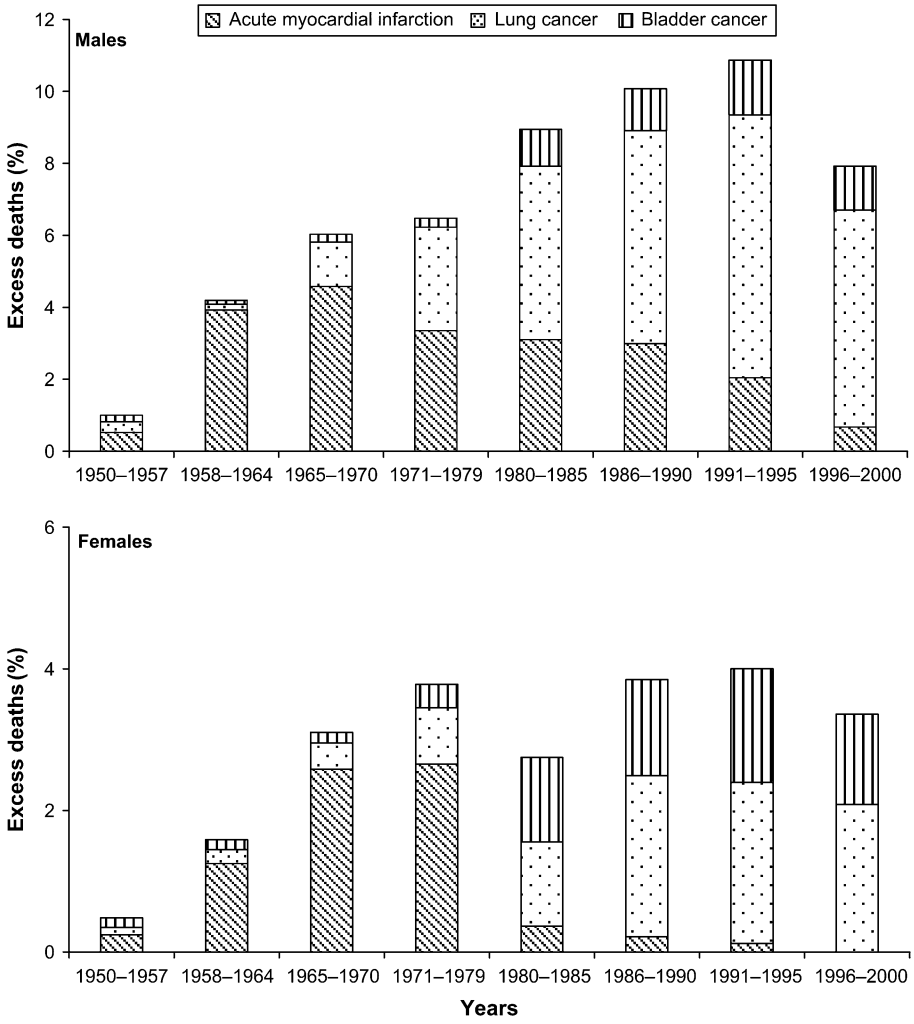

FIGURE 3. Excess deaths as a percentage of total deaths due to acute myocardial infarction, lung cancer, and bladder cancer for males and females, region II (exposed) compared with region V (unexposed), Chile, 1950–2000. (Note: The years 1950–1957 were prior to exposure, followed by high exposure from 1958 to 1970. During 1971–1985, there was intermediate exposure, and in 1986–2000, low exposure.)

The second reason for rejecting confounding as an explanation relates to the magnitude of mortality rate ratios identified. The rate ratio estimate for AMI mortality among men in region II was 1.48 (95 percent CI: 1.37, 1.59) during the high-exposure period, compared with region V (table 2). We estimated the magnitude of differences in smoking prevalence between region II and region V that would be needed to produce a mortality rate ratio of 1.48 between the regions using the method first proposed by Axelson (24). We obtained a relative risk estimate for smokers from a large cohort study of about 140,000 men that found that the AMI mortality rate ratio was 2.11 for current cigarette smokers who have smoked more than 20 pack-years compared with never smokers (25). Using relative risk estimates for smokers, we estimated that, if 20 percent of men smoked in region V, then at least 70 percent of men in region II would have to smoke to produce a rate ratio of 1.45 or more. If 15 percent of men had smoked in region V, then at least 60 percent would have to have been smokers in region II to result in a population rate ratio of at least 1.43. Such temporary differences in smoking practices are extremely unlikely when the data we have from 1990 show no evidence of any difference in smoking between the regions. Given this example with a strong risk factor such as smoking, it is also unlikely that other confounding factors, including diet and exercise or a combination of them, could produce the magnitude of rate ratios that we found and their trends over time. For all these reasons, we believe that confounding is unlikely and, although the study is ecologic in design, that it provides strong evidence of a causal relation between arsenic in drinking water and AMI mortality.

An important finding from this mortality study is the large number of excess deaths attributed to arsenic. In 1991–1995, around 35 years after the highest arsenic exposures commenced, this amounted to about 10 percent of all deaths among men in this period and 4 percent among women.

Such high proportions of deaths are unprecedented for any long-term general population environmental exposures. The higher impact on men than women could partly be due to the synergistic effect of arsenic exposure with cigarette smoking, which has already been demonstrated for lung cancer (17).

This study is the first epidemiologic study to report the impact of early life arsenic exposure on mortality from AMI. We recently reported markedly increased mortality from lung cancer and bronchiectasis in the same birth cohort of young adults aged 30–49 years in region II of Chile after probable exposure to arsenic in utero and in early childhood, a finding which we noted provided ''some of the first human evidence of effects from environmental exposures to toxic chemicals *in utero* and early childhood resulting in disease in adults'' (26, p. 1296). With the current findings, we can add mortality from AMI in young adults as another possible consequence of early life arsenic exposure.

Evidence of associations between arsenic in water supplies and circulatory disease mortality has previously been found in several high-dose studies from Taiwan (5, 6, 8–13). Previous systematic reviews concerning arsenic in drinking water and cardiovascular disease have been inconclusive as to whether or not there is a causal relation (27, 28). We believe that the clear-cut evidence concerning AMI mortality that has emerged from this mortality study in Chile makes an important addition to our knowledge about arsenic and cardiovascular disease.

Concerning other circulatory disease outcomes, we found no evidence of increased cerebrovascular disease mortality and little evidence of an increase in peripheral vascular disease mortality and hypertensive heart disease mortality. Regarding cerebrovascular disease, findings in Taiwan in relation to arsenic are weaker than the evidence concerning cardiovascular disease mortality (6, 10). Interestingly, Hertz-Picciotto et al. (29) presented evidence from studies of workers inhaling arsenic in the workplace showing that there might be increased mortality from cardiovascular disease and not from cerebrovascular disease.

We conclude that the major impact of arsenic in drinking water on circulatory disease involves AMI and that, in the initial years, it is the main cause of death from arsenic in drinking water, superseded in later years by excess mortality from lung and bladder cancer. Based on the large proportion of excess deaths that we identified, the overall increase in mortality due to arsenic in drinking water in the population of region II of Chile is greater than ever found for mortality from any other environmental exposure in any other population in the world.

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