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doi:10.1289/ehp.8832 (available at http://dx.doi.org/)
Online 27 March 2006
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Running Title: **Childhood arsenic exposure and mortality**

Article descriptors: COPD; Children’s health

Keywords: arsenic, bronchiectasis, childhood exposure, chronic obstructive pulmonary disease, drinking water, *in utero* exposure

Abbreviations:
CI-confidence interval
COPD-chronic obstructive pulmonary disease
HRCT-high-resolution computed tomography
IARC-International Agency for Research on Cancer
ICD-International Classification of Diseases
NRC-National Research Council
SMR-standardized mortality ratio

Acknowledgments:
This research was supported by the National Institute of Environmental Health Sciences grants R01 ES10033-03 and P42-ES04705, and the University of California Center for Occupational and Environmental Health. The authors declare they have no competing financial interests.
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ABSTRACT
Arsenic in drinking water is an established cause of lung cancer, and preliminary evidence suggests that ingested arsenic may also cause non-malignant lung disease. Antofagasta is the second largest city in Chile and had a distinct period of very high arsenic exposure which began in 1958 and lasted until 1971, when an arsenic removal plant was installed. This unique exposure scenario provides a rare opportunity to investigate the long term mortality impact of early-life arsenic exposure. In this paper, we compare mortality rates in Antofagasta in the period 1989-2000 with the rest of Chile, focusing on subjects who were born during or just before the peak exposure period and who were aged 30-49 at the time of death. For the birth cohort born just before the high exposure period (1950-1957), and exposed in early childhood, the standardized mortality ratio (SMR) for lung cancer was 7.0 (CI 5.4-8.9, p<0.001) and the SMR for bronchiectasis was 12.4 (CI 3.3-31.7, p<0.001). For those born during the high exposure period (1958-1971) with probable exposure in utero and early childhood, the corresponding SMRs were 6.1 (CI 3.5-9.9, p<0.001) for lung cancer, and 46.2 (CI 21.1-87.7, p<0.001) for bronchiectasis. These findings suggest that exposure to arsenic in drinking water during early childhood or in utero has pronounced pulmonary effects greatly increasing subsequent mortality in young adults from both malignant and non-malignant lung disease.

(227 words)
**Introduction**

The International Agency for Research on Cancer (IARC) has classified arsenic in drinking water as a Group 1 carcinogen that causes skin cancer, bladder cancer, and lung cancer (IARC 2002). Substantial evidence supports the biological plausibility that exposure to arsenic can lead to skin and bladder cancer. For example, arsenic concentrates in the skin and is known to cause non-malignant skin lesions (National Research Council (NRC) 2001), and the major pathway of excretion is in urine, giving plausibility to increased bladder cancer rates (NRC 2001). While it is known that inhalation of arsenic may cause lung cancer, the findings of increased lung cancer mortality following ingestion in drinking water were unexpected since all other known lung carcinogens act via inhalation. However, the evidence based on multiple studies in Taiwan (Chen et al. 1985; Chen and Wang 1990; Chen et al. 1988; Wu et al. 1989), Chile (Ferreccio et al. 2000; Smith et al. 1998), Argentina (Hopenhayn-Rich et al. 1998) and Japan (Tsuda et al. 1995; Tsuda et al. 1989) is sufficient to conclude that there is a causal relationship. In fact, lung cancer is the main long-term cause of death from ingesting arsenic in drinking water (NRC 2001). In Region II of Chile, which includes the city of Antofagasta, overall lung cancer mortality rates for men and women were previously found to be at least three-fold higher than for the rest of Chile (Smith et al. 1998), and lung cancer relative risk estimates increased nearly nine-fold in those with the highest exposures (Ferreccio et al. 2000).
Several known lung carcinogens cause chronic non-malignant respiratory diseases, including cigarette smoking which causes COPD, asbestos which causes asbestosis, and silica which causes silicosis. To date, however, relatively little attention has been given to whether or not ingestion of arsenic in drinking water causes nonmalignant pulmonary disease. The first reports of chronic respiratory symptoms came from small investigations in Antofagasta in the 1970s (Zaldivar 1974; Zaldivar 1977; Zaldivar 1980; Zaldivar and Ghai 1980). Prior to 1958, the water supply in the main city of Antofagasta had an arsenic concentration of about 90 µg/L. A growing population led to supplementation of Antofagasta’s water supply in the late 1950’s with water from rivers with arsenic concentrations near 1,000 µg/L. Because this area is among the driest places on earth, there are very few individual water supplies and almost everyone drinks water from the same municipal sources. After the installation of a new treatment plant in 1971, arsenic levels in Antofagasta water dropped abruptly to about 90 µg/L, and have been progressively reduced further in recent years (Ferreccio et al. 2000). These data are shown in Figure 1.

In a 1998 publication concerning Region II, increased COPD mortality was reported for the age group 30-39 (Smith et al. 1998). Based on the time period in which mortality was assessed (1989-1993), subjects in the age group 30-39 would have been in utero or young children at the time of the peak exposure period in Antofagasta. These results were based on a small number of cases but were later supported by findings from other arsenic exposed regions. For example, increases in symptoms of chronic respiratory disease were found to be associated with arsenic ingestion in studies in West Bengal, India (De et
al. 2004; Guha Mazumder et al. 2000) and Bangladesh (Milton and Rahman 2002). Recently, two studies in West Bengal involving participants with arsenic-caused skin lesions reported major deficits in pulmonary function (von Ehrenstein et al. 2005), and a 10-fold increase in prevalence of bronchiectasis identified by high resolution computed tomography (HRCT) (Guha Mazumder et al. 2005).

The distinct period of high arsenic exposure in Antofagasta from 1958 to 1970 offers the opportunity to investigate the health effects of early life arsenic exposure. In this study, we take advantage of this unique situation in order to assess adult mortality in those born during the high exposure period who would have experienced exposure in utero, as well as early childhood, and those born just before 1958 who would have experienced high exposure during childhood, but not in utero.

Methods

Computerized mortality data were obtained for the period 1989-2000 from the Ministry of Health for all thirteen regions of Chile. Deaths were divided into two groups, those who were residents of Antofagasta and neighboring Mejillones, neighboring cities which have the same water source, and those who were residents in all regions of Chile other than Region II in which Antofagasta and Mejillones are located. Two birth cohorts were defined for this investigation: those born in the period 1958-1970 (probable in utero exposure if resident in Antofagasta/Mejillones), and those born in 1950-57 (probable childhood exposure if born in Antofagasta/Mejillones). Causes of death were coded
according to the 9th revision of the International Classification of Diseases (ICD-9), including lung cancer (ICD 162), and chronic respiratory disease (ICD 490, ICD 491, ICD 492, ICD 494, ICD 496). Annual estimates of the population living in Antofagasta/Mejillones in Region II, and for the rest of Chile excluding Region II, were obtained for the period 1989-2000 from the National Institute of Statistics (Instituto Nacional de Estadísticas) stratified by age and sex.

In the year 2000, the last year of mortality data, the oldest persons in the first birth cohort born in the period 1950-1957 would have been 50 years old. We therefore calculated standardized mortality ratios (SMRs) for men and women separately, aged 30-49, using ten-year age groups, 30-39 and 40-49, for standardization. Mortality in younger ages was not included, since death from lung cancer or chronic respiratory disease is extremely rare under age 30. SMRs were calculated as the observed number of deaths divided by the expected number of deaths, using all regions in Chile outside of Region II as the referent population. SMRs were estimated for lung cancer, for bronchiectasis, and for other COPD causes of death excluding bronchiectasis. SMRs were also estimated for all other causes of death excluding lung cancer and COPD. Tests of significance and confidence intervals were calculated based on the Poisson distribution (Selvin 1995). In view of the clear direction of the a priori hypotheses for arsenic and both malignant and nonmalignant pulmonary diseases, 1-tailed tests of significance were conducted for increases in these outcomes. Tests for effect modification by age group (comparing age group 30-39 and 40-49), and tests for effect modification by gender, and for differences
between those born in 1950-1957 and 1958-1970, were assessed by testing the pertinent Poisson regression interaction terms with 2-tailed tests.

Results

SMRs for lung cancer and COPD are given in Table 1 for ages 30-39 and 40-49 separately and combined, and for men and women separately and combined. Based on the Poisson regression interaction terms, there was no evidence of differences in rate ratios between age groups 30-39 and 40-49 for lung cancer and COPD causes of death, and we therefore focus on the SMRs for the overall age range 30-49. For lung cancer, the SMR for ages 30-49 was increased for those born in the period 1950-1957 for both men (SMR = 8.2, CI 6.2-10.8, p <0.001) and women (SMR = 4.7, CI 2.7-7.7, p <0.001). The lung cancer SMR was also increased for those born in 1958-1970 (women SMR = 2.9, CI 0.6-8.5, p = 0.087; men SMR = 8.1, CI 4.3-13.9, p <0.001). Concerning COPD mortality, bronchiectasis SMRs were markedly increased for both men and women, especially for those born in the high exposure period 1958-1970 (women SMR = 50.1, CI 20.0-103, p <0.001; men SMR = 36.4, CI 4.1-132, p = 0.001). SMRs for other COPD causes of death excluding bronchiectasis were elevated, but much less than for bronchiectasis. Finally, for all other causes of death combined, there was little evidence of increased mortality for either birth cohort, as shown in Table 1.
The lung cancer relative risks are higher for men than women, but the confidence intervals for women are wide in view of relatively small numbers, and overlap the lung cancer SMR for men (point estimate for men age 30-49 was 8.1, CI for women 0.6-8.5, Table 1). Testing Poisson regression interaction terms, there was little evidence of effect modification by gender for the period 1950-58 (p=0.23), but testing for effect modification for those born in the period 1958-71 yields a p-value of 0.04, with higher relative risks in men than women (8.1 for men and 2.9 for women). The pooled results are presented, highlighted, in Table 1 and graphically in Figure 2. It can be seen that lung cancer rates are greatly increased for both those born in 1950-1957 with childhood exposure, and for those born in 1958-1970, who would have experienced in utero exposure. However, for bronchiectasis, and to a lesser extent for other COPD mortality, the SMRs are much higher for those born in 1958-1970 (SMR=46.2, CI 21.1-87.7, p < 0.001) than for those born in 1950-1957 before the very high exposures started (SMR=12.4, CI 3.3-31.7, p<0.001, Poisson regression test for difference in bronchiectasis rate ratios for the two periods p=0.02).

Discussion

Region II of Chile provides a unique opportunity to investigate arsenic health effects. It is one of the driest areas of the world, and water used in major cities and towns comes from single sources with known arsenic concentration. Furthermore, there was an abrupt onset of high exposure in 1958 in Antofagasta, the major city of Region II with a population at that time of about 200,000 (Zaldivar 1974), and an abrupt reduction in exposure in 1971
when the first large arsenic removal plant in the world was installed there. Such clear-cut exposure patterns are rare in environmental epidemiology, perhaps with the exception of radiation exposure from use of the atomic bomb in Hiroshima and Nagasaki, and to a lesser extent, ionizing radiation from accidents at nuclear reactors.

The magnitude of the effects found on lung cancer and bronchiectasis mortality has no parallel with effects of other environmental exposures occurring in utero and/or in early childhood. No lung cancer cases were reported in 40 years among the in utero exposed survivors of the atomic bombing of Hiroshima and Nagasaki (Yoshimoto et al. 1988). Children with the highest gamma radiation exposure in Hiroshima and Nagasaki under age 10 did not experience increased lung cancer risks as adults, but those exposed in the age range of 10-19 years of age had lung cancer relative risk estimate of about 2.5 as young adults aged 30-39 (from Figure 2 in Shimizu et al. 1990). The evidence for an effect of childhood exposure to ETS on adult lung cancer rates is mixed, with a meta-analysis published in 2000 finding no overall evidence of increased risks (Boffetta et al. 2000). However, a recent publication involving a prospective study reported a relative risk estimate of 3.6 (95%CI 1.2-11.1) based on 4 lung cancer cases among those with “many hours” of daily exposure (Vineis et al. 2005). By contrast, we report here a total of 84 deaths from lung cancer following childhood exposure to high concentrations of arsenic in drinking water in Chile, a 6- and 7-fold increase above rates in the rest of Chile (Table 1).
There is some supportive evidence providing biological plausibility for arsenic having effects *in utero*. Arsenic crosses the placenta in animals and humans, and there is human evidence that arsenic is a developmental toxicant affecting birthweight and reproductive outcomes (Concha et al. 1998; Hanlon and Ferm 1987; Hopenhayn et al. 2003; Hopenhayn-Rich et al. 2000; Hopenhayn-Rich et al. 1999). Recently, a study conducted in Bangladesh showed an increased risk for stillbirth (OR: 2.5; 95% CI: 1.5, 4.9) and spontaneous abortion (2.5; 1.5, 4.3) in women with current arsenic exposure ≥100 µg/L in water (Milton et al. 2005), and a study in West Bengal found increased risks of stillbirths (OR: 6.1; 95% CI: 1.5, 24.0) (von Ehrenstein et al. In press). As a whole, these epidemiologic data provide evidence that arsenic exposure *in utero* could be associated with a number of adverse effects. The current study however, is the first to provide evidence that early life exposures may result in effects manifesting themselves in adults.

Oral dose animal studies demonstrate arsenic teratogenicity (Chattopadhyay et al. 2002; Vahter 1994). Of particular relevance to our study is evidence that arsenic is a transplacental carcinogen in mice (Waalkes et al. 2000). The offspring of pregnant mice who were given high doses of arsenic in their drinking water developed tumors at multiple sites, including the lung in female offspring with lung carcinoma increased to 5/24 (21%) compared to 0/25 (0%) in the unexposed controls.

Strengths of our study include the extensive documentation of arsenic in drinking water in the Antofagasta water system. Records of arsenic levels in Antofagasta have been kept for the last 50 years and almost all residents drink from the same water supply. One
potential limitation of this study is that it is ecological in nature, since overall mortality rates in the cities of Antofagasta/Mejillones were compared with the rest of Chile. Residence was determined from death certificates and relates to residence at the time at death. We cannot be certain that those manifesting the increased mortality were actually born in Antofagasta/Mejillones. However, the increases in relative risks are far too great to result from bias due to in-migration of very high risk persons born elsewhere. We conclude that the effects are most probably due to arsenic in the water, and that if anything they are diluted by in-migration of people who were born and grew up elsewhere in Chile.

The study has a weakness in its reliance on death certificates, even though Chile mortality records are well-documented: laws require that deaths be registered with the Civilian Registration Service (Servicio de Registro Civil), while another branch of government, the National Institute of Statistics (Instituto Nacional de Estadísticas) oversees validation of the generated data. Death certificates are coded according to the standard International Classification of Disease (ICD), and the 1996 World Health Statistics cited Chile as having 100%, 100% and 98% of all estimated deaths registered for the years 1991, 1993 and 1994 respectively (World Health Organization 1998). However, while death certificates are reasonably good for lung cancer studies, they have known limitations for identifying death from chronic respiratory disease (Selikoff and Seidman 1992). This leads one to question if medical practices in Region II might have led to over-diagnosis of chronic respiratory disease as a cause of death placed on death certificates, in particular from bronchiectasis. However, separating out the findings
concerning bronchiectasis from other COPD causes of death was conducted with a clear
*a priori* hypothesis. Although previous mention had been made in the literature of
bronchiectasis and arsenic, it was the recent finding of a ten-fold increase in
bronchiectasis prevalence in persons with high exposure to arsenic and arsenic-caused
skin lesions in West Bengal, India (Guha Mazumder et al. 2005) that led us specifically
to evaluate bronchiectasis in this study.

While smoking is strongly associated with mortality from lung cancer and COPD,
confounding due to smoking is unlikely. Smoking is not a strong risk factor for
bronchiectasis and so would not confound our findings regarding this disease (Barker
2002). And even in extreme form, confounding could not produce the marked elevation
of lung cancer relative risks we have found (Axelson 1980). In addition, smoking data do
not indicate higher smoking rates in Region II than in the rest of Chile, according to a
national survey conducted in 1990 (CASEN 1992). The survey included the two largest
cities in Region II (Antofagasta and Calama), which comprise 80% of the Region II
population; the proportion of smokers in these two cities was found to be lower than the
rest of Chile, and the two cities also had a smaller proportion of people who smoked
more than one pack per day (Table 2) (Smith et al. 1998). While there is some evidence
that exposure of children to passive smoking in their homes increases the risk of adult
lung cancer (Lee et al. 2000; Vineis et al. 2005), an earlier meta-analysis estimated the
relative risk to be 0.91 (95% CI 0.8-1.05) (Boffetta et al. 2000). Even if passive smoking
does increase the risk of adult lung cancer, such exposure occurs throughout Chile.
Finally, occupational exposures to arsenic, such as in the mining and refining of copper,
could contribute to COPD and lung cancer mortality, but these occupational exposures mainly involve men and our study found similar increases in mortality in both men and women.

In conclusion, we have demonstrated pronounced increases in mortality from lung cancer and bronchiectasis in persons with probable exposure to high concentrations of arsenic in drinking water \textit{in utero} and early childhood. These findings are important in that they provide some of the first human evidence of effects from environmental exposures to toxic chemicals \textit{in utero} and early childhood resulting in disease in adults. A marked increase in mortality in young adults is also of public health importance and should be taken into consideration in setting arsenic drinking water standards.
References


Table 1. SMRs for bronchiectasis, other COPD, all other deaths, and lung cancer for Antofagasta/Mejillones, for age 30-49, for men and women separately as well as pooled

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Cause of Death</th>
<th>Born 1950-57</th>
<th></th>
<th></th>
<th>Born 1958-70</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>O</td>
<td>E</td>
<td>SMR (CI)</td>
<td>p-value</td>
<td>O</td>
<td>E</td>
<td>SMR (CI)</td>
</tr>
<tr>
<td>30-39</td>
<td>Male</td>
<td>Lung Cancer</td>
<td>15</td>
<td>1.17</td>
<td>12.8 (7.1-21.1)</td>
<td>&lt;0.001</td>
<td>12</td>
<td>1.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchiectasis</td>
<td>3</td>
<td>0.15</td>
<td>19.4 (4.0-56.8)</td>
<td>0.001</td>
<td>2</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other COPD</td>
<td>1</td>
<td>0.21</td>
<td>4.7 (0.1-26.0)</td>
<td>0.193</td>
<td>1</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
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<td>All other deaths</td>
<td>129</td>
<td>155.78</td>
<td>0.8 (0.7-1.0)</td>
<td>0.987</td>
<td>305</td>
<td>304.41</td>
</tr>
<tr>
<td>30-39</td>
<td>Female</td>
<td>Lung Cancer</td>
<td>2</td>
<td>0.48</td>
<td>4.2 (0.5-15.1)</td>
<td>0.084</td>
<td>3</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchiectasis</td>
<td>0</td>
<td>0.04</td>
<td>0</td>
<td>-</td>
<td>6</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other COPD</td>
<td>2</td>
<td>0.14</td>
<td>13.9 (1.7-50.2)</td>
<td>0.009</td>
<td>4</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
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<td>All other deaths</td>
<td>74</td>
<td>64.95</td>
<td>1.1 (0.9-1.4)</td>
<td>0.145</td>
<td>145</td>
<td>113.73</td>
</tr>
<tr>
<td>30-39</td>
<td>Pooled</td>
<td>Lung Cancer</td>
<td>17</td>
<td>1.65</td>
<td>10.3 (6.0-16.5)</td>
<td>&lt;0.001</td>
<td>15</td>
<td>2.14</td>
</tr>
<tr>
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<td></td>
<td>Bronchiectasis</td>
<td>3</td>
<td>0.19</td>
<td>15.8 (3.2-46.0)</td>
<td>0.001</td>
<td>8</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other COPD</td>
<td>3</td>
<td>0.36</td>
<td>8.4 (1.7-24.5)</td>
<td>0.006</td>
<td>5</td>
<td>0.79</td>
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<td>All other deaths</td>
<td>203</td>
<td>220.73</td>
<td>0.9 (0.8-1.0)</td>
<td>0.891</td>
<td>450</td>
<td>418.14</td>
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<tr>
<td>40-49</td>
<td>Male</td>
<td>Lung Cancer</td>
<td>37</td>
<td>5.14</td>
<td>7.2 (5.1-9.9)</td>
<td>&lt;0.001</td>
<td>1</td>
<td>0.29</td>
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<td>Bronchiectasis</td>
<td>0</td>
<td>0.10</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
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<td></td>
<td>Other COPD</td>
<td>3</td>
<td>1.30</td>
<td>2.3 (0.5-6.7)</td>
<td>0.144</td>
<td>1</td>
<td>0.10</td>
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<tr>
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<td>All other deaths</td>
<td>270</td>
<td>292.37</td>
<td>0.9 (0.8-1.0)</td>
<td>0.911</td>
<td>21</td>
<td>19.66</td>
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<tr>
<td>40-49</td>
<td>Female</td>
<td>Lung Cancer</td>
<td>14</td>
<td>2.90</td>
<td>4.8 (2.6-8.1)</td>
<td>&lt;0.001</td>
<td>0</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchiectasis</td>
<td>1</td>
<td>0.04</td>
<td>27.6 (0.7-154)</td>
<td>0.036</td>
<td>1</td>
<td>0.0</td>
</tr>
<tr>
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<td></td>
<td>Other COPD</td>
<td>2</td>
<td>0.76</td>
<td>2.6 (0.3-9.5)</td>
<td>0.177</td>
<td>1</td>
<td>0.04</td>
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<tr>
<td></td>
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<td>All other deaths</td>
<td>178</td>
<td>147.78</td>
<td>1.2 (1.0-1.4)</td>
<td>0.009</td>
<td>17</td>
<td>11.92</td>
</tr>
<tr>
<td>40-49</td>
<td>Pooled</td>
<td>Lung Cancer</td>
<td>51</td>
<td>8.04</td>
<td>6.3 (4.7-8.3)</td>
<td>&lt;0.001</td>
<td>1</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchiectasis</td>
<td>1</td>
<td>0.13</td>
<td>7.5 (0.2-42.0)</td>
<td>0.124</td>
<td>1</td>
<td>0.0</td>
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<tr>
<td></td>
<td></td>
<td>Other COPD</td>
<td>5</td>
<td>2.06</td>
<td>2.4 (0.8-5.7)</td>
<td>0.059</td>
<td>2</td>
<td>0.13</td>
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<td></td>
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<td>All other deaths</td>
<td>448</td>
<td>440.15</td>
<td>1.0 (0.9-1.1)</td>
<td>0.361</td>
<td>38</td>
<td>31.58</td>
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<tr>
<td>30-49</td>
<td>Male</td>
<td>Lung Cancer</td>
<td>52</td>
<td>6.31</td>
<td>8.2 (6.2-10.8)</td>
<td>&lt;0.001</td>
<td>13</td>
<td>1.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchiectasis</td>
<td>3</td>
<td>0.25</td>
<td>12.0 (2.4-34.9)</td>
<td>0.002</td>
<td>2</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other COPD</td>
<td>4</td>
<td>1.52</td>
<td>2.6 (0.7-6.7)</td>
<td>0.068</td>
<td>2</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All other deaths</td>
<td>399</td>
<td>448.15</td>
<td>0.9 (0.8-1.0)</td>
<td>0.991</td>
<td>326</td>
<td>324.07</td>
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<tr>
<td>30-49</td>
<td>Female</td>
<td>Lung Cancer</td>
<td>16</td>
<td>3.38</td>
<td>4.7 (2.7-7.7)</td>
<td>&lt;0.001</td>
<td>3</td>
<td>1.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchiectasis</td>
<td>1</td>
<td>0.07</td>
<td>13.9 (0.2-77.1)</td>
<td>0.070</td>
<td>7</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other COPD</td>
<td>4</td>
<td>0.90</td>
<td>4.4 (1.2-11.3)</td>
<td>0.014</td>
<td>5</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All other deaths</td>
<td>252</td>
<td>212.73</td>
<td>1.2 (1.0-1.3)</td>
<td>0.005</td>
<td>162</td>
<td>125.64</td>
</tr>
<tr>
<td>30-49</td>
<td>Pooled</td>
<td>Lung Cancer</td>
<td>68</td>
<td>9.69</td>
<td>7.0 (5.4-8.9)</td>
<td>&lt;0.001</td>
<td>16</td>
<td>2.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchiectasis</td>
<td>4</td>
<td>0.32</td>
<td>12.4 (3.3-31.7)</td>
<td>&lt;0.001</td>
<td>9</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other COPD</td>
<td>8</td>
<td>2.42</td>
<td>3.3 (1.4-6.5)</td>
<td>0.004</td>
<td>7</td>
<td>0.92</td>
</tr>
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<td></td>
<td></td>
<td>All other deaths</td>
<td>651</td>
<td>660.88</td>
<td>1.0 (0.9-1.1)</td>
<td>0.655</td>
<td>488</td>
<td>449.71</td>
</tr>
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</table>
Table 2. Smoking habits among men and women in the two major cities in Region II in 1990 compared with data for the rest of Chile

<table>
<thead>
<tr>
<th></th>
<th>Nonsmokers</th>
<th>Occasional</th>
<th>1-9</th>
<th>10-19</th>
<th>≥20</th>
<th>Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Antofagasta</td>
<td>163,500</td>
<td>76.4</td>
<td>13,223</td>
<td>6.2</td>
<td>27,445</td>
<td>12.8</td>
<td>1,800</td>
</tr>
<tr>
<td>Calama</td>
<td>92,214</td>
<td>80.4</td>
<td>8,268</td>
<td>7.2</td>
<td>10,944</td>
<td>9.5</td>
<td>1,788</td>
</tr>
<tr>
<td>Rest of Chile</td>
<td>5,443,466</td>
<td>75.1</td>
<td>581,686</td>
<td>8.0</td>
<td>837,878</td>
<td>11.6</td>
<td>228,617</td>
</tr>
</tbody>
</table>

aData were obtained from the Ministerio de Planificacion y Coordinacion Nacional Republica de Chile IIIa, Encuesta CASEN.
Figure 1. Arsenic concentrations in Antofagasta/Mejillones water by year. An arsenic removal plant was installed in 1971.

Figure 2. COPD Standard Mortality Ratios for Antofagasta/Mejillones for 30-49 year olds, pooled.
Figure 1.
Figure 2.