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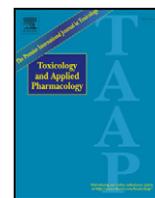Acevedo, J
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High risks of lung disease associated with early-life and moderate lifetime arsenic exposure in northern Chile

Craig Steinmaus [a,*], Catterina Ferreccio [b,c], Johanna Acevedo [b,c], John R Balmes [a,d], Jane Liaw [a], Patricia Troncoso [e,f], David C Dauphiné [a], Anthony Nardone [g], Allan H Smith [a]

[a] Arsenic Health Effects Research Program, UC Berkeley School of Public Health, Berkeley, CA, USA
[b] School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile
[c] Advanced Center for Chronic Diseases (ACCDiS), FONDAP, Santiago, Chile
[d] Department of Medicine, University of California, San Francisco, San Francisco, CA, USA
[e] Laboratorio de Anatomía Patológica Dra. Patricia Troncoso, Iquique, Chile
[f] Hospital Felix Bulnes, Departamento de Anatomía Patológica, Santiago, Chile
[g] Global Health Sciences Program, University of California, San Francisco, San Francisco, CA, USA

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ABSTRACT

Background: Arsenic in drinking water has been associated with increases in lung disease, but information on the long-term impacts of early-life exposure or moderate exposure levels are limited.
Methods: We investigated pulmonary disease and lung function in 795 subjects from three socio-demographically similar areas in northern Chile: Antofagasta, which had a well-described period of high arsenic water concentrations (860 μg/L) from 1958 to 1970; Iquique, which had long-term arsenic water concentrations near 60 μg/L; and Arica, with long-term water concentrations ≤10 μg/L.
Results: Compared to adults never exposed >10 μg/L, adults born in Antofagasta during the high exposure period had elevated odds ratios (OR) of respiratory symptoms (e.g., OR for shortness of breath = 5.56, 90% confidence interval (CI): 2.68–11.5), and decreases in pulmonary function (e.g., 224 mL decrease in forced vital capacity in nonsmokers, 90% CI: 97–351 mL). Subjects with long-term exposure to arsenic water concentrations near 60 μg/L also had increases in some pulmonary symptoms and reduced lung function.
Conclusions: Overall, these findings provide new evidence that in utero or childhood arsenic exposure is associated with non-malignant pulmonary disease in adults. They also provide preliminary new evidence that long-term exposures to moderate levels of arsenic may be associated with lung toxicity, although the magnitude of these latter findings were greater than expected and should be confirmed.

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Millions of people worldwide are exposed to arsenic-contaminated drinking water, and ingested arsenic is an established cause of lung cancer (IARC, 2004). Studies have also linked it to non-malignant lung disease, but most studies have involved subjects with recent exposures and study areas with high exposure levels (NRC, 2014). To date, little is known about more moderate exposure levels or whether exposures in utero or in early childhood might lead to pulmonary disease in adults.

Northern Chile is the driest habitable place on earth and almost all drinking water comes from a small number of municipal supplies. Arsenic concentrations have been measured in all of these, with measurements dating back 50 years or more. Arsenic concentrations in this area have ranged from <10 to >800 μg/L and, except for in cities where arsenic treatment plants have been installed, have been stable over time (Ferreccio et al., 2000). Until recently, relatively few people used bottled water or water filters (Steinmaus et al., 2013). A consequence of all these factors is that one simply needs to know the cities in which a person has lived, and when, to have a good estimate of that person's lifetime arsenic exposure. In the largest city in the region, Antofagasta, to cater to a growing population, two rivers with high arsenic concentrations (about 860 μg/L) were diverted to the city for drinking in 1958. In 1970, an arsenic treatment plant was installed and arsenic concentrations quickly fell to about 100 μg/L and then, with improvements to the treatment plant, more gradually to about 10 μg/L today (Ferreccio et al., 2000), creating a distinct period of very high exposure from 1958 to 1970.

Earlier studies reported high rates of bronchopulmonary disease in both adults and children in Antofagasta during this high exposure period (Borgono et al., 1977; Zaldivar, 1974; Zaldivar, 1977; Zaldivar and Ghai, 1980). More recently, we identified elevated rates of lung cancer in adults who were born or were young children during this period (Smith et al., 2006; Steinmaus et al., 2014a). We also identified evidence

that people in neighboring areas with long-term exposures near 60 μg/L have increases in lung cancer (Steinmaus et al., 2014b). Here, we further explored the long-term impacts of early-life and moderate arsenic exposures by collecting data on pulmonary symptoms, disease, and function in people born during the high exposure period who are now adults, and in people with long-term exposures near 60 μg/L. This is the largest study ever to examine the non-malignant pulmonary impacts associated with these two exposure scenarios.

1. Methods

Subjects were recruited from three of the four largest cities in northern Chile: Arica, Iquique, and Antofagasta. As described above, Antofagasta had a distinct period of very high arsenic water concentrations of about 860 μg/L from 1958 to 1970. Water concentrations in Iquique and Arica have been very stable over time at about 8–10 and 60 μg/L, respectively, until recently when water concentrations in Iquique were lowered to <10 μg/L to meet new regulations (Ferreccio et al., 2000; Steinmaus et al., 2013). All subjects were randomly selected from the Chile Electoral Registry, which contains >90% of all people over age 40 years, with an initial goal of selecting 200 people from Arica, 200 from Iquique, and 400 from Antofagasta. Only subjects of the ages where they would have been born during the high exposure period in Antofagasta, and only subjects who were born in and lived at least 80% of their lives in their respective cities were recruited. The study was approved by institutional review boards in the US and Chile. All participants gave written informed consent.

Interviews and lung function tests were conducted by trained staff from 2009 to 2011. Each participant was administered a structured questionnaire to assess lifetime residential and occupational history, water sources, and medical history. Smoking histories included ages started and quit, years smoked, and average cigarettes smoked per day. Information on secondhand smoke included whether someone smoked regularly in the same room at home (child or adult) or at work. Subjects were asked about types of fuels used at home, as well as specific workplace exposures like asbestos, silica, and arsenic. Subjects were asked about their typical diet and drinking water intakes currently and 20 years ago. Socioeconomic (SES) scores were based on 12 items, including ownership of household appliances (e.g., refrigerator, microwave), car, computer, and use of domestic help.

Questions on symptoms such as chronic cough and shortness of breath were derived from the British Medical Research Council respiratory questionnaire and adapted to local Spanish (Cotes, 1987). Additional questions asked about physician-diagnosed asthma, bronchitis, emphysema, and other pulmonary and medical conditions; all medications used; and childhood hospitalizations.

After height and weight were measured by nurse-interviewers, lung function was assessed per American Thoracic Society guidelines using an EasyOne spirometer (ndd Medical Technologies, Zurich, Switzerland) in diagnostic mode (ATS, 1995). Subjects were asked to perform 3 to 8 maximum forced expiratory efforts while seated without a nose clip. The main lung function values assessed were forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC). Each subject's best effort (largest sum of FEV1 and FVC) was included in the analyses.

Municipal drinking water arsenic records, obtained from water suppliers, government agencies, and research studies, were linked with participants' residential histories to obtain estimated arsenic drinking water concentrations for each year of each subject's life (Ferreccio et al., 2000; Smith et al., 2012). These yearly arsenic concentrations were then used to develop several exposure indices, including the highest exposure for any one year, the highest exposure averaged over any contiguous 5-, 20-, or 40-year period, cumulative exposure (calculated by summing the yearly concentrations), average lifetime exposure (cumulative exposure divided by age at interview), and the highest drinking water concentration during lung development (ages 0–20). Subjects were then categorized by tertiles in all subjects or on the exposure

distribution of the main study cities. Water intake had little impact on categorizing subjects so was not used here. Some subjects lived in cities other than the three recruitment cities at some points in their lives, but arsenic water measurements were available for all large cities in Chile (accounting for >90% of the country's population) and these were also used to assign yearly arsenic concentrations. Bottled water and residences without arsenic measurements were assigned values of zero.

Logistic regression was used to calculate unadjusted and adjusted odds ratios (OR) for respiratory symptoms and disease prevalence, comparing subjects with low, medium and high levels of arsenic. Age (<44, 45–49, and 50 + years), sex, and smoking (never-smokers, and average daily cigarettes smoked categories of 1–5, 6–19, and 20 +) were entered in models a priori. Additional adjustments were done for occupational exposures (ever vs. never exposed to silica, asbestos, wood dust and other pulmonary toxins or mining work), past daily fruit and vegetable intake (tertiles), body mass index (tertiles), household fuel (wood, coal, kerosene, electricity as indicator variables), secondhand smoke (regular exposure for >1 year), highest education achieved (less than high school, high school, some post-high school, university), and race, but these had little impact and so were not included in final models. Adjustments for pack-years and average cigarettes smoked as continuous variables also had little impact. Interaction between smoking and arsenic was assessed using stratified analyses and interaction terms.

Age (one-year intervals), height (meters) and gender-adjusted FEV1 and FVC residuals were calculated using multiple linear regression (Willett and Stampfer, 1998), and mean residuals were compared across arsenic exposure categories, using the lowest as the reference. Aymara were the common indigenous population in our study, and Aymara ethnicity was included in final models since the percentage of Aymara subjects differed across arsenic categories and Aymara subjects had lower pulmonary function values. Adjusting for the other factors mentioned above or for EasyOne quality scores had little impact on results. All data were analyzed using SAS 9.2 (SAS Institute Inc., Cary, NC).

In order to examine associations at moderate arsenic exposures, we calculated symptom ORs and spirometry results, comparing subjects with ≥30 years exposure at 60 μg/L (but never higher, and they did not report bottled water consumption) to subjects never exposed >10 μg/L. Because we had a clear a priori hypotheses that arsenic would adversely impact lung health, 90% confidence intervals (CI) and one-sided p-values are presented unless otherwise indicated.

2. Results

Of the 281, 257, and 442 subjects contacted about the study in Arica, Iquique, and Antofagasta, respectively, 37 (13.2%), 36 (14.0%), and 29 (6.6%) declined participation. Of the remaining, 35 (16.7%), 26 (13.3%), and 22 (5.6%), respectively, were ineligible due to residency or spirometry criteria. The remaining participants included 204, 208, and 383 people with the highest known arsenic water concentrations of <11 μg/L (median = 10 μg/L, range 0–10 μg/L), 11–200 μg/L (median = 60 μg/L, range = 14–110 μg/L), and >200 μg/L (median = 860 μg/L, range 250–860 μg/L). Mean ages, smoking rates, education, and SES were similar across arsenic categories (Table 1). BMI and work-related exposures were higher in subjects in the middle exposure category than the low and high categories, and there were no subjects of Aymara descent in the high exposure category. The percentages of subjects using gas for cooking 20 years ago in the low, medium, and high arsenic areas were 94.3, 96.7, and 97.6%, respectively, with even higher percentages currently (data not shown). Everyone in the >200 μg/L category lived most of their lives in Antofagasta. The large majority of people in the 11–200 μg/L category lived most of their lives in Iquique (60 μg/L), although eight people in this group lived in Antofagasta but reported using some bottled water or other water source and had adjusted highest known exposures of 60–200 μg/L. Arsenic water

Table 1
Demographic variables by categories of highest known arsenic concentration in drinking water (μg/L).

Variable	Arsenic:	<11		11–200		>200	
	Group	N	%	N	%	N	%
Age (years)	<44	56	27.5	58	27.9	102	26.6
	44–49	113	55.4	95	45.7	183	47.8
	>49	35	17.2	55	26.4	98	25.6
Sex	Female	118	57.8	102	49.0	173	45.2
	Male	86	42.2	106	51.0	210	54.8
Ethnicity	Hispanic	130	63.7	164	78.8	382	99.7
	Aymara	58	28.4	35	16.8	0	0
	Other	16	7.8	9	4.3	1	0.3
Ever smoker	No	107	52.5	99	47.6	194	50.7
	Yes	97	47.5	109	52.4	189	49.3
Smoking rate (cigs/day)[a]	>0–5	63	64.9	62	56.9	103	54.8
	5–19	29	29.9	37	33.9	65	34.6
	20+	5	5.2	10	9.2	20	10.6
Secondhand smoke[b]	No	97	90.7	79	84.9	175	90.2
	Yes	10	9.3	14	15.1	19	9.8
Socioeconomic status score[c]	Low	62	30.4	55	26.4	107	27.9
	Medium-high	142	69.6	153	73.6	276	72.1
Body mass index (kg/m²)	<25	49	24.0	44	21.2	95	24.8
	25–29	105	51.5	91	43.8	204	53.3
	30+	50	24.5	73	35.1	84	21.9
Education (highest grade)	High school	50	24.5	61	29.3	112	29.2
	Some college	85	41.7	84	40.4	163	42.6
	College	69	33.8	63	30.3	108	28.2
Occupational exposure[d]	No	158	77.5	143	68.8	299	78.1
	Yes	46	22.5	65	31.3	84	21.9
Spirometry grade	<4	3	1.5	2	1.0	32	8.4
	≥4	201	98.5	206	99.0	351	91.6

[a] Average cigarettes smoked per day when smoking, only in smokers.
[b] At least six months exposure as a child or adult in never smokers.
[c] Low, lower tertile; High, higher two tertiles.
[d] Ever vs. never exposed to fiberglass, silica, diesel exhaust, wood dust, arsenic, asbestos, welding fumes, other fumes, coke oven emissions, soot, acrylic, beryllium, or radon at work.

measurements were available for residences comprising 97.9% of the subjects' lifetimes.

For shortness of breath, adjusted prevalence ORs for lifetime highest single year exposures of <11, 11–200, and >200 μg/L were 1.00, 5.48 (90% CI, 2.55–11.8), and 5.56 (2.68–11.5), respectively (Table 2). Similar ORs were seen when exposure categories were based on highest known exposures during ages 0–20 years. For tertiles of lifetime cumulative exposure, ORs were lower (OR = 2.55, 90% CI: 1.49–4.37 and OR = 2.82, 90% CI: 1.63–4.88 for the middle and upper tertiles, respectively). ORs were also elevated for chronic cough, chronic phlegm, childhood respiratory hospitalizations, and bronchitis in the highest exposure categories. Too few subjects had emphysema (n = 2), bronchiectasis (n = 2), or other pulmonary conditions to calculate robust ORs. Adjustments for workplace exposures, SES, and other factors had little impact on ORs (Appendix Fig. A1). For both asthma and wheeze, elevated ORs were seen in the middle but not upper exposure categories. For example, for highest single year exposure, ORs for wheeze for exposures of 11–200 μg/L and >200 μg/L were 4.35 (90% CI: 2.00–9.46) and 2.05 (90% CI: 0.94–4.48) respectively. Results in subjects with long-term exposures near 60 μg/L had ORs similar to those with highest single year exposures between 11 and 200 μg/L (Table A1), although the number of cases were small for some outcomes such as chronic cough and phlegm. Clear evidence of interaction between arsenic and smoking was not seen for pulmonary symptoms.

Never-smokers with highest single-year arsenic water concentrations of 11–200 and >200 μg/L had adjusted FVC residuals of −175 mL (90% CI: −303 to −47) and −224 mL (90% CI: −351 to −97), respectively (Table 3). A 224 mL decrease represents about a 6.1% decrease in FVC (median FVC = 3681 mL). Similar decrements were not seen in smokers or for FEV1 (Table A2). Spirometry results in subjects with long-term exposures at 60 μg/L were similar to those for the 11–200 μg/L group (Table 3).

3. Discussion

Overall, we identified associations between high arsenic exposures in early-life and increases in pulmonary symptoms and decrements in FVC, although the latter was only seen in never-smokers. A number of other studies have also reported associations between arsenic exposure and these same outcomes (Milton and Rahman, 2002; Olivas-Calderon et al., 2015; Parvez et al., 2008; Rahman et al., 2011; Smith et al., 2013; von Ehrenstein et al., 2005; Das et al., 2014; Farzan et al., 2016; Parvez et al., 2010; Parvez et al., 2013; Recio-Vega et al., 2015). Importantly, though, almost all of them have involved populations with fairly recent exposures. A novel aspect of our study is that it includes adults with very high exposures in utero and during early childhood, with much lower exposures after, and as such provides novel new evidence that these early-life exposures could have impacts that continue well into later life. This is the largest study to date to report this type of finding.

Other work in northern Chile supports these findings. In ecologic analyses, we found high rates of bronchiectasis (standardized mortality ratio (SMR) = 18.4, 95% CI: 10.3–30.4) and other chronic obstructive pulmonary disease (SMR = 2.9, 95% CI: 1.7–4.5) mortality in Antofagasta in those born during or just before the high exposure period (Smith et al., 2012). And, in an earlier pilot study in Arica and Antofagasta, we reported preliminary evidence that early-life arsenic exposure was associated with increases in respiratory symptoms and declines in FVC, with the latter also being greater in never-smokers (Dauphine et al., 2011). Decrements were also seen for FEV1, although sample sizes were small (n = 32) and subjects were a convenience sample of mostly health care workers. A number of findings support the biologic plausibility of our results. For example, ingested arsenic is known to cross the placenta (NRC, 1999), and is known to accumulate in the lung more than in most other organs, possibly due to its binding affinity to sulfhydral groups abundant in lung tissue (NRC, 1999). Also, ingested arsenic is an established human carcinogen of the lung; it not only reaches this organ, but causes toxicity there (IARC, 2012).

The reason we saw arsenic-associated FVC declines in never-smokers but not in smokers is unknown. One possibility could be that the toxic effects of smoking may mask those due to arsenic but this is speculative. Several studies have reported evidence of positive synergy between smoking and arsenic for lung cancer (Ferreccio et al., 2000; Chen et al., 2004; Ferreccio et al., 2013), but evidence for similar effects for non-malignant lung disease is less clear. For example, in the large Health Effects of Arsenic Longitudinal Study in Bangladesh, arsenic-associated FVC declines were similar in smokers and non-smokers (Parvez et al., 2013). Overall, further research is needed to more clearly delineate the impact of smoking on non-malignant lung disease related to arsenic.

After the treatment plant was installed in Antofagasta in 1970, arsenic concentrations decreased rapidly from about 860 μg/L to about 100 μg/L. Improvements in the treatment process have resulted in gradual reductions from 100 μg/L to <10 μg/L today. It's possible that some of the associations we identified in subjects from Antofagasta were due to the more moderate exposures (e.g., 10–100 μg/L) that occurred after 1971. For shortness of breath, the magnitude of the associations in those with high early-life exposure were similar to those in subjects with long-term exposure at 60 μg/L. Importantly, though, this was not the case for most of the outcomes we assessed. For chronic cough, chronic phlegm, childhood respiratory hospitalizations, and FVC, effect sizes were higher in those with high early-life exposure than in those with long-term moderate exposures. These differences provide some evidence that the adverse outcomes identified in Antofagasta were at least partially due to the specific effects of early-life exposure.

Although there is abundant evidence linking high arsenic water concentrations (e.g., >100 μg/L) to adverse health effects, the toxicity at lower concentrations is less clear. We identified five-fold increases in shortness of breath and 2–4-fold increases in wheeze and asthma in

Table 2
Logistic regression prevalence odds ratios for respiratory symptoms and disease by various metrics and levels of arsenic exposure.

Symptom	Highest lifetime (µg/L)					Highest age 0–20 years (µg/L)					Cumulative (µg/L-years)				
				Unadjusted	Adjusted[a]				Unadjusted	Adjusted[a]				Unadjusted	Adjusted[a]
	As	Case	Cont	OR (90% CI)	OR (90% CI)	As	Case	Cont	OR (90% CI)	OR (90% CI)	As	Case	Cont	OR (90% CI)	OR (90% CI)
Shortness of breath	<11	6	198	1.00 (ref)	1.00 (ref)	<11	6	202	1.00 (ref)	1.00 (ref)	<2342	15	249	1.00 (ref)	1.00 (ref)
	11–200	28	180	5.13 (2.40, 11.0)	5.48 (2.55, 11.8)	11–200	28	176	5.36 (2.51, 11.4)	5.70 (2.65, 12.2)	2342–5430	35	231	2.52 (1.48, 4.27)	2.55 (1.49, 4.37)
	>200	52	331	5.18 (2.51, 10.7)	5.56 (2.68, 11.5)	>200	52	331	5.29 (2.56, 10.9)	5.65 (2.72, 11.7)	>5430	36	229	2.61 (1.54, 4.42)	2.82 (1.63, 4.88)
Chronic cough	<11	3	201	1.00 (ref)	1.00 (ref)	<11	4	204	1.00 (ref)	1.00 (ref)	<2342	9	255	1.00 (ref)	1.00 (ref)
	11–200	8	200	2.68 (0.87, 8.26)	2.69 (0.87, 8.32)	11–200	7	197	1.81 (0.64, 5.15)	1.81 (0.63, 5.15)	2342–5430	16	250	1.81 (0.90, 3.65)	1.75 (0.86, 3.56)
	>200	58	325	12.0 (4.47, 32.0)	12.3 (4.55, 33.0)	>200	58	325	9.10 (3.84, 21.6)	9.29 (3.90, 22.1)	>5430	44	221	5.64 (3.03, 10.5)	5.80 (3.05, 11.0)
Chronic phlegm	<11	5	199	1.00 (ref)	1.00 (ref)	<11	6	202	1.00 (ref)	1.00 (ref)	<2342	8	256	1.00 (ref)	1.00 (ref)
	11–200	7	201	1.39 (0.52, 3.68)	1.31 (0.49, 3.50)	11–200	6	198	1.02 (0.39, 2.67)	0.96 (0.36, 2.52)	2342–5430	10	256	1.25 (0.57, 2.76)	1.27 (0.57, 2.83)
	>200	35	348	4.00 (1.80, 8.91)	3.83 (1.71, 8.60)	>200	35	348	3.39 (1.61, 7.10)	3.22 (1.52, 6.82)	>5430	29	236	3.93 (2.01, 7.71)	3.53 (1.76, 7.08)
Wheeze	<11	6	198	1.00 (ref)	1.00 (ref)	<11	6	202	1.00 (ref)	1.00 (ref)	<2342	13	251	1.00 (ref)	1.00 (ref)
	11–200	24	184	4.30 (1.99, 9.29)	4.35 (2.00, 9.46)	11–200	24	180	4.49 (2.08, 9.69)	4.51 (2.08, 9.80)	2342–5430	22	244	1.74 (0.96, 3.15)	1.95 (1.06, 3.59)
	>200	22	361	2.01 (0.93, 4.35)	2.05 (0.94, 4.48)	>200	22	361	2.05 (0.95, 4.43)	2.09 (0.96, 4.55)	>5430	17	248	1.32 (0.71, 2.47)	1.12 (0.59, 2.12)
Child hospitalization[b]	<11	7	197	1.00 (ref)	1.00 (ref)	<11	7	201	1.00 (ref)	1.00 (ref)	<2342	9	255	1.00 (ref)	1.00 (ref)
	11–200	8	200	1.13 (0.47, 2.68)	1.16 (0.48, 2.77)	11–200	8	196	1.17 (0.49, 2.79)	1.20 (0.50, 2.87)	2342–5430	19	247	2.18 (1.10, 4.31)	2.07 (1.04, 4.13)
	>200	44	339	3.65 (1.84, 7.25)	3.88 (1.94, 7.74)	>200	44	339	3.73 (1.88, 7.39)	3.94 (1.97, 7.87)	>5430	31	234	3.75 (1.98, 7.12)	4.72 (2.40, 9.25)
Asthma	<11	9	195	1.00 (ref)	1.00 (ref)	<11	9	199	1.00 (ref)	1.00 (ref)	<2342	13	251	1.00 (ref)	1.00 (ref)
	11–200	18	190	2.05 (1.03, 4.10)	2.21 (1.10, 4.45)	11–200	18	186	2.14 (1.07, 4.28)	2.28 (1.13, 4.59)	2342–5430	23	243	1.83 (1.01, 3.30)	2.09 (1.14, 3.82)
	>200	26	357	1.58 (0.82, 3.03)	1.76 (0.91, 3.41)	>200	26	357	1.61 (0.84, 3.09)	1.79 (0.92, 3.46)	>5430	17	248	1.32 (0.71, 2.47)	1.33 (0.70, 2.54)
Chronic bronchitis	<11	3	201	1.00 (ref)	1.00 (ref)	<11	3	205	1.00 (ref)	1.00 (ref)	<2342	4	260	1.00 (ref)	1.00 (ref)
	11–200	7	201	2.33 (0.74, 7.34)	2.35 (0.74, 7.45)	11–200	7	197	2.43 (0.77, 7.64)	2.42 (0.76, 7.67)	2342–5430	10	256	2.54 (0.95, 6.79)	2.72 (1.00, 7.41)
	>200	14	369	2.54 (0.88, 7.31)	2.66 (0.92, 7.73)	>200	14	369	2.59 (0.90, 7.45)	2.70 (0.93, 7.84)	>5430	10	255	2.55 (0.95, 6.82)	2.34 (0.85, 6.43)

Abbreviations: As, arsenic water concentration; CI, confidence interval; Cont, controls; OR, odds ratios.
[a] Adjusted for age, gender, and smoking.
[b] Ever hospitalized for a respiratory infection as a child.

Table 3
Results from multiple linear regression analyses of age, gender, height-adjusted forced vital capacity (FVC) residuals (milliliters) by various metrics and levels of arsenic exposure, stratified by smoking status.

Arsenic exposure		Never-smokers					Smokers				
		N	Unadjusted		Adjusted[a]		N	Unadjusted		Adjusted[a]	
Metric	As level		Residual	(90% CI)	Residual	(90% CI)		Residual	(90% CI)	Residual	(90% CI)
Lifetime highest (µg/L)	<11	107					97				
	11–200	99	−151	(−277, −26)	−175	(−303, −47)	109	−89	(−207, 29)	−64	(−180, 51)
	>200	194	−164	(−274, −53)	−224	(−351, −97)	189	27	(−94, 149)	43	(−89, 175)
Highest age 0–20 years (µg/L)	<11	107					101				
	11–200	99	−151	(−277, −26)	−175	(−303, −47)	105	−93	(−211, 24)	−64	(−180, 51)
	>200	194	−164	(−274, −53)	−224	(−351, −97)	189	27	(−94, 148)	43	(−88, 174)
Lifetime cumulative (µg/L-years)	<2342	137					127				
	2342–5430	124	−84	(−198, 31)	−104	(−222, 13)	142	−57	(−164, 50)	−57	(−163, 50)
	>5430	139	−191	(−296, −87)	−229	(−343, −115)	126	101	(−21, 223)	125	(−003, 252)
Long-term moderate (µg/L)	<11	107					97				
	≈60	60	−164	(−317, −11)	−192	(−351, −34)	73	−87	(−215, 41)	−62	(−189, 64)

Abbreviations: As, arsenic; CI, confidence interval.

[a] Adjusted for smoking (in smokers) and Aymara race.

subjects with long-term moderate exposures near 60 µg/L. These findings were unexpected, since most studies identifying clear associations between arsenic and respiratory symptoms have reported much lower relative risks (Milton and Rahman, 2002; von Ehrenstein et al., 2005; Parvez et al., 2013; Guha Mazumder et al., 2000). For example, in the prospective Health Effects of Arsenic Longitudinal Study in Bangladesh, the hazard ratio for having any respiratory symptom was 1.39 (95% CI, 1.19–1.63) for arsenic water concentrations of 40–90 µg/L and 1.43 (1.22–1.68) for arsenic concentrations of >178 µg/L (Parvez et al., 2010). The reason why we identified higher relative risks in our moderately exposed group is unknown. However, almost everyone in our moderately exposed group was exposed at birth and remained exposed throughout most of their lives, and it's possible this early-life and/or long-term continuous exposure resulted in the high relative risks we identified. Most other studies only assessed exposure at one or only a few points in time, so early-life exposure or lifetime exposure patterns are unknown and could differ in these other studies.

Another possible cause of the associations we identified in Iquique is an over-reporting bias, although we know of no obvious reason why symptoms would be over-reported here. The same standardized questionnaire was used in all cities, interviewers were instructed not to over-interpret questions or lead subjects, and staff from all three cities attended the same training sessions. Major selection bias is unlikely since recruitment protocols were the same in the three study cites and the relatively small differences in participation rates across the three cities are unlikely to cause the high symptom odds ratios or fairly large spirometric declines we identified. Confounding is another possible explanation. However, we adjusted for the most prevalent determinants of lung health and function including age, gender, height, ethnicity, smoking, second hand smoke, and occupational exposures and these had little impact on results. All three cities are coastal cities with somewhat elevated albeit similar $PM_{2.5}$ levels (e.g. 10–20 µg/m³) (Ministerio del Medio Ambiente, 2015; WHO, 2014). No obvious source of allergens is known in Iquique. We did not have detailed data on other air pollutants (NO₂, ozone) or traffic patterns, although these factors typically are associated with effect sizes that are fairly low. For example, in the U.S. Sister Study (n = 50,884), interquartile range increases in $PM_{2.5}$ and NO₂ (3.6 µg/m³ and 5.8 ppb, respectively), were associated with ORs for wheeze of 1.14 (95% CI: 1.04–1.26) and 1.08 (1.00–1.17), respectively (Young et al., 2014). In Los Angeles children, $PM_{2.5}$ differences of 30 µg/m³ were associated with shortness of breath and wheeze ORs of 1.08 (95% CI: 1.00–1.17) and 1.06 (1.01–1.11), respectively (Ostro et al., 2001). These ORs are much lower than the ORs of 2–5 we identified in our study, suggesting that these air pollutants were not responsible for the associations reported here.

Exposure misclassification in this study could have resulted from missing exposure data, inaccurate recall, or arsenic from non-water sources. Because exposure was assessed similarly in all subjects, most of this was likely non-differential and biased ORs towards the null. In addition, exposure was based mostly on residences, and errors in recalling this information are likely minimal. Adjustments for occupational arsenic exposure had little impact on our results and arsenic air concentrations in the three cities are similar (Ferreccio and Sancha, 2006). Most food in this area comes from outside the region, and non-differential misclassification due to arsenic inherent in this outside food would likely bias results towards the null (Ferreccio and Sancha, 2006; Sancha and Frenz, 2000). Arsenic intake may result from the use of contaminated water to grow local crops or to prepare foods. While this does not alter our conclusions regarding arsenic water-lung disease associations, it would need to be considered in risk assessments seeking to examine dose-response relationships for total arsenic intake.

Overall, we identified evidence of associations in both adults with very high exposures in early-life, and in subjects with long-term, moderate exposures. A variety of information from other studies and data on biologic plausibility support our early-life findings. Major reporting bias or confounding seem unlikely but cannot be ruled out. Our findings regarding moderate exposure levels are particularly novel in that they are the first with lifetime exposure information to show these types of associations. Given this novelty, and given the fact that tens of millions of people worldwide are exposed to levels close to this, it would be especially important to confirm these findings in a population with similar exposure levels, good information on relevant confounders, and accurate data on arsenic exposure during all life stages.

Conflict of interest

The authors of "High risks of lung disease associated with early-life and moderate lifetime arsenic exposure in northern Chile" declare they have no conflicts of interest. Dr. Craig Steinmaus has done consulting work on the health effects of arsenic for industry and environmental organizations.

Transparency document

The Transparency document associated with this article can be found, in online version.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.taap.2016.10.006.

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