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The impact of BMI on non-malignant respiratory symptoms and lung function in arsenic exposed adults of Northern Chile



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ABSTRACT

Background: Elevated body mass index (BMI) and arsenic are both associated with cancer and with non-malignant lung disease. Using a unique exposure situation in Northern Chile with data on lifetime arsenic exposure, we previously identified the first evidence of an interaction between arsenic and BMI for the development of lung cancer.

Objectives: We examined whether there was an interaction between arsenic and BMI for the development of non-malignant lung disease.

Methods: Data on lifetime arsenic exposure, respiratory symptoms, spirometry, BMI, and smoking were collected from 751 participants from cities in Northern Chile with varying levels of arsenic water concentrations. Spirometry values and respiratory symptoms were compared across subjects in different categories of arsenic exposure and BMI.

Results: Adults with both a BMI above the 90th percentile ($> 33.9 \text{ kg/m}^2$) and arsenic water concentrations $\geq 11 \mu\text{g/L}$ exhibited high odds ratios (ORs) for cough (OR = 10.7, 95% confidence interval (CI): 3.03, 50.1), shortness of breath (OR = 14.2, 95% CI: 4.79, 52.4), wheeze (OR = 14.4, 95% CI: 4.80, 53.7), and the combined presence of any respiratory symptom (OR = 9.82, 95% CI: 4.22, 24.5). In subjects with lower BMIs, respiratory symptom ORs for arsenic water concentrations $\geq 11 \mu\text{g/L}$ were markedly lower. In never-smokers, reductions in forced vital capacity associated with arsenic increased as BMI increased. Analysis of the FEV₁/FVC ratio in never-smokers significantly increased as BMI and arsenic concentrations increased. Similar trends were not observed for FEV₁ alone or in ever-smokers.

Conclusions: This study provides preliminary evidence that BMI may increase the risk for arsenic-related non-malignant respiratory disease.

1. Introduction

Hundreds of millions of people worldwide are exposed to arsenic through contaminated food or water (Naujokas et al., 2013). Multiple studies have linked chronic arsenic exposure to increased risks of cancers including lung, bladder, kidney, and skin cancer, as well as diabetes, cardiovascular disease, and other adverse health outcomes (Smith et al., 1998; Hopenhayn-Rich et al., 1998; Chen et al., 1992, 1996; Tseng, 1977; Benbrahim-Tallaa and Waalkes, 2008; Tsuda et al., 1995; Maull et al., 2012). The International Agency for Research on

Cancer has listed ingested arsenic as a class I human lung carcinogen (IARC Working Group on the Evaluation of Carcinogenic Risk, 2012). In the US, it has been estimated that about 12% of all public water systems have arsenic concentrations close to the US and World Health Organization (WHO) regulatory drinking water standard of $10 \mu\text{g/L}$ (Schulman, 2000; The World Health Organization, 2016). It is estimated that concentrations near this level may be associated with one excess case of cancer for every 300 individuals exposed, which is about 50 times higher than the estimated risk for any other regulated contaminant (National Research Council, 2001; Smith et al., 2002).

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It is increasingly thought that lung cancer is the most common cause of mortality in those with prolonged arsenic exposure, suggesting that the human lung may be particularly susceptible to ingested arsenic (Smith and Steinmaus, 2009). Arsenic exposure also increases the risk of non-malignant pulmonary disease and abnormal auscultation findings (National Research Council, 2014; Sanchez et al., 2016). Chronic cough, shortness of breath (SOB), and abnormal lung sounds are increased in those exposed to ingested arsenic (Sanchez et al., 2016; Mazumder et al., 2000). Multiple studies, many of which involve exposure levels that overlap those in Northern Chile, have also demonstrated a relationship between arsenic exposure and decreases in forced vital capacity (FVC) and forced expiratory volume in the first second (FEV₁) (Sanchez et al., 2016; von Ehrenstein et al., 2005; Ghosh, 2013; Smith et al., 2013; Das et al., 2014; Nafees et al., 2011; Parvez et al., 2010, 2013; Dauphiné et al., 2011; Steinmaus et al., 2016). FVC and FEV₁ are common spirometric measurements, the first being a measurement of the total volume of air forcefully exhaled after one complete inhalation, and the second a measurement of the total volume of air forcefully exhaled in one second after one complete inhalation. These measurements can be used as indicators for varying types of lung dysfunction (Ranu et al., 2011; Pellegrino et al., 2005).

The mechanisms of arsenic pathogenesis are largely unknown, but may involve increased circulation of inflammatory agents and oxidative stress, both of which have been strongly linked to cancer and lung disease progression (Coussens and Werb, 2002; Reuter et al., 2010). While high arsenic exposure is limited to certain geographic regions, elevated body mass index (BMI) is a globally widespread health concern and also increases systemic inflammation, oxidative stress, and cancer risk (Furukawa et al., 2004; Aviv, 2004; Fantuzzi, 2005; Shoelson and Herrero, 2007; Rocha and Libby, 2009; Pischon et al., 2007; de Heredia et al., 2012; Belkina and Denis, 2012; Weisberg et al., 2003; World Health Organization, 2016; Secretan et al., 2016). Both arsenic exposure and elevated BMI have been shown to trigger inflammatory reactions in the lungs (National Research Council, 1999; Mancuso et al., 2010). Obesity is also associated with increased odds of chronic cough and SOB (Jarvis et al., 2002). The joint ability of arsenic and elevated BMI to individually cause inflammation, oxidative stress, and potentially alter adipocyte protein synthesis highlights the possibility that the two could interact to increase disease risks (Thomas et al., 2000; Mantzoros et al., 1997; Gossai et al., 2015; Ahmed et al., 2010).

Our research group has been studying the long-term health effects of arsenic using a uniquely exposed area in Northern Chile. The Antofagasta Region located in the Atacama Desert is one of the driest habitable places on earth, receiving less than two millimeters of rain annually (McKay et al., 2003; Schwerdtfeger, 1976; Benner et al., 2000). Because it is so dry there are few individual water sources, and each city has a single municipal water supply. These water supplies have had a wide range of arsenic concentrations from current-day concentrations of ≤ 10 $\mu\text{g/L}$ to over 800 $\mu\text{g/L}$ from the late 1950s through the 1960s. Since arsenic records are available on all of the major water sources in this area for many decades in the past, lifetime arsenic exposures can be assessed fairly accurately simply by knowing which city a person has lived in during which years (Ferreccio et al., 2000). To date, we have identified major increases in lung cancer, bladder cancer, lung symptoms, spirometry decrements, and other health outcomes associated with high arsenic exposures in this area. Most recently, we found that the odds ratios of lung cancer associated with arsenic were over three times greater in people with BMIs above the 90th percentile compared to people with lower BMIs (Steinmaus et al., 2015). Given these substantial findings for lung cancer and that both arsenic and obesity are associated with increased risks of non-malignant lung symptoms and disease, we used data from this unique study area to evaluate whether arsenic and elevated BMI could interact to increase non-malignant lung disease risks.

2. Methods

2.1. Subject ascertainment

This analysis is part of a parent study of arsenic and non-malignant lung disease conducted in Northern Chile between 2009 and 2011 (Steinmaus et al., 2016). Study participants were adults aged 39–60 years who were randomly selected from the Chilean Electoral Registry for three of the four largest cities in Northern Chile, which had variable arsenic water concentrations. Because the focus of the parent study was on the impacts of early-life exposure, all study participants were born between the years of 1958–1970, the high exposure period in Antofagasta. These cities included Arica (population of 157,568; mean arsenic water concentrations near 10 $\mu\text{g/L}$), Iquique (population of 181,773; mean historical arsenic water concentrations of 60 $\mu\text{g/L}$), and Antofagasta (population of 391,832). Antofagasta had a distinct period of high exposure (mean arsenic water concentrations of 860 $\mu\text{g/L}$) beginning in 1958 when two rivers with high arsenic concentrations were diverted to the city for drinking purposes and ending in 1970 when an arsenic treatment plant was installed. Following the installation of this plant, concentrations initially dropped to about 100 $\mu\text{g/L}$ and eventually to 10 $\mu\text{g/L}$ by 2003 with further improvements to the plant (Ferreccio et al., 2000).

All subjects provided written consent prior to participation. Participants who lived less than 80% of their lives in the city where their interview was conducted, were born in Santiago, exhibited a BMI at the time of interview of < 18.5 kg/m^2 , had lung cancer, or had a poor spirometry grade (greater than 150 ml difference in FEV₁ across two best trials) were excluded from the main analyses presented here (Fig. 1). Individuals born in Santiago were excluded due to historically high air pollution (Ostro et al., 1996). Since our analyses assumed a unidirectional relationship between lung function and BMI, individuals with a BMI < 18.5 kg/m^2 were excluded, as this BMI level is associated with higher rates of mortality (Flegal et al., 2005).

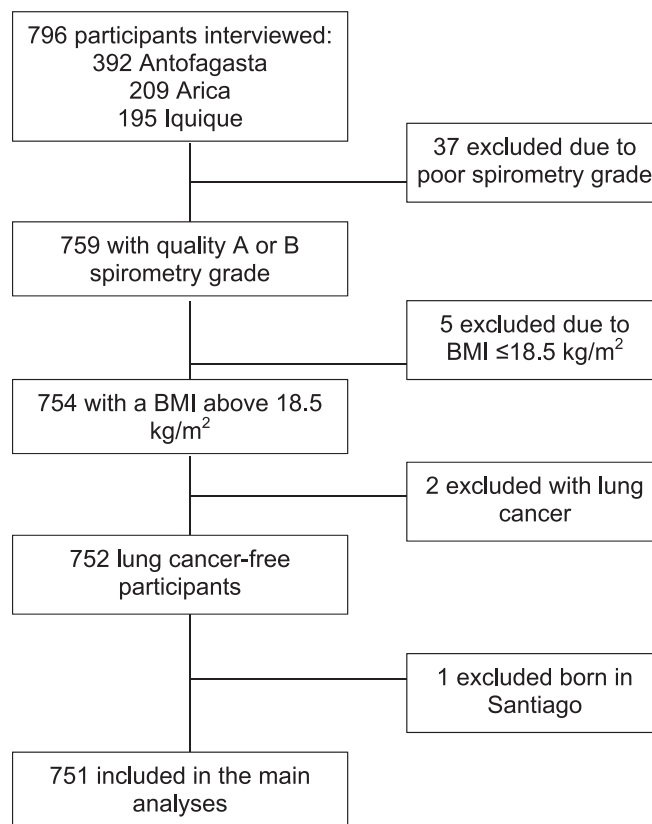


Fig. 1. Data analysis inclusion criteria.

2.2. Questionnaires and BMI

Trained staff administered one-time study interviews and pulmonary function tests. Structured questionnaires were administered to collect data on lifetime residential history; occupational history (e.g. mining or smelter work); water sources used (e.g. public water supply, bottled water); typical water intake; ages of and duration of tobacco use; secondhand smoke exposure in childhood and adulthood; specific occupational lung irritant exposures like asbestos, arsenic, and silica; socioeconomic status; typical diet currently and 20 years ago; illnesses like diabetes and hypertension; and ethnicity/race. Socioeconomic status (SES) scores were calculated on a 12-point scale based on self-reported ownership of household appliances, electronics, car, or employment of domestic help. Diet is strongly related to obesity and was assessed as a potential confounder. Participants were also asked about potential pulmonary disease symptoms such as cough, shortness of breath (SOB), wheeze, and phlegm production. Questions on pulmonary symptoms were based on the British Medical Research Council respiratory questionnaire and translated to local Spanish (Cotes, 1987). Information on cough was ascertained by asking, “Do you cough almost every day for three consecutive months or more during the year?” and if so, “For how many years have you had this cough?” Participants answering yes to the first were considered to have cough. Participants answering two years or more for the second question were considered to have chronic cough. Participants were also asked about shortness of breath when walking with people their own age on level ground, when hurrying or walking uphill, or when walking quickly on level ground or uphill. They were also asked about duration, frequency, and hospitalizations for wheeze, and about other prior hospitalizations, all medication use, and prior physician-diagnosed asthma, bronchitis, emphysema, and other pulmonary diagnoses. The Spanish version of these questions are shown in Fig. S1. Height and weight were measured by the study nurses at the time of interview using standard protocols and were used to calculate BMI.

2.3. Spirometry

Spirometry measurements were collected using an EasyOne spirometer in diagnostic mode (NDD Medical Technologies, Zurich, Switzerland) according to protocol guidelines of the American Thoracic Society (Miller et al., 2005). Participants were asked to provide a minimum of three forced exhalation efforts from the seated position without a nose clip or bronchodilator. Although use of a nose clip is standard protocol, research suggests it has little impact on FVC or FEV₁ (Newall et al., 2007). Only participants with spirometry grades A or B (i.e. at least two acceptable maneuvers with FEV₁ values less than 150 ml apart) based on the EasyOne spirometry guidelines were included in our main analyses, although separate analyses including all subjects regardless of grade were also done. Each subject's best effort (largest sum of FEV₁ and FVC) was included in the analyses.

2.4. Arsenic exposure assessment

Arsenic exposure was assessed using historical municipal drinking water records for all cities and towns in the study area and nearly all subjects reported use of public water supplies. These records were collected from government agencies and water suppliers and were linked to each participant's residential history in order to create an arsenic exposure estimate for each year of each subjects life, from birth to interview (Borgoño et al., 1977). These yearly estimates were then used to develop several exposure metrics including the participant's highest arsenic water concentration for any single year of their lives; the highest average arsenic water concentration over any contiguous 5, 20, or 40-year period; cumulative exposure (calculated by summing the yearly concentrations); average lifetime arsenic water concentration; and the highest arsenic water concentration during the first 20 years of

life. Although some participants lived outside of the three recruitment cities at some point in their lives, almost all of these residences were in Chile and arsenic exposure information was available for almost all of these other cities. Bottled water use and residences without arsenic measurements were assigned values of zero. Overall, arsenic water concentration data were available for 97.9% of all life-years of the study participants.

2.5. Data analysis

All statistical analyses were conducted using the open-source statistical analysis software R (Version 0.99.486 2015). The major non-malignant lung disease variables of interest were the presence of respiratory symptoms (coughing, wheezing, SOB) and the spirometric measurements FEV₁ and FVC. Age, height, FEV₁, and FVC were assessed as continuous variables. Sex, smoking pack-years (by tertile), BMI level (18.5– < 25 kg/m² defined as normal, 25–30 kg/m² defined as overweight, and > 30 kg/m² defined as obese), and single year lifetime highest arsenic exposure (< 11 µg/L, 11–200 µg/L, and ≥ 200 µg/L) were assessed as categorical variables. These cutoff points for arsenic exposure were based on the highest arsenic concentrations in the drinking water of the largest cities in the study area (Steinmaus et al., 2016). Participants in the ≥ 200 µg/L category lived most of their lives in Antofagasta, while all but eight in the 11–200 µg/L group had lived majority of their lives in Iquique. All participants in the < 11 µg/L category lived most of their lives in Arica. Although our primary exposure metric was the single highest year, most subjects lived in the area for many years and thus had many years of exposure.

First, we conducted bivariate analysis in order to examine socio-demographic characteristics between the different BMI categories. Odds ratios were calculated to determine potential associations, using people with a normal BMI as the reference category. Next, we calculated odds ratios to evaluate associations between the socio-demographic variables and the prevalence of respiratory symptoms such as cough, wheezing, and SOB, as well a combined measure for any one of these three symptoms.

We then used logistic regression to calculate odds ratios (ORs) for respiratory symptom prevalence in participants with high and low arsenic exposure and with high and low BMI. In these analyses, low and high arsenic exposures were defined as having a single year highest exposure below or ≥ 11 µg/L, respectively. This cut-off was selected because the WHO's recommended limit for arsenic in water is 10 µg/L (The World Health Organization, 2016). Low and high BMI were defined as being below or above the cohort's 90th percentile, respectively. The 90th percentile was selected for our main analyses since this was the cut-off point used in our previous evaluation of arsenic-BMI interaction for lung cancer, although analyses using other cutoff points (e.g. the median and 30 kg/m²) were also performed. Additional analyses with alternative arsenic exposure cutoff-points and alternative metrics (e.g. cumulative exposure) were also conducted. ORs were adjusted *a priori* by age, sex, and tertiles of pack-years smoked. In these analyses, arsenic exposure and BMI were each categorized into two groups based on sample size considerations.

Because there were no widely accepted standard reference values for our study area, we used FVC and FEV₁ residuals as our primary spirometry outcome metric. Residuals were calculated using multiple linear regression and data from the study subjects themselves. Here, subjects FEV₁s or FVCs were entered in the multiple linear regression equation as the dependent variable and their ages, sex, and heights were entered as the independent variables. Residuals were then calculated as the difference between the subjects observed FEV₁ or FVC and that predicted for them based on the linear regression equation and their age, sex, and height. Race had little impact on results and was not included. The R² of the linear regression model with FVC as the dependent variable and age, sex, and height as the independent variables was 0.56. For FEV₁ this value was 0.51.

FEV₁ and FVC residuals were compared across various socio-demographic groups using Student's *t*-tests. To analyze whether BMI may impact arsenic-related changes on FVC or FEV₁, participants were stratified into groups based on highest single year arsenic exposures of < 11, 11–200, and ≥ 200 µg/L and normal, overweight, and obese BMI levels. Because smoking is a strong predictor of respiratory disease, subjects were further stratified into ever- vs. never-smokers (Burchfiel et al., 1995). Differences in mean FEV₁ and FVC across the various arsenic-BMI groups were then calculated using linear regression models adjusted by age, sex, and height.

Interaction between arsenic and BMI on spirometric outcomes was evaluated in linear regression analyses by adding a product term for arsenic and BMI. Here, BMI was entered as a continuous variable and arsenic as a dichotomous categorical variable (< 11 µg/L or ≥ 11 µg/L). Potential biologic interaction between arsenic and BMI on respiratory symptoms was calculated using synergy indices and the methods described by Andersson et al. (Andersson et al. (2005) For synergy calculations, a value of 0.5 was entered for cells with zero subjects. A synergy index greater than one indicates a greater than additive relationship.

2.6. Ethics review

The study protocol has approval from the institutional review boards at the University of California, Berkeley and the Pontificia Universidad Católica de Chile.

3. Results

3.1. Participant characteristics

In total, 751 participants were included in the analyses presented here, including 198 from the low-exposure city of Arica, 202 from the middle exposure city of Iquique, and 351 from the high exposure city of Antofagasta. The socio-demographic characteristics of the participants stratified by BMI categories are shown in Table 1. Overall, 178 subjects had normal BMI (18.5 ≤ BMI < 25 kg/m²), 375 were overweight (25 ≤ BMI ≤ 30 kg/m²), and 198 were obese (BMI > 30 kg/m²). Males were more likely to be obese than females (OR = 1.92, 95% CI: 1.28, 2.90). Those with an occupational exposure to a known lung irritant were more likely to be overweight (OR = 1.81, 95% CI: 1.18, 2.78) but not obese (OR = 0.94, 95% CI: 0.56, 1.57). There were no associations between highest arsenic exposure and age (*p* = 0.20), pack-years smoked (*p* = 0.62), or SES (*p* = 0.62) (data not shown).

Table S1 presents respiratory symptoms ORs for various socio-demographic characteristics. Older age (> 49 years) was associated with cough (OR = 2.28, 95% CI: 1.06, 4.89) and with having any respiratory symptom (OR = 1.74, 95% CI: 1.02, 2.96). Obesity was associated with wheeze (OR = 2.47, 95% CI: 1.11, 5.49), SOB (OR = 1.72, 95% CI: 0.88, 3.34), and any respiratory symptom (OR = 1.44, 95% CI: 0.85, 2.45) although only the association with wheeze was statistically significant. A single year lifetime highest arsenic exposure of 11–200 µg/L was associated with SOB (OR = 4.94, 95% CI: 1.99, 12.2), wheeze (OR = 3.91, 95% CI: 1.55, 9.87), and any symptom (OR = 4.07, 95% CI: 2.07, 7.99) when compared to the low exposure group (< 11 µg/L). Arsenic exposures > 200 µg/L were also associated with increases in cough (OR = 10.6, 95% CI: 3.24, 29.2), SOB (OR = 4.47, 95% CI: 1.87, 10.7), and any symptom (OR = 4.07, 2.15, 7.70) when compared to the low exposure group. Those with cumulative smoking histories of 20 pack-years or more were more likely to report any respiratory symptom (OR = 2.40, 95% CI: 1.09, 5.30) compared to never-smokers (not shown).

Table 2 shows the mean sex, age, and height adjusted residuals of FEV₁ and FVC by various socio-demographic categories. Compared with BMI of 18.5 to 25 kg/m², the upper category of BMI was associated with decreased FVC and FEV₁ residuals although results were not

statistically significant. While ≥ 20 pack-year cumulative smoking histories were also associated with decrements in FVC (127 ml) and FEV₁ (70 ml) compared to never smokers (data not shown), these decreases were also not statistically significant.

3.2. Arsenic, BMI and respiratory symptoms

ORs for respiratory symptoms adjusted for sex, age, and smoking by categories of arsenic exposure and BMI, using subjects with lower BMI (< 90th percentile of 33.9 kg/m²) and low arsenic exposure (< 11 µg/L) as the reference group, are shown in Fig. 2. Symptom ORs in subjects never exposed to arsenic concentrations ≥ 11 µg/L, but having a BMI > 33.9 kg/m² were above 1.0 for SOB, wheeze, and any symptom combined but were not statistically significant. In subjects with low BMIs, arsenic exposures ≥ 11 µg/L were associated with cough (OR = 6.24, 95% CI: 2.23, 26.0), SOB (OR = 5.96, 95% CI: 2.39, 19.9), wheeze (OR = 2.56, 95% CI: 0.97, 8.82), and any symptom combined (OR = 4.46, 95% CI: 2.31, 9.74). Having both an arsenic exposure ≥ 11 µg/L and a high BMI was associated with even greater increases in cough (OR = 10.7, 95% CI: 3.03, 50.1), SOB (OR = 14.2, 95% CI: 4.79, 52.4), wheeze (OR = 14.4, 95% CI: 4.80, 53.7), and any symptom combined (OR = 9.82, 95% CI: 4.22, 24.5). ORs for chronic cough were similar to those for cough. Synergy indexes for cough (*S* = 2.29, 95% CI: 0.92, 5.70), SOB (*S* = 1.49, 95% CI: 0.51, 4.36), wheeze (*S* = 2.76, 95% CI = 0.60, 12.7), and any symptom combined (*S* = 1.61, 95% CI: 0.62, 4.17) were all above 1.0 but not statistically significant. Similar findings were seen when other cutoff points for BMI were used, although with overall somewhat lower synergy indices (Table S2). Findings were also similar when other arsenic exposure metrics were used, including lifetime average, cumulative exposure, and cumulative exposure between birth and age 20 (data not shown). No associations with phlegm production or asthma were observed.

3.3. Arsenic, BMI and spirometry

FVC and FEV₁ spirometry results for participants in various arsenic exposure and BMI categories, stratified by smoking status, are presented in Table 3. In never smokers with BMIs > 30 kg/m², arsenic exposures of 11–200 (n = 43) and ≥ 200 µg/L (n = 36) were associated with a 311 ml (95% CI: 54, 569) and 353 ml (95% CI: 88, 618) decrease in FVC, respectively, compared to those never exposed to arsenic concentrations ≥ 11 µg/L (n = 24). Given a median FVC value of 3.65 L in never smokers, this 353 ml decrease represents a 9.7% decrease in FVC. In never smokers with BMIs of 25–30 kg/m², arsenic exposures of 11–200 (n = 36) and ≥ 200 µg/L (n = 94) were also associated with decreases in FVC compared to those never exposed ≥ 11 µg/L (n = 58) although the differences were smaller (189 ml and 138 ml, respectively). Similar results for FVC were seen in analyses including all subjects regardless of spirometry grade (Table 3). Clear associations were not seen for FEV₁ (Table S3). In analyses adjusted for age, gender, and height, the arsenic-BMI interaction term for FVC in never smokers had a *p*-value of 0.04 (data not shown). This *p*-value was lower when all subjects regardless of spirometry grade were included (*p* = 0.01). Clear evidence of arsenic-BMI interaction was not seen in ever-smokers or for FEV₁ (data not shown).

Additional adjustments for mining work, secondhand smoke exposure, occupational lung irritant exposures, socioeconomic status, diabetes, or typical weekly fruit and vegetable consumption had little impact on spirometry and symptom results (Fig. S2 and Table S4). Further excluding individuals with emphysema, bronchitis, and asthma from the analysis do not significantly alter the results presented in Table 2, Table 3 or Fig. 2, but did decrease the *p*-value of the arsenic-BMI interaction term for FVC in never-smokers from 0.04 to 0.01. Using other arsenic exposure metrics including cumulative lifetime exposure, cumulative exposure from ages 0–20, or yearly lifetime average did not significantly alter the findings.

Table 1
Socio-demographic characteristics stratified by BMI category.

N = 751	Normal BMI (N = 178)		Overweight BMI (N = 375)			Obese BMI (N = 198)		
	N	%	N	%	OR (95% CI)	N	%	OR (95% CI)
Age (years)								
< 44	44	24.7%	102	27.2%	1.00 (ref)	59	29.8%	1.00 (ref)
44–49	87	48.9%	191	50.9%	0.95 (0.61, 1.45)	93	47.0%	0.80 (0.49, 1.30)
> 49	47	26.4%	82	29.1%	0.75 (0.45, 1.25)	46	23.2%	0.73 (0.42, 1.28)
Sex								
Female	107	60.1%	220	58.7%	1.00 (ref)	87	43.9%	1.00 (ref)
Male	71	39.9%	155	41.3%	1.06 (0.74, 1.53)	111	56.1%	1.92 (1.28, 2.90)
Arsenic exposure^a								
< 11 µg/L	46	25.8%	102	27.2%	1.00 (ref)	50	25.3%	1.00 (ref)
11–200 µg/L	41	23.0%	88	23.5%	0.97 (0.58, 1.61)	73	36.9%	1.64 (0.94, 2.85)
≥ 200 µg/L	91	51.1%	185	49.3%	0.92 (0.60, 1.41)	75	37.8%	0.76 (0.46, 1.25)
Ever-smoker								
No	87	48.9%	188	50.1%	1.00 (ref)	103	52.0%	1.00 (ref)
Yes	91	51.1%	187	49.9%	0.95 (0.67, 1.36)	95	48.0%	0.88 (0.59, 1.32)
Smoking level^b								
Light	32	35.2%	60	32.1%	0.87 (0.81, 1.13)	32	33.7%	0.84 (0.48, 1.49)
Moderate	29	31.9%	63	33.7%	1.01 (0.60, 1.67)	30	31.6%	0.87 (0.49, 1.57)
Heavy	30	32.9%	64	34.2%	0.99 (0.60, 1.63)	33	34.7%	0.93 (0.52, 1.64)
Secondhand smoke^c								
No	52	59.8%	114	60.6%	1.00 (ref)	68	66.0%	1.00 (ref)
Yes	35	40.2%	74	39.4%	0.96 (0.57, 1.62)	35	34.0%	0.76 (0.42, 1.38)
Ethnicity								
Hispanic	154	87.0%	321	85.8%	1.00 (ref)	161	82.1%	1.00 (ref)
Aymara	15	8.5%	45	12.0%	1.44 (0.78, 2.66)	25	12.8%	1.59 (0.81, 3.14)
Other	8	4.5%	8	2.2%	0.48 (0.18, 1.30)	10	5.1%	1.20 (0.46, 3.11)
Education level								
College	55	30.9%	109	29.1%	1.00 (ref)	60	30.3%	1.00 (ref)
Some college	84	47.2%	149	39.7%	0.90 (0.59, 1.36)	83	41.9%	0.91 (0.56, 1.46)
High school	39	21.9%	117	31.2%	1.51 (0.93, 2.46)	55	27.8%	1.29 (0.75, 2.24)
SES score^d								
High	133	74.7%	272	72.5%	1.00 (ref)	138	69.7%	1.00 (ref)
Low	45	25.3%	103	27.5%	1.12 (0.74, 1.68)	60	30.3%	1.29 (0.82, 2.02)
Occupational exposure^e								
No	143	80.3%	260	69.3%	1.00 (ref)	161	81.3%	1.00 (ref)
Yes	35	19.7%	115	30.7%	1.81 (1.18, 2.78)	37	18.7%	0.94 (0.56, 1.57)

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; ref, reference category; SES, socioeconomic status.

^a Single year lifetime highest drinking water arsenic concentration.

^b Light, moderate, and heavy refer to ≤ 2.4 , > 2.4 to < 8.5 , and ≥ 8.5 pack-years. Never smokers used as the reference group.

^c Amongst never-smokers only.

^d High, upper two tertiles; Low, lower tertile.

^e Includes mining work and exposure to silica, asbestos, wood dust, arsenic, and fiberglass.

FEV₁/FVC ratios for various arsenic-BMI exposure categories are shown in Fig. 3 (never smokers) and Fig. 4 (smokers). Never-smoking adults with a BMI below the 90th percentile (≤ 33.9 kg/m²) and a single year highest arsenic exposure below 11 µg/L had a mean ratio of 0.77 (95% CI: 0.76, 0.79). Those with high BMI-low arsenic, low BMI-high arsenic, and high BMI-high arsenic exposures had corresponding ratios of 0.78, 0.79, and 0.81. The p-value for the difference in the mean FEV₁/FVC ratio between the low BMI-low arsenic group and the high BMI-high arsenic group was 0.005. In ever smokers, those in the low BMI-low arsenic, high BMI-low arsenic, low BMI-high arsenic, and high BMI-high arsenic groups had FEV₁/FVC ratios of 0.79, 0.80, 0.79, and 0.77, respectively. The p-value for the difference between the low BMI-low arsenic group and high BMI-high arsenic group was 0.54.

4. Discussion

Overall, we identified high ORs for several respiratory symptoms and fairly large decreases in FVC in never-smoking individuals who were exposed to high levels of arsenic and had elevated BMIs. Although synergy indices were not statistically significant, they were above 1.0 and arsenic-associated ORs for SOB, wheeze, and all symptoms combined were markedly higher in subjects with a BMI above the 90th percentile than in those with lower BMIs. Arsenic-associated decrements in FVC were also markedly greater in subjects with higher BMIs,

although this relationship was only evident in FVC for never-smokers. We also identified a significant increase in the FEV₁/FVC ratio in never-smokers as joint arsenic exposure and BMI increased, which was primarily driven by the decreases in FVC demonstrated in Table 3. Overall, these findings provide preliminary evidence that the combined adverse effects of arsenic and elevated BMI on the lung could be at least additive and possibly greater.

This study is the first to our knowledge to investigate the impact of BMI on lung function and health in arsenic-exposed individuals. Although mechanisms may differ, previous studies have identified somewhat similar associations with other chemical exposures, supporting the idea that the adverse effects of chemical exposures and elevated BMI can be synergistic (Weichenthal et al., 2014). In our recent study in the same area in Northern Chile, we identified evidence of major synergy (i.e. greater than additive associations) between arsenic exposure and excess BMI for lung and bladder cancer, two outcomes commonly linked with arsenic ingestion (Steinmaus et al., 2015). In that study, data was available on current BMI, and for BMI based on self-reported height and weights at ages 20 and 40 years. Lung cancer odds ratios for arsenic exposures > 800 µg/L were nearly 3-times higher in subjects with a BMI in the upper 90th percentile at age 20 (OR = 6.98, 95% CI: 1.84, 26.56) than in those with BMIs below this level (OR = 2.31, 95% CI: 1.63, 3.29) (synergy index = 4.08, 95% CI: 1.01, 16.4). Even higher odds ratios were seen in subjects whose BMI

Table 2

Multiple linear regression analyses of age, gender, and height-adjusted forced vital capacity (FVC) residuals, forced expiratory volume in one second (FEV1) residuals, and FEV₁/FVC ratio means by various socio-demographic categories.

	N	FVC residual (ml)			FEV ₁ residual (ml)			FEV ₁ /FVC		
		Mean res.	95% CI ^a	p ^b	Mean res.	95% CI ^a	p ^b	Mean	95% CI ^a	p ^b
BMI (kg/m²)										
18.5–25	178	21	−63, 104	Ref	18	−55, 90	Ref	0.78	0.77, 0.79	Ref
25–30.0	375	12	−48, 73	0.88	13	−38, 63	0.91	0.79	0.79, 0.80	0.01
> 30	198	−56	−136, 25	0.20	−47	−117, 24	0.21	0.80	0.79, 0.81	0.01
As exposure (µg/L)^c										
< 11	198	39	−35, 113	Ref	−9	−68, 51	Ref	0.78	0.77, 0.79	Ref
11–200	202	−59	−137, 19	0.07	−27	−95, 41	0.69	0.80	0.79, 0.80	0.004
≥ 200	351	3	−63, 69	0.48	17	−40, 74	0.54	0.79	0.79, 80	0.005
Smoking^d										
Never	378	7	−53, 68	Ref	−8	−60, 44	Ref	0.79	0.78, 0.80	Ref
Light	124	1	−99, 101	0.92	18	−66, 103	0.60	0.79	0.78, 0.80	0.94
Moderate	122	−59	−156, 39	0.26	−21	−102, 60	0.79	0.79	0.78, 0.80	0.58
Heavy	128	16	−91, 122	0.89	16	−74, 107	0.64	0.79	0.78, 0.80	0.73
Ethnicity										
Hispanic	636	−14	−60, 33	Ref	−1	−41, 39	Ref	0.79	0.79, 0.80	Ref
Aymara	85	70	−37, 178	0.16	14	−74, 102	0.59	0.78	0.77, 0.79	0.15
Other	30	55	−123, 233	0.45	26	−124, 177	0.60	0.80	0.78, 0.82	0.60
Education										
College	224	64	−190, 146	Ref	39	−34, 111	Ref	0.79	0.78, 79	Ref
Some college	316	−58	−119, 2	0.02	−38	−89, 142	0.09	0.79	0.79, 0.80	0.18
High school	208	10	−70, 90	0.36	10	−55, 75	0.57	0.79	0.78, 0.80	0.49
SES score^e										
High	543	−9	−59, 41	Ref	−12	−55, 31	Ref	0.79	0.79, 0.80	Ref
Low	208	11	−64, 87	0.65	24	−39, 87	0.35	0.79	0.78, 0.80	0.86
Occupational exposure^f										
No	564	10	−37, 57	Ref	7	−33, 47	Ref	0.79	0.79, 0.80	Ref
Yes	187	−47	−139, 44	0.27	−32	−109, 46	0.38	0.79	0.78, 0.79	0.38

Abbreviations: BMI, body mass index; CI, confidence interval; Ref, reference group; res, residual; SES, socioeconomic status.

^a 95% CIs are for the mean FEV1 or FVC residual for this category.

^b P-value for the difference between the mean FEV1 or FVC residual in the corresponding category and the reference category.

^c Single year lifetime highest arsenic water concentration.

^d Light, moderate, and heavy refer to ≤2.4, > 2.4 to < 8.5, and ≥8.5 pack years. Never smokers used as the reference group.

^e High, upper two tertiles; Low, lower two tertiles.

^f Includes mining work and exposure to silica, asbestos, wood dust, arsenic, and fiberglass.

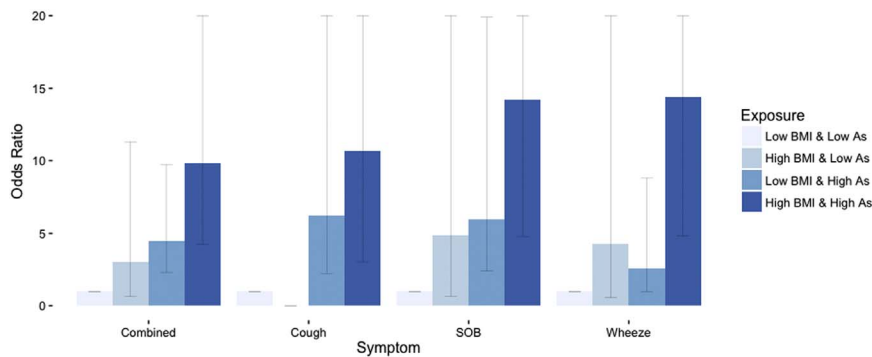


Fig. 2. Logistic regression prevalence odds ratios for respiratory symptoms by categories of BMI and single year highest arsenic water concentration. Abbreviations: As, arsenic; BMI, body mass index; CI, confidence interval; OR, odds ratio; SOB, shortness of breath. Odds ratios were adjusted age, sex, and tertiles of pack-years of smoking; low and high BMI constitutes a BMI below and above the 90th percentile of 33.9 kg/m², respectively. Low and high arsenic constitutes a single year lifetime highest exposure below and ≥11 µg/L, respectively. All categories were mutually exclusive. Horizontal error bars indicate confidence intervals. The upper limits were capped at 20 for illustrative purposes. Actual upper limit values for the symptom odds ratios were as follows: combined, 24.5 (high BMI & high As); cough, 50.1 (high BMI & high As), 26.0 (low BMI & high As); SOB, 52.4 (high BMI & high As), 27.2 (high BMI & low As); wheeze, 53.7 (high BMI & high As), 24.2 (high BMI & low As).

remained high throughout their adult lives. In the study presented here, data on past BMI were not available so it is unknown whether a similar temporal pattern might occur for non-malignant lung disease. Regardless, the high arsenic-associated respiratory symptom ORs and major arsenic-associated decrements in FVC we identified here in subjects with elevated BMI provide at least some evidence that the overall synergistic relationship we identified for lung cancer might also occur, although possibly to a lesser extent, for non-malignant lung disease.

While the precise mechanism by which arsenic damages the lungs is unknown, arsenic ingestion has been linked to increased levels of inflammatory markers and oxidative stress (Wu et al., 2003; Dutta et al., 2015; Qi et al., 2014; Liu et al., 2014; Andrew et al., 2008; Fujino et al., 2005; Weimann et al., 2002; Jomova et al., 2011). Likewise, obesity also is an established cause of increased inflammation and oxidative

stress (Furukawa et al., 2004; Aviv, 2004; Fantuzzi, 2005; Shoelson and Herrero, 2007; Rocha and Libby, 2009; Pischon et al., 2007; de Heredia et al., 2012; Belkina and Denis, 2012; Weisberg et al., 2003; Valdes et al., 2005). More specifically, both arsenic exposure and obesity are known to trigger inflammatory reactions in lung tissue which could lead to additive or possibly even synergistic impacts on lung damage (National Research Council, 1999; Mancuso et al., 2010). In mice, arsenic significantly increased inflammation in overweight mice (Tan et al., 2011). One or more of many different pathways could be involved. In humans, arsenic exposure may decrease respiratory immune function by suppressing chlorine secretion of epithelial lung tissue (Bomberger et al., 2012). Adipocytes specifically respond to inflammatory signals triggered in lung tissue. In particular, lung irritants in mice have been shown to trigger release of interleukin-6 by

Table 3
Age, height, and sex adjusted forced vital capacity (FVC) residuals (ml) by categories of arsenic water concentrations and BMI.

	As ($\mu\text{g/L}$) ^a	BMI 18.5–24.99 kg/m^2				BMI 25–30 kg/m^2				BMI > 30 kg/m^2			
		N	β	95% CI	p	N	β	95% CI	p	N	β	95% CI	p
Quality spirometry grade A and B only (N = 751) ^b	Never smokers (N = 87)												
	11–200	17	227	–131, 584	0.21	36	–189	–437, 60	0.14	43	–311	–569, –54	0.02
	≥ 200	46	–18	–131, 275	0.90	94	–138	–335, 58	0.17	36	–353	–618, –88	0.01
	Ever smokers (N = 91)												
11–200	23	–55	–427, 316	0.77	52	–137	–371, 98	0.25	30	76	–189, 341	0.57	
≥ 200	45	–46	–370, 278	0.78	91	91	–58, 365	0.15	39	–52	–301, 196	0.68	
All participants (N = 787)^c	Never smokers (N = 89)												
	11–200	17	215	–145, 576	0.24	37	–206	–452, 40	0.10	43	–307	–560, –53	0.02
	≥ 200	48	–25	–314, 263	0.86	105	–180	–372, 12	0.07	41	–365	–620, –109	0.01
	Ever smokers (N = 93)												
	11–200	23	–54	–422, 313	0.77	53	–143	–375, 92	0.23	30	69	–194, 333	0.60
	≥ 200	47	–40	–358, 278	0.80	99	113	–94, 320	0.28	43	–77	–320, 166	0.53

Abbreviations: As, arsenic; BMI, body mass index; β , linear regression coefficient (values represent the difference in adjusted mean FVC between the arsenic exposure categories shown and the reference category of < 11 $\mu\text{g/L}$); CI, confidence interval.

^a Single year lifetime highest arsenic exposure. Subjects with highest exposures < 11 $\mu\text{g/L}$ are used as the reference group.

^b Only includes participants who had at least two acceptable trials in which their FEV1 and FVC differed by less than 150 ml.

^c Includes all participants regardless of their spirometry grade.

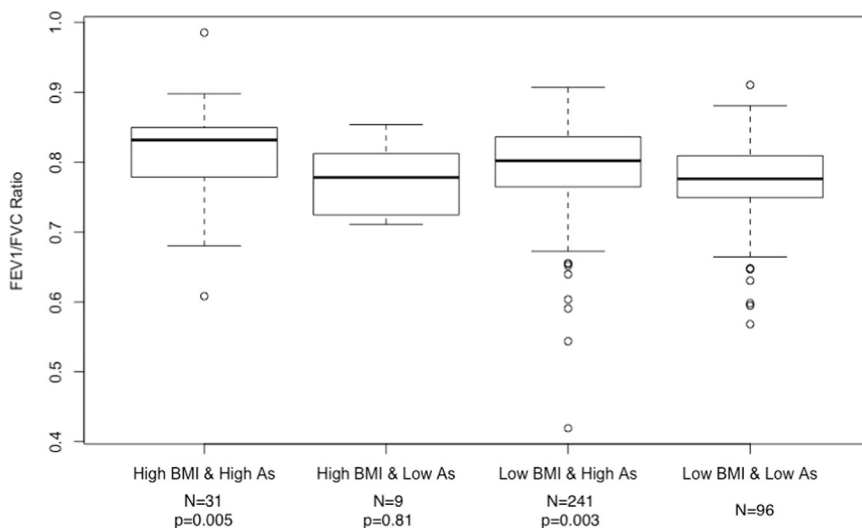


Fig. 3. FEV₁/FVC ratio by categories of BMI and single year lifetime highest arsenic exposure categories in never smokers. Abbreviations: As, single year lifetime highest arsenic water concentration; BMI, body mass index; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity (FVC). Names along x-axis correspond to categories of arsenic exposure and BMI. Low and high BMI constitutes a BMI below and above the 90th percentile of 33.9 kg/m^2 , respectively. Low and high arsenic constitutes a single year lifetime highest exposure below and ≥ 11 $\mu\text{g/L}$, respectively. All categories were mutually exclusive.

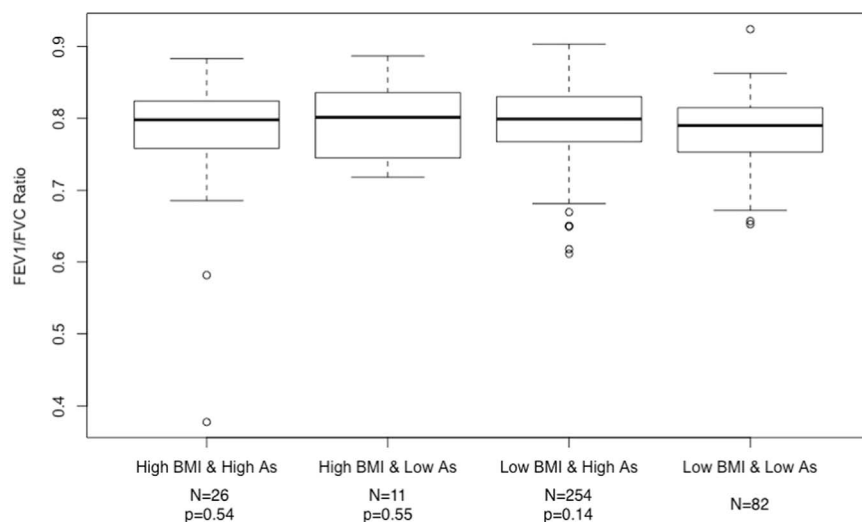


Fig. 4. FEV₁/FVC ratio by categories of BMI and single year lifetime highest arsenic exposure categories in ever-smokers. Abbreviations: As, single year lifetime highest arsenic water concentration; BMI, body mass index; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity (FVC). Names along x-axis correspond to categories of arsenic exposure and BMI. Low and high BMI constitutes a BMI below and above the 90th percentile of 33.9 kg/m^2 , respectively. Low and high arsenic constitutes a single year lifetime highest exposure below and ≥ 11 $\mu\text{g/L}$, respectively. All categories were mutually exclusive.

adipocytes, a cytokine that has been shown to increase metastasis of arsenic-exposed respiratory tissue (Qi et al., 2014; Liu et al., 2014; Lang et al., 2008). Receptors of adiponectin, a cytokine produced by adipose tissue, are expressed in the lungs and play an anti-inflammatory role;

however, as more fat tissue accumulates, secretion of adiponectin decreases (Shore, 2008; Koerner et al., 2005). Genetically modified mice unable to produce adiponectin had overall poor lung health, suggesting a link between healthy lung function and the adipocytokine (Summer

et al., 2008). Leptin is another molecule produced by adipocytes, is involved in satiety, energy balance, and fat mass, and is proinflammatory, mitogenic, and antiapoptotic; arsenic has been linked to both increased leptin and to decreased adiponectin levels (Gossai et al., 2015; Ahmed et al., 2010; Booth et al., 2015; Ntikoudi et al., 2014; Huang et al., 2015). Overall, these common links between arsenic and BMI on a number of common pathological processes like inflammation or adipocyte expression support the hypothesis that these two factors could produce additive or synergistic effects through a variety of mechanisms. Obesity can also cause a restrictive pattern on spirometry by a purely mechanical pathway. An obese abdomen pushes the diaphragm up and reduces thoracic cavity volume. If arsenic causes decreased lung volumes due to a biological effect on growth of lung function, then obesity could also have an interactive effect with arsenic exposure through a purely mechanical pathway.

Some misclassification of arsenic exposure may have occurred in our study. However, our arsenic exposure data were based primarily on residential history, which can be recalled with good accuracy. Records of arsenic water concentrations covered more than 90% of all persons-years in our study subjects, and because arsenic exposure was assessed similarly in all participants, any misclassification of exposure is most likely to have been non-differential and therefore most likely to have biased results towards the null. In addition to water, arsenic may also come from air, food, or workplace exposure. However, arsenic air concentrations were low and similar in all three study cities (Ferreccio and Sancha, 2006). Because Northern Chile has little rainfall, most food comes from outside the study area where arsenic water concentrations are low (Vera, 2017). As such, arsenic from food is unlikely to have caused major bias in our findings. Misclassification of past diet likely occurred to some extent, but diet was assessed similarly in all participants so this would most likely be non-differential and not likely have caused the positive associations we identified here. Differential recall of diet is possible but we could find no evidence that this would likely cause major bias.

We cannot eliminate the possibility of confounding in our results. For example, the impacts we identified for BMI could be related to some other factor associated with elevated BMI such as diet or an obesity-related disease like diabetes. Adjustments for several factors related to BMI and lung disease including fruit and vegetable intake, occupational exposures to known lung irritants, diabetes, and exposure to second hand smoke had little impact on our results (Table S4 and Fig. S2). Specific dietary factors or nutrients were not evaluated here, and their impacts could be evaluated in future research. Air pollution may also impact lung function and increase respiratory symptoms. However, subjects who lived in Santiago were excluded, and air pollution levels (e.g. PM₁₀) are similar in the three study cities and generally below US standards (Cifuentes et al., 1999).

The reason we saw arsenic-associated FVC declines in never-smokers but not in smokers is unknown. It may be the toxic effects of smoking masked those due to arsenic but this is speculative. Several studies have identified synergy between smoking and arsenic for lung cancer but evidence for similar effects for non-malignant lung disease is less consistent (Ferreccio et al., 2000, 2013; Chen et al., 2004). 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). Further research is needed to more clearly delineate the combined impacts of smoking and arsenic on non-malignant lung disease.

Overall, we found evidence that adults exposed to arsenic with an increased BMI are at an elevated risk for non-malignant respiratory symptoms and overall poorer lung function. Furthermore, our study also suggests that arsenic and obesity could interact, and is the first study to specifically investigate the impact of coupled arsenic exposure and elevated BMI on lung function and health. Lastly, we also observed the highest FEV₁/FVC ratios in those with the highest combined arsenic exposure and BMI in never-smokers. Because the results here are novel

and the statistical power to evaluate interaction was mostly low, they should be considered preliminary. In addition, our goal was to assess long-term impacts of arsenic, so any impacts occurring in the past that may have resolved or any impacts occurring in children could not be assessed here. Future research involving larger sample sizes, detailed data on past BMI, and markers of potential mechanisms like inflammation and oxidative stress could help clarify the issues we've studied here. Given the globally rising rates of obesity and widespread arsenic exposure worldwide identifying risk factors for arsenic-related damage such as BMI could have important and far-reaching public health implications.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.envres.2017.06.024>.

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