Lung Function and Respiratory Symptoms after Tuberculosis in an American Indian Population

The Strong Heart Study

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Abstract

Rationale: Permanent lung function impairment after active tuberculosis infection is relatively common. It remains unclear which spirometric pattern is most prevalent after tuberculosis.

Objectives: Our objective was to elucidate the impact of active tuberculosis survival on lung health in the Strong Heart Study (SHS), a population of American Indians historically highly impacted by tuberculosis. As arsenic exposure has also been related to lung function in the SHS, we also assessed the joint effect between arsenic exposure and past active tuberculosis.

Methods: The SHS is an ongoing population-based, prospective study of cardiovascular disease and its risk factors in American Indian adults. This study uses tuberculosis data and spirometry data from the Visit 2 examination (1993–1995). Prior active tuberculosis was ascertained by a review of medical records. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), and FEV₁/FVC were measured by spirometry. An additional analysis was conducted to evaluate the potential association between active tuberculosis and arsenic exposure.

Results: A history of active tuberculosis was associated with reduced percent predicted FVC and FEV₁, an increased odds of

airflow obstruction (odds ratio = 1.45, 95% confidence interval = 1.08–1.95), and spirometric restrictive pattern (odds ratio = 1.73, 95% confidence interval = 1.24–2.40). These associations persisted after adjustment for diabetes and other risk factors, including smoking. We also observed the presence of cough, phlegm, and exertional dyspnea after a history of active tuberculosis. In the additional analysis, increasing urinary arsenic concentrations were associated with decreasing lung function in those with a history of active tuberculosis, but a reduced odds of active tuberculosis was found with elevated arsenic.

Conclusions: Our findings support existing knowledge that a history of active tuberculosis is a risk factor for long-term respiratory impairment. Arsenic exposure, although inversely associated with prior active tuberculosis, was associated with a further decrease in lung function among those with a prior active tuberculosis history. The possible interaction between arsenic and tuberculosis, as well as the reduced odds of tuberculosis associated with arsenic exposure, warrants further investigation, as many populations at risk of developing active tuberculosis are also exposed to arsenic-contaminated water.

Keywords: tuberculosis; arsenic; American Indian; Strong Heart Study; spirometry

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Tuberculosis, a preventable and treatable infectious disease when drug therapies are successful, largely affects vulnerable populations, including indigenous peoples, such as American Indians. Worldwide, indigenous populations are at a higher risk of tuberculosis than nonindigenous populations due to a higher-than-average prevalence of predisposing risk factors, including diabetes, smoking, and socioeconomic circumstances (1). Historically, tuberculosis was an important cause of mortality in American Indians, with peak disease likely around 1910 (2). Even as mortality, morbidity, and risk of infection from tuberculosis have greatly decreased among American Indians, incidence rates remain above that of the non-foreign-born, non-Hispanic white population (1, 3).

A recent systematic review found that pulmonary impairment is relatively common among those with a history of tuberculosis (4). Even after microbiologic cure of the infectious disease, tuberculosis can be associated with long-term pulmonary damage, and this impairment, which can involve airflow obstruction and/or spirometric restrictive pattern defects (4), contributes to an unmeasured burden of chronic lung disease (5, 6).

In this study, we evaluated the relationship between a history of active tuberculosis and subsequent lung function in American Indians participating in the Strong Heart Study (SHS), a population-based study that represents Tribal Nations across four states in the United States. We assessed this association using data from a medical record–based history of active tuberculosis, spirometric measurements, and self-reported respiratory symptoms.

We also conducted an additional analysis to evaluate the potential association between tuberculosis and arsenic. In the United States, elevated exposure to arsenic disproportionately affects populations relying on private well water. This includes many American Indian communities where naturally occurring arsenic is often above 10 $\mu\text{g/L}$, the current U.S. Environmental Protection Agency safety standard. In the SHS population, arsenic levels in drinking water were stable and relatively high before 2006, when new water systems were introduced in some of the communities to comply with the U.S. Environmental Protection Agency safety standard. For decades, participants were thus exposed to relatively high arsenic levels (7). At present,

one study found high arsenic exposure associated with higher tuberculosis mortality in Chile (8). In the SHS cohort, low–moderate arsenic exposure ($<100 \mu\text{g/L}$), which is widely prevalent in study communities (7), was positively associated with a spirometric restrictive pattern, airflow obstruction, and lower lung function, independent of active tuberculosis history (9). There is also prior knowledge that arsenic is an immunosuppressant (10, 11). Given these previous findings, we examined whether a history of active tuberculosis was associated with arsenic exposure and possible interaction between arsenic and tuberculosis on lung disease.

The SHS provides a unique opportunity to examine the lung health of participants who have been previously treated for active tuberculosis, allowing for the assessment of this burden compared with community members not affected by active tuberculosis, in a population-based study. We undertook this study to characterize the association of an active tuberculosis diagnosis on long-term functional pulmonary impairment in an American Indian population.

Methods

Study Population

The SHS is an ongoing, population-based, prospective study of cardiovascular disease and its risk factors in American Indian adults. The SHS recruited 4,549 residents of Tribal Nations located in Arizona (AZ), Oklahoma (OK), and North and South Dakota (ND/SD) in the United States. Study enrollment rates of eligible participants were 71.8% in AZ, 61.5% in OK, and 55.3% in ND/SD (12). All men and women aged 45–74 years at the baseline visit in 1989–1991 were invited to participate. Compared with nonparticipants, participants were similar in age, body mass index (BMI), and diabetes status, and were more likely to be female (12). Participants were invited to subsequent clinical visits between 1993–1995 and 1998–1999 (13).

This study uses tuberculosis data and spirometry data from the Visit 2 examination (1993–1995), available in 2,625 participants. We further excluded 123 participants missing data on cigarette pack-years, 33 participants missing diabetes status, and 36 missing BMI and waist

circumference, leaving 2,463 individuals for this study.

Data Collection

Visit 1 (1989–1991) and Visit 2 (1993–1995) included biospecimen collection, a physical exam, and an interviewer-administered standardized questionnaire. Visits were performed by trained and certified examiners. Methods have been previously described (13).

Tuberculosis. At Visit 2, a medical record review for a history of active and treated tuberculosis (class III tuberculosis) was performed. Case definition for class III tuberculosis involved having a positive culture for *Mycobacterium tuberculosis* from a body fluid or tissue or having a clinical picture suggestive of tuberculosis that responded to treatment with antitubercular medications. If any of those criteria were identified on a discharge diagnosis or on a problem list, they were considered to have a history of active tuberculosis. How the individual met the case definition, positive culture versus response to treatment, was not available. If there was uncertainty about whether the laboratory results met the case definition, the medical record was reviewed by T.K.W., coauthor of this study. T.K.W., a retired physician from the U.S. Indian Health Service and expert in clinical tuberculosis, developed the SHS data collection protocol and oversaw data collection and the identification of active tuberculosis based on available data in medical records at Visit 2. Participants received the diagnosis of active tuberculosis several years before the study visit (median [interquartile range (IQR)] for the year of diagnosis was 1968 [1955–1979]).

Tuberculosis status was specifically added to the SHS Visit 2 research protocol to establish prevalence of tuberculin positivity, refer study participants with positive tuberculin tests to Indian Health Service for appropriate evaluation and treatment, and establish a prevalence of history of active tuberculosis. A history of an active tuberculosis diagnosis was not differentiated between pulmonary and extrapulmonary.

Spirometry for identification of airflow obstruction and restrictive pattern.

Spirometry was performed by centrally trained and certified nurses and technicians at Visit 2 (14). Prebronchodilator testing was conducted in the sitting position, except for participants with a BMI greater than 27 kg/m^2 who stood.

Maneuvers were considered acceptable according to then-current American Thoracic Society recommendations. Methods have been previously described (14, 15).

Spirometric measurements of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), and their ratio (FEV₁/FVC) were used in analyses. Reference values to determine the normal range of spirometry results for SHS participants were derived previously (14), yielding FVC % predicted and FEV₁ % predicted. Airflow obstruction was defined two ways: 1) by a fixed ratio (FEV₁/FVC < 0.70) using crude FEV₁ and FVC values (16); and 2) by the lower limit of normal (LLN), (FEV₁/FVC < LLN), which classifies the bottom 5% of the “healthy” population as abnormal (for the SHS, negative predictors of FEV₁ were used to exclude participants from the healthy subset) (14). Spirometric-based restrictive pattern was defined two ways: 1) as a low FVC (FVC < 80% predicted) together with a preserved ratio (FEV₁/FVC ≥ 0.70) (17); and 2) as the LLN (FEV₁/FVC ≥ LLN and FVC < LLN). Normal spirometry was defined as those with no obstruction and no restriction (fixed ratio defined as: FEV₁/FVC ≥ 0.70 and FVC > 80% predicted; LLN defined as FEV₁/FVC ≥ LLN and FVC > LLN).

Symptoms and lung disease. At Visit 2, participants were asked to report respiratory symptoms, including the presence of cough, frequent cough, cough with phlegm, shortness of breath when walking up a slight hill, and stopping for breath while walking 100 yards.

Urine arsenic. Morning spot urine samples collected during the baseline visit were used to measure arsenic species (inorganic arsenic [iAs], methylarsonate, and dimethylarsinate) using high-performance liquid chromatography/inductively coupled plasma–mass spectrometry (13). Quality control and quality assurance methods and laboratory procedures for urine arsenic analysis were conducted in 2009–2010 using highly precise laboratory methods that are still state-of-the-art today (18). We used the sum of iAs and methylated arsenic species (iAs + methylarsonate + dimethylarsinate) as the biomarker of exposure to iAs in drinking water and food. Arsenobetaine levels were low, confirming that seafood intake is rare in the population. Urine

creatinine was measured by an automated alkaline picrate methodology run on a rapid flow analyzer. To account for urine dilution in spot urine samples, urine arsenic (μg/L) was divided by urine creatinine concentrations (g/L) (the concentrations of total urine arsenic and its species were expressed in μg/g creatinine).

Other variables. Models were progressively adjusted for relevant lung health variables to correct for potential confounding, using data from Visit 2. In model 1, we adjusted for age, sex, education, and study site, potential demographic confounders. In our study population, arsenic levels in drinking water are higher in AZ, lower in OK, and intermediate in ND/SD, yet levels still overlap across sites, allowing us to adjust for site. Education is associated with arsenic exposure in our study, mostly related to the fact that those in AZ have, on average, a lower education level. In model 2, we adjusted for smoking status and cigarette pack-year, a well-established risk factor for lung disease, with smoking status categorized as never, former (smoked ≥ 100 cigarettes, but no longer smoking), or current (smoking at then-present day). In model 3, we adjusted for BMI, waist circumference, and percent body fat to account for adiposity impact on respiratory system compliance (19, 20). In model 4, we adjusted for diabetes, a highly prevalent risk factor found in the SHS cohort. Diabetes was defined as a fasting glucose level of 126 mg/dL or greater, a 2-hour postload plasma glucose level of 200 mg/dL or greater, an HbA1c level of 6.5% or greater, or use of an oral hypoglycemic agent or insulin (21). To minimize any missing data, if Visit 2 data were missing for an individual, then baseline measurement was used (waist circumference, *n* = 5; body fat, *n* = 34; cigarette pack-years, *n* = 279; smoking status, *n* = 63).

Statistical Analysis

We conducted descriptive statistics to evaluate differences in participant demographic and lifestyle variables by tuberculosis status and by obstruction/restrictive spirometry-based pattern. We used logistic regression to estimate the odds ratio (OR) for presence of obstruction/restrictive pattern and respiratory symptoms by tuberculosis status, and linear regression to assess the mean difference of spirometric measurements by tuberculosis status. Effect modification of

the association between active tuberculosis and lung outcomes was evaluated in fully adjusted models by including an interaction term for active tuberculosis status with indicator variables for sex (male/female), age (<59.9 yr/≥59.9 yr), smoking status (never/former/current), BMI (<25 kg/m²/≥25 to <30/≥30), diabetes (yes/no), and arsenic (tertile: ≤6.0, 6.1 to 11.9, ≥12.0 μg/g). *P* values for interactions were obtained using Wald test for multiple coefficients. For the additional analysis, we estimated the OR of active tuberculosis by urinary arsenic modeled as a categorical variable, comparing tertiles of arsenic exposure, and as a continuous variable to compare an IQR increase of log urinary arsenic. *P* values for trend were obtained from modeling log-arsenic as continuous. All analyses were performed using Stata software, version 15.1 (StataCorp LLC), and figures were made in R (www.r-project.org).

Results

A total of 14% of participants (344/2,463) had a history of active tuberculosis. Participants with a history of active tuberculosis were more likely to be older (mean [IQR]: 60.8 [55.5–66.8] yr vs. 58.5 [53.0–65.3] yr) and completed a lower level of education (no high school: 19.5% vs. 16.8%) (Table 1) compared with those without active tuberculosis. Those with versus those without a history of active tuberculosis had a lower FEV₁ % predicted (mean [IQR]: 88.5 [75.5–100.7] vs. 94.1 [82.2–104.8]), FVC % predicted (91.1 [78.3–100.7] vs. 94.4 [83.3–105.3]), and FEV₁/FVC% (75.6 [69.0–80.6] vs. 76.7 [71.5–80.1]). Those with a history of active tuberculosis were more likely to report presence of usual cough, frequent cough, production of phlegm with cough, and needing to stop for breath while walking for a few minutes (Table 1).

Using the fixed-ratio definition (FEV₁/FVC < 0.70), airway obstruction was present in 21.2% (521/2,463) overall (Table 2) and in 27.3% of those with active tuberculosis history (Table 1). A spirometric based restrictive pattern was present in 15.0% (369/2,463) overall and in 18.6% of those with active tuberculosis; the prevalence of diabetes in those with restriction was 68.0% (Table 2). Using the LLN definition (FEV₁/FVC < LLN),

Table 1. Participant characteristics by cumulative prevalence of history of medical-record tuberculosis (N = 2,463)

	No Tuberculosis (n = 2,119)	Tuberculosis (n = 344)
Age, yr	58.5 (53.0–65.3)	60.8 (55.5–66.8)
Female, n (%)	1,274 (60.1)	226 (65.7)
Education, n (%)		
No HS	356 (16.8)	67 (19.5)
Some HS	491 (23.2)	97 (28.2)
Completed HS or higher	1,271 (60.0)	180 (52.2)
BMI, kg/m ²	30.1 (26.8–34.4)	30.0 (26.5–33.8)
Waist circumference (cm)	105 (96–114)	104 (95–114)
% Body fat	36.1 (29.3–43.0)	37.1 (30.1–42.5)
Diabetes, n (%)	1,091 (51.5)	187 (54.4)
Urine Σ As*	8.5 (5.1–14.0)	7.6 (5.0–12.9)
% iAs	7.5 (5.4–10.8)	7.6 (5.4–10.7)
% MMA	14.1 (10.9–17.6)	14.2 (11.1–18.2)
% DMA	77.9 (71.9–82.8)	77.8 (71.7–82.9)
Smoking status, n (%)		
Never	640 (30.2)	100 (29.1)
Former	741 (35.0)	115 (33.4)
Current	738 (34.8)	129 (37.5)
Cigarette pack-years (current/former)	3 (0–18)	3 (0–16.5)
FEV ₁ , L	2.5 (2.1–3.0)	2.3 (1.8–2.8)
FVC, L	3.3 (2.7–4.0)	3.0 (2.4–3.8)
FEV ₁ /FVC, %	76.7 (71.5–80.1)	75.6 (69.0–80.6)
% Predicted		
FEV ₁	94.1 (82.2–104.8)	88.5 (75.5–100.7)
FVC	94.4 (83.3–105.3)	91.1 (78.3–100.7)
Airflow obstruction (fixed), n (%)	427 (20.2)	94 (27.3)
Airflow obstruction (LLN), n (%)	141 (6.7)	33 (9.6)
Restrictive pattern (fixed), n (%)	305 (14.4)	64 (18.6)
Restrictive pattern (LLN), n (%)	148 (7.0)	30 (8.7)
Self-reported cough, n (%)	451 (21.3)	98 (28.5)
Cough 4–6×/wk, n (%)	286 (13.5)	59 (17.2)
Phlegm with cough, n (%)	276 (13.1)	70 (20.4)
Shortness of breath, n (%)	959 (45.8)	171 (50.3)
Stopping for breath, n (%)	332 (15.9)	75 (22.1)

Definition of abbreviations: Σ As = inorganic arsenic plus methylated species; BMI = body mass index; DMA = dimethylarsinate; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; HS = high school; iAs = inorganic arsenic; LLN = lower limit of normal; MMA = methylarsonate. Data are median (interquartile range) or n (% of column).

* μ g/g creatinine.

obstruction was present in 6.7% (141/2,463) overall and in 9.6% of those with active tuberculosis; spirometric restriction was present in 7.0% (148/2,463) overall and in 8.7% of those with active tuberculosis (Table 1).

After full adjustment (Table 3, model 3), the OR (95% confidence interval [CI]) comparing those with a history of active tuberculosis to those without was 1.45 (1.08–1.95) for obstruction and 1.73 (1.24–2.40) for spirometric restrictive pattern (Table 3). When the LLN definition was used, the OR for was nonsignificant for obstruction (1.24 [0.81–1.89]) and nonsignificant for spirometric restrictive pattern (1.47 [0.97–2.29]) (Table 3), although the direction of the association was

consistent with the findings based on the fixed ratio definitions.

The mean difference (95% CI) for FEV₁ % predicted comparing active tuberculosis cases to those free of active tuberculosis was -5.84 (-7.91 to -3.77). For FVC % predicted, the mean difference was -5.23 (-7.45 to -3.39 ; Table 4). Among the normal group (FEV₁/FVC > 0.70 and FVC > 80% predicted), both FEV₁ % predicted and FVC % predicted remained significantly reduced in those with a history of active tuberculosis. No association was seen between a history of active tuberculosis and FEV₁/FVC.

A history of active tuberculosis was associated with self-reported respiratory symptoms at Visit 2: cough (OR [95% CI]

= 1.43 [1.10–1.87]; $P = 0.008$) and production of phlegm when coughing (1.64 [1.21–2.22]; $P = 0.001$) (Table 5). A history of active tuberculosis was not significantly associated with frequent cough (4–6×/d), stopping for breath while walking, or shortness of breath when hurrying on the level or walking up a slight hill.

We found no effect modification for the association of prior active tuberculosis with airflow obstruction or spirometric restriction by sex, age, diabetes, or BMI (Figure 1). By smoking status, effect modification was significant for a spirometric restrictive pattern (P interaction = 0.04), with the association being markedly stronger among former smokers (OR [95% CI] = 3.01 [1.77–5.13]).

Additional Analysis of Arsenic and Tuberculosis

For airflow obstruction and spirometric restrictive pattern, the association with prior active tuberculosis became slightly stronger when models were additionally adjusted for arsenic when using the fixed ratio (obstruction, 1.47 [1.07–2.02]; restriction, 1.90 [1.34–2.70]; Table 3, model 4). When using the LLN, results remained nonsignificant.

By arsenic exposure tertile, effect modification was statistically significant for the spirometric restrictive pattern (P interaction = 0.03), with stronger ORs for those in arsenic tertile 2 (2.70 [1.44–5.10]) and tertile 3 (2.63 [1.39–4.99]) compared with tertile 1 (1.17 [0.60–2.28]) (Figure 1). No interaction was observed between arsenic and prior active tuberculosis for obstruction (P interaction = 0.2), although a stronger association between prior active tuberculosis and obstruction was observed among those in the highest arsenic tertile (2.27 [1.28–4.05]).

For FEV₁ % predicted, the mean difference (95% CI) comparing those with and without a history of active tuberculosis was further reduced with each increasing arsenic exposure tertile, with the largest reduction in those exposed to the highest levels (-3.32 [-7.02 to 0.39], -5.97 [-9.91 to -2.04], -8.86 [-13.08 to -4.64] % for tertiles 1, 2, and 3, respectively; Figure 2). The same pattern was seen for FVC % predicted (-3.93 [-7.19 to -0.66], -6.27 [-10.36 to -2.19], -6.48 [-10.64 to -2.32] %, respectively). However, the interaction was not statistically significant for

Table 2. Participant characteristics by airflow obstruction and spirometric restrictive pattern ($N=2,463$)

	Airflow Obstruction FEV ₁ /FVC < 0.70 ($n=521$)	Restrictive Pattern FEV ₁ /FVC ≥ 0.70 FVC < 80% Predicted ($n=369$)	Normal FEV ₁ /FVC ≥ 0.70; FVC ≥ 80% Predicted ($n=1,573$)
Age, yr	63.5 (56.7–69.7)	59.8 (54.1–65.7)	57.2 (52.3–63.8)
Female, n (%)	256 (50.9)	246 (66.7)	998 (63.5)
Education, n (%)			
No HS	134 (25.7)	80 (21.7)	209 (13.3)
Some HS	132 (25.3)	94 (25.5)	362 (23.0)
Completed HS or higher	255 (48.9)	194 (52.7)	1,002 (63.7)
Smoking status, n (%)			
Never	122 (23.4)	121 (32.8)	491 (31.6)
Former	170 (32.6)	131 (35.5)	555 (35.3)
Current	229 (44.0)	117 (31.7)	521 (33.1)
Smoking pack-years	9.0 (0–33.0)	3.0 (0–15.0)	2.0 (0–14.0)
BMI, kg/m ²	28.1 (25.0–31.9)	31.6 (27.9–36.3)	30.5 (27.3–34.4)
Diabetes, n (%)	231 (44.3)	251 (68.0)	796 (50.6)
Urine ΣAs, μg/g creatinine*	10.1 (5.7–14.6)	9.1 (5.1–16.2)	7.8 (4.9–13.0)
FEV ₁ , % predicted	79.9 (63.9–93.8)	75.2 (69.3–80.8)	99.2 (91.8–108.5)
FVC, % predicted	95.5 (79.2–108.6)	72.0 (65.7–76.9)	97.4 (89.7–106.3)
FEV ₁ /FVC, %	65.2 (58.7–68.1)	80.5 (76.3–85.3)	77.9 (74.8–81.3)
Self-reported symptoms, n (%)			
Cough	155 (29.8)	101 (27.5)	293 (18.7)
Cough 4–6×/wk	105 (20.2)	63 (17.2)	177 (11.3)
Phlegm with cough	101 (19.4)	60 (16.4)	185 (11.8)
Shortness of breath	255 (49.4)	197 (55.0)	678 (43.5)
Stopping for breath	113 (21.9)	80 (22.5)	214 (13.8)
History of active tuberculosis, n (%)	94 (18.0)	64 (17.3)	186 (11.8)

Definition of abbreviations: ΣAs=inorganic arsenic plus methylated species; BMI=body mass index; FEV₁=forced expiratory volume in 1 second; FVC=forced vital capacity; HS=high school.

All analyses are weighted. Data are n (% of column), or median (interquartile range).

*μg/g creatinine; arsenic measured from visit 1 (1989–1991).

either FEV₁ % predicted or FVC % predicted.

Arsenic exposure was significantly associated with a reduced odds of a past active tuberculosis diagnosis (Table 6). In fully adjusted models, the OR (95% CI) comparing the highest to lowest arsenic tertile (≥ 12.0 vs. ≤ 6.0 μg/g creatinine) was 0.71 (0.56–0.89).

Discussion

From our findings, lung function and respiratory symptoms of cough and cough with phlegm appear worse in participants who had a history of active tuberculosis compared with those who did not. A history of active tuberculosis was associated with reduced FEV₁ % predicted and FVC % predicted and increased odds of airflow obstruction and a spirometric restrictive pattern, with a stronger association with the restrictive pattern, when based on the fixed-ratio definition. The associations were significant after adjustment for diabetes and major risk factors, including smoking.

Although the interaction analysis was underpowered and none of the P values reached significance, the effect estimates showed lower FEV₁ % predicted and lower FVC % predicted with preserved FEV₁/FVC ratio comparing tuberculosis to no tuberculosis among those with arsenic levels in the highest (>12.0 μg/L) compared with the lowest tertile (≤ 6.0 μg/L).

Our findings support existing knowledge that a history of active tuberculosis is a risk factor for long-term respiratory impairment (4). An increasing number of population-based studies has shown a consistent positive association between a history of active tuberculosis and the presence of airflow obstruction, with a recent meta-analysis finding a history of active tuberculosis to be associated with chronic obstructive pulmonary disease in adults over 40 years of age (pooled OR = 3.05 [2.42–3.85]) (22). A study of 14,050 adults from 18 countries found that a history of self-reported tuberculosis increased risk for airflow obstruction (adjusted OR = 2.51 [1.83–3.42] using the LLN definition) (23). The study also found

an association with spirometric restriction (2.13 [1.42–3.19]). In our study, the associations with the study outcomes based on the LLN were not statistically significant, possibly because of the smaller number of cases and a lack of power. The GOLD (Global Initiative for Obstructive Lung Disease) threshold of less than 0.70 for FEV₁/FVC is thought to often misclassify normal spirometry as airflow obstruction in nonsmokers, particularly in older adults (24). The American Thoracic Society recommends using the LLN instead of the fixed GOLD ratio. However, it is likely that the LLN misses individuals with mild airflow obstruction (25). In a population with a high burden of lung disease, as it appears to be in the SHS, underdiagnosis of obstruction may be a larger problem than overdiagnosis (26). Overall, however, why the associations are stronger with the ratio versus LLN definition is unclear.

Fewer studies have examined posttuberculosis respiratory health in an indigenous population, with none in an American Indian population. One descriptive study ($n=121$) examined

Table 3. Odds ratio (95% confidence interval) of airflow obstruction and spirometric restrictive pattern by history of active tuberculosis

	No Tuberculosis	Tuberculosis	P Value
Obstruction* fixed ratio/normal [†]	427/1,387	94/186	
Model 1	1.00 (Ref)	1.43 (1.07–1.91)	0.02
Model 2	1.00 (Ref)	1.47 (1.09–1.97)	0.01
Model 3	1.00 (Ref)	1.45 (1.08–1.95)	0.01
Model 4	1.00 (Ref)	1.47 (1.07–2.02)	0.02
Obstruction* lower limit of normal/normal [†]	141/1,830	33/281	
Model 1	1.00 (Ref)	1.28 (0.85–1.92)	0.24
Model 2	1.00 (Ref)	1.28 (0.84–1.94)	0.25
Model 3	1.00 (Ref)	1.24 (0.81–1.89)	0.33
Model 4	1.00 (Ref)	1.27 (0.80–2.00)	0.31
Restrictive [‡] fixed ratio/normal [†]	305/1,387	64/186	
Model 1	1.00 (Ref)	1.72 (1.25–2.37)	0.001
Model 2	1.00 (Ref)	1.73 (1.25–2.39)	0.001
Model 3	1.00 (Ref)	1.73 (1.24–2.40)	0.001
Model 4	1.00 (Ref)	1.90 (1.34–2.70)	<0.001
Restrictive [‡] lower limit of normal/normal [†]	148/1,830	30/281	
Model 1	1.00 (Ref)	1.53 (1.00–2.34)	0.05
Model 2	1.00 (Ref)	1.52 (0.99–2.33)	0.05
Model 3	1.00 (Ref)	1.47 (0.97–2.29)	0.07
Model 4	1.00 (Ref)	1.38 (0.86–2.22)	0.19

Definition of abbreviations: FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; LLN = lower limit of normal; Ref = reference group.

Model 1—adjusted for age, sex, education, and site; model 2—further adjusted for smoking status and smoking pack-year; model 3—further adjusted for body mass index, waist circumference, percent body fat, and diabetes; model 4—further adjusted for arsenic.

*Airflow obstruction: fixed ratio—FEV₁/FVC < 0.70; lower limit of normal—FEV₁/FVC < LLN.

[†]Normal: fixed ratio, FEV₁/FVC ≥ 0.70 and FVC > 80% predicted; LLN, FEV₁/FVC ≥ LLN and FVC > LLN.

[‡]Restrictive pattern: fixed ratio, FEV₁/FVC ≥ 0.70 and FVC < 80% predicted; LLN, FEV₁/FVC ≥ LLN and FVC < LLN.

respiratory health after tuberculosis, comparing indigenous to nonindigenous people from Brazil, and found a high prevalence of respiratory symptoms, obstruction, and obstruction with reduced FVC in both groups (27).

It is proposed that the chronic inflammatory response and long-term

anatomic alterations induced by pulmonary tuberculosis are the main pathological basis for long-term impairment of lung function (28). A number of mechanisms may account for the development of airflow obstruction after pulmonary tuberculosis infection, including the structural damage of large and small airways, including bronchiolar

Table 4. Mean difference (95% confidence interval) of lung function measures comparing participants with versus without history of active tuberculosis

	n	Mean Difference (95% CI)	P Value
FEV ₁ , % predicted			
All	2,462	−5.84 (−7.91 to −3.77)	<0.001
Normal*	1,573	−2.73 (−4.64 to −0.83)	0.005
FVC, % predicted			
All	2,462	−5.23 (−7.45 to −3.39)	<0.001
Normal*	1,573	−2.70 (−4.51 to −0.89)	0.004
FEV ₁ /FVC ratio (%)			
All	2,462	−0.43 (−1.40 to 0.54)	0.38
Normal*	1,573	−0.04 (−0.71 to 0.64)	0.92

Definition of abbreviations: CI = confidence interval; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity.

*Normal: FEV₁/FVC ≥ 0.70 and FVC > 80% predicted.

Adjusted for: age, sex, education, site, smoking status, cigarette pack-year, body mass index, waist circumference, % body fat, and diabetes.

narrowing and bronchiolitis obliterans resulting from peribronchial fibrosis, as well as accelerated emphysematous change caused by residual chronic or recurrent inflammation (29, 30). Restriction in patients with tuberculosis may be explained by structural changes in the lung as a result of aberrant lung tissue repair, such as bronchovascular distortion, fibrotic bands, and pleural thickening (4). There also could be significant overlap of obstruction and restrictive impairment mechanisms in those with tuberculosis, with some researchers suggesting that immune mediators and pathways that drive caseous necrosis and pulmonary cavitation, which can lead to airflow obstruction, during the disease may also set up for later fibrosis (4). Rather than a direct toxic effect of arsenic on the lung, an inflammation-mediated immunologic basis has been suggested (31), as arsenic is known to alter key functions of the innate and adaptive immune system (32–35). In mice, exposure of low to moderate concentrations of arsenic in drinking water (10–100 µg/L) led to a decrease in immune gene expression and aberration in inflammatory protein expression (10, 36), resulting in susceptibility to airway inflammation (11). Both arsenic (37, 38) and tuberculosis (22) are known to be associated with increased risk of developing bronchiectasis, suggesting some potential common pathophysiology for the long-term impact of arsenic and tuberculosis on lung disease. In both tuberculosis-associated lung injury and arsenic-induced effects on airway physiology, matrix metalloproteinases (MMPs), degradation enzymes, are likely central; MMPs can promote different stages of lung remodeling during tuberculosis, including promoting alveolar destruction (39) and, in arsenic-exposed individuals, MMP-9 impairs repair mechanisms in human lung epithelial cells (40).

In the additional analysis, the effect estimates for the association between history of tuberculosis and lung function indices, FEV₁ % predicted and FVC % predicted, were progressively decreased by increasing urinary arsenic concentrations; however, the P values for interaction were not statistically significant. Despite this dose response, elevated arsenic exposure was unexpectedly associated with reduced odds of a history of active tuberculosis. This is inconsistent with the one previous study also examining this relationship, an ecological study from Chile, which found increased mortality from

Table 5. Odds ratio (95% confidence interval) of self-reported respiratory symptom by history of active tuberculosis

	No Tuberculosis	Tuberculosis	P Value
Cough/no cough*	451/1,663	98/246	
Model 1	1.00 (Ref)	1.41 (1.09–1.83)	0.01
Model 2	1.00 (Ref)	1.44 (1.10–1.88)	0.007
Model 3	1.00 (Ref)	1.44 (1.11–1.88)	0.007
Model 4	1.00 (Ref)	1.43 (1.10–1.87)	0.008
Model 5	1.00 (Ref)	1.34 (1.01–1.79)	0.04
Cough 4–6×/d [†] /no	286/1,826	59/285	
Model 1	1.00 (Ref)	1.29 (0.94–1.76)	0.11
Model 2	1.00 (Ref)	1.31 (0.95–1.80)	0.10
Model 3	1.00 (Ref)	1.32 (0.96–1.82)	0.09
Model 4	1.00 (Ref)	1.31 (0.95–1.81)	0.10
Model 5	1.00 (Ref)	1.22 (0.86–1.71)	0.26
Phlegm/no phlegm [‡]	276/1,836	70/274	
Model 1	1.00 (Ref)	1.59 (1.19–2.14)	0.002
Model 2	1.00 (Ref)	1.63 (1.21–2.21)	0.001
Model 3	1.00 (Ref)	1.65 (1.22–2.23)	0.001
Model 4	1.00 (Ref)	1.64 (1.21–2.22)	0.001
Model 5	1.00 (Ref)	1.53 (1.10–2.11)	0.01
Shortness of breath/no [§]	959/1,134	171/169	
Model 1	1.00 (Ref)	1.08 (0.86–1.37)	0.50
Model 2	1.00 (Ref)	1.09 (0.86–1.39)	0.46
Model 3	1.00 (Ref)	1.12 (0.88–1.43)	0.35
Model 4	1.00 (Ref)	1.12 (0.88–1.43)	0.36
Model 5	1.00 (Ref)	1.13 (0.87–1.46)	0.37
Stop for breath/no	332/1,756	75/264	
Model 1	1.00 (Ref)	1.28 (0.95–1.72)	0.10
Model 2	1.00 (Ref)	1.30 (0.97–1.75)	0.08
Model 3	1.00 (Ref)	1.34 (0.99–1.80)	0.05
Model 4	1.00 (Ref)	1.33 (0.99–1.80)	0.06
Model 5	1.00 (Ref)	1.35 (0.98–1.86)	0.07

Definition of abbreviation: Ref = reference group.

Model 1—adjusted for age, sex, education, site; model 2—further adjusted for smoking status and smoking pack-year; model 3—further adjusted for body mass index, waist circumference, percent body fat; model 4—further adjusted for diabetes; model 5—further adjusted for arsenic.

*Do you usually have a cough? If yes:

[†]Do you usually cough as much as 4–6 times/day, 4 or more days/week?

[‡]Do you usually bring up phlegm when you cough?

[§]Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill? If yes:

^{||}Do you ever have to stop for breath while walking about 100 yards or a few minutes on the level?

pulmonary tuberculosis associated with arsenic in drinking water (8). We hypothesize that our findings may be due to survival bias. For example, those with more severe tuberculosis may have died before participation in the SHS. It is also possible that those with higher arsenic exposure were more likely to progress from latent to active tuberculosis, or, at the time of active tuberculosis development, also had higher risk of death. We were not able to determine if arsenic could have increased the incidence of active tuberculosis or increased mortality among infected individuals. Relevant to this population, older age, diabetes, and chronic obstructive pulmonary disease have been associated with an increased risk of death during tuberculosis treatment (41). In these scenarios, our sample of patients with tuberculosis could be overrepresenting those

with better survival after treatment, including participants with lower arsenic exposure. This could have attenuated effect estimates, undervaluing the relationship between tuberculosis and arsenic exposure. In addition, if the most severely affected patients with tuberculosis were not included in the study, all effect estimates shown, including the main analyses and possible interaction with arsenic, could be underestimated.

Being able to run analyses for both active tuberculosis and a positive tuberculosis diagnostic test (suggestive of latent tuberculosis) could have provided additional clarity to the relationship with lung health and with arsenic, potentially to help determine if there was an increased risk of tuberculosis activation in those with both latent tuberculosis and higher arsenic

exposure. This could help us assess arsenic's contribution to pulmonary impairment through tuberculosis activation. A commonality among the majority of risk factors for tuberculosis activation, such as human immunodeficiency virus (HIV) and malnutrition, is an impaired immune response (42). Part of the toxic effects of arsenic is likely through acting as an immunosuppressant (43) and producing a state that favors opportunistic infections (44), like tuberculosis. Animal studies have demonstrated immune suppression that is suspected to affect the pulmonary defense system (45), and studies in children have shown associations between increased urinary arsenic and reduced proliferative response to mitogens, percentage of CD4 T cells, and IL-2 secretion levels, suggesting immunosuppression (46). Our analyses are based on a clinical diagnosis of active tuberculosis, and not the purified protein derivative (PPD) test, a tuberculin skin test. This is because the administration of the Bacille Calmette-Guerin (BCG) vaccine could have interfered with the interpretation of the PPD test, as those who have received the vaccination also test positive for the PPD skin test. The source population for the SHS was part of a large BCG vaccination trial in the period 1935–1938, during which children and adults aged 1 month to 20 years who had normal chest radiographs received the BCG vaccine or placebo (47). We did not have individual records of vaccination status.

This study benefitted from several strengths. The SHS is a well-established cohort with high-quality laboratory methods, high participation retentions, standardized variable collection, and strong support from the communities involved. We had individual spirometric measures standardized to American Thoracic Society recommendations. We also had American Indian reference values derived from the SHS population, which allowed us to assess lung function against predicted values for better interpretation of results. However, the subgroup used to calculate predicted values did not exclude those with tuberculosis or high arsenic exposure.

Our study has several limitations. Outcome misclassification could have occurred from inaccurate recall of symptom and use of symptom questionnaires based on yes/no answers, which might be difficult for participants to choose from compared with scale-based questionnaires.

Figure 1. Odds ratio (OR) (95% confidence interval [CI]) for airflow obstruction and restrictive pattern (fixed ratio) when history of tuberculosis is compared across participant characteristics. ORs were stratified by each subgroup of interest, and associated *P* values for interaction were obtained from models with interaction terms and using Wald tests for multiple coefficients. Age values presented are means. Adjusted for: age, sex, education, location, smoking status, cigarette pack-year, body mass index (BMI), waist circumference, percent body fat, and diabetes.

Determination of prior active tuberculosis infection was dependent on the completeness and accuracy of medical records. If any information pertaining to tuberculosis was inadequately documented, it would have been missed in our analysis; however, as diagnosis of tuberculosis among American Indians has long been a major concern, misdiagnosis is thought unlikely

(47). More importantly, even if some cases were missed, diagnosis based on laboratory test and the combination of radiological criteria with tuberculosis treatment ensures the high specificity of the case definition. Although we did not have confirmation of whether the active tuberculosis was pulmonary or extrapulmonary, around 80% of active tuberculosis cases in American

Indians in the United States are pulmonary (48); however, this could have led to an underestimation of effect estimates for pulmonary tuberculosis, as the number of cases was likely slightly diluted by extrapulmonary cases. Although we had no information on HIV infection, the strongest known risk factor for progressing latent tuberculosis infection to tuberculosis

Figure 2. Mean difference (95% confidence interval [CI]) of lung function (forced expiratory volume in 1 second [FEV₁], forced vital capacity [FVC] % predicted) by tuberculosis and urine arsenic tertile. Adjusted for: age, sex, education, location, smoking status, cigarette pack-year, body mass index (BMI), waist circumference, percent body fat, and diabetes. TB = tuberculosis.

disease, HIV infection among American Indian patients with active tuberculosis is comparatively lower than for other racial/ethnic groups (48). Our study is cross-sectional, and precludes us from drawing temporal conclusions. The diagnosis of active tuberculosis happened in the past, and was based on medical records; we do not know when airflow obstruction or spirometric restriction developed, and we cannot discount the possibility that they were present before tuberculosis. In addition, due to incomplete data collection for year of tuberculosis diagnosis, we were

not able to use it with confidence in our analyses, further preventing us from examining temporality. We did not account for multiple comparisons, because, although we examined two exposures (arsenic and tuberculosis) individually with each outcome, we were not interpreting the results separately. Rather, the multiple outcomes were not independent and provided complementary information, as we examined several ways to assess the pattern of lung impairment (obstructive vs. restrictive), looking for patterns of associations with the study outcomes that

allowed us to assess the contribution of tuberculosis and joint effect with arsenic. We lacked information on possible additional confounders, such as exposure to indoor air pollutants, including exposure to smoke from cooking fires or heating fuel, and dietary information, including consumption levels of marine fatty acids and fresh fruit and vegetables (49). Regarding socioeconomic status, we used education status, which is a proxy commonly used by the SHS, but that might not completely capture study participants' socioeconomic status.

Table 6. Odds ratio (95% confidence interval) of history of tuberculosis by urinary arsenic concentration*

	Inorganic Plus Methylated Arsenic Species (µg/g Creatinine)			75th vs. 25th Percentile [†]	P Trend [‡]
	Tertile 1 (≤6.0)*	Tertile 2 (6.1–11.9)*	Tertile 3 (≥12.0)*		
History of tuberculosis/no tuberculosis	111/606	100/625	88/608	299/1,839	
Model 1	1.00 (Ref)	0.71 (0.52–0.97)	0.61 (0.43–0.88)	0.74 (0.59–0.92)	0.007
Model 2	1.00 (Ref)	0.71 (0.52–0.97)	0.61 (0.43–0.87)	0.73 (0.59–0.91)	0.006
Model 3	1.00 (Ref)	0.71 (0.52–0.96)	0.59 (0.41–0.85)	0.72 (0.57–0.90)	0.004
Model 4	1.00 (Ref)	0.70 (0.51–0.96)	0.58 (0.41–0.84)	0.71 (0.56–0.89)	0.003

Model 1—adjusted for age, sex, education, and site; model 2—further adjusted for smoking status and smoking pack-year; model 3—further adjusted for body mass index, waist circumference, percent body fat; model 4—further adjusted for diabetes.

*Tertiles are ranges, calculated based on overall population, sum of inorganic arsenic, methylarsonate, dimethylarsinate µg/g creatinine.

[†]Comparison of the 75th and 25th percentiles (interquartile range) of urinary arsenic concentrations (14.3 vs. 5.1 µg/g creatinine)

[‡]P trend calculated modeling log-arsenic as continuous.

Conclusions

A prior active tuberculosis diagnosis was associated with impaired pulmonary function, including airflow obstruction and a spirometric restrictive pattern, and respiratory symptoms among American Indians in the SHS, a population historically at elevated risk for tuberculosis infection

and disease. We also found suggestive evidence of a possible interaction between arsenic exposure and a history of active tuberculosis with worse lung function, especially spirometric restrictive-related outcomes. The possible interaction between arsenic and active tuberculosis, as well as the reduced odds of active tuberculosis

associated with arsenic exposure, warrants further investigation, as many populations at risk of developing tuberculosis are also exposed to arsenic-contaminated water. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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