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Environmental exposure and systemic hypertension are risk factors for decline in lung function

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Abstract

Background: Chronic lung disease is a leading contributor to the global disease burden; however, beyond tobacco smoke, we do not fully understand what risk factors contribute to lung function decline in low-and middle-income countries (LMICs).

Methods: We collected sociodemographic and clinical data in a randomly selected, age-, sex-, and site-stratified population-based sample of 3,048 adults aged ≥ 35 years from four resource-poor settings in Peru. We assessed baseline and annual pre-and post-bronchodilator lung function over three years. We used linear mixed effects models to assess biological, socioeconomic, and environmental risk factors associated with accelerated lung function decline.

Results: Mean ± SD enrollment age was 55.4 ± 12.5 years, 49.2% were male, and mean follow-up time was 2.36 (SD = 0.61) years. Mean annual pre-bronchodilator FEV₁ decline was 30.3 mL/yr (95% CI 28.6 to 32.0) and pre-bronchodilator FVC decline was 32.2 mL/yr (30.0 to 34.4). Using multivariable linear mixed effects regression, we found that urban living, high altitude dwelling, and having hypertension accounted for 25.9% (95% CI 15.7 to 36.1), 21.3% (11.1 to 31.5), and 15.7% (3.7 to 26.9) of the overall mean annual decline in pre-bronchodilator FEV₁/

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height², respectively. Corresponding estimates for pre-bronchodilator FVC/height² were 42.1% (95% CI 29.8 to 54.4), 36.0% (23.7 to 48.2), and 15.8% (2.6 to 28.9) of the overall mean annual decline, respectively.

Conclusion: Urbanization, living at high altitude, and hypertension were associated with accelerated lung function decline in a population with low daily smoking prevalence.

INTRODUCTION

Chronic lung disease is a leading cause of death worldwide, and accelerated decline in lung function is associated with increased hospitalizations [1], cardiovascular morbidity [2,3], and all-cause mortality [1,4,5]. Accelerated lung function decline is indicated by faster than average annual decrease in FEV₁ and FVC. In low-and middle-income countries (LMIC) where chronic cardiovascular and respiratory diseases are the leading causes of death [6], there has been limited exploration into the understanding of accelerated lung function decline.

One of the most widely recognized risk factors for accelerated lung function decline is cigarette smoking [7,8]. However, there remains variable data regarding the influence of other environmental exposures including ambient and traffic-related air pollution [9,10], and household air pollution from biomass fuel smoke exposure [11,12]. It is unclear whether other risk factors including urbanization, underlying lung disease [13], and poorer cardiovascular health contribute to accelerated lung function decline in LMICs [2,12,14]. Understanding the burden of environmental risk factors and comorbid medical conditions in LMIC settings can direct health systems and policy interventions geared towards disease prevention and identification of at-risk subgroups.

Previous cross-sectional analyses by our group identified risk factors associated with respiratory disease burden in our four diverse settings in Peru [15]. We found that household air pollution was associated with a higher prevalence of COPD and hypertension [16,17], that urbanization was associated with a higher prevalence of asthma [18], and that both household air pollution and urbanization were associated with a higher prevalence of chronic bronchitis [19]. In this longitudinal evaluation of the CRONICAS cohort study, we aimed to determine environmental and comorbid risk factors for accelerated lung function decline. Specifically, we evaluated the effect of urbanization, altitude, household air pollution, asthma, chronic bronchitis, history of post-treatment pulmonary tuberculosis, hypertension, body mass index, systemic inflammation as measured by hs-CRP and diabetes and the relationship of each of these risk factors with longitudinal lung function.

METHODS

Study setting

We conducted a longitudinal, population-based study aimed to better understand the progression towards chronic pulmonary and cardiovascular diseases across four disparate regions in Peru. The study has been described in detail elsewhere and involved collection of sociodemographic and clinical data from adults aged ≥ 35 years in four diverse populations in Peru [15]. The four settings under study varied based on degrees of urbanization, living at

high altitude, and prevalence of daily biomass fuel use (Table 1). The diverse demographics of our study sites allowed us to evaluate unique environmental risk factors, specifically urbanization, altitude and biomass fuel smoke, and comorbid conditions including hypertension, obesity, diabetes, chronic bronchitis and COPD.

Design

We enrolled an age-(35–44, 45–54, 55–64 and 65 years), sex-, and site-stratified sample of eligible subjects. Recruitment began in September 2010 and was conducted until approximately 1,000 participants with complete information per site were enrolled. Only one participant per household was enrolled. In Puno, we stratified recruitment to include 500 participants each from the urban and rural settings. Patients were followed for a total of three years after their enrollment date. Inclusion criteria were being 35 years of age, being a full-time resident in the specified setting, and capacity to understand procedures and consent to the study. Exclusion criteria were being pregnant, having a physical disability that prevented measurement of blood pressure or anthropometry, or having active pulmonary tuberculosis. All participants provided verbal informed consent due to high illiteracy rates, especially in rural areas. The study was approved by the Institutional Review Boards of Universidad Peruana Cayetano Heredia and A.B. PRISMA, in Lima, Peru, and the Johns Hopkins Bloomberg School of Public Health in Baltimore, USA.

Data collection

Each participant was evaluated three times over three years. At enrollment, participants responded to a questionnaire on sociodemographics, smoking history, respiratory symptoms, past medical history, and family history of disease. A detailed questionnaire also evaluated frequency and duration of cooking with biomass fuels. Spirometry was conducted annually for a total of three tests per participant using the Easy-On-PC spirometer (ndd, Zurich, Switzerland). Pre-bronchodilator examinations were conducted on all three visits, whereas post-bronchodilator examinations using 200 mcg of inhaled salbutamol via a spacer were conducted in the first and third visits only. Trained technicians measured spirometry in participants following joint American Thoracic Society and European Respiratory Society guidelines [20]. We adapted a standardized grading system for quality control, review, and interpretation [21]. Participants with low quality spirometry were asked to repeat the test on another day for a total of three attempts. Blood samples were collected in the first and third visits.

Definitions

To assess lung function decline, we looked at subject-specific change in pre-bronchodilator FEV_1/height^2 , FVC/height^2 , and FEV_1/FVC over time [22]. All results are presented as mL/m^2 , or percent difference from mean baseline values. FEV_1/height^2 was calculated by dividing forced expiratory volumes (in milliliters) by height (in meters) squared. We also presented results as lung volumes adjusted by height and Z-scores for sensitivity analysis. All of the following risk factors for lung function decline were assessed using baseline clinical data from visit one. We defined chronic bronchitis as having self-reported phlegm production for at least three months each year in two successive years. We created a wealth index according to assets, household facilities, household income, and occupation [23]. We

defined biomass fuel use as using biomass fuels for cooking at least once daily. We defined daily smoking as having at least one cigarette a day; hypertension as having systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, self-report of a physician diagnosis or current use of anti-hypertensive medications; diabetes as a fasting glucose ≥ 126 mg/dL, self-report of physician diagnosis or current use of anti-hyperglycemic medications; and tuberculosis as self-reported past medical history of tuberculosis infection. Urban or rural dwelling was defined according to site. Lima and urban Puno were classified as urban, whereas Tumbes and rural Puno were classified as rural based on city density and traffic (Table 1). Rural and urban Puno were considered high altitude sites, whereas Lima and Tumbes were considered sea-level communities.

Biostatistical methods

We sought to characterize average lung function decline in our study populations, and identify potential factors that were associated with an accelerated decline. As such, we used multivariable linear mixed effects models with random intercepts and random slopes by individual to assess the potential factors associated with longitudinal lung function values. The use of random effects in longitudinal data analysis accounts for the heterogeneity in subject-specific lung function values at baseline (intercept) and change over time (slope). All models were adjusted for the following *a priori* selected baseline factors: age, sex, height, environmental exposures (self-reported smoking, self-reported daily biomass fuel use, urbanization, living at high altitude, wealth index), comorbid conditions (hypertension, diabetes, chronic bronchitis, asthma, history of post-treatment pulmonary tuberculosis), body mass index (BMI), and high-sensitivity C-reactive protein (hs-CRP). In place of adjusting for site, we decomposed site into multiple components including degree of urbanization and altitude. For continuous variables such as BMI and hs-CRP, we scaled the effect size to the interquartile range, i.e., difference between the 75th and 25th percentiles of these variables. We then conducted sex-specific subset analyses of above models. Attributable annual decline in lung function (as a percentage) for each risk factor were calculated as the estimated change in lung function for that specific factor divided by the average annual decline in lung function in the population, multiplied by 100 (e.g., an expected decline of 6 mL for a risk factor modeled in our regression with regard to the observed average 30 mL annual decline in pre-bronchodilator FEV₁ corresponds to a 20% percent decline above expected). We used Local Polynomial Regression to estimate the smoothed mean and 95% confidence interval for values in Figure 1 [24]. Analyses were conducted in R (www.r-project.org) and linear mixed effects models used the package lme4.

RESULTS

Participant characteristics

A total of 3,048 people completed at least one spirometry testing in any of the three visits and 2,956 (97%) participants of these had complete data on all other variables included in the longitudinal models. Of the 2,956 participants with complete data, 2,180 (72.2%) had spirometry measurements in all three visits, 537 (17.6%) had spirometry measurements on two visits, and 309 (10.1%) had a spirometry measurement at just one visit. Non-participation in subsequent data collection was due to death, participant declining further

testing or questioning, or incomplete data collection. There were no differences in sex ($p=0.56$), having COPD ($p=0.86$), or age ($p=0.12$) between participants who were included in analysis when compared to those who were not; however, participants included higher BMI ($p=0.05$) than those who were not.

Among the 3,048 participants with spirometry, average age at enrollment was 55.4 ± 12.5 years and 49.2% were male. The four sites were heterogeneous with respect to BMI, wealth index, cigarette and biomass fuel exposures, clinical history and data, and lung function (Table 2). Tumbes and Lima (sea-level settings) had higher average BMI and hs-CRP, and higher prevalence of hypertension. Lima, the urban sea-level population with high outdoor air pollution, had the highest prevalence of post-treatment tuberculosis, asthma, and chronic bronchitis. Urban and rural Puno (high altitude settings), also had high prevalence of chronic bronchitis, but rural Puno, when biomass fuel is predominantly used, there is a marked increased prevalence of COPD compared to all other study sites. Prevalence of daily cigarette smoking was highest in Lima, but overall it was relatively low across all settings (Table 2).

Overview of lung function decline

Average annual decline in pre-bronchodilator FEV_1 and FEV_1/height^2 was 30.3 mL (95% CI 28.6 to 32.0 mL) and 10.8 mL/m² (10.3 to 11.4 mL/m²) per year, respectively (Table 2 and Figure 1). Lima and rural Puno had similar FEV_1 annual decline whereas urban Puno had the fastest and Tumbes had the lowest annual decline (Table 2). Mean annual decline in pre-bronchodilator FVC and FVC/height^2 was 32.2 mL (30.0 to 34.4 mL) and 11.4 mL/m² (10.3 to 11.4 mL/m²) per year, respectively. Compared to participants who at sea level, those who lived at high altitude had a faster decline in lung function (Table 2). There was substantial heterogeneity in annual decline of both pre-bronchodilator FEV_1 and FVC across participants (Figure 1). Moreover, adults with higher pre-bronchodilator forced expiratory volumes at baseline also had a faster annual decline in their lung function (Figure 2).

Factors that may affect lung function decline

We found varying trends between risk factors when looking at lung function decline with age (Figure 3). Urbanization, high altitude, and hypertension were responsible for an additional 2.8 mL/m² (95% CI 1.7 to 3.9 mL/m²), 2.3 mL/m² (1.2 to 3.4 mL/m²), and 1.7 mL/m² (0.4 to 2.9 mL/m²) decrease in overall average annual decline in FEV_1/height^2 , respectively (table 3). This corresponds to an additional 25.9% (95% CI 15.7% to 36.1%), 21.3% (11.1% to 31.5%), and 15.7% (3.7% to 26.9%) higher than average annual decline in FEV_1/height^2 , respectively. When looking at FVC/height^2 , we found that urbanization, high altitude, and hypertension were responsible for an additional 4.8 mL/m² (95% CI 3.4 mL/m² to 6.2 mL/m²), 4.1 mL/m² (2.7 to 5.5 mL/m²), and 1.8 mL/m² (0.3 to 3.3 mL/m²) (table 3). This corresponds to an additional 42.1% (95% CI 29.8% to 54.4%), 36.0% (23.7% to 48.2%), and 15.8% (2.6% to 28.9%) higher than average annual decline for urbanization, high altitude, and hypertension, respectively. Daily smokers trended towards having higher annual declines in pre-bronchodilator FEV_1 ($p=0.06$) and FVC ($p=0.18$). Daily biomass fuel smoke exposure was not associated with a higher than average annual decline in pre-bronchodilator FEV_1/height^2 ($p=0.33$), but there was a trend towards a higher average

annual decline in FVC/height² ($p=0.08$). Urbanization and high altitude were associated with slower annual decline in pre-bronchodilator FEV₁/FVC ratio of 0.07 (0.02 to 0.11) and 0.05 (0.01 to 0.10), respectively. A history of post-treatment tuberculosis was the only factor associated with a higher annual decline in pre-bronchodilator FEV₁/FVC (-0.10 , 95% CI -0.20 to -0.01).

Sensitivity analysis

We performed sensitivity analysis with Z-scores and absolute FEV₁ and FVC values and found effect sizes were similar (Figure 4, Figure 5, and Table 3). To evaluate the effects of underlying lung disease on lung function decline, we performed a sensitivity analysis using the same regression model but excluding those with COPD. We found similar mean estimates and 95% CIs (E-Table 1 and E-Table 2).

DISCUSSION

In this multicenter, population-based longitudinal study of adults in Peru, we found that living at high altitude and living in an urban setting was associated with accelerated lung function decline. Smoking trended towards having accelerated decline in lung function in our population, but may have not achieved statistical significance because of the low prevalence of daily smokers. Biomass fuel smoke exposure also trended towards having accelerated decline in FVC/height². Having hypertension at baseline was associated with an accelerated decline in both FEV₁/height² and FVC/height² in our study population. In contrast, other comorbid conditions including obesity, diabetes, and chronic bronchitis did not show accelerated lung function decline.

Several findings reported in our study are consistent with existing literature from high-income countries and provide novel reports of longitudinal lung function in LMICs. Average FEV₁ decline in our study was 30.4 mL/year; similar to the 33 ± 2 mL/year observed by the ECLIPSE investigators [25], the 27 mL/year observed in a non-smoking population in the Lung Health Study [26], and within the age-related decline of 23.7 to 39 mL/year for adults aged 25 to 75 years found across multiple US cities [27]. The mean rate of FVC decline in our study was 32.5 mL/year, which is also within the range of the NHANES age-related predictions [25].

There is a paucity of research evaluating lung function decline in LMICs, and the majority of these existing studies focus on biomass fuel smoke exposure. A study in Mexico that followed participants with COPD for 15 years found a lower rate of FEV₁ decline (23 mL/year) in their biomass-exposed group compared to the decline observed in our rural Puno group (33.5 mL/year), a setting where biomass fuels are used for cooking on daily basis in approximately 95% of study households [16]. A prospective cohort study in China found a similar FEV₁ decline of 35 mL/year in participants who used biomass fuels for cooking compared to a much slower decline of 18 mL/year among participants using alternative clean fuels and improved ventilation [12]. Other groups have seen associations between biomass fuel and decline in FVC [28]. Proposed mechanisms for accelerated decline in FVC involve the development of scarring and interstitial lung abnormalities in the setting of biomass fuel exposure [28]. Our study did not show a significant relationship between

biomass fuel and FEV₁ or FEV₁/FVC ratio. Biomass fuel exposure trended towards an accelerated decline in FVC, however this trend did not achieve statistical significance at the 0.05 level. These discrepancies could be attributed to either shorter follow up time or the complexity of multiple other environmental and comorbid risk factors found in our cohort that can also contribute to lung function decline. Our findings are similar to the RESPIRE cookstove intervention trial which had a slightly longer follow-up period than our study (5.6 years). [11] Furthermore, similar to what we found with cigarette smoke and traffic related air pollution, any effects of biomass on lung function decline may be diminished by the fact that only certain groups are susceptible to such environmental influences [29–31]. Gene by environment interactions related to household air pollution need further exploration.

Other environmental exposures highlighted in our study included the effects of high altitude and urbanization on accelerated lung function decline. At high altitude, hypoxia and inflammation likely play a role in lung function decline [32,33]. Hypoxia itself induces systemic inflammation by activating hypoxia-inducible factor 1-alpha in hypertrophied obese adipose tissues [34,35]. Higher inflammation has been associated with worse outcomes in COPD populations. In highly urbanized settings, outdoor air pollution and comorbid conditions likely play a role in lung function decline [9,14]. Cross-sectional evaluation from the ESCAPE study found that an increase in NO₂ exposure was associated with lower baseline FEV₁ and FVC [10], whereas work by Rice *et al* found an association with long-term exposure to traffic and PM_{2.5} [9]. However, other studies have found no significant association between ambient PM_{2.5} levels and lung function decline [36].

What causes environmental factors to influence disease in one individual but not in another remains unclear. There has been significant discussion regarding genetic predisposition to COPD leading some but not all daily cigarette smokers to develop pulmonary disease. It is likely that indoor air pollution from biomass fuels, outdoor air pollution, and other environmental exposure similarly affect predisposed individuals [37]. Given the variable effects of exposures on lung function, to develop targeted interventions, it is important to find clinical and biological identifiers for at risk individuals among high exposure populations. In this study, we took a novel approach and simultaneously evaluated effects of both environmental and comorbid conditions on lung function decline. Hypertension has been associated with pulmonary disease in previous work from both NHANES III and BOLD [3,38]. Similarly, the BOLD study [38], the Whitehall II study [39], and the MESA study have reported an association with lower baseline FVC and markers of cardiovascular disease including arterial stiffness and hypertension [40]. Going beyond a cross-sectional association, the CARDIA study looked at this same question from a different angle and demonstrated accelerated decline in FEV₁ and FVC predicted future incident of hypertension in an otherwise generally healthy population [2]. One proposed mechanism connecting cardiovascular disease and lung function is a parallel physiologic degradation pathway of arterial and airway elasticity. The MESA study observed a positive association between small arterial elasticity and lung function [40]. A second hypothesis proposes systemic endothelial dysfunction mediates the association between FEV₁ and atherosclerosis, however in a recent study, airflow limitation and endothelial dysfunction were found to be unrelated and independent predictors of atherosclerosis [41]. Finally, a

third related hypothesis poses that systemic inflammation related to lung disease facilitates a prothrombotic state and augments atherosclerosis.

Our study has several strengths. First, this is one of few longitudinal studies evaluating lung function decline in LMICs. Second, we collected detailed demographic, clinical, and environmental data that allows us to explore competing factors contributing to lung function decline. Third, the low prevalence of tobacco smoking provides a unique opportunity to examine other risk factors contributing to lung function decline. Finally, we used longitudinal analysis methods that model subject specific trajectories [42,43]. A specific concern was how to account for baseline lung function in our analyses. To address this concern, we accounted for heterogeneity in subject-specific baseline lung function through the use of random intercepts. This allowed us to evaluate population-averaged trends while accounting for the heterogeneity (i.e., variation) in baseline forced expiratory volumes among individuals.

Our study also has some potential limitations. First, we were not powered to determine risk factors stratified by site, however we are able to evaluate key components of each site including altitude and urbanization. Second, because of the number of risk factors evaluated in our analysis, it is possible that we were not powered to measure the effects of competing conditions such as diabetes [44], and chronic bronchitis which have been previously described [45]. Third, our follow up time is only a short to intermediate time frame with respect to decline in FEV1 and FVC and therefore we may not see the significant effects from some risk factors that one might expect like chronic bronchitis. Finally, some of our clinical data including asthma, chronic bronchitis, and history of post-treatment pulmonary tuberculosis are self-reported and therefore potentially subject to bias and error.

Conclusion

In four diverse settings in Peru with low tobacco use prevalence, we found that urbanization, high altitude, and hypertension, were associated with accelerated decline in forced expiratory volumes. This study highlights possible environmental and comorbid factors that contribute to accelerated lung function decline in LMICs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is the key question?

Beyond cigarette smoke exposure, what are the major risk factors for worsened lung function decline in low-and middle-income settings?

What is the bottom line?

Hypertension, urban dwelling, and high altitude are all independently related to greater than average annual decline in lung function.

Why read on?

Results propose new relationships between lung function and various risk factors for disease including biomass fuel smoke exposure, urbanization, altitude, and cardiovascular health.

Figure 1:

Histogram of annual declines in mL/year for pre-bronchodilator FEV₁ (left panel) and FVC (right panel) for all study participants, expressed as a proportion of the total number of participants. All values were calculated using the 2,793 (90.0%) participants with at least one follow-up visit.

Figure 2:

Annual decline in pre-bronchodilator FEV₁ (left panel) and FVC (right panel) as a function of the corresponding baseline forced expiratory volume. Smooth lines (in blue) and 95% confidence bands (grey area) were obtained using local polynomial regression adjusted for age, sex, wealth index, diabetes, asthma, history of post-treatment tuberculosis, and high-sensitivity C-reactive protein levels, daily smoking, daily biomass fuel exposure, having hypertension at baseline, chronic bronchitis, body mass index interquartile range, urbanization, and high altitude.

Figure 3:

Adjusted mean annual decline in pre-bronchodilator FEV₁/height² (left panel) and FVC/height² (right panel) as a function of daily smoking (non-smoker or non-daily smoker is reference), daily biomass fuel exposure (no exposure or nondaily is reference), having hypertension at baseline, chronic bronchitis, body mass index interquartile range (difference between 75th and 25th percentile), urbanization, and high altitude. The diamonds represent adjusted mean differences in lung function decline and horizontal lines represent the corresponding 95% confidence intervals. Adjusted means were obtained from regression models that included age, sex, wealth index, diabetes, asthma, history of post-treatment tuberculosis, high-sensitivity C-reactive protein levels (hs-CRP), daily smoking, daily biomass exposure, living at high altitude, and urbanization.

Figure 4:

Adjusted mean annual decline in pre-bronchodilator FEV₁ (left panel) and FVC (right panel) Z scores as a function of daily smoking (non-smoker or non-daily smoker is reference), daily biomass fuel exposure (no exposure or nondaily is reference), having hypertension at baseline, chronic bronchitis, body mass index interquartile range (difference between 75th and 25th percentile), urbanization, and high altitude. The diamonds represent adjusted mean differences in lung function decline and horizontal lines represent the corresponding 95% confidence intervals. Adjusted means were obtained from regression models that included age, sex, wealth index, diabetes, asthma, history of post-treatment tuberculosis, high-sensitivity C-reactive protein levels (hs-CRP), daily smoking, daily biomass exposure, living at high altitude, and urbanization. Z-scores were calculated using NHANES Mexican-American reference equations.

Figure 5:

Adjusted mean annual decline in pre-bronchodilator FEV₁ (left panel) and FVC (right panel) as a function of daily smoking (nonsmoker or nondaily smoker is reference), daily biomass fuel exposure (no exposure or nondaily is reference), having hypertension at baseline, chronic bronchitis, body mass index interquartile range (difference between 75th and 25th percentile), urbanization, and high altitude. The diamonds represent adjusted mean differences in lung function decline and horizontal lines represent the corresponding 95% confidence intervals. Adjusted means were obtained from regression models that included age, sex, wealth index, diabetes, asthma, history of post-treatment tuberculosis, high-sensitivity C-reactive protein levels (hs-CRP), height, daily smoking, daily biomass exposure, living at high altitude, and urbanization.

Study site classification by urbanization, indoor and outdoor pollution, and altitude. Table adapted from previous work (20).

Table 1:

	Degree of urbanization	Use of biomass fuel	Outdoor air pollution	Altitude
Lima	Highly urbanized	Rare	High	Sea level
Tumbes	Semi-urban	Moderately prevalent	Low	Sea level
Puno, urban	Urban	Rare	Low	3825 m above sea level
Puno, rural	Rural	Highly prevalent	Low	3825 m above sea level

Table 2:

Demographic, clinical, and lung function characteristics stratified by site.

n (%) or mean $\pm$ SD (or 95% CI where indicated)	Lima (n=1,014)	Tumbes (n=990)	Urban Puno (n=516)	Rural Puno (n=528)	Overall (n=3048)	p-value
Age (years)	Urban, sea level 55.0 $\pm$ 11.8	Semi-urban/rural, sea level 55.8 $\pm$ 13.3	Urban, high altitude 55.3 $\pm$ 12.2	Rural, high altitude 55.8 $\pm$ 12.7	55.4 $\pm$ 12.5	0.43
Sex (reference is male)	496 (48.9)	498 (50.3)	254 (49.2)	251 (47.5)	1499 (49.2)	0.78
Height (cm)	154.9 $\pm$ 8.5	158.4 $\pm$ 8.8	156.9 $\pm$ 9.0	155.5 $\pm$ 8.0	156.5 $\pm$ 8.7	<0.001
Weight (kg)	68.1 $\pm$ 12.0	71.1 $\pm$ 13.2	68.7 $\pm$ 11.9	60.9 $\pm$ 10.6	67.9 $\pm$ 12.6	<0.001
BMI (kg/m ²)	28.4 $\pm$ 4.5	28.3 $\pm$ 4.8	27.9 $\pm$ 4.4	25.2 $\pm$ 3.7	27.7 $\pm$ 4.6	<0.001
Low (BMI < 18 kg/m ²)	1 (0.1)	4 (0.4)	3 (0.6)	4 (0.8)	12 (0.4)	
Normal (BMI 18–24 kg/m ²)	327 (32.2)	312 (31.5)	138 (26.7)	55 (10.4)	832 (27.3)	
Overweight (BMI 25–29 kg/m ²)	227 (22.4)	238 (24.0)	118 (22.9)	276 (52.3)	859 (28.2)	
Obese (BMI $\geq$ 30 kg/m ²)	459 (45.3)	436 (44.0)	257 (49.8)	193 (36.6)	1345 (44.1)	<0.001
Wealth Index						
Low	123 (12.1)	324 (32.7)	122 (23.6)	373 (70.6)	942 (30.9)	
Middle	375 (37.0)	404 (40.8)	132 (25.6)	140 (26.5)	1051 (34.5)	
Upper	516 (50.9)	262 (26.5)	262 (50.8)	15 (2.8)	1055 (34.6)	<0.001
Exposures						
Daily smoking	33 (3.3)	56 (5.7)	11 (2.2)	1 (0.2)	101 (3.3)	<0.001
Daily biomass fuel use for cooking	63 (6.2)	229 (23.1)	25 (5.0)	484 (96.6)	801 (26.3)	<0.001
Clinical data						
COPD	58 (5.7)	17 (1.7)	25 (4.8)	44 (8.3)	143 (4.7)	<0.001
Chronic Bronchitis	94 (9.3)	15 (1.5)	35 (7.0)	39 (7.8)	182 (6.1)	<0.001
Asthma	51 (5.0)	9 (0.9)	6 (1.2)	0 (0.0)	117 (3.9)	<0.001
History of post-treatment tuberculosis	72 (7.1)	7 (0.7)	3 (0.6)	7 (1.4)	89 (3.0)	<0.001
Hypertension	200 (19.7)	261 (26.4)	57 (11.0)	59 (11.2)	576 (18.9)	<0.001
Diabetes	55 (5.5)	101 (10.2)	34 (6.8)	16 (3.2)	207 (6.9)	<0.001
hs-CRP log mg/L	3.6 $\pm$ 6.1	4.0 $\pm$ 6.6	2.9 $\pm$ 5.2	2.4 $\pm$ 9.1	3.4 $\pm$ 6.7	<0.001
Pre-bronchodilator lung function						

		Lima (n=1,014)	Tumbes (n=990)	Urban Puno (n=516)	Rural Puno (n=528)	Overall (n=3048)	p-value
n (%) or mean $\pm$ SD (or 95% CI where indicated)		Urban, sea level	Semi-urban/rural, sea level	Urban, high altitude	Rural, high altitude		
FEV ₁ (mL)		2.6 $\pm$ 0.8	2.5 $\pm$ 0.7	2.8 $\pm$ 0.8	2.7 $\pm$ 0.8	2.6 $\pm$ 0.8	<0.001
FEV ₁ Z score		0.7 $\pm$ 1.3	0.1 $\pm$ 1.1	0.9 $\pm$ 1.3	0.8 $\pm$ 1.4	0.5 $\pm$ 1.3	<0.001
FVC (mL)		3.4 $\pm$ 1.0	3.2 $\pm$ 0.9	3.7 $\pm$ 1.1	3.6 $\pm$ 1.1	3.4 $\pm$ 1.0	<0.001
FVC Z score		1.0 $\pm$ 1.4	0.2 $\pm$ 1.1	1.4 $\pm$ 1.3	1.4 $\pm$ 1.4	0.9 $\pm$ 1.4	<0.001
FEV ₁ /FVC (%)		77.4 $\pm$ 7.5	79.4 $\pm$ 5.9	75.9 $\pm$ 6.0	75.2 $\pm$ 7.4	77.4 $\pm$ 6.9	<0.001
FEV ₁ /FVC Z scores		-0.5 $\pm$ 1.1	-0.2 $\pm$ 0.8	-0.8 $\pm$ 0.9	-0.8 $\pm$ 1.0	-0.5 $\pm$ 1.0	<0.001
FEV ₁ decline in mL/yr, mean (95% CI)		-31.1 (-34.0, -28.2)	-22.2 (-24.8, -19.7)	-38.7 (-43.2, -34.2)	-33.2 (-37.8, -28.6)	-30.3 (-32.0, -28.6)	<0.001
FVC decline in mL/yr, mean (95% CI)		-34.5 (-38.3, -30.7)	-12.0 (-15.5, -8.5)	-51.9 (-57.9, -45.8)	-40.1 (-46.1, -34.1)	-32.2 (-34.4, -30.0)	<0.001

Unadjusted and adjusted mean effect of covariates on pre-bronchodilator $FEV_1/height^2$ and $FVC/height^2$ over time (mL/m^2 per year). All of the variables included in the table were used in adjusted models. Reported values are adjusted mean differences and corresponding 95% confidence intervals.

Table 3 –

	$FEV_1/height^2$		$FVC/height^2$	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Sex (male is reference)	0.66 (−0.27, 1.59)	0.44 (−0.49, 1.38)	−0.21 (−1.37, 0.95)	−0.31 (−1.45, 0.83)
Wealth index (middle)	−0.97 (−2.29, 0.34)	−0.63 (−1.80, 0.54)	−0.86 (−2.59, 0.87)	−0.44 (−1.86, 0.99)
Wealth index (highest)	0.16 (−1.22, 1.53)	0.85 (−0.46, 2.15)	−0.31 (−2.12, 1.49)	1.03 (−0.56, 2.62)
Daily smoking	−2.18 (−5.65, 1.29)	−2.83 (−5.75, 0.08)	−0.17 (−4.73, 4.38)	−2.45 (−6.02, 1.11)
Daily biomass fuel exposure	−0.02 (−1.27, 1.23)	−0.65 (−1.97, 0.66)	−0.54 (−2.19, 1.10)	−1.47 (−3.08, 0.13)
Hypertension	−1.52 (−2.96, −0.08)	−1.65 (−2.89, −0.41)	−0.95 (−2.84, 0.94)	−1.82 (−3.34, −0.31)
Diabetes	−0.42 (−2.98, 2.14)	−0.09 (−2.23, 2.04)	0.40 (−2.95, 3.75)	0.28 (−2.32, 2.89)
Chronic bronchitis	−1.39 (−3.61, 0.84)	−0.41 (−2.26, 1.45)	−2.68 (−5.61, 0.25)	−1.10 (−3.37, 1.17)
Asthma	2.39 (−1.21, 6.00)	0.39 (−2.66, 3.45)	2.81 (−1.94, 7.56)	0.46 (−3.28, 4.19)
History of post-treatment tuberculosis	−2.49 (−5.80, 0.83)	−1.36 (−4.10, 1.37)	−2.75 (−7.10, 1.59)	−0.96 (−4.28, 2.36)
BMI (IQR)	0.15 (0.02, 0.27)	0.36 (−0.25, 0.98)	0.17 (0.01, 0.32)	0.24 (−0.51, 0.99)
High-sensitivity C-reactive protein levels (IQR)	0.31 (0.09, 0.54)	0.06 (−0.13, 0.24)	0.51 (0.22, 0.80)	0.03 (−0.19, 0.26)
Urbanization	−2.68 (−3.77, −1.60)	−2.80 (−3.92, −1.68)	−5.35 (−6.77, −3.94)	−4.81 (−6.18, −3.44)
High altitude	−2.93 (−4.10, −1.76)	−2.27 (−3.40, −1.15)	−6.29 (−7.82, −4.77)	−4.14 (−5.51, −2.77)