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Prevalence and risk factors of restrictive spirometry in a cohort of Peruvian adults

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SUMMARY

INTRODUCTION: Few studies have described the prevalence of and lung function decline among those with a restrictive spirometric pattern (RSP) in low- and middle-income countries.

METHODS: We analyzed prospective data from 3055 adults recruited across four diverse settings in Peru over a 3-year period. Multivariable logistic regression was used to study the association between the presence of restriction and associated risk factors. Multivariable linear mixed models were used to determine lung function decline.

RESULTS: Among 3055 participants, the average age was 55.4 years (SD 12.4); 49% were male. Overall prevalence of RSP was 4.7%, ranging from 2.8% (Lima) to 6.9% (Tumbes). The odds of having RSP were higher among those who lived in a rural environment (OR 2.19, 95%CI 1.43–3.37), had a diagnosis of diabetes (OR 1.94, 95%CI 1.10–3.40) and among women (OR 2.09, 95%CI 1.41–3.09). When adjusting for baseline lung function, adults with RSP had accelerated decline in forced expiratory volume in 1 s (FEV₁) compared with non-obstructed, non-restricted individuals.

DISCUSSION: RSP is prevalent particularly among women and in individuals living in rural settings of Peru. When adjusted for baseline lung function, participants with RSP had accelerated rates of FEV₁ decline. Our findings are consistent with the notion that RSP is an insidious inflammatory condition with deleterious effects of lung function decline.

RESUME

Peu d'études ont décrit la prévalence et le déclin de la fonction pulmonaire des patients ayant un profil de spirométrie restrictif (RSP) dans les pays à revenu faible et moyen.

Nous avons analysé les données prospectives de 3055 adultes recrutés dans quatre zones diverses du Pérou sur une période de 3 ans. Une régression logistique multivariées a été utilisée pour étudier les facteurs de risque associés à la présence de restriction. Des modèles linéaires multivariés mélangés ont été utilisés pour déterminer le déclin de la fonction pulmonaire.

Parmi 3055 participants, l'âge moyen a été de 55,4 ans (déviations standard 12,4) et 49% ont été des hommes. La prévalence d'ensemble du RSP a été de 4,7%, avec une fourchette de 2,8% (Lima) à 6,9% (Tumbes). Les risques d'avoir un RSP ont été plus élevés parmi les patients vivant dans un environnement rural (OR 2,19; 1,43–3,37), ayant eu un diagnostic de diabète (OR 1,94; IC95% 1,10–3,40) et parmi les femmes (OR 2,09; IC95% 1,41–3,09). Après ajustement sur la fonction pulmonaire de base, les adultes ayant un RSP ont eu un déclin accéléré du volume expiratoire maximal par seconde (VEMS) en comparaison aux individus sans obstruction ni restriction.

Le RSP est surtout prévalent parmi les femmes et chez les individus vivant dans des zones rurales du Pérou. Après ajustement sur la fonction pulmonaire de départ, les participants atteints de RSP ont eu des taux accélérés de déclin du VEMS. Nos résultats sont en accord avec la notion que le RSP est une pathologie inflammatoire insidieuse avec des effets délétères sur le déclin de la fonction pulmonaire.

RESUMEN

Pocos estudios han descrito la prevalencia de perfiles restrictivos de las pruebas funcionales respiratorias (RSP) con deterioro de la función pulmonar en los pacientes de países de ingresos bajos y medianos.

Se analizaron datos prospectivos de 3055 adultos inscritos en cuatro entornos diferentes en el Perú durante un período de 3 años. Se evaluó la presencia de un perfil restrictivo y los factores asociados mediante un modelo de regresión logística multivariante. El deterioro de las pruebas funcionales respiratorias se analizó con un modelo lineal multivariante.

En los 3055 participantes, el promedio de la edad fue 55,4 años (desviación típica 12,4) y 49% era de sexo masculino. La prevalencia general de un RSP fue 4,7%, con un intervalo entre 2,8% (Lima) y 6,9% (Tumbes). La posibilidad de un RSP fue más alto en las personas que vivían en medio rural (OR 2,19; IC95% 1,43–3,37), las que tenían un diagnóstico de diabetes (OR 1,94; IC95% 1,10–3,40) y en las mujeres (OR 2,09; IC95% 1,41–3,09). Al ajustar con respecto a las RSP iniciales, los adultos con un perfil restrictivo presentaban un deterioro acelerado del volumen espiratorio forzado en el primer segundo (VEF₁) al compararlos con las personas sin restricción ni obstrucción.

El perfil restrictivo de la espirometría predomina sobre todo en las mujeres y en las personas que viven en medio rural en el Perú. Cuando se ajustó con respecto a la función pulmonar inicial, se observaron tasas de deterioro acelerado del VEF₁ en los pacientes con un perfil restrictivo. Estos resultados coinciden con la noción de que perfil restrictivo de la espirometría corresponde a un proceso inflamatorio insidioso que provoca una agravación de la función pulmonar.

Keywords

chronic lung disease; lung function decline

CHRONIC RESPIRATORY DISEASE affects approximately 1 billion people globally, and accounts for 7% of all deaths worldwide.¹ The majority of the deaths related to chronic respiratory conditions occur in low- and middle-income countries (LMICs), and the burden of disease is expected to increase in many LMICs due to rapid urbanization and increased tobacco consumption.²

Over the past decade, population-based cross-sectional studies have examined obstructive lung disease in LMICs.^{3–5} Among those studies, a percentage of participants were found to have restrictive spirometric values demonstrating reduced forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁), with a preserved overall FEV₁/FVC ratio.^{6–8} Although restriction in spirometry does not denote restrictive lung disease, which typically requires measurement of total lung capacity and/or gas transfer, studies in high-income settings have shown that restrictive spirometric patterns (RSPs) can result in a higher risk of morbidity (respiratory symptoms and limitation of function) as well as all-cause mortality among individuals who present with these findings.⁸

Global estimates for RSPs range from 2.3% in Santiago, Chile, to 68% among women in Mumbai, India, although this variability may be a result of different definitions of RSP and reference populations.^{6,7} RSPs have been most commonly associated with obesity, tobacco exposure and female sex in these settings.^{3,6} In addition, countries with a high prevalence of biomass cooking fuel use and tuberculosis (TB) also have a higher prevalence of RSPs, although potential associations between biomass, TB and RSPs have not been studied at a household level.^{4,9}

While population-based studies have shown varying prevalence of RSPs in LMIC settings, associated morbidity, environmental risk factors and longitudinal health outcomes among these groups remain poorly defined.^{6,7} Our primary objective was to describe the prevalence of and attributable risk factors for RSPs across four geographically diverse settings in Peru. We also examined respiratory symptoms, functional status and decline in lung function among those with RSPs over a 3-year follow-up.

METHODS

Study setting

We conducted a longitudinal, population-based study in Peru to determine the prevalence of chronic pulmonary and cardiovascular diseases across four disparate regions. This study has been described in detail elsewhere.⁵ Four settings were selected based on the degree of urbanization and altitude: Pampas de San Juan de Miraflores, an urbanized community south of Lima; Tumbes, a semi-urban, sea-level community in northern Peru; Puno, an urban setting 3825 m above sea level; and the rural communities around Puno.⁵

Study design

We analyzed data from approximately 3000 adults aged ≥35 years enrolled in a longitudinal population-based study, with annual follow-up from 2010 to 2013. All subjects were randomly selected using a single-stage random selection process, and only one participant

per household was enrolled. In Puno, recruitment was stratified to include 500 participants each from urban and rural settings. Inclusion criteria were age ≥ 35 years, a full-time resident in the specified setting, and capacity to understand procedures and consent to the study. Exclusion criteria were pregnancy, physical disability that prevented measurement of blood pressure or anthropometry, or active pulmonary TB.

The study protocol was approved by the Institutional Review Boards of the Universidad Peruana Cayetano Heredia Asociación Bénéfica Prisma, in Lima, Peru, and the Johns Hopkins Bloomberg School of Public Health in Baltimore, MD, USA.

Data collection

Participants responded to a questionnaire on sociodemographic factors, current smoking status, respiratory symptoms, past medical history, and family history of non-communicable disease and biomass exposure. Field workers measured weight and height in triplicate in all three phases. Spirometry was conducted using the Easy-On-PC spirometer (nidd, Zurich, Switzerland) before and after inhalation of salbutamol (200 μg) via a spacer according to joint American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines.¹⁰ Participants with low-quality spirometry results (that did not meet acceptability and reproducibility criteria) were asked to repeat the test on another day for a total of three attempts. Overall, 95% met ATS/ERS criteria, including a minimum exhalation time of 6 s or 12 s, if no plateau was present.¹¹ Participants were then invited to attend annual follow-up visits for 3 years for repeat spirometry and phlebotomy. Bronchodilation was conducted at baseline and on the third follow-up visit.¹²

Definitions

We defined RSP as a pre-bronchodilator FVC below the fifth percentile (Z score -1.64) and a post-bronchodilator FEV_1/FVC ratio above the fifth percentile (Z score -1.64) of a reference population,⁸ and chronic obstructive pulmonary disease (COPD) as a post-bronchodilator FEV_1/FVC ratio below the fifth percentile of a reference population. Post-bronchodilator measurements were used to exclude individuals with reversible airway obstruction from the diagnosis of RSP.⁸ As there are no established reference equations for lung function among Peruvians, we used the Global Lung Function Initiative (GLI) mixed ethnic reference population.¹³ For longitudinal analysis, we included participants with at least one follow-up visit within the 3-year period.

Biostatistical methods

For prevalence estimates, we included all participants who completed study questionnaires and had post-bronchodilator spirometry at baseline. Baseline risk factors for RSPs were analyzed using multivariable logistic regression. We evaluated risk factors for RSP, including sex, age, urbanization, altitude, daily smoking, daily use of biomass fuel, history of TB, chronic bronchitis, high-sensitivity C-reactive protein (hs-CRP) level, diabetes mellitus (DM), hypertension and body mass index (BMI). We compared respiratory symptoms among those with RSP vs. COPD vs. non-restricted, non-obstructed spirometry at baseline to assess respiratory symptoms. For other analyses, we used χ^2 tests or Fisher's

exact tests to compare proportions, *t*-tests to compare continuous values, and Kruskal-Wallis tests to compare categorical values between subgroups, as appropriate.

We then built multivariable linear mixed effects models with a random intercept and random slope by individual to analyze the effect of having an RSP at baseline on longitudinal decline in pre-bronchodilator FEV₁ and FVC.¹⁴ All models were adjusted for sex, daily use of biomass fuels, daily tobacco smoking, living in an urban setting, and living at high altitude. We then used the estimated subject-specific random slopes divided by baseline lung function to characterize the subject-specific decline in lung function as a percentage of baseline FEV. To calculate 95% confidence intervals (CIs) for the mean decline in lung function as a percentage of baseline FEV, we used the 2.5th and 97.5th percentiles of 3000 bootstrap resamples by individual.¹⁵ Analyses were performed in R (www.r-project.org).^{16–18}

RESULTS

Participant characteristics

There were 3055 participants with complete data. Participant characteristics are shown in Tables 1 and 2. Those included in the analysis had an average age of 55.4 ± 12.4 years; 49% were male. Reported biomass exposure (5%–97%) and tobacco exposure (<1–6%) varied between settings. Overall, 27.3% of participants had a BMI ≥ 30 kg/m² ($n = 833$) and 7% had DM ($n = 207$) at baseline. A low percentage of individuals reported a history of TB ($n = 89$, 3%), with the majority located in Lima ($n = 72$). Across the sample, 6% of individuals reported symptoms of chronic bronchitis ($n = 183$).

Prevalence and risk factors for a restrictive spirometric pattern

The overall prevalence of restriction was 4.7%, with a range of 2.8% (Lima) to 6.9% (Tumbes) when using the GLI mixed ethnic reference population (Figure 1). Being female was associated with higher odds of RSP (OR 2.09, 95%CI 1.41–3.09; Figure 2). Living in a rural area was associated with higher odds of having an RSP (OR 2.19, 95%CI 1.43–3.37) as well as DM (OR 1.94, 95%CI 1.10–3.40). There was a moderate association of increased hs-CRP level (interquartile OR 1.05, 95%CI 1.03–1.08) and diagnosis of RSP. Daily smoking, daily use of biomass fuels, site (urbanization and high altitude), age, BMI, history of TB, hypertension, and chronic bronchitis were not by themselves associated with having an RSP.

Respiratory symptoms associated with presence of restrictive spirometric pattern at baseline

Adults with RSP did not have more respiratory symptoms, including cough in the past 12 months (4.2% vs. 4.0%, $P = 0.87$), phlegm in the past 12 months (3.5% vs. 5.5%, $P = 0.34$), ever wheeze (19.0% vs. 16.2%, $P = 0.29$), dyspnea on exertion (9.2% vs. 8.1%, $P = 0.57$), hospitalization for respiratory problems in the past 12 months (1.4% vs. 0.4%, $P = 0.08$), or missed work due to respiratory problems in the past 12 months (2.8% vs. 2.1%, $P = 0.50$) (Figure 3). Mean scores $\pm$ standard deviation (SD) on the St George's Respiratory Symptoms Questionnaire did not differ among those with an RSP compared with non-restricted, non-obstructed individuals (8.1 ± 15.9 vs. 7.2 ± 12.8). In contrast, adults

with COPD had average scores of 12.9 ± 18.9 . Similarly, the modified Medical Research Council (mMRC) Dyspnoea Scale scores were not different between participants with RSP and those who were non-restricted and non-obstructed at either baseline (mean mMRC scores 1.17 vs. 1.18; $P = 0.72$) or at 3 years of follow-up (1.32 vs. 1.26; $P = 0.31$).

Restrictive spirometric pattern and change in lung function over time

We report lung function decline both as an absolute value and as a percentage of baseline lung function. There was an inverse relationship between post-bronchodilator FEV₁ Z scores and percentage decline in lung function from baseline (Figure 4). Participants with RSP had a slower absolute rate of lung function decline than non-restricted, non-obstructed individuals (pre-bronchodilator FEV₁, 19.2 vs. 26.6 ml/year, $P = 0.002$); however, we found that participants with RSP had an accelerated pre-bronchodilator FEV₁ decline when baseline pre-bronchodilator FEV₁ was taken into account (1.15%/year vs. 1.06%/year, respectively; $P = 0.003$) (Table 3).

DISCUSSION

In this population-based, longitudinal study, we described the prevalence and risk factors for RSP across four sites with different degrees of urbanization, geography, and altitude in Peru. Although other studies have examined the risk factors for RSP in LMICs, this study is among the first to assess the prevalence and associated risk factors for RSP and longitudinal lung function decline. We found overall low rates of RSP, particularly in urban areas. Similarly, while for those living in a rural environment, DM and increased hs-CRP level were associated with RSP, those exposed to smoking and biomass did not have an increased risk for RSP. After adjustment for baseline FEV₁, participants with RSP had a small but significant accelerated rate of FEV₁ decline compared with non-restricted, non-obstructed individuals.

Published data show wide variations in RSP prevalence among LMICs. In the Burden of Obstructive Lung Disease (BOLD) Study, rates of RSP ranged from 4.2% to 48.7%, with higher RSP rates found among LMICs using fixed-per cent predicted cut-offs to diagnose RSP.⁶ Our results were consistent with the prevalence in other Latin American countries in the PLATINO study, which found rates of RSP ranging from 2.3% to 7%, and used lower limit of normal (LLN) cut-offs than we did.⁷

Several negative health outcomes among those with RSP have been examined in longitudinal studies, including increased respiratory symptoms, metabolic syndrome, and mortality.^{8,19–22} In high-income settings, those with RSP have been shown to have an increased burden of respiratory symptoms compared with those with normal spirometry, and perform worse on symptom-based questionnaires.^{22,23} While our results demonstrate a trend towards more severe symptoms among those with RSP than those with normal spirometry, there were no significant differences between participants with RSP and those with normal spirometry, as opposed to the significant differences between those with COPD and those with normal spirometry.

In high-income settings, where obesity is most closely linked to RSP, there is evidence that RSPs may be linked to pro-inflammatory conditions independent of obesity.^{8,24,25} We found a diagnosis of diabetes to be positively associated with RSP similar to other LMIC-based studies.⁸ When examining inflammatory biomarkers, studies have demonstrated elevated levels of hs-CRP among those with lower FVC values.^{25–27} Elevated hs-CRP levels were associated with having RSP in Peru. Living in a rural setting was also found to be associated with RSP when controlling for biomass exposure. One explanation for this finding may be the low socio-economic status of rural groups and lower lung volumes secondary to malnutrition.²⁸

The diagnosis of RSP resulted in an accelerated decline in FEV_1 as a percentage of baseline lung function compared with non-restrictive, non-obstructive individuals in our longitudinal analysis. Lung function decline had a strong relationship with baseline lung function across the cohort, emphasizing the importance of adjusting estimates of lung function decline for baseline lung function. While few studies have examined RSPs in LMIC settings, those conducted in high-income settings have shown RSPs to result in accelerated absolute decline in lung function.^{8,29}

One strength of our study was its large population-based sample derived from four diverse geographic and social settings across Peru. We defined RSP as a pre-bronchodilator FVC below the LLN, which may explain the lower prevalence of RSP than earlier studies, which used fixed cut-offs. The definition for RSP has varied among studies and has included $FVC < 80\%$, FVC , LLN and $FEV_1 < 80\%$.⁸ A definition including both FEV_1 and FVC may further identify phenotypes at risk for negative health outcomes. One limitation of this study was the short follow-up time of 3 years. The high prevalence of biomass use in rural areas vs. low use in urban areas also made these variables difficult to interpret separately.

In general, the Peruvian population with RSP included in this study differed in both respiratory symptoms and showed a small, but significantly increased decline in lung function compared with non-restricted, non-obstructed individuals, which raises the question as to whether RSP is a diagnosis that confers risk for negative health outcomes. We did find elevated hs-CRP levels among those with RSP, independent of obesity and other comorbidities, indicating that a similar inflammatory pattern found in high-income settings may apply to those with RSP in low-income settings. In many LMIC settings, diagnostic equipment for assessing restriction is prohibitively expensive, and requires a steady supply of mixed gas, and skilled technicians. While a diagnosis of RSP does not indicate restriction, it may prove a valuable proxy for systemic inflammatory disease processes that require further analyses, particularly in LMIC settings.

CONCLUSIONS

This multisite, population-based study showed that RSPs were prevalent in Peru; being female, having a diagnosis of DM and living in a rural environment were associated with increased odds of having a lower FVC with a high normal or preserved FEV_1/FVC ratio. Those with RSP had accelerated lung function decline compared with non-restricted, non-obstructed individuals. This observation is consistent with previous findings whereby

RSP was hypothesized to be an insidious inflammatory process with deleterious, measurable effects of lung function decline.

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Figure 1.

RSP prevalence stratified by age category and sex. Diagnosis was made using a GLI mixed ethnic reference population. RSP = restrictive spirometric pattern; GLI = Global Lung Function Initiative.

Figure 2.

ORs of having RSP for a rural environment vs. urban, women vs. men, living at high altitude (3800 m) vs. low altitude (sea level), diabetes vs. no diabetes, hs-CRP (75th vs. 25th percentile), daily biomass exposure vs. non-daily, and daily smoking vs non-daily. OR = odds ratio; RSP = restrictive spirometric pattern; hs-CRP = high-sensitivity C-reactive protein.

Figure 3.

Prevalence of negative health outcomes and respiratory symptoms (missed work days because of respiratory problems in the last 12 months, hospitalization for respiratory problems in the last 12 months, dyspnea upon exertion, ever wheeze, phlegm, and cough in the last 12 months) between groups (RSP vs. COPD vs. No RSP or COPD). RSP = restrictive spirometric pattern; COPD = chronic obstructive pulmonary disease.

Figure 4.

Baseline pre-bronchodilator Z scores vs. change in lung function as a percentage of baseline, stratified by FEV₁ and FVC. Longitudinal models were adjusted for sex, biomass exposure, tobacco exposure, urbanization and altitude. Data were grouped by baseline Z score (20 bins for FEV₁ and 21 bins for FVC). The mean values for lung function decline (with error bars showing $\pm$ one standard deviation) are plotted in black, with the non-binned values plotted in gray. FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity.

Table 1

Sociodemographic and disease characteristics according to site

	Tumbes (<i>n</i> = 991) <i>n</i> (%)	Rural Puno (<i>n</i> = 530) <i>n</i> (%)	Urban Puno (<i>n</i> = 520) <i>n</i> (%)	Lima (<i>n</i> = 1014) <i>n</i> (%)
Age, years, mean $\pm$ SD	56.1 $\pm$ 13.3	55.8 $\pm$ 12.6	55.4 $\pm$ 12.2	55.1 $\pm$ 11.8
RSP-positive when using a GLI mixed ethnic reference population	68 (6.9)	27 (5.1)	19 (3.7)	28 (2.8)
Males	498 (50)	253 (48)	255 (49)	496 (49)
Chronic bronchitis	15 (2)	39 (8)	35 (7)	94 (9)
Daily biomass use	229 (23)	484 (97)	25 (5)	63 (6)
BMI $\geq$ 30 kg/m ²	312 (32)	55 (10)	139 (27)	327 (32)
Daily smokers	56 (6)	1 (0)	11 (2)	33 (3)
Diabetes	102 (10)	16 (3)	34 (7)	55 (6)
hs-CRP, mean $\pm$ SD	4.0 $\pm$ 6.7	2.5 $\pm$ 9.6	2.8 $\pm$ 5.1	3.6 $\pm$ 5.9
Tuberculosis	7 (1)	7 (1)	3 (1)	72 (7)
Wealth index				
Lowest	324 (33)	373 (71)	122 (24)	123 (12)
Middle	401 (41)	132 (26)	132 (26)	375 (37)
Highest	262 (50)	15 (3)	262 (50)	516 (51)

SD = standard deviation; RSP = restrictive spirometric pattern; GLI = Global Lung Function Initiative; BMI = body mass index; hs-CRP = high-sensitivity C-reactive protein.

Baseline sociodemographic and disease characteristics of RSP vs. non-obstructed, non-restricted and COPD using a GLI mixed ethnic reference population

Table 2

	RSP (<i>n</i> = 142) <i>n</i> (%)	No RSP or COPD (<i>n</i> = 2719) <i>n</i> (%)	COPD (<i>n</i> = 194) <i>n</i> (%)
Age, years, mean $\pm$ SD	56.7 $\pm$ 13.6	55.3 $\pm$ 12.3	58.4 $\pm$ 13.9
Males	47 (33.1)	1333 (49.0)	122 (62.9)
Daily biomass use	39 (28.1)	690 (25.8)	72 (37.5)
BMI 30 kg/m ²	41 (28.9)	760 (28.0)	32 (16.5)
Daily smokers	6 (4.3)	89 (3.3)	6 (3.1)
Diabetes	17 (12.8)	173 (6.7)	4 (2.1)
hs-CRP, mean $\pm$ SD	4.6 $\pm$ 9.1	3.3 $\pm$ 6.5	4.3 $\pm$ 8.1
Tuberculosis	4 (10.9)	64 (2.4)	21 (10.9)
Wealth index			
Lowest	55 (38.7)	807 (29.7)	80 (41.2)
Middle	48 (33.8)	937 (34.5)	60 (34.0)
Highest	39 (27.5)	969 (35.7)	48 (24.7)
Pre-bronchodilator spirometry <i>Z</i> scores, mean $\pm$ SD			
FVC	-1.60 $\pm$ 1.26	1.04 $\pm$ 1.24	0.61 $\pm$ 1.71
FEV ₁	-1.55 $\pm$ 1.11	0.75 $\pm$ 1.14	-0.82 $\pm$ 1.46
FEV ₁ /FVC	-0.14 $\pm$ 1.30	-0.41 $\pm$ 0.84	-2.24 $\pm$ 0.95
Post-bronchodilator spirometry <i>Z</i> scores, mean $\pm$ SD			
FVC	-1.18 $\pm$ 1.21	1.13 $\pm$ 1.21	0.96 $\pm$ 1.66
FEV ₁	-1.01 $\pm$ 1.08	1.12 $\pm$ 1.16	-0.34 $\pm$ 1.48
FEV ₁ /FVC	0.25 $\pm$ 1.07	0.02 $\pm$ 0.76	-1.97 $\pm$ 0.82

RSP = restrictive spirometric pattern; COPD = chronic obstructive pulmonary disease; GLI = Global Lung Initiative; SD = standard deviation; BMI = body mass index; hs-CRP = high-sensitivity C-reactive protein; FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 s.

Table 3

Average change per year in lung function (ml/year) and percentage change from baseline adjusted for sex, biomass exposure, tobacco exposure, urbanization and high altitude compared to non-restricted, non-obstructed individuals stratified by reference population used for diagnosis of RSP

	No RSP or COPD			RSP		
	FEV ₁ (95%CI)	FVC (95%CI)	FEV ₁ (95%CI)	FVC (95%CI)	FEV ₁ (95%CI)	FVC (95%CI)
Estimated lung function decline, ml/year	26.6 (25.6–27.7)	28.7 (27.3–30.1)	19.2 (14.7–23.6)	22.2 (16.5–27.9)		
Estimated lung function decline as a percentage of baseline FEV ₁ , %/year	1.06 (1.04–1.07)	0.89 (0.88–0.90)	1.15 (1.10–1.22)	1.15 (1.10–1.22)		

RSP = restrictive spirometric pattern; COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in 1 s; CI = confidence interval.