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

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ABSTRACT

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

Methods: We analysed prospective data from 2,957 adults recruited across four diverse settings in Peru over a three-year period. Multivariable logistic regression was used to study the association between the presence of restriction and associated risk factors. Multivariable linear mixed models was used to determine lung function decline.

Results: Among 2,957 participants, average age was 55.4 years (SD=12.4) and 49.3% were male. Overall prevalence of RSP was 4.7% with a range of 2.8% (Lima) to 6.9% (Tumbes). The odds of having a diagnosis of restriction were higher among those who lived in a rural environment (OR=2.19; 1.43-3.39), had a diagnosis of diabetes (OR = 1.93, 95% CI 1.10-3.39) and among women (OR=2.09, 95% CI 1.42-2.11). Adjusted for baseline lung function, adults with RSP had accelerated decline in FEV_1 when compared to 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 FEV_1 decline. Our findings are consistent with the notion that RSP is an insidious inflammatory condition with deleterious effects of lung function decline.

INTRODUCTION

Chronic respiratory disease affects 1 billion people globally and accounts for 7% of all deaths worldwide [1]. The majority of 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 among LMICs [3-5]. Among these 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 (FEV_1) with preserved overall FEV_1/FVC ratio [6-8]. Although restriction in spirometry is not 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 (RSP) can result in higher risk of morbidity (respiratory symptoms and function status limitation) as well as all-cause mortality among individuals who present with these findings [8].

Global estimates for RSP range from 2.3% in Santiago, Chile to 68% among women in Mumbai, India, though this variability may be a result of different definitions for RSP and reference populations [6,7]. RSP has been most commonly associated with obesity, tobacco exposure and female gender in these settings [3,6]. In addition, countries with a high prevalence of biomass cooking fuel use and tuberculosis also had higher

prevalence of RSP, though potential associations between biomass, tuberculosis and RSP have not been studied at a household level [4,9].

While population-based studies have shown varying prevalence of RSP 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 RSP across four geographically diverse settings in Peru. We additionally examine respiratory symptoms and functional status among those with RSP, and decline in lung function during three 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 was 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 3,825 meters above sea-level; and the rural communities around Puno [5].

Study Design

We analysed data from approximately 3,000 adults aged ≥35 years enrolled in a longitudinal population-based study with annual follow-up from 2010-2013. 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 the 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 tuberculosis. 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

Participants responded to a questionnaire on socio-demographics, 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 (ndd, Zurich, Switzerland) before and after 200 mcg of inhaled salbutamol via a spacer following joint American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines[10]. Participants with low quality spirometry were asked to repeat the test on another day for a total of three attempts. Overall 95% met ATS/ERS criteria including minimum exhalation time of 6 seconds or 12 seconds if no plateau.[11] Participants were then invited to follow up annually for three years for repeat spirometry and phlebotomy. Bronchodilation was conducted at baseline and on the third follow-up visit [12].

Definitions

We defined restrictive spirometric patterns as a pre-bronchodilator FVC below the 5th percentile (Z score ≤ -1.64) and a post-bronchodilator FEV_1/FVC ratio above the 5th percentile (Z score ≥ -1.64) of a reference population[8], and COPD as a post-bronchodilator FEV_1/FVC ratio below the 5th percentile of a reference population. Post-bronchodilator measurements were utilized to exclude individuals with reversible airways obstruction from a diagnosis of RSP.[8] Since there are no established reference equations for lung function among Peruvians, we utilized the Global Lungs Initiative (GLI) mixed ethnic reference population. For longitudinal analysis, we included participants with at least one follow-up visit within the three-year period.

Biostatistical Methods

For prevalence estimates we included all participants who completed study questionnaires and had acceptable post-bronchodilator spirometry at baseline. Baseline risk factors for RSP were analysed using multivariable logistic regression. We evaluated risk factors for having a diagnosis of RSP including sex, age, urbanization, altitude, daily smoking, daily use of biomass fuel, history of tuberculosis, chronic bronchitis, hs-CRP, diabetes, hypertension and body-mass index (BMI). We compared respiratory symptoms among those with RSP vs. COPD vs. non-restricted, non-obstructed spirometry at baseline assessing respiratory symptoms. For other analysis we used chi-squared 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 analyse the effect of having RSP at baseline on longitudinal decline in pre-bronchodilator FEV_1 and FVC [13]. 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 lung function decline as a percent of baseline forced expiratory volumes. To calculate 95% confidence intervals for the mean lung function decline as a percent of baseline forced expiratory volumes, we used the 2.5^{th} and 97.5^{th} percentiles of 3,000 bootstrap resamples by individual [14]. Analyses were performed in R (www.r-project.org) [15-17].

RESULTS

Participant characteristics

There were 2,957 participants with complete data. We report participant characteristics in Tables 1 and 2. Those included in analysis had an average age of 55.4 ± 12.4 years, 49% of whom were male. Reported biomass exposure (1%-97%) and tobacco exposure (<1%-6%) varied between settings. 27.3% of participants had a BMI ≥ 30 kg/m^2 (n=833) and 7% had diabetes (n=207) at baseline. A low percentage of individuals reported a history of tuberculosis (3%, n=89), 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 RSP

The overall prevalence of restriction was 4.6%, 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 1.42-2.11) (Figure 2). Similarly, living in a rural area was associated with a higher odds of having RSP (OR=2.19; 95% CI 1.43 to 3.39) as well as diabetes (OR = 1.93, 95% CI 1.10-3.39). There was a moderate association of elevated hs-CRP (interquartile OR=1.05; 95% CI 1.00-1.10) and a diagnosis of RSP. Daily smoking, daily use of biomass fuels, site (urbanization and high altitude), age, BMI, history of tuberculosis, hypertension, and chronic bronchitis were not by themselves associated with having RSP.

Respiratory symptoms associated with presence of RSP at baseline

Adults with RSP did not have more respiratory symptoms including cough in the past 12 months (4.5% vs. 4.2%, p=0.87), phlegm in the past 12 months (3.8% vs. 5.7%, p=0.35), ever wheeze (20.3% vs. 16.7%, p=0.28), difficulty walking/shortness of breath (9.8% vs. 8.3%, p=0.56), hospitalization for respiratory problems in the past 12 months (1.5% vs. 0.4%, p=0.08), and missed work due to respiratory problems in the past 12 months (3.0% vs. 2.1%, p=0.50) (Figure 3). Mean scores ± SD for the St. George's Respiratory Symptoms Questions did not differ between groups among those with RSP compared to 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 MRC (mMRC) Dyspnea Scale scores were not different between 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).

RSP and change in lung function over time

We report lung function decline both as an absolute value and as a percent of baseline lung function. There was an inverse relationship between post-bronchodilator FEV_1 Z-scores and percent decline in lung function from baseline (Figure 4). Participants with RSP had a slower absolute rate of lung function decline when compared to non-restricted, non-obstructed individuals (19.2 mL/year vs. 26.6 mL/year, p=0.002); however, we found that participants with RSP had an accelerated pre-bronchodilator FEV_1 decline when baseline pre-bronchodilator FEV_1 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 describe 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 risk factors for RSP in LMICs, this study is among the first to assess 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 living in a rural environment, diabetes, and elevated hs-CRP were associated with RSP, those exposed to smoking and biomass did not have an increased risk for RSP. Adjusted for baseline FEV_1, participants with RSP had a small but significant accelerated rate of FEV_1 decline when compared to non-restricted, non-obstructed individuals.

Published data show wide variation in prevalence of RSP among LMICs. In BOLD, the rates of RSP ranged from 4.2% to 48.7%, with higher rates of RSP found among LMIC using fixed-percent predicted cut offs to diagnose RSP [6]. Our results were consistent

with the prevalence of other Latin American countries in PLATINO, which found rates of RSP ranging from 2.3% to 7%, and used LLN cut-offs as we did [7].

A number of negative health outcomes among those with RSP have been examined in longitudinal studies including increased respiratory symptoms, metabolic syndrome, and mortality [8,18-21]. In high-income settings, those with restrictive spirometry patterns have been shown to have increased burden of respiratory symptoms, when compared to those with normal spirometry, and perform worse on symptom-based questionnaires.[21,22] While our results demonstrate a trend towards greater symptoms among those with RSP compared to those with normal spirometry, there were no significant differences between groups as seen with COPD.

In high-income settings, where obesity is most closely linked to RSP, there is evidence that RSP may be linked to pro-inflammatory conditions independent of obesity [8,23,24]. We found a diagnosis of diagnosis 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 levels of FVC [24-26]. Elevated hs-CRP was similarly associated with having RSP in Peru. Living in rural settings was also found to be associated with RSP when controlling for biomass exposure. One explanation for this may be due to low socioeconomic status among rural groups and lower lung volumes secondary to malnutrition [27].

A diagnosis of RSP resulted in accelerated decline in FEV_1 as a percentage of baseline lung function when compared to non-restrictive individuals, non-obstructive individuals in

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 RSP in LMIC settings, those conducted in high income settings have shown RSP to result in accelerated absolute lung function decline [8,28].

A strength of this study is its large population-based sample derived from four diverse geographical and social settings across Peru. We defined RSP as a pre-bronchodilator FVC below the LLN, which may explain the lower prevalence of RSP when compared to earlier studies which used fixed cut-offs. The definition for RSP has varied among previous studies and have 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. Limitations in this study include a short follow up time of three years. The high prevalence of biomass use in rural areas vs low utilization in urban areas additionally made these variables difficult to interpret separately.

Ultimately, the Peruvian population with RSP included in this study differed in both respiratory symptoms and showed small but significantly increased lung function decline compared to non-restricted, non-obstructed individuals, which raises the question of whether RSP is a diagnosis which confers risk for negative health outcomes. We did find elevated hs-CRP among those with RSP, independent of obesity and other comorbid conditions, 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 prohibitive, requiring high expense, a steady

supply of mixed-gas, and skilled technicians. While a diagnosis of RSP does not necessitate restriction, it may prove a valuable proxy for systemic inflammatory disease processes which warrant further analysis particularly in LMIC settings.

Conclusions

This multi-site population-based study showed that RSP was prevalent in Peru and being female, diagnosis of diabetes and living in a rural environment were associated with increased odds of having lower forced vital capacity with a high normal or preserved FEV_1/FVC ratio. Those with RSP had accelerated lung function decline when compared to non-restricted, non-obstructed individuals. This is consistent with previous findings, whereby RSP is hypothesized to be an insidious inflammatory process with deleterious, measurable effects of lung function decline.

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Table 1. Sociodemographic and disease characteristics by site

	Tumbes	Rural Puno	Urban Puno	Lima
Age in years, mean (SD)	56.1 (13.3)	55.8 (12.6)	55.4 (12.2)	55.1 (11.8)
RSP positive when using GLI Mixed Ethnic reference population, % (n)	6.9 (68)	5.1 (27)	3.7 (19)	2.8 (28)
Percentage of Males (n)	50 (498)	48 (253)	49 (255)	49 (496)
Chronic bronchitis, % (n)	2 (15)	8 (39)	7 (35)	9 (94)
Use biomass daily, % (n)	23 (229)	97 (484)	1 (25)	6 (63)
BMI ≥ 30 kg/m^2, % (n)	32 (312)	10 (55)	27 (139)	32 (327)
Daily smokers, % (n)	6 (56)	0 (1)	2 (11)	3 (33)
Diabetes, % (n)	10 (102)	3 (16)	7 (34)	6 (55)
hs-CRP, mean (SD)	4.0 (6.7)	2.5 (9.6)	2.8 (5.1)	3.6 (5.9)
Tuberculosis, % (n)	1 (7)	1 (7)	1 (3)	7 (72)
Wealth index, % (n)				
Lowest	33 (324)	71 (373)	24 (122)	12 (123)
Middle	41 (401)	26 (140)	26 (132)	37 (375)
Highest	26 (263)	3 (15)	50 (262)	51 (516)

Table 2. Baseline sociodemographic and Disease Characteristics of RSP vs. Non-obstructed, Non-restricted and COPD using GLI Mixed Ethnic reference population.

	RSP	Non obstructed or restricted	COPD
Age in years, mean (SD)	55.7 (13.0)	55.2 (12.3)	58.4 (13.9)
Number of Males (%)	43 (32.3)	1296 (49.1)	118 (63.4)
Use biomass daily, n (%)	39 (29.3)	681 (25.9)	70 (37.6)
BMI ≥ 30 kg/m^2, n (%)	38 (28.6)	740 (28.1)	32 (17.3)
Daily smokers, n (%)	5 (3.8)	87 (3.3)	5 (2.7)
Diabetes, n (%)	17 (12.8)	173 (6.7)	4 (2.2)
hs-CRP, mean (SD)	4.8 (9.4)	3.3 (6.5)	4.3 (8.2)
Tuberculosis, n (%)	4 (3.0)	62 (2.9)	20 (10.8)
Wealth index, n (%)			
Lowest	48 (36.1)	780 (29.6)	74 (39.8)
Middle	47 (35.3)	906 (34.4)	65 (34.9)
Highest	38 (28.6)	948 (36.0)	47 (25.3)
Pre-bronchodilator spirometry Z scores			
FVC, mean (SD)	-1.53 (1.25)	1.05 (1.24)	0.70 (1.6)
FEV$_1$, mean (SD)	-1.50 (1.12)	0.76 (1.14)	-0.76 (1.4)
FEV$_1$/FVC, mean (SD)	-0.16 (1.32)	-0.41 (0.84)	-2.2 (0.95)
Post-bronchodilator spirometry Z scores			
FVC, mean (SD)	-1.18 (1.20)	1.32 (1.21)	1.0 (1.6)
FEV$_1$, mean (SD)	-1.01 (1.08)	1.12 (1.16)	-0.29 (1.4)
FEV$_1$/FVC, mean (SD)	0.25 (1.07)	0.02 (0.76)	-1.95 (0.80)

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.

	Non-restricted, non-obstructed		Restrictive spirometric pattern	
	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 forced expiratory volume (%/yr)	1.06% (1.04%, 1.07%)	0.89% (0.88%, 0.90%)	1.15% (1.10%, 1.22%)	1.06% (1.01%, 1.12%)

Figure 1: Prevalence of RSP by age category, stratified by sex.

Figure 2: **Odds Ratio of having RSP for rural environment vs. urban, women vs. men, living at high altitude (3800m) vs. low altitude (sea level), diabetes vs. no diabetes, hs-CRP (75^{th} vs 25^{th} percentile), daily biomass exposure vs non-daily, and daily smoking vs non-daily, stratified by sex.**

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 on exertion, ever wheeze, phlegm, and cough in last 12 months) between groups (RSP vs. Non-restricted, non-obstructed vs. COPD).

Figure 4: Baseline pre-bronchodilator Z scores vs change in lung function as a percentage of baseline, stratified by FEV_1 and FVC. Longitudinal models were adjusted for sex, biomass exposure, tobacco exposure, urbanization and altitude. Data was grouped by baseline Z-score (20 bins for FEV_1 and 21 bins for FVC). The mean values for lung function decline (with error bars showing ± one standard deviation) were plotted in black, with the non-binned values plotted in grey.