

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

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47 **ABSTRACT**

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

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

55 **Results:** Among 2,957 participants, average age was 55.4 years (SD=12.4) and 49.3%  
56 were male. Overall prevalence of RSP was 4.7% with a range of 2.8% (Lima) to 6.9%  
57 (Tumbes). The odds of having a diagnosis of restriction were higher among those who  
58 lived in a rural environment (OR=2.19; 1.43-3.39), had a diagnosis of diabetes (OR =  
59 1.93, 95% CI 1.10-3.39) and among women (OR=2.09, 95% CI 1.42-2.11). Adjusted for  
60 baseline lung function, adults with RSP had accelerated decline in FEV<sub>1</sub> when compared  
61 to non-obstructed, non-restricted individuals.

62 **Discussion:** RSP is prevalent particularly among women and in individuals living in rural  
63 settings of Peru. When adjusted for baseline lung function, participants with RSP had  
64 accelerated rates of FEV<sub>1</sub> decline. Our findings are consistent with the notion that RSP  
65 is an insidious inflammatory condition with deleterious effects of lung function decline.

66 **INTRODUCTION**

67 Chronic respiratory disease affects 1 billion people globally and accounts for 7% of all  
68 deaths worldwide <sup>1</sup>. The majority of deaths related to chronic respiratory conditions  
69 occur in low- and middle-income countries (LMICs), and the burden of disease is  
70 expected to increase in many LMICs due to rapid urbanization and increased tobacco  
71 consumption <sup>2</sup>.

72

73 Over the past decade, population-based, cross-sectional studies have examined  
74 obstructive lung disease among LMICs <sup>3-5</sup>. Among these studies, a percentage of  
75 participants were found to have restrictive spirometric values demonstrating reduced  
76 forced vital capacity (FVC) and forced expiratory volume in one second (FEV<sub>1</sub>) with  
77 preserved overall FEV<sub>1</sub>/FVC ratio <sup>6-8</sup>. Although restriction in spirometry is not restrictive  
78 lung disease, which typically requires measurement of total lung capacity and/or gas  
79 transfer, studies in high-income settings have shown that restrictive spirometric patterns  
80 (RSP) can result in higher risk of morbidity (respiratory symptoms and function status  
81 limitation) as well as all-cause mortality among individuals who present with these  
82 findings <sup>8</sup>.

83

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

89 prevalence of RSP, though potential associations between biomass, tuberculosis and  
90 RSP have not been studied at a household level <sup>4,9</sup>.

91  
92 While population-based studies have shown varying prevalence of RSP in LMIC  
93 settings, associated morbidity, environmental risk factors and longitudinal health  
94 outcomes among these groups remain poorly defined <sup>6,7</sup>. Our primary objective was to  
95 describe the prevalence of and attributable risk factors for RSP across four  
96 geographically diverse settings in Peru. We additionally examine respiratory symptoms  
97 and functional status among those with RSP, and decline in lung function during three  
98 year follow up.

99

## 100 **METHODS**

### 101 **Study Setting**

102 We conducted a longitudinal, population-based study in Peru to determine the  
103 prevalence of chronic pulmonary and cardiovascular diseases across four disparate  
104 regions. This study was described in detail elsewhere <sup>5</sup>. Four settings were selected  
105 based on the degree of urbanization and altitude: Pampas de San Juan de Miraflores,  
106 an urbanized community south of Lima; Tumbes, a semi-urban, sea-level community in  
107 northern Peru; Puno, an urban setting 3,825 meters above sea-level; and the rural  
108 communities around Puno <sup>5</sup>.

109

### 110 **Study Design**

111 We analysed data from approximately 3,000 adults aged  $\geq 35$  years enrolled in a  
112 longitudinal population-based study with annual follow-up from 2010-2013. All subjects

113 were randomly selected using a single-stage random selection process and only one  
114 participant per household was enrolled. In Puno, recruitment was stratified to include  
115 500 participants each from the urban and rural settings. Inclusion criteria were age  $\geq 35$   
116 years, a full-time resident in the specified setting, and capacity to understand procedures  
117 and consent to the study. Exclusion criteria were pregnancy, physical disability that  
118 prevented measurement of blood pressure or anthropometry, or active pulmonary  
119 tuberculosis. The study was approved by the Institutional Review Boards of Universidad  
120 Peruana Cayetano Heredia and A.B. PRISMA, in Lima, Peru, and the Johns Hopkins  
121 Bloomberg School of Public Health in Baltimore, USA.

122

### 123 **Data collection**

124 Participants responded to a questionnaire on socio-demographics, current smoking  
125 status, respiratory symptoms, past medical history, and family history of non-  
126 communicable disease and biomass exposure. Field workers measured weight and  
127 height in triplicate in all three phases. Spirometry was conducted using the Easy-On-PC  
128 spirometer (ndd, Zurich, Switzerland) before and after 200 mcg of inhaled salbutamol via  
129 a spacer following joint American Thoracic Society and European Respiratory Society  
130 (ATS/ERS) guidelines<sup>10</sup>. Participants with low quality spirometry were asked to repeat  
131 the test on another day for a total of three attempts. Overall 95% met ATS/ERS criteria  
132 including minimum exhalation time of 6 seconds or 12 seconds if no plateau.<sup>11</sup>  
133 Participants were then invited to follow up annually for three years for repeat spirometry  
134 and phlebotomy. Bronchodilation was conducted at baseline and on the third follow-up  
135 visit <sup>12</sup>.

136

137 **Definitions**

138 We defined restrictive spirometric patterns as a pre-bronchodilator FVC below the 5<sup>th</sup>  
139 percentile (Z score  $\leq -1.64$ ) and a post-bronchodilator FEV<sub>1</sub>/FVC ratio above the 5<sup>th</sup>  
140 percentile (Z score  $\geq -1.64$ ) of a reference population<sup>8</sup>, and COPD as a post-  
141 bronchodilator FEV<sub>1</sub>/FVC ratio below the 5<sup>th</sup> percentile of a reference population. Post-  
142 bronchodilator measurements were utilized to exclude individuals with reversible airways  
143 obstruction from a diagnosis of RSP.<sup>8</sup> Since there are no established reference  
144 equations for lung function among Peruvians, we utilized the Global Lungs Initiative  
145 (GLI) mixed ethnic reference population. For longitudinal analysis, we included  
146 participants with at least one follow-up visit within the three-year period.

147

148 **Biostatistical Methods**

149 For prevalence estimates we included all participants who completed study  
150 questionnaires and had acceptable post-bronchodilator spirometry at baseline. Baseline  
151 risk factors for RSP were analysed using multivariable logistic regression. We evaluated  
152 risk factors for having a diagnosis of RSP including sex, age, urbanization, altitude, daily  
153 smoking, daily use of biomass fuel, history of tuberculosis, chronic bronchitis, hs-CRP,  
154 diabetes, hypertension and body-mass index (BMI). We compared respiratory symptoms  
155 among those with RSP vs. COPD vs. non-restricted, non-obstructed spirometry at  
156 baseline assessing respiratory symptoms. For other analysis we used chi-squared tests  
157 or Fisher's exact tests to compare proportions, t-tests to compare continuous values,  
158 and Kruskal-Wallis tests to compare categorical values between subgroups as  
159 appropriate.

160

161 We then built multivariable linear mixed effects models with a random intercept and  
162 random slope by individual to analyse the effect of having RSP at baseline on  
163 longitudinal decline in pre-bronchodilator FEV<sub>1</sub> and FVC<sup>13</sup>. All models were adjusted for  
164 sex, daily use of biomass fuels, daily tobacco smoking, living in an urban setting, and  
165 living at high altitude. We then used the estimated subject-specific random slopes  
166 divided by baseline lung function to characterize the subject-specific lung function  
167 decline as a percent of baseline forced expiratory volumes. To calculate 95% confidence  
168 intervals for the mean lung function decline as a percent of baseline forced expiratory  
169 volumes, we used the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles of 3,000 bootstrap resamples by  
170 individual<sup>14</sup>. Analyses were performed in R ([www.r-project.org](http://www.r-project.org))<sup>15-17</sup>.

171

## 172 **RESULTS**

### 173 **Participant characteristics**

174 There were 2,957 participants with complete data. We report participant characteristics  
175 in Tables 1 and 2. Those included in analysis had an average age of 55.4 ± 12.4 years,  
176 49% of whom were male. Reported biomass exposure (1%-97%) and tobacco exposure  
177 (<1%-6%) varied between settings. 27.3% of participants had a BMI ≥ 30 kg/m<sup>2</sup> (n=833)  
178 and 7% had diabetes (n=207) at baseline. A low percentage of individuals reported a  
179 history of tuberculosis (3%, n=89), with the majority located in Lima (n=72). Across the  
180 sample, 6% of individuals reported symptoms of chronic bronchitis (n=183).

181

### 182 **Prevalence and risk Factors for RSP**

183 The overall prevalence of restriction was 4.6%, with a range of 2.8% (Lima) to 6.9%  
184 (Tumbes) when using the GLL mixed ethnic reference population (Figure 1). Being

185 female was associated with higher odds of RSP (OR=2.09; 95% CI 1.42-2.11) (Figure  
186 2). Similarly, living in a rural area was associated with a higher odds of having RSP  
187 (OR=2.19; 95% CI 1.43 to 3.39) as well as diabetes (OR = 1.93, 95% CI 1.10-3.39).  
188 There was a moderate association of elevated hs-CRP (interquartile OR=1.05; 95% CI  
189 1.00-1.10) and a diagnosis of RSP. Daily smoking, daily use of biomass fuels, site  
190 (urbanization and high altitude), age, BMI, history of tuberculosis, hypertension, and  
191 chronic bronchitis were not by themselves associated with having RSP.

192

### 193 **Respiratory symptoms associated with presence of RSP at baseline**

194 Adults with RSP did not have more respiratory symptoms including cough in the past 12  
195 months (4.5% vs. 4.2%, p=0.87), phlegm in the past 12 months (3.8% vs. 5.7%, p=0.35),  
196 ever wheeze (20.3% vs. 16.7%, p=0.28), difficulty walking/shortness of breath (9.8% vs.  
197 8.3%, p=0.56), hospitalization for respiratory problems in the past 12 months (1.5% vs.  
198 0.4%, p=0.08), and missed work due to respiratory problems in the past 12 months  
199 (3.0% vs. 2.1%, p=0.50) (Figure 3). Mean scores  $\pm$  SD for the St. George's Respiratory  
200 Symptoms Questions did not differ between groups among those with RSP compared to  
201 non-restricted, non-obstructed individuals ( $8.1 \pm 15.9$  vs.  $7.2 \pm 12.8$ ). In contrast, adults  
202 with COPD had average scores of  $12.9 \pm 18.9$ . Similarly, the modified MRC (mMRC)  
203 Dyspnea Scale scores were not different between RSP and those who were non-  
204 restricted and non-obstructed at either baseline (mean mMRC scores 1.17 vs. 1.18;  
205 p=0.72) or at 3-years of follow-up (1.32 vs. 1.26; p=0.31).

206

### 207 **RSP and change in lung function over time**



208 We report lung function decline both as an absolute value and as a percent of baseline  
209 lung function. There was an inverse relationship between post-bronchodilator FEV<sub>1</sub> Z-  
210 scores and percent decline in lung function from baseline (Figure 4). Participants with  
211 RSP had a slower absolute rate of lung function decline when compared to non-  
212 restricted, non-obstructed individuals (19.2 mL/year vs. 26.6 mL/year, p=0.002);  
213 however, we found that participants with RSP had an accelerated pre-bronchodilator  
214 FEV<sub>1</sub> decline when baseline pre-bronchodilator FEV<sub>1</sub> was taken into account  
215 (1.15%/year vs. 1.06%/year, respectively; p=0.003) (Table 3).

216

## 217 **DISCUSSION**

218 In this population-based, longitudinal study we describe the prevalence and risk factors  
219 for RSP across four sites with different degrees of urbanization, geography, and altitude  
220 in Peru. Although other studies have examined risk factors for RSP in LMICs, this study  
221 is among the first to assess prevalence and associated risk factors for RSP, and  
222 longitudinal lung function decline. We found overall low rates of RSP particularly in  
223 urban areas. Similarly while living in a rural environment, diabetes, and elevated hs-CRP  
224 were associated with RSP, those exposed to smoking and biomass did not have an  
225 increased risk for RSP. Adjusted for baseline FEV<sub>1</sub>, participants with RSP had a small  
226 but significant accelerated rate of FEV<sub>1</sub> decline when compared to non-restricted, non-  
227 obstructed individuals.

228

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

232 with the prevalence of other Latin American countries in PLATINO, which found rates of  
233 RSP ranging from 2.3% to 7%, and used LLN cut-offs as we did <sup>7</sup>.

234  
235 A number of negative health outcomes among those with RSP have been examined in  
236 longitudinal studies including increased respiratory symptoms, metabolic syndrome, and  
237 mortality <sup>8,18-21</sup>. In high-income settings, those with restrictive spirometry patterns have  
238 been shown to have increased burden of respiratory symptoms, when compared to  
239 those with normal spirometry, and perform worse on symptom-based questionnaires.<sup>21,22</sup>  
240 While our results demonstrate a trend towards greater symptoms among those with RSP  
241 compared to those with normal spirometry, there were no significant differences  
242 between groups as seen with COPD.

243  
244 In high-income settings, where obesity is most closely linked to RSP, there is evidence  
245 that RSP may be linked to pro-inflammatory conditions independent of obesity <sup>8,23,24</sup>. We  
246 found a diagnosis of diagnosis positively associated with RSP similar to other LMIC-  
247 based studies.<sup>8</sup> When examining inflammatory biomarkers, studies have demonstrated  
248 elevated levels of hs-CRP among those with lower levels of FVC <sup>24-26</sup>. Elevated hs-CRP  
249 was similarly associated with having RSP in Peru. Living in rural settings was also found  
250 to be associated with RSP when controlling for biomass exposure. One explanation for  
251 this may be due to low socioeconomic status among rural groups and lower lung  
252 volumes secondary to malnutrition <sup>27</sup>.

253  
254 A diagnosis of RSP resulted in accelerated decline in FEV<sub>1</sub> as a percentage of baseline  
255 lung function when compared to non-restrictive individuals, non-obstructive individuals in

256 longitudinal analysis. Lung function decline had a strong relationship with baseline lung  
257 function across the cohort emphasizing the importance of adjusting estimates of lung  
258 function decline for baseline lung function. While few studies have examined RSP in  
259 LMIC settings, those conducted in high income settings have shown RSP to result in  
260 accelerated absolute lung function decline <sup>8,28</sup>.

261  
262 A strength of this study is its large population-based sample derived from four diverse  
263 geographical and social settings across Peru. We defined RSP as a pre-bronchodilator  
264 FVC below the LLN, which may explain the lower prevalence of RSP when compared to  
265 earlier studies which used fixed cut-offs. The definition for RSP has varied among  
266 previous studies and have included FVC <80%, FVC <LLN and FEV<sub>1</sub> <80% <sup>8</sup>. A  
267 definition including both FEV<sub>1</sub> and FVC may further identify phenotypes at risk for  
268 negative health outcomes. Limitations in this study include a short follow up time of three  
269 years. The high prevalence of biomass use in rural areas vs low utilization in urban  
270 areas additionally made these variables difficult to interpret separately.

271  
272 Ultimately, the Peruvian population with RSP included in this study differed in both  
273 respiratory symptoms and showed small but significantly increased lung function decline  
274 compared to non-restricted, non-obstructed individuals, which raises the question of  
275 whether RSP is a diagnosis which confers risk for negative health outcomes. We did find  
276 elevated hs-CRP among those with RSP, independent of obesity and other comorbid  
277 conditions, indicating that a similar inflammatory pattern found in high-income settings  
278 may apply to those with RSP in low-income settings. In many LMIC settings, diagnostic  
279 equipment for assessing restriction is prohibitive, requiring high expense, a steady

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

283

## 284 **Conclusions**

285 This multi-site population-based study showed that RSP was prevalent in Peru and  
286 being female, diagnosis of diabetes and living in a rural environment were associated  
287 with increased odds of having lower forced vital capacity with a high normal or preserved  
288 FEV<sub>1</sub>/FVC ratio. Those with RSP had accelerated lung function decline when compared  
289 to non-restricted, non-obstructed individuals. This is consistent with previous findings,  
290 whereby RSP is hypothesized to be an insidious inflammatory process with deleterious,  
291 measurable effects of lung function decline.

292

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**Table 1. Sociodemographic and disease characteristics by site**

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

372  
373

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

	<b>RSP</b>	<b>Non obstructed or restricted</b>	<b>COPD</b>
<b>Age in years, mean (SD)</b>	55.7 (13.0)	55.2 (12.3)	58.4 (13.9)
<b>Number of Males (%)</b>	43 (32.3)	1296 (49.1)	118 (63.4)
<b>Use biomass daily, n (%)</b>	39 (29.3)	681 (25.9)	70 (37.6)
<b>BMI <math>\geq</math> 30 kg/m<sup>2</sup>, n (%)</b>	38 (28.6)	740 (28.1)	32 (17.3)
<b>Daily smokers, n (%)</b>	5 (3.8)	87 (3.3)	5 (2.7)
<b>Diabetes, n (%)</b>	17 (12.8)	173 (6.7)	4 (2.2)
<b>hs-CRP, mean (SD)</b>	4.8 (9.4)	3.3 (6.5)	4.3 (8.2)
<b>Tuberculosis, n (%)</b>	4 (3.0)	62 (2.9)	20 (10.8)
<b>Wealth index, n (%)</b>			
<b>Lowest</b>	48 (36.1)	780 (29.6)	74 (39.8)
<b>Middle</b>	47 (35.3)	906 (34.4)	65 (34.9)
<b>Highest</b>	38 (28.6)	948 (36.0)	47 (25.3)
<b>Pre-bronchodilator spirometry Z scores</b>			
<b>FVC, mean (SD)</b>	-1.53 (1.25)	1.05 (1.24)	0.70 (1.6)
<b>FEV<sub>1</sub>, mean (SD)</b>	-1.50 (1.12)	0.76 (1.14)	-0.76 (1.4)
<b>FEV<sub>1</sub>/FVC, mean (SD)</b>	-0.16 (1.32)	-0.41 (0.84)	-2.2 (0.95)
<b>Post-bronchodilator spirometry Z scores</b>			
<b>FVC, mean (SD)</b>	-1.18 (1.20)	1.32 (1.21)	1.0 (1.6)
<b>FEV<sub>1</sub>, mean (SD)</b>	-1.01 (1.08)	1.12 (1.16)	-0.29 (1.4)
<b>FEV<sub>1</sub>/FVC, mean (SD)</b>	0.25 (1.07)	0.02 (0.76)	-1.95 (0.80)

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**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.**

	<b>Non-restricted, non-obstructed</b>		<b>Restrictive spirometric pattern</b>	
	<b>FEV<sub>1</sub> (95% CI)</b>	<b>FVC (95% CI)</b>	<b>FEV<sub>1</sub> (95% CI)</b>	<b>FVC (95% CI)</b>
<b>Estimated lung function decline (ml/year)</b>	26.6 (25.6, 27.7)	28.7 (27.3, 30.1)	19.2 (14.7, 23.6)	22.2 (16.5, 27.9)
<b>Estimated lung function decline as a percentage of baseline forced expiratory volume (%/yr)</b>	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<sup>th</sup> vs 25<sup>th</sup> 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<sub>1</sub> 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<sub>1</sub> and 21 bins for FVC). The mean values for lung function decline (with error bars showing  $\pm$  one standard deviation) were plotted in black, with the non-binned values plotted in grey.**