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Relationship between symptoms and results on spirometry in adults seen in non-tertiary public health facilities presenting with preserved ratio impaired spirometry

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Abstract

Preserved ratio impaired spirometry (PRISm), defined by reduced forced expiratory volume in 1 second (FEV_1) without meeting criteria for airway obstruction, is often encountered in clinical practice. The management of this heterogeneous condition in individuals with chronic respiratory symptoms is challenging, especially under limited diagnostic resources. Since 2020, all consecutive patients referred for spirometry at our institution have been invited to participate in our registry. Other than spirometry, no other physiological lung function testing is available in this public health service. Therefore, we reviewed our databank with the aim of assessing: i) the proportion of symptomatic patients aged 18 years or older referred for spirometry presenting with PRISm; ii) the rate of inhaled medication used in this group, suggesting a referral diagnosis of obstructive airway disease (OAD); and iii) the relationship between symptoms and results on spirometry in PRISM compared to a group with obstruction matched by FEV_1. To this end, the COPD Assessment Test (CAT) and the Asthma Control Test (ACT) were conjointly responded to by 1032 participants, irrespective of the clinical suspicion. We found that 22% had PRISM, of whom 200 were paired with obstruction by FEV_1 (68±10% of predicted). The CAT and ACT results were well-correlated in both groups (r=-0.727 and -0,698, respectively; $p<0.001$) and used to measure symptoms. Participants in the final sample (n=400) were aged 62±13 years; 70% were ever smokers; and 55% reported household exposure to biomass smoke (at least 5 years). The CAT responses were in the range of moderate symptoms (17±9) and ACT borderline for uncontrolled symptoms (19±5). The main differences were higher body mass index (33±7 *versus* 29±7 kg/m^2; $p<0.001$) and proportion of females (72 *versus* 49%; $p<0.001$) in PRISm compared to obstruction. This group had lower exposure to tobacco (65 *versus* 76% of ever-smokers) but greater exposure to biomass smoke (61 *versus* 49%) ($p<0.05$ for all). The rate of inhaled medication use was as high in PRISm as in obstruction (80%). Notwithstanding matched FEV_1, we found less prominent signs of airway disease in PRISM: marginally reduced FEV_1/forced vital capacity (FVC) ratio (94±8% of predicted); higher expiratory flow between 25% and 75% of vital capacity, despite presumed lower lung volumes (lower FVC); and lower rate of bronchial hyperresponsiveness. In an identical multivariate model, FEV_1 predicted symptoms of obstruction only. In conclusion, these data raise suspicion of a substantial rate of misclassification of individuals with PRISM as having OAD in healthcare facilities with constraints on diagnostic resources.

Key words: spirometry, airway diseases, diagnosis, preserved ratio impaired spirometry.

Introduction

Spirometry may show no airway obstruction but abnormal values [1]. In such circumstances, reductions in the Forced Vital Capacity (FVC) and Forced Expiratory Volume in 1 second (FEV_1) often occur together [2]. Although the term "restrictive spirometry" is traditionally used to describe this pattern, a low FVC is a poor predictor of restrictive ventilatory disorder in unselected cases [3]. The FEV_1, instead, might be the chief abnormality, because: obstructive airway disorders (OAD) are by far more numerous than restrictive ventilatory diseases [4]; in OAD, minor FEV_1 changes already signal substantial involvement of small airways [5]; any attendant reduction in FVC influences the diagnosis of obstruction, and a pseudonormalization of the FEV_1/FVC ratio may result from difficulty in completing a full exhalation (e.g., by older, frail individuals) or air trapping during the forced maneuver (e.g., by obese individuals) [1,6]. Based on this rationale, Preserved Ratio Impaired Spirometry (PRISm) has been proposed to describe the pattern of FEV_1 impairment with a preserved FEV_1/FVC ratio [7]. Since then, cohorts of smokers and general population have shown that, compared to normal spirometry, individuals with PRISm are older, have greater body mass index (BMI) and tobacco exposure [7-12]. In these comparisons, PRISM also have greater burden of respiratory symptoms and respiratory-related hospitalizations [10-13]. There is no clear guidance on how to manage symptomatic individuals showing PRISm. Most of them show no clinical or radiological feature of restrictive ventilatory disorders. Regarding OAD, measurement of lung volumes is needed to unmask obstruction in PRISm, but the tools required to accomplish this task (e.g., plethysmography) are unavailable in healthcare facilities with limited resources. The fact is that, in clinical practice, individuals with PRISm are more likely to receive diagnoses of Asthma and Chronic Obstructive Airway Disease (COPD) and inhaled medications are often prescribed, although evidence of their widespread efficacy in this scenario is lacking [7,8,14]. Therefore, in a public health system in Brazil equipped with no further lung physiological tests other than spirometry, we are interested in investigating: (1) the proportion of symptomatic adult patients referred to spirometry presenting with PRISm; (2) the rate of inhaled medication used in this group, suggesting a referral diagnosis of obstructive airway disease (OAD); (3) the relationship between symptoms of OAD (assessed by questionnaires) with the findings on spirometry compared to a FEV_1-matched group with obstructive pattern. We reasoned that in our setting the frequency of inhaled therapy will be high in PRISm and symptoms more loosely related to the degree of FEV_1 impairment in this group compared to the obstruction.

Materials and Methods

Since July 2020, all consecutive subjects referred for spirometry at our institution have been invited to participate in our registry. Tests are ordered mainly by general practitioners and

pulmonologists pertaining to secondary level of care, comprising a public health system designed to assist the diagnosis of respiratory disorders of around 400,000 inhabitants, living predominantly in urban environment in the southeast of Brazil. Our service is responsible for performing and interpreting the spirometries and the clinical management of patients is entirely at the discretion of the referring physician. We have only enrolled participants with chronic respiratory symptoms, as defined by use of inhaled medication, or the presence of dyspnea, cough or sputum for more than 3 months. Participants unable to perform spirometry maneuvers according to American Thoracic Society (ATS) standards [15] have been not included, as well as individuals with cognitive impairment. The research protocol has been approved by the Ethics Committee (number 2.198.023) and all participants signed the informed consent before inclusion in the registry. For the present study, we analyzed participants in the databank aged 18 years or older and enrolled up to August 2022, because along this period the research protocol stipulated all participants to answer both Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT) and Asthma Control Test (ACT), irrespective of the clinical suspicion. This procedure enabled the use of these tools as complementary measures of the burden of respiratory symptoms in this population. Pregnant women were excluded of the present analyses.

Study procedures

A pulmonologist of the research team obtained all clinical and demographic information. Comorbidities were assessed by clinical interview and prescription analysis. The CAT and ACT questionnaires were responded through a structured interview by all participants, to take into account the low average level of scholarship of the studied population. The CAT and ACT questionnaires are widely used for clinical and research purposes in COPD and Asthma, respectively, and details of these tools are available elsewhere [16,17]. Of note, as opposed to CAT, lower values in ACT indicate higher burden of symptoms.

The spirometry tests were performed with a Koko PDS® device and 400 mcg of salbutamol were administrated to check for bronchodilator responsiveness (assessed by ERS/ATS 2020 criteria). Trained physiotherapists conducted the spirometry tests according to the ATS protocol [15]. PRISM was defined as having a post-bronchodilator (BD) FEV_1/FVC ratio LLN and $FEV_1<$ LLN; and obstructive spirometry was defined as a FEV_1/FVC ratio <LLN. The decision to use LLN, instead of a fixed threshold, was based on the availability of reference equations previously published for our population [18]; the influence of age on the diagnosis of obstruction [1]; and our local practice to prepare the reports sent to the physicians who ordered the tests.

Statistical analysis

Data analysis was performed using IBM SPSS software version 25. A random matching process using a 5% tolerance factor for FEV_1 was performed in the software to find case-control pairs (groups with PRISm and obstruction). Then, a Student's t-test ascertained a non-significant difference in FEV_1 between the two new paired groups. To compare matched-groups, we used the Student's t-test (Mann-Whitney U Test, if appropriate) for continuous variables and the chi-square test for categorical variables. Correlation analyzes between continuous variables were performed by Pearson's method and the obtained correlation coefficients were compared by Fischer's z-test. A multiple linear regression was used to test FEV_1 as an independent predictor of worsening symptoms (CAT and ACT scores). The other variables selected for the model, chosen *a priori*, were age, gender, current smoking status, and BMI. Comorbidities with expected influence on symptoms, among those systematically inquired according to the research protocol, were added if univariate analysis showed uneven prevalences between groups. The candidate predictor variables were inserted in a single step into the model. The model was run 4 times, separately for PRISM and obstruction groups, with CAT and ACT each time as the dependent variables. A p value of less than 0.05 was indicative of statistical significance.

Results

The flowchart of the study is described in Figure 1. Briefly, from August 2020 to July 2022, 1,532 participants aged 18 years or later with adequate spirometry maneuvers were included in our registry. The number of individuals with PRISM was 336 (22%). Of the remaining, 637 (42%) had normal spirometry and 559 (36%) obstruction.

For the present study, 500 eligible participants in the databank were excluded because incomplete answering of ACT or CAT questionnaires. This occurred at a similar rate across the 3 groups (Figure 1). We were able to match by FEV_1 200 participants (out of 217 participants with PRISM and completed questionnaires data) with individuals showing obstruction. Therefore, the final sample (N = 400, Table 1) consisted of individuals aged 62±13 years old; predominantly female (61%); with the distribution of severity of FEV_1impairment into the moderate range (68±10%). Around 80% were using inhaled therapy in both groups ($p > 0.05$). The CAT results showed a moderate-to-high level of symptoms (17±9) and the ACT values were within a threshold below which symptoms are considered uncontrolled when applied to asthmatics (19±5).

Starting the comparisons between PRISM and obstruction groups regarding sociodemographic data, Table 1 showed that the age was similar (63±13 vs 61±15; $p = 0.152$). The age of reported onset of symptoms varied widely and was alike in the two groups (35±24 vs 32±26; $p = 0.229$).

PRISM had higher proportion of females (72 vs 49%; $p < 0.001$) and BMI values (33±7 vs 29±7; $p < 0.001$). The smoking status distribution was different between groups (p=0.007), owing to less current smoking in PRISm and higher rate of never smokers in this group compared to obstruction. Conversely, the pack-years were not different (38±32 vs 42±38; p = 0.349) and the reported household exposure (5 years) to biomass smoke was greater in PRISM than in obstruction (61 vs 49%; p = 0.016). Occupational exposure to fine dust was alike in both groups ($p > 0.05$).

The main pulmonary function results are also presented in Table 1. Despite matched post-BD FEV_1 (69±9 vs 67±11% of predicted; p = 0.171), FVC was lower in PRISM than in obstruction (74±10 vs 93±13% of predicted; $p < 0.001$), as expected. However, the FEV_1 was only mildly reduced in proportion to FVC in PRISM, since FEV_1/FVC ratio in this group was very close to the predicted values (94±8 vs 73±10%, $p < 0.001$). The forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}) was less impaired in PRISM compared to obstruction (59±21 vs 34±12% of predicted; $p < 0.001$). The proportion of individuals showing BD responsiveness was lower in PRISM than in obstruction, considering both FEV_1 and FVC criteria (12 vs 24% and 11 vs 27%, respectively; all $p < 0.005$). Also, BMI correlated positively to FEV_1 decline in the PRISM group (r = -0.182; p = 0.010) but not in obstruction (r = 0.095; p = 0.179). Of note, these correlation coefficients were different (p = 0.006).

Regarding clinical data (Table 1), the combination of corticosteroids with bronchodilators was the predominant modality of therapy in both groups and the distribution of pharmacological classes prescribed was not different between groups ($p > 0.05$). The CAT and ACT total scores showed no differences in the burden of symptoms between groups ($p >0.05$). Figure 2A shows that the individual components of the CAT were rated similar or slightly higher in PRISM compared to obstruction (*Activities at home* reached higher statistical significance). As expected by its inverse scale, this pattern was the opposite in ACT (Figure 2B), except for the use of rescue medication (significantly lower in PRISM). Figure 3 illustrates the inverse and moderate-to-strong correlations between CAT and ACT that were found both in PRISM and obstruction (r= -0.727 and -0,698, respectively; $p <0.001$ for all). The correlation coefficients were not different between groups (p=0,559).

The analysis of comorbidities showed that hypertension, diabetes, and dyslipidemia had higher prevalences in PRISM than obstruction (all $p<0.005$). However, considering those with a major putative influence on respiratory symptoms, only depression/anxiety occurred more frequently in PRISM compared to obstruction (21 vs 10%; p = 0.001).

Therefore, the final multivariate linear regression model proposed to assess whether FEV_1 independently predicts symptoms (CAT and ACT scores, tested alternately as dependent variables) was adjusted for age, gender, current smoking status, BMI, and depression/anxiety.

Table 2 shows that the model had statistical significance when run separately in obstruction and PRISM for both CAT and ACT scores ($p < 0.05$ in all 4 scenarios). The main finding was that the FEV_1 decline independently predicted worse symptoms in obstruction only (CAT and ACT scores), not in PRISm.

In relation to the results of the other candidate variables tested in the model, higher BMI had distinct effects in each group: in PRISM it was a consistent predictor of worse symptoms (CAT and ACT scores); but in obstruction its influence varied from neutral (CAT) to beneficial (ACT). Current smoking negatively impacted symptoms in PRISM only, when assessed by CAT. Female sex worsened symptoms in practically all four scenarios ($p = 0.056$ for ACT in PRISM; others < 0.05). In obstruction only, depression/anxiety led to worse ACT values and higher age was associated with better ACT scores.

Discussion

In a public healthcare service structured only with spirometry as a physiological lung function test designed to evaluate respiratory symptoms in the population, we observed that about fifth of the referred individuals had PRISm. Compared to a FEV_1-matched group with obstruction, PRISm showed less remarkable signs of OAD in the spirometry and the burden of respiratory symptoms in this group was unrelated to the degree of FEV_1 impairment. Despite these findings, we noted that the rate of prescription of inhaled therapy was similarly high in PRISm as in the group with obstruction (~80%).

The prevalence of PRISm in our study seems high (22%) but falls relatively well into the upper range of that reported in the cohort of smokers and the general population (7-20%) [7-14]. On the other hand, the prevalence of OAD in PRISm reported by those studies was as low as 1,3% and reached a maximum of 28% [7,8,14], whereas this equivalent proportion in our study was much higher (80%). A more informative comparison is with cohorts restricted to symptomatic individuals. In this sense, there is a scarcity of data, and we are aware of a single study analogous to ours, which showed that 24% of a clinical cohort of spirometry had PRISm (quite similar to our study), but only 16% with a referral diagnosis of OAD [19]. Beyond differences in local epidemiology and the criteria used to define OAD, participants in that study were followed in a tertiary level of care and all of them had plethysmography data, which supports the contention that advanced testing is advisable to properly identify patients with OAD among those with PRISm.

In this context of a high rate of perceived diagnosis of OAD in PRISm in our setting, we could not demonstrate that symptoms in this group were related to the degree of lung function impairment. A possible negative effect in this investigation of considering groups composed of mixed etiologies (mainly COPD and asthma) as a single population (i.e., OAD) is minimized

by the accepted view in the literature of the CAT as a valid instrument to capture the burden of respiratory symptoms in non-COPD population [20]. Furthermore, ACT was simultaneously employed, and the demonstration of a strong correlation between the results of these questionnaires in both groups strengthens their use in our study to collect symptoms.

Obesity is a striking feature of PRISm, and it is interesting to note that higher BMI affected both symptoms and FEV_1 only in this group. This finding may be attributed to a complex interplay between many factors: greater severity of obesity in PRISm compared to obstruction; the intrinsic consequence of obesity on pulmonary function and respiratory well-being [9]; a paradoxical effect of obesity on mitigation of dyspnea in individuals with (true) obstruction, explained by a deflator effect [20]; greater prevalence of cardiometabolic diseases related to obesity in PRISm (hypertension, diabetes, and dyslipidemia), which have been associated with lower lung function in the population [21,22], besides being risk factors for cardiovascular diseases that mimic OAD or worsen its symptoms [23].

Current smoking also had a distinct effect on symptoms in PRISM. Current smoking causes non-obstructive chronic bronchitis, the symptoms of which are easier to prevail over those related to OAD diagnosed on disputable pathophysiological grounds. Smoking cessation [24], but not inhaled medication is routinely recommended to improve symptoms [20]. Finally, the effect of sex on symptoms, regardless of their mechanisms (biological, physiological, or psychological), was apparent in both groups. Of note, this is in line with the literature showing adult women have increased susceptibility for asthma; COPD development following smoking exposure; and respiratory symptoms for a given level of lung function impairment [25].

Study limitations

Our study has several limitations. First, we performed a cross-sectional study, and longitudinal cohorts have documented that individuals who initially present with PRISM often change to normal or obstructive patterns. Also, we have made assumptions concerning diagnosis based on the pharmacological management, which were ultimately typical of OAD. And, among the various etiologies witin this group, we only considered those whose prevalence is notably superior (asthma and COPD). Finally, in face of the limited collected data relative to the task of distinguishing between COPD, asthma or their overlap in a mostly elderly population, we decided to simultaneously address these entities by applying the CAT and ACT in concert.

Conclusions

We conclude that PRISm is a frequent finding in adults with respiratory symptoms in the community. Notwithstanding the evidence gap in the management of this group, we observed that 4 in every 5 patients with this type of ventilatory impairment are receiving inhaled therapy

in a non-tertiary public healthcare. In this context, symptoms were less supported by abnormalities on spirometry in this group compared to a FEV_1-matched group with airway obstruction. These data, coupled to a much lower rate of diagnosis of OAD in PRISm reported by a corresponding study performed at the tertiary level, raise concern of overtreatment of individuals presenting with PRISm in healthcare facilities with limited diagnostic resources.

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Table 1. Epidemiological, clinical and spirometry tests data.

Variables	All N = 400	PRISM N = 200	Obstruction N = 200	*P* Value
Age, years	62±13	63±13	61±15	0.152
Gender, % female	61%	72%	49%	**<0.001**
BMI, kg/m^2	31±7	33±7	29±7	**<0.001**
Formal education, years	6.8±5.0	6.8±4.9	6.8±5.1	0.966
Age of onset of symptoms, years	33±25	35±24	32±26	0.229
Smoking status, %				
Never	30%	35%*	24%	
Former	45%	45%	45%	**0.007**
Current	25%	20%*	31%	
Smoking, pack-years	40±35	38±32	42±38	0.349
Smoke from biomass fuels exposure,%	55%	61%	49%	**0.016**
Occupational exposure to fine dust, %	18%	16%	20%	0.276
Treatment modality, %				
No medication	19%	20%	19%	
Rescue only	15%	15%	14%	0.085
IC or Long acting BD in isolation	13%	17%	9%	
Long-acting BD + IC	53%	48%	58%	
CAT score (0-40)	17±9	17±10	16±9	0.213
ACT score (5-25)	19±5	19±5	19±5	0.724
Comorbidities, %				
Hypertension	68%	75%	61%	**0.003**
Diabetes	27%	37%	17%	**<0.001**
Dyslipidemia	31%	38%	24%	**0.004**
Depression/Anxiety	15%	21%	10%	**0.001**
Heart Failure	7%	8%	5%	0.224
Coronary artery disease	7%	8%	5%	0.224
Post-BD Pulmonary Function				
FEV1/FVC ratio, absolute values	0.67±0.11	0.75±0.06	0.58±0.08	**<0.001**
FEV1/FVC ratio, % of predicted	84±13	94±8	73±10	**<0.001**
FEV_1, % of predicted	68±10	69±9	67±11	0.171
FVC, % of predicted	83±15	74±10	93±13	**<0.001**
FEF_{25-75}, % of predicted	47±21	59±21	34±12	**<0.001**
BD responsiveness	18%	12%	24%	**0.002**
FEV_1, criteria, % yes	19%	11%	27%	**<0.001**
FVC criterion, % yes				

BMI, body mass index; IC, inhaled corticosteroids; BD, bronchodilators; CAT, COPD Assessment Test; ACT, Asthma Control Test.

Table 2. Multiple linear regression model alternately applied for CAT and ACT as the dependent variables, separately in the groups with PRISM and obstruction.

	PRISM		Obstruction	
Dependent: CAT	$p < 0.001$; $R^2 = 0.147$		$p = 0.001$; $R^2 = 0.082$	
Predictors:	β standardized	p value	β standardized	p value
FEV_1	0.021	0.768	-0.147	**0.043**
BMI	0.315	**<0.001**	-0.013	0.858
Female	0.181	**0.010**	0.268	**<0.001**
Depression/Anxiety	0.106	0.132	0.073	0.309
Age	0.011	0.160	-0.087	0.241
Current smoking	0.147	**0.035**	0.075	0.298
Dependent: ACT	$p = 0.020$; $R^2 = 0.048$		$p < 0.001$; $R^2 = 0.139$	
Predictors:	β standardized	p value	β standardized	p value
FEV_1	0.091	0.223	0.239	**0.001**
BMI	-0.174	**0.023**	0.144	**0.049**
Female	-0.141	0.056	-0.178	**0.012**
Depression/Anxiety	-0.034	0.644	-0.200	**0.004**
Age	0.066	0.372	0.253	**0.001**
Current smoking	0.002	0.976	0.074	0.292

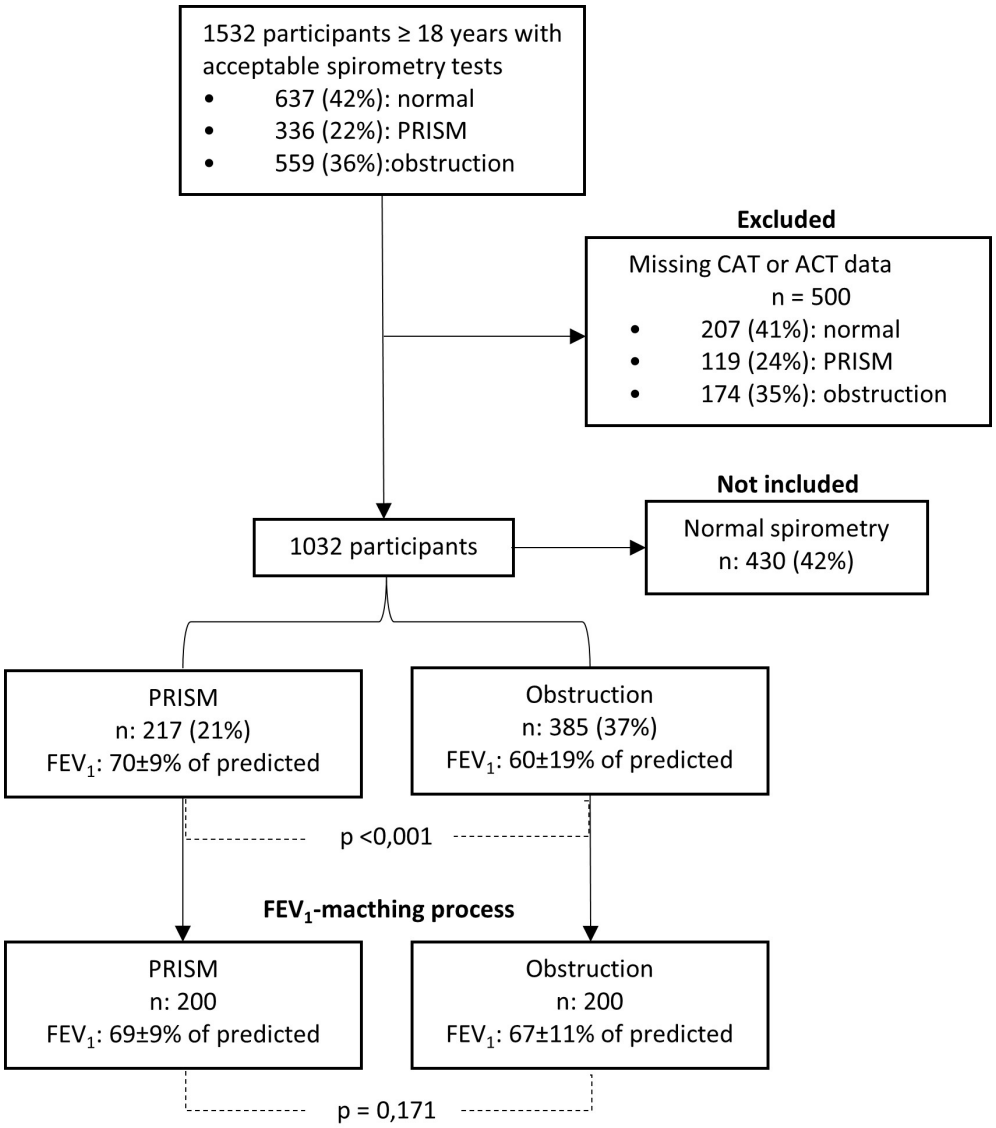

Figure1. Flowchart of the study population.

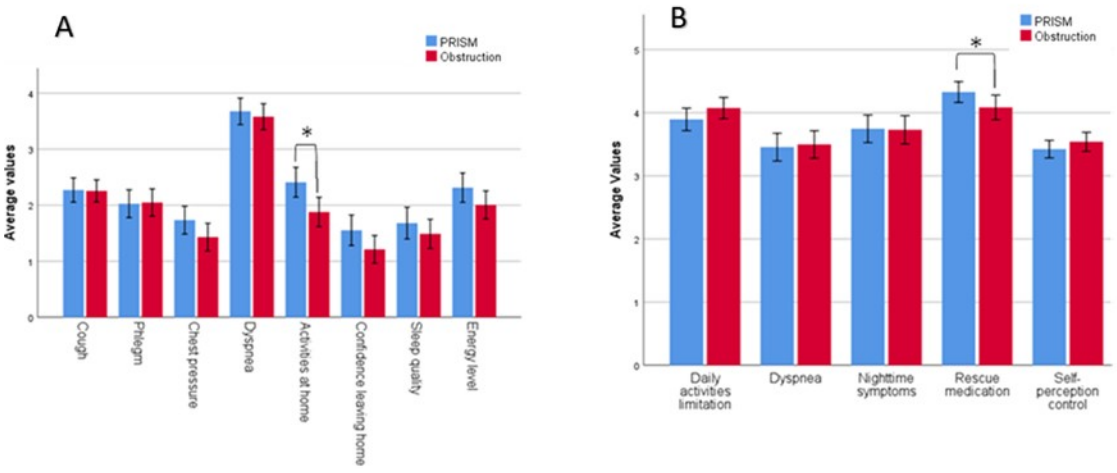

Figure 2. Scores of the individual domains of the CAT (A) and ACT (B) questionnaires.

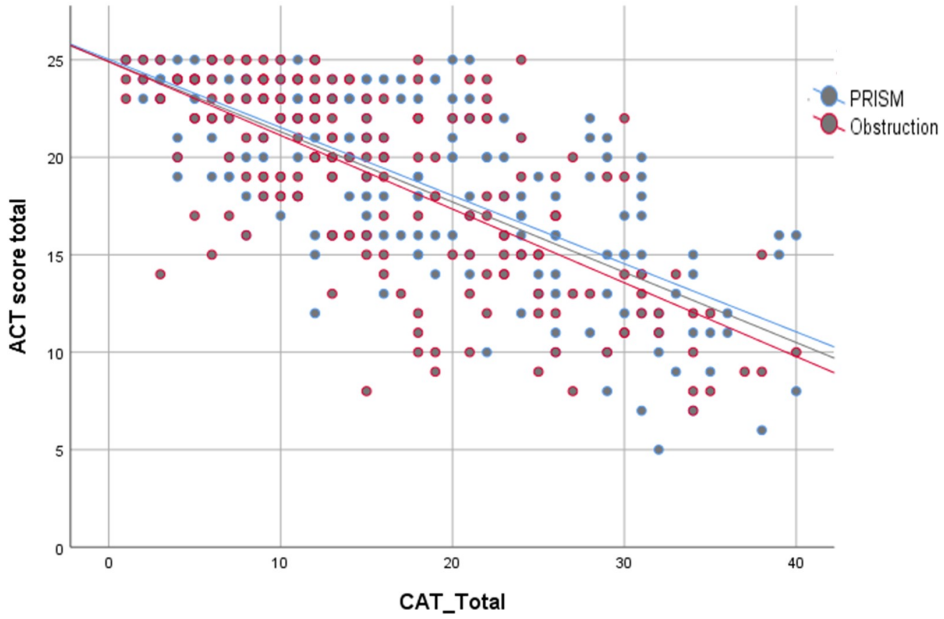

Figure 3. Correlation between ACT and CAT values in PRISM and obstruction groups.