



## Restrictive pattern on spirometry: association with cardiovascular risk and level of physical activity in asymptomatic adults

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### ABSTRACT

**Objective:** To determine whether a restrictive pattern on spirometry is associated with the level of physical activity in daily life (PADL), as well as with cardiovascular disease (CVD) risk factors, in asymptomatic adults. **Methods:** A total of 374 participants (mean age, 41 ± 14 years) underwent spirometry, which included the determination of FVC and FEV<sub>1</sub>. A restrictive pattern on spirometry was defined as an FEV<sub>1</sub>/FVC ratio > 0.7 and an FVC < 80% of the predicted value. After conducting demographic, anthropometric, and CVD risk assessments, we evaluated body composition, muscle function, and postural balance, as well as performing cardiopulmonary exercise testing and administering the six-minute walk test. The PADL was quantified with a triaxial accelerometer. **Results:** A restrictive pattern on spirometry was found in 10% of the subjects. After multivariate logistic regression, adjusted for confounders (PADL and cardiorespiratory fitness), the following variables retained significance (OR; 95% CI) as predictors of a restrictive pattern: systemic arterial hypertension (17.5; 1.65-184.8), smoking (11.6; 1.56-87.5), physical inactivity (8.1; 1.43-46.4), larger center-of-pressure area while standing on a force platform (1.34; 1.05-1.71); and dyslipidemia (1.89; 1.12-1.98). **Conclusions:** A restrictive pattern on spirometry appears to be common in asymptomatic adults. We found that CVD risk factors, especially systemic arterial hypertension, smoking, and physical inactivity, were directly associated with a restrictive pattern, even when the analysis was adjusted for PADL and cardiorespiratory fitness. Longitudinal studies are needed in order to improve understanding of the etiology of a restrictive pattern as well as to aid in the design of preventive strategies.

**Keywords:** Spirometry; Hypertension; Motor activity; Sedentary lifestyle; Smoking.

### INTRODUCTION

Lung restriction is a multifactorial clinical condition, characterized by a reduction in lung volumes, and worsens with age. A restrictive pattern on spirometry is seen in approximately 12% of the general population.<sup>(1)</sup> The diagnosis of lung restriction requires the measurement of static lung volumes. However, a reduction in FVC, without bronchial obstruction, is commonly used as a proxy for lung restriction. Although it remains unclear whether a restrictive pattern has clinical relevance in the absence of respiratory symptoms, signs of pulmonary fibrosis, or other clinical changes, a different ventilatory strategy might be employed during exercise.<sup>(2)</sup> In addition, a restrictive pattern has been associated with various cardiovascular disease (CVD) risk factors, including obesity,<sup>(3)</sup> diabetes mellitus,<sup>(4)</sup> dyslipidemia,<sup>(5)</sup> and systemic arterial hypertension (SAH),<sup>(6)</sup> as well as with high mortality.<sup>(7)</sup>

Studies have shown that physical inactivity is associated with worse cardiorespiratory fitness and respiratory function.<sup>(8)</sup> Although previous studies have shown

that a restrictive pattern on spirometry is associated with cardiovascular risk and disease,<sup>(9)</sup> there is little information about the possible confounding effect of the level of accelerometer-measured physical activity and of cardiorespiratory fitness, despite the fact that physical inactivity is associated with all of the aforementioned comorbidities.<sup>(9)</sup> A better understanding of the factors related to restrictive lung disease could enable primary care providers to intervene early and prevent problems associated with the abnormality. We hypothesized that a restrictive pattern is also associated with the level of physical activity in daily life (PADL), and that the associations between a restrictive pattern and CVD risk factors could be confounded by the levels of PADL and cardiorespiratory fitness. Therefore, we aimed to determine whether a restrictive pattern is associated with PADL and CVD risk factors in asymptomatic adults, even when the analysis of the latter is adjusted for PADL and cardiorespiratory fitness. A secondary objective was to assess the prevalence of this spirometric abnormality in a sample of the Brazilian population.

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## METHODS

### *Participants and study design*

This was a cross-sectional study involving 374 participants, with a mean age of  $41 \pm 14$  years (91 males and 283 females), selected from among those enrolled in an ongoing study—the Epidemiological Study of Human Movement and Hypokinetic Diseases. All participants underwent spirometry. The classic definition of a restrictive pattern on spirometry is low FVC in the presence of a normal  $FEV_1/FVC$  ratio. However, restrictive lung disease is characterized by a decrease in total lung capacity (TLC).<sup>(10)</sup> There are two gold standard methods for the determination of TLC: helium dilution; and plethysmography. Both methods are costly and time consuming in comparison with simple spirometry. Various epidemiological studies have used the Global Initiative for Chronic Obstructive Lung Disease spirometry criteria for identifying a restrictive pattern, including an  $FVC < 80\%$  of the predicted value and a fixed ratio of  $FEV_1$  to FVC (in absolute values)  $\geq 70\%$ .<sup>(7,11-13)</sup> To make our results comparable to those available in the literature, we decided to employ the latter definition. To calculate the predicted spirometric variables, we used reference values for the Brazilian population.<sup>(14)</sup> We collected demographic and anthropometric data, as well as data related to CVD risk factors. We also assessed PADL (with accelerometry), body composition, muscle function, and postural balance, as well as performing cardiopulmonary exercise testing (CPET) and administering the six-minute walk test. The inclusion criteria were being between 18 and 90 years of age and having no cardiac or pulmonary diseases. The exclusion criteria were having orthopedic problems, having a recent history of respiratory infections, having had angina (unstable or stable) in the last four weeks, having a recent history of myocardial infarction, and having undergone angioplasty or cardiac surgery in the last three months. The participants were informed of the potential risks and discomforts of the procedures proposed in the present study, and all gave written consent. The study was approved by the Human Research Ethics Committee of the Federal University of São Paulo (Protocol no. 186.796).

In the present study, we evaluated a convenience sample of volunteers who were recruited through postings disseminated via social networks and brochures distributed at universities in the region, as well as through announcements in local magazines and newspapers. During the initial clinical evaluation, we asked all participants to complete the Physical Activity Readiness Questionnaire,<sup>(15)</sup> in order to identify any contraindications to undergoing CPET. To investigate the history of asthma and exposure to pollutants, as well as to determine smoking status, we used a respiratory questionnaire based on that developed for the American Thoracic Society Epidemiology Standardization Project.<sup>(16)</sup> The risk of CVD was stratified according to the American College of Sports Medicine guidelines.<sup>(17)</sup> On the basis of the verifiable and self-report data

collected, we investigated the major risk factors for CVD, including age (male  $\geq 45$  years; female  $\geq 55$  years); family history of premature coronary heart disease (confirmed myocardial infarction before 55 years of age in the father or before 65 years of age in the mother or in another first-degree relative); SAH; diabetes; dyslipidemia; and current smoking.

### *Procedures*

Spirometry was performed with a hand-held spirometer (Quark PFT; Cosmed, Pavona di Albano, Italy), in accordance with the criteria established by the American Thoracic Society.<sup>(18)</sup> We determined  $FEV_1$ , FVC, and the  $FEV_1/FVC$  ratio. After determining body weight and height, we calculated the BMI. Body composition was determined with a tetrapolar bioimpedance analyzer (310e; Biodynamics, Seattle, WA, USA), following the procedure described by Kyle et al.<sup>(19)</sup> Lean body mass and fat body mass were calculated using the regression equations developed for healthy individuals.<sup>(20)</sup>

The maximal symptom-limited exercise capacity was assessed during CPET with a ramp protocol on a treadmill (ATL; Inbrasport, Porto Alegre, Brazil). After 3 min at rest, the speed and inclination were automatically increased according to the estimated maximal oxygen consumption, the aim being to complete the test in approximately 10 min. Cardiovascular, respiratory, and metabolic variables were analyzed breath by breath with a gas analyzer (Quark PFT; Cosmed). Oxygen uptake ( $VO_2$ ), carbon dioxide production ( $VCO_2$ ), the rate of gas exchange ( $VCO_2/VO_2$ ), minute ventilation, and heart rate were monitored throughout the test. The data were filtered every 15 s for further analysis. The peak  $VO_2$  (in mL/min, mL/min/kg, and % of predicted) was defined as the average values in the last 15 s of the incremental exercise.

Functional exercise capacity was assessed by means of a six-minute walk test performed rigorously in accordance with the American Thoracic Society guidelines.<sup>(21)</sup> The six-minute walk distance was recorded in meters and in percentage of the predicted value.<sup>(22)</sup>

Postural balance was evaluated by collecting kinetic data on center-of-pressure (COP) dynamics during postural balance assessment on a force platform (400 BIOMECH; EMG System do Brasil, São José dos Campos, Brazil). The frequency of platform data acquisition was 100 Hz. Participants were instructed to remain as immobile as possible, and the COP area (in  $cm^2$ ) was registered while each participant was standing with eyes open or eyes closed. Each condition was maintained for 30 s.

Muscle function was assessed by determining the peak torque (PT) of the quadriceps and biceps on an isokinetic dynamometer (Biodex; Lumex Inc., Ronkonkoma, NY, USA). The PT (in N m) was evaluated in two trials of 5 movements each at  $60^\circ/s$ . After a rest period of at least 3 min, participants performed two tests of isometric force (also in N m) against fixed resistance

in a 60° range of knee flexion. After another similar rest period, participants performed 30 movements at 300°/s to record the total work (in kJ). In all tests, the highest value was selected for analysis.

The level of PADL was assessed with an ActiGraph triaxial accelerometer (MTI, Pensacola, FL, USA), the use of which has previously been validated.<sup>(23)</sup> Participants were asked to wear the device on an elasticized belt over their dominant hip for 7 days. A valid day was defined as one on which a participant wore the device for at least 12 h. Participants were instructed to remove it for water-related activities, such as bathing and swimming, and at bedtime. The triaxial accelerometer measures the duration and intensity of physical activity. The device incorporates an inclinometer, which records the time spent lying, sitting, and standing. We analyzed the accelerometry data only for the participants who had used the device for at least 4 (valid) days. Physical activity in the sedentary, low intensity, moderate intensity, vigorous, and very vigorous strata were defined as described by Freedson et al.<sup>(24)</sup> The minimum PADL, in terms of quantity and intensity, was defined as 150 min/week of moderate to vigorous intensity.<sup>(25)</sup> Individuals who did not reach this level of PADL were considered physically inactive.

### Statistical analysis

We first conducted descriptive analysis of the data, including frequencies, histograms, measures of central tendency, and variability. To assess the association between a restrictive pattern on spirometry and the studied variables, we calculated unadjusted and adjusted odds ratios, together with the respective 95% confidence intervals. We then selected the most significant variables and performed a multivariate logistic regression analysis using a restrictive pattern as the outcome variable. The model was adjusted for age, gender, race, level of education (higher education or not), self-reported CVD risk factors (SAH, diabetes, dyslipidemia, smoking, obesity, and physical inactivity), body composition (fat body mass), peripheral muscle function (PT of the quadriceps and biceps), postural balance (COP area while standing with eyes open), and cardiorespiratory fitness (peak  $\text{VO}_2$ ). Obesity was defined as a BMI > 29.9 kg/m<sup>2</sup>. The probability of a type I error was set at 5%. Statistical analysis was performed with the Statistical Package for the Social Sciences, version 15.0 (SPSS Inc., Chicago, IL, USA).

## RESULTS

Of the 374 subjects evaluated, 37 (9.9%) presented a restrictive pattern on spirometry and 6 presented an obstructive pattern ( $\text{FEV}_1/\text{FVC}$  ratio < 0.7). In comparison with rest of the sample, the 37 participants with a restrictive pattern were older. In addition, the proportions of females and obese individuals were greater among the participants with a restrictive pattern, who also had more CVD risk factors and used

a higher number of medications. In the sample as a whole, the prevalence of SAH was 11%, the prevalence of self-reported dyslipidemia was 21%, the prevalence of self-reported diabetes was 0.07%, the prevalence of current smoking was 11%, and the prevalence of accelerometer-measured physical inactivity was 19%. The characteristics of the sample are described in Table 1. After being adjusted for confounders, the multivariate logistic regression indicated that the variables SAH, smoking, physical inactivity, dyslipidemia, and COP retained their significance as predictors of a restrictive pattern (Table 2).

## DISCUSSION

We found an overall prevalence of a restrictive pattern on spirometry of 10%. To our knowledge, this is first study to show an association between a restrictive pattern and PADL through accelerometry. A restrictive pattern was also associated with SAH, smoking, and dyslipidemia, even after the analysis was adjusted for PADL and cardiorespiratory fitness. In a multicenter, population-based study carried out in Spain,<sup>(26)</sup> the reported prevalence of a restrictive pattern was 12.7%, similar to that found in the present study. In another population-based study, conducted in the greater metropolitan area of São Paulo, Brazil, the prevalence of COPD was found to be 15.8%.<sup>(27)</sup> It can be hypothesized that the major initiatives that have targeted an obstructive pattern on spirometry, regardless of the definition of COPD employed, have missed an important public health target by not exploring the frequency of a restrictive pattern.

Previous studies have reported that individuals with a restrictive pattern on spirometry are at increased risk for all-cause and cardiovascular mortality.<sup>(28)</sup> In the present study, the strongest predictor of a restrictive pattern was SAH. In fact, the association between SAH and pulmonary function abnormalities has been previously described.<sup>(6)</sup> However, the mechanism of that association remains unknown.

It is known that SAH is associated with increased systemic and pulmonary vascular resistance, as well as with increased vessel stiffness. Given the highly vascular nature of the lung and the intimate anatomic coupling of vascular parenchymal elements, it is quite possible that a loss of elasticity of the pulmonary vascular tree would, independently of any pulmonary parenchymal change, adversely affect vital capacity and  $\text{FEV}_1$ . In the Normative Aging Study, Sparrow et al.<sup>(29)</sup> concluded that a reduction in FVC precedes the onset of SAH. Inflammation, on the other hand, seems to play a critical role in the development of SAH, because individuals with elevated levels of high-sensitivity C-reactive protein seem to be more likely to develop SAH during the first 5 years of follow-up.<sup>(30)</sup>

Another CVD risk factor directly associated with a restrictive pattern on spirometry was, as expected, current smoking. Classically, smoking history and the heaviness of smoking are associated with obstructive

**Table 1.** Characteristics of the 374 participants.<sup>a</sup>

Characteristic	Pattern on spirometry	
	Normal (n = 337)	Restrictive (n = 37)
Age, years	42 ± 15	47 ± 16*
Gender (%)		
Female	53.3	73.0**
Male	43.8	27.0
FVC, L	3.92 ± 1.00	2.75 ± 0.85**
FVC, % of predicted	98 ± 12	74 ± 9**
FEV <sub>1</sub> , L	3.21 ± 0.80	2.13 ± 0.64**
FEV <sub>1</sub> , % of predicted	98 ± 11	71 ± 6**
FEV <sub>1</sub> /FVC, %	82 ± 5	80 ± 5*
Race (%)		
White	59.7	57.1
Black	7.6	5.7
Mulatto	30.0	31.4
Asian	2.1	0.0
Indigenous	0.6	5.7*
Weight, kg	75 ± 18	77 ± 20
Height, cm	165 ± 97	161 ± 98
BMI, kg/m <sup>2</sup>	27 ± 6	29 ± 7**
Fat body mass, %	28 ± 8	33 ± 10*
Lean body mass, kg	53 ± 12	50 ± 11
Peak VO <sub>2</sub> , mL/min	2,383 ± 863	1,928 ± 814**
Peak VO <sub>2</sub> , mL/min/kg	32 ± 10	25 ± 10**
Peak VO <sub>2</sub> , % of predicted	100 ± 20	91 ± 19**
6MWD, m	605 ± 90	519 ± 118**
6MWD, % of predicted	105 ± 13	93 ± 17**
CVD risk factors (%)		
Family history	24.6	16.2
Obesity	26.1	40.5**
Hypertension	9.5	21.6*
Dyslipidemia	21.1	27.0
Diabetes	5.9	16.2*
Current smoking	10.4	21.6*
Physical inactivity	16.8	36.4*
Use of medications (%)	26.7	43.2*
Occurrence of falls (%)	5.3	18.9*
Higher education complete (%)		
Yes	40.2	27.0
No	59.7	72.9**

VO<sub>2</sub>: oxygen uptake; 6MWD: six-minute walk distance; and CVD: cardiovascular disease.<sup>a</sup>Values expressed as mean ± SD, except where otherwise indicated.

breathing patterns and with COPD. Smoking is also able to trigger the inflammatory pathway and cause profound histological changes. There is loss of elastic tissue and resistive material because the inflammatory process involves a tissue repair phase, in which the lung parenchyma is replaced by fibrotic tissue. Similar results were found by Twisk et al.,<sup>(31)</sup> who also reported that smoking was related to decreases in FVC and FEV<sub>1</sub>.

Previous studies have reported that subjects with higher levels of PADL also have higher levels of FEV<sub>1</sub> and FVC.<sup>(8)</sup> However, that association has been poorly investigated in the general population. In the present

study, accelerometer-measured physical inactivity was selected as an independent predictor of a restrictive pattern on spirometry. The biological plausibility of the influence of physical inactivity on the decline of lung function relies on the elevated levels of inflammatory mediators seen in physically inactive subjects. A low level of PADL has been associated with elevated plasma levels of interleukin-6 and C-reactive protein, independently of obesity.<sup>(32)</sup> In a review of 40 observational studies, Hamer<sup>(33)</sup> found that 27 of those studies reported that PADL was inversely associated with one or more inflammatory markers, and that those associations

**Table 2.** Multiple logistic regression analysis of risk factors for a restrictive pattern on spirometry.

Factor	OR	Adjusted model	
		Lower limit	95% CI Upper limit
Age	1.016	0.917	1.126
Gender	0.115	0.006	2.093
CVD-related			
Obesity	1.756	0.194	15.930
SAH	17.513*	1.659	184.819
Dyslipidemia	1.896*	1.127	1.988
Diabetes	3.549	0.382	33.011
Current smoking	11.699*	1.564	87.504
Physical inactivity	8.176*	1.439	46.461
Fat body mass	1.012	0.913	1.121
PTQ	1.015	0.991	1.039
PTB	1.012	0.929	1.101
COP-EO	1.347*	1.056	1.718
Peak VO <sub>2</sub>	0.982	0.838	1.150
6MWD	0.997	0.985	1.009
Use of medications	0.242	0.039	1.495

CVD: cardiovascular disease; SAH: systemic arterial hypertension; PTQ: peak torque of quadriceps; PTB: peak torque of biceps; COP-EO: center of pressure-eyes open; VO<sub>2</sub>: oxygen uptake; and 6MWD: six-minute walk distance. \*Significant, after adjustment for confounders, as a predictor of a restrictive pattern on spirometry.

remained significant even after being adjusted for measures of obesity.

In our multiple regression model, adjusted for confounders, dyslipidemia was also selected as an independent predictor of a restrictive pattern on spirometry, an association that has not been extensively investigated. Yeh et al.<sup>(3)</sup> reported that individuals with metabolic syndrome have high serum levels of inflammatory markers, and that those increases seem to be related to the reduction in FVC. Accordingly, the authors found that reduced lung function presents before the development of metabolic syndrome. Restrictive lung disease has been associated with high levels of inflammatory mediators, such as C-reactive protein and fibrinogen.<sup>(12)</sup> Many pathological mechanisms (ranging from obesity to interstitial lung disease) can cause restrictive lung disease. The underlying mechanisms of the association between this type of metabolic disorder and impaired lung function remain unclear.

One interesting finding of the present study is that poor static postural balance was associated with a restrictive pattern on spirometry, regardless of age, gender, or comorbidities. Similar results have been obtained in patients with asthma or COPD.<sup>(34)</sup> Kayacan et al.<sup>(35)</sup> concluded that, in individuals with COPD, airflow obstruction and disease duration can reduce the conduction velocity of peripheral nerves and cause neurophysiological changes, such as balance deficits. That mechanism might be related to the systemic inflammation present in such individuals, as well as in those with a restrictive pattern. To our knowledge, ours is the first study to assess the correlations between measurements obtained on a force platform and spirometric indices in asymptomatic individuals. Clinically, it might be important to know that individuals

with a restrictive pattern could be at increased risk of falls, which should be taken into consideration during the management of this condition. We believe that the inflammatory cascade can also affect postural balance, as can being physically inactive, being a smoker and having hypertension. However, because we did not assess inflammation, that falls into the realm of supposition. Therefore, such interactions should be investigated further.

Although diabetes has been shown to be associated with lower FVC<sup>(4)</sup> and vice versa,<sup>(36)</sup> that was not found to be the case in the present study. The self-report nature of the data regarding diabetes might have influenced our results, given that the prevalence of the self-reported diagnosis was below that previously reported for the region.<sup>(37)</sup> Nevertheless, those reports either did not consider the confounding effects of PADL and cardiorespiratory fitness or assessed PADL only by questionnaire.

In the present study, obesity was more prevalent among subjects with a restrictive pattern on spirometry than among the remaining participants. However, in the adjusted model, obesity was not selected as a significant predictor of a restrictive pattern. Although several studies have reported an association between obesity and poor lung function, they have not taken comorbidities or a low level of PADL into consideration as possible confounders. In addition, BMI is not the best variable to evaluate in investigating this association. We know that excess adipose tissue exerts a mechanical effect on the lungs, whereby fat tissue within the abdominal region reduces the capacity of the diaphragm to shift downward, thereby limiting lung inflation. We found it surprising that Scott et al.<sup>(38)</sup> observed no significant associations between

fat mass and lung function in males, nor was fat mass a significant predictor of lung function in either of the regression models employed in their study. Furthermore, systemic inflammation seems to have a greater impact on dynamic lung function than do the mechanical effects of obesity.<sup>(38)</sup>

Our study has certain limitations, one of which is related to the selection of subjects. Because we evaluated a convenience sample, our obese subjects might have shown above-normal cardiorespiratory fitness, which could have influenced the results, given that fitness is positively associated with lung function. In addition, this was a cross-sectional study, and we were therefore unable to determine the causes of a restrictive pattern on spirometry. Furthermore, the fact that the diagnoses of SAH, diabetes, and dyslipidemia were based on self-reported data might have resulted in those conditions being underdiagnosed in our sample. Moreover, we did not measure TLC, take chest X-rays, or obtain chest CT scans in order to diagnose true pulmonary restriction. Nevertheless, the participants were asymptomatic and had no history of exposure to known predisposing factors for restrictive lung disease. We believe that a restrictive pattern can be related to nonpulmonary diseases, given the association found with other factors, including systemic inflammatory mechanisms (such as SAH), physical inactivity, and dyslipidemia. Neither abnormal chest X-rays nor a history of pleural disease have been shown to be predictors of

a restrictive pattern on spirometry. Although interstitial lung diseases clearly result in pulmonary restriction, they do not appear to be the main factor associated with a restrictive pattern on spirometry in a population.<sup>(7)</sup> Most other large epidemiological cohort studies have identified a restrictive pattern on the basis of the pre-bronchodilator values; we did not employ that methodology, which is another limitation of our study. However, our participants with a restrictive pattern did not show any sign or symptom of airflow obstruction or airway hyperresponsiveness. Another study, using pre-bronchodilator spirometry, reported that subjects with a restrictive pattern are at increased mortality risk.<sup>(4)</sup> Because we did not quantify the TLC, we can not affirm that participants with a reduction in FVC also had a lower TLC. Therefore, the reduction in FVC could be a nonspecific respiratory disorder.

We can conclude that a restrictive pattern on spirometry is common among asymptomatic adults. To our knowledge, this is the first study reporting an association between a restrictive pattern and PADL objectively measured. We also found that a restrictive pattern was associated with CVD risk factors, even after adjusting for PADL and cardiorespiratory fitness. There is a need for additional, longitudinal, studies in order to gain a better understanding of the etiology of a restrictive pattern on spirometry as well as to inform decisions regarding the design of preventive strategies.

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