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TESI DOCTORAL

DETERMINANTS AND EFFECTS OF EXERCISE CAPACITY DECLINE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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A sa meva família més propera,

per donar-me suport durant aquests anys.

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LIST OF ABBREVIATIONS

6MWT	6-minute walk test
6MWD	6-minute walk distance
ATS	American Thoracic Society
BMI	Body mass index
CAT	COPD assessment test
CFI	Comparative fit index
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise test
DL_{CO}	Diffusing capacity for carbon monoxide
EELV	End-expiratory lung volume
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in 1 second
FFMI	Fat free mass index
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HADS	Hospital anxiety and depression scale
HRCT	High resolution computed tomography
IC	Inspiratory capacity
ICD	International classification of diseases
MCID	Minimal clinically important difference
MEP	Maximum expiratory pressures
MIP	Maximum inspiratory pressures
mMRC	Modified Medical Research Council dyspnoea scale

PaO_2	Arterial oxygen tension
RMSEA	Root mean square error of approximation
RV	Residual volume
SEM	Structural equations modelling
SGRQ	Saint George's respiratory questionnaire
TLC	Total lung capacity
VO_{2max}	Maximal oxygen consumption
Vt	Tidal volume
YPAS	Yale physical activity survey

1. INTRODUCTION

1.1. CHRONIC OBSTRUCTIVE PULMONARY DISEASE

1.1.2. Definition

Chronic obstructive pulmonary disease (COPD) is a respiratory disease characterised by airflow limitation that is progressive and not fully reversible. This airflow limitation is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking [1]. COPD also has some significant extra-pulmonary effects, such as skeletal muscle impairment and exercise intolerance, which importantly affect patient's activities of daily living and lead to a considerable loss in health-related quality of life [2].

1.1.3. Diagnosis and classification

The clinical diagnosis of COPD should be considered in any subject who is older than 40 years of age and refers dyspnoea, chronic cough or sputum, and a history of exposure to risk factors for the disease. The diagnosis should be confirmed by spirometry; a post-bronchodilator forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio <0.70 confirms the presence of airflow limitation that is not fully reversible [1].

Spirometry is commonly used to classify disease severity. According to the American Thoracic Society and the European Respiratory Society (ATS/ERS), and the Global Initiative for Chronic Obstructive Lung Disease (GOLD), patients can be classified in 4 different groups based on their post-bronchodilator FEV_1 (Table 1) [1, 3].

Table 1. Spirometric classification of chronic obstructive pulmonary disease severity based on post-bronchodilator FEV_1 [1, 3].

COPD severity	Post-bronchodilator FEV_1
Mild	$FEV_1 \geq 80\%$ predicted
Moderate	$50\% \leq FEV_1 < 80\%$ predicted
Severe	$30\% \leq FEV_1 < 50\%$ predicted
Very severe	$FEV_1 < 30\%$ predicted

Although COPD classification has been usually established according to the level of airflow limitation, at present FEV_1 is recognized to be an unreliable marker of the impact of the disease on COPD patients. For instance, it is difficult to predict the degree of dyspnoea, exercise limitation, and impaired health related quality of life, based on FEV_1 at an individual level [4]. Therefore, GOLD proposes that the classification of COPD should be based on patient's level of dyspnoea and future risk of exacerbations, in addition to airflow limitation, and propose a total of 4 groups (A to D) as illustrated in Figure 1 [1]. This approach is consistent with previous research suggesting that multidimensional grading systems, such as the body mass index, airway obstruction, dyspnoea and exercise capacity (BODE) index, or the age, dyspnoea, and airflow obstruction (ADO) index, provide a better categorisation and prediction of mortality than FEV_1 alone [5, 6]. In fact, these indexes have already been adopted for disease severity classification in the Spanish COPD Guidelines [7].

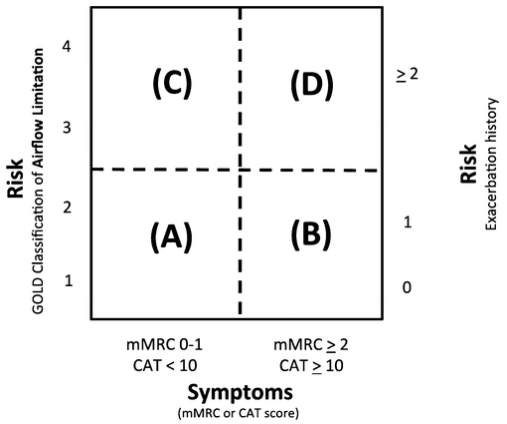


Figure 1. Combined COPD assessment proposed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Adapted from Vestbo et al. [1].

1.1.4. Prevalence, morbidity and mortality

The prevalence of COPD varies across countries and across different groups within countries, mainly due to differences in the exposure to tobacco smoking, the increased life span of the population and the method used to diagnose the disease [1].

The results of a large epidemiological study conducted in Spain demonstrated an overall prevalence of COPD in the population between 40 and 80 years of age of 10.2% using spirometric criteria [8]. This information is in accordance with a meta-analysis based on 26 spirometric estimates from different countries all over the world that reported a median prevalence of 10.1%. However, a large dispersion of data was observed, since prevalence ranged from 2.1 to 26.4% [9]. A common finding of studies from general population and primary care is that a high proportion of individuals fulfilling COPD diagnosis criteria remain undiagnosed [8, 10].

COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing, particularly in developing countries [11]. Morbidity measurements traditionally include health resources utilization, such as hospitalisations, and disability-adjusted life years (DALYs). In this sense, COPD represented

a 28.2% of hospital discharges for respiratory illnesses in patients between 45 and 85 years in 2013 in Spain [12], and was the ninth leading cause of DALYs lost in the world in 2010 [1]. With regards to mortality, COPD, which ranked fourth as a cause of death in the world in 1990, became the third one in 2010 [11]. In Spain, COPD mortality rate was 339 per 100,000 inhabitants in men and 492 per 100,000 inhabitants in women in 2008 [7]. This increasing morbidity and mortally is mainly due to the expansive epidemic of tobacco smoking.

1.1.5. Natural history of COPD

COPD is a disease that fluctuates between periods of relative stability and episodes in which the patient experiences a sustained clinical worsening, referred as exacerbations. Exacerbations are characterized by an increase in respiratory symptoms beyond normal day-to-day variations that requires a change in regular treatment [13].

The severity of exacerbations is classified as mild when the increase in respiratory symptoms require a change of inhaled treatment by the patient, moderate when they require a medical intervention including a short course of antibiotic and/or oral steroids, and severe when they require hospitalisation [1]. COPD exacerbations are an important cause of unscheduled physician's visits and hospital admissions [13]. Thus, COPD exacerbations have high socioeconomic costs. In Spain, a 44% of the total annual cost of COPD is due to hospital admissions [14].

COPD exacerbations also have a negative impact on the health status of these patients. It has been shown that COPD patients who suffer a greater number of exacerbations during the course of the disease, experience a higher decline in lung function and health related quality of life, have a higher reduction in muscle force and physical activity, and have an increased risk of mortality [15–19]. It is partly for these reasons that an appropriate treatment and monitoring of exacerbations is considered to be a very important aspect in the management of COPD [1, 13].

1.2. EXERCISE CAPACITY

1.2.1. The concept of exercise capacity

Exercise capacity refers to the maximum amount of physical exertion that an individual can sustain, operationalised as the maximum work load that can be achieved during an exercise capacity test [20].

During exercise, there is a gradual increase in ventilation, cardiac output and oxygen consumption in the skeletal muscle. These physiological changes are driven by the central nervous system, which is responding to direct cortical input and to neural and humoral feedback from exercising muscles. Therefore, exercise capacity reflects a coordinated response of respiratory, cardiovascular and neural function along with the action of exercising muscles (Figure 2), which is not adequately reflected through the measurement of individual system function [21].

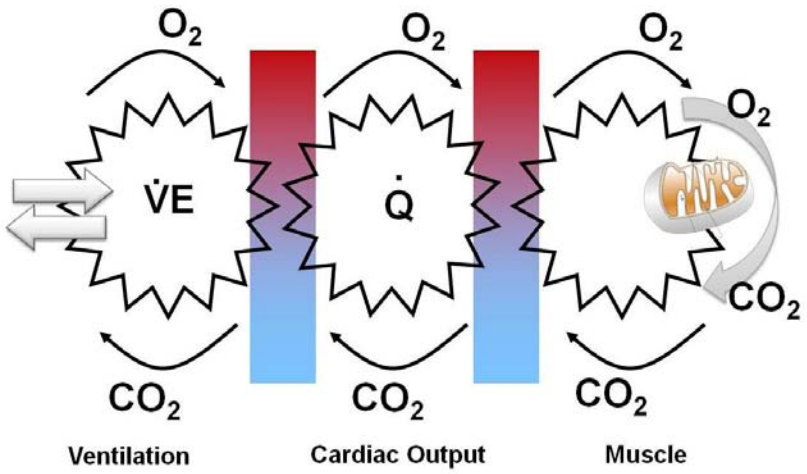


Figure 2. Diagram to illustrate the interrelationships between pulmonary, cardiovascular, and musculoskeletal function during exercise. VE: ventilation; Q: cardiac output. Adapted from *Wasserman K, et al.* [21] .

In healthy subjects, each system has reserve capacity far in excess of that needed to sustain normal, asymptomatic body functioning at rest and during modest exertion. However, many disease processes affecting the cardiovascular and/or respiratory systems reduce this reserve, thus leading to a progressive loss of function and limitation during exercise [20]. Since some diseases may produce symptoms and physiological abnormalities only with strenuous effort, exercise testing becomes relevant for the diagnosis of exercise capacity limitation and exercise related symptoms [22].

1.2.2. Assessment of exercise capacity

There are several modalities available for the objective evaluation of functional exercise capacity. Exercise performance tests might be divided into: i) laboratory treadmill or cycle ergometer tests (cardiopulmonary tests); and ii) field-based walking tests. The modality used should be chosen based on the clinical question to be addressed and availability of resources [22, 23].

The **cardiopulmonary exercise test** (CPET) is considered to be the *gold standard* for the measurement of exercise capacity in respiratory patients [24]. This relatively non-invasive test permits the evaluation of peak exercise response (maximal oxygen consumption: VO_{2max}) by progressively increasing work rate. It also allows to define the factors contributing to exercise limitation [21]. Two modes of exercise are commonly employed in cardiopulmonary exercise tests: treadmill and cycle ergometer. In most clinical circumstances, cycle ergometry is the preferable mode of exercise testing in respiratory patients. Cardiopulmonary test involves the measurement of respiratory gas exchange (oxygen consumption and carbon dioxide output), and minute ventilation, in addition to monitoring electrocardiography, blood pressure, and pulse oximetry. When appropriate, arterial sampling is also performed [22]. The conduct of the test is quite complex and should only be supervised by very qualified personnel. Moreover, very sophisticated equipment is necessary. Therefore, cost and

complexity of equipment limit its widespread use and it cannot be suggested for everyday clinical practice.

Field-based walking tests, and specially the **6-minute walk test** (6MWT), have gained popularity in the clinical evaluation of patients with chronic cardiopulmonary disorders, mainly because of their simplicity, safety, good standardization and because they give a better reflection of activities of daily living than other exercise tests do [25].

The 6MWT consists of walking as fast as possible in a long, flat, straight corridor that is seldom travelled. The walking course should be 30 meters in length. The turnaround points should be marked with traffic cones or similar marks (Figure 3) [23].

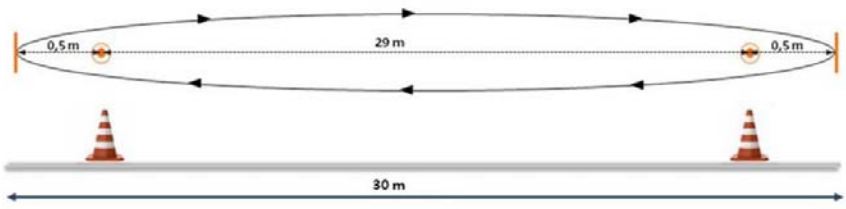


Figure 3. Course layout for the 6-minute walk test. Cones are inset 0.5 m from either end to avoid abrupt changes in direction.

During the test the patient is encouraged every minute using standard phrases and is informed of the elapsed time [26]. At the beginning and end of the test, oxygen saturation and heart rate are measured. Besides, the grade of dyspnoea and lower limb fatigue is evaluated using the modified Borg score. The total distance covered (6-minute walking distance, 6MWD) is calculated at the end of the test by counting the number of laps completed by the patient (multiplying the laps by the length of the walking course) and any additional distance covered (the number of metres in the final partial lap, if applicable) [23].

There is strong evidence of a learning effect for the 6MWD. Then, when conducted for the first time, two tests are recommended and the highest 6MWD obtained should be reported [27].

6MWD is the parameter that indicates the functional exercise capacity of the individual and it has been shown to correlate well with the VO_{2max} achieved during a CPET [28]. However, the 6MWT is a sub-maximal exercise test and since most activities of daily living are performed at sub-maximal exercise level, this test may give a better reflection of the functional exercise capacity of subjects to carry out their daily physical activities [23, 29]. Also, compared with incremental cycle testing, the 6MWT is more sensitive for detecting oxygen desaturation in patients with COPD [30]. Moreover, the 6MWD has been shown a better predictor of mortality than the CPET [31].

6MWD also appears to be a good tool to detect responses to different treatments in patients with COPD [27]. In this sense, the minimal clinically important difference (MCID), which is the smallest difference in an outcome measurement that can be detected and helps to drive clinical decisions, has been reported at 35 m in patients with mild to moderate COPD [32].

1.2.3. Exercise capacity in COPD

Limitation of exercise capacity is one of the cardinal manifestations of COPD [1, 24]. Many studies have demonstrated that patients with COPD have reduced exercise capacity levels compared to their healthy peers, irrespective of the method used for this purpose [33, 34].

Exercise intolerance in individuals with COPD is multifactorial and results from complex interactions between physical, both pulmonary and non-pulmonary, and psychological factors [35–37].

Among the pulmonary mechanisms that contribute to exercise limitation in these patients, ventilatory constraints seem to be of special relevance [38,

39]. It is known that progressive expiratory airflow limitation and the loss of lung elastic recoil lead to an increase in end-expiratory lung volume (EELV), usually known as **static lung hyperinflation** [40]. The negative consequences of hyperinflation are manifested during physical activity or other circumstances leading to increased ventilatory demand [41]. In healthy subjects, EELV and inspiratory capacity (IC) are maintained throughout exercise. Thus, tidal volume (Vt) is normally increased to accommodate the increased metabolic demand. However, in patients with COPD, the delayed lung emptying process and the increased EELV already present at rest are further aggravated during exercise, so Vt expands during exercise to quickly reach a critically low IC (Figure 4) [40, 42]. This phenomenon, termed **dynamic lung hyperinflation** [41], concomitantly increases the work of breathing and impairs inspiratory muscle function, leading to dyspnoea and early termination of exercise [43]. Accordingly, both static and dynamic pulmonary hyperinflation have been consistently identified as important correlates of exercise capacity in cross-sectional studies [44–46].

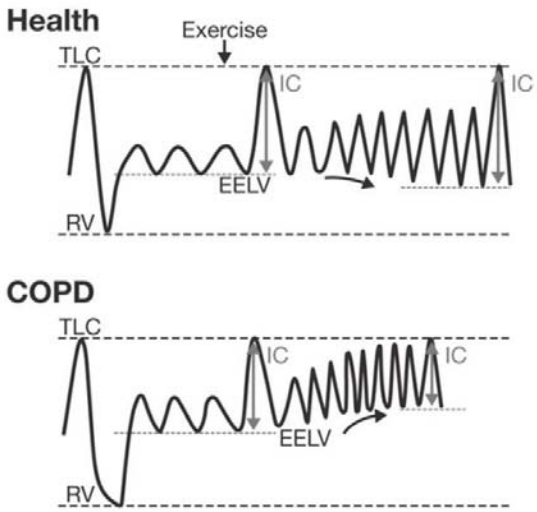


Figure 4. Lung volumes at rest and during exercise in healthy subjects and in patients with chronic obstructive pulmonary disease (COPD). EELV: end-expiratory lung volume; IC: inspiratory capacity; RV: residual volume; TLC: total lung capacity. Adapted from *O'Donnell DE* [42].

Other pulmonary-related factors, apart from lung hyperinflation, have also been associated with exercise capacity in patients with COPD. These include **airflow limitation** (FEV_1) [37, 47], **diffusing capacity** of the lung (diffusing capacity for carbon monoxide (DLco)) [36], and oxygen desaturation during exercise as a marker of **hypoxemia** [48].

Muscle dysfunction may significantly contribute to exercise limitation in COPD. Although, it is accepted that patients with COPD experience dyspnoea on exertion, Killian and co-workers identified that a surprisingly high number of patients with COPD also experience symptoms of leg fatigue [33]. Then, further studies observed that peripheral and respiratory muscle weakness are important determinants of exercise limitation in these patients [49].

During the course of COPD, **cardiovascular abnormalities** such as pulmonary hypertension and right ventricular failure may develop due to an elevated load imposed on the right ventricle and/or risk factors shared between COPD and cardiovascular diseases [1]. In these patients, exercise capacity is not only reduced due to pulmonary, but also cardiac impairment [24]. Then, exercise limitation may be predicted by assessment of right ventricle functions, such as pulmonary artery pressures, in patients with severe COPD [50].

1.2.4. Relevance of exercise capacity in COPD

Exercise capacity limitation is a marker of disability and it worsens health status in COPD [51]. Besides, exercise capacity predicts mortality better than other traditional markers of disease severity such as FEV_1 or BMI [52, 53]. In fact, exercise capacity, measured by means of the 6MWD, is one of the four domains included in the BODE grading system because of its ability to predict mortality independent of other relevant prognostic factors in COPD [5].

Exercise capacity has also a role in the disease vicious circle of dyspnoea-inactivity, a theoretical model that has been put forward to explain the clinical course of patients with COPD (Figure 5). Briefly, dyspnoea, the hallmark symptom in these patients, leads to inactivity and reduces exercise capacity, further aggravating dyspnoea [54, 55].

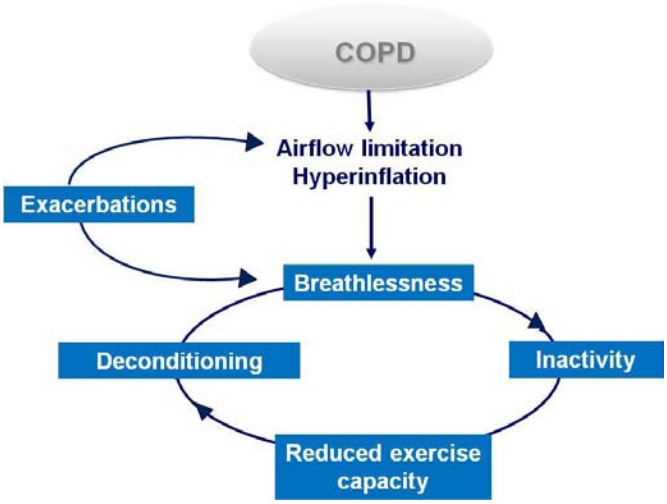


Figure 5. Vicious circle of dyspnoea-inactivity in COPD, showing the clinical course of COPD. Adapted from *Cooper CB* [54] and *Decramer M* [55].

1.2.5. Relevance of exercise capacity decline in COPD

Exercise capacity often declines over time [31, 52, 56, 57]. This decline appears to be independent of longitudinal changes in airflow limitation [52, 57] and it is also a strong predictor of mortality [31, 52, 57].

Exercise capacity declines in a greater extent than other functional variables such as FEV_1 [57]. This fact suggests that repeated measurements of exercise capacity might be a more sensitive marker of changes in clinical status in these patients than measurements of pulmonary function. However, there is a limited understanding of the factors that affect exercise capacity decline over time in COPD.

To date, only a few studies have investigated risk factors associated with exercise capacity decline in COPD, mainly using 6MWD as an index of exercise capacity [56, 58, 59]. These studies identified that older age [37], lower BMI [37], more severe airflow limitation (FEV_1), [37, 56, 58] and a lower level of regular physical activity [58], were related to exercise capacity deterioration. However, the relationship between lung hyperinflation, a variable that has been shown to be an important predictor of exercise performance in cross-sectional studies [43–45, 60] and exercise capacity decline, has not been assessed in any of the abovementioned studies. The effect of hospital admissions in exercise capacity decline has not been studied so far, either.

1.2.6. Interventions to improve exercise capacity in COPD

Several interventions have been tested in the past to improve exercise capacity in COPD patients. There is some evidence that supports the use of bronchodilators, oxygen therapy and pulmonary rehabilitation for this purpose.

Lung hyperinflation and dyspnoea can be reduced using optimal **bronchodilator therapy** and ventilatory capacity can be maximized, as well. Therefore, bronchodilators allow better exercise performance in COPD [61–63]. However, the magnitude of the effect is lower than that observed with more specific interventions, such as exercise training [64].

Oxygen therapy may have a role in improving exercise performance in some COPD patients [65, 66]. However, results are inconsistent among studies [67]. A meta-analysis of randomized controlled trials in which patients exercised while breathing either supplemental oxygen or ambient air, noticed an increase in cycle exercise endurance and a reduction in dyspnoea, but did not find a difference in maximum exercise capacity and 6MWD [68].

Pulmonary rehabilitation is a multidisciplinary programme of care that is individually tailored and designed to optimise physical and social performance, and autonomy. The pulmonary rehabilitation programme includes exercise training, education, psychosocial/behavioural intervention, nutritional therapy, outcome assessment and promotion of long-term adherence to the rehabilitation recommendations. Remarkably, exercise training remains the cornerstone of rehabilitation programmes [24].

Pulmonary rehabilitation increases exercise capacity, but also reduces dyspnoea and fatigue, improves muscle force and health related quality of life [64], and reduces health-care resource utilization [69]. These positive effects appear to occur irrespective of age and disease severity [24].

Pulmonary rehabilitation can be initiated at any stage of the disease, either during periods of clinical stability, or during or immediately after COPD exacerbations [24]. Pulmonary rehabilitation programmes conducted in the context of a COPD exacerbation are effective and safe interventions [69].

Although present COPD guidelines recommend that pulmonary rehabilitation should be considered in any COPD patient who refers dyspnoea and functional limitation [1, 3], currently, pulmonary rehabilitation programmes are available for only a small fraction of patients with COPD [70]. This is mainly due to a lack of facilities, as well as cost constraints of healthcare systems in many countries [71–73]. Identifying those patients at risk to experience a loss in exercise capacity may be helpful to select candidates who could potentially benefit the most from pulmonary rehabilitation.

2. RATIONALE

Exercise capacity limitation is a hallmark of patients with COPD and relates with poor health outcomes. Further, previous studies have clearly shown that exercise capacity declines over time in patients with COPD, and this decline is indicative of poor survival. However, there is a limited understanding of the factors that predict exercise deterioration in COPD. Identifying such factors in the clinical setting may help to guide therapeutic interventions to reduce the decline in exercise capacity.

Static lung hyperinflation is an important predictor of exercise performance in cross-sectional studies and it contributes to dyspnoea, morbidity and mortality [43, 74, 75]. However, the role of static lung hyperinflation as a determinant of exercise capacity decline in COPD is still unknown.

On the other hand, hospital admissions are associated with physical inactivity and prolonged bed rest [18, 76]. Thus, it is possible that hospital admissions due to COPD exacerbations play a role in the deterioration of exercise capacity in these patients. This hypothesis has not been explored so far.

Furthermore, a disease vicious circle has been conceptualized in COPD, in which dyspnoea leads to inactivity, yielding substantial exercise capacity deterioration and muscle dysfunction that further exacerbates dyspnoea on exertion. But this concept has never been validated to date and the role of exercise capacity limitation, in such disease vicious circle, has not been formally studied.

3. OBJECTIVES

General objective

To study the determinants of exercise capacity decline in COPD and its effects in the clinical course of the disease.

Specific objective 1

To estimate the effect of static lung hyperinflation on exercise capacity decline in a cohort of COPD patients.

Specific objective 2

To estimate the effect of hospital admissions on exercise capacity decline in a cohort of COPD patients.

Specific objective 3

To assess the role of exercise capacity in the COPD vicious circle of dyspnoea-inactivity and validate this concept using longitudinal data from a COPD cohort.

4. METHODS

The research conducted in the frame of the present doctoral thesis is based on the sample of COPD patients participating in the Phenotype and Course of COPD (PAC-COPD) study [77].

This section includes information on the general methodology followed in the PAC-COPD study that mainly applies to the conduct of the 3 objectives previously mentioned, and also includes specific information for developing each of them.

4.1. GENERAL METHODOLOGY

4.1.1. Study design and participants

Subjects in the PAC-COPD study were recruited during their first hospitalization due to a COPD exacerbation in 9 teaching hospitals in Spain between January 2004 and March 2006. The diagnosis of COPD ($FEV_1/FVC<0.70$) was confirmed in stable clinical conditions at least 3 months after discharge. The study included: i) a recruitment visit; ii) a first complete evaluation visit in stable condition (visit 1), at least 3 month after hospital discharge; iii) a short telephone interview 9 to 12 months after discharge (visit 2); and iv) a second complete evaluation visit (visit 3) conducted between 21 to 27 months after discharge (Figure 6).

Figure 6. PAC-COPD design and visit schedule.

The Clinical Research Ethical Committee of all participating hospitals approved the study and written informed consent was obtained from all participants.

4.1.2. Measurements

The current section describes methods followed to assess the variables related to the objectives of this thesis. Detailed information about the methods, questionnaires, standardization of the tests, and fieldwork supervision has been previously reported [77]. Figure 7 depicts measurements conducted at each PAC-COPD visit.

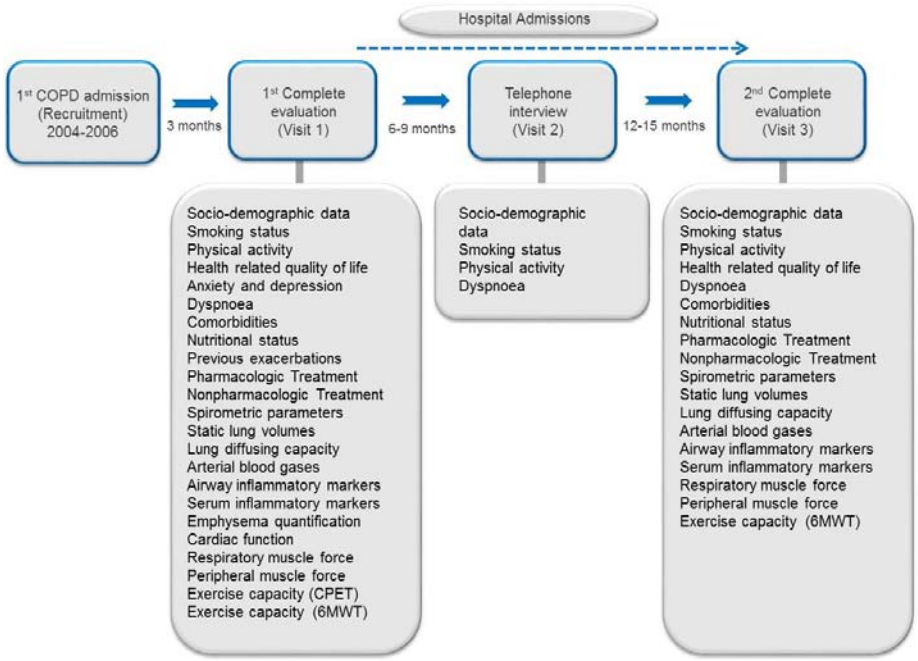


Figure 7. PAC-COPD visit time points and measurements.

4.1.2.1. Measurements conducted during complete evaluation visits (visits 1 and 3)

Exercise capacity

Exercise capacity was assessed by the 6MWT [78]. In the first complete evaluation visit, patients completed two tests with at least a 30-min rest between them, and the longest of both 6MWD was used for analysis. Only one test was conducted during visit 3. The annual rate of change in exercise

capacity was defined as the difference between the distance walked at the second evaluation minus that at baseline divided by follow-up time in each subject. Heart rate, oxygen saturation, dyspnoea and fatigue score (Borg scale) [79] were collected before and at the end of each exercise test. Patients were classified according to what is considered a MCID for exercise capacity decline [32], as having a clinically significant loss (≥35 m/year), or a less than clinically significant decline (<35 m/yr).

A CPET using an electromagnetically braked cycle ergometer was also available in a subsample of 200 participants at visit 1. The CPET was conducted following international guidelines [22] and consisted of the following: i) a rest phase before exercise (3 min), ii) exercise without load (3 min), and iii) progressive increases in load (10-20 W/min) until the tolerance limit was reached (approximately 10 min).

Pulmonary function and blood gases

Patients underwent complete lung function tests, including forced spirometry (before and after bronchodilator), static lung volumes by whole-body plethysmography, diffusing capacity for carbon monoxide (DLco), arterial blood gases and maximum inspiratory and expiratory pressures (MIP and MEP, respectively) [80, 81]. Static lung hyperinflation was considered as any value of total lung capacity (TLC) above 120% of predicted [82]. Inspiratory-to-total lung capacity (IC/TLC) ratio was taken as an index of inspiratory constraint derived from static hyperinflation of the lung [74], and residual volume-to-total lung capacity (RV/TLC) ratio was considered as an index of gas trapping. For analysis, disease severity was classified according to the ATS/ERS criteria [3].

Additional measurements

Patients also answered a computerized epidemiological questionnaire that included socio-demographic data, life-style information, the modified Medical Research Council (mMRC) scale for the assessment of dyspnoea [83], and

self-reported co-morbid conditions. The Charlson index of comorbidity [84] was calculated using comorbidites identified by physicians in patients medical records. Physical activity was assessed using the Yale Physical Activity Survey (YPAS) [85] in its Spanish version validated for COPD patients [86]. Both YPAS total score and estimated energy expenditure (kcal/week) were considered for analysis. The validated Spanish-language version [87] of the St George's Respiratory Questionnaire (SGRQ) [88] was used to measure health status. Anxiety and depression were assessed using the validated Spanish-language version [89] of the Hospital Anxiety and Depression Scale (HAD) [90]. Information on concomitant medications use, continuous long-term oxygen therapy, and participation in pulmonary rehabilitation programmes were also collected.

Weight and height were measured, the body mass index (BMI) was calculated and the fat free mass index (FFMI) was obtained by bioimpedance. Data on airway inflammatory markers (interleukin [IL] -1ß, IL-6, and IL-8 concentration) and bronchial colonisation were collected and assessed as previously reported [91]. Serum levels of C-reactive protein and tumour necrosis factor-α were also determined, as reported elsewhere [77, 91]. C-reactive protein levels greater than 5 mg/L were considered as elevated [92]. A hand dynamometer was used to measure peripheral muscle function. Only during first complete evaluation visit (visit 1), cardiac function was assessed by Doppler echocardiography following standardized methodology and emphysema quantification was assessed by High-Resolution Computed Tomography (HRCT) [93, 94]. Emphysema was defined as sharply delineated low-density areas subdivided into acinar, panlobular or subpleural in both lungs. Emphysema was expressed as a dichotomous variable (presence or absence). Detection of emphysema in any lobe was considered as the presence of emphysema [95].

4.1.2.2. Measurements conducted during the short telephone interview (visit 2)

Physical activity by the YPAS and dyspnoea according to the mMRC were measured as detailed above.

4.1.2.3. Hospital admissions during follow up

Information on hospital admissions, including dates and causes, from visit 1 to visit 3 was obtained from the Minimum Basic Dataset (CMBD), a national administrative database. Hospitalization rate was defined as the number of hospitalizations (all-causes) during follow-up divided by follow-up time in each subject. Causes of admission were classified according to the International Classification of Diseases (ICD), 9th revision. Patients were classified in two main groups: i) patients with “only COPD” hospitalizations, due exclusively to a COPD exacerbation (primary cause of admission at discharge ICD-9 codes 490-496, or primary cause ICD-9 466 or 518.81 if second cause was ICD-9 491.21), and ii) patients with “non-Respiratory” hospitalizations, due to causes unrelated to respiratory conditions (primary cause different than ICD-9 460-519). A third group of patients combining respiratory and non-respiratory admissions was labelled as “mixed cause” hospitalizations, and used only for descriptive purposes. In patients who required hospitalization at least once during follow-up, we computed the cumulative hospital stay as defined by the total number of days of admission (all-cause admissions) during follow-up. We also calculated the time from the last discharge to visit 3.

4.2. SPECIFIC METHODOLOGY TO ANSWER OBJECTIVE 1

Objective 1: To estimate the effect of static lung hyperinflation on exercise capacity decline in a cohort of COPD patients

4.2.1. Study design

Prospective longitudinal study nested in the PAC-COPD project.

4.2.2. Participants

PAC-COPD patients that participated in visit 1 and visit 3 who had repeated measurements of exercise capacity.

4.2.3. Measurements

Figure 8 shows (highlighted in black) PAC-COPD time points and measurements included in these analyses.

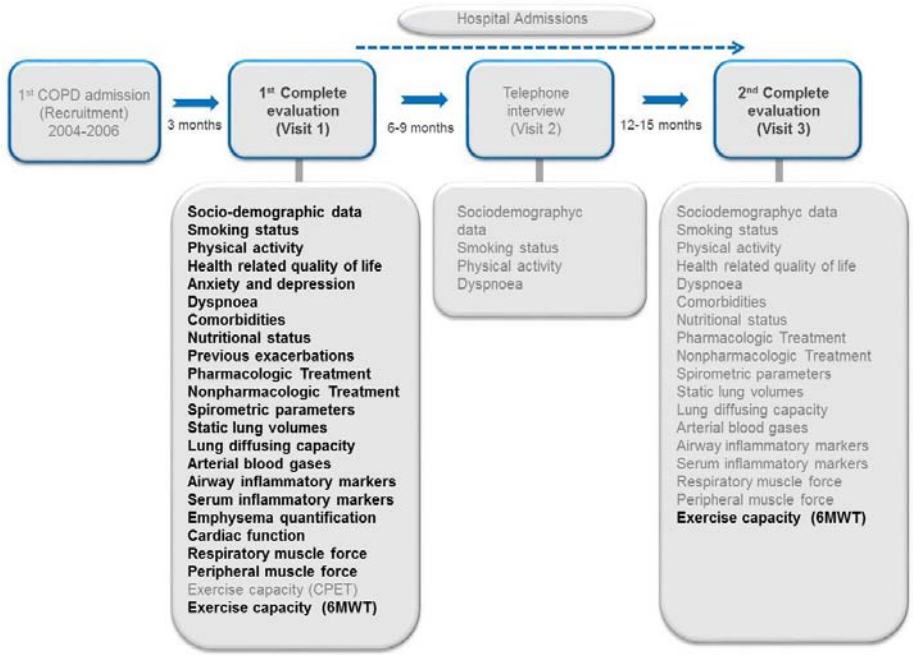


Figure 8. PAC-COPD time points and measurements included in the conduct of Objective 1.

4.2.4. Statistical analysis

A sample size of 342 was fixed by the primary scientific objectives of the PAC-COPD Study [94]. Prior to any analysis we calculated, using the program GRANMO 5.2 [96], that statistical power was 96% using data from the literature on 6MWD [97, 98], assuming a difference of 40 m in 6MWD between two equally sized groups, and accepting an alpha risk of 0.05 in a two-sided contrast.

Of the 342 patients enrolled in the PAC-COPD, 226 (66%) had exercise capacity measurements in the two complete evaluation visits. To account for selective attrition and missing values, we used multiple imputation. Moreover, other variables had a small proportion (<15%) of missing values that, assuming ignorability holds, were considered either completely at random or at random [99]. Thus, multiple imputation through chained equations was used, replacing missing values by imputations drawn from the predictive distribution of each variable [100], which was obtained from a regression model (logistic, lineal, or politomous, depending on the type of variable), where variables that were associated with the quantities of main interest and variables that were associated with the probability of missingness were used as covariates (age, sex, Charlson index of comorbidity, mMRC dyspnoea score, SGRQ total score, YPAS physical activity index, BMI, FFMI, FEV_1, IC/TLC, DL_{CO}, PaO_2, MIP, handgrip muscle force, baseline 6MWD and hospitalisation rate). To account for the additional uncertainty produced by the fact that missing values are substituted by estimates [101], we imputed missing values 20 times.

IC/TLC, as a continuous variable or categorized in tertiles, was selected a priori as the main exposure variable. The bivariate association between IC/TLC, as well as other potential determinants of exercise capacity decline, and change in 6MWD (dependent variable) were analysed using Students' t test or ANOVA, as appropriate depending on the number of categories of the exposure variable. Those variables that were strongly and/or significantly related to the outcome were then included in a multiple linear

regression model to identify independent risk factors of exercise capacity decline, after adjusting for baseline 6MWD. Variables were kept in the model if they were significantly associated with the outcome and/or they modified (at least 10%) the coefficient for other variables in the model. Goodness of fit was assessed by means of normality of residuals, heteroscedasticity, linearity, collinearity and identification of influential data. Because previous research has identified different determinants of exercise capacity in obese and normal weighted COPD patients [102], we stratified the models according to BMI. Additional analyses using RV/TLC as a marker of air trapping were also implemented. Finally, sensitivity analyses were conducted: i) using complete case analyses, ii) measuring changes in the 6MWD as percentage with respect to baseline level, iii) excluding patients enrolled in pulmonary rehabilitation programmes, and iv) forcing into the model variables previously related to 6MWD decline [56, 58, 59].

4.3. SPECIFIC METHODOLOGY TO ANSWER OBJECTIVE 2

Objective 2: To estimate the effect of hospital admissions on exercise capacity decline in a cohort of COPD patients

4.3.1. Study design

Prospective longitudinal study nested in the PAC-COPD project.

4.3.2. Participants

PAC-COPD patients that participated in visit 1 and visit 3 who had repeated measurements of exercise capacity.

4.3.3. Measurements

Figure 9 shows (highlighted in black) PAC-COPD time points and measurements included in these analyses.

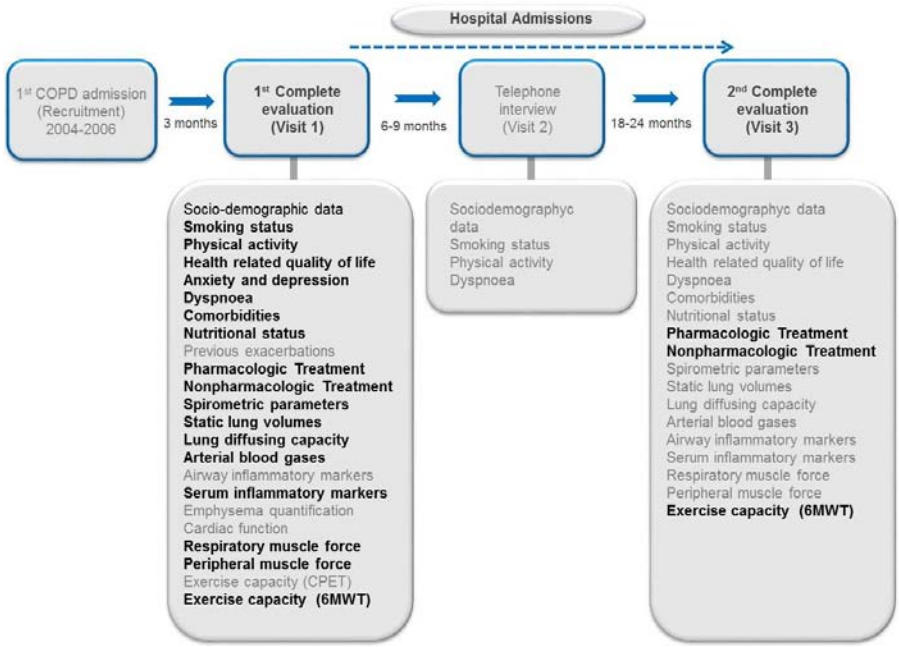


Figure 9. PAC-COPD time points and measurements included in the conduct of Objective 2.

4.3.4. Statistical analysis

Provided sample size was fixed by the primary scientific objectives of the PAC-COPD study [94], prior to any analysis we calculated whether the available number of patients would allow for identification of significant differences in 6MWD decline between groups (admitted *vs*. non-admitted during follow-up). Calculations using the program GRANMO 5.2 [96] showed that, assuming a standard deviation of 100 meters in the 6MWD [97, 98], a 1:2 ratio of hospitalised: not hospitalised [94], a correlation between first and second measurements of 0.84 [52], and accepting an alpha risk of 0.05 and a beta risk of 0.20 in a two-sided contrast, a sample size of 342 patients allows for a 20 meter or more difference in the 6MWD decline between groups to be identified as statistically significant. This difference is lower than the test's minimal important difference [32], suggesting the sample has sufficient power to provide clinically meaningful results.

To account for selective attrition and missing values, we used the same imputation strategy described in Objective 1.

The bivariate association between hospitalisation and the annual rate of change in the 6MWD was analysed using either unpaired t-test, analysis of variance, Chi-square, or Fischer's exact tests, as appropriate. Multivariate linear regression models were used to assess the effect of hospitalisations on 6MWD decline and adjusting for baseline 6MWD. Age, sex, smoking history, working status, daily physical activity, Charlson index of comorbidity, BMI, mMRC dyspnoea scale, SGRQ scores, HAD depression scale, severity of airflow limitation (FEV_1), gas trapping (RV/TLC) and lung hyperinflation (IC/TLC), pulmonary diffusion impairment (DL_{CO}), arterial oxygenation (PaO_2), muscle force (handgrip, MIP and MEP), serum TNFα, inhaled corticosteroids use, and participation in pulmonary rehabilitation programs, were tested as potential confounders and included in the final model if (i) related to both the exposure and the outcome, (ii) modified (>10% change in regression coefficient) the estimates of the remaining variables, or (iii) there was consistent evidence in the literature on their association with exercise

capacity. To assess whether exercise capacity decline was different depending on the causes of hospitalization, linear regression models were stratified according the main cause of the hospitalization using patients groups described in the general methodology. Further stratification analyses according to sex, age, BMI, daily physical activity, FEV_1 and muscle force (handgrip, MIP and MEP) were conducted in order to study possible interactions, using the median as cut off point for continuous variables. Goodness of fit was assessed by means of normality of residuals, heteroscedasticity, linearity, collinearity and identification of influential data. Sensitivity analysis was conducted (i) using the cut-off point of 26 meters/yr as the clinically significant threshold of exercise capacity decline, as this cut-off has been proposed for severe COPD patients [103], (ii) excluding subjects who participated in any pulmonary rehabilitation programme during follow-up, and (iii) using a complete case approach analysis.

4.4. SPECIFIC METHODOLOGY TO ANSWER OBJECTIVE 3

Objective 3: To assess the role of exercise capacity in the COPD vicious circle of dyspnoea-inactivity and validate this concept using longitudinal data from a COPD cohort.

4.4.1. Systematic review

We conducted a systematic review to identify all previously published conceptual models for the dyspnoea-inactivity vicious circle in COPD following the handbooks of the Centre for Reviews and Dissemination [104], the Cochrane Collaboration [105], and the PRISMA statement for reporting systematic reviews [106]. All methods were specified in advance and documented in a protocol (see Annex 1).

Data source and searches: We searched the PubMed/Medline and SCOPUS databases from the earliest record to May 2015. We browsed for additional data in the references of retrieved articles. A full search strategy was listed in a protocol (see Annex 1).

Study selection: Two reviewers (MAR, EGS) independently reviewed the title and abstract of every citation retrieved by the database searches. We ordered all articles that were deemed potentially eligible by at least one of them. The same two reviewers independently evaluated the retrieved full texts and made a decision on inclusion or exclusion according to the predefined selection criteria. In case of disagreement a third reviewer (JGA) decided upon close attention to the inclusion/exclusion criteria.

We included articles fulfilling the following criteria: i) Population: patients with COPD; ii) Content: studies that discussed the conceptual model for the dyspnoea-inactivity vicious circle either in a diagram or in the body text. A conceptual model for the dyspnoea-inactivity vicious circle in COPD was defined *a priori* as a list of proposed causal linkages believed to be related to the concept of interest [107]. We did not include articles that: i) reported other vicious circle than dyspnoea-inactivity; ii) articles containing previously

published models (e.g. repeated diagrams). Language restrictions were not imposed in this search.

Data extraction: The following information was extracted from eligible studies: i) first author name; ii) publication year; iii) aim of the article; iv) type of article; and v) diagram depicting the conceptual model of interest and/or list of variables involved in the dyspnoea-inactivity vicious circle as listed in the body text.

Data synthesis: For each study presenting a diagram, we built an acyclic graph depicting the (hypothesised) longitudinal relationships (both direct and indirect) between variables involved in the dyspnoea-inactivity vicious circle. All authors of original papers were contacted and all agreed with our adaptation of their conceptual model.

4.4.2. Study design

Prospective longitudinal study nested in the PAC-COPD project.

4.4.3. Participants

PAC-COPD patients that participated in visit 1, 2 and 3, who had repeated measurements of dyspnoea and physical activity.

4.4.4. Measurements

Figure 10 shows (highlighted in black) PAC-COPD time points and measurements included in these analyses.

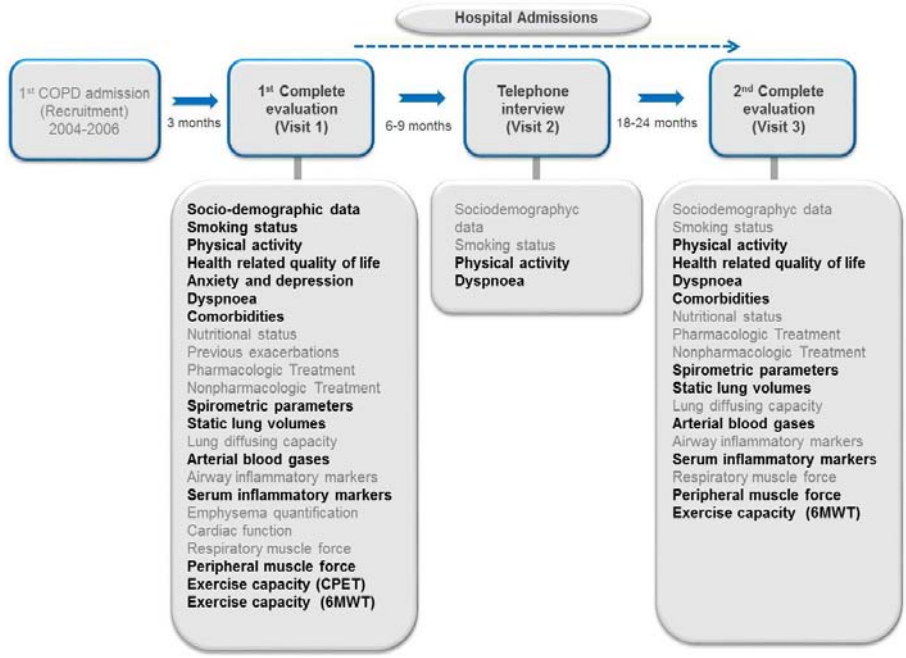


Figure 10. PAC-COPD time points and measurements included in the conduct of Objective 3.

4.4.5. Statistical analysis

The sample size was fixed by the primary scientific objectives of the PAC-COPD study [94]. Before any analysis, we calculated whether the available number of patients (210 patients with repeated measures of dyspnoea and physical activity) would provide enough statistical power for the implementation of structural equations modelling (SEM) techniques. To our knowledge, there are no sample size calculation formulas for SEM. However, our sample was greater than the proposed 10 cases per variable rule-of-thumb conventionally used to guide sample size selection in SEM [108]. Further, some recent investigations have proposed to evaluate sample size requirements in SEM in retrospect, with the specific model at hand, according to the variance explained by the direct effects [109]. Using this approach after the conduct of the analysis, our sample size was sufficient to answer the research objective with enough precision.

To validate each of the diagrams depicting the conceptual model for the dyspnoea-inactivity vicious circle obtained from the systematic review we used SEM, which allow the estimation of direct and indirect associations between variables in a path diagram or conceptual model [110]. SEM has proven effective for testing and estimating causal relations of hypothesized models in the past, using a combination of statistical data and qualitative causal assumptions [111]. To allow comparison between path coefficients, standardized coefficients were used. To test model fit we used the following criteria: i) low x^2 relative to degrees of freedom with a insignificant p value ($p>0.05$), which indicates that a non-significant amount of variance in the data remains unexplained; ii) the root mean square error of approximation (RMSEA), which assesses how well the model reaches the data by determining the lack of fit of the model to the covariance matrix (a RMSEA less than 0.07 is an acceptable threshold level and values less than 0.03 represent excellent fit); and iii) the comparative fit index (CFI) that analyses the association between all measured variables (a CFI equal or higher than 0.95 is presently recognised as indicative of good fit) [112]. Finally, variables identified either in a diagram or body text of each included study were

combined in search of the most comprehensive and valid model. Variables were kept in the model if they showed a statistically significant association with at least one of the remaining variables and/or if they significantly improved the model fit.

5. RESULTS

5.1. DETERMINANTS OF EXERCISE CAPACITY DECLINE IN COPD PATIENTS

5.1.1. CHARACTERISTICS OF THE SAMPLE TO STUDY THE DETERMINANTS OF EXERCISE CAPACITY DECLINE IN COPD PATIENTS

Of the 342 patients originally recruited into the PAC-COPD study [113] 226 (66%) had measurements of exercise capacity in the two complete evaluation visits (Figure 11).

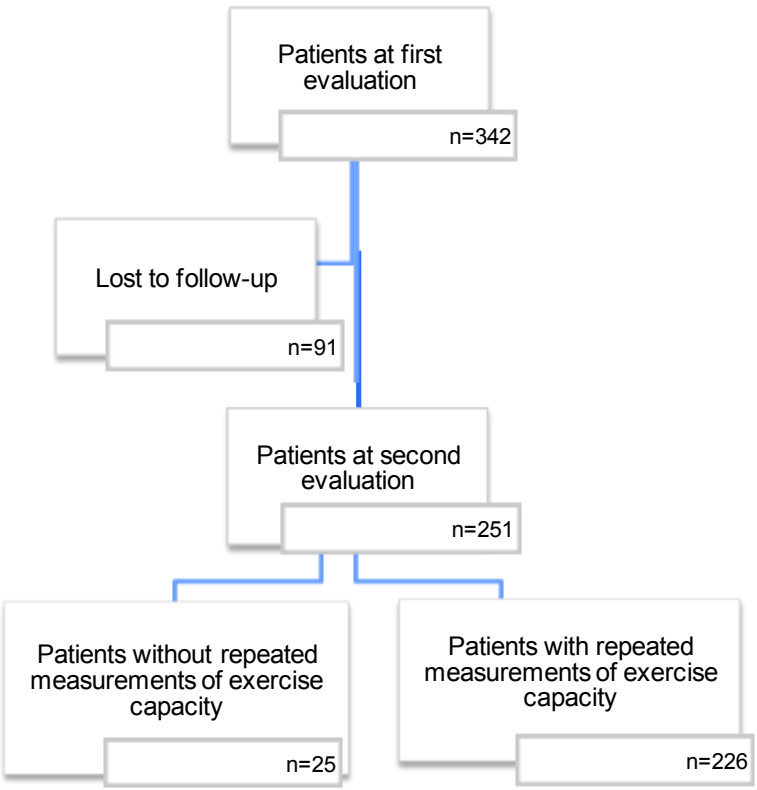


Figure 11. Flow chart of patients enrolled in the PAC-COPD study.

Subjects lost to follow-up were older, had more co-morbidities and lower FEV_1 compared with the remaining patients (Tables 2 and 3).

Table 2. Comparison between participants with repeated measurements of exercise capacity and patients lost to follow-up.

	Participants followed (n=226)	**Lost to follow-up (n=91)**	**p**
Sex: Males	209 (9)	85 (93)	0.773
Age (years)	67.4 ± 8.3	67.9 ± 9.4	0.658
Smoking: current smoker	78 (35)	35 (38)	0.507
YPAS index (score 0 to 137)	36 (23-53)	31 (18-49)	0.139
Charlson index ≥2	115(51)	61 (67)	0.009
BMI kg/m^2	28.2 ± 4.6	27.7 ± 4.8	0.307
FFMI kg/m^2	19.8 ± 3.2	19.0 ± 2.7	0.063
Significant dyspnoea (mMRC ≥2)	95 (42)	48 (53)	0.083
PostBD FEV_1 (% pred)	54 ± 17	49 ± 16	0.019
PostBD FEV_1/FVC (%)	54 ± 12	52 ± 12	0.099
COPD severity*			
Mild (FEV_1 ≥80%)	15 (7)	4 (4)	0.289
Moderate (FEV_1 ≥50%, <80%)	111 (49)	37 (41)	
Severe (FEV_1 ≥30%, <50%)	85 (37)	40 (44)	
Very severe (FEV_1 <30%)	15 (7)	10 (11)	
IC (% pred)	70.4 ± 21.2	65.2 ± 18.9	0.126
IC/TLC (%)	31.6 ± 9.3	30.3 ± 10.1	0.276
TLC (% pred)	101.3 ± 17.8	100.3 ±20.0	0.674
RV/TLC (%)	55.1 ± 10.1	56.5 ± 10.1	0.298
DLco (% pred)	66.5 ± 20.7	62.8 ± 19.9	0.189
PaO_2 (mmHg)	74.9 ± 11.2	72.6 ± 9.4	0.094
Handgrip muscle force (Kg)	31.3 ± 8.3	29.1 ± 8.1	0.043
Baseline 6MWD (m)†	444 ± 83	411 ± 107	0.066

Data are presented as n (%), mean±SD or median (P_{25}-P_{75}). mMRC: modified Medical Research Council dyspnoea scale; FEV_1: forced espiratory volume in 1 second; FEV_1/FVC: forced espiratory volume in 1 second/forced vital capacity; IC: inspiratory capacity; IC/TLC: inspiratory capacity/total lung capacity; RV/TLC: Residual Volume/Total Lung Capacity; DLCo: diffusing capacity for carbon monoxide; PaO_2: arterial oxygen tension. *According to the American Thoracic Society/European Respiratory Society criteria [3]. †The best of two six-minute walk distance tests separated by ≥30 min.

Table 3. Comparison between participants with repeated measurements of exercise capacity and subjects that attended all visits but did not have repeated measurements.

	Participants with repeated measurements of 6MWD (n=226)	**Participants without repeated measurements of 6MWD (n=25)**	**p**
Sex: Males	209 (92)	24 (96)	0.999
Age (years)	67.4 ± 8.3	72.5 ± 7.0	0.003
Smoking: current smoker	78 (35)	7(28)	0.657
YPAS index (score 0 to 137)	36 (23-53)	29 (19–46)	0.260
Charlson index ≥2	115(50.88)	18 (72)	0.045
BMI (kg/m^2)	28.2 ± 4.6	29.5 ± 4.6	0.194
FFMI (kg/m^2)	19.78 ± 3.2	20.6 ± 2.5	0.226
Significant dyspnoea (mMRC ≥2)	95 (42)	15 (60)	0.094
PostBD FEV_1 (% pred)	54 ± 17	52 ± 12	0.648
PostBD FEV_1/FVC (%)	54 ± 12	55 ± 11	0.798
COPD severity*			
Mild (FEV_1 ≥80%)	15 (7)	0	0.379
Moderate (FEV_1 ≥50%, <80%)	111 (49)	16 (64)	
Severe (FEV_1 ≥30%, <50%)	85 (37)	7 (28)	
Very severe (FEV_1 <30%)	15 (7)	2 (8)	
IC (% pred)	70.4 ± 21.2	61.9 ± 14.9	0.076
IC/TLC (%)	31.6 ± 9.3	31.1 ± 8.7	0.786
TLC (% pred)	101.3 ± 17.8	92.7 ± 17.0	0.027
RV/TLC (%)	55.1 ± 10.1	55.7 ± 9.5	0.798
DLco (% pred)	66.5 ± 20.7	61.2 ± 22.9	0.259
PaO_2 (mmHg)	74.9 ± 11.2	74.6 ± 9.0	0.903
Handgrip muscle force (Kg)	31.3 ± 8.3	28 ± 8.3	0.068
Baseline 6MWD (m)†	444 ± 83	415 ± 98	0.251

Data are presented as n (%), mean±SD or median (P_{25}-P_{75}). FEV_1: forced espiratory volume in 1 second; FEV_1/FVC: forced espiratory volume in 1 second/forced vital capacity; IC: inspiratory capacity; IC/TLC: inspiratory capacity/total lung capacity; RV/TLC: Residual Volume/Total Lung Capacity; DLCo: diffusing capacity for carbon monoxide; PaO_2: arterial oxygen tension. *According to the American Thoracic Society/European Respiratory Society criteria [3]. † The best of two six-minute walk distance tests separated by ≥30 min.

Given that 34% of patients without repeated measurements of exercise capacity exhibited some differences compared with the remaining patients, and that selective attrition is known to introduce bias into analysis if using a complete case strategy [114], we used multiple imputation to compensate for the underrepresentation of the older, more severe population (refer to methods section for details).

Table 4 (A and B) shows the main clinical and functional characteristics of the 342 study participants at baseline using imputed datasets. Patients were mostly male (92) with a mean±SD age of 67.9±8.6 years. Airflow limitation was moderate to severe in the majority of patients (mean post-bronchodilator FEV_1 was 54±17% of predicted) but there was significant variability. Static hyperinflation was present in 67 (20%) patients. Thirteen (5%) patients were enrolled in pulmonary rehabilitation programmes, 8 (2%) were on continuous long-term oxygen therapy, and 120 (35%) on chronic inhaled steroids.

Table 4-A. Characteristics of study participants.

	All patients* **n=342**
Anthropometric and clinical data	
Males	314 (92)
Age (years)	67.9 ± 8.6
Current smokers	120 (35)
Active workers	61 (18)
YPAS physical activity index (score 0 to 137)	34 (20-53)
SGRQ total score (0 to100)	33 (23-48)
Charlson index ≥2	194 (57)
Body mass index (kg/m^2)	28.2 ± 4.7
Fat free mass index (kg/m^2)	19.7 ± 3.1
mMRC dyspnoea score (0 to 4)	2 (2-3)
Exacerbation in previous year >1†	141 (41)
Inflammatory markers	
Interleukin-6 (pg/ml)	128 (43-259)
C-reactive protein (mg/l)	3.8 (1.7-7.1)
Tumour necrosis factor-α (pg/l)	2.1 (0.5-10.2)

Data are presented as n (%), mean±SD or median (P_{25}-P_{75}). YPAS: Yale physical activity survey; SGRQ: Saint George's respiratory questionnaire; mMRC: modified Medical Research Council dyspnoea scale.*:Descriptive analyses conducted using imputed datasets where existing missing data. †: All patients had at least one exacerbation in the previous year, as they were recruited during their first COPD admission.

Table 4-B. Characteristics of study participants.

	All patients* **n=342**
Pulmonary function and blood gases	
Postbronchodilator FEV_1 (% pred)	54.4 ± 17.2
Airflow limitation severity†	
Mild (FEV_1 ≥80%)	19 (6)
Moderate (FEV_1 ≥50%, <80%)	164 (48)
Severe (FEV_1 ≥30%, <50%)	132 (38)
Very severe (FEV_1 <30%)	27 (8)
IC (% pred)	67.3 ± 20.2
IC/TLC (%)	30.9 ± 9.8
TLC (% pred)	100.4 ± 18.4
RV/TLC (%)	55.9 + 10.5
DLco (% pred)	64.4 ± 22.7
PaO_2 (mmHg)	74.4 ± 10.9
Cardiac function	
Left Ventricle Ejection Fraction (%)	59.0 ± 8.9
Transtricuspid regurgitant velocity (m/sec)	2.4 ± 0.9
Right ventricle-Mid end-diastolic diameter (mm)	31.6 ± 4.5
Muscle force and Exercise capacity	
Respiratory muscle force (MIP, %)	68 ± 27
Peripheral muscle force (hand-grip, Kg)	30.5 ± 8.5
6MWD at baseline (m)	433 ± 93
6MWD at follow-up visit (m)	396 ± 99
Annual change in 6MWD (m/year)	-21.9 ± 51.0
Patients with clinically significant decline in 6MWD (≥ 35 m/year)	113 (33)

Data are presented as n (%), mean±SD or median (P_{25}-P_{75}). FEV_1: forced expiratory volume in 1 second; IC: inspiratory capacity; IC/TLC: inspiratory capacity/total lung capacity; TLC: total lung capacity; RV/TLC: residual volume/total lung capacity; DLco: diffusing capacity for carbon monoxide; PaO_2: arterial oxygen tension; MIP: maximum inspiratory pressure; 6MWD: 6-minute walk distance. *: Descriptive analyses conducted using imputed datasets where existing missing data. †: According to the criteria of the ATS/ERS [3].

Subjects were followed-up for a mean±SD of 1.7±0.34 years. The mean±SD 6MWD was 433±93 m at baseline and 396±99 m at the second evaluation. Mean change in 6MWD was -21.9±51.0 m/year (Figure 12). About 20% of patients experienced an increase in exercise capacity during follow-up. A 6MWD decline ≥35 m/year (MCID) occurred in 113 (33%) subjects.

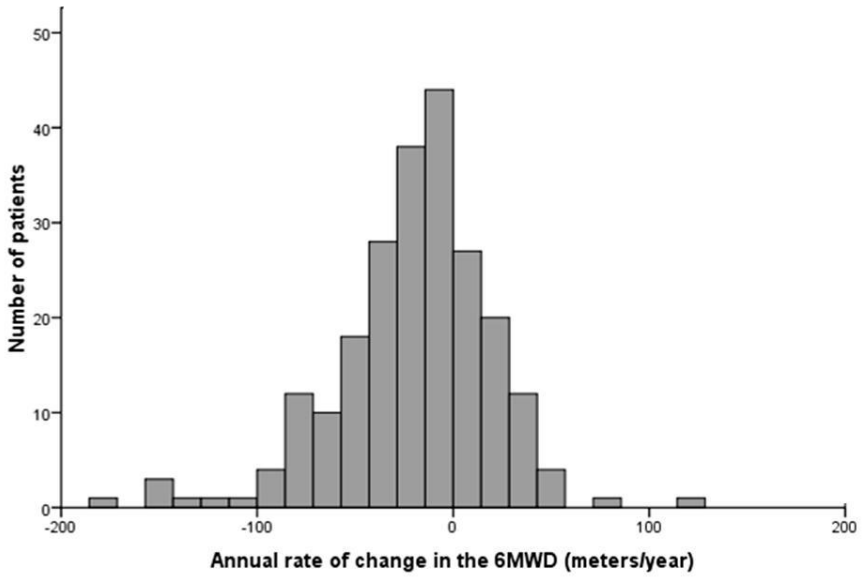


Figure 12. Distribution of annual 6MWD change in 342 COPD patients followed over 1.7 years.

5.1.2. STATIC PULMONARY HYPERINFLATION AND EXERCISE CAPACITY DECLINE IN PATIENTS WITH COPD

5.1.2.1. Crude association between baseline socio-demographic, clinical and functional factors and annual change in 6MWD

In the bivariate analysis, patients with higher levels of IC/TLC as a surrogate of static hyperinflation had greater 6MWD decline (-27.4±42.5, -24.9±36.5 and -13.4±39.9 m/year in the 1st, 2nd and 3rd tertile of IC/TLC, respectively; p-for-trend=0.018). From other potential risk factors considered, dyspnoea, health status, serum C-reactive protein and Borg dyspnoea score at the end of the exercise test were related to exercise capacity decline in the bivariate analyses (Figure 13).

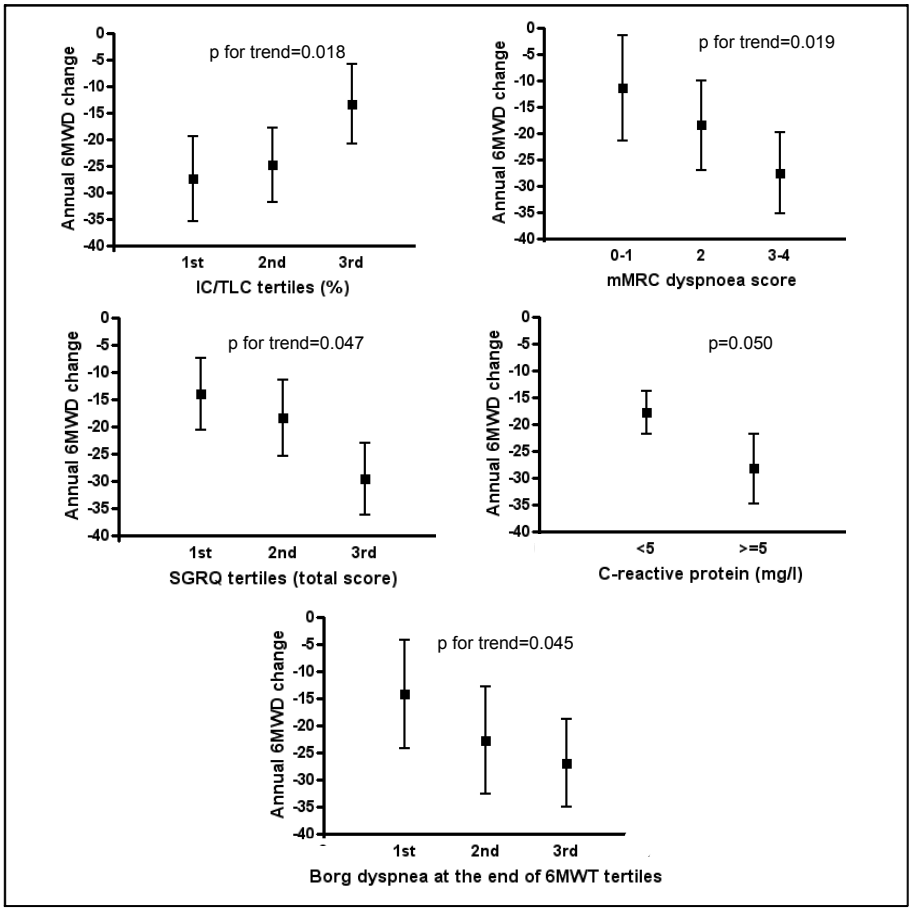


Figure 13. Factors associated with the annual change in 6MWD in 342 COPD patients. Data are presented as mean and 95% confidence intervals. Change in 6-minute walk distance is shown in meters/year. Negative values represent decline. 6MWD: 6-minute walk distance; IC/TLC: inspiratory capacity/total lung capacity; mMRC: Modified Medical Research Council dyspnoea scale; SGRQ: Saint George's respiratory questionnaire; 6MWT: 6-minute walk test.

Other potential determinants were not related to 6MWD decline (Figures 14-16). FEV_1 was not associated with exercise capacity decline neither as a continuous nor as a categorical variable.

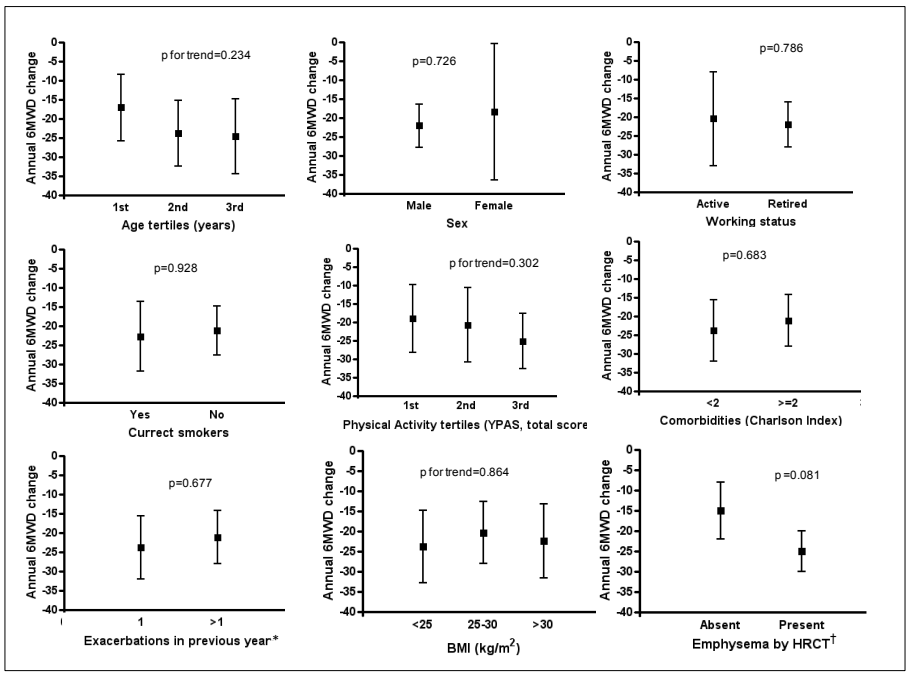


Figure 14. Relationship between relevant socio-demographic, life-style and clinical data and the annual change in 6MWD in 342 COPD patients. Data are presented as mean and 95% confidence intervals. Change in 6-minute walk distance is shown in meters/year. Definition of abbreviation: 6MWD: 6-minute walk distance; YPAS: Yale physical Activity Survey; BMI: Body Mass Index; HRCT: High-Resolution Computed Tomography. *:All patients had at least one exacerbation in the previous year, as they were recruited during their first COPD admission. †:Emphysema was defined as sharply delineated low-density areas subdivided into acinar, panlobular or subpleural types in both lungs.

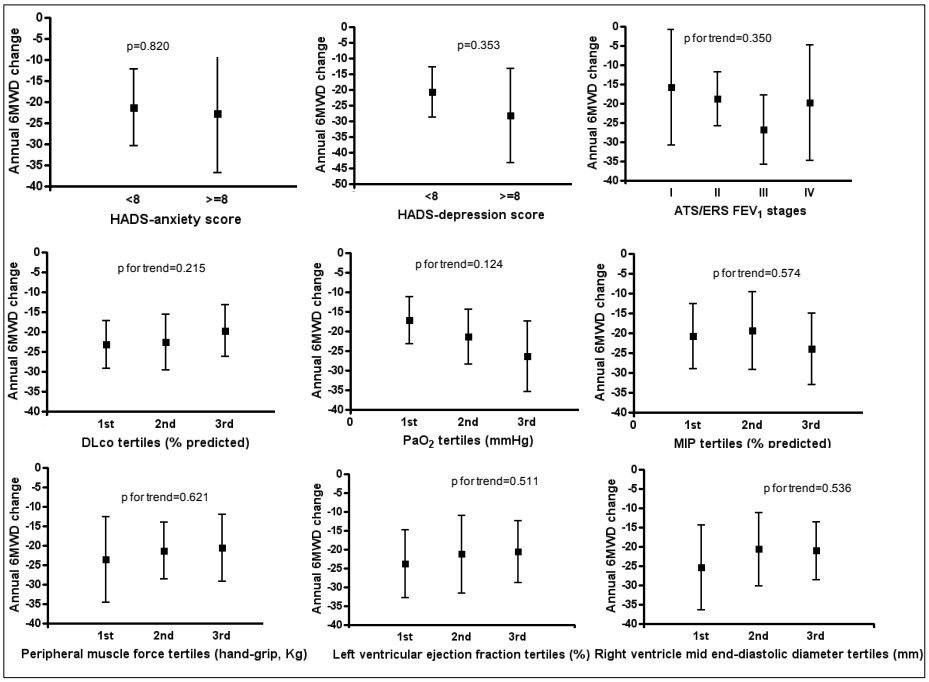


Figure 15. Relationship between anxiety and depressive symptoms, lung function parameters, blood gases, muscle force, cardiac function and the annual change in 6MWD in 342 COPD patients. Data are presented as mean and 95% confidence intervals. Change in 6-minute walk distance is shown in meters/year. Definition of abbreviation: 6MWD: 6-minute walk distance; HADS: Hospital Anxiety and Depression scale; FEV_1: forced expiratory volume in 1 second; DLco: diffusing capacity for carbon monoxide; PaO_2: arterial oxygen tension; MIP: maximum inspiratory pressure.

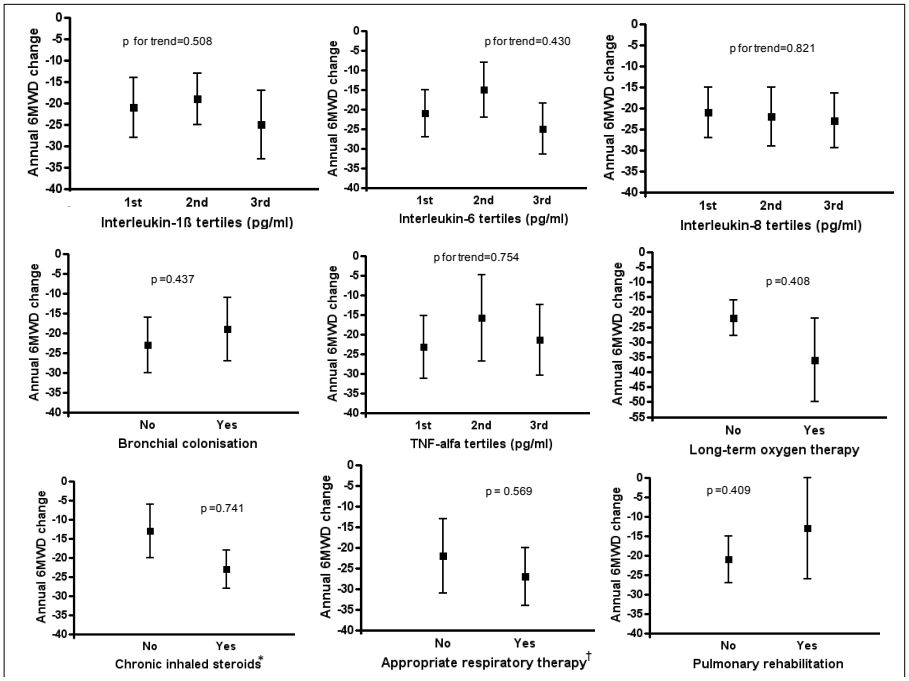


Figure 16. Relationship between relevant inflammatory markers, bronchial colonisation and respiratory treatments at baseline and the annual change in 6MWD in 342 COPD patients. Data are presented as mean and 95% confidence intervals. Change in 6-minute walk distance is shown in meters/year. Definition of abbreviation: 6MWD: 6-minute walk distance; TNF: Tumour necrosis factor. *: Alone or in combination with other drug treatments; †: Defined as some kind of long-acting beta adrenergic, corticosteroids, or a combination of both.

5.1.2.2. Adjusted association between baseline sociodemographic, clinical and functional factors and annual change in 6MWD

In multivariate models (Table 5), only IC/TLC ratio and dyspnoea remained significantly associated with the 6MWD decline, after adjusting for baseline 6MWD.

Table 5. Adjusted predictive factors of 6MWD decline in 342 COPD patients followed-up for 1.7 years.

	All patients (n=342)	
	Coefficient† (95%CI)	p
Constant*	-14.3 (-21.8; -6.7)	<0.001
Baseline IC/TLC (%)	0.7 (0.2; 1.2)	0.007
Significant dyspnoea (mMRC≥2) at baseline	-14.6 (-26.2; -3.1)	0.013
SGRQ at baseline	-0.1 (-0.5; 0.3)	0.691
C-reactive protein at baseline (mg/l)	-0.4 (-2.8; 2.1)	0.777
Borg dyspnoea at the end of 6MWT	-0.8 (-2.9; 1.3)	0.457
Baseline 6MWD (m)	-0.2 (-0.3; -0.1)	<0.001
Adjusted R^2	*0.137*	

95% CI: 95% confidence interval; mMRC: Modified Medical Research Council dyspnoea scale; IC/TLC: inspiratory capacity/total lung capacity; SGRQ: Saint George's respiratory questionnaire; 6MWD: 6-minute walk distance; 6MWT: 6-minute walk test. *: Adjusted mean value based on the linear regression equation corresponding to the mean change in 6-minutes walking distance in a subject with mMRC<2 and mean IC/TLC ratio, SGRQ, C-reactive protein, Borg dyspnoea at the end of 6MWT and mean baseline 6-minute walk distance. Negative values represent decline. †: Coefficients are expressed as changing meters of the six-minute walk distance per (i) each unit of the continuous covariates, or (ii) a change with respect to reference category in categorical covariates.

The adjusted predicted change in 6MWD (and 95% confidence interval) was plotted against IC/TLC ratio (Figure 16), and showed that the lower the baseline IC/TLC ratio, the greater the longitudinal decline in exercise capacity in a linear dose-response shape.

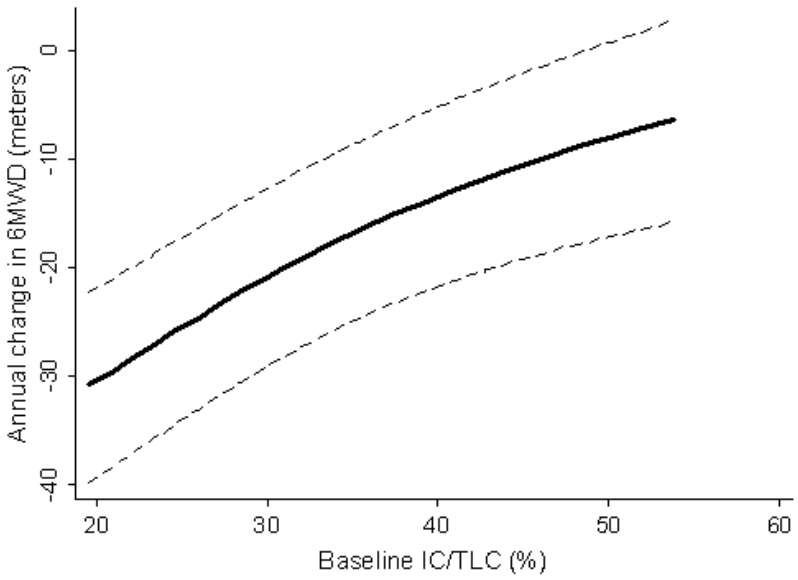


Figure 16. Mean (and 95% confidence intervals) annual decline in 6MWD according to IC/TLC. From a linear regression model with IC/TLC as a continuous variable, and adjusted for dyspnoea, quality of life, C-reactive protein, and baseline 6MWD.

Additional analyses using RV/TLC as a marker of air trapping (Table 6), stratification according to BMI (Table 7), as well as sensitivity analyses (i) using a complete case strategy (Table 8); (ii) measuring changes in 6MWD as percentage with respect to baseline level (Table 9); (iii) excluding patients enrolled in pulmonary rehabilitation programmes (Table 10); and (iv) forcing into the model variables previously related to 6MWD decline (Table 11), yielded very similar results. Linear regression goodness of fit tests did not reveal any abnormality.

Table 6. Adjusted predictive factors of exercise capacity decline in 342 COPD patients followed-up for 1.7 years (linear regression model), using RV/TLC as a marker of air trapping.

	Using RV/TLC as a marker of air trapping (n=342)		**Using IC/TLC as a marker of lung hyperinflation (n=342)**	
	Coefficient† (95%CI)	p	Coefficient† (95%CI)	p
Constant*	-14.1 (-21.7;-6.6)	0.001	-14.3 (-21.8; -6.7)	<0.001
Baseline RV/TLC (%)	-0.7 (-1.2; -0.1)	0.016	--	--
Baseline IC/TLC (%)	--	--	0.7 (0.2; 1.2)	0.007
Significant dyspnoea (mMRC ≥2) at baseline	-14.6 (-26.1; -3.2)	0.012	-14.6 (-26.2; -3.1)	0.013
SGRQ at baseline	-0.1 (-0.5; 0.2)	0.503	-0.1 (-0.5; 0.3)	0.691
C-reactive protein at baseline (mg/l)	-0.11 (-2.6; 2.3)	0.928	-0.4 (-2.8; 2.1)	0.777
Borg dyspnoea at the end of 6MWT	-1.2 (-8.2; 5.6)	0.742	-0.8 (-2.9; 1.3)	0.457
Baseline 6MWD (m)	-0.2 (-0.3; -0.1)	<0.001	-0.2 (-0.3; -0.1)	<0.001
Adjusted R^2	*0.134*		*0.137*	

95% CI: 95% confidence interval; mMRC: modified Medical Research Council dyspnoea scale; RV/TLC: residual volume/total lung capacity; IC/TLC: inspiratory capacity/total lung capacity; SGRQ: Saint George's respiratory questionnaire 6MWD: 6-minute walk distance; 6MWT: 6-minute walk test. *: Adjusted mean value based on the linear regression equation corresponding to the mean change in 6-minutes walking distance in a subject with mMRC<2 and mean RV/TLC ratio (or mean IC/TLC), SGRQ, C-reactive protein, Borg dyspnoea at the end of 6MWT and mean baseline 6-minute walk distance. Negative values represent decline. †: Coefficients are expressed as changing meters of the six-minute walk distance per (i) each unit of the continuous covariates, or (ii) a change with respect to reference category in categorical covariates.

Table 7. Adjusted predictive factors of exercise capacity decline in 342 COPD patients followed during 1.7 years (linear regression model), according to baseline BMI.

	BMI<30 kg.m^{-2} (n=221)		**BMI≥30 kg.m^{-2} (n=121)**	
	Coefficient† (95%CI)	p	Coefficient† (95%CI)	p
Constant*	-11.7 (-22.5; -1.0)	0.035	-11.8 (-31.2; 7.4)	0.223
Baseline IC/TLC (%)	0.9 (0.3; 1.6)	0.006	0.6 (-0.3; 1.6)	0.196
Significant dyspnoea (mMRC ≥2) at baseline	-15.7 (-29.2;-2.2)	0.028	-15.0 (-35.8; 5.7)	0.154
SGRQ at baseline	-0.2 (-0.6; 0.26)	0.430	0.1 (-0.68; 0.77)	0.910
C-reactive protein at baseline (mg/l)	-0.2 (-4.0; 3.7)	0.938	0.4 (-3.2; 3.9)	0.855
Borg dyspnoea at the end of 6MWT	0.2 (-2.3; 2.7)	0.882	-1.7 (-5.6; 2.2)	0.385
Baseline 6MWD (m)	-0.2 (-0.2; -0.1)	0.002	-0.2 (-0.3; -0.1)	0.008
Adjusted R^2	*0.165*		*0.120*	

95% CI: 95% confidence intervals; IC/TLC: inspiratory capacity/total lung capacity; mMRC: modified Medical Research Council dyspnoea scale; SGRQ: Saint George's respiratory questionnaire; 6MWD: 6-minute walk distance. *: Adjusted mean value based on the linear regression equation corresponding to the mean change in 6-minutes walking distance in a subject with mMRC<2 and mean IC/TLC ratio, SGRQ, C-reactive protein, Borg dyspnoea at the end of 6MWT and mean baseline six-minute walk distance. Negative values represent decline. †: Coefficients are expressed as changing meters of the six-minute walk distance per (i) each unit of the continuous covariates, or (ii) a change with respect to reference category in categorical covariates.

Table 8. Adjusted predictive factors of exercise capacity decline in 342 COPD patients followed during 1.7 years (linear regression model), using complete cases and imputed datasets.

	Complete cases (n=226)		**Multiple imputation (n=342)**	
	Coefficient† (95%CI)	p	Coefficient† (95%CI)	p
Constant*	-14.8 (-22.1; -7.4)	<0.001	-14.3 (-21.8; -6.7)	<0.001
Baseline RV/TLC (%)	0.8 (0.3; 1.4)	0.003	0.7 (0.2; 1.2)	0.007
Significant dyspnoea (mMRC ≥2) at baseline	-9.4 (-21.9; 3.1)	0.140	-14.6 (-26.2; -3.1)	0.013
SGRQ at baseline	-0.1 (-0.5; 0.2)	0.639	-0.1 (-0.5; 0.3)	0.691
C-reactive protein at baseline (mg/l)	-0.1 (-2.6; 2.5)	0.928	-0.4 (-2.8; 2.1)	0.777
Borg dyspnoea at the end of 6MWT	-1.7 (-3.9; 0.5)	0.101	-0.8 (-2.9; 1.3)	0.457
Baseline 6MWD (m)	-0.1 (-0.2; -0.1)	<0.001	-0.2 (-0.3; -0.1)	<0.001
Adjusted R^2	*0.101*		*0.137*	

95% CI: 95% confidence interval; IC/TLC: inspiratory capacity/total lung capacity; mMRC: Modified Medical Research Council dyspnoea scale; SGRQ: Saint George's respiratory questionnaire 6MWD: 6-minute walk distance. *: Adjusted mean value based on the linear regression equation corresponding to the mean change in 6-minutes walking distance in a subject with mMRC<2 and mean IC/TLC ratio, SGRQ, C-reactive protein, Borg dyspnoea at the end of 6MWT and mean baseline 6-minute walk distance. Negative values represent decline. †: Coefficients are expressed as changing meters of the six-minute walk distance per (i) each unit of the continuous covariates, or (ii) a change with respect to reference category in categorical covariates.

Table 9. Adjusted predictive factors of exercise capacity decline expressed in absolute values and as percentage with respect to baseline level in 342 COPD patients followed during 1.7 years (linear regression model).

	6MWD decline, meters (n=342)		**6MWD decline, % from baseline (n=342)**	
	Coefficient† (95%CI)	p	Coefficient† (95%CI)	p
Constant*	-14.3 (-21.8; -6.7)	<0.001	-2.15 (-4.98; 0.68)	0.133
Baseline IC/TLC (%)	0.7 (0.2; 1.2)	0.007	0.14 (0.11; 0.18)	0.045
Significant dyspnoea (mMRC ≥2) at baseline	-14.6 (-26.2; -3.1)	0.013	-5.00 (-9.48; -0.71)	0.023
SGRQ at baseline	-0.1 (-0.5; 0.3)	0.691	0.02 (-0.13; 0.16)	0.825
C-reactive protein at baseline (mg/l)	-0.4 (-2.8; 2.1)	0.777	0.14 (-0.92; 1.19)	0.792
Borg dyspnoea at the end of 6MWT	-0.8 (-2.9; 1.3)	0.457	-0.02 (-0.76; 0.73)	0.966
Baseline 6MWD (m)	-0.2 (-0.3; -0.1)	<0.001	-0.04 (-0.04; -0.03)	<0.001
Adjusted R^2	*0.137*		*0.080*	

95% CI: 95% confidence interval; IC/TLC: inspiratory capacity/total lung capacity; mMRC: modified Medical Research Council dyspnoea scale; SGRQ: Saint George's respiratory questionnaire 6MWD: 6-minute walk distance. *: Adjusted mean value based on the linear regression equation corresponding to the mean change in 6-minutes walking distance in a subject with mMRC<2, and mean IC/TLC ratio, SGRQ, C-reactive protein, Borg dyspnoea at the end of 6MWT and mean baseline 6-minute walk distance. Negative values represent decline.†: Coefficients are expressed as changing meters of the six-minute walk distance per (i) each unit of the continuous covariates, or (ii) a change with respect to reference category in categorical covariates.

Table 10. Adjusted predictive factors of exercise capacity decline in 342 COPD patients followed during 1.7 years (linear regression model), excluding patients enrolled in pulmonary rehabilitation programs.

	All patients (n=342)		**Patient not enrolled in pulmonary rehabilitation (n=329)**	
	Coefficient† (95%CI)	p	Coefficient† (95%CI)	p
Constant*	-14.3 (-21.8; -6.7)	<0.001	-11.3 (-20.6; -1.9)	0.018
Baseline RV/TLC (%)	0.7 (0.2; 1.2)	0.007	0.9 (0.4; 1.4)	0.001
Significant dyspnoea (mMRC ≥2) at baseline	-14.6 (-26.2; -3.1)	0.013	-11.8 (-24.0; 0.4)	0.052
SGRQ at baseline	-0.1 (-0.5; 0.3)	0.691	-0.1 (-0.5; 0.3)	0.522
C-reactive protein at baseline (mg/l)	-0.4 (-2.8; 2.1)	0.777	0.1 (-2.6;2.8)	0.934
Borg dyspnoea at the end of 6MWT	-0.8 (-2.9; 1.3)	0.457	-1.0 (-3.2; 1.1)	0.352
Baseline 6MWD (m)	-0.2 (-0.3; -0.1)	<0.001	-0.1 (-0.2; -0.1)	<0.001
Adjusted R^2	*0.137*		*0.156*	

95% CI: 95% confidence interval; IC/TLC: inspiratory capacity /total lung capacity; mMRC: modified Medical Research Council dyspnoea scale; SGRQ: Saint George's respiratory questionnaire 6MWD: 6-minute walk distance. *: Adjusted mean value based on the linear regression equation corresponding to the mean change in 6-minutes walking distance in a subject with mMRC<2, and mean IC/TLC ratio, SGRQ, C-reactive protein, Borg dyspnoea at the end of 6MWT and mean baseline 6-minute walk distance. Negative values represent decline. †: Coefficients are expressed as changing meters of the six-minute walk distance per (i) each unit of the continuous covariates, or (ii) a change with respect to reference category in categorical covariates.

Table 11. Adjusted predictive factors of exercise capacity decline in 342 COPD patients followed during 1.7 years (linear regression model), forcing variables previously related to 6MWD decline.

	Original model (n=342)		**Model after forcing variables previously related to 6MWD decline (n=342)**	
	Coefficient† (95%CI)	p	Coefficient† (95%CI)	p
Constant*	-14.3 (-21.8; -6.7)	<0.001	-14.4 (-22.3; -6.5)	<0.001
Baseline RV/TLC (%)	0.7 (0.2; 1.2)	0.007	0.9 (0.3; 1.6)	0.007
Significant dyspnoea (mMRC ≥2) at baseline	-14.6 (-26.2; -3.1)	0.013	-13.8 (-25.3; -2.3)	0.019
SGRQ at baseline	-0.1 (-0.5; 0.3)	0.691	-0.2 (-0.6; 0.2)	0.361
C-reactive protein at baseline (mg/l)	-0.4 (-2.8; 2.1)	0.777	-0.3 (-2.8; 2.2)	0.826
Borg dyspnoea at the end of 6MWT	-0.8 (-2.9; 1.3)	0.457	-0.7 (-2.9; 1.6)	0.560
Baseline 6MWD (m)	-0.2 (-0.3; -0.1)	<0.001	-0.2 (-0.3; -0.1)	<0.001
Age at baseline	--	--	-0.7 (-1.4; -0.1)	0.037
Body Mass Index (Kg/m^2)	--	--	-0.3 (-1.5; 0.9)	0.657
FEV_1 (% pred)	--	--	0.1 (-0.6; 0.5)	0.515
YPAS physical activity index	--	--	-0.1 (-0.3; 0.1)	0.303
Adjusted R^2	*0.137*		*0.164*	

95% CI: 95% confidence interval; IC/TLC: inspiratory capacity /total lung capacity; mMRC: modified Medical Research Council dyspnoea scale; SGRQ: Saint George's respiratory questionnaire 6MWD: 6-minute walk distance; FEV_1: forced expiratory volume in 1 second; YPAS:Yale physical activity survey. *: Adjusted mean value based on the linear regression equation corresponding to the mean change in 6-minutes walking distance in a subject with mMRC<2, and mean IC/TLC ratio, SGRQ, C-reactive protein, Borg dyspnoea at the end of 6MWT, 6-minute walk distance, age, Body Mass Index, FEV_1 and mean baseline YPAS physical activity index. Negative values represent decline.†: Coefficients are expressed as changing meters of the six-minute walk distance per (i) each unit of the continuous covariates, or (ii) a change with respect to reference category in categorical covariates

5.1.3. HOSPITAL ADMISSIONS AND EXERCISE CAPACITY DECLINE IN PATIENTS WITH COPD

5.1.3.1. Characteristics of hospital admissions during follow-up

During follow-up, 153 (45%) patients were hospitalised (all-causes). The most frequent cause of admission during follow-up was a COPD exacerbation (52%). Table 12 (A and B) presents detailed information on the characteristics of hospitalisations during follow-up.

Table 12-A. Hospital admissions during 1.7 year follow-up of 342 COPD patients.

	All patients n=342
Any (all-cause) admission during follow-up, n (%)	153 (45)
Rate (number per year) of (all-cause) admissions during follow-up, n (%)	
0	189 (55)
>0 and ≤1	73 (21)
>1	80 (24)
Distribution of patients according to admissions and their causes, n (%)	
No admission	189 (55)
Only COPD admission(s)	77 (23)
Only non-Respiratory admission(s)	43 (13)
Mixed causes	33 (10)
Cumulative hospital stay (days), median (P25-P75) [n=153]	13 (5-28)
Time from last discharge to second evaluation (days), median (P25-P75) [n=153]	206 (103-363)

Table 12-B. Hospital admissions during 1.7 year follow-up of 342 COPD patients.

	All admissions n=376 (153 patients)	
	Cause of admission* n (%)	**Length of hospital stay (days) median (P25-P75)**
All-cause admissions	376 (100)	6 (3-10)
COPD (ICD9 490-496)	196 (52)	6 (3-9)
Other respiratory non-COPD (ICD9 460-519 except 490-496)	46 (12)	7 (4-10)
Cardiovascular (ICD9 390-459)	38 (10)	7 (3-14)
Cancer (ICD9 140-239)	28 (7)	6 (3-10)
Digestive (ICD9 520-579)	21 (6)	4 (3-8)
Genitourinary (ICD9 580-629)	17 (5)	6 (5-9)
Aftercare (ICD9 V50-V69)	7 (2)	4 (2-8)
Musculoskeletal (ICD9 710-739)	7 (2)	8 (7-8)
Infectious and parasitic diseases (001-139)	4 (1)	36 (7.5-80)
Injury and poisoning (ICD9 800-999)	3 (0.8)	8 (6-17)
Nervous system and sense organs (ICD9 320-389)	3 (0.8)	17 (2-25)
Diseases of skin (ICD9 680-709)	3 (0.8)	5 (2-13)
Diseases of the blood (ICD9 280-289)	1 (0.3)	12
Endocrine disorders (ICD9 240-279)	1 (0.3)	15
Mental disorders (ICD9 290-319)	1 (0.3)	2

*Ordered by frequency. There were no admission causes other than those included in the table.

5.1.3.2. Crude association between hospitalisations and change in 6MWD

Hospitalisations during follow-up, as well as the frequency of all-cause hospitalisations, were associated with a significantly higher decline in 6MWD in unadjusted analyses (Figure 17, Table 13). The rate of 6MWD decline was higher in patients with only-COPD admissions as compared to patients admitted for non-Respiratory causes, but this difference was not statistically significant (Figure 18, Table 13). A higher proportion of patients with only-COPD admissions experienced a clinically significant loss in the 6MWD

compared to patients with non-Respiratory admission (53% vs. 29%, p=0.040). There was no association between 6MWD decline and cumulative length of hospital stay(s) or time elapsed from last hospital discharge to the second evaluation (Table 13).

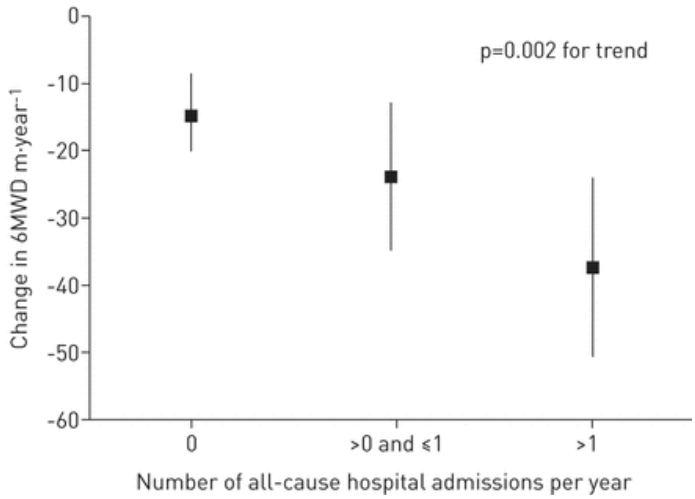


Figure 17. Mean and 95% CI annual rate of change in the 6MWD according to annual rate of hospitalizations during 1.7 year follow-up in 342 COPD patients.

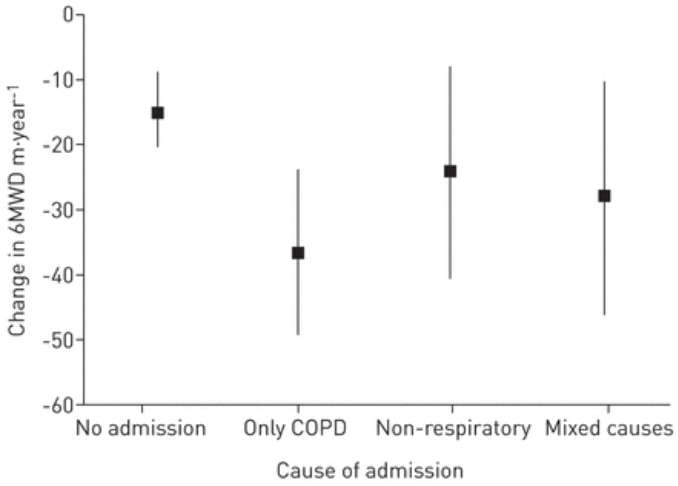


Figure 18. Mean and 95% CI annual rate of change in the 6MWD according to cause of admission(s) during 1.7 year follow-up in 342 COPD patients**.**

Table 13. Crude relationship between hospitalizations and change in 6MWD* in the 342 COPD patients followed for 1.7 years.

	Change in 6MWD		**Clinically significant loss†**		
	n=342 m±SD	**p**	**No n= 229 n (%)**	**Yes n=113 n (%)**	**p**
Any all-cause hospitalisation during follow-up					
No	-13.8 ± 35.9	0.003	142 (75)	47 (25)	0.002
Yes	-32.5 ± 51.7		87 (57)	66 (43)	
All-cause hospitalisation rate					
0 per year	-13.8 ± 32.9	0.002¶	142 (75)	47 (25)	0.001¶
>0 and ≤1 per year	-26.1 ± 51.9		46 (63)	27 (37)	
>1 per year	-38.4 ± 70.9		41 (52)	39 (48)	
Cause of hospitalisation	*[n=153]*				
Only COPD	-36.2 ± 56.2	0.236§	36 (47)	41 (53)	0.040§
Non-Respiratory	-24.2 ± 48.9		31 (71)	12 (29)	
Mixed causes	-28.2 ± 48.7		20 (61)	13 (39)	
Cumulative hospital stay (days)	*[n=153]*				
1st quartile (1 to ≤5)	-29.8 ± 37.6	0.610¶	25 (61)	16 (39)	0.682¶
2nd quartile (>5 to ≤13)	-33.1 ± 48.7		20 (51)	18 (49)	
3rd quartile (>13 to ≤28)	-29.1 ± 49.8		23 (64)	13 (36)	
4th quartile (>28)	-38.1 ± 51.5		19 (50)	19 (50)	
Time from last discharge to 2nd evaluation (days)	*[n=153]*				
1st quartile (0 to ≤103)	-36.3 ± 42.1	0.445¶	21 (52)	18 (48)	0.735¶
2nd quartile (>103 to ≤206)	-33.8 ± 48.9		23 (60)	15 (40)	
3rd quartile (>206 to ≤363)	-36.1 ± 49.4		20 (53)	18 (47)	
4th quartile (>363)	-25.8 ± 46.4		23 (60)	15 (40)	

*: 6MWD is presented both as a continuous variable (mean and SD) and according to clinically significant change, for a better understanding of the effect of hospitalizations. Each combination of hospitalisation variables and change in the 6MWD is a single unadjusted model. †: Clinically significant loss in 6MWD defined as a decline higher or equal to 35m/year (see text). ¶: P for trend §: P-value comparing "only COPD" vs "non-Respiratory". The group with "mixed causes" is only presented for descriptive purposes.

5.1.3.3. Adjusted relationship between hospitalisations and change in 6MWD

Table 14 shows that, after adjusting for age, sex, dyspnoea, BMI, RV/TLC, PaO_2 and baseline 6MWD, suffering one or more than one (all-cause) hospitalisation/year was associated with an increase in the mean annual decline in 6MWD by 7.4 and 26.1 m, respectively, as compared with patients who were not hospitalised during follow-up ($p=0.211$ and $p<0.001$, respectively). This decline was similar in the different groups of causes of admissions.

Table 14. Adjusted association between hospitalisation rate and annual change in the 6MWD in 342 COPD patients followed during 1.7 years (linear regression model), in all patients and according to cause of admission(s).

	All patients (n=342)		**Patients with "Only COPD admissions" (n=77) *vs* "No admissions" (n=189)**		**Patients with "Only non-Respiratory admissions" (n=43) *vs* "No admissions" (n=189)**	
	Coefficient† (95%CI)	**p**	**Coefficient† (95%CI)**	**p**	**Coefficient† (95%CI)**	**p**
Constant*	-7.3 (-15.8; 1.2)	0.088	-7.7 (-15.8; 0.6)	0.068	-8.5 (-16.7; -0.3)	0.043
Hospitalisation Rate:						
0 per year	*(reference)*		(*reference*)		(*reference*)	
>0 and ≤1 per year	-7.4 (-19.1; 4.3)	0.211	-13.8 (-28.2; 2.1)	0.092	-1.5 (-18.7; 15.7)	0.865
>1 per year	-26.1 (-38.6; -13.1)	<0.001	-28.0 (-45.1; -10.7)	0.002	-27.3 (-48.9; -5.6)	0.014
Significant dyspnoea (mMRC ≥2) at baseline	-17.2 (-27.8; -6.6)	0.002	-16.9 (-28.3; -5.4)	0.004	-15.3 (-26.4; -4.1)	0.008
Age at baseline (years)	-0.6 (-1.3; 0.01)	0.057	-0.6 (-1.2; 0.1)	0.089	-0.6 (-1.3; 0.1)	0.098
Sex (women)	-11.1 (-30.2; 7.9)	0.249	-8.6 (-29.1; 11.9)	0.407	-4.3 (-24.9; 16.3)	0.679
Baseline Body Mass Index (Kg/m^2)	-0.3 (-1.5; 0.9)	0.664	-0.2 (-1.4; 1.1)	0.782	-0.6 (-1.8; 0.7)	0.389
Baseline RV/TLC (%)	-0.5 (-1.0; 0.04)	0.069	-0.5 (-1.2; 0.1)	0.087	-0.4 (-0.9; 0.2)	0.223
Baseline PaO_2 (mmHg)	0.1 (-0.2; 0.4)	0.692	0.1 (-0.3; 0.4)	0.726	0.1 (-0.2; 0.5)	0.398
Baseline 6MWD (m)	-0.2 (-0.3; -0.1)	<0.001	-0.2 (-0.3; -0.1)	<0.001	-0.2 (-0.3; -0.1)	<0.001
Adjusted R^2	*0.223*		*0.229*		*0.193*	

mMRC: modified Medical Research Council dyspnoea scale; RV/TLC: residual volume/total lung capacity; PaO_2: arterial oxygen tension; 6MWD: 6-minute walk distance. *Adjusted mean value based on the linear regression equation corresponding to the mean change in 6-minutes walking distance in a subject with 0 COPD hospitalisations/year, mMRC<2, male, and mean age, Body Mass Index, RV/TLC, PaO_2 and mean baseline six-minute walk distance. Negative values represent decline. †Coefficients are expressed as changing meters of the six-minute walk distance per (i) each unit of the continuous covariates, or (ii) a change with respect to reference category in categorical covariates.

Stratification according to sex, age, BMI, daily physical activity, FEV_1 and muscle force (handgrip, MIP and MEP) did not show any difference. Sensitivity analyses (i) using the cut-off point of 26 m/yr as the clinically significant threshold of exercise capacity decline; (ii) excluding subjects who participated in any pulmonary rehabilitation programme during follow-up; and (iii) using a complete case analysis yielded very similar results (Table 15 compares main results using both complete case and imputed datasets).

Table 15. Adjusted association between hospitalisation rate and annual change in the 6MWD in 342 COPD patients followed during 1.7 years (linear regression model), using complete cases and imputed datasets.

	Complete cases (n=226)		**Multiple imputation (n=342)**	
	Coefficient† (95%CI)	**p**	**Coefficient† (95%CI)**	**p**
Constant*	-6.4 (-14.5; 1.6)	0.117	-7.3 (-15.8; 1.2)	0.088
Hospitalisation Rate:				
0 per year	(*reference*)		*(reference)*	
>0 and ≤1 per year	-13.6 (-26.7; -0.5)	0.042	-7.4 (-19.1; 4.3)	0.211
>1 per year	-34.2 (-49.3; -19.1)	<0.001	-26.1 (-38.6;-13.1)	<0.001
Significant dyspnoea (mMRC ≥2) at baseline	-15.3 (-26.6; -4.1)	0.008	-17.2 (-27.8; -6.6)	0.002
Age at baseline (years)	-0.7 (-1.4; 0.02)	0.058	-0.6 (-1.3; 0.01)	0.057
Sex (women)	-12.8 (-33.0; 6.9)	0.198	-11.1 (-30.2; 7.9)	0.249
Baseline Body Mass Index (Kg/m^2)	-0.6 (-1.8; 0.7)	0.631	-0.3 (-1.5; 0.9)	0.664
Baseline RV/TLC (%)	-0.5 (-1.0; 0.1)	0.079	-0.5 (-1.0; 0.04)	0.069
Baseline PaO_2 (mmHg)	0.1 (-0.2; 0.4)	0.586	0.1 (-0.2; 0.4)	0.692
Baseline 6MWD (m)	-0.2 (-0.3; -0.1)	<0.001	-0.2 (-0.3; -0.1)	<0.001
Adjusted R^2	*0.203*		*0.223*	

95% CI: 95% confidence interval; mMRC: modified Medical Research Council dyspnoea scale; RV/TLC: residual volume/total lung Capacity; PaO_2: arterial oxygen tension; 6MWD: 6-minute walk distance. *Adjusted mean value based on the linear regression equation corresponding to the mean change in 6-minutes walking distance in a subject with 0 COPD hospitalisations/year, mMRC<2, male, and mean age, Body Mass Index, RV/TLC, PaO_2 and mean baseline six-minute walk distance. Negative values represent decline. †Coefficients are expressed as changing meters of the six-minute walk distance per (i) each unit of the continuous covariates, or (ii) a change with respect to reference category in categorical covariates.

5.1.4. THE COMBINED EFFECT OF STATIC PULMONARY HYPERINFLATION AND HOSPITAL ADMISSIONS ON EXERCISE CAPACITY DECLINE

In the previous sections, we have reported an association between baseline static lung hyperinflation (IC/TLC) and dyspnoea and the longitudinal decline in 6MWD in COPD patients, independent of other covariates. Also, an independent relationship between hospital admissions during the course of the disease and 6MWD decline was observed. In the light of these results, and as a *post hoc* analysis, we tried to ascertain to which extent the observed effect of IC/TLC on exercise capacity decline could be mediated by hospitalisations during follow-up, as lung hyperinflation is an important risk factor for hospital admission in this group of patients [75]. To this aim, we analysed sequentially the role of dyspnoea, IC/TLC and FEV_1 on hospital admissions, and their role, independent of admissions, on 6MWD decline (Tables 16 and 17 below).

Table 16. Effect of dyspnoea, IC/TLC and FEV_1 on hospital admissions (logistic regression; outcome: hospital admission (yes/no) during follow-up).

	Model 1 OR (p-value)	**Model 2 OR (p-value)**	**Model 3 OR (p-value)**	**Model 4 OR (p-value)**	**Model 5 OR (p-value)**	**Model 6 OR (p-value)**	**Model 7 OR (p-value)**
mMRC ≥2	1.18 (0.002)	--	--	1.17 (0.004)	1.15 (0.009)	--	1.16 (0.008)
IC/TLC (%)	--	0.99 (0.040)	--	0.99 (0.087)	--	0.99 (0.517)	0.99 (0.433)
FEV_1 (% pred)	--	--	0.99 (0.014)	--	0.99 (0.079)	1.00 (0.165)	1.00 (0.436)

Table 17. Effect of dyspnoea, hyperinflation, and FEV_1, combined with the effect of hospital admissions on exercise capacity decline (linear regression; outcome 6MWD change (in m) between final and baseline).

	Model 1 Coef (p-value)	**Model 2 Coef (p-value)**	**Model 3 Coef (p-value)**	**Model 4 Coef (p-value)**	**Model 5 Coef (p-value)**	**Model 6 Coef (p-value)**	**Model 7 Coef (p-value)**
mMRC ≥2	-8.22 (0.107)	--	--	-6.76 (0.177)	-7.45 (0.154)	--	-8.27 (0.112)
IC/TLC (%)	--	0.68 (0.011)	--	0.64 (0.016)	--	0.89 (0.011)	0.92 (0.008)
FEV_1 (% pred)	--	--	0.15 (0.351)	--	0.10 (0.551)	-0.19 (0.371)	-0.26 (0.227)
Hospitalisations	-11.23 (0.006)	-15.21 (0.002)	-16.05 (0.002)	-14.12 (0.005)	-15.02 (0.003)	-15.58 (0.002)	-14.4 (0.004)

Results from previous tables, summarised graphically in the following Figure 19, show that: i) dyspnoea is the only factor independently related to hospital admissions (reflected in Figure 19 with an arrow from dyspnoea to hospital admission); ii) the loss of statistical significance of the association between IC/TLC and hospitalisations after adjusting for dyspnoea suggests that the effect of IC/TLC on hospitalisations is confounded by dyspnoea (reflected in Figure 19 as a lack of an arrow from IC/TLC to hospitalisations and an arrow from IC/TLC to dyspnoea); iii) the same occurs for FEV_1 (reflected in Figure 19 as a lack of an arrow from FEV_1 to hospitalisations and an arrow from FEV_1 to dyspnoea); iv) IC/TLC and hospital admissions are independently related to 6MWD decline (reflected in Figure 19 with an arrow from both IC/TLC and hospital admission to 6MWD decline); and v) the loss of statistical significance in the association between dyspnoea and 6MWD decline after adjusting for admissions suggests that the effect of dyspnoea on 6MWD decline is mediated by hospital admissions (reflected in Figure 19 as a lack of a direct arrow from dyspnoea to 6MWD decline).

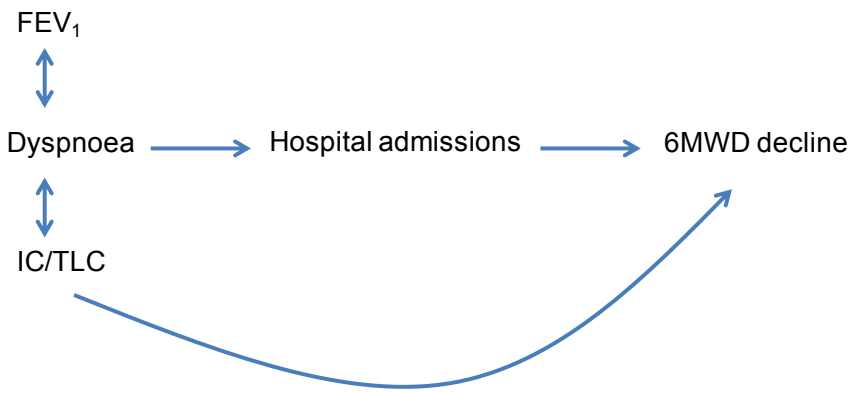


Figure 19. Direct and indirect association between dyspnoea, IC/TLC, FEV_1, hospital admission and exercise capacity decline in COPD patients. FEV_1: forced expiratory volume in 1s; IC/TLC: inspiratory capacity /total lung capacity; 6MWD: 6-minute walk distance.

5.2. EXERCISE CAPACITY AND THE VICIOUS CIRCLE OF DYSPNOEA-INACTIVITY IN PATIENTS WITH COPD

5.2.1. Characteristics of the dyspnoea-inactivity vicious circles identified in the systematic review

Figure 20 depicts the flowchart of the systematic literature search. From 13 studies included, 9 reported the dyspnoea-inactivity vicious circle in a diagram while the other 4 only reported it in text.

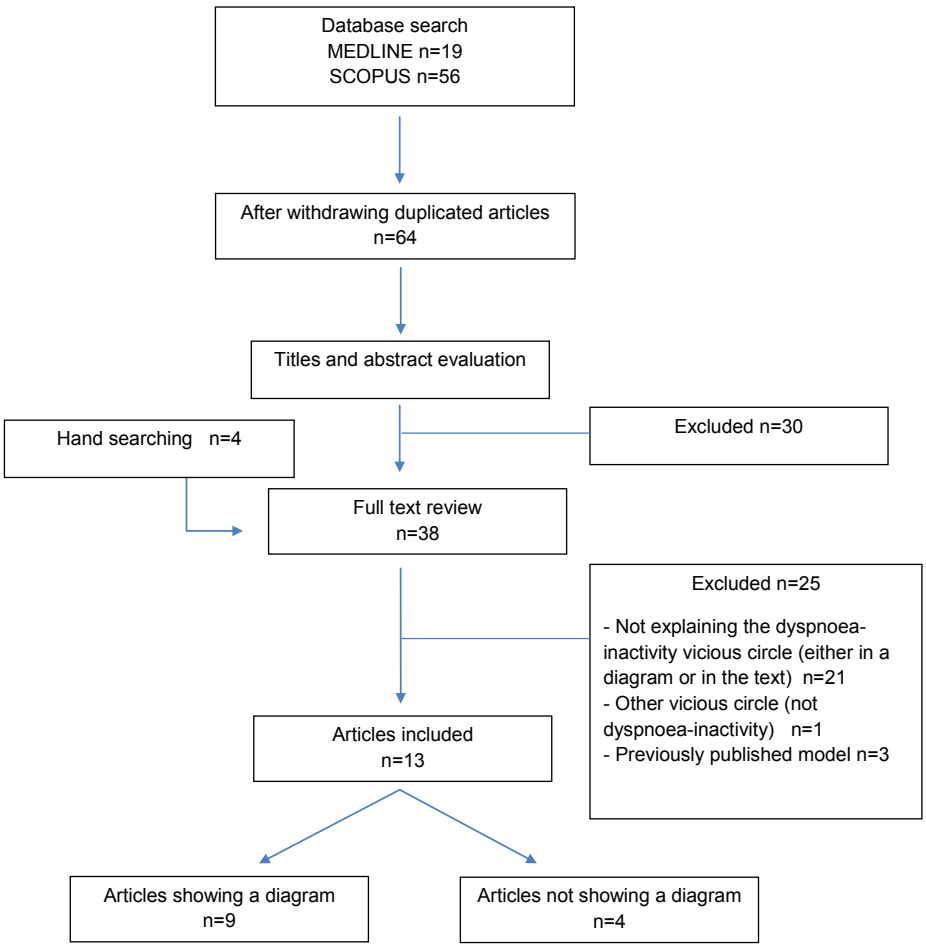


Figure 20. Flow diagram of study selection procedure.

Table 18 shows detailed information from each included article. Important differences were observed among components and order of the components in each conceptual model. Most of the models included dyspnoea as the starting variable of the vicious circle [115–117, 120, 122, 124–126], whereas airflow limitation or systemic inflammation were considered the initial factor in the few remaining models [54, 118, 119, 121, 123]. Exercise capacity was present in 6 (46%) models [54, 115, 117, 118, 123, 125] (Table 18).

Table 18. Information of 13 articles explaining the dyspnoea-inactivity vicious circle identified in the systematic review.

Reference (Chronological order)	Type of article	Dyspnoea-inactivity vicious circle explained in a diagram	Dyspnoea-inactivity vicious circle explained in the text	Factors involved in the dyspnoea-inactivity vicious circle
Cooper CB 2001, Med Sci Sport Exer.[115]	Review	Yes	Yes	Dyspnoea, exercise capacity, muscle force, ventilatory requirements.
Polkey MI 2006, Clin Med.[116]	Review	Yes	Yes	Dyspnoea, muscle force, anaerobic metabolism, hyperinflation, dyspnoea.
Cooper CB 2006, Am J Med. [54]	Review	Yes	Yes	Airflow limitation, hyperinflation, dyspnoea, physical activity, anxiety, tachypnea, hypoxemia, exercise capacity, ventilator requirements, health related quality of live.
Reardon JZ 2006, Am J Med. [117]	Review	Yes	Yes	Dyspnoea, physical activity, exercise capacity.
Decramer M 2006, Eur Respir Rev. [118]	Review	Yes	Yes	Airflow limitation, hyperinflation, dyspnoea, physical activity, exercise capacity, muscle force, COPD exacerbation, health related quality of live.
Polkey MI 2009, Eur Respir J. [119]	Editorial	No	Yes	Systemic inflammation, muscle force, anaerobic metabolism, physical activity, exacerbations.
Casaburi R 2011, Proc Am Thorac Soc. [120]	Discussion	No	Yes	Dyspnoea, physical activity, muscle force, health related quality of life.
Polkey MI 2011, Clin Med. [121]	Discussion	No	Yes	Systemic inflammation, muscle force, anaerobic metabolism, ventilator requirements, dyspnoea, physical activity.

(Continuation of Table 18)

Reference (Chronological order)	Type of article	Dyspnoea-inactivity vicious circle explained in a diagram	Dyspnoea-inactivity vicious circle explained in the text	Factors involved in the dyspnoea-inactivity vicious circle
Donaldson AV 2012, Int J Chron Obstruct Pulmon Dis. [122]	Review	Yes	Yes	Dyspnoea, physical activity, muscle force, anaerobic metabolism.
Maltais F 2013, Physician Sportmed. [123]	Review	Yes	Yes	Airflow limitation, hyperinflation, dyspnoea, physical activity, muscle force, comorbidities, exercise capacity, health related quality of live.
Thomas M 2013, Prim Care Respir J. [124]	Review	No	Yes	Dyspnoea, physical activity, deconditioning, health related quality of life.
Garcia-Aymerich J 2014, Clin Chest Med. [125]	Review	Yes	Yes	Dyspnoea, physical activity, muscle force, exercise capacity.
Corhay J 2014, Int J Chron Obstruct Pulmon Dis. [126]	Review	Yes	Yes	Dyspnoea, physical activity, depression, anxiety.

5.2.2. Validation of dyspnoea-inactivity vicious circles identified in the systematic review

Of the 342 COPD patients included in the PAC-COPD cohort, 210 patients had dyspnoea and physical activity data available at visit 1, 2 and 3 and were, therefore, included in the present analysis. Patients lost to follow-up had more comorbidities, worst quality of life and lower muscle force at baseline (Table 19).

Table 19. Comparison of baseline characteristics between participants and non-participants in the study.

	Participants (n=210)	Non-participants (n=132)	p
Anthropometric and clinical data			
Males	195 (92.9)	123 (93.2)	0.909
Age (years)	67.5 ± 82	68.6 ± 9.1	0.259
Active smokers	74 (35.2)	46 (34.9)	0.945
YPAS, Kcal/week	6056 (3345-9085)	4980 (2310-8664)	0.095
SGRQ total score (0-100)	31.2 (22.2-44.1)	37.8 (25.3-53.4)	0.007
HAD anxiety	4 (2-7)	5 (2-9)	0.390
HAD depression	3 (1-5)	4 (2-7)	0.003
Charlson index of comorbidity	2 (1-2)	2 (1-3)	0.003
mMRC dyspnoea score	2 (2-3)	2 (2-3)	0.189
Respiratory frequency	18 (16-20)	20 (16-22)	0.628
Lung function			
Postbronchod FEV_1 (% pred)	53.5 ± 16.6	50.7 ± 15.5	0.123
IC/TLC (%)	31.4 ± 0.9	30.9 ± 0.9	0.638
PaO_2 (mmHg)	74.8 ± 11.3	73.5 ± 9.4	0.253
Exercise capacity and muscle force			
6MWD (m)	445 ± 84	415 ± 101	0.077
$V_{E\ max}$, (L/min)	42.2 ± 12.7	44.9 ± 15.5	0.192
Lactic acid, (mM)	4.8 ± 2.2	4.8 ± 1.9	0.843
Handgrip muscle force (Kg)	31.4 ± 8.2	29.0 ± 8.3	0.013

Data are presented as n (%), mean±SD or median (P_{25}-P_{75}). YPAS: Yale physical activity survey; SGRQ: Saint George's respiratory questionnaire; HADS: Hospital Anxiety and Depression Scale; mMRC: modified Medical Research Council dyspnoea scale; FEV_1: forced espiratory volume in 1 second; IC/TLC: inspiratory capacity/total lung Capacity; PaO_2: arterial oxygen tension; 6MWD: 6-minute walk distance, V_{Emax}: maximum ventilation during incremental cycloergometer test.

Patients used to validate the identified conceptual models were mostly male (93%) with a mean±SD FEV_1 of 53.5±16.6 % predicted (Tables 19 and 20). At baseline, weekly energy expenditure was 6056 (3345-9085) kcal/week according to the YPAS and the majority of patients had an mMRC score of 2 or higher. Physical activity, dyspnoea, as well as other clinical and functional variables, worsened during follow-up (Table 20).

Table 20. Descriptive characteristics of the 210 COPD patients at different study time points.

	Visit 1	**Visit 2**	**Visit 3**
Anthropometric and clinical data			
Males	195 (92.9)	-	-
Age (years)	67.5 ± 82	-	-
Active smokers	74 (35.2)	-	77 (36.7)
YPAS, Kcal/week	6056 (3345-9085)	5123 (2982-8280)	5010 (3368-7358)
SGRQ total score (0-100)	31.2 (22.2-44.1)	-	27.3 (16.0-44.7)
HADS-anxiety	4 (2-7)	-	-
HADS-depression	3 (1-5)	-	-
Charlson index	2 (1-2)	-	2 (1-3)
mMRC dyspnoea score	2 (2-3)	2 (2-3)	2 (3-4)
Exacerbations rate*	-	-	0.3 ± 0.7
Respiratory frequency	18 (16-20)	-	20 (16-22)
Lung function			
Post FEV_1 (% pred)	53.5 ± 16.6	-	50.8 ± 15.8
IC/TLC(%)	31.4 ± 0.9	-	29.8 ± 0.9
PaO_2 (mmHg)	74.8 ± 11.3	-	73.7 ± 10.0
Exercise capacity and muscle force			
6MWD (m)	445 ± 84	-	412 ± 93
$V_{E\ max,}$ (L/min)	42.2 ± 12.7	-	-
Lactic acid (mM)	4.8 ± 2.2	-	-
Handgrip force (Kg)	31.4 ± 8.2	-	28.5 ± 9.1

Data are presented as n (%), mean±SD or median (P_{25}-P_{75}). YPAS: Yale physical activity survey; SGRQ: Saint George's respiratory questionnaire; HADS: Hospital Anxiety and Depression Scale; mMRC: modified Medical Research Council dyspnoea scale; FEV_1: forced espiratory volume in 1 second; IC/TLC: inspiratory capacity/total lung Capacity; PaO_2: arterial oxygen tension; 6MWD: 6-minute walk distance, $V_{E\ max}$: maximum ventilation during incremental cycloergometer test. *COPD exacerbations requiring hospitalisation between visit 1 and 3.

Original diagrams were adapted to acyclic graphs for proper validation with SEM. All original authors agreed with the adaptation. Graphs are presented in Figures 21 to 29 together with the results from the SEM analysis, which details the magnitude of each hypothesised association (standardized coefficients) as well as the goodness of fit of each theorised model to the real data. Most of the associations between variables in each conceptual model were statistically significant. However, in all cases, RMSEA values (from 0.176 to 0.352), CIF values (from 0.347 to 0.629), and *p* values of the model (all <0.05) indicated a poor fit of the model to the data (*e.g.*, the associations hypothesised in the models are not similar to matrices containing the relationships in the actual data)

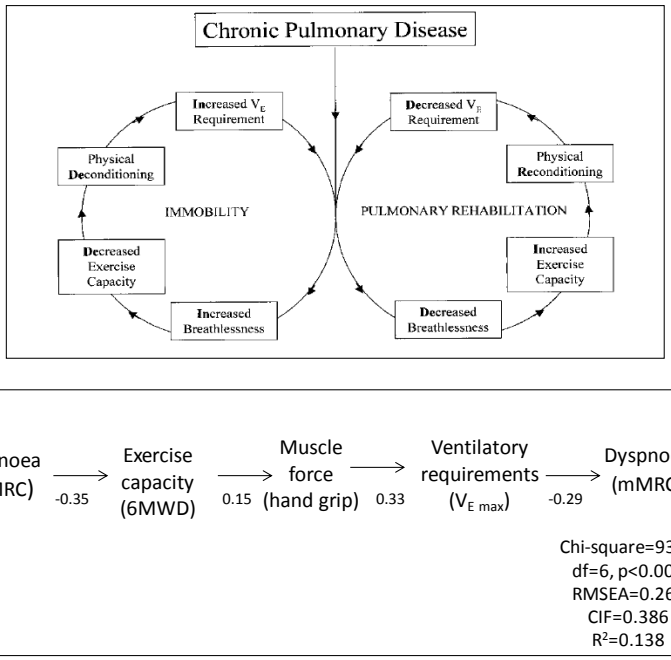
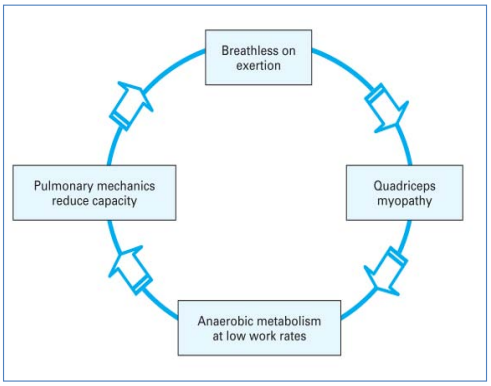


Figure 21. Validation of the conceptual model for the dyspnoea-inactivity vicious circle proposed by *Cooper* in 2001 [115]. Relationship and standardized regression coefficients between variables. mMRC: modified Medical Research Council dyspnoea scale 6MWD: 6-minute walk distance; V_{Emax}: maximum ventilation during incremental cycloergometer test.



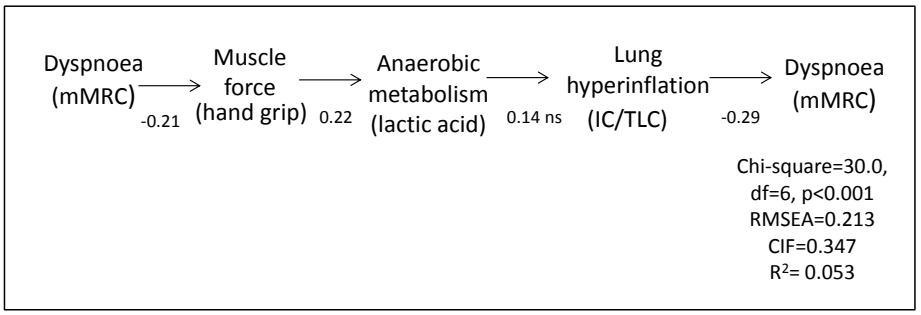
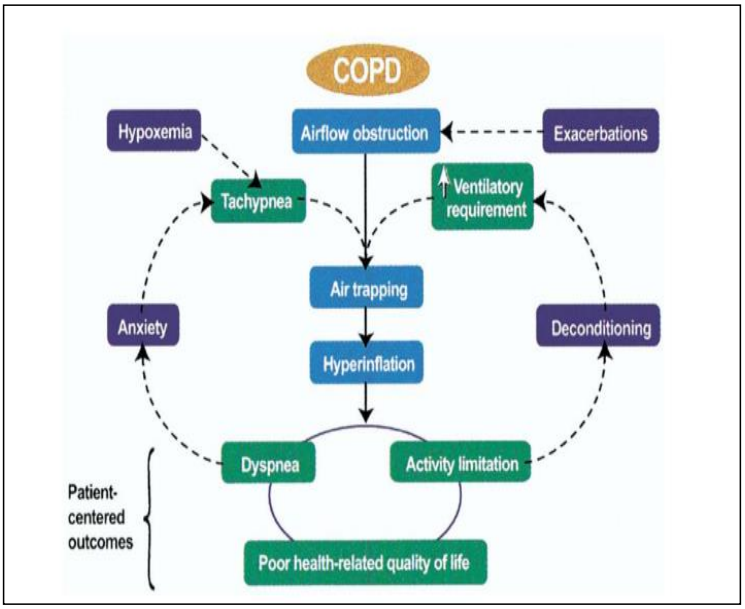


Figure 22. Validation of the conceptual model for the dyspnoea-inactivity vicious circle proposed by *Polkey et al.* in 2006 [116]. Relationship and standardized regression coefficients between variables. mMRC: modified Medical Research Council dyspnoea scale; IC/TLC: inspiratory capacity /total lung capacity; ns: non-significant association.



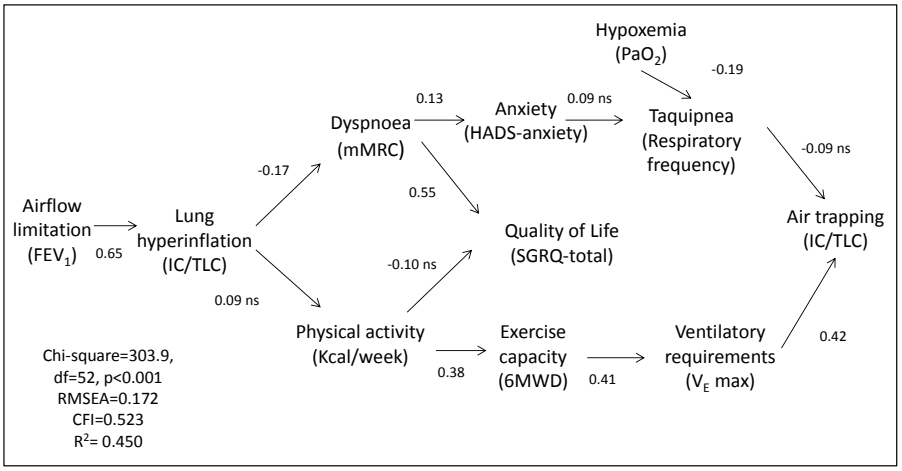
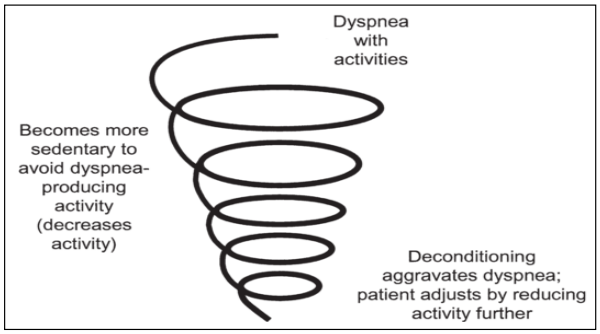


Figure 23. Validation of the conceptual model for the dyspnoea-inactivity vicious circle proposed by *Cooper* in 2006 [54]. Relationship and standardized regression coefficients between variables. FEV_1: forced expiratory volume in 1s; IC/TLC: inspiratory capacity /total lung capacity; mMRC: modified Medical Research Council dyspnoea scale; HADS: Hospital *Anxiety* and Depression Scale; PaO_2: arterial oxygen tension; SGRQ: Saint George's respiratory questionnaire; 6MWD: 6-minute walk distance; V_{Emax}: maximum ventilation during incremental cycloergometer test; ns: non-significant association.



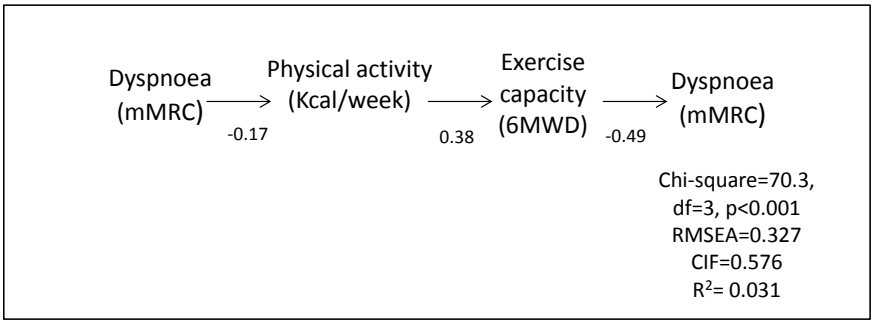
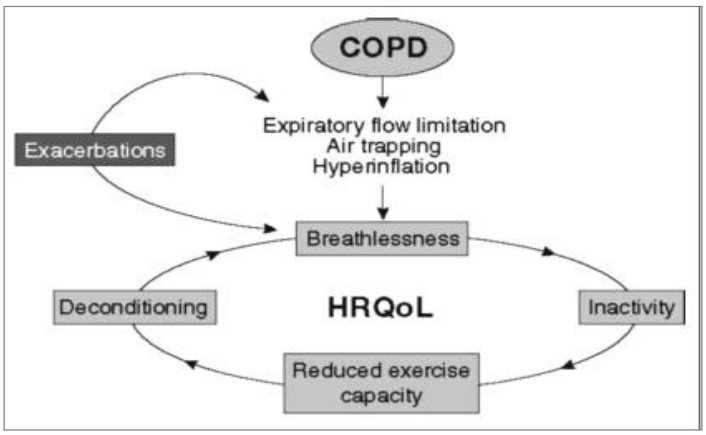


Figure 24. Validation of the conceptual model for the dyspnoea-inactivity vicious circle proposed by *Reardon et al.* in 2006 [117]. mMRC: modified Medical Research Council dyspnoea scale; 6MWD: 6-minute walk distance.



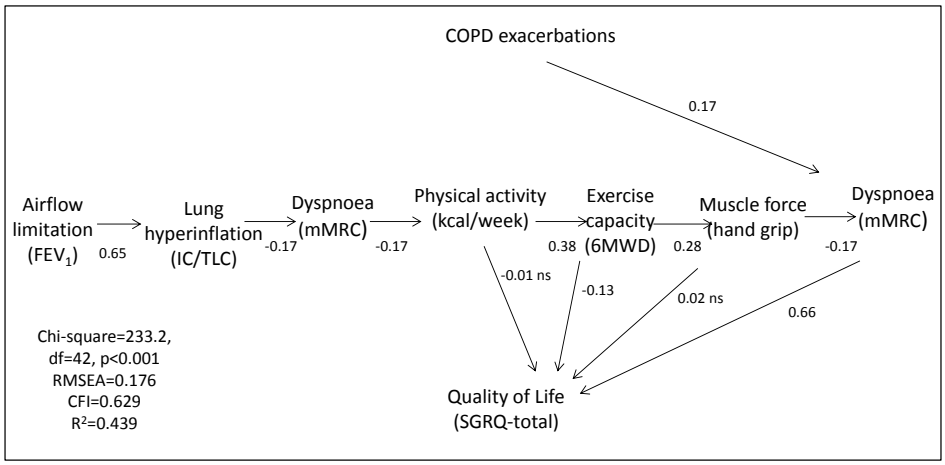
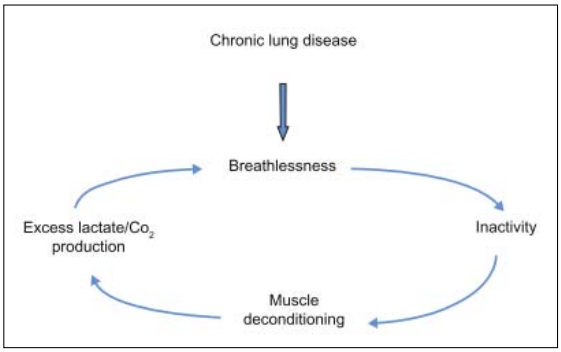


Figure 25. Validation of the conceptual model for the dyspnoea-inactivity vicious circle proposed by *Decramer* in 2006 [118]. Relationship and standardized regression coefficients between variables. FEV_1: forced expiratory volume in 1s; IC/TLC: inspiratory capacity /total lung capacity; mMRC: modified Medical Research Council dyspnoea scale; 6MWD: 6-minute walk distance; SGRQ: Saint George's respiratory questionnaire; ns: non-significant association.



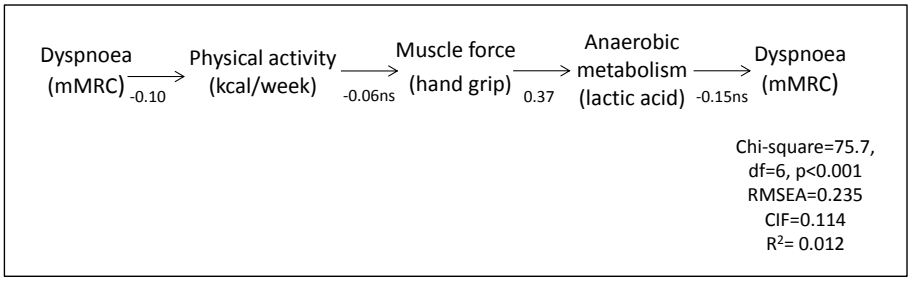
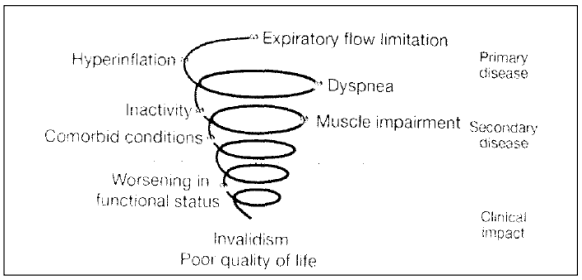


Figure 26. Validation of the conceptual model for the dyspnoea-inactivity vicious circle proposed by *Donaldson et al.* in 2012 [116]**.** Relationship and standardized regression coefficients between variables. mMRC: modified Medical Research Council dyspnoea scale; ns: non-significant association.



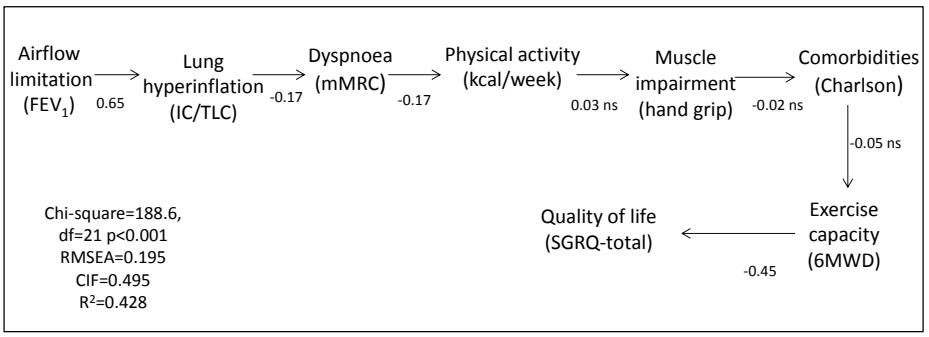
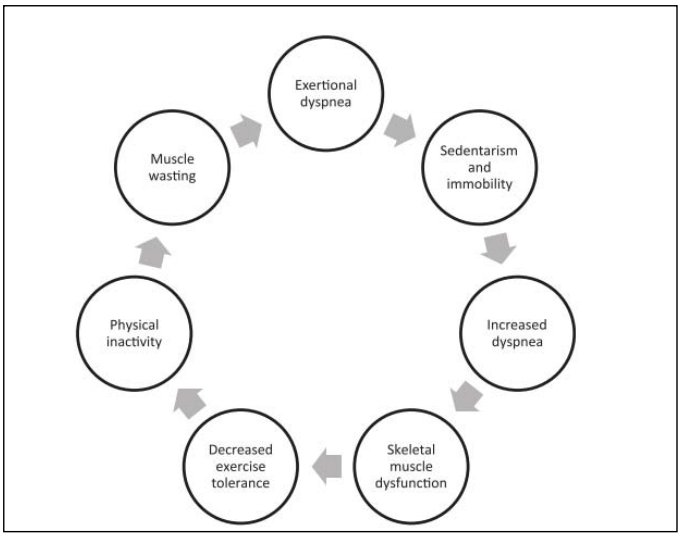


Figure 27. Validation of the conceptual model for the dyspnoea-inactivity vicious circle proposed by *Maltais.* in 2013 [123]**.** Relationship and standardized regression coefficients between variables. FEV_1: forced expiratory volume in 1s; IC/TLC: inspiratory capacity /total lung capacity; mMRC: modified Medical Research Council dyspnoea scale; 6MWD: 6-minute walk distance; SGRQ: Saint George's respiratory questionnaire; ns: non-significant association.



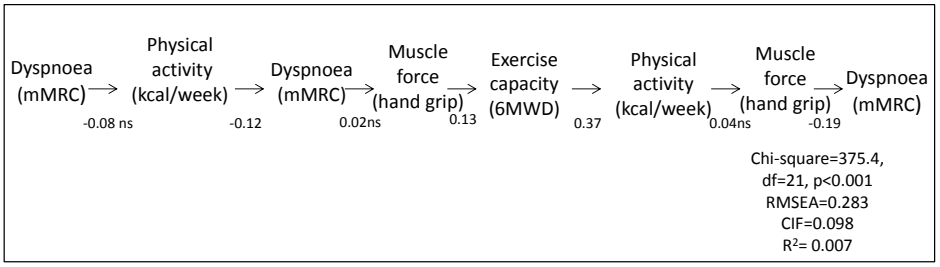


Figure 28. Validation of the conceptual model for the dyspnoea-inactivity vicious circle proposed by *Garcia-Aymerich et al.* in 2014 [125]. Relationship and standardized regression coefficients between variables. mMRC: modified Medical Research Council dyspnoea scale; 6MWD: 6-minute walk distance; ns: non-significant association.

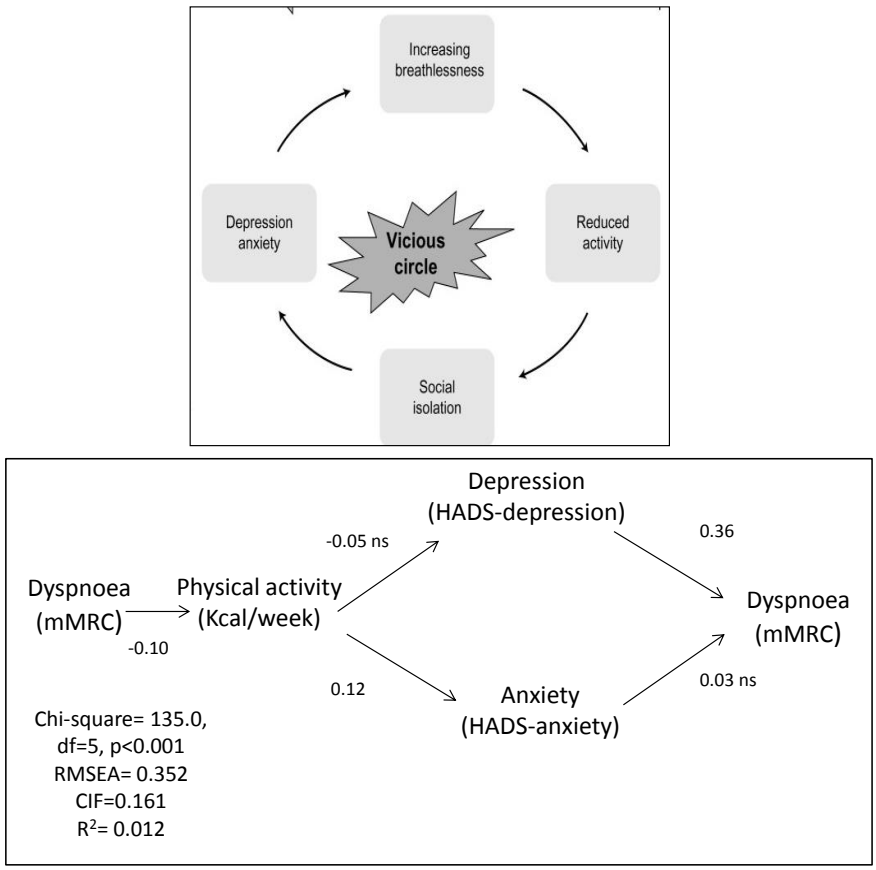


Figure 29. Validation of the conceptual model for the dyspnoea-inactivity vicious circle proposed by *Corhay et al.* in 2014 [126]. Relationship and standardized regression coefficients between variables. mMRC: modified Medical Research Council dyspnoea scale; HADS: Hospital Anxiety and Depression Scale; ns: non-significant association.

5.2.3. Proposal and validation of a comprehensive dyspnoea-inactivity vicious circle in COPD

Because none of the existing models identified in the systematic review fitted well with real data we built an alternative model based on previous ones and evidence from the literature. In this alternative model, two parallel paths were hypothesized in the disease vicious circle; one derived from airflow limitation and another from systemic inflammation (Figure 30). We speculated that airflow limitation leads to lung hyperinflation, hyperinflation to dyspnoea, dyspnoea to anxiety, anxiety to a reduction in physical inactivity, and inactivity to a limitation in exercise capacity, which finally leads to dyspnoea aggravation. From the other path, we presumed that systemic inflammation has negative effects on the peripheral muscle, which in turns leads to exercise capacity limitation, aggravating dyspnoea as well. Finally, COPD exacerbations that take place during the course of the disease affect physical activity, exercise capacity and worsen dyspnoea too. Other direct effects among some of these variables were hypothesised based on previous models and data from the literature.

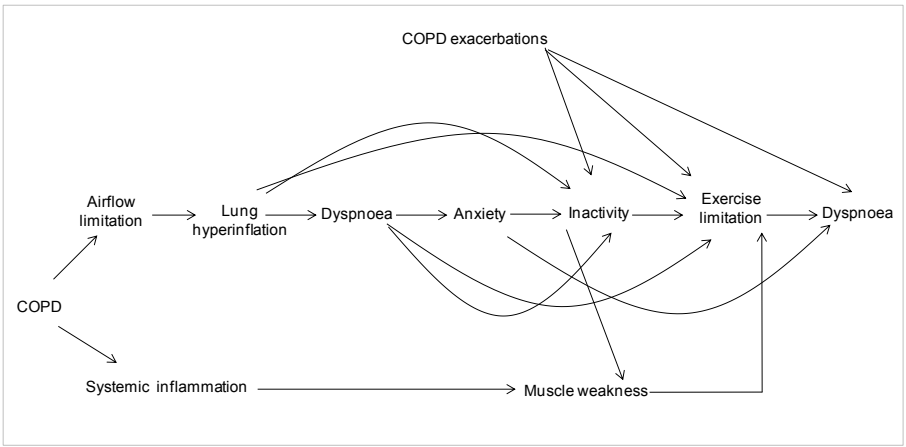


Figure 30. Hypothesized associations between variables in the dyspnoea-inactivity vicious circle.

After several SEM analyses, we kept in the model the variables with statistically significant direct effects on at least another variable in the model. Some variables such as anxiety were removed. Some direct arrows (e.g., lung hyperinflation to physical activity) were eliminated as well. Figure 31 depicts final variables kept with their direct relationships and standardised regression coefficients. The final model shows that dyspnoea deterioration is directly affected by prior exercise capacity limitation, while airflow limitation, lung hyperinflation, physical activity, muscle force and COPD exacerbations only affect dyspnoea indirectly, always mediated by effects on exercise capacity. Analysis of this model fit showed a x^2=32.7, df=18, p= 0.066, a RMSEA of 0.048 and a CIF of 0.964, indicating a good fit of the model to the data.

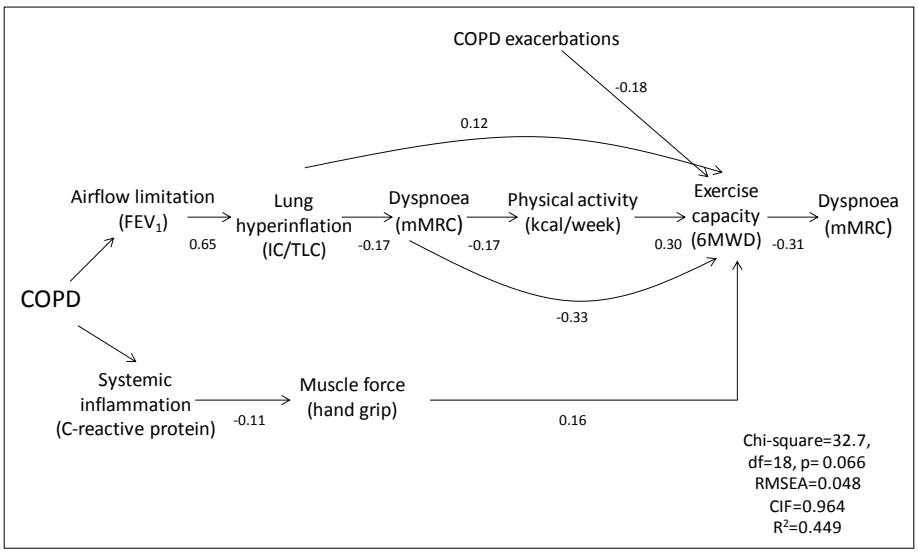


Figure 31. Relationship and standardized regression coefficients between variables in the dyspnoea-inactivity vicious circle in patients with COPD. FEV_1: forced expiratory volume in 1s; IC/TLC: inspiratory capacity /total lung capacity; mMRC: modified Medical Research Council dyspnoea scale; 6MWD: 6-minute walk distance.

6. DISCUSSION

The major findings of the research conducted in the frame of this doctoral thesis are that: i) static lung hyperinflation and dyspnoea are independent determinants of exercise capacity decline in stable COPD patients; ii) hospital admissions are related to a greater decline in exercise capacity; iii) the existing conceptual models for the dyspnoea-inactivity vicious circle described in COPD are not supported by real data from COPD patients; and iv) a new dyspnoea-inactivity vicious circle has been developed using real patients data, in which exercise capacity appears as an important contributor.

The discussion that follows includes a review of previous literature on the field as well as considerations on the relevance and implications of our findings. Further, the strengths and limitations of our research are exposed.

6.1. DETERMINANTS OF EXERCISE CAPACITY DECLINE IN PATIENTS WITH COPD

6.1.1. Previous studies and interpretation of findings

Exercise capacity declines over time and it is an important determinant of health status and prognosis in patients with COPD [31, 52, 56, 57]. To date, only few studies have investigated risk factors associated with 6MWD decline in COPD [56, 58, 59, 127]. Spruit *et al.* [59] reported in the ECLIPSE cohort that age, BMI and GOLD grades of airflow limitation were significantly related (after adjustment) to exercise capacity deterioration. In the Bergen COPD cohort, Frisk *et al.* [58] found that airflow limitation severity and self-reported physical activity predicted changes in 6MWD in a multivariate regression model. Casanova *et al.* [56], using data from the BODE cohort, found that 6MWD declined significantly only in patients with FEV_1 lower than 50% of predicted, although the association was not adjusted for potentially relevant confounders. Finally, Bu *et al.* [127] reported that the duration of COPD exacerbations had an impact on 6MWD in a small COPD sample (56 patients), but did not distinguish between exacerbations requiring hospital care and those managed in the community, and did not collect information

about admissions due to comorbidities either. None of these studies tested the role of pulmonary function tests other than forced spirometry (i.e., lung volumes), hospital admissions due to COPD and other comorbidities, systemic inflammation, cardiac function, skeletal muscle force and/or concomitant treatments, among others.

A novel finding of our research is that IC/TLC, an index of inspiratory constraint derived from static lung hyperinflation, predicts exercise capacity decline. Moreover, according to our data, the effect of IC/TLC on exercise capacity decline is independent from other important clinical and functional factors and it is not mediated by relevant events that take place during the course of the disease, such as hospital admissions. Lung hyperinflation is frequently observed in patients with COPD. Furthermore, it has potentially negative pulmonary and cardiovascular consequences [128] and it is also a powerful predictor of mortality in these patients [74]. We add to this knowledge by showing that COPD patients with lower IC/TLC experience a higher longitudinal decline in 6MWD. This is in agreement with previous cross-sectional studies demonstrating that a low IC/TLC predisposes to critical mechanical constraints on tidal volume expansion as ventilatory requirements increase, which in turn, results in lower exercise capacity [43, 129].

Secondly, we found that exertional dyspnoea, a cardinal symptom of patients with COPD [1], was also related to the decline in exercise capacity. A strong association between dyspnoea and exercise capacity has been reported in previous cross-sectional studies [130]. Also, some interventions, such as pulmonary rehabilitation, result in an improvement of both parameters [24]. Then, it is plausible that those COPD patients with worse baseline dyspnoea in our study showed a greater decline in exercise capacity during follow-up.

Finally, the results of our research identify a clear and statistically significant association of all-cause hospitalisation with exercise capacity decline in COPD. Several potential mechanisms can be conceived to explain this relationship. For instance, it is well known that both bed rest and physical

inactivity impair skeletal muscle mass and function [18, 76]. However, the fact that, in our study, neither the total duration of hospital stay, nor the time from hospital discharge to the second evaluation, were related to the annual 6MWD decline, suggest that other specific mechanisms may play a more active and important pathogenic role than simply the passive physical inactivity associated with any hospitalisation event. Likewise, all-cause hospitalisations can be markers of poor general health, hence poor prognosis. Other more specific factors may also operate in particular causes of admissions including: i*)* a burst of systemic inflammation, known to occur during exacerbations of COPD [13] or acute cardiovascular diseases [131], which can reduce quadriceps strength and exercise capacity [19]; or ii) the use of systemic corticosteroid therapy [1, 13], commonly used in case of COPD admissions, which can cause skeletal muscle dysfunction [132]. Certainly, further clinical and experimental research is needed to identify these mechanisms, since this issue is usually beyond the scope of epidemiological studies.

At variance with previous studies, we did not observe an association between baseline FEV_1 and exercise capacity decline. Two explanations can be conceived to understand this discrepancy. First, we might consider the potential role of differences in patients' characteristics among studies, given that our COPD patients walked somewhat more at baseline than those from the ECLIPSE and the BODE cohort (mean 369 m and 388 m, respectively), and had lower airflow limitation than participants in the BODE cohort (mean FEV_1=39% predicted). This fact could have led to the detection of different determinants of exercise capacity decline. In the second place, and specially from a methodological point of view, the fact that previous studies did not consider patients lost to follow up in the analysis could also be responsible for the different results. Between 16% and 45% of patients were lost to follow-up in these previous studies, and they were not included in the analysis. Because patients lost to follow-up in longitudinal studies usually have poorer health status and lower FEV_1 values (as also observed in our PAC-COPD cohort), the fact of not including them in the analysis may lead to biased results (usually called survival bias) [114]. Among the several statistical techniques to

deal with survival bias, we used multiple imputation [100]. To test the hypothesis that lack of consideration of survival bias in previous studies may have been responsible of the differences between theirs and our results, we performed a *post-hoc* analysis, comparing results obtained with multiple imputation (our main approach to reduce bias) with results obtained with a complete case approach (previous' studies approach). Results show a linear relationship between FEV_1 and 6MWD decline only with the complete case approach, suggesting that this approach results in a *spurious* association between FEV_1 and 6MWD decline. Therefore, consideration of patients lost to follow-up in longitudinal analyses using appropriate statistical techniques not only prevents missing relevant information, but, most importantly, reduces bias which increases the validity of the estimates [101].

Finally, at difference with Spruit *et al.* [59], BMI did not play a role in 6MWD annual decline in our study patients. This may be partly due to the small variability in BMI and the low prevalence of undernourishment in our COPD study group, preventing us to detect possible association or interactions with exercise capacity decline.

6.1.2. Clinical and research implications

Timed walking tests, and specially 6MWT, have been extensively used in the clinical evaluation of patients with COPD, mainly because of their simplicity, reliability and safety. At present, it is recognized that 6MWT adds useful information for the clinical staging of patients (e.g., the BODE index [5]). Moreover, longitudinal changes in the 6MWD are strong predictors of mortality [31, 52, 57]. It is therefore important to identify factors associated with this decline in exercise capacity in order to better tailor potential therapeutic interventions, such as pulmonary rehabilitation, which can modify this course.

National and international COPD guidelines highlight that any symptomatic or exercise-limited individual with a chronic respiratory disease, such as COPD, could be referred to a pulmonary rehabilitation programme [1, 3, 7]. However, in real life, such programmes are not accessible to many COPD patients from

around the world due to the cost-constraint situation in many healthcare systems. In this sense, the 2013 ATS/ERS Task Force statement on pulmonary rehabilitation suggests that the identification of key indicators for pulmonary rehabilitation is a priority in COPD research [24].

Our current analyses throw some light on this question and show that severe dyspnoea and IC/TLC, because of their strong and independent association with exercise capacity decline, could be used as indicators to prioritise candidates for pulmonary rehabilitation. Also, our research demonstrates that hospital admissions may accelerate the decline in exercise capacity in these patients [133], suggesting that patients admitted to hospital during the course of their disease are also potential candidates to benefit the most from pulmonary rehabilitation. In fact, pulmonary rehabilitation programs starting within a few days of hospital admission, or immediately after discharge, have been shown to produce clinically meaningful improvements in exercise capacity and quadriceps strength in COPD patients [134]. In addition, a meta-analysis of randomized controlled trials concluded that post-exacerbation rehabilitation can reduce hospital re-readmissions and mortality in COPD patients [69]. Thus, our data complement and extend these previous observations and support the need for pulmonary rehabilitation in COPD patients during or immediately after hospitalisation. The high proportion (56%) of patients with a clinically relevant loss of exercise capacity among those admitted only for COPD-related causes as compared to other conditions, makes COPD admission a highly specific target for such interventions. Unfortunately, only a small proportion (5%) of our hospitalised COPD patients were enrolled in pulmonary rehabilitation programmes, so we were not able to explore the potential effectiveness of such programmes in our study population.

Besides, our results may help to identify those COPD patients who could benefit most from treatments that enable to increase tidal volume during activities, including some drugs (e.g., long-acting β2-agonists) and eventually lung volume reduction strategies, thus reducing exertional dyspnoea and interrupting the vicious circle of worsening exercise capacity [135, 136].

Finally, all these potential implications of our research would require further clinical trials to specifically ascertain whether patients with the previously mentioned characteristics are the ones who would get the most benefit from such pharmacologic and non-pharmacologic therapeutic interventions.

6.2. EXERCISE CAPACITY AND THE VICIOUS CIRCLE OF DYSPNOEA-INACTIVITY IN PATIENTS WITH COPD

6.2.1. Previous studies

COPD can be viewed as a vicious circle of disabling symptoms that leads to physical inactivity, deconditioning, and worsening symptoms. Although the concept has been used for a long time [137], Cooper was the first one to depict this idea in a diagram in 2001 [115]. Since then, many other different conceptual models have emerged in the scientific literature, according to our systematic review [54, 115–126]. Surprisingly, although authors from each model intended to represent the same idea, quite important differences are observed among them; most of the conceptual models have divergent components and even when the same components are considered the order of events is usually inconsistent.

To our knowledge, none of the identified conceptual models have been previously validated. Interestingly, the results of our study suggest that none of these models properly address the dyspnoea-inactivity vicious circle in COPD. In particular, we could not reproduce some of the hypothesised associations using repeated measurements over time in a COPD cohort. Also, goodness of fit was poor in all tested models according to different fit indices, indicating a weak representation of the underlying theory (the dyspnoea-inactivity vicious circle). Therefore, we propose a new conceptual model for the dyspnoea-inactivity vicious circle in COPD, based on previously published literature on this topic, which seems more comprehensive and valid than the current ones.

At variance with most of previous conceptual models, which usually depicted the concept in only one pathway [115–118, 122, 123, 125, 126], our results indicate that two parallel paths are involved in the disease vicious circle: one derived from airflow limitation and the other from the systemic inflammation, usually observed in COPD patients. This observation is consistent with the current definition of the disease [1]. However, although the role of systemic inflammation in the vicious circle has been discussed before [119, 121] it is not present in any of the previous published diagrams. Ignoring this variable in earlier models might partly explain their observed lack of validity. Also, COPD exacerbations, an important marker for disease progression [16, 18, 133], was rarely considered in earlier works [54, 118] and their inclusion could have improved model fit as well. Figure 32 highlights in blue the main additions to previous research of our proposed conceptual model for the dyspnoea-inactivity vicious circle in COPD.

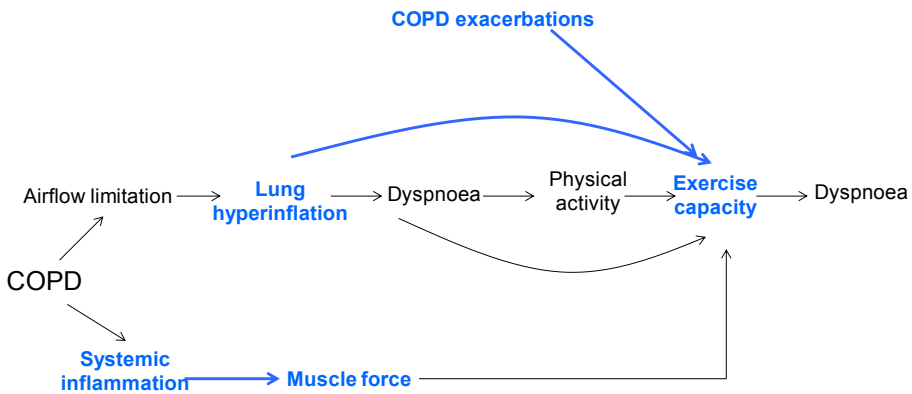


Figure 32. Relationship between variables in our conceptual model for the dyspnoea-inactivity vicious circle in patients with COPD. Main differences from previous models are highlighted in blue.

6.2.2. Interpretation of findings

The new conceptual model for the dyspnoea-inactivity vicious circle in COPD that we propose agrees with current pathophysiological knowledge in this disease. Progressive expiratory airflow limitation, the pathophysiological hallmark of COPD, leads to an increase in resting lung volumes (known as lung hyperinflation). The increase in resting lung volumes limits the ability to extend ventilation in response to the increasing metabolic demands of exertion [138]. As a result of this, activities such as walking lead to dynamic hyperinflation in many COPD patients [60], which importantly contributes to the development of a shallow breathing pattern and the rise of dyspnoea [43, 46]. Therefore, COPD patients often ratchet down their physical activity to reduce the discomfort of symptoms. Then, the reduction in daily activity levels from adopting a more sedentary lifestyle, in turn, deteriorates their exercise capacity, thrusting the patient into a vicious circle leading to further dyspnoea. In parallel, the chronic systemic inflammation that is linked to COPD induces muscle dysfunction [139]. Supporting this contention is the inverse relation observed between systemic levels of some pro-inflammatory cytokines and limb muscle mass [140] and strength [19] in these patients. Although the peripheral muscle dysfunction in COPD is related to diverse pathophysiological changes in the skeletal muscle, systemic inflammation could have a role [139] and increase the susceptibility to muscular fatigue, and an early termination of exercise [49], leading again to an increase in the perception of dyspnoea. Finally, COPD exacerbations also promote the reduction in exercise performance [133], accelerating the path of this vicious circle.

6.2.3. Clinical and research implications

The results of the present study should be taken into account for further research, specifically, to study the potential effects of drug and non-drug treatments to stop or delay the disease vicious circle in COPD. A number of strategies could play a part in breaking this circle. First, bronchodilators, a treatment that improves expiratory flow limitation and decreases pulmonary constraints, might interrupt the vicious circle of faster breathing and activity

avoidance, as lung hyperinflation is closely associated with patient-reported symptoms like dyspnoea [42]. In fact, recent studies have shown that treatment with long-acting bronchodilators provide significant improvements in lung hyperinflation, and that physical activity measured by a multisensory accelerometer can be significantly increased [141]. Second, pulmonary rehabilitation has proven effective to ameliorate dyspnoea and exercise capacity, two key variables in the dyspnoea-inactivity vicious circle. Also, muscle dysfunction can be improved, in part, and hospital admissions can be reduced with pulmonary rehabilitation as well [24]. Finally, preventive therapeutic interventions, such as smoking cessation, influenza vaccination and physical activity counselling, may reduce lung and systemic inflammation and risk of COPD exacerbations, thus improving the natural history of COPD [1].

Logically, further research is needed to validate our conceptual model for the dyspnoea-inactivity vicious circle in other COPD population different to that included in the PAC-COPD project.

6.3. STRENGHS AND LIMITATIONS

The large sample size, the careful phenotypic characterization of participants [90], the relatively long period of follow-up with availability of repeated measurements, and the novelty of the hypotheses investigated are clear strengths of the research included in this doctoral thesis. In addition to this, we applied advanced epidemiological and statistical methods to properly address our objectives: i) we used multiple imputations to account for selective attrition and missing values, as missing data could have introduced bias in our estimates (although it was not possible for SEM since it has not been implemented yet) [114]; ii) we conducted several sensitivity analyses; iii) we followed a rigorous systematic review methodology and used a prespecified protocol to identify previously published models for the dyspnoea-inactivity vicious circle; and iv) SEM was the method of choice to validate all existing models for the dyspnoea-inactivity vicious circle, which

provides an extensive insight into the complex relationship between variables involved in a underlying theory.

Some limitations of our study should also be noted and further discussed. First, since patients were recruited at their first COPD hospitalisation they may not represent the COPD population at large. Also, even though the PAC-COPD study had no exclusion criteria in relation to sex, few women were included reflecting the current prevalence of COPD by sex in our geographical area, so we cannot generalise the results to both sexes. Likewise, we do not have information on quadriceps strength, which is a strong correlate of exercise capacity in COPD. Instead, we did test hand-grip strength as well as respiratory muscle force. Thus, considering that both upper and lower muscle function can be impaired in COPD patients [49], we believe that any residual confounding effect should be relatively small.

7. CONCLUSIONS

From the research conducted in the course of this doctoral thesis, we can conclude that:

1) IC/TLC, a marker of ventilator constraint due to static lung hyperinflation, is an independent determinant of exercise capacity decline in patients with COPD.

2) Dyspnoea is an independent determinant of exercise capacity decline in patients with COPD. Its effect is partly mediated by hospital admissions.

3) Hospital admissions of any cause during the course of the disease are independently related to exercise capacity decline in patients with COPD.

4) Existing conceptual models for the dyspnoea-inactivity vicious circle are not supported by analysis with real patients' data.

5) A new conceptual models for the dyspnoea-inactivity vicious circle including two paths (one from airflow limitation and one from systemic inflammation) has been validated with real patients' data and shows that exercise capacity has a central role in the process.

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ANNEX I

Protocol for the systematic review of articles describing the vicious circle of dyspnoea-inactivity in COPD

PROTOCOL FOR THE SYSTEMATIC REVIEW OF ARTICLES DESCRIBING THE VICIOUS CIRCLE OF DYSPNOEA-INACTIVITY IN COPD

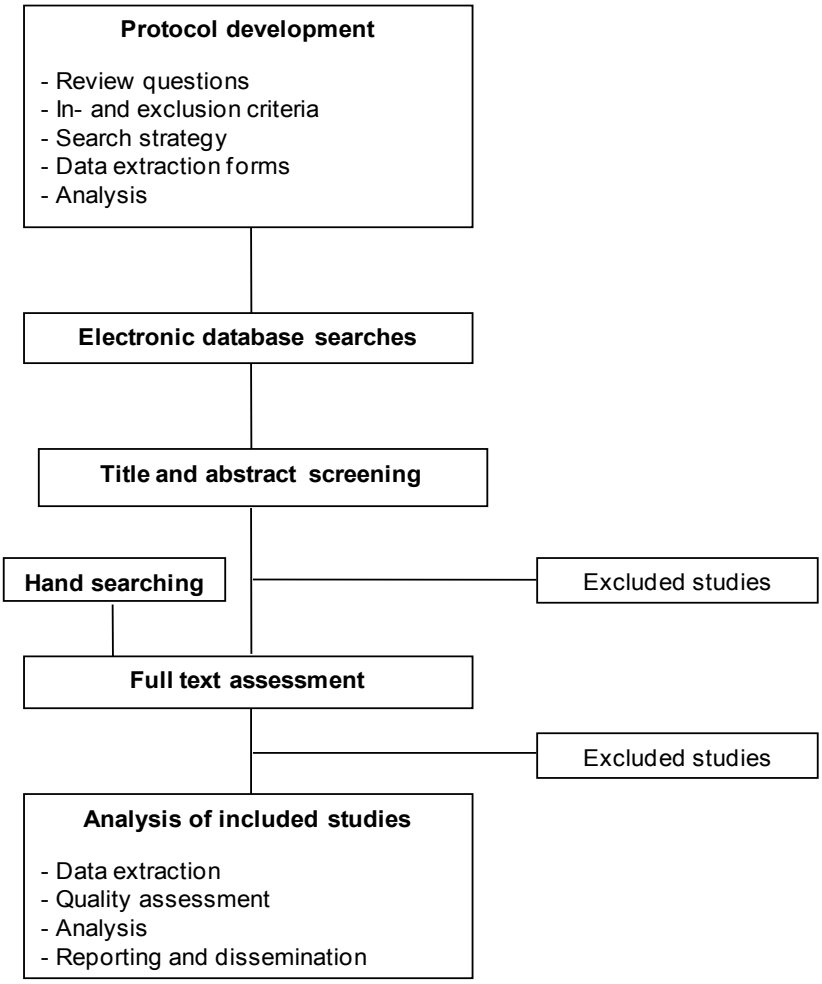
1. BACKGROUND

A disease vicious circle theory of symptom-induced inactivity has been put forward to explain the clinical course of patients with chronic obstructive pulmonary disease (COPD). Several conceptual models describing this notion have arisen in the past years. Interestingly, discrepancies are observed among them.

We aim to conduct a systematic review to identify previously published conceptual models for the dyspnoea-inactivity vicious circle in COPD and validate them in search of the most comprehensive model.

2. METHODS

We will follow standard systematic review methodology following handbooks of the Centre for Reviews and Dissemination (York, UK) and the Cochrane Collaboration. The figure shows the steps we will follow for the present review and the protocol below provides details on each step:



Main objective

Identify those articles in which the dyspnoea-inactivity vicious circle in COPD is described.

Inclusion criteria:

We will include articles fulfilling the following criteria:

- Population: Patients with COPD.
- Content: Studies that discuss or explain the dyspnoea-inactivity vicious circle either in a diagram or in the text.

Exclusion criteria:

- Other population than COPD.
- Other vicious circle than dyspnoea-inactivity.

- Articles containing previously published models (ex. repeated diagrams)
- No date restrictions imposed.
- No language restrictions imposed.

Databases
Pubmed/Medline and SCOPUS.

Strategy of search

(COPD OR “chronic lung disease” OR “chronic obstructive lung disease” OR “chronic bronchitis” OR emphysema)

AND

(“cycle decline” OR “vicious spiral” OR “downward spiral” OR “downward adjustment” OR “vicious cycle” OR “clinical path” OR “disease spiral” OR “circle decline” OR “vicious circle”)

AND

(dyspnea OR dyspnoea OR “shortness of breath” OR “breath shortness” OR “breath shortnesses” OR breathlessness OR breathlessnesses)

AND

(“physical activity” OR functioning OR function OR “motor activity” OR “locomotor activity” OR “chronic limitation of activity” OR “limitation of activity” OR “activity limitation” OR “sedentary lifestyle” OR “physical exertion” OR “physical effort” OR “activities of daily living” OR “daily living activities” OR “daily living activity”)

Study selection

- Abstracts and titles screening: The title and abstract of every citation retrieved by the database searches will be scrutinized independently by 2 researchers (MAR, EGS). We will order all articles that are deemed potentially eligible by at least one member of the consortium. Decisions of the reviewers will be recorded (for example, 0=exclude; 1=order full text; 2=related study (e.g. reviews). Do not order but may be useful reference) in the screening file. If the Abstract is not clear enough on the eligibility criteria or does not contain the necessary information, reviewers will be conservative and will order full text.
- Full text screening: Two researchers will then independently evaluate the retrieved full texts and make a decision on inclusion or exclusion according to the predefined selection criteria. They will record their

decision about in- or exclusion and will record the reason if the paper is decided to be excluded. Any disagreements will be resolved by consensus with close attention to the inclusion/exclusion criteria. In case of persistent disagreement a third member (JGA) will decide upon in- an exclusion.

Dealing with duplication

Multiple papers may be published for a number of reasons including translations, results at different follow-up period or reporting of different outcomes.

Reporting study selection

We will use a flow chart to describe the study selection process according to the PRISMA STATEMENT (http://www.prisma-statement.org/) diagram.

Pilot the study selection process

Initially, members of the consortium will pilot the selection process by applying the inclusion and exclusion criteria to a sample of 5 randomly selected papers. Inclusion and exclusion criteria will be refined and clarified.

Management of references

Screening form for title and abstract assessment process

Reviewer:……

1st Author	Year	COPD population (0:no/1:yes)	Mention the the dyspnoea-inactivity vicious circle (0:no/1:yes)	Order for full text (0:no/1:yes/2:related study)

Screening form for full text assessment process

Reviewer:……

1st Author	Year	COPD population (0:no/1:yes)	Dyspnoea-inactivity vicious circle explained in a diagram (0:no/1:yes)	Dyspnoea-inactivity vicious circle explained in the text (0:no/1:yes)	Included (0:no/1:yes/ 2:related study)	Reason for exclusion*

*1: Not COPD patient group; 2: Does not mention dyspnoea-inactivity vicious circle either in a diagram or a the text; 3: Other (specify)

Data extraction strategy

Data extraction from study reports will be performed independently by 2 reviewers (MAR and EGS). A data collection form adapted for this review will be used to recollect the data. The form will be tested by the reviewers to identify if it is confusing or incomplete. The data form could be modified after consensus between the reviewers.

The following information will be extracted from each included article: (i) bibliographic details such as first author, year, journal, and aim of the article; (ii) type of article; (iii) figure with a diagram or a conceptual model explaining the dyspnoea-inactivity vicious circle; (iv) variables involved in the dyspnoea-inactivity vicious circle explained in the body text of the manuscript.

The reviewers will extract the information from the report following the data extraction form criteria. The information must be explicit and detailed (using 'not reported' or 'unclear' if is necessary), the original information must write in quotes. In case of the reviews were unable to extract the whole information from the report they would contact with study authors.

The reviewers will share the information at the end of the data extraction process. Any disagreements will be resolved by consensus with close attention to the data extraction form. In case of persistent disagreement, a third member of the consortium will resolve it.

Data extraction form:

Reviewer (Surname, Name):

a. Identifying information

1st author (Surname, Name)	
Year	
Journal	
Aim of the article	

b. Type of article (tick with a "x")

Discussion article	
Other (specify)	

c. Diagram/conceptual model of dyspnoea-inactivity vicious circle (tick with a "x"):

Yes	
No	

If "yes", paste below the original diagram/conceptual model identified:

d. List of variables identified in the body text explaining the dyspnoea-inactivity vicious circle:

Variables indentified

Methods of analysis and synthesis

A structural equation model will be build for each of the conceptual models identified in the databases, with longitudinal data of patients from the PAC-COPD cohort. To allow comparison between path coefficients, standardized coefficients will be used. To test model fit the following criteria will be considered: i) low x^2 relative to degrees of freedom with a insignificant p value ($p>0.05$), which indicates that a non-significant amount of variance in the data remains unexplained; ii) the root mean square error of approximation (RMSEA), which assesses how well the model reaches the data by determining the lack of fit of the model to the covariance matrix (a RMSEA less than 0.07 is an acceptable threshold level and values less than 0.03 represent excellent fit); and iii) the comparative fit index (CFI) that analyses the association between all measured variables (a CFI equal or higher than 0.95 is presently recognised as indicative of good fit). All analyses were performed with a statistical software package (Stata, version 12.1; Stata Corp LP; College Station, TX).

Dealing with interpretation of information

In order to deal with interpretation of information, we will contact the corresponding authors of manuscripts in which a diagram for the vicious circle of dyspnoea-inactivity is shown to know whether they agree with our adaptation of the published model.