Measure and effects of physical activity in patients with Chronic Obstructive Pulmonary Disease (COPD)

Doctoral Program in Physical Activity and Sport Science

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Barcelona, 23 September 2015

Universitat Ramon Llull

C.I.F. G: 59069740 Universitat Ramon Lull Fundació Privada. Rgtre. Fund. Generalitat de Catalunya núm. 472 (28-02-90)

TESI DOCTORAL

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ACKNOWLEDGEMENTS

Para empezar, quiero dar las gracias abiertamente a todas las personas que han conformado y conforman el CREAL porque desde que llegué no he recibido otra cosa que apoyo, comprensión y cariño. En pocos días, el CREAL pasó de ser un lugar nuevo e imponente al más familiar y estimulante lugar en el que podría haber trabajado. Gran parte de este sentimiento de acogida es gracias a los compañeros del PAC-EPOC, pero no hubiera sido lo mismo sin mis compañeros de sala, siempre haciendo suyas las dudas o retos de los demás, el grupo de gestoras, un grupo cariñoso como pocos, y mi directora de tesis, por haber apostado por mí.

Del grupo PAC-EPOC, mis sinceras gracias a Ignasi por medir la importancia de las cosas con "seny", su entrega y su buen humor que comparte y contagia a todo los que le rodean. A Jordi de Batlle por ser mi ejemplo como doctorando y una de las personas con las que es más fácil trabajar. A Marta Benet, la guardiana de los datos, por su seguridad en sí misma, rapidez trabajando y por mantener bajo un perfecto control cualquier dato necesitado. A Josep Maria Antó, curioso incansable, de espíritu crítico y gran dialéctica, por elevar el nivel de cualquier disertación, gracias al ejercicio de una reflexión epistemológica continua.

En mi sala de trabajo, cualquier tema de conversación es una fiesta a la que todo el mundo está invitado. Especialmente gracias a Glòria por brindarme su amistad desde el primer instante, preocuparse de forma sincera por mí y conseguir distraerme siempre que lo necesité. Gracias a Esther Gracia por siempre encontrar tiempo para inspirarme y muy especialmente por tener la paciencia de ayudarme a programar mi primera función para extraer los episodios de actividad física. Gracias a Claudio por ser un inconformista y mostrarme que uno hace su camino. Gracias a Mireia por compartir conmigo su pragmatismo, sentido común y entusiasmo. Gracias a Maribel por escucharme pacientemente siempre. No podría olvidarme de los técnicos como Jaume Matamala, grandísima persona y compañero de trabajo, por recorrer conmigo Barcelona entera, uno o dos sábados al mes, comprobando que los puntos de muestreo del estudio TAPAS fueran apropiados. Asimismo, gracias a Albert, Tania y Ariadna por no desfallecer y conseguir preguntar, reclutar y entrevistar al número necesario de participantes (18000,1600, 800, respectivamente).

Mención aparte merece David Martínez, pobre, no sabía donde había ido a parar. Siempre dispuesto a ayudar y a explicar el concepto más complicado de la manera más pragmática y sencilla posible. Y así, casi sin darme cuenta y por las muchas veces que acudí a él (perdón!!!), se convirtió en mi persona de confianza, un gran amigo y compañero de trabajo. Gracias a él, he aprendido todo lo que se de R y me he atrevido a realizar análisis tan complicados.

Al grupo de gestoras (G. Punyet, G. Perelló, I. Molina, M. Ferrer), siempre atendiendo con empatía las necesidades siempre apremiantes de un grupo muy demandante y no siempre paciente. Gracias especialmente a Gema Punyet por ser tan fan de los doctorandos y reconocer de forma genuina y contextualizada la importancia de nuestros esfuerzos por cambiar la realidad que rodea a las familias, amigos y sociedad.

Gracias también a Jordi Sunyer, Michael Jerrett, Audrey de Nazelle y especialmente a Mark Nieuwenhuijsen, grandes investigadores que me han hecho descubrir otras ramas de la epidemiología.

Gracias a Miriam por aceptarme en su grupo de investigación, por pensar en mí cuando llegó la oferta del CREAL, hacer de puente con la universidad y estar siempre que la he necesitado.

Judith, gracias por enseñarme y guiarme por el mundo de la epidemiología y especialmente por haberme apoyado siempre. Gracias a ti, mi doctorado ha sido la experiencia más intensa, comprometida y enriquecedora de mi vida. Me faltan palabras para poder expresar lo agradecido que te estoy. Espero algún día poder corresponder a todo lo que lo que tú me has dado.

No podría terminar sin dar gracias de corazón a mis amigos, por entender y apoyar mi pasión por la investigación, y a mi familia, que siempre me ha animado y demostrado que con sacrificio todo llega, "más vale el que quiere que el que puede". Gracias yaya por preocuparte de si me gusta lo que hago y ser un ejemplo de carácter y fuerza. Gracias a mi hermano por dejarme que le ayudara con la tesina y por ser tan inocente y genuino. Gracias a mi madre por creer en mí y hacerme sentir capaz de lo más osado.

A Ariadna por ser más motivada que nadie y divertirse con todos y cada uno de los desafíos, pero sobretodo por soportarme y ayudarme durante el último pero no pequeño empujón.

A todos, muchas gracias.

ABSTRACT

BACKGROUND AND OBJECTIVES

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of worldwide mortality and disability. Physical activity is one of the few modifiable factors that decelerate COPD evolution. Nonetheless, the dose and characteristics of physical activity responsible for the deceleration are still unknown. In consequence, the aims of this thesis are to move forward and refine the methodology and instruments to evaluate the physical activity of COPD patients, go in depth in the knowledge about the characteristics and the pattern of their physical activity, and determine which physical activity characteristics improve the prognosis of COPD patients.

METHODS

177 patients with stable COPD selected from 8 hospitals in Spain have participated (94% male, mean±SD age 71±8 years, forced expiratory volume in 1 s 52±16% predicted and body mass index 29±5 $kg{\cdot}m^{-2}$). Physical activity was measured with an accelerometer (SenseWear® Pro2 Armband) and with a questionnaire (Yale Physical Activity Survey, YPAS). The sociodemographic (age, sex, civil status, educational level, socioeconomic status, employment status, and tobacco habit) and clinical variables (airflow limitation, lung hyperinflation, dyspnoea, gas exchange, local and systemic inflammation, body composition, comorbidities, quality of life, and exercise capacity), were obtained using validated tools and following international standards. Information about the evolution of the disease (Hospital Admissions and Mortality) was obtained from government registries.

RESULTS

(Objective 1) The YPAS is a valid tool for the detection of COPD patients' inactivity [the area under the ROC curve is 0.71 (95% CI: 0.63–0.79)]. (Objective 2) The 97% of COPD patients are able to perform 10-minutes bouts of moderate-to-vigorous physical activity. More than 50% of the COPD patients met the World Health Organization recommendation of physical activity for the elderly. The quantity of physical activity, the percentage of activity done in bouts and the frequency of bouts decreased with increasing COPD severity. (Objective 3) The quantity and the intensity of physical activity are independent determinants of the COPD evolution. Every additional 1000 daily steps at low-average intensity reduce by 20% the risk of COPD hospitalisation. However, a greater quantity of daily steps at high-average intensity does not influence the risk of COPD hospitalisation (HR 1.01, p=0.919).

CONCLUSIONS

The YPAS is a valid instrument for the early screening of COPD patients who run the risk of sedentarism. Patients with severe and very severe COPD perform fewer bouts of physical activity and less quantity of physical activity, and have lower ratio between bouts and quantity than those in mild and moderate stages. Higher quantity of low-intensity physical activity reduces the risk of COPD hospitalization.

RESUM

ANTECEDENTS I OBJECTIUS

La Malaltia Pulmonar Obstructiva Crònica (MPOC) és una de les principals causes de mortalitat i discapacitat a nivell mundial. L'activitat física és un dels pocs factors modificables que desacceleren l'evolució de la MPOC. No obstant, la dosi i les característiques de l'activitat física responsables de la desacceleració són encara desconegudes. En conseqüència, els objectius d'aquesta tesi són avançar i perfeccionar la metodologia i els instruments per avaluar l'activitat física realitzada pels malalts amb MPOC, aprofundir en el coneixement sobre les característiques i els patrons de la seva activitat física i determinar quines característiques de l'activitat física milloren el pronòstic dels malalts amb MPOC.

MÈTODES

Han participat 177 individus amb MPOC estable seleccionats de 8 hospitals a Espanya (94% homes, edat mitjana±DE 71±8 anys, volum expiratori forçat en 1 s 52±16% i índex de massa corporal 29±5 kg·m^{-2}). L'activitat física va ser mesurada per un acceleròmetre (SenseWear® Pro2 Armband) i per un qüestionari (Yale Physical Activity Survey, YPAS). Les variables sociodemogràfiques (edat, sexe, estat civil, nivell educatiu, nivell socioeconòmic, situació laboral i hàbit tabàquic) i les variables clíniques (limitació al flux d'aire, hiperinsuflació pulmonar, díspnea, intercanvi de gasos, inflamació sistèmica i local, composició corporal, comorbiditats, qualitat de vida i capacitat d'exercici), es van obtenir utilitzant instruments validats i seguint les normes internacionals. La informació sobre l'evolució de la malaltia (els ingressos hospitalaris i la mortalitat) es va obtenir dels registres dels governs.

RESULTATS

(Objectiu 1) El YPAS és una eina vàlida per a la detecció precoç de la inactivitat dels individus amb MPOC [àrea sota la corba ROC (95% IC) = 0.71 (0,63-0,79)]. (Objectiu 2) El 97% dels individus amb MPOC són capaços de realitzar episodis de 10 minuts d'activitat física moderada-vigorosa. Més del 50% dels individus amb MPOC compleixen amb les recomanacions de l'Organització Mundial de la Salut sobre l'activitat física per a la gent gran. La quantitat d'activitat física, la proporció d'aquesta activitat realitzada en episodis de 10 minuts i la freqüència d'aquests episodis va disminuir amb l'augment de la gravetat de la MPOC. (Objectiu 3) La quantitat i la intensitat de l'activitat física són determinants independents de l'evolució de la MPOC. El risc d'hospitalització per MPOC és un 20% menor per cada 1000 passos diaris addicionals realitzats en baixa intensitat. No obstant, una major quantitat de passos diaris a una alta intensitat mitjana no influeix en el risc d'hospitalització per MPOC (HR = 1.01; p = 0,919).

CONCLUSIONS

El YPAS és una eina vàlida per a la detecció precoç dels individus amb MPOC físicament inactius. Els pacients amb MPOC greu i molt greu realitzen menys episodis i quantitat d'activitat física, i tenen menor la ràtio entre episodis i quantitat que en aquells en estat lleu i moderat. Una major quantitat d'activitat física de baixa intensitat redueix el risc d'hospitalització per MPOC.

RESUMEN

ANTECEDENTES Y OBJETIVOS

La Enfermedad Pulmonar Obstructiva Crónica (EPOC) es una de las principales causas de mortalidad y discapacidad a nivel mundial. La actividad física es uno de los pocos factores modificables que desaceleran la evolución de la EPOC. Sin embargo, la dosis y las características de la actividad física responsables de la desaceleración son todavía desconocidas. En consecuencia, los objetivos de esta tesis son avanzar y perfeccionar la metodología e instrumentos para evaluar la actividad física realizada por los enfermos con EPOC, profundizar en el conocimiento sobre las características y patrones de su actividad física y determinar qué características de la actividad física mejoran el pronóstico de los enfermos con EPOC.

MÉTODOS

Han participado 177 individuos con EPOC estable seleccionados de 8 hospitales en España (94% hombre, edad media±DE 71±8 años, volumen espiratorio forzado predicho en 1 s 52±16% e índice de masa corporal 29±5 kg·m^{-2}). La actividad física fue medida por un acelerómetro (SenseWear® Pro2 Armband) y por un cuestionario (Yale Physical Activity Survey, YPAS). Las variables sociodemográficas (edad, sexo, estado civil, nivel educativo, nivel socioeconómico, situación laboral y hábito tabáquico) y las variables clínicas (limitación al flujo aereo, hiperinsuflación pulmonar, disnea, intercambio de gases, inflamación sistémica y local, composición corporal, comorbilidades, calidad de la vida y capacidad de ejercicio), se obtuvieron utilizando instrumentos validados y siguiendo las normas internacionales. La información sobre la evolución de la enfermedad (ingresos hospitalarios y mortalidad) se obtuvo de los registros gubernamentales.

RESULTADOS

(Objetivo 1) El YPAS es una herramienta válida para la detección precoz de la inactividad de los individuos con EPOC [área bajo la curva ROC (95% IC) = 0.71 (0.63-0.79)]. (Objetivo 2) El 97% de los individuos con EPOC son capaces de realizar episodios de 10 minutos de actividad física moderada-vigorosa. Más del 50% de los individuos con EPOC cumplen con la recomendación de la Organización Mundial de la Salud sobre actividad física para las personas mayores. La cantidad de actividad física, la proporción de ésta realizada en episodios de 10 minutos y la frecuencia de estos episodios disminuyó con el aumento de la gravedad de la EPOC. (Objetivo 3) La cantidad y la intensidad de la actividad física son determinantes independientes de la evolución de la EPOC. El riesgo de hospitalización por EPOC es un 20% menor por cada 1000 pasos adicionales realizados en baja intensidad

media. Sin embargo, una mayor cantidad de pasos diarios a una alta intensidad media no influye en el riesgo de hospitalización por EPOC (HR = 1.01; p = 0,919).

CONCLUSIONES

El YPAS es una herramienta válida para la detección precoz de los individuos con EPOC físicamente inactivos. Los pacientes con EPOC grave y muy grave realizan menos episodios y cantidad de actividad física, y tienen menor el ratio entre episodios y cantidad que en aquellos en estado leve y moderado. Una mayor cantidad de actividad física de baja intensidad reduce el riesgo de hospitalización por EPOC.

PREFACE

Due to population aging and increased tobacco consumption, a worldwide rise in the prevalence of chronic obstructive pulmonary disease (COPD) is expected. Physical activity has been found to be one of the few behavioural factors that improve COPD evolution. However, the assessment of physical activity and their effects upon COPD are still very basic and inaccurate. Therefore, this thesis consists in a compilation of three scientific publications attempting to better understand how to measure COPD patients' physical activity, what are their regular levels of physical activity and which characteristics of physical activity are responsible of the deceleration of COPD course. According to the procedures of the PhD program of the Department of **Salut, Activitat Física i Esport**, the thesis includes an abstract, a general introduction, a rationale, the objectives, the results (3 original scientific papers), a discussion, and final conclusions. The scientific papers included in this thesis are based on data from the Phenotype and Course of Chronic Obstructive Pulmonary Disease (PAC-COPD) study, a Spanish multi-centric cohort study aiming to improve the understanding about the phenotypic heterogeneity of COPD and its relationship with the clinical prognosis. At the end of this thesis, in annexes, other publications regarding physical activity or ambulatory assessment that I have co-authored during the predoctoral period are included, altogether with a list of congress contributions.

Barcelona, July 2015

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BACKGROUND

Chronic Obstructive Pulmonary Disease (COPD)

Definition

Chronic obstructive pulmonary disease (COPD) is a "preventable and treatable pulmonary disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases" [1].

The airflow limitation that characterizes COPD is usually measured by the ratio between forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). A ratio below 0.7 (FEV_1 / FVC ≤0.70) is the standardized operational definition of COPD [2]. Moreover, this reduction of expiratory airflow serves to characterize the severity of the disease, being this light, moderate, severe or very severe when the FEV_1 is ≥80%; 80-50%, 50-30% or <30% of expected according to age, sex and height of patients (Table 1) [2]. In addition, following the recognition of the multifactoriality of COPD severity, new measures of COPD severity have appeared with a more holistic approach. This is the case of the Combined COPD Assessment proposed by The Global Initiative for Chronic Obstructive Lung Disease (GOLD) that takes into account the airflow limitation, frequency of exacerbations, and quality of life (Table 1) [3].

Table 1. Classification of COPD severity according to ATS/ERS guidelines [2] and to GOLD initiative [3].

Spirometric Classification	**ATS/ERS classification**	**GOLD classification**		**Risk**
$FEV_1 \geq 80$	I. Mild COPD	A (Low Risk & Less Symptoms)	B (Low Risk & More Symptoms)	Low Risk ($FEV_1 \geq 50$ & ≤ 1 Exacerbations)
$50 \leq FEV_1 > 80$	II. Moderate COPD			
$30 \leq FEV_1 > 50$	III. Severe COPD	C (High Risk & Less Symptoms)	D (High Risk & More Symptoms)	High Risk ($FEV_1 < 50$ or ≥ 2 Exacerbations)
$FEV_1 < 30$	IV. Very severe COPD			
		Less Symptoms (mMRC<2 or CAT<10)	More Symptoms (mMRC≥2 or CAT≥10)	
		Symptoms		

FEV_1: predicted post-broncodilatador forced expiratory volume in 1 s; mMRC: modified Medical Research Council Disnea scale; CAT: COPD assessment test

Prevalence, morbidity and mortality

In 2006, the worldwide prevalence of COPD in the population older than 40 years (~1000 million) was 8-12%, being one of the highest among chronic non-communicable diseases [4]. Moreover, it is expected that this prevalence increases as a result of the changing age structure of populations (the number of people aged 60 and over will nearly triple in size in 2050) [5], the tobacco abuse during the past decades, and the longer life expectancy of patients with COPD achieved through the improvement of management of COPD [6]. In 2007, the prevalence of COPD in Spain was lower than the worldwide prevalence (7.1% of men and 2% of women aged 40-80 years) [7], due to the delayed acquisition of smoking habit, especially among women. However, at the same time, in 2007, Spanish people were at the head of Europe regarding smoking population, which portends that Spain will become in few years one of the developed countries with higher prevalence of COPD.

COPD morbidity accounts for 8.2% of medical visits (primary care and external consultations), 8.3% of emergency visits and 4.3% of hospitalizations [8], being the third and fourth leading cause of hospitalization in men and women older than 45 years, respectively in Spain [9]. The most frequent cause of COPD morbidity (medical consultation and hospital admission) is the COPD exacerbation [2, 10]. COPD exacerbation is "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication"[3]. Patients with COPD experience from one to three COPD exacerbations on average per year [11–13]. COPD exacerbations increase the decline of lung function [14] and jeopardize both quality of life [15] and survival amongst these patients [16]. Therefore, reducing the frequency of COPD exacerbations is a major therapeutic goal [3].

COPD mortality is difficult to assess due to the lack of an accepted and standardized code for COPD and the limited validity of current death certificates [17]. However, COPD is recognized as one of the leading causes of mortality worldwide. Between 1990 and 2010, COPD moved from fourth to third leading cause of death worldwide, being responsible of more than 8% of deaths due to non-communicable diseases [18]. Despite this, life expectancy for smokers in their mid-fifties at ten years is 75% amongst smoker adult people with no lung disease, 65% for people with COPD symptoms, and 63%, 58% and 15% for patients with light, moderate, and severe-to-very severe COPD, respectively [19].

Prognostic factors of COPD evolution

Several factors play a role in COPD evolution, including **biological factors** (such as airflow limitation, lung hyperinflation, gas exchange, pulmonary hypertension, COPD exacerbations, lung infections, deficiency of alpha 1-antitrypsin, and/or exercise capacity), **pharmacological** (such as inhaled steroids, long-acting bronchodilators or flu vaccine), **environmental** (such as air pollution and/or occupational exposure) and **behavioural** (such as tobacco habit, diet and/or physical activity) [20–22].

In the current thesis, we focus on physical activity, which depends on individual's behaviour and therefore is potentially modifiable, and plays an important role in the morbidity and mortality of COPD patients [23].

Physical Activity

Definition

Physical activity is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" [24]. Physical activity is a complex, modifiable and multidimensional behaviour, performed in bouts during occupational and/or leisure time, based on personal interests or needs. Physical activity can be characterized by the frequency, duration, intensity, amount and type of activity performed [55, 56]. It is important to distinguish physical activity from exercise or physical fitness. The exercise is the part of physical activity in which planned and structured bodily movements are performed to improve or maintain physical fitness [24]. Physical fitness is a set of attributes that people have or achieve that relates to the ability to perform physical activity [24].

Physical activity prevents the 9% of premature deaths and the 6-10% of the burden of non-communicable diseases [25, 26]. Despite these well-known benefits, there is a widespread trend towards rising physical inactivity levels worldwide [27]. In 2008, physical inactivity was considered one of the most important public health problems, affecting around one-third of adult population worldwide [28] and causing approximately 32 million of years lost due to ill-health, disability or early death (DALYs) worldwide, representing about 2.1% of global DALYs each year [29].

It could be argued that the elderly population with chronic disease, such as patients with COPD, are even more at risk to be affected by the deleterious effects of physical inactivity because of their pathophysiological limitations like lung hyperinflation, limited gas exchange, recurrent exacerbations, and reduced physical fitness [23].

Measurement of physical activity in COPD patients

Accurate assessment of daily physical activity is essential in COPD patients because of its effect on disease prognosis [30]. Importantly, the physical activity measurement is more complex for COPD patients than for the general population because of the abovementioned characteristics, which alter patients' movement efficiency.

The existing tools to measure physical activity include direct (diaries, doubly labeled water (DLW), accelerometers) and indirect (oxygen uptake, heart rate, body temperature, ventilation monitors, and questionnaires) methods. Most of existing epidemiological studies measured physical activity by questionnaires and/or more recently with accelerometers [31].

The questionnaires have allowed the identification of the health benefits of physical activity in many chronic diseases and conditions. The questionnaires are low cost, easy to use, a unique kind of tool able to assess type and purpose of activity, have generalized applicability, and are the elected technique to measure physical activity in large epidemiological studies [32–34]. However, they are not able to characterise individual-level physical activity because of their poor accuracy [31].

The specific characteristics of COPD patients preclude the use of any physical activity questionnaire if it has not been previously validated for this population. Before this thesis some questionnaires were used to assess physical activity in COPD population [35]. Evidence concerning reliability, validity and responsiveness of these questionnaires for COPD physical activity assessment was mainly inexistent [30]. Only Vilaró and colleagues [36] validated the Modified Baecke Physical Activity Questionnaire specifically for COPD population, but this questionnaire is mainly focused on rating the physical activity level (classifying subjects in sedentary, moderately sedentary and active) instead of quantifying or characterizing the physical activity performed by patients with COPD.

The accelerometer is becoming the most accepted method to measure physical activity in COPD patients due to its higher accuracy and reliability at the individual level [31]. Accelerometers use the acceleration in the subjects' movements to quantify intensity over short epochs of time. In COPD patients, the accelerometers have been shown to have high reliability (Interclass Correlation Coefficient, ICC= 0.84) between three sequential 6-min walk distances (6MWDs) [37]. Accelerometers are able to distinguish between different intensities of physical activity and between populations with different amount of physical activity (e.g., healthy vs COPD). It has been suggested that accelerometers are more accurate for quantification and differentiation of body movements than for estimation of energy expenditure, especially at slow speeds [30]. However, using multisensor monitors, such as SenseWear® Pro2 Armband, instead of regular accelerometers could also provide valid assessments of both physical activity and energy expenditure in COPD patients [38]. The responsiveness of accelerometers to interventions has not been evaluated because of the lack of effective interventions to increase physical activity in COPD patients.

Other tools are rarely used in COPD patients to study physical activity for several reasons. Briefly, diaries are not used because they are burdensome for participants and are affected by respondent error and low resolution. Methods based on physiological assessments (DLW, oxygen uptake, ventilation rate, heart rate, or body temperature) are not appropriate to assess physical activity of COPD patients because the physiological response to physical activity depends on movement efficiency which change across COPD severity [30].

Characteristics of COPD patients' physical activity

Since the launch of the accelerometers, research on the physical activity of COPD patients has consistently shown that COPD patients perform lower volume of physical activity than their healthy peers [39, 40]. The changes in physical activity start in the early stage of the disease [41, 42], where the speed and intensity of walking are the main physical activity aspects affected [43–45]. Only at severe and very severe stages of the airflow limitation, the time spent in moderate-to-vigorous physical activity is reduced, when compared with healthy subjects [42]. However, there are huge differences in physical activity volume across countries [46, 47] that cannot be fully explained by severity or age differences.

On the other hand, and despite all previous evidence about the reduction of the volume of physical activity in COPD patients, there are no studies providing information on what features of the pattern of physical activity explain this reduction of physical activity volume. Indeed, this lack of information on the pattern of physical activity of COPD patients may have limited our ability to **design interventions with realistic goals for this population[48].**

Benefits of physical activity upon COPD

Until 2003 there were almost no evidences regarding the beneficial effects of physical activity upon COPD. The lack of a validated tool to measure physical activity in this population was one of the reasons. However, from 2003, the literature regarding the relationship between physical activity and COPD started growing, as well as the consistency of its beneficial effect, despite of the limited accuracy of the used questionnaires [23]. It is worth noting the beneficial effects found in longitudinal designs about COPD morbidity [44, 49–55] and mortality [52, 53, 56–60], where those COPD patients that spent 2 hours or more per week performing physical activity had a 30% and 20% reduction in risk of hospitalization and death because of COPD, respectively, compared to those who did not achieve these 2 hours per week [52]. Furthermore, it is also remarkable the cross-sectional associations found between physical activity and forced expiratory volume [61, 62], dyspnoea [62, 63], health-related quality of life [56, 62, 64, 65], exercise capacity [47, 63, 66, 67] or systemic inflammation [41, 63, 68]. However, and despite the evidences on the relationship between keeping physically active and COPD evolution, it remains unexplained what is the required dose of physical activity, whether there is a minimum necessary threshold of physical activity, whether the benefit is independent of the type of physical activity, or whether this benefit depends on the stage of disease severity.

RATIONALE

COPD has become a challenge for the health systems that it is expected to worsen in the future due to population aging and the widespread abuse of tobacco consumption. Without dismissing the importance of anti-tobacco health policies, we need parallel measures that help to prevent COPD development or decelerate COPD course. Physical activity is one of the most promising factors because of its susceptibility of modification through behavioural interventions and because its demonstrated effects on COPD evolution.

However, there are important gaps in the knowledge about physical activity and COPD which prevent the design and implementation of interventions to achieve the precise dose of physical activity that could improve COPD evolution [48]. Specifically, there is a lack of a free, quick, accurate and specifically validated tool to quantify physical activity in COPD patients. Also, the characteristics of physical activity pattern in COPD patients have never been assessed. Finally, it what is not known, is the potential differential role of the several characteristics of physical activity on its beneficial effect on COPD course.

OBJECTIVES

General Objective

The present thesis aims to deep and improve the knowledge about the measure and effects of physical activity in COPD patients, specifically to move forward and refine the methodology and instruments to evaluate the physical activity of COPD patients, go in depth in the knowledge about the characteristics and pattern of their physical activity, and determine which characteristics of their physical activity are responsible of decelerating the COPD evolution.

To reach our objective, two physical activity measures were included, one self-reported measured using the Yale Physical Activity questionnaire and another objectively measured with the SenseWear® Pro2 Armband accelerometer, in a cohort of COPD patients thoroughly characterized who participated in the Phenotype and Course of Chronic Obstructive Pulmonary Disease (PAC-COPD) study.

Specific Objectives

1. To study the validity of the Yale Physical Activity questionnaire to quantify and classify physical activity levels in COPD patients.

2. To describe the overall physical activity volume and pattern of physical activity bouts in patients with COPD.

3. To assess how the overall physical activity volume and pattern of physical activity bouts differ according to airflow limitation of COPD patients.

4. To explore whether COPD patients meet the general guidelines for physical activity for elderly.

5. To assess the independent effect of the quantity and intensity of physical activity on the risk of hospitalisation due to a COPD exacerbation.

HYPOTHESES

The Yale Physical Activity questionnaire is a valid instrument to quantify the volume of physical activity at the population level and determine inactive COPD patients.

The volume and characteristics of COPD patients' physical activity pattern differ across the severity of airflow limitation. COPD patients with severe and very severe airflow limitation perform their daily activities in fewer and shorter bouts than those with mild and moderate stages.

COPD patients that usually perform higher quantity and intensity of physical activity have lower risk of hospitalization for COPD exacerbation than those performing lower quantity or intensity of physical activity.

RESULTS

Paper I: Validation of the Yale Physical Activity Survey in Chronic Obstructive Pulmonary Disease patients

Donaire-Gonzalez D, Gimeno-Santos E, Serra I, Roca J, Balcells E, Rodríguez E, Farrero E, Antó JM, Garcia-Aymerich J; on behalf of PAC-COPD Study Group. Validation of the Yale Physical Activity Survey in chronic obstructive pulmonary disease patients. Arch Bronconeumol. 2011;47(11):552-60.*

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Arch Bronconeumol. 2011;47(11):552–560

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Original Article

Validation of the Yale Physical Activity Survey in Chronic Obstructive Pulmonary Disease Patients☆

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A R T I C L E   I N F O

Article history:
Received 8 March 2011
Accepted 7 July 2011
Available online 6 December 2011

Keywords:
Chronic obstructive pulmonary disease (COPD)
Validation studies
Epidemiology
Motor activity
Questionnaires

A B S T R A C T

Background: Patients with chronic obstructive pulmonary disease (COPD) perform limited physical activity. Surprisingly, there is a lack of research in COPD about the validity of physical activity questionnaires. Our aim was to validate the Yale Physical Activity Survey in COPD patients in order to quantify and classify their levels of physical activity.
Methods: 172 COPD patients from 8 university hospitals in Spain wore an accelerometer (SenseWear® Pro_2 Armband) for 8 days and answered the questionnaire 15 days later. Statistical analyses used to compare both tools measures included: (i) Spearman's correlation coefficient, (ii) intraclass correlation coefficient (ICC) and Bland–Altman plots, (iii) distribution of accelerometer measurements according to tertiles of the questionnaire, and (iv) receiver operating characteristic (ROC) curves to detect sedentary patients.
Results: 94% of participants were men, 28% were active smokers and 7% were currently working. Mean (standard deviation) age was 70 (8) years, mean post-bronchodilator FEV_1 was 52 (15)% predicted, and median (p25–p75) steps taken was 5702 (3273–9253) steps per day^{-1}. Spearman correlations were low to moderate (from 0.29 to 0.52, all $P<.001$). ICCs showed weak agreement (from 0.34 to 0.40, all $P<.001$). A wide variability in agreement was observed in the Bland–Altman plots. Significant differences in accelerometer measurements were found according to questionnaire tertiles (all $P<.001$). The area under the ROC for identifying sedentarism was 0.71 (95% CI: 0.63–0.79).
Conclusions: The Yale Physical Activity Survey may be a valid tool to classify, but not to quantify, physical activity performed by COPD patients. The summary index of this questionnaire, based on seven short questions, shows the best validity properties. This suggests that it should be considered as a screening tool to identify patients at risk for sedentarism.

☆ Please cite this article as: Donaire-Gonzalez D, et al. Validación del cuestionario de actividad física de Yale en pacientes con enfermedad pulmonar obstructiva crónica. Arch Bronconeumol. 2011;47:552–60.
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Validación del cuestionario de actividad física de Yale en pacientes con enfermedad pulmonar obstructiva crónica

Palabras clave:
Enfermedad pulmonar obstructiva crónica (EPOC)
Estudios de validación
Epidemiología
Actividad motora
Cuestionarios

R E S U M E N

Introducción: Los pacientes con enfermedad pulmonar obstructiva crónica (EPOC) se caracterizan por una actividad física limitada. Sorprendentemente, apenas se dispone de investigación sobre los cuestionarios para medir la actividad física en la EPOC. El objetivo del presente estudio fue validar el cuestionario Yale Physical Activity Survey en pacientes con EPOC.
Métodos: Un total de 172 pacientes de 8 hospitales universitarios españoles usaron un acelerómetro (SenseWear® PrO_2 Armband) durante 8 días y contestaron el cuestionario. Los análisis estadísticos de comparación de ambos instrumentos incluyeron: a) correlación de Spearman; b) coeficiente de correlación intraclase (CCI) y gráficos de Bland–Altman; c) distribución de las medidas del acelerómetro según los terciles del cuestionario, y d) la curva *receiver operating characteristic* (ROC) para detectar a los pacientes sedentarios.
Resultados: El 94% de los participantes eran hombres, el 28% eran fumadores y el 7% eran trabajadores activos; la edad media (±DE) fue de 70 (8) años, el volumen espiratorio medio en el primer segundo (VEMS) posbroncodilatador fue de 52 (15) como porcentaje del valor de referencia, y la mediana (p25–p75) de pasos fue de 5.702 (3.273–9.253) pasos/día. Las correlaciones de Spearman fueron débiles o moderadas (desde 0,29 hasta 0,52, todas las p < 0,001). Los CCI mostraron concordancias débiles (desde 0,34 hasta 0,40, todas las p < 0,001). Los gráficos de Bland–Altman mostraron una gran variabilidad en la concordancia. Se encontraron diferencias significativas en las medidas del acelerómetro según los terciles del cuestionario (todas las p < 0,001). El área bajo la curva ROC para identificar el sedentarismo fue de 0,71 (intervalo de confianza del 95%: 0,63–0,79).
Conclusión: El cuestionario Yale Physical Activity Survey es una herramienta válida para clasificar la actividad física que realizan los pacientes con EPOC, pero no para cuantificarla. El índice resumen del cuestionario, originado de tan solo 7 preguntas, muestra los mejores resultados de validez, sugiriendo que debería considerarse un instrumento de cribado para identificar a los pacientes que corren riesgo de sedentarismo.

Introduction

Frequent physical activity has been related with a reduction in risk for hospitalization and mortality in patients with chronic obstructive pulmonary disease (COPD).[1–3] Consequently, there is a growing interest in measuring physical activity in these patients in order to study its determinants and effects as well as its clinical evaluation. There are several tools used to measure physical activity, and research on their ease of use, validity and reliability for monitoring physical activity in patients with COPD has grown exponentially. Similarly, the use of these monitors in clinical research of physical activity and COPD has increased,[4] despite some disagreements about their interpretation.[5] Nevertheless, there is a lack of research in COPD about the ease of use, validity or reliability of questionnaires,[4] which are widely used instruments for measuring physical activity in other fields of research. Physical activity questionnaires have identified the health benefits of physical activity in numerous diseases and chronic processes. The questionnaires have a generalized applicability, are low-cost, easy to use and are the method of choice for measuring physical activity in large-scale epidemiological studies.[6–8] The specific sociodemographic characteristics of COPD patients (seniors, retirees) and their functional limitations impede the use of any questionnaire that has not been previously validated in this population. We selected the Yale Physical Activity Survey (YPAS)[9] because it is one of the most detailed, available for senior subjects and whose validity, reliability and sensitivity to change have been previously published.[9–11] The YPAS reflects the volume, frequency and intensity of physical activity, expressed as metabolic equivalents of task (MET), meaning MET-h/week, which are able to estimate the effects of physical activity as a continuous parameter even in the lowest levels of activity (predictable in COPD).[8]

The objective of the present study is to validate the YPAS in COPD patients in order to quantify the levels of physical activity and classify the patients according to these levels using a physical activity monitor (accelerometer) as a reference.

Methods

Study Type

A concurrent validity study.

Participants

This study is part of the study entitled “Phenotypic Characterization and Evolution of Chronic Obstructive Pulmonary Disease (PAC-COPD)”.[12,13] Briefly, the individuals were recruited during their first hospitalization due to COPD exacerbation and the diagnosis of COPD (post-bronchodilator forced expiratory volume in one second [FEV_1] – forced vital capacity [FVC] ratio [FEV_1/FVC] < 0.70)[14] was confirmed under stable clinical conditions at least 3 months after hospitalization. After 18 months, the patients were invited to participate in a validation protocol of physical activity in patients who continued to survive and were candidates (n=257) after a pilot test in a reduced sample of patients not included in the PAC-COPD.[15] Among these, 75 patients (29%) did not participate (8 belonged to a hospital that did not participate in the study on physical activity, one patient could not use the monitor as he was missing his right arm, 58 refused to use the accelerometer and 8 did not answer the questionnaire). The comparison of the characteristics between participants and non-participants demonstrated that there was a greater proportion of retired individuals among the participants (93% vs 84%, *P*=.019) than among the non-participants. There were no differences in other variables for sociodemographics, dyspnea, quality of life, comorbidities, smoking, lung function, nutritional state or capacity for exercise. Lastly, out of the 182 patients who completed the validation study, 10 were excluded because they used the accelerometer less than the minimum previously defined time, which left a total of 172 patients for the analysis. The study was approved by the research committees of all the participating hospitals and informed consent was given by all the individuals. More details about the selection process have been previously described.[16]

Determination Tools and Variables

The study was carried out under conditions of clinical stability and at least 3 months after the last COPD exacerbation. The data from the monitor were obtained before the survey was completed and, consequently, following the general recommendations that, when administering a sequence of measurements, the first should be the least sensitive to the objectives of the study, expectations of the researcher or knowledge about the following measurement.[17] The questionnaire was administered 2 weeks later since the questions referred to the 4 weeks prior and included the period of the accelerometer.

Physical activity was determined with the SenseWear® Pro_2 Armband monitor (SWA; Body Media, Pittsburgh, PA), which has shown to be a valid parameter for physical activity in COPD patients.[18] The patients used the monitor for 8 consecutive days and the minimum use time was previously defined as at least 3 days registering more than 70% of the daytime hours (from 8 a.m. to 10 p.m.).[19] The first and last days were not used for the analysis because they were not representative of usual physical activity.[19] The congruency of the monitor data was tested using the intraclass correlation coefficient (ICC) of the steps taken per day among all the possible 3-day combinations (ICC=0.95, 95% CI: 0.93–0.96). Accelerometers measure the magnitude of the changes in acceleration of the center of the body mass during movement. The monitor used in this present study is biaxial, registering the movement on the axes *X* and *Y*. The armband system was placed on the right arm and it registered the movements of the upper and lower thirds of the subjects' bodies, proving a minute-by-minute report of the two movement axes, thermal flow, galvanic response of the skin, skin temperature and environmental temperature near the body. For each patient, the data obtained included the number of steps taken per day as well as time (h/day), intensity (MET-h/day), and energy output (cal/day), physical activity of any, light or moderate intensity (defined as activities $\geq$1.4, $\geq$2.5 and $\geq$3.6 MET, respectively). As an indicator of sedentarism, a cut-point was defined as <30 min/day of moderate activity, as recommended by the American College of Sports and Medicine.[20]

Two weeks after the accelerometer register, two experienced interviewers administered the validated Spanish version[10] of the Yale survey.[9] This questionnaire compiles information (frequency, intensity and duration) for an extensive list of activities performed in the last 4 weeks (therefore it includes the period in which the accelerometer was used). Since some of the patients were actively working, we slightly modified the original questionnaire, adding a question about the physical activity done at work, as has been previously published.[21] The final version of the questionnaire is available on our website (http://www.creal.cat). From the list of activities of the questionnaire, we obtained two summarizing parameters: time per day (in h) and daily intensity (MET-h) of the physical activity $\geq$1.4 MET. The YPAS also includes 7 questions that combine the frequency and intensity of the activities in general, which provides an index that summarizes the activity with a score that varies between 0 and 137.[9] In addition, we calculated the energy expenditure of the physical activity, multiplying the MET of each individual by body weight, following the formula 1 MET=1 kcal/h/kg.[22]

We obtained other pertinent variables, including sociodemographic factors, the Charlson comorbidity index, the St. George's Respiratory questionnaire in order to evaluate health-related quality of life, dyspnea, lung function (FEV1, FVC, FEV1/FVC and partial arterial oxygen and carbon dioxide pressures [PaO_2, $PaCO_2$]), nutritional state (body mass index), and 6-min walk test. The details about these procedures have been previously published.[13,16]

Statistical Analysis

It was estimated that at least 107 individuals were necessary in order to identify correlations $\geq$0.3, accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-tailed test (bilateral) and anticipating a drop-out rate of 20%.

The characteristics of the individuals are presented as number (percentage) for the categorical variables, means ($\pm$standard deviation [SD]) for the continuous variables with normal distribution, or medians (P25–P75) for continuous variables with abnormal distribution.

The validation of the questionnaires was done with different strategies. First of all, in order to evaluate the linear relationship between the continuous variables of the questionnaire, the accelerometer and the distance walked in 6 min, a Spearman's correlation was used. In accordance with the previous data of the physical activity questionnaires, the expected correlations ranged between 0.35 and 0.45.[9,10,23]

Secondly, the agreement between the questionnaire and the monitor for time, intensity (MET) and energy expenditure during activity $\geq$1.4 MET was examined by means of the intraclass correlation coefficient (ICC) and Bland–Altman plots. For this effect, all the variables were transformed in order to approach normal distribution using the squared root. We used an ICC with random effect for a factor, which can be conceived as the ratio of the intra-individual variance over the total variance.[24] The Bland–Altman plots show for each variable the difference between the accelerometer and the questionnaire compared with the mean value of both instruments. The limits of agreement between the accelerometer and the questionnaire were, by default, the mean difference $\pm$2 SD. However, depending on the previous estimations of the intra-individual biological and analytical variation of the daily energy expenditure,[24,25] we defined *a priori* a stricter limit of agreement, established at $\pm$30% of the mean estimation of the accelerometer.

Thirdly, the distribution of the accelerometer parameters in accordance with the tertiles of the questionnaire parameters was evaluated using the Kruskal–Wallis test. Lastly, we tested the capability of the questionnaire for detecting sedentary individuals using the morphologic study of the receiver operating characteristic (ROC) curve.

In addition, we tested which are the possible determinants of the differences between the quantitative parameters of the questionnaire and the monitor, using a linear regression adjusted for the quantity of physical activity, as defined by the accelerometer. We constructed a stratified analysis of the validation analyses (correlations, Bland–Altman plots, ICC and ROC curves) according to the determinants identified in the previous linear regression models. As an analysis of sensitivity, we repeated all the analyses: (a) using only the individuals up until the 95th percentile in the questionnaire or accelerometer; and (b) with exclusion of the individuals with acute health problems during the administration of the questionnaire and/or the accelerometer (n=4). The analyses were done using the R 2.6.2 program (2008 The R Foundation for Statistical Computing).

Results

Table 1 demonstrates the characteristics of the sample. The patients used the accelerometer a mean of 6 days and registered a mean of 95% of the daytime hours (13.5 h out of a maximum of 14 h). A total of 79 (48%) patients did a minimum of 30 min of at least

Table 1
Sociodemographic, Clinical and Physical Activity Data for 172 Patients With Chronic Obstructive Pulmonary Disease (COPD).

	Total Sample n=172[a] n (%)/mean (±SD)
Sex: males	161 (94)
Age, years	70 (8)
Marital status: married	141 (82)
Occupation: actively employed	12 (6.98)
Low socioeconomic level (IV, V)	126 (80.25)
Smoking: current smoker	47(28)
BMI, kg/m^2	28.5 (4.76)
Severe dyspnea: scores 3, 4, 5 of the MMRC	81 (47.4)
Charlson comorbidity index (score from 0 to 30)	2.14 (1)
Health-related quality of life (St. George's Respiratory Questionnaire)	32 (18)
COPD severity stage	
I – mild (FEV1 ≥80%)	8 (5.03)
II – moderate (FEV1 50%–80%)	80 (50.31)
III – severe (FEV1 30%–50%)	57 (35.85)
IV – very severe (FEV1 <30%)	14 (8.81)
FEV1, post-bronchodilator, % reference value	52 (15)
FEV1/FVC, post-bronchodilator, %	54 (13)
PaO_2, mm Hg	74 (10)
$PaCO_2$, mm Hg	41 (5)
Distance walked in the 6-min walk test, m	414 (104)
Physical activity recorded by the monitor (SenseWear® Pro$_2$ Armband)	median (P_{25}–P_{75})
Number of steps, n/day	5702 (3273–9253)
Time of any activity (≥1.4 MET), h/day	2.9 (1.9–4.6)
Time of mild activity (≥2.5 MET), h/day	1.1 (0.5–2.0)
Time of moderate activity (≥3.6 MET), h/day	0.4 (0.2–1.1)
MET of any activity (≥1.4 MET), MET-h/day	8 (4–12)
Energy expenditure during activity ≥1.4 MET, kcal/day	556 (337–939)
Physical activity of the questionnaire (Yale Physical Activity Survey)	median (P_{25}–P_{75})
Time of any activity (≥1.4 MET), h/day	3.3 (2.1–5.3)
MET of any activity (≥1.4 MET), MET-h/day	11 (7–16)
Summary index of physical activity (score 0–137)	45 (30–63)
Energy expenditure during activity, kcal/day	871 (514–1300)

MMRC: modified Medical Research Council dyspnea scale; BMI: body mass index.
[a] Some data are missing for certain variables: 5 for smoking, 7 for PaO_2 and 11 for 6-min walk test.

moderate physical activity (56%, 45%, 49%, and 40%, in mild, moderate, severe and very severe COPD, respectively). All the physical activity parameters of the questionnaire positively correlated with the parameters of the accelerometer, with Spearman's coefficients that varied from 0.29 to 0.52 (all P<.001; Table 2).

The intraclass correlation coefficients for the time spent performing activity, intensity (MET) and energy expenditure were 0.397, 0.360 and 0.339, respectively, showing that less than half of the variance of the concordance was attributable to the variability of the individuals. The corresponding Bland–Altman plots showed that the mean values were significantly different between the questionnaire and the accelerometer (Fig. 1). There was a wide variability in the agreement; in 45%, 56%, and 57% of the cases it was higher than the previously defined limit for agreement for the time spent in each activity, the intensity and the energy expenditure, respectively.

The mean values of the physical activity variables recorded by the monitor increased in accordance with the tertiles of the corresponding parameters in the questionnaire (all the P < 0.001) (Fig. 2). Fig. 3 shows that the area under the ROC curve between the summary of the activity according to the questionnaire and sedentarism was 0.71 (95% CI: 0.63–0.79). Table 3 shows three different cut-points with high sensitivity and specificity for identifying the sedentary individuals based on the questionnaire.

Table 2
Correlation Between the Physical Activity Parameters of the Monitor and the Questionnaire and the Distances Walked in the 6-min Walk Test in 172 Patients With Chronic Obstructive Pulmonary Disease (COPD).

	Physical Activity Monitor				Distance Walked in the 6-min Walk Test, m
	Steps, *n*/Day	Time of Activity ≥1.4 MET, h/Day	MET of Activity ≥1.4 MET, MET-h/Day	Energy Expenditure of Activity ≥1.4 MET, kcal/Day	
	r	*r*	*r*	*r*	*r*
Questionnaire					
Time of activity ≥1.4 MET, h/day	0.34[a]	0.38[a]	0.35[a]	0.36[a]	0.37[a]
MET of activity ≥1.4 MET, MET-h/day	0.38[a]	0.41[a]	0.38[a]	0.40[a]	0.37[a]
Activity energy expenditure ≥1.4 METs, kcal/day	0.32[a]	0.32[a]	0.29[a]	0.37[a]	0.33[a]
Summary index of physical activity (score 0–137)	0.52[a]	0.38[a]	0.42[a]	0.43[a]	0.40[a]
Distance walked in the 6-min walk test, m	0.47[a]	0.46[a]	0.47[a]	0.45[a]	–

[a] All P<.001.

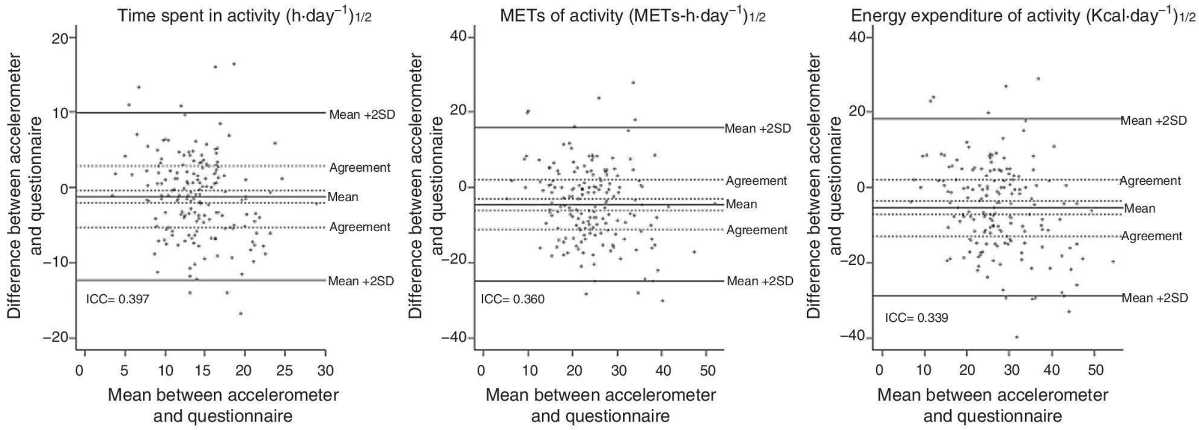

Figure 1. Intraclass correlation coefficients (ICC) and Bland–Altman plots of the physical activity parameters of the monitor and the survey in 172 patients with chronic obstructive pulmonary disease (COPD) (the ICC is a proper statistic for evaluating the degree of agreement between measurements of the same construct, and can be conceived as the ratio of the intra-individual variance over total variance).

Table 4 shows that: (a) being a current smoker and being actively employed led to higher values in the questionnaire than in the accelerometer; and (b) growing levels of activity as defined by the accelerometer were related with a decrease in the differences between instruments. There was no statistically significant interaction or modification of the effect between being a smoker and active worker. Other potential determinants showed no association in the bivariate or multivariate models.

The stratified validation analyses showed very similar results for the ex-smokers and/or retired individuals, while in current smokers (n=47 [28%]) and/or in those actively employed (n=12 [7%]) we observed lower correlations and a poorer classification of the physical activity parameters. The sensitivity analysis, detailed in Section “Methods”, showed very similar levels for all the analyses (data not shown).

Discussion

The present study evaluated the validity of a self-administered physical activity questionnaire in a COPD population by means of the comparison of the YPAS questionnaire with the SenseWear® Pro_2 Armband accelerometer. In order to evaluate the valid properties of the survey, several strategies were used that demonstrated the following: (a) positive correlations that were statistically

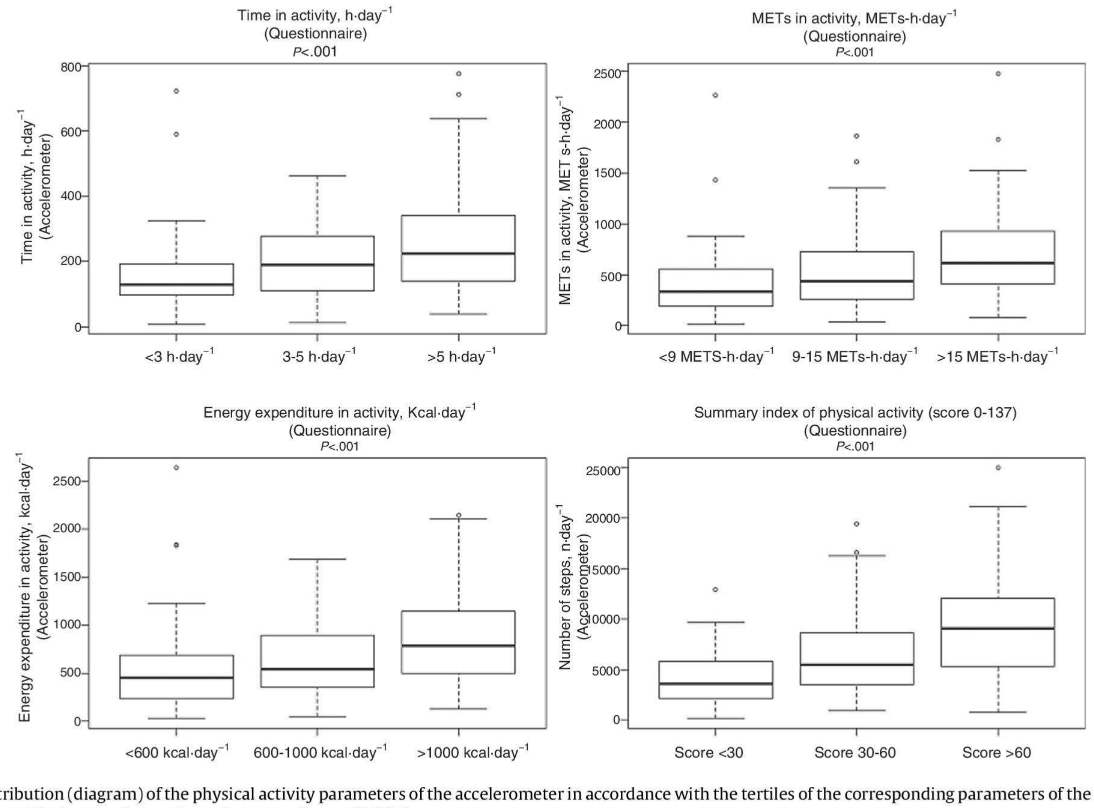

Figure 2. Distribution (diagram) of the physical activity parameters of the accelerometer in accordance with the tertiles of the corresponding parameters of the questionnaire in 172 patients with chronic obstructive pulmonary disease (COPD).

Table 3
Performance of the Physical Activity Summary Index of the YPAS in Order to Identify the Sedentary Individuals (Defined as <30 min/Day of Moderate Physical Activity) in 172 Patients With Chronic Obstructive Pulmonary Disease (COPD).

Activity Summary Index[a]	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Kappa
Score 38	54%	81%	78%	59%	0.32
Score 47	71%	64%	71%	64%	0.35
Score 51	75%	59%	69%	66%	0.34

[a] In theory, the summary index varies from 0 to 137, and in the sample of the present study, from 4 to 88. The analysis of the ROC curve identifies three cut-points with different sensitivities and specificities for detecting sedentary individuals based on the questionnaire. For instance, using a score of 38 as the cut-point (which means, defining as sedentary those patients with a score ≤38 in the questionnaire), 54% of the actual sedentary individuals (based on the monitor) would be identified as sedentary, 81% of the actual non-sedentary subjects (based on the monitor) would be identified as non-sedentary, and the proportion of sedentary/non-sedentary subjects correctly identified by the questionnaire would be, respectively, 78% and 59%.

Table 4
Mutually Adjusted Determinants[a] of the Differences Between the Physical Activity Parameters of the Monitor and the Questionnaire (Multivariate Linear Regression) in 172 Patients With Chronic Obstructive Pulmonary Disease (COPD).

	All Individuals n=172[b]		
	Coefficient	(95% CI)	*P*-Value
Time of maintained activity, h/day			
Constant[c]	−0.11	(−0.55 to 0.33)	0.621
Current smokers (*n* = 47)	−1.31	(−2.16 to −0.47)	0.002
Work situation: currently employed (n=12)	−3.12	(−4.67 to −1.57)	0.000
Level of monitor, h/day	0.61	(0.44 to 0.79)	0.000
		R^2 adjusted	0.27
MET of activity, MET-h/day			
Constant[c]	−2.5	(−4.1 to −0.9)	0.002
Current smoker (n=47)	−3.7	(−6.7 to −0.7)	0.015
Work situation: currently employed (n=12)	−8.4	(−13.8 to −2.9)	0.002
Level of monitor, MET-h/day	0.5	(0.3 to 0.7)	0.000
		R^2 adjusted	0.17
Energy expenditure in activity, kcal/day			
Constant[c]	−227	(−355 to −100)	0.000
Current smoker (n=47)	−279	(−525 to −33)	0.025
Work situation: currently employed (n=12)	−734	(−1,179 to −289)	0.001
Level of monitor, kcal/day	0.5	(0.2 to 0.7)	0.000
		R^2 adjusted	0.14

[a] The potential determinants included age, sex, marital status, socioeconomic level, smoking, comorbidities, dyspnea, body weight, height, BMI, quality of life, PaO_2, $PaCO_2$, post-bronchodilator FEV_1, post-bronchodilator FVC and FEV_1/FVC ratio.
[b] Five values omitted in smoking.
[c] Mean difference between the monitor parameters and the survey in individuals who were ex-smokers, were not employed and had average levels of physical activity according to the monitor.

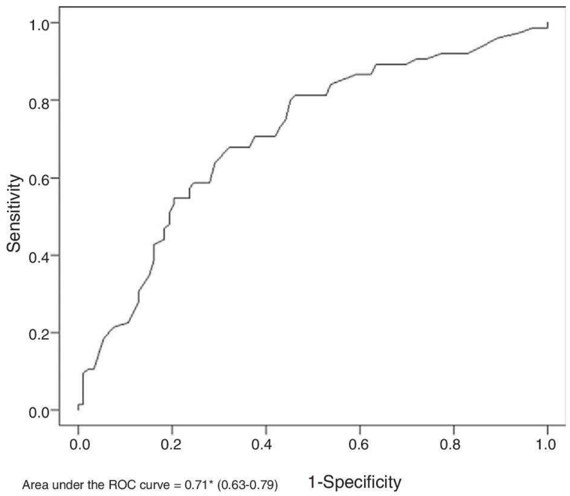

Figure 3. Receiver operating characteristic (ROC) curve of the summary index of activity, determined from the questionnaire, compared with sedentarism, defined as <30 min/day of moderate physical activity based on the monitor, in 172 patients with chronic obstructive pulmonary disease (COPD). An area under the curve of 0.71 means that, if two individuals are selected randomly (one above and another under the cut-points of the questionnaire), 71% of the time they will be correctly classified as sedentary/non-sedentary, in accordance with the monitor.

significant between both tools; (b) a reduced agreement between instruments and a substantial overestimation of physical activity by the questionnaire; (c) statistically significant differences in the parameters of the monitor in accordance with the tertiles of the questionnaire; and (d) satisfactory performance for the identification of sedentary patients.

The correlations between the questionnaire and the monitoring system varied from low to moderate (0.30–0.48) in the sample of patients with COPD in the present study, which corresponds with the values from 0.35 to 0.45 that are predictable based on the studies published in healthy individuals of older age.[9,10,23] In addition, it is much greater than the value of 0.14 observed in a small-scale study done in COPD patients which compared the units of movement of the vector of a tri-axial accelerometer and a questionnaire of the activity over the previous 4 days.[26] The greatest correlation coefficient was obtained between the survey summary index and the steps taken as measured by the monitor, which are the most widely accepted parameters of each tool.[4] As was expected, the 6-min walk distance (an objective parameter for exercise capacity) exhibited slightly higher correlation coefficients with the accelerometer (an objective parameter for physical activity) than with the questionnaire (a subjective parameter of physical activity). Nevertheless, it is interesting to comment that the questionnaire correlated better with the monitor than with the distance walked in 6 min, which supports the opinion that physical activity is a concept different from that of capacity for exercise.[27]

Until now, no studies have ever examined the agreement between the quantitative parameters of the YPAS questionnaire and the parameters of the accelerometer. The data of the present study show statistically significant differences between instruments in the means of the physical activity parameters, all of which are higher in the questionnaire. The ICC estimations imply that half of the variance in the physical activity parameters can be attributed to the tool more than to the individual. In addition, the prevalence of cases that surpassed the previously defined limits of agreement (±30% of the mean estimation of the accelerometer) was around 50%. This great variability could be explained in part by the weakness of the questionnaire. The effect of social desireability[28] when responding to a questionnaire (a self-administered instrument) could entail exaggerating socially accepted activities, which would lead to an overestimation of the time dedicated to the physical activity in the survey. Regardless of the cause, these data suggest that the YPAS should not be used for individual quantitative estimations of physical activity parameters.

It is worth mentioning that the analysis of the possible determinants for the differences between the accelerometer and the questionnaire only identified two variables in addition to physical activity. Being a current smoker or being actively employed increased the difference between the two instruments. One possible explanation of the first is that current smokers may over-report their physical activity due to the effect of what is socially desirable. As for the patients who were actively employed, it is possible that the questionnaire requires more direct, clear questions about the degree of physical activity done during work instead of the individual question that we added about activity at work. Lastly, it is reasonable that the levels of physical activity are also independently related with the differences between the questionnaire and the monitor, with fewer differences in the lower levels of physical activity. As a whole, and, although the variance in the differences of physical activity explained by these variables is lower than 30%, this analysis suggests that, in future research on the Yale survey in COPD patients, adjustments could be necessary for these specific populations.

The present study is the first that examines the capacity of the YPAS for discriminating physical activity among groups and for identifying sedentary individuals. As the health benefits of physical activity have been evaluated in general with physical activity in ordinal categories more than as a continuous variable,[20] the results of the present study regarding the increase in mean accelerometer values in accordance with the tertiles of the questionnaire is exceedingly important. It is not known to what point the selection of cut-points (either statistically or clinically pertinent) could influence in these results. However, and given that the degrees of physical activity change through studies and questionnaires, the use of categories based on percentiles is a common practice. For the identification of sedentarism, the authors used an accepted cut-point,[20] and the questionnaire seemed useful for identifying this circumstance. As long as COPD patients have a lower degree of physical activity than healthy adults of the same age[29]—related with their poorer state of health and poorer outcome[30]—the questionnaire could contribute to the early detection and treatment of sedentarism in clinical practice. From the several cut-points obtained in the analysis of the ROC curve with high sensitivity and specificity, it is proposed to use a cut-point score of 51 in the summary index of the YPAS questionnaire for the identification of sedentary patients. The reason for this choice is that the authors gave priority to the sensitivity over the specificity in the identification of sedentary individuals given the absence of harmful psychological effects associated with the diagnosis of sedentarism and the lack of adverse effects related with the recommendation of performing physical activity.

One limitation of the present study is that it does not evaluate reliability. Previous studies have demonstrated that the YPAS has an appropriate reliability in healthy individuals of older age (ICC=0.65), which could be very similar in the case of patients with COPD.[10] Second, the calculation of the energy expenditure in the questionnaire could have led to an incorrect estimation of the energy expenditure in the COPD population due to the use of absolute intensities (MET values) derived from healthy individuals.[22] In addition, the use of a physical activity monitor as a reference for energy expenditure could be debatable because the application of the reference algorithm of the monitor could translate into an erroneous estimation of physical activity.[31] Other parameters, like the doubly labeled water method (DLW), provide more valid information about energy expenditure.[7] Unfortunately, the DLW is limited to experimental studies due to its complexity, the material necessary and cost. The authors considered that the SenseWear® accelerometer is an appropriate instrument for validating the questionnaire because previous studies have demonstrated an appropriate agreement (ICC 0.54–0.73) in the physical activity parameters of its measurements and those using indirect calorimeter.[32] It has been previously validated for low-intensity activities in COPD pacients,[18] and it has been demonstrated that, for senior patients with low cultural levels, it is inoffensive and appropriate.[15] Lastly, the sample of the present study included mostly men, which represents the actual distribution of sexes in COPD in Spain. Although it is probable that the degree of physical activity may be different in the sample of the present study than in others with a different male:female proportion, it is highly unlikely that this were to cause bias in evaluating the validity of the questionnaire.

It could be debated whether a validated questionnaire for physical activity in COPD patients is necessary or not, given the recent technological progress made in monitoring the activity of this population. Several authors coincide in affirming that the selection of the tool for measuring physical activity in COPD patients depends on the characteristics and the objectives of the research.[4,5,19] Without belittling the relevance of monitoring activity, questionnaires (if these are validated and reliable) are still the most cost-efficient instruments for epidemiological research and control.[33] This could also be the reason for discussion if the instruments that monitor physical activity provide data comparable to the self-evaluated experience of physical activity in COPD patients, which is unknown due to the lack of a conceptual physical activity framework in this population. One of the main advantages is the use of agreement and discrimination parameters to quantify and classify physical activity in COPD patients in addition to the generally used exclusive correlation analysis. An additional advantage comes from the use of the accelerometer for a mean of 6 days as a reference because recent studies have demonstrated systematic changes during the week[19] that otherwise would have only been covered by the questionnaire. A final, novel advantage is that, in order to improve the results obtained with the questionnaire, we included patient body weight in the calculation of energy expenditure based on physical activity instead of assuming that all the subjects weighed 60 kg, which is the usual strategy.[9]

We conclude that the Yale Physical Activity Survey is a valid tool for classifying the physical activity in patients with COPD, but not for quantifying it. Its use in large-scale epidemiological studies, including either COPD patients or patients with similar chronic processes, will provide an adequate and cost-efficient estimation of the effects of physical activity levels in these patients. Given that the summary index of the questionnaire demonstrated adequate capacity for discriminating sedentarism, the use of the series of questions that make up this index (which is a very small part of the questionnaire) should be considered a screening instrument for identifying patients who run the risk of sedentarism.

Funding

The present study was funded by the Health-Care Research Fund [FIS PI052292], the Spanish Society of Pulmonology and Thoracic Surgery [SEPAR 2004/136] and the College of Physiotherapists of Catalonia [R02/08-09]. Judith Garcia-Aymerich has a research grant from the Instituto de Salud Carlos III [CP05/00118], Ministry of Health, Spain. The PAC-COPD study is funded with grants from: the Health-Care Research Fund [FIS PI020541], Ministry of Health, Spain; the Agència d'Avaluació de Tecnologia i Recerca Mèdiques [AATRM 035/20/02], Catalonian regional government; Spanish Society of Pulmonology and Thoracic Surgery [SEPAR 2002/137]; Catalonian Pulmonology Foundation [FUCAP 2003 Beca Marià Ravà]; RESPIRA Network [RTIC C03/11]; RCESP Network[RTIC C03/09]; Health-Care Research Fund [PI052486]; Health-Care Research Fund [PI052302]; La Marató de TV3 Foundation [num. 041110]; DURSI [2005SGR00392]; Novartis Pharmaceuticals, Spain; AstraZeneca Pharmaceuticals, Spain. CIBERESP and CIBERES receive funding from the Instituto de Salud Carlos III, Ministry of Health, Spain. The sources of funding did not participate in either the study design, data collection, data analysis or interpretation, the drafting of the manuscript or the decision to present the article for publication. The researchers are independent from the funding sources.

Acknowledgements

The authors would like to express their thanks to Dr. Milo Puhan for his useful comments about the previous version of the manuscript, and to Ms. Esther Gracia for her help in processing the data from the monitors.

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Paper II: Physical activity in COPD patients: patterns and bouts

Donaire-Gonzalez D, Gimeno-Santos E, Balcells E, Rodríguez DA, Farrero E, de Batlle J, Benet M, Ferrer A, Barberà JA, Gea J, Rodriguez-Roisin R, Antó JM, Garcia-Aymerich J. Physical activity in COPD patients: patterns and bouts. Eur Respir J. 2013;42(4):993-1002. *

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Physical activity in COPD patients: patterns and bouts

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ABSTRACT The present study aims to describe the pattern of physical activity and the frequency, duration and intensity of physical activity bouts in patients with chronic obstructive pulmonary disease (COPD), to assess how these patterns differ according to COPD severity, and to explore whether these patients meet the general guidelines for physical activity for older adults.

177 patients (94% male, mean $\pm$SD age 71$\pm$8 years and forced expiratory volume in 1 s 52$\pm$16% predicted) wore the SenseWear Pro_2 Armband accelerometer for eight consecutive days. Physical activity bouts were defined as periods of $\geqslant$10 min above 1.5 metabolic equivalent tasks and classified according to their median intensity.

Patients engaged in activity a median of 153 min$\cdot$day^{-1} and 57% of that time was spent in bouts. Median frequencies of bouts per day were four and three for all and moderate-to-vigorous intensities, respectively. With increasing COPD severity, time in physical activity, proportion of time in bouts and frequency of bouts decreased. 61% of patients fulfilled the recommended physical activity guidelines.

In conclusion, COPD patients of all spirometric severity stages engage in physical activity bouts of moderate-to-vigorous intensities. Patients with severe and very severe COPD perform their daily activities in fewer and shorter bouts than those in mild and moderate stages.

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Patients with severe COPD perform their daily activities in fewer, shorter bouts than those in mild and moderate stages http://ow.ly/nug7k

This article has supplementary material available from www.erj.ersjournals.com

Received: July 02 2012 | Accepted after revision: Nov 29 2012 | First published online: Dec 20 2012

Conflict of interest: Disclosures can be found alongside the online version of this article at www.erj.ersjournals.com

Introduction

Among patients with chronic obstructive pulmonary disease (COPD), reduced levels of physical activity have been found to be related to an increased risk of hospital admissions and mortality [1–3]. In addition, research on the physical activity levels of COPD patients has consistently shown that COPD patients have lower physical activity levels than their healthy peers [4, 5]. Most previous studies have reported accurate measurements of the physical activity level without addressing the pattern of activity. Indeed, physical activity is recognised as a multi-faceted behaviour that involves frequency, intensity, time and type (FITT principle) as modifiable components that are specifically used for guiding and testing interventions [6, 7]. Consistent with this concept, the recommendations from the American College of Sports Medicine and the American Heart Association advise that older adults "should perform moderate-intensity aerobic (endurance) physical activity for a minimum of 30 min on 5 days each week or vigorous-intensity aerobic activity for a minimum of 20 min on 3 days each week" [8]. Importantly, current physical activity guidelines explicitly acknowledge that the recommendations should be used in the context of the subject's needs, goals and initial abilities; thus, the 30 consecutive minutes of activity could be replaced by two or three bouts of at least 10 min each [9]. This adaptation is especially useful for COPD patients, given their limitations engaging in more activity [10]. Unfortunately, the lack of information on the pattern of physical activity in COPD patients with respect to the bouts of activity may have limited our ability to design interventions with realistic goals for this population [11]. For patients with other diseases, such as arterial hypertension, information on bout frequency, duration and intensity has enabled the development of recommendations for the primary prevention, treatment and control of this condition [12]. The present study aims to describe the pattern of physical activity and the frequency, duration and intensity of physical activity bouts in patients with COPD, to assess how these patterns differ according to COPD severity, and to explore whether these patients meet the general guidelines for physical activity for older adults.

Methods

Participants

This study is part of the Phenotype and Course of Chronic Obstructive Pulmonary Disease (PAC-COPD) cohort. Patients with a diagnosis of COPD (ratio of the post-bronchodilator forced expiratory volume in 1 s (FEV_1) to the forced vital capacity (FVC) <70%) [13] were recruited at nine tertiary hospitals in Spain [14, 15] and their spirometric severity was classified according to American Thoracic Society/European Respiratory Society criteria [13]. Of the 342 COPD patients included in the PAC-COPD cohort, 177 patients had physical activity data available and were, therefore, included in the present analysis. There were no differences between these patients and the remaining PAC-COPD patients, as previously reported [16]. The study was approved by the ethics committees of all of the participating hospitals and written informed consent was obtained from all of the subjects.

Variables and instruments of measurement

All study tests were carried out on patients in clinically stable conditions at least 3 months after the last recorded exacerbation. Physical activity levels and bouts, and adherence to recommendations were measured using the SenseWear Pro_2 Armband accelerometer (Body Media, Pittsburgh, PA, USA), which has proven a valid tool to measure physical activity in COPD patients [17]. The accelerometer was worn for eight consecutive days and the minimal time was defined, *a priori*, as at least 3 days recording more than 70% of daily time (08:00–22:00 h) [18]. The consistency of accelerometer data was tested by the intra-class correlation coefficient (ICC) of steps per day between all possible combinations of 3 days (ICC 0.95, 95% CI 0.93–0.96). The accelerometer was worn on the right arm and recorded the subjects' movements from lower and upper body. More details on the accelerometer wearing time and recording have been previously published [16].

Support statement: Supported by Fondo de Investigación Sanitaria (FIS PI052292) and Spanish Society of Pneumology and Thoracic Surgery (SEPAR 2004/136). J. Garcia-Aymerich has a researcher contract from the Instituto de Salud Carlos III (CP05/00118), Ministry of Health, Spain. J. de Batlle had a predoctoral fellowship from the Instituto de Salud Carlos III (FI05/01022), Ministry of Health, Spain. D.A. Rodríguez has a long-term research fellowship from the European Respiratory Society (2006/191). The PAC-COPD Study is funded by grants from Fondo de Investigación Sanitaria (FIS PI020541), Ministry of Health, Spain; Agència d'Avaluació de Tecnologia i Recerca Mèdiques (AATRM 035/20/02), Catalonia Government; Spanish Society of Pneumology and Thoracic Surgery (SEPAR 2002/137); Catalan Foundation of Pneumology (FUCAP 2003 Beca Marià Ravà); Red RESPIRA (RTIC C03/11); Red RCESP (RTIC C03/09), Fondo de Investigación Sanitaria (PI052486); Fondo de Investigación Sanitaria (PI052302); Fundació La Marató de TV3 (number 041110); DURSI (2005SGR00392); and an unrestricted educational grant from Novartis Farmacèutica, Spain. CIBERESP and CIBERES are funded by the Instituto de Salud Carlos III, Ministry of Health, Spain. No involvement of funding sources in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication. The researchers are independent from the funders.

 DOI: 10.1183/09031936.00101512

The accelerometer provided a minute-by-minute report for each subject, with values for the number of steps and the metabolic equivalent tasks (METs) that were used to compute the variables of interest.

First, the physical activity was characterised using energy expenditure (MET·min·day^{-1}), time (min·day^{-1}), intensity (METs), time spent in minutes with ⩾1.5 MET and steps (steps per day). Secondly, physical activity bouts were defined as any period of at least 10 min with an intensity ⩾1.5 MET and classified as light, moderate or vigorous according to their median intensity (in METs). The thresholds for moderate and vigorous physical activity were set at 50% and 65% of the maximum oxygen consumption [19] from an incremental test (mean 16 mL·min^{-1}·kg^{-1}, reported elsewhere) [15], following the most recent recommendations on the best practices for the use of objective methods to assess physical activity in studies for adults with functional limitations [20], and resulted in 2.6 and 3.4 MET, respectively [19]. We computed the frequency (bouts per day), duration (minutes per bout), intensity (METs) and total time (min·day^{-1}) in bouts. To exemplify the latter, figure 1 shows a minute-by-minute METs report from the accelerometer in a sample day of a COPD patient, together with the graphical illustration of six physical activity bouts and their duration and median intensity. The ratio of time in physical activity bouts to time in physical activity was also obtained. Thirdly, the adherence to the recommendation for older adults was defined as spending ⩾30 min in moderate activity ⩾5 days per week or spending ⩾20 min in vigorous activity ⩾3 days per week [8]. For both definitions, we distinguished if the minimum time spent in activity was achieved through consecutive minutes or through the accumulation of bouts.

Self-reported physical activities were obtained with the Spanish version of the Yale Physical Activity Survey [21], as previously validated for our COPD population [16]. This questionnaire collects information

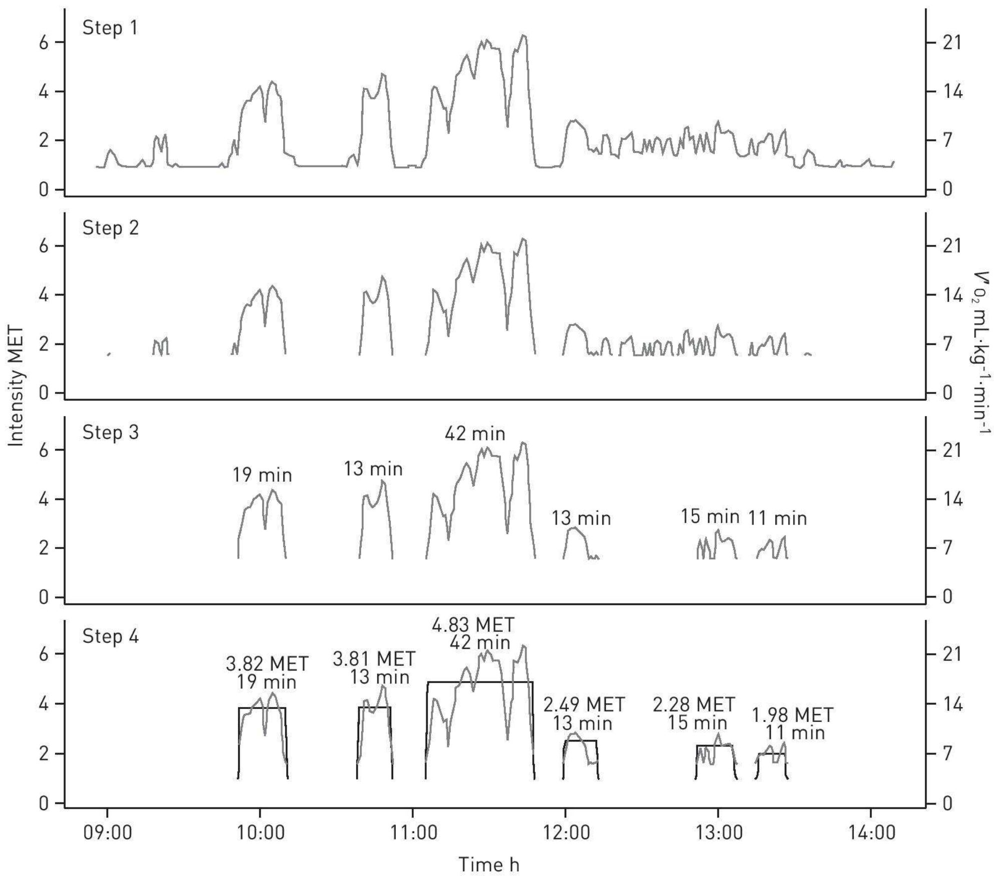

FIGURE 1 Graphical illustration of the process to identify physical activity bouts from the minute-by-minute metabolic equivalent tasks (METs) report of the accelerometer during a sample day in a chronic obstructive pulmonary disease patient. The continuous grey line represents the minute-by-minute MET values recorded by the accelerometer. Step 1 (if required): to format data into the minute-by-minute report of MET values; step 2: to keep minutes in which activity is ⩾1.5 MET; step 3: to calculate the duration of consecutive minutes and keep periods ⩾10 min; step 4: to calculate the average intensity of each bout, to be classified into light, moderate or vigorous according to each population threshold. $V'O_2$: oxygen uptake.

(frequency and duration) on a wide range of activities performed in a typical week of the previous month. Other relevant variables included sociodemographic factors, smoking, Charlson comorbidity index, dyspnoea, the St George's Respiratory Questionnaire, lung function measurements (post-bronchodilator FEV_1, FVC and FEV_1/FVC, residual volume (RV), total lung capacity (TLC), RV/TLC, and arterial oxygen tension, body mass index, fat-free mass index and the 6-min walking distance. Details of these procedures have been published previously [14, 15].

Statistical analysis

Sample size calculations are available in the online supplementary material. The subjects' characteristics and physical activity characteristics are presented as n (%) for categorical variables and mean±SD or median (interquartile range) for continuous variables with normal and non-normal distributions, respectively. Physical activity variables were modelled using Poisson regression. Tests for trends across COPD severity stages were obtained by treating the COPD severity stages as a continuous variable. For sensitivity analyses, we repeated all analyses: 1) using standard cut-off points for intensity of physical activity (3 MET for moderate and 6 MET for vigorous physical activity [9]); and 2) excluding subjects with extreme values (above the 95th percentile) in the number of daily steps recorded by the accelerometer. All analyses were conducted using R 2.14.1 (the R Project for Statistical Computing, www.r-project.org). The scripts for the calculation of bouts are available in the online supplementary material.

Results

Table 1 shows the main characteristics of the patients. Patients wore the accelerometer for a mean of 6 days and recorded a mean of 95% of daily time (13.5 h of 14-h maximum). Almost all COPD patients (98%) participated in physical activity bouts on a daily basis and 57% of their physical activity was performed in bouts (table 2). Median number of daily bouts was 4.4 and 2.6 for all intensities and moderate-to-vigorous intensities, respectively. The median duration of the bouts was ~20 min, irrespective of their intensity. Overall, our patients exhibited moderate exercise limitation and were reasonably active. Exercise capacity and physical activity were moderately correlated (Spearman r=0.54; p<0.001) (online supplementary fig. S1).

TABLE 1 Sociodemographic and clinical characteristics according to levels of chronic obstructive pulmonary disease (COPD) severity

	All COPD patients	Mild COPD	Moderate COPD	Severe COPD	Very Severe COPD
Subjects	177 (100)	9 (5)	87 (49)	64 (36)	17 (10)
Male	166 (94)	6 (67)	82 (94)	63 (98)	15 (88)
Age years	71±8	69±10	71±8	72±7	66±8
Working status: active	15 (8)	0 (0)	10 (11)	4 (6)	1 (6)
Low (IV, V) socioeconomic status#	130 (80)	7 (78)	64 (82)	47 (80)	12 (75)
Current smokers	57 (32)	3 (33)	28 (32)	18 (28)	8 (47)
BMI $kg \cdot m^{-2}$	29±5	28±4	30±5	28±4	25±5
FFMI $kg \cdot m^{-2}$ **#**	20±3	18±3	20±3	19±3	18±3
Dyspnoea mMRC score¶	2.5±1.6	1.3±1.2	2.1±1.5	3.0±1.5	3.5±1.3
Charlson index score+	2.2±1.4	1.7±0.7	2.3±1.5	2.0±1.3	2.2±1.4
SGRQ total score§	32±18	16±12	25±16	37±16	51±17
FEV_1 % pred	52±16	87±7	61±8	41±5	25±4
FEV_1/FVC %#	54±13	67±7	60±9	47±11	35±8
RV/TLC %#	58±10	46±5	54±8	62±8	69±7
P_{aO_2} mmHg#	74±10	81±8	76±10	72±10	69±9
6-min walking distance m#	407±96	450±91	423±86	395±102	349±103
V'_{O_2max} $mL \cdot kg^{-1} \cdot min^{-1}$ **#**	16±4	19±4	16±4	16±5	15±4
V'_{O_2max} MET#	5±1	5±1	5±1	4±1	4±1

Data are presented as n (%) or mean±SD. BMI: body mass index; FFMI: fat-free mass index; mMRC: modified Medical Research Council; SGRQ: St George's Respiratory Questionnaire; FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; P_{aO_2}: arterial oxygen tension; V'_{O_2max}: maximal oxygen uptake; MET: metabolic equivalent task. #: some values are missing for certain variables (15 in socioeconomic status, 13 in FFMI, one in FEV_1/FVC, 11 in RV/TLC, six in P_{aO_2}, 10 in 6-min walking distance and 66 in V'_{O_2max}); missing values were distributed at random and were mainly due to the hospital logistics and patients' availability, as previously published [15]. ¶: out of five; +: out of 30; §: out of 100.

DOI: 10.1183/09031936.00101512

TABLE 2 Characteristics of physical activity and physical activity bouts in chronic obstructive pulmonary disease patients

	All intensities (⩾1.5 MET)	Moderate-to-vigorous intensities (⩾2.6 MET)[#]
Characteristics of physical activity		
Steps per day	5876 (3316–9571)	
Energy expenditure in physical activity MET·min·day^{-1}	424 (234–724)	
Time in physical activity min·day^{-1}	153 (88–232)	
Intensity of physical activity MET	2.7 (2.4–3.1)	
Characteristics of physical activity bouts		
Participation in physical activity bouts n (%)	174 (98)	172 (97)
Frequency bouts·day^{-1}[¶]	4.4 (2–6.5)	2.6 (1.2–4.8)
Duration min·bout^{-1}[¶]	19 (15–24)	20 (16–25)
Intensity MET[¶]	3.1 (2.8–3.5)	3.6 (3.4–3.8)
Time in bouts min·day^{-1}[¶]	86 (34–145)	57 (20–106)
Time in bouts out of total time in activity %[¶]	57 (39–70)	37 (19–52)

Data are presented as median (interquartile range), unless otherwise stated. n=177 patients. MET: metabolic equivalent task; [#]: cut-off points for definition of intensity of physical activity are based on the mean values of maximal oxygen uptake at cardiopulmonary incremental exercise test peak in this population (see methods). [¶]: the frequency, duration, intensity, time in bouts and time in bouts out of total time in activity were only computed for subjects that had at least one bout in the whole recording period.

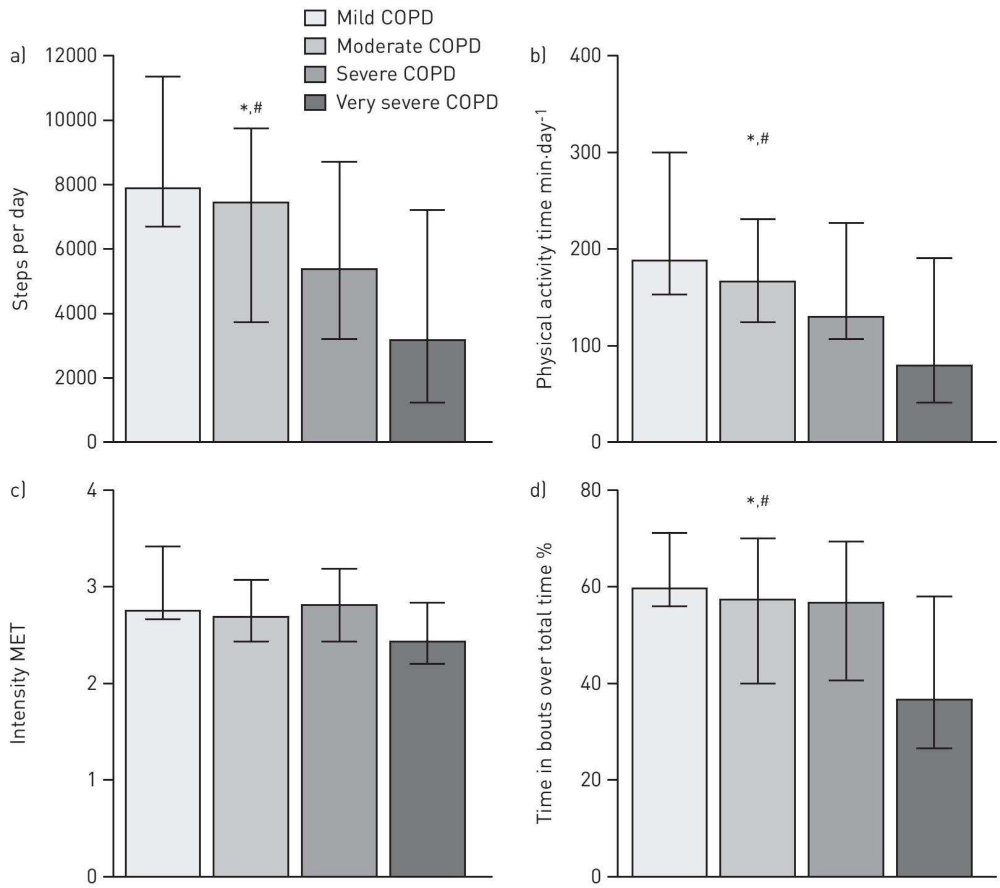

FIGURE 2 Characteristics of physical activity across levels of chronic obstructive pulmonary disease (COPD) severity. Bar plots represent the medians and error bars the interquartile range. a) Total number of steps per day, b) total time in physical activity ⩾1.5 metabolic equivalent tasks (METs), c) mean intensity in physical activity and d) percentage of time in physical activity bouts out of the total time in physical activity. *: p-trend across COPD severity stages <0.05; [#]: p-value comparing mild-to-moderate *versus* severe-to-very-severe COPD <0.05.

Figure 2 shows that the number of steps, time in physical activity and proportion of time in bouts over total time in physical activity exhibited a significant, steady decrease with increasing COPD severity, but no differences in intensity were found. The frequency of the bouts, as well as the total time spent in bouts, decreased with increasing COPD severity (fig. 3). Patients with severe-to-very-severe COPD reported lower participation and less time spent in some of the leisure time activities (gardening and exercising) compared to those with mild-to-moderate COPD, while there were no differences in participation and time spent in household activities or recreational activities (online supplementary table S1).

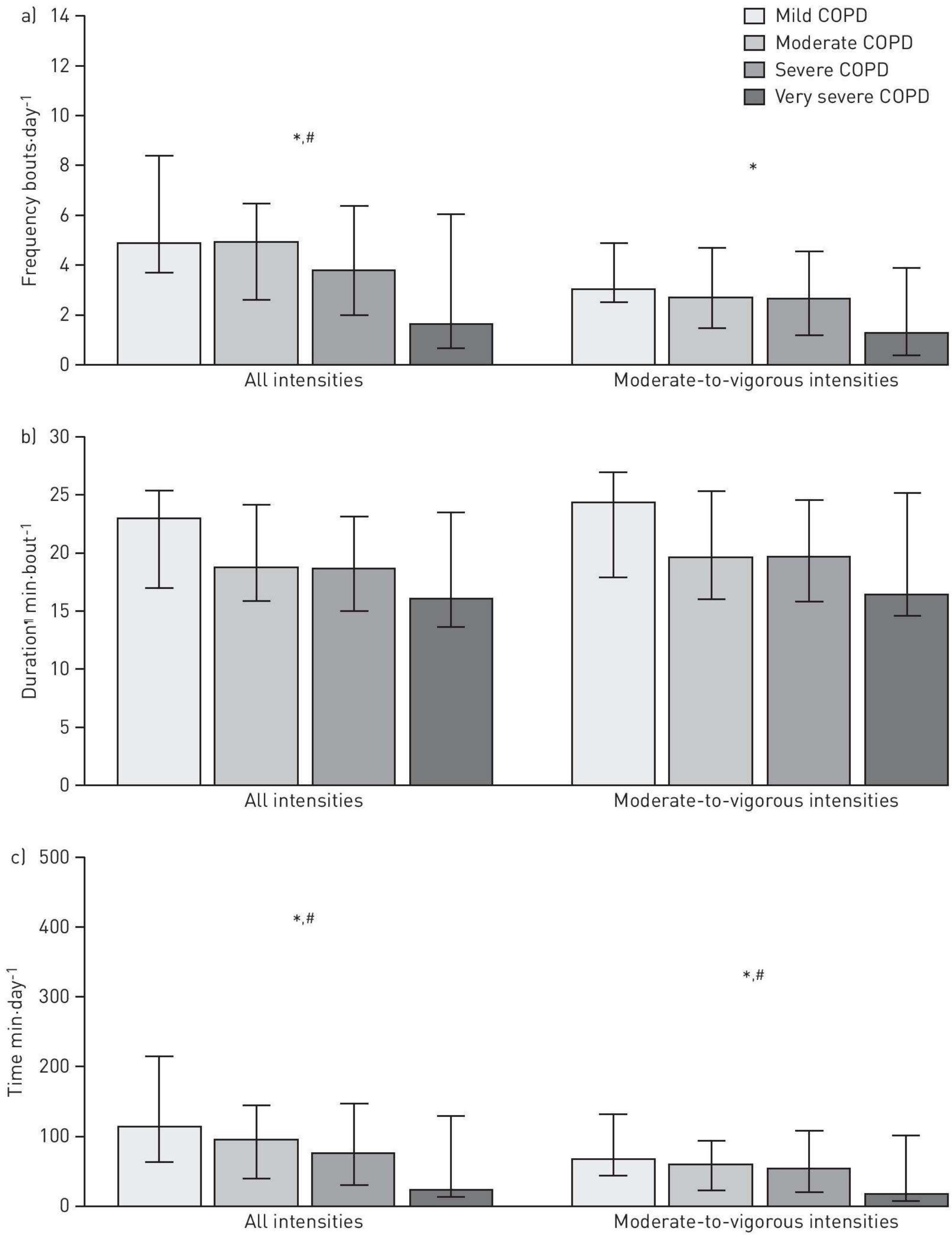

FIGURE 3 Frequency, duration and time in physical activity bouts of all and moderate-to-vigorous intensities, across levels of chronic obstructive pulmonary disease (COPD) severity. Bar plots represent the medians and error bars the interquartile range. a) Number of physical activity bouts per day, b) mean duration of the physical activity bouts and c) total amount of time in physical activity bouts. *: p-trend across COPD severity stages <0.05; #: p-value comparing mild-to-moderate *versus* severe-to-very-severe COPD <0.05; ¶: only patients who participated in bouts.

DOI: 10.1183/09031936.00101512

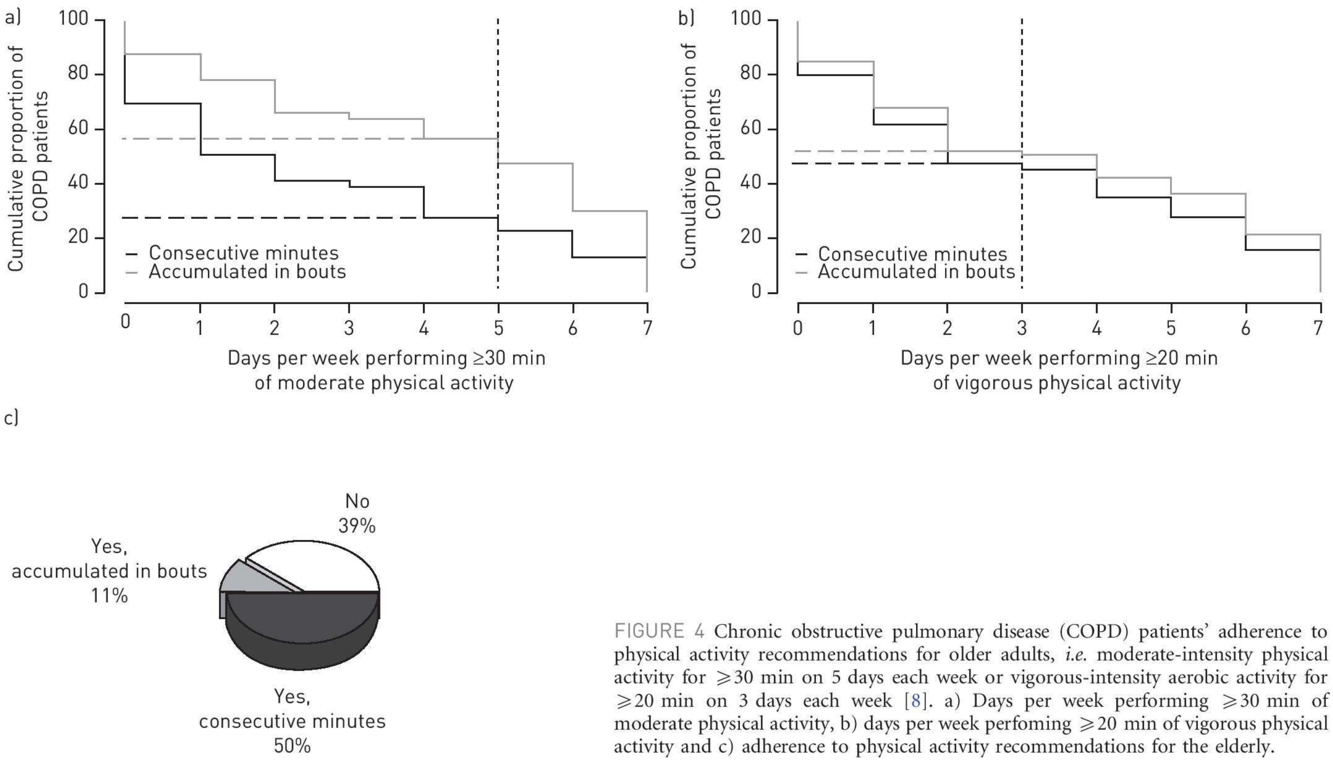

FIGURE 4 Chronic obstructive pulmonary disease (COPD) patients' adherence to physical activity recommendations for older adults, *i.e.* moderate-intensity physical activity for ⩾30 min on 5 days each week or vigorous-intensity aerobic activity for ⩾20 min on 3 days each week [8]. a) Days per week performing ⩾30 min of moderate physical activity, b) days per week perfoming ⩾20 min of vigorous physical activity and c) adherence to physical activity recommendations for the elderly.

Figure 4 shows that about 25% of the COPD patients fulfilled the recommendation of engaging in ⩾30 consecutive minutes of moderate physical activity five or more days per week. The proportion increased to almost 60% when the duration of ⩾30 min per day was achieved through the accumulation of bouts of ⩾10 min duration. Overall, 61% of COPD patients fulfilled the physical activity recommendation for older adults. Table 3 shows that the patients who adhered to this recommendation had reported higher time in leisure activity, primarily yard-work or gardening and recreational activities.

All analyses were repeated using standard cut-off points for the definition of moderate and vigorous intensities of physical activity (online supplementary tables S2 and S3 and figs S2 and S3). Results for participation, frequency, duration and intensity of bouts were very similar. The proportion of COPD

TABLE 3 Self-reported (Yale Physical Activity Survey) time spent weekly in physical activities, according to the adherence to physical activity recommendation for older adults#

	Adherence to physical activity recommendation			p-value¶
	No	Yes, accumulated in bouts ⩾10 min	Yes, in consecutive minutes	
Subjects n (%)	66 (39)	17 (10)	86 (51)	
Household activities h·week^{-1}	8.1±8.1	6.3±7.1	11.5±12.1	0.054
Work activities h·week^{-1}	3.7±11.8	2.4±9.7	5.7±15.2	0.411
Leisure time activities h·week^{-1}	11.6±11	16.2±13.4	16.4±12.3	0.007
Yard work/gardening h·week^{-1}	1.1±4.3	4.1±6.9	3±10.2	0.035
Caretaking h·week^{-1}	0.9±4.5	0±0	0.9±3.5	0.266
Exercise h·week^{-1}	0.7±1.5	2.5±7.6	1.5±3.5	0.217
Recreational activities h·week^{-1}	9±10	9.6±9.6	10.9±7.3	0.017

Data are presented as mean±SD, unless otherwise stated. #: moderate-intensity physical activity for ⩾30 min on 5 days each week or vigorous-intensity aerobic activity for ⩾20 min on 3 days each week [8]; ¶: Kruskal–Wallis test to compare the three groups of adherence to recommendations.

patients fulfilling the physical activity recommendation was reduced from 61% to 50% (online supplementary fig. S3). Sensitivity analysis excluding subjects with extreme values yielded notably similar results.

Discussion

This report is the first assessing bouts of physical activity in COPD patients. It shows that these subjects are able to perform bouts of moderate-to-vigorous physical activity. The severity of COPD is inversely associated with the frequency of bouts. More than 60% of our COPD patients fulfilled the physical activity recommendation for older adults.

Comparison with previous studies

Our results on the patterns of physical activity can be compared with previous research. The COPD patients included in our study walked more (according to steps per day or walking time measures) than COPD patients who participated in previous studies from four different geographic locations [18, 22, 23]. Our patients were older than, and had similar airflow limitation and exercise capacity to patients in these former studies. Interestingly, the time spent in activity was similar across studies, suggesting a higher participation, duration or speed during walking activities in our population. In fact, a previous study found that COPD patients walk 25% slower than healthy age-matched controls [23]. Akin to this finding, only 7% of the walking time in our patients was reported as brisk walking, as compared to 75% in a study with healthy subjects of similar age and geographical location using an identical physical activity questionnaire [24]. Another difference between previous studies and ours is that the earlier studies recruited patients with an established diagnosis of COPD from outpatient clinics, whereas our sample was made up of patients who were recruited after their first COPD admission, one-third of whom were undiagnosed as COPD [14]. Thus, the limiting effects of COPD on activity may be more related to the specific time-point in the course of the disease, rather than to its spirometric severity.

Our results, consistent with previous data that showed that the severity of airflow limitation is related to the level of physical activity [4, 5], provide, for the first time, information on the activity pattern that is behind the differences in levels. Our very severe COPD patients spent a lower proportion of their activity time in bouts, at the expense of reducing bout frequency (fig. 2). The lack of differences in bout duration across severity stages needs to be interpreted with caution; the very severe COPD patients perform bouts that have similar duration to those of patients in other severity stages. However, the lower proportion of time spent in bouts implies that their physical activity is performed in episodes of <10 min duration. The lack of differences in intensity of physical activity across severity stages is well known. It has been hypothesised that COPD patients increase the intensity of their daily physical activities as a result of "trying to perform activities as fast as possible so as to alleviate the unease caused by physical activity" [5]. In our study, patients kept doing both household and recreational activities; the former are likely practised despite disease severity because they are compulsory for daily living, while the latter, more specifically in the case of leisure walking, because they are perceived as healthy, social or simply pleasant. Altogether our findings suggest that the exercise limitation in COPD primarily affects the way patients distribute their periods of activity over time, towards fewer and shorter episodes of uninterrupted activity.

The proportion of COPD patients meeting the physical activity recommendation has been reported to be an important subject for COPD research [10] that had not previously been assessed. We approached this subject by using an objective tool for defining bouts in agreement with the definitions of the international physical activity guidelines, which are widely known, disseminated and implemented in Spain. The comparison with findings from other studies [25, 26] should consider the current evidence that geographical, cultural and lifestyle factors affect the practice of physical activity.

Applicability of the results

There is an emerging need for interventions that aim to increase the physical activity level of COPD patients [10, 27]. These interventions include, but are not restricted to, pulmonary rehabilitation and/or community health promotion programmes and should be considered in addition to the promotion of the light intensity activities frequently performed during daily life [8]. Our detailed assessment of physical activity patterns provides important insight into the design of such interventions. First, the proportion of patients achieving the recommended physical activity levels is elevated when shorter bouts are grouped together, rather than when definitions are restricted to consecutive minutes. Thus, fulfilling the recommendation with short bouts may be more feasible and not necessarily less effective because several clinical trials have demonstrated similar effects in aerobic fitness, weight loss, and other cardiovascular risk factors with either long-bout ($\geqslant 20$ min) or short-bout ($\geqslant 10$ min) interventions [28–30]. Interestingly, in our study, patients fulfilling the recommendation also reported more time engaged in recreational activities. Secondly, it is interesting to note that the way COPD patients seem to adapt to exercise limitation (towards less and shorter periods of

DOI: 10.1183/09031936.00101512

activity, as discussed above) matches with the strategy of interval training that is used in pulmonary rehabilitation, specifically in the most severe patients. We suggest that a meaningful focus of rehabilitation programmes is increasing the frequency of bouts rather than prolonging the duration of current bouts. This is supported by a previous 6-month pulmonary rehabilitation programme, which found that the increase in time spent walking after the intervention was due to an increase in the frequency of short activity blocks (<1 min) rather than to a lengthening of existing periods [31]. Finally, the differing physical activity levels observed between the patients in the current study and the patients from other studies with similar COPD severities or other populations suggest that interventions designed for COPD patients should not only be based on pathophysiology-related limitations but also on the "subjects' needs, goals, and initial abilities", as advocated by the recommendations [8, 9].

Limitations and strengths

The current study has several limitations. The cross-sectional design does not allow for the differences to be interpreted across COPD severity stages, such as the evolution of physical activity over time. The lack of a control (non-COPD) group may be seen as a limitation. However, because the aim of the project was to describe the characteristics of physical activity in COPD patients, we believe that the population addresses the needs of the research question. Unfortunately, the small number of patients in the mild and very severe COPD groups could have led to reduced statistical power to identify as statistically significant the observed differences in physical activity. Despite this fact, our study still includes a considerable number of patients with moderate and severe COPD, which is more than in previous COPD studies [5]. We defined a bout as a minimum of 10 consecutive minutes in activity, according to public health recommendations [32, 33], a definition that has not been consistently applied as yet, such that the comparison of our results with existing research is currently limited. Finally, our findings on physical activity levels and patterns may not be applicable to other COPD groups with more impaired exercise capacity or in other geographical areas, which may differ with respect to climate or lifestyle. However, the relationship between activity levels and patterns with disease severity is still valid and original.

One strength of our study is the large number of patients who were assessed using accelerometry during a period of eight consecutive days. Other physical activity instruments or shorter recording periods would have not allowed for the calculation of weekly patterns of physical activity bouts. The fact that all patients were recruited at the same time-point during the clinical course of COPD allows for the avoidance of the potential confounding factors produced by changes during the course of disease. Finally, we defined the MET cut-off points for moderate and vigorous physical activity according to the mean maximal oxygen uptake during a cardiopulmonary incremental exercise test in the same patients [15, 19]. Setting the cut-off points in this manner is a clear advantage in comparison with previous COPD research that used only the standard intensity cut-offs for the general population, which results in higher relative intensities when applied to older and less fit individuals [19, 20].

Conclusions

In conclusion, COPD patients of all spirometric severity stages engage in physical activity bouts of moderate-to-vigorous intensities. Patients with severe and very severe COPD perform their daily activities in fewer and shorter bouts than those in mild and moderate stages. Interventions that aim to increase the physical activity levels of COPD patients, including physical activity advice and pulmonary rehabilitation programmes, should focus on maximising endurance capacity of the patients.

Acknowledgements

The authors acknowledge E. Gracia and D. Martinez (Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain) for their help in extracting data from the accelerometers. This manuscript was reviewed by two professional medical editors, Mark C and Sarah B, from American Journal Experts.

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DOI: 10.1183/09031936.00101512

SUPPLEMENTARY MATERIAL FOR THE *ERJ* ONLINE DEPOSITORY (PAPER II)

PHYSICAL ACTIVITY IN COPD PATIENTS: PATTERNS AND BOUTS

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SAMPLE SIZE CALCULATIONS

Sample size calculations were performed with the program GRANMO 7.10 [1] and using data from previous research on physical activity from the SenseWear® Pro_2 Armband accelerometer in COPD patients [2,3].

For the estimation of physical activity levels, 163 subjects would have to be recruited to obtain values of steps per day with a precision of +/- 500 units (steps) for an estimated standard deviation of 3000 in the population, assuming that such population is equal to 999999 subjects, accepting an alpha risk of 0.05 for a two-sided test, and anticipating a non-responses rate of 15%. Similarly, and using the same assumptions, 99 subjects would be needed to estimate values of minutes per day in activity with a precision of +/- 15 units (minutes) for an estimated standard deviation of 70 in the population.

Regarding the study of differences across severity groups, the above maximum estimated figure of 163 would allow identifying as statistically significant differences greater than or equal to 1500 steps between two groups of severity, which is lower than differences reported in the literature, accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test.

Finally, the estimated figure of 163 would allow identifying a proportion of 50% or lower in the adherence to physical activity recommendations with a precision of +/- 7 units, under the same assumptions stated above.

The total available sample of 177 COPD patients exceeded the requirements and therefore allows answering the research questions.

R FUNCTION TO CALCULATE BOUTS OF PHYSICAL ACTIVITY

Description

The function `pabout` identifies the bouts performed for an individual, gives the total days registered (n), and characterizes their bouts with the median intensity (METs), duration (min/bout), and time (day).

Usage

`pabout(int,tim,database)`

Arguments

`int`	a numeric value specifying the intensity threshold (in METs) of the bouts
`tim`	a numeric value specifying the minimal duration (in minutes) of the bouts
`database`	name of the accelerometer data.frame in R

The accelerometer data.frame is unique for each subject and includes a row per minute, being all minutes consecutive, with information on only two variables: `date` (as POSIXt class) and `mets`, as follows:

```
date                  mets
2006-09-13 13:32:00   1.216434121
2006-09-13 13:33:00   1.407135248
2006-09-13 13:34:00   1.327723145
```

```
2006-09-13 13:35:00  1.191337228
2006-09-13 13:36:00  0.908973336
2006-09-13 13:37:00  1.057457089
2006-09-13 13:38:00  0.896382630
2006-09-13 13:39:00  0.890199065
…
```

Results

The function results in a database with a single row per each physical activity bout with the following variables:

`id.bout`	identification number of bout
`intensity`	median energy expenditure (METs) per physical activity bout
`duration`	mean time spent per physical activity bout (minutes/bout)
`day`	day when physical activity bouts where registered
`ndays`	total number of days registered

Function

```
pabout <-function(int,tim,database)
{
       require(doBy)
       names(database)<-tolower(names(database))

       if (!is.numeric(int)|!is.numeric(tim))
              stop("\n variable 'int'&'tim' must be a numeric")

       if (!is.data.frame (database))
              stop("\n variable 'database' must be a data.frame")

       if (sum(names(database)=="mets")==0)
              stop("\n No variable called 'mets' in 'database'")

       if (sum(names(database)=="date")==0)
              stop("\n No variable called 'date' in 'database'")

       if (!any(class(database$date)=="POSIXt"))
              stop("\n variable 'date' in 'database' must be a POSIXt")

       if(!max(difftime(tail(database$date,n=-1),head(database$date,n=-
1),units="mins"))==1)
              stop("\n variable 'date' in 'database' must be contain consecutive
minutes")

with(database,{
       pa <- 0
       pa[mets>=int] <- 1

       duration<-rep.int(rle(pa)$lengths, rle(pa)$lengths)
       day<- format(date,format="%Y-%m-%d")
```

```
        nbout<-NA

        bout<-data.frame(id.bout=0,intensity=NA,duration=NA,
              day=0,ndays=length(rle(as.character(day))$values))

        if(length(rle(pa)$lengths[rle(pa)$values==1 &
                    rle(pa)$lengths>=tim])!=0){
                    nbout[duration >=tim & pa ==1]<-
                    rep.int(1:length(rle(pa)$values[rle(pa)$values==1 &
                    rle(pa)$lengths>=tim]),
                    rle(pa)$lengths[rle(pa)$values==1 &
                    rle(pa)$lengths>=tim])

        bout<-data.frame(id.bout=1:max(nbout,na.rm=T),
                    intensity=sapply(1:max(nbout,na.rm=T),function(y)
                    median(mets[nbout==y],na.rm=T)),
                    duration=rle(pa)$lengths[rle(pa)$values==1 &
                    rle(pa)$lengths>=tim],
                    day=sapply(as.data.frame(unclass(table(day,nbout))),whi
                    ch.max),
                    ndays=length(rle(as.character(day
                    [!is.na(day)]))$values)
                    )
        bout}
})
}
```

ADDITIONAL RESULTS (PAPER II)

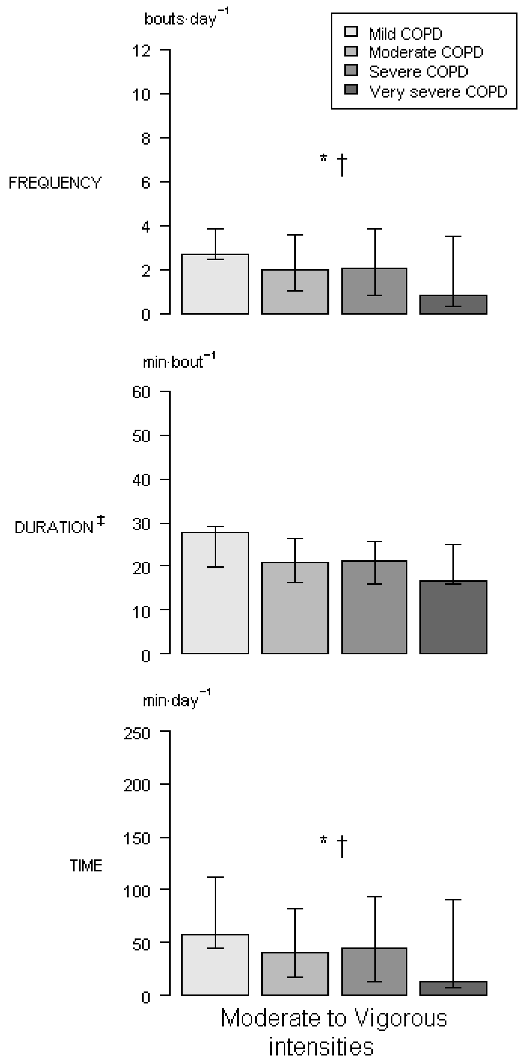
Table S1. Characteristics of physical activity bouts in COPD patients using standard definition of intensity.

	Moderate-to-vigorous intensities (≥ 3 METs)*
	median (25^{th}-75^{th} percentile)
Characteristics of physical activity bouts	
Participation in physical activity bouts, n (%)	168 (95%)
Frequency ($bouts \cdot day^{-1}$) †	2.2 (1-3.9)
Duration ($min \cdot bout^{-1}$) †	21 (16-27)
Intensity (METs) †	3.8 (3.5-4.0)
Time in bouts ($min \cdot day^{-1}$) †	45 (17-91)
Time in bouts out of total time in activity (%)†	29 (16-49)

n: number; m: mean; SD: standard deviation; MET: metabolic equivalent tasks.
* Standard definition of intensity of physical activity [4].

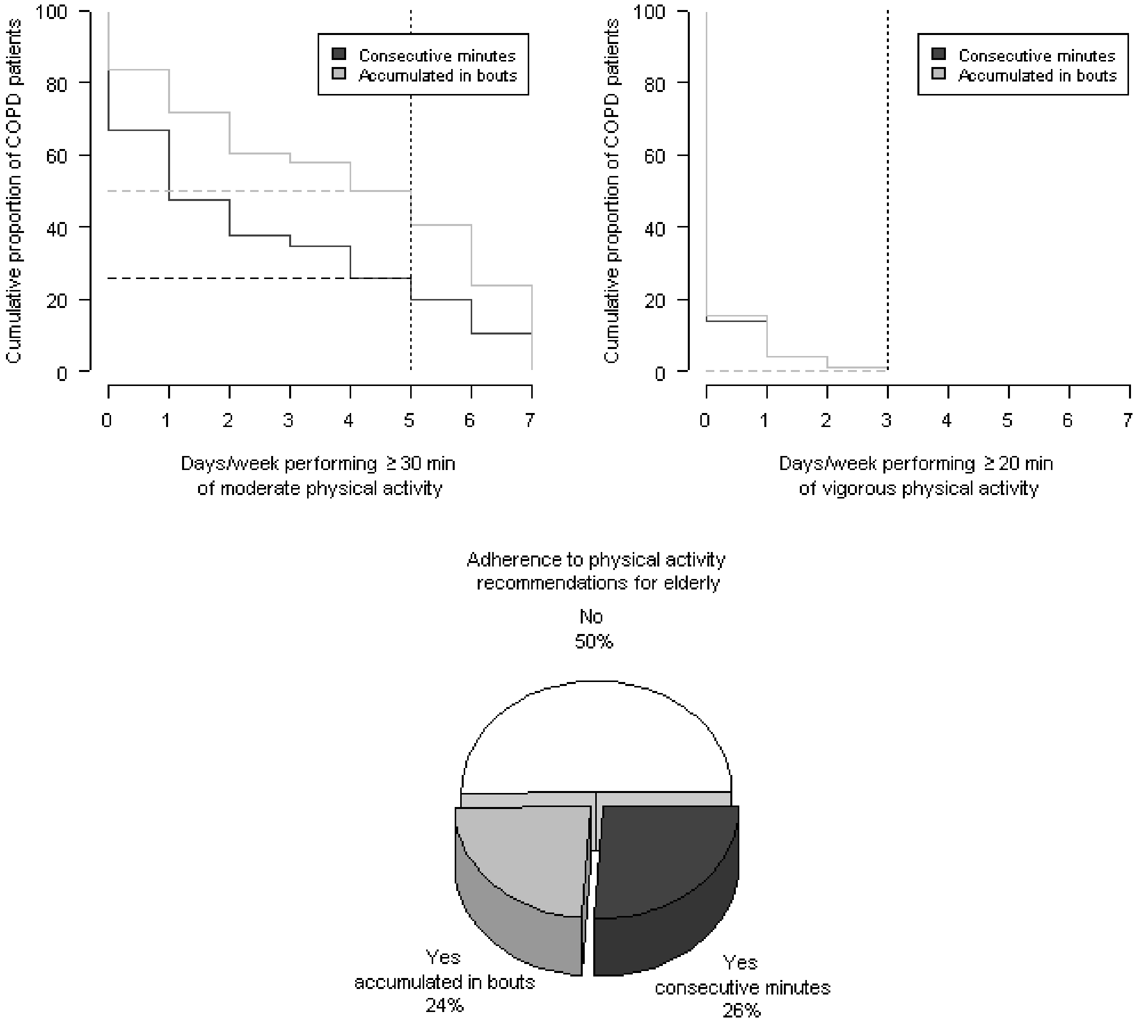
† The frequency, duration, intensity, time in bouts, and time in bouts out of total time in activity were only computed for subjects that had at least one bout in the whole recording period

Figure S1. Frequency, duration, and time in physical activity bouts of moderate-to-vigorous intensities using standard definition of intensity, across levels of COPD severity



* p-trend across COPD severity stages <0.05.
† p-value comparing mild-to-moderate *versus* severe-to-very severe COPD <0.05.
‡ Only patients who participated in bouts.

Figure S2. COPD patients adherence to physical activity recommendations for older adults* using standard definition of physical activity intensity†.



* Moderate-intensity physical activity for a minimum of 30 min on five days each week or vigorous-intensity aerobic activity for a minimum of 20 min on three days each week [5].
† 3 METs for moderate and 6 METs for vigorous physical activity [4].

Table S2. Self-reported (Yale Physical Activity Survey) time spent weekly in physical activities, according to the adherence to physical activity recommendations for older adults* defined using standard cut-offs of intensity†.

	Adherence to physical activity standard recommendations			
	No	**Yes, accumulated in bouts ≥10 min**	**Yes, in consecutive min**	**p-value**
	n= 85 (50%)	**n= 40 (24%)**	**n= 44 (26%)**	
Household activities (h·week^{-1}), m (SD)	8.2 (8.1)	11.7 (13.6)	10.6 (11)	0.322
Work activities (h·week^{-1}), m (SD)	4.5 (12.7)	3.6 (14.1)	5.8 (14.4)	0.53
Leisure time activities (h·week^{-1}), m (SD)	12.3 (11.4)	15.4 (10.6)	18 (13.9)	0.007
Yard work/gardening (h·week^{-1}), m (SD)	1.5 (4.7)	1.7 (4.3)	4.6 (13.7)	0.255
Caretaking (h·week^{-1}), m (SD)	1.1 (4.6)	0.3 (1.4)	0.8 (3.3)	0.519
Exercise (h·week^{-1}), m (SD)	1.2 (4)	1.8 (3.8)	1 (2.3)	0.281
Recreational activities (h·week^{-1}), m (SD)	8.5 (9.3)	11.5 (9.3)	11.5 (6.4)	0.001

* Moderate-intensity physical activity for a minimum of 30 min on five days each week or vigorous-intensity aerobic activity for a minimum of 20 min on three days each week [5]

† Standard cut-offs of intensity of physical activity: 3 METs for moderate and 6 METs for vigorous physical activity [4].

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Paper III: Benefits of physical activity on Chronic Obstructive Pulmonary Disease Hospitalisation depend on Intensity

Donaire-Gonzalez D, Gimeno-Santos E, Balcells E, de Batlle J, Ramon MA, Rodríguez E, Farrero E, Benet M, Guerra S, Sauleda J, Ferrer A, Barberà JA, Rodriguez-Roisin R, Gea J, Agustí A, Antó JM, Garcia-Aymerich J. Benefits of physical activity on Chronic Obstructive Pulmonary Disease Hospitalisation depend on Intensity. Eur Respir J. 2015;XX(X):xxx-xxxx.*

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ERJ Express. Published on July 23, 2015 as doi: 10.1183/13993003.01699-2014

ORIGINAL ARTICLE
COPD

Benefits of physical activity on COPD hospitalisation depend on intensity

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ABSTRACT The present study aims to disentangle the independent effects of the quantity and the intensity of physical activity on the risk reduction of chronic obstructive pulmonary disease (COPD) hospitalisations.

177 patients from the Phenotype Characterization and Course of COPD (PAC-COPD) cohort (mean±SD age 71±8 years, forced expiratory volume in 1 s 52±16% predicted) wore the SenseWear Pro 2 Armband accelerometer (BodyMedia, Pittsburgh, PA, USA) for eight consecutive days, providing data on quantity (steps per day, physically active days and daily active time) and intensity (average metabolic equivalent tasks) of physical activity. Information on COPD hospitalisations during follow-up (2.5±0.8 years) was obtained from validated centralised datasets.

During follow-up 67 (38%) patients were hospitalised. There was an interaction between quantity and intensity of physical activity in their effects on COPD hospitalisation risk. After adjusting for potential confounders in the Cox regression model, the risk of COPD hospitalisation was reduced by 20% (hazard ratio (HR) 0.79, 95% CI 0.67–0.93; p=0.005) for every additional 1000 daily steps at low average intensity. A greater quantity of daily steps at high average intensity did not influence the risk of COPD hospitalisations (HR 1.01, p=0.919). Similar results were found for the other measures of quantity of physical activity.

Greater quantity of low-intensity physical activity reduces the risk of COPD hospitalisation, but high-intensity physical activity does not produce any risk reduction.

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This article has supplementary material available from erj.ersjournals.com

Received: Sept 17 2014 | Accepted after revision: May 28 2015

Introduction

Reducing the frequency of exacerbations in patients with chronic obstructive pulmonary disease (COPD) is a major therapeutic goal [1], since exacerbations accelerate decline in lung function and exercise capacity and jeopardise both quality of life and survival in these patients [1–3]. Moreover, COPD exacerbations are the most frequent cause of medical consultation and hospitalisation in COPD and cause 50–75% of the healthcare costs associated with COPD.

Currently, tobacco smoking cessation and pharmacological treatment of COPD reduce and prevent COPD exacerbations, but lifestyle factors, such as physical activity or diet also modulate them beneficially [3–5]. The evidence from prospective studies supporting the beneficial effects of physical activity in preventing COPD exacerbations is consistent across studies involving different physical activity measures, severity of disease and geographical areas [6]. Yet common limitations of all these previous studies are the lack of control for the previous history of COPD exacerbations, which is now known to be the best predictor of further exacerbations [7], and, in most cases, the lack of an objective physical activity assessment. Similarly, whether these beneficial effects of physical activity are due to its quantity and/or its intensity has never been assessed, despite the fact that intensity of physical activity has been proven important for health benefits in other diseases [8, 9]. This is important because it may give guidance to the implementation of research findings in clinical practice, since no COPD-specific recommendations for an adequate physical activity are available so far.

We hypothesised that both higher quantity and intensity of physical activity could prevent COPD hospitalisations. To test this hypothesis, we assessed the independent effects of the quantity and intensity of objectively measured physical activity on the risk of hospitalisation due to a COPD exacerbation in the Phenotype Characterization and Course of COPD (PAC-COPD) study cohort [10].

Methods

Study design, participants and ethics

This is a prospective longitudinal study nested in the PAC-COPD project, whose methodology and main results have been reported previously [10]. In brief, COPD patients were enrolled during their first hospitalisation due to COPD exacerbation in nine teaching hospitals in Spain. Patients were evaluated 3 months after discharge, when clinically stable (baseline). The diagnosis of COPD was established according to the American Thoracic Society/European Respiratory Society (ERS) guidelines. Patients were invited to participate in a second visit for follow-up assessment 18–24 months later, while clinically stable. In this second visit, a sample of 177 patients, representative of the PAC-COPD cohort [11], accepted the monitoring of their physical activity with an accelerometer (see later). All patients were followed-up until December 31, 2010 or date of death, whichever came first (median 2.6 years). The ethics committees of all the participating hospitals approved the study, and written informed consent was obtained from each participant.

Measurements

Patients were instructed to wear an accelerometer (SenseWear Pro 2 Armband; BodyMedia, Pittsburgh, PA, USA) placed on the right arm during waking hours (08:00–10:00 h) over eight consecutive days. On average, they wore the accelerometer for 6 days and recorded a mean 95% of daytime hours (13.5 h of a maximum 14 h) [11]. The quantity of physical activity was assessed using 1) the number of steps per day; 2) the number of days per week that the patient could be considered physically active, operationally defined by $\geqslant$5000 steps per day [12]; and 3) time (minutes) per day spent in physical activity (defined as any minute with $\geqslant$1.5 metabolic equivalent tasks (METs)). The intensity of physical activity was assessed by the average METs over the time spent in physical activity.

Support statement: Supported by Fondo de Investigación Sanitaria (FIS PI052292) and the Spanish Society of Pneumology and Thoracic Surgery (SEPAR 2004/136). The Phenotype Characterization and Course of COPD (PAC-COPD) study is funded by grants from Fondo de Investigación Sanitaria (FIS PI020541), Ministry of Health, Spain; Agència d'Avaluació de Tecnologia i Recerca Mèdiques (AATRM 035/20/02), Catalonia Government; the Spanish Society of Pneumology and Thoracic Surgery (SEPAR 2002/137); the Catalan Foundation of Pneumology (FUCAP 2003 Beca Marià Ravà); Red RESPIRA (RTIC C03/11); Red RCESP (RTIC C03/09); Fondo de Investigación Sanitaria (PI052486); Fondo de Investigación Sanitaria (PI052302); Fundació La Marató de TV3 (041110); DURSI (2005SGR00392); and unrestricted educational grants from Novartis Farmacèutica (Spain) and AstraZeneca Farmacéutica (Spain). CIBERESP (CIBER Epidemiología y Salud Pública) and CIBERES (CIBER de Enfermedades Respiratorias) are funded by the Instituto de Salud Carlos III, Ministry of Health, Spain. There is no involvement of funding sources in study design; in the collection, analysis, and interpretation of data; in the writing of the report; nor in the decision to submit the article for publication. Researchers are independent from funders. Funding information for this article has been deposited with FundRef.

Conflict of interest: Disclosures can be found alongside the online version of this article at erj.ersjournals.com

 DOI: 10.1183/13993003.01699-2014

The information about COPD hospitalisations (dates and diagnoses at discharge) during the 12 months prior to enrolment (from 2005 to 2006) and during follow-up (from 2006 until December 31, 2010) was obtained from a national administrative database (online supplementary material).

Other measurements included sociodemographic factors, pharmacological and nonpharmacological treatment, smoking habit, dietary habits, comorbidities, health-related quality of life, dyspnoea, complete lung function (including forced spirometry, body plethysmography, diffusing capacity and arterial blood gases), nutritional status, exercise capacity, lung density and structure and systemic inflammation (online supplementary material).

Statistical analysis

Provided that sample size was fixed by the primary scientific objectives of the PAC-COPD study, prior to any analysis we calculated the statistical power to answer our research question with 177 patients using the software GRANMO 7.10 (www.imim.cat/ofertadeserveis/en_granmo.html). Accepting an α risk of 0.05 in a two-sided test, and using our own data about the distribution of physically active:physically inactive COPD patients [11], the statistical power to recognise as statistically significant a risk reduction in COPD hospitalisation was 84%, similar to that reported in previous literature [6].

The relationship between baseline physical activity outcomes and risk of COPD hospitalisation was first tested using the Kruskal–Wallis test and then using Cox proportional hazard regression models. To test the independent effect of quantity and intensity of physical activity, we stratified the association between the three outcomes of quantity of physical activity and COPD hospitalisation according to the average of intensity of physical activity (categorised by its median value in our population (2.7 METs)). Because the effect of quantity variables was restricted to the low-intensity group, multivariate models included an interaction term between each variable of physical activity quantity and intensity (see Results). The treatment of potential confounders and the goodness-of-fit tests are detailed in the online supplementary material. Final models were stratified according to 1) severity of airflow limitation (⩾50% and <50% forced expiratory volume in 1 s (FEV_1)) [2] and 2) having had a COPD hospitalisation in the previous year. We performed additional analysis using the volume of physical activity ($METs \cdot min^{-1} \cdot day^{-1}$) as the exposure. As sensitivity analyses we 1) excluded subjects with extreme values (>95th percentile) in the accelerometer measures; 2) used COPD hospitalisation or all-cause mortality as the outcome; 3) used all-cause hospitalisation as the outcome; and 4) categorised intensity of physical activity in three groups. All analyses were conducted using R 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

We enrolled 177 COPD patients (94% male, mean±SD 71±8 years, FEV_1 52±16% predicted). Table 1 shows their main anthropometric, clinical and functional characteristics. Table 2 shows that patients walked a mean±SD 6663±4675 $steps \cdot day^{-1}$ and were physically active (>5000 $steps \cdot day^{-1}$) a median 4 days per week. During follow-up, 67 (38%) patients suffered at least one COPD hospitalisation. Additionally, 10 patients died during follow-up without having had any hospitalisation; they exhibited lower physical activity levels in all variables than survivors (online supplementary table E1).

The number of daily steps and physically active days at baseline was lower in patients who were hospitalised during follow-up than in those who were not, while no differences were observed with regard to time in activity or intensity of physical activity (table 2). All physical activity variables decreased according to increased severity of airflow limitation in a statistically significant linear pattern (online supplementary table E2). When patients were stratified above or below the median of the average intensity of physical activity (⩾2.7 METs), we observed that the relationship between variables describing the quantity of physical activity and risk of COPD hospitalisations was restricted to those with low average intensity of physical activity (online supplementary table E3). Consequently, physical activity intensity was included as an interaction term in all subsequent analyses.

The multivariate Cox model, adjusted both for potential confounders and the interaction term between intensity and daily steps, showed that for every additional 1000 daily steps at low average intensity, the risk of COPD hospitalisation was reduced by ~20% (hazard ratio (HR) 0.79, 95% CI 0.67–0.93; p=0.005) (table 3). However, increasing the number of daily steps when average intensity of physical activity was high did not result in any reduction in risk of COPD hospitalisation (table 3). This is illustrated in figure 1. Similar results were observed for the other two variables describing the quantity of physical activity (number of physically active days and time in activity) (table 3). After stratification according to airflow limitation, in patients with severe to very severe airflow limitation (FEV_1 <50% pred) high quantity of activity at high average intensity was associated with a higher risk of COPD hospitalisation (fig. 2 and online supplementary table E4). Stratification of patients by hospitalisation for COPD in the previous year (online supplementary table E5), additional analysis using volume of physical activity as the exposure

TABLE 1 Sociodemographic, clinical and functional characteristics of participants

	All	COPD hospitalisation		p-value
		No	Yes	
Baseline				
Subjects n	177	110	67	
Male	166 (94)	103 (94)	63 (94)	1.000
Age years	71±8	70±8	71±8	0.725
Marital status married	146 (83)	94 (86)	52 (78)	0.222
Family >2 members	79 (45)	52 (47)	27 (40)	0.436
Primary education or higher	106 (60)	69 (63)	37 (55)	0.346
Active workers	15 (8)	12 (11)	3 (5)	0.171
Low socioeconomic status (level IV or V)#	130 (80)	82 (80)	48 (80)	1.000
Current smokers	57 (33)	37 (34)	20 (30)	0.765
BMI $kg \cdot m^{-2}$	29±5	29±5	28±5	0.054
FFMI# $kg \cdot m^{-2}$	20±3	20±3	19±3	0.168
Dyspnoea mMRC score 0–4	1 (1–2)	1 (0–2)	2 (1–4)	<0.001
Charlson index score 0–30	2 (1–3)	2 (1–3)	2 (1–3)	0.537
Cardiovascular disease	30 (17)	18 (16)	12 (18)	0.838
SGRQ total score 0–100	32±18	26±16	41±18	<0.001
FEV_1 % pred	52±16	57±16	43±14	<0.001
COPD grade				
Mild (FEV_1 ≥80% pred)	9 (5)	9 (8)	0 (0)	<0.001
Moderate (FEV_1 50–80% pred)	87 (49)	67 (61)	20 (30)	
Severe (FEV_1 30–50% pred)	64 (36)	31 (28)	33 (49)	
Very severe (FEV_1 <30% pred)	17 (10)	3 (3)	14 (21)	
RV/TLC# %	58±10	56±10	61±9	<0.001
D_{LCO}# % pred	63±21	67±20	57±20	0.004
P_{aO_2}# mmHg	74±10	76±9	70±10	<0.001
6-min walking distance# m	407±96	424±91	379±100	0.003
V'_{O_2max}#,¶ % pred	16±4	17±4.6	15±3.9	0.028
≥1 COPD hospitalisation in the previous 12 months	29 (16)	6 (6)	23 (34)	<0.001
Previous COPD hospitalisations in the previous 12 months+	1.4 (0.8)	1.0 (0.0)	1.5 (0.9)	<0.001
CRP ≥3 $mg \cdot L^{-1}$	119 (67)	75 (74)	44 (69)	0.596
Lung density# HU	−842±41	−849±26	−832±55	0.215
Emphysema# % lung tissue <−950 HU	31±14	31±15	30±13	0.681
Bronchial wall thickness extension score# (0–3)	2.0±1.4	1.8±1.4	2.1±1.3	0.295
Follow-up				
Duration of follow-up years	2.6 (2.0–3.2)			
Participation in any pulmonary rehabilitation programme	19 (11)			
COPD hospitalisation during follow-up	67 (38)			
COPD hospitalisations§ n	2 (1–3)			
Time to first COPD hospitalisation§ years	0.7 (0.3–1.3)			
Mortality	28 (16)			

Data are presented as n, n (%), mean±SD or median (interquartile range), unless otherwise stated. COPD: chronic obstructive pulmonary disease; BMI: body mass index; FFMI: fat-free mass index; mMRC: modified Medical Research Council; SGRQ: St George's Respiratory Questionnaire; FEV_1: forced expiratory volume in 1 s; RV: residual volume; TLC: total lung capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; % pred: % predicted; P_{aO_2}: arterial oxygen tension; V'_{O_2max}: maximal oxygen uptake; CRP: C-reactive protein. #: some variables have missing values: socioeconomic status (n=15), FFMI (n=13), RV/TLC (n=11), D_{LCO} (n=17), P_{aO_2} (n=6), 6-min walking distance (n=10), V'_{O_2max} (n=66), CRP (n=11), lung density and emphysema (n=112) and bronchial wall thickness (n=96). Missing values were distributed at random and were mainly due to the hospital logistics and patient availability, as previously published [10]. ¶: during exercise testing using the reference values of NEDER *et al.* [13]; +: n=29; §: n=67.

(online supplementary table E6), as well as the sensitivity analyses (online supplementary tables E7, E8, E9 and E10) all yielded similar results.

Discussion

The main finding of our study is that increased quantity of physical activity reduces the risk of future COPD hospitalisations when the average intensity of physical activity is low. The finding that high quantity of physical activity at high average intensity of physical activity may be unhelpful in COPD patients with severe to very severe airflow limitation was unexpected and will require replication. The sensitivity analyses showed that our results were very stable in relation to changes in the selection of subjects, variables and the use of different outcome measures.

DOI: 10.1183/13993003.01699-2014

TABLE 2 Characteristics of patients' physical activity at baseline and according to hospitalisations for chronic obstructive pulmonary disease (COPD) during follow-up

	All patients	COPD hospitalisation		p-value
		No	Yes	
Subjects	177	110	67	
Physical activity steps·day^{-1}	6663±4675	7470±4939	5339±3890	0.003
Physically active days per week#	4 (1–7)	5 (2–7)	2 (0–7)	0.007
Time in physical activity min·day^{-1}	176±123	185±131	160±108	0.272
Average intensity of physical activity METs	2.8±0.5	2.8±0.5	2.8±0.6	0.258

Data are presented as n, mean±SD or median (interquartile range), unless otherwise stated. METs: metabolic equivalent tasks. #: defined as ⩾5000 steps·day^{-1} [12].

Comparison with previous studies

This is the first study that unravels the independent role of the quantity and the intensity of physical activity on the risk of COPD hospitalisations. Previous research consistently demonstrated that higher quantity of physical activity reduces the risk of future COPD exacerbation/hospitalisation [6]. However, some of these previous studies [14–16] measured the quantity of physical activity using variables of energy expenditure (MET-h per week or -kcal per day) that also included intensity in their calculation [17]. In view of the results of the study, this should be taken into account more carefully since it could reduce the beneficial effects of physical activity on COPD hospitalisation risk. It is worth noting that the only study that has used an objective tool (pedometer) to assess the quantity of physical activity found a risk reduction almost identical to that observed in the study (20% for every additional 1000 steps) [18].

TABLE 3 Adjusted# association between physical activity variables and hospitalisation for chronic obstructive pulmonary disease (COPD) (multivariate Cox proportional hazards regression)

	HR (95% CI)	p-value	R^2
Subjects n	177		
Steps per day (change for each 1000 steps per day)	0.79 (0.67–0.93)	0.005	0.33
High average intensity of physical activity (⩾2.7 METs)	2.71 (1.27–5.81)	0.010	
Interaction: steps×intensity	1.28 (1.06–1.53)	0.009	
⩾1 COPD hospitalisation in the previous 12 months	5.17 (2.95–9.06)	<0.001	
FEV_1 % pred	0.96 (0.95–0.98)	<0.001	
Physically active days per week (change for 1 day per week)	0.79 (0.67–0.93)	0.005	0.32
High average intensity of physical activity (⩾2.7 METs)	2.12 (1.10–4.09)	0.025	
Interaction: days×intensity	1.37 (1.10–1.70)	0.005	
⩾1 COPD hospitalisation in the previous 12 months	5.19 (2.97–9.07)	<0.001	
FEV_1 % pred	0.96 (0.94–0.98)	<0.001	
Time in physical activity (change for 1 h per day)	0.79 (0.63–0.99)	0.039	0.31
High average intensity of physical activity (⩾2.7 METs)	1.64 (0.95–2.85)	0.078	
Interaction: time×intensity	1.36 (1.01–1.82)	0.041	
⩾1 COPD hospitalisation in the previous 12 months	5.51 (3.16–9.62)	<0.001	
FEV_1 % pred	0.96 (0.94–0.98)	<0.001	

Data are presented as n, unless otherwise stated. An increase of 1000 steps per day at low average intensity of physical activity is related to reduced COPD hospitalisation risk (hazard ratio (HR) 0.79); high average intensity of physical activity without increasing the number of steps is related to increased COPD hospitalisation risk (HR 2.71); an increase of 1000 steps per day at high average intensity of physical activity is not related to COPD hospitalisation risk (HR 0.79×1.28=1.01). METs: metabolic equivalent tasks; FEV_1: forced expiratory volume in 1 s. #: other potential confounders (sex, age, education, marital status, family members, working status, socioeconomic status, inhaled bronchodilators or corticosteroids, smoking status, smoking duration and intensity, Charlson index, cardiovascular comorbidities, modified Medical Research Council dyspnoea score, health-related quality of life, forced vital capacity, residual volume/total lung capacity, diffusing capacity of the lung for carbon monoxide, arterial oxygen tension, body mass index, fat-free mass index, 6-min walking distance, maximal oxygen uptake, lung density and structure, C-reactive protein, tumour necrosis factor-α, participation in a pulmonary rehabilitation programme and consumption of fruits, vegetables and cured meats) were not finally included in multivariate models because they did not relate to the outcome nor did they modify the coefficient estimate for the exposure >10%.

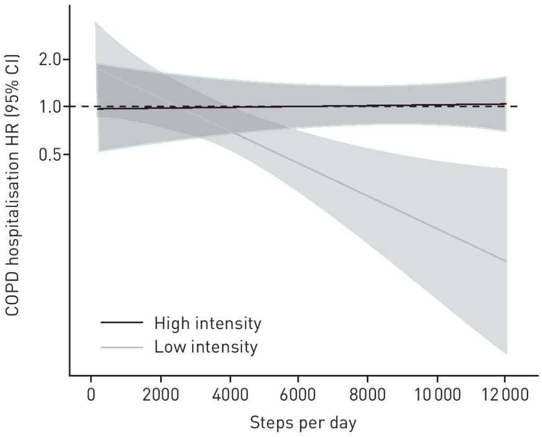

FIGURE 1 Dose–response relationship between steps per day and hazard ratio (HR) of hospitalisation for chronic obstructive pulmonary disease (COPD), according to intensity of physical activity (multivariate Cox proportional hazards regression). Hazard ratio was computed at each intensity value as the rate between hazard at each intensity value and average hazard of the sample. The model was adjusted for confounders as detailed in table 3.

The modifying effect of intensity of physical activity in the reported associations between its quantity and the risk of future hospitalisation is a novel finding in the COPD literature, although it has been previously reported in healthy elderly people, where health benefits were mainly related to low intensity of physical activity [8, 19, 20]. Specifically in the elderly, low-intensity physical activity has been shown to provide wellbeing benefits that were not found with moderate-to-vigorous physical activity [19]. It has been suggested that individuals engaging in more activities in the low intensity range (*e.g.* leisure-time walking) are more likely to have less stress, increased socialisation and greater quality of life [19]. Furthermore, low-intensity physical activity shows slight advantages over vigorous physical activity in reducing tumour necrosis factor-α and rising insulin-like growth factor binding protein-3 levels in aged people [20].

Interpretation of findings

The interpretation of the results for intensity of physical activity requires prior clarification. First, the intensity of physical activity is usually measured by METs, which express the ratio of energy expenditure

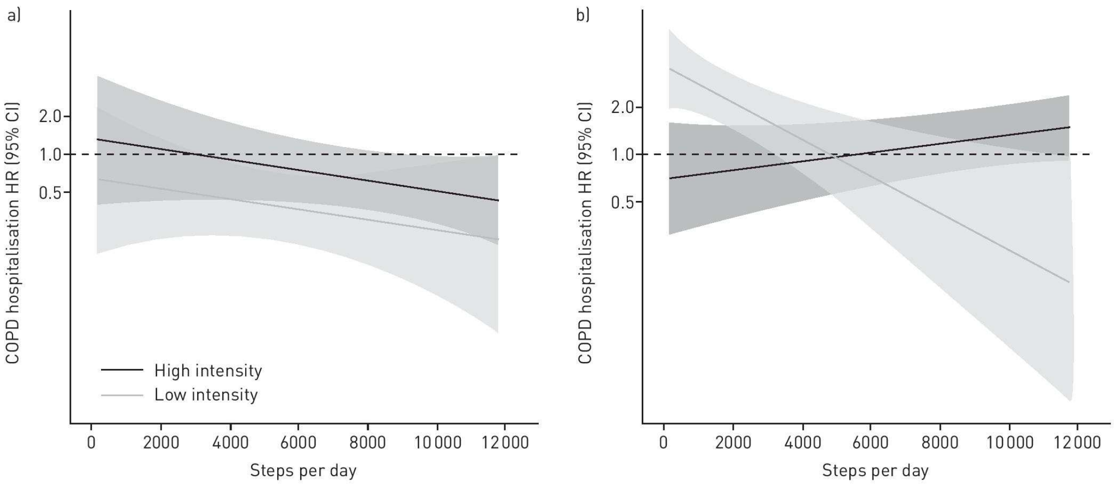

FIGURE 2 Dose–response relationship between steps per day and hazard ratio (HR) of hospitalisation for chronic obstructive pulmonary disease (COPD), according to intensity of physical activity and severity of airflow limitation: a) severe to very severe (forced expiratory volume in 1 s (FEV_1) ⩾50% pred); b) mild to moderate (FEV_1 <50% pred). Hazard ratio was computed at each intensity value as the rate between hazard at each intensity value and the average hazard of the sample. The model was adjusted for confounders as detailed in table 3.

DOI: 10.1183/13993003.01699-2014

during a specific physical activity in relation to the energy expenditure at rest. However, the relative metabolic demand (and, as a result, symptom perception) produced by a specific physical activity does not depend only on its MET value but also on the maximum intensity achievable by each subject. In fact, it is well known that for a given activity, COPD patients use a higher proportion of their metabolic and ventilatory capacities than their healthy peers [21]. Thus, the consideration about what is low- or high-intensity physical activity differs depending on the population under study [17]. Second, it is also important to consider that the intensity was defined in our study as the average of METs during all periods spent in physical activity. This included basic activities of daily living, which represent the greater part of patients' time, and have an intensity of ~1.5 METs. Thus, to achieve a mean of 3 METs over 1 week, patients need to spend a large proportion of time at very high intensities most days of the week. Third, similarly to the framework that considers physical activity and exercise as different concepts [22], our average intensity of physical activity was conceptually different to an average intensity of exercise. Consequently, our results should not be interpreted as a contradiction of pulmonary rehabilitation programmes, which may include exercise of high intensity, because the impact of the latter on the daily average intensity of physical activity will be very small. In summary, our results support a beneficial effect of physical activity when the average of intensity is low, *i.e.* if only a small proportion of the daily time in physical activity is spent at high intensity levels. By contrast, when a large proportion of the time in physical activity is spent at higher intensities, physical activity appears no longer beneficial, a finding that will require replication.

Several mechanisms have been proposed as responsible for the beneficial effects of physical activity in COPD patients which could ultimately reduce the risk of exacerbations (and subsequent hospitalisations). First, moderate levels of physical activity have been shown to reduce the circulating levels of a number of inflammatory markers, both in experimental and observational studies, as well as in COPD populations [23–25]. Second, the regular practice of physical activity promotes more efficient oxygen delivery to respiratory muscles and improves the oxidative capacity of the muscles in COPD patients [26]. Regular physical activity has also been associated with higher levels of diffusing capacity of the lung for carbon monoxide, maximal expiratory pressure, 6-min walking distance and maximal oxygen uptake in COPD patients [25]. Studies on the effects of physical activity suggest that additional mechanisms may play a role in our observed increased risk of hospitalisation in the inactive patients, including 1) reduced nitric oxide production leading to deleterious vascular effects and loss of its bronchodilator effect [27]; 2) deregulation of gene expression of the β_2-adrenergic receptor, therefore possibly inducing a poorer response to therapy [28]; and 3) increased susceptibility to respiratory infections in COPD patients due to a reduction in the number and function of cells mediating cytotoxic activity [29].

Our novel findings of an unhelpful effect of higher quantity of high-intensity physical activity in severe to very severe COPD patients are supported by previous research in COPD patients, healthy subjects, elite athletes and animals. First, strenuous exercise is accompanied by an increase in circulating pro-inflammatory and inflammation-responsive cytokines [30], a response that is exaggerated in specific populations, such as overweight children [31]. In COPD patients, high-intensity exercise alters the nitroso-redox balance, which cannot be balanced by antioxidant mechanisms [26]. Studies in elite athletes have shown an association between high intensity of physical activity and increased airways inflammatory cells, as well as respiratory infections [32], which has been attributed to exercise-induced immune-suppressive effects of exercise, mostly affecting cell immunity. Finally, studies in animals suggest additional effects of high intensity of physical activity, such as the induction to apoptosis of inflammatory cells, mostly in elderly animals [33]. The complex role of physical activity in the immune system is still a matter of debate, more so in diseases with a high inflammatory component, such as COPD [29].

Clinical implications of results

Several of the observations of our study can have clinical implications for the recommendations about daily physical activity to COPD patients. This is an added value in the management of these patients, since no COPD-specific recommendations are available so far [1, 2]. The linear dose–response relationship between quantity of low-intensity physical activity and the risk of COPD hospitalisations (fig. 2) suggests that there is no threshold, either low or high, to achieve clinical benefits. In addition to existing research [6], our results provide evidence to consider in the current COPD guidelines/strategies that COPD patients in general should be encouraged to perform an extra quantity of low-intensity physical activity during their daily life. Furthermore, the data suggest that research aiming to assess the effectiveness of physical activity interventions should consider several physical activity outcomes, including the proportion of individuals meeting certain physical activity goals [34], extra steps per day [35] and the changes, if any, in average intensity.

Strengths and limitations

Our study has several strengths and limitations. The extensive clinical, physiological and biological characterisation of participants within the framework of the PAC-COPD study [10] allowed the inclusion of potential confounders in the analysis, including history of previous COPD hospitalisations, which was not considered in previous studies [15, 16, 36]. Likewise, the use of an objective method to quantify physical activity (and the high compliance level) contrasts with previous studies that mainly used self-reported questionnaires [14, 15, 36, 37], reduces misclassification and allows the dissection of the role of different physical activity characteristics. In theory, our results could be explained by reverse causation, *i.e.* that hospitalisations reduce physical activity. Against this possibility is the fact that we recruited participants prospectively during their first COPD hospitalisation, that we followed them up for several years, that we restricted our current analysis to the next COPD hospitalisation and that we included the history of previous COPD hospitalisations as an adjusting variable. Another potential limitation of our study is the possibility of survival bias, namely that patients may die (and are therefore censored) before a COPD hospitalisation occurs. However, given that these patients performed low levels of physical activity (online supplementary table E1), the magnitude of the protective effect of physical activity on COPD hospitalisations is probably reduced. Likewise, the technological restrictions of the accelerometer to assess certain activities, such as cycling or swimming, could also be seen as a limitation. Similarly, the activity monitors can not yet be sufficiently accurate to identify small variations in the intensity of physical activities. However, it is now well recognised that accelerometers constitute the best tool to evaluate the quantity and intensity of physical activity during the activities of daily life; moreover, the specific accelerometer that we used is among the most valid [38]. It could also be argued that a single week of physical activity measurement may have resulted in some misclassification of patients' usual physical activity, because of season variation or low representativeness of that particular week. In either case, this would result in a reduction of the effect of physical activity. Our sample size was not large enough to assess the role of other physical activity characteristics such as frequency and duration of physical activity bouts, nor to assess the effects of physical activity on specific subgroups, such as patients with mild and very severe COPD. Finally, although the characteristics of our population, *i.e.* mainly retired, low socioeconomic status and having at least one previous COPD hospitalisation, may be characteristics that differ from other COPD cohorts, this probably does not affect the observed association of quantity and intensity of physical activity with COPD hospitalisations. In keeping with patterns of tobacco consumption in Europe, a majority of our patients were male; as there is evidence of sex-related differences in the effects of physical activity there is a need to replicate this study in females [39].

In conclusion, a greater quantity of low-intensity physical activity reduces the risk of COPD hospitalisation. The observation that high-intensity daily-life physical activity does not generate additional protective effects in the most severe COPD patients will require replication.

Acknowledgements

Members of the Phenotype Characterization and Course of COPD (PAC-COPD) Study Group are as follows. Josep M. Antó (Principal Investigator), Judith Garcia-Aymerich (project coordinator), Marta Benet, Jordi de Batlle, Ignasi Serra, David Donaire-Gonzalez and Stefano Guerra: Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain; Joaquim Gea (centre coordinator), Eva Balcells, Àngel Gayete, Mauricio Orozco-Levi and Ivan Vollmer: Hospital del Mar-IMIM, Barcelona; Joan Albert Barberà (centre coordinator), Federico P. Gómez, Carles Paré, Josep Roca, Robert Rodriguez-Roisin, Àlvar Agustí, Xavier Freixa, Diego A. Rodriguez, Elena Gimeno-Santos and Karina Portillo: Hospital Clínic-Institut D'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona; Jaume Ferrer (centre coordinator), Jordi Andreu, Esther Pallissa and Esther Rodríguez: Hospital General Universitari Vall D'Hebron, Barcelona; Pere Casan (centre coordinator), Rosa Güell and Ana Giménez: Hospital de la Santa Creu i Sant Pau, Barcelona; Eduard Monsó (centre coordinator), Alicia Marín and Josep Morera: Hospital Universitari Germans Trias i Pujol, Badalona, Spain; Eva Farrero (centre coordinator) and Joan Escarrabill: Hospital Universitari de Bellvitge, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), L'Hospitalet de Llobregat, Spain; Antoni Ferrer (centre coordinator): Hospital de Sabadell, Corporació Parc Taulí, Institut Universitari Parc Taulí (Universitat Autònoma de Barcelona), Sabadell, Spain; Jaume Sauleda (centre coordinator) and Bernat Togores: Hospital Universitari Son Dureta, Palma de Mallorca, Spain; Juan Bautista Gáldiz (centre coordinator) and Lorena López: Hospital Universitario de Cruces, UPV, Barakaldo, Spain; José Belda: Instituto Nacional de Silicosis, Oviedo, Spain.

The authors acknowledge Milo Puhan (Johns Hopkins University, Baltimore, MD, USA) for his helpful comments on a previous version of the manuscript, Esther Gracia and David Martinez from the Centre for Research in Environmental Epidemiology (CREAL) for their help in extracting data from the accelerometers, and the Conjunto Mínimo Básico de Datos de Altas Hospitalarias (CMBDAH) from Catalonia, the Basque Country and the Balearic Islands for providing the information on hospitalisation data.

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ONLINE SUPPLEMENT (PAPER III)

BENEFITS OF PHYSICAL ACTIVITY ON CHRONIC OBSTRUCTIVE PULMONARY DISEASE HOSPITALISATION DEPEND ON INTENSITY

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METHODS (complete version)

RESULTS:

- **Table E1.** Characteristics of physical activity at baseline, according to outcomes (hospitalisation or death) during follow-up.
- **Table E2.** Characteristics of physical activity of the patients at baseline, according to levels of COPD severity.
- **Table E3.** Characteristics of physical activity at baseline, according to intensity and COPD hospitalisation during follow-up.
- **Table E4.** Adjusted association between physical activity quantity (steps per day) and COPD hospitalisation, according to spirometric COPD severity (multivariate Cox proportional hazards regression).
- **Table E5.** Adjusted association between physical activity quantity (steps per day) and COPD hospitalisation, according to having had a COPD hospitalisation in the previous 12 months (multivariate Cox proportional hazards regression).
- **Table E6.** Adjusted association between volume and intensity of physical activity and COPD hospitalisation (multivariate Cox proportional hazards regression).
- **Table E7.** Adjusted association between physical activity quantity (steps per day) and COPD hospitalisation, after excluding patients with extreme values (>95th percentile) in steps per day (multivariate Cox proportional hazards regression).
- **Table E8.** Adjusted association between physical activity quantity (steps per day) and COPD hospitalisation or all-cause mortality (multivariate Cox proportional hazards regression).
- **Table E9.** Adjusted association between physical activity variables and all-cause hospitalisation (multivariate Cox proportional hazards regression).
- **Table E10.** Adjusted association between physical activity quantity (steps per day) and COPD hospitalisation categorising intensity in three groups (multivariate Cox proportional hazards regression).

SUPPLEMENT REFERENCES

METHODS (complete version)

Study Design, Participants and Ethics

The design, methodology and main results of the "Phenotype characterisation and course of chronic obstructive pulmonary disease" (PAC-COPD) study have been reported before[1, 2]. In brief, COPD patients were enrolled during their first hospitalisation due to COPD exacerbation in nine teaching hospitals in Spain. Patients were evaluated three months after discharge, when clinically stable (baseline). The diagnosis of COPD was established according to the ATS-ERS guidelines (post-bronchodilator forced expiratory volume in the first second to forced vital capacity ratio (FEV_1/FVC) <0.70). Patients were invited to participate in a second visit for follow-up assessment 18-24 months later while clinically stable. From 251 patients who were participating in the PAC-COPD study in this second visit, 177 (70%) accepted to measure PA with an activity monitor (see below). There were no differences between them and those who did not participate, as previously shown[3]. All patients were followed up until December 31st, 2010 or date of death, whichever came first (median 2.6 years). The Ethics Committees of all the participating hospitals approved the study, and written informed consent was obtained from all subjects.

Measurements

Patients were instructed to wear an accelerometer (SenseWear® Pro2 Armband. SWA; Body Media, Pittsburgh, PA) placed on the right arm during waking hours (aprox, from 8.00 am through 10.00 pm) in 8 consecutive days, just after the clinical examination (described below). On average, they wore the accelerometer six days, and recorded a mean of 95% of daytime (13.5 h of 14 h maximum)[4]. This device provides minute by minute information on subjects' movements and physiological response, which allowed obtaining measures of quantity and intensity of PA. The *quantity* of PA was assessed using: (i) the number of steps per day, (ii) the number of days per week that the patient could be considered physically active, operationally defined by ≥ 5000 steps per day[5, 6]; and (iii) time (minutes) per day spent in PA (defined as any minute with ≥ 1.5 Metabolic Equivalent Tasks (METs)). The *intensity* of PA was assessed by the average of METs during the time spent in PA.

We obtained information about hospitalisations (dates and diagnoses on discharge) during the 12 months prior to enrollment (i.e. from 2005 to 2006) and during follow up (from 2006 until December 31st, 2010), from the Minimum Basic Dataset (CMBD) that covers all Spanish hospitals. We defined a COPD hospitalisation as any hospitalisation whose primary cause of hospitalisation at discharge corresponds to codes 490-496, or primary cause is 466 or 518.81 if second cause was 491.21, according to the International Classification of Diseases, 9th revision.

As reported elsewhere in detail[1] other measurements included socio-demographic factors, pharmacologic and non-pharmacologic treatment (e.g., pulmonary rehabilitation, long-term oxygen therapy), smoking habit, dietary habits, co-morbidities (Charlson index), health-related quality of life (St George Respiratory Questionnaire (SGRQ)), dyspnoea (modified Medical Research Council dyspnoea scale (mMRC)), complete lung function (including forced spirometry (post-bronchodilator FEV_1, FVC, FEV_1/FVC), static lung volumes by body plethysmography (residual volume (RV), total lung capacity (TLC), RV/TLC), single-breath carbon monoxide lung diffusing capacity (DLco), and arterial blood gases), nutritional status (body mass index (BMI) and fat free mass index (FFMI) by body impedance), exercise tolerance (six-min walking distance (6MWD) and oxygen consumption (VO2max) during a cardiopulmonary incremental exercise test with cycloergometer), lung density, emphysema quantification and semiquantitative evaluation of bronchial wall thickness from computarised tomographies, and systemic inflammation (C-reactive protein (CRP) and tumor necrosis factor alpha (TNF-α)).

Statistical analysis

Provided sample size was fixed by the primary scientific objectives of the PAC-COPD Study, prior to any analysis we calculated the statistical power to answer our research question with 177 patients using the software GRANMO 7.10. Accepting an alpha risk of 0.05 in a two-sided test, and using own data about the distribution of physically active:physically inactive COPD patients[3], the statistical power was 84% to recognise as statistically significant a risk reduction in COPD hospitalisation similar to that reported in previous literature[7].

Results are presented as mean (standard deviation), n (%) or median (25^{th}-75^{th} percentile), as appropriate. The relationship between baseline PA variables and risk of COPD hospitalisation was first tested using the Kruskal Wallis test and then using Cox proportional hazards regression models. To test the independent effect of quantity and intensity of PA, we stratified the association between the three quantity variables and COPD hospitalisation according to intensity levels (categorised by its median value in our population (≥2.7 METs)). Because the effect of quantity variables was restricted to the low average intensity group, multivariate models included an interaction term between each variable of PA quantity and intensity. Potential confounders considered in the analysis were sex, age, education, marital status, family members, working status, socio-economic status, inhaled treatment (bronchodilators and corticosteroids), smoking status, smoking duration and intensity, Charlson index, cardiovascular comorbidities (ischaemic heart disease, cardiac heart failure or cerebrovascular disease), dyspnoea score, health-related quality of life, COPD hospitalisations in the previous 12months, FEV_1, FVC, RV/TLC, DLco, PaO_2, BMI, FFMI, 6MWD, VO_{2max}, lung density and structure, CRP, TNF-α, participation in a pulmonary rehabilitation programme, and consumption of fruits, vegetables and cured meats. Final multivariate models were built, adjusting for variables that were independently associated with the outcome ($p<0.05$) or modified the coefficient estimate for the exposure (>10% change). The proportionality of Cox models was checked by plotting the Schoenfeld residuals of each predictor variable of the model according to survival time. Collinearity between variables was checked by the variance inflation factor approach.

To test for potential effect modification, final models were stratified according to (i) severity of airflow limitation (above and below 50% FEV_1)[8], and (ii) having had a COPD hospitalisation in the previous year. We performed additional analysis using the volume of physical activity (METs-min per day) as the exposure. As sensitivity analyses, we repeated all analyses (i) excluding subjects with extreme values (>95th percentile) in the accelerometer measures, (ii) using COPD hospitalisation or all-cause mortality as the outcome, (iii) using all-cause hospitalisation as the outcome, and (iv) categorising PA intensity in three groups. All analyses were conducted using R 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

Table E1. Characteristics of physical activity at baseline, according to outcomes (hospitalisation or death) during follow-up.

	No COPD hospitalisation n= 100 m (SD)	**COPD hospitalisation n= 67 m (SD)**	**Death before hospitalisation n= 10 m (SD)**
Steps per day	7705 (4597)	5339 (3890)	5115 (7496)
Physically active days/week, median (25^{th}-75^{th} percentile)	6 (2 - 7)	2 (0 - 7)	1 (0 - 4)
Time in PA (min/day)	190 (129)	160 (108)	135 (149)
Average intensity of PA (METs)	2.8 (0.5)	2.8 (0.6)	2.8 (0.6)

n: number; m: mean; SD: standard deviation; MET: metabolic equivalent tasks.

Table E2. Characteristics of physical activity of the patients at baseline, according to levels of COPD severity.

	Mild COPD n=9 (5%) m (SD)	**Moderate COPD** n=87 (49%) m (SD)	**Severe COPD** n=64 (36%) m (SD)	**Very Severe COPD** n=17 (10%) m (SD)	**p-value**	**p- trend**
Steps per day	9755 (4968)	7233 (4721)	5793 (3786)	5381 (6318)	0.010	0.032
Physically active days/week*, median (25^{th}-75^{th} percentile)	6 (6 - 7)	6 (1 - 7)	4 (0 - 7)	1 (0 - 6)	0.017	0.010
Time in PA (min/day)	220 (117)	186 (117)	157 (105)	169 (198)	0.061	0.337
Average intensity of PA (METs)	3.1 (0.6)	2.8 (0.5)	2.8 (0.5)	2.5 (0.5)	0.069	0.058

n: number; m: mean; SD: standard deviation; p-value: significance of Kruskal Wallis test comparing the four groups; p-trend: significance of the linear trend across COPD severity stages, treating the COPD severity stages as a interval variable; MET: metabolic equivalent tasks.
* Physically active days defined as ≥5000 steps per day[5] (see methods).

Table E3. Characteristics of physical activity at baseline, according to intensity and COPD hospitalisation during follow-up.

	Low Intensity (average <2.7 METs)				**High Intensity (average ≥2.7 METs)**			
	All **n= 86** **m (SD)**	**No COPD hospitalisation** **n= 54** **m (SD)**	**COPD hospitalisation** **n= 32** **m (SD)**	**p-value**	**All** **n= 86** **m (SD)**	**No COPD hospitalisation** **n= 53** **m (SD)**	**COPD hospitalisation** **n= 33** **m (SD)**	**p-value**
Steps per day	4797 (3397)	5751 (3670)	3253 (2182)	0.001	8550 (5038)	9188 (5455)	7487 (4114)	0.250
Physically active days/week, median (25th-75th percentile)	2 (0 - 6)	5 (1 - 7)	0 (0 - 2)	<0.001	7 (4 - 7)	7 (4 - 7)	7 (2 - 7)	0.795
Time in PA (min/day)	140 (112)	154 (124)	116 (86)	0.116	212 (123)	216 (131)	205 (111)	0.901
Average intensity of PA (METs)	2.4 (0.2)	2.4 (0.2)	2.3 (0.2)	0.002	3.2 (0.4)	3.2 (0.4)	3.2 (0.4)	0.894

n: number; m: mean; SD: standard deviation; MET: metabolic equivalent tasks.

Table E4. Adjusted association between physical activity quantity (steps per day) and COPD hospitalisation, according to spirometric COPD severity (multivariate Cox proportional hazards regression).

	Mild-to-moderate ($FEV_1 \geq 50\%$) n=96; n events= 20		Severe-to-very severe ($FEV_1 < 50\%$) n= 81; n events= 47	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Steps per day *(change for each 1000 steps per day)*	0.87 (0.77-1.00)	0.042	0.66 (0.51-0.84)	0.001
High average intensity of PA (≥2.7 METs)	2.46 (0.95-6.39)	0.064	3.08 (1.13-8.36)	0.028
Interaction: Steps × Intensity	-	-	1.61 (1.22-2.13)	0.001
At least one COPD hospitalisation in the previous 12 months	2.81 (0.76-10.39)	0.122	8.01 (3.98-16.15)	<0.001
		$R^2=0.08$		$R^2=0.39$

n: number; n events: number of COPD patients who have had a COPD hospitalisation during follow-up; HR: hazard ratio; MET: metabolic equivalent tasks.

Table E5. Adjusted association between physical activity quantity (steps per day) and COPD hospitalisation, according to having had a COPD hospitalisation in the previous 12 months (multivariate Cox proportional hazards regression).

	Previous COPD hospitalisation		**No previous COPD hospitalisation**	
	n= 29; n events= 23		**n= 148; n events= 44**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Steps per day *(change for each 1000 steps per day)*	0.80 (0.56-1.13)	0.205	0.79 (0.66-0.95)	0.012
High average intensity of PA (≥2.7 METs)	3.00 (1.13-7.94)	0.027	2.03 (0.79-5.23)	0.140
Interaction: Steps x Intensity	1.43 (0.96-2.13)	0.077	1.26 (1.03-1.54)	0.023
FEV_1 (% predicted)	0.96 (0.92-1.00)	0.034	0.97 (0.95-0.99)	0.004
		R^2=0.42		*R^2=0.15*

n: number; n events: number of COPD patients who have had a COPD hospitalisation during follow-up; HR: hazard ratio; MET: metabolic equivalent tasks; FEV_1: forced expiratory volume in the first second.

Table E6. Adjusted association between volume and intensity of physical activity and COPD hospitalisation (multivariate Cox proportional hazards regression).

	All subjects n= 177; n events= 67	
	HR (95% CI)	**p-value**
Volume of physical activity (METs-min per day)	0.91 (0.84-0.98)	0.009
High average intensity of PA (≥2.7 METs)	2.54 (1.20-5.36)	0.015
Interaction: Energy Expenditure x Intensity	1.10 (1.02-1.19)	0.011
At least one COPD hospitalisation in the previous 12 months	5.10 (2.91-8.91)	<0.001
FEV_1 (% predicted)	0.96 (0.94-0.98)	<0.001
		R^2=0.32

n: number; n events: number of COPD patients who have had a COPD hospitalisation during follow-up; HR: hazard ratio; MET: metabolic equivalent tasks; FEV_1: forced expiratory volume in the first second.

Table E7. Adjusted association between physical activity quantity (steps per day) and COPD hospitalisation, after excluding patients with extreme values (>95th percentile) in steps per day (multivariate Cox proportional hazards regression).

	n= 166; n events= 66	
	HR (95% CI)	**p-value**
Steps per day *(change for each 1000 steps per day)*	0.79 (0.66-0.93)	0.006
High average intensity of PA (≥2.7 METs)	2.27 (1.15-4.48)	0.018
Interaction: Steps x Intensity	1.34 (1.10-1.64)	0.003
At least one COPD hospitalisation in the previous 12 months	5.31 (3.02-9.32)	<0.001
FEV_1 (% predicted)	0.96 (0.94-0.98)	<0.001
		R^2=0.33

n: number; n events: number of COPD patients who have had a COPD hospitalisation during follow-up; HR: hazard ratio; MET: metabolic equivalent tasks; FEV_1: forced expiratory volume in the first second.

Table E8. Adjusted association between physical activity quantity (steps per day) and COPD hospitalisation or all-cause mortality (multivariate Cox proportional hazards regression).

	All subjects	
	n= 177; n events= 77	
	HR (95% CI)	**p-value**
Steps per day *(change for each 1000 steps per day)*	0.76 (0.65-0.89)	0.001
High average intensity of PA (≥2.7 METs)	3.02 (1.44-6.33)	0.004
Interaction: Steps × Intensity	1.31 (1.10-1.56)	0.002
At least one COPD hospitalisation in the previous 12 months	4.70 (2.76-8.01)	<0.001
FEV_1 (% predicted)	0.97 (0.95-0.98)	<0.001
		R^2=0.34

n: number; n events: number of COPD patients who have had a COPD hospitalisation or died (all-cause) during follow-up; HR: hazard ratio; MET: metabolic equivalent tasks; FEV_1: forced expiratory volume in the first second.

Table E9. Adjusted association between physical activity quantity (steps per day) and all-cause hospitalisation (multivariate Cox proportional hazards regression).

	All subjects	
	n= 177; n events= 102	
	HR (95% CI)	**p-value**
Steps per day *(change for each 1000 steps per day)*	0.86 (0.77-0.96)	0.006
High average intensity of PA (≥2.7 METs)	1.90 (1.13-3.21)	0.016
Interaction: Steps × Intensity	1.16 (1.03-1.31)	0.018
At least one COPD hospitalisation in the previous 12 months	3.32 (2.06-5.37)	<0.001
FEV_1 (% predicted)	0.98 (0.97-0.99)	0.005
		R^2=0.23

n: number; n events: number of COPD patients who have had a hospitalisation (all-cause) during follow-up; HR: hazard ratio; MET: metabolic equivalent tasks; FEV_1: forced expiratory volume in the first second.

Table E10. Adjusted association between physical activity quantity (steps per day) and COPD hospitalisation categorising intensity in tertiles (multivariate Cox proportional hazards regression).

	All subjects	
	n= 177; nº events= 77	
	HR (95% CI)	**p-value**
Steps per day *(change for each 1000 steps per day)*	0.83 (0.64-1.07)	0.153
Average intensity of PA:		
Average intensity of PA 1.81 – 2.39 METs	1.59 (0.44-5.73)	0.482
Average intensity of PA 2.40– 2.69 METs	ref	
Average intensity of PA ≥2.7 METs	3.15 (1.27-7.82)	0.013
Interaction: Steps x Intensity:		
Interaction: Steps x Intensity 1.81 – 2.39 METs	0.99 (0.70-1.39)	0.933
Interaction: Steps x Intensity 2.40– 2.69 METs	ref	
Interaction: Steps x Intensity ≥2.7 METs	1.21 (0.93-1.58)	0.159
At least one COPD hospitalisation in the previous 12 months	5.16 (2.96-9.00)	<0.001
FEV_1 (% predicted)	0.96 (0.94-0.98)	<0.001
		R^2=0.33

n: number; n events: number of COPD patients who have had a COPD hospitalisation during follow-up; HR: hazard ratio; MET: metabolic equivalent tasks; FEV_1: forced expiratory volume in the first second.

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SUMMARY AND GENERAL DISCUSSION

This section is meant to be a global discussion, avoiding reiterating what has been already discussed in each of the papers conforming this doctoral thesis. Therefore, this section will build up and expand upon previous discussions on: (i) which has been the contribution of this thesis about the role of physical activity in COPD; (ii) which have been the main troubles and limitations that we have faced; (iii) which are the clinical implications of this thesis; and finally, (iv) which are the research implications of this thesis in order to improve the knowledge on the role of physical activity in COPD course.

Contribution to the current knowledge

Physical Activity Measurement of COPD patients

Contribution of Paper I & II

Before this thesis started, only the Baecke Physical Activity Questionnaire had been validated for the Spanish COPD population [36]. Although the Baecke Questionnaire is the most utilized questionnaire to study COPD patients physical activity [39], it is mainly focused on rating the physical activity level (classifying subjects in sedentary, moderately sedentary and active) instead of quantifying or characterizing it. Therefore, amongst all the current methods to assess physical activity in people with COPD, this thesis has added a valid questionnaire for both the surveillance of the physical activity volume of COPD populations and the screening of physical inactive COPD patients.

On the other hand, regarding the objective assessment of physical activity in COPD patients, there were only experimental studies showing high validity of accelerometers to assess physical activity performed by COPD patients when this thesis began. Therefore, there was no guidance on the minimum requirements to obtain a valid and reliable accelerometer assessment of regular physical activity performed by COPD patients. As a consequence, one of our contributions, and in agreement with other studies published during this thesis [42, 69], has been the reporting that any combination of three days of physical activity provides a high reliable estimate of COPD patients' physical activity.

Before this thesis started, the adaptation of objective physical activity assessment to COPD patients' capacities (walking speed) was only applied by Coronado and colleagues [70]. In this sense, we have taken one step forward through the adaptation of physical activity definition according to the aerobic capacity, following the American College Sport Medicine criterion [71]. Furthermore, and taking advantage of this objective assessment, we have introduced the evaluation of the pattern of physical activity bouts in COPD population, which, as explained later, has become a crucial improvement to understand how physical activity differs according to the degree of the air obstruction severity of COPD patients.

Last but not least important, the second paper of this thesis was the first study that combined a subjective and an objective physical activity assessment to achieve a comprehensive assessment of the quantification of physical activity [71, 72].

Volume and Pattern of Physical Activity in COPD patients

Contribution of Paper II

When the present thesis started, Pitta and colleagues had shown that COPD patients walk less and slowly than healthy patients [73]. In 2009, two cross-sectional studies described the physical activity volume across severity of airflow obstruction [42, 74] showing that there is a significant difference in the volume of physical activity across severity of the airflow limitation. Furthermore, they found that the reduction in the moderate-to-vigorous physical activity volume of COPD patients in relationship to healthy patients began to be statistically significant from the GOLD stage II of airflow obstruction.

Our research shows that COPD patients of all spirometric severity stages engage in moderate-to-vigorous physical activity bouts during their daily life activities and more than a half of them reach the World Health Organization recommendation of physical activity to promote or maintain physical health. Thanks to this thesis, we also know that the reduction in the volume of physical activity across severity of airflow obstruction is because of the reduction in the frequency rather than the duration of moderate-to-vigorous physical activity bouts, which is not made up for the rest of the overall physical activity. Moreover, we have shown that those COPD patients with more severe airflow obstruction experienced a reduction in the percentage of the volume of physical activity performed in bouts out of overall physical activity. Finally, we have shown that the leisure physical activity is the first and the most affected domain/purpose of physical activity amongst COPD patients.

Benefits of Physical Activity upon COPD Patients evolution

Contribution of Paper III

As mentioned in the introduction section, since 2003 and despite using inaccurate assessment tools, low levels of physical activity have been consistently associated with higher risk of COPD exacerbations and mortality [23]. In consequence, and because of the low precision of questionnaires [34], the appropriate dose required to maximize physical activity benefits upon COPD evolution is still a matter of study.

The third paper of this thesis was the first study that unraveled the independent role of the quantity and the intensity of physical activity upon the risk of COPD hospitalizations, using an objective physical activity measurement. The results support linear dose-response relationship between quantity of low-intensity physical activity and the risk of COPD hospitalisations. However, the finding that high quantity of high-intensity physical activity may be unhelpful for COPD patients with severe-to-very severe airflow limitation was unexpected and will require replication. In the light of these results, future studies should take into account the quantity and intensity of physical activity separately since otherwise it could reduce the observed magnitude of the association between physical activity and COPD hospitalization risk.

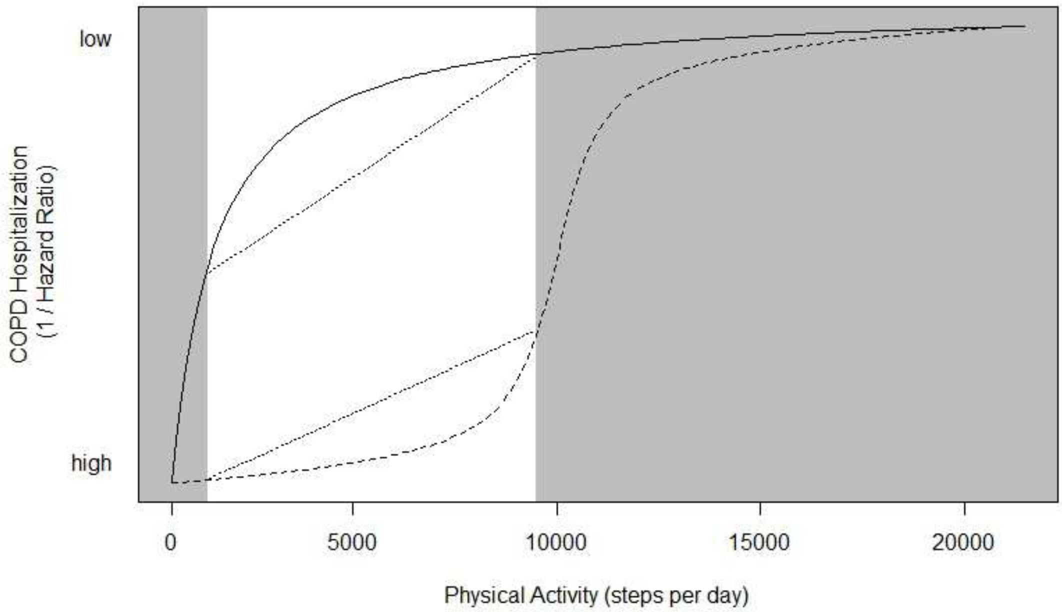
Strengths and Limitations

The use of the PAC-COPD cohort allowed the follow-up of a large and representative sample of incipient COPD patients. They had been systematically recruited during their first hospitalization due to a COPD exacerbation. This recruitment approach prevented a possible selection bias that might have happened if other recruitment strategies had been used (e.g., selecting patients at outpatient clinics, rehabilitation settings or lung function laboratories). Moreover, the extensive clinical, radiological and biological characterization of participants within the frame of the PAC-COPD study [75] allowed the control for confounders, which usually are very difficult to obtain in clinical epidemiology research.

The choice of a historic questionnaire, which asks specifically for each activity of daily life, instead of a recall questionnaire, which asks about self-perceived intensities, was a clear improvement in both internal and external validity of physical activity measurement because the intensities of activities remain almost constant, while self-perception of intensity depends mainly on physical fitness of COPD patients. The SenseWear® Pro2 Armband was the most precise objective tool to assess the physical activity performed by COPD subjects. It is a multi-sensor worn on the arm allowing to capture light activities of daily life such as personal care and it has been shown to be valid specifically for COPD patients [38] and in comparison to indirect calorimeter [76]. The evaluation of aerobic capacity prior to definition of physical activity thresholds of the objective assessment together with the intensive monitoring of at least 12 hours per day during a period of eight consecutive days are a guarantee of the validity of the physical activity measurement. The combination of the subjective and objective physical activity assessments, together with the development of a new computational method to assess physical activity bouts have been clear improvements in the validity of the study of physical activity patterns in comparison with previous studies. These measurements allow both the characterization of the frequency, duration, intensity, type and purpose of physical activity and the study of the relationship between the overall and bouts of physical activity.

A potential limitation of this study is that physically inactive COPD patients could have been overrepresented because physical inactivity is a risk factor of COPD hospitalization and patients were recruited during a COPD hospitalization. It could be argued that, as a consequence of the PAC-COPD design, the volume and range of physical activity could have been underestimated, and the relationship between physical activity and subsequent COPD hospitalisations underestimated or overestimated depending to the dose-response relationship between them (Figure 1). A second limitation related to subjects' selection is that physical activity assessment was done 24 months after the start of PAC-COPD study, i.e., 24 months after the first COPD hospitalization, which increased the chance of survival bias. Actually, 12 patients died during their first hospitalization and 19 died after engaging in the PAC-COPD study but before the physical activity assessment. The likelihood that lost patients were less physically active could have reduced more the range of physical activity and changed again the estimated relationship between physical activity and COPD hospitalization (Figure 1).

Figure 1. The sampling and survival effect on the dose-response analysis between physical activity and COPD hospitalization.



Explanation: data from the literature support that the effect of physical activity upon COPD hospitalization can follow a radical (solid line) or sigmoidal (dashed line) dose-response shape [77, 78]. The shaded area at the right of the figure represents that patients with high levels of physical activity were not included in our study because recruitment was done during a COPD admission (see text). The shaded area at the left of the figure represents that patients with very low levels of physical activity were not included in our study because they died during follow-up (see text). The two dotted lines represent the association between physical activity and COPD hospitalization as estimated in our study. Differences between each dotted line and its corresponding radical or sigmoidal lines support overall validity of our estimates, although magnitude of the effect of physical activity may be slightly different for some specific physical activity levels.

A second set of limitations is related to the methods used to assess physical activity. The technological restriction of the objective tool to assess certain activities like cycling or swimming was a limitation of the present objective physical activity evaluation. This weakness would affect more those COPD patients who are more active and led to undervaluing the benefits of physical activity upon COPD evolution. It is known that SenseWear® Pro2 Armband overestimates the intensity of arm activities, which could lead to some differential misclassification if the prevalence of these activities were related to some characteristics of COPD. However, it must be noted that the Paper I of this thesis shows no differences between the questionnaire and the physical activity monitor according to COPD characteristics. Furthermore, a single week of physical activity monitoring may have resulted in some non-differential misclassification because of seasonal variation and/or low representativeness of that particular week.

The lack of repeated measures of physical activity may have prevented to establish the causal relationship between physical activity and COPD hospitalization. Putting together previous hospitalizations and current physical activity levels will not remove all residual confounding, because the relationship between these two determinants could be also confounded by previous physical activity levels, as it was previously suggested by Garcia-Aymerich and colleagues [58].

Finally, the male predominance in our cohort (94%), which is in agreement with COPD gender distribution in Spain, prevented the generalization of the found benefits of physical activity upon COPD hospitalisation to the females, because there is evidence of sex-related differences in the effects of physical activity [79].

Implications for Clinical Practice

This thesis has direct, relevant, inexpensive and feasible implications for clinical practice. Once demonstrated the beneficial effects of physical activity on the evolution of COPD (Paper III), the relevance to implement interventions that promote physical activity from the early stages of the disease is evident. Thanks to the YPAS validation (Paper I), the health care systems have a valid, effective, free and easy tool for the early identification of COPD patients physically inactive. Moreover, and thanks to the findings of Paper II, it is known that the first domain of physical activity that will manifest a reduction and needs promotion is the leisure time. Consequently, a systematic anamnesis of leisure time physical activity might also help to identify the COPD patients at risk of physical inactivity.

Having been highlighted the need for physical activity promotion and being the ability to identify its target population, the next aim is to define the type of intervention. According to the findings of Paper II, interventions must be directed to increase the total amount of physical activity undertaken by COPD patients by performing new bouts of physical activity during leisure time, instead of extending the already performed bouts. The activities promoted should be especially focused on resistance capacity, being the long duration and light-to-moderate intensity activities the most desirable according to the findings of Paper III. Furthermore, as a consequence of the different physical activity levels observed across countries and populations, interventions designed for COPD patients should not only be based on pathophysiology-related limitations but also on the ''subjects' needs, goals, and initial abilities'', as advocated by the recommendations [8, 9]. Therefore, it will be advisable the prescription of achievable amounts of physical activity, as it occurs with a pharmacologic treatment, for the prevention of accelerated COPD course. Finally, to assess the effectiveness of physical activity interventions several physical activity outcomes should be considered, including the proportion of patients meeting certain physical activity goals [80], the extra steps per day [81], and the changes, if any, in average intensity.

Implications for future research

To date, epidemiological and clinical studies have consistently shown that higher volume of physical activity reduces the risk of mortality and hospitalization in COPD patients [23]. However, the potential role of physical activity in other relevant health outcomes of COPD patients is still unknown. In addition, the causal nature of some of the reported relationship needs to be established. The next paragraphs will provide some insight on the contributions of this thesis to future research that will need to fill in the gaps on physical activity and COPD. These contributions are mostly in the area of study design and assessment of physical activity.

Study Design

During this thesis we have identified several limitations common to most existing studies about effects of physical activity on COPD evolution that could be overcome by using alternative study designs and/or subjects' selection. These limitations cover: (i) residual confounding, including that related to physical activity levels prior to study design; (ii) potential for reverse causation as an explanation of study findings; and (iii) outcome misclassification because of the lack of information about exacerbations characteristics (e.g., viral or bacterial infection, other).

One of the potential solutions solving two of the mentioned limitations is to complement existing information coming from prospective cohort studies with **randomized controlled trials** to assess the role of physical activity on COPD evolution. The use of stratified or covariate adaptive randomization would help to prevent differences between groups regarding infrequent factors, such as not having suffered previous COPD hospitalization or the severity of these previous COPD hospitalizations [82]. The most important challenge for this proposal is the identification of an appropriate intervention to modify physical activity, which in turn would lead to reduce exacerbations. Several recent and ongoing initiatives can help in this regard [81, 83].

An additional possibility to reduce confounding by early events in COPD course and reducing the potential reverse causation interpretation is to select COPD patients at early stages of the disease, ideally before its clinical manifestation. A **cohort study of long-term heavy smokers** in their mid-fifties, without a history of COPD exacerbations, would allow not only to improve the study of temporal relationship between physical activity and COPD hospitalizations, but also the assessment of determinants of physical activity changes over time. However, such a study requires a large sample and a long follow-up [84, 85].

Finally, given the anti-inflammatory properties of physical activity [63], it is likely that its effects are restricted to exacerbations with high inflammatory burden, such as viral or bacterial infections. Therefore, a **thorough characterization of COPD exacerbations**, irrespective of study design and subjects' selection, is a must for all future research studies.

Physical Activity assessment

The current thesis builds the assessment of physical activity (and its effects) on the Caspersen's definition of physical activity, which, as detailed in the Introduction, clearly delimitates between physical activity, exercise and physical fitness. However, results from this thesis as well as ongoing research in other areas reveal that a more holistic approach for physical activity is needed if we want to succeed in understanding the concept, measuring it and assessing its effects. Among other theories, the crisis theory and its Individual Zone of Optimal Functioning model deserve discussion for their potential applicability to COPD. They define physical activity as a multidimensional behaviour broken down in physiological (behavioural & biological components) and psychological (cognitive & affective components) dimensions [86]. The behavioural component is characterized by the volume, frequency, duration, intensity, and type of physical activity performed. The biological component contextualizes the behavioural one regarding the physical fitness of patients (aerobic capacity, strength, flexibility, and resistance). The cognitive component assesses subjects' beliefs upon each physical activity (frustration, fear, tolerance, and/or voluntary participation). Finally, the affective component characterizes the social part of each physical activity (support, interaction, and/or recognition).

To date, research in COPD has mostly focused on the physiological dimension of physical activity, though still with a restricted approach. To improve its assessment, future studies should consider a more detailed measurement of its behavioural component, including the type of activity in addition to frequency, duration and intensity, using accelerometers on different parts of the body and/or applying machine learning algorithms [87]. The identification of the type of activity would help to study whether different types of activities have different impact on disease evolution [88, 89], and will allow the improvement of the estimation of the activity intensity [90]. In the specific case of questionnaires aimed to quantify physical activity, there is still no clear answer regarding how to adapt the task-related intensities distinctive of able-bodied population to disabled population, such as COPD patients [91–94].

Regarding the biological component of the physiological dimension, future studies need to incorporate fitness capacity evaluation in order to standardize the physical activity intensity with respect to each individual capabilities [71, 95]. This would make future studies about the effects of physical activity intensity more comparable and replicable between them, and at the same time, it would also allow to study the potentially different effect of aerobic and anaerobic physical activity upon COPD hospitalization. Interestingly, the fitness assessment and distinction between aerobic and anaerobic activities could be incorporated into physical activity questionnaires.

The potential role of the psychological dimension of physical activity on COPD evolution is underexplored, although it can be hypothesized that part of the benefits of physical activity come from the cognitive and affective components [89, 96]. To delve into this dimension of physical activity, some studies based on healthy subjects and young people have begun to simultaneously evaluate the location and physical activity in order to contextualize the activity [97]. At the same time, other studies have gone a step further and have included emotional momentary assessment tools to capture the emotional and affective components of the activities undertaken by individuals [98]. Finally, the addition of information regarding desirability to physical activity questionnaires would help controlling the over- and underreporting of physical activity.

Overall, the integration of the several dimensions of physical activity and their components, both using questionnaires and activity monitors, will help to understand this behaviour as a whole and will increase our ability to assess its health effects.

CONCLUSIONS

1. The Yale Physical Activity Survey is a valid tool for classifying the physical activity in patients with COPD, but not for quantifying it.

2. The summary index of the Yale Physical Activity Survey should be considered a screening instrument for identifying patients who run the risk of sedentarism.

3. COPD patients of all spirometric severity stages engage in physical activity bouts of moderate-to-vigorous intensities.

4. Patients with severe and very severe COPD perform fewer bouts and less quantity of physical activity, and have lower ratio between bouts and quantity than those in mild and moderate stages.

5. Higher quantity of low-intensity physical activity reduces the risk of COPD hospitalization.

6. High-intensity daily-life physical activity does not generate additional protective effects in the most severe COPD patients.

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ANNEXES

Apart from the original papers included in the present thesis, the PhD candidate has also published other papers, two as first author on physical activity and three as second author on personal monitoring assessment.

Other papers as first or second author

Donaire-Gonzalez D, de Nazelle A, Cole-Hunter T, Curto A, Rodriguez D, Mendez M, Garcia-Aymerich J, Basagaña X, Ambros A, Jerrett M, Nieuwenhuijsen MJ.The Added Benefit of Bicycle Commuting on the Regular Amount of Physical Activity Performed. Am J Prev Med. 2015: (in Press).

Rivas I, **Donaire-Gonzalez D**, Bouso L, Esnaola M, Pandolfi M, de Castro M, Viana M, Alvarez-Pedrerol M, Nieuwenhuijsen M, Alastuey A, Sunyer J, Querol X. Spatio-temporally resolved black carbon concentration, schoolchildren's exposure and dose in Barcelona. Indoor Air. 2015: (in Press).

Nieuwenhuijsen MJ, **Donaire-Gonzalez D**, Rivas I, de Castro M, Cirach M, Hoek G, Seto E, Jerrett M, Sunyer J. Variability in and agreement between modeled and personal continuously measured black carbon levels using novel smartphone and sensor technologies. Environ Sci Technol. 2015;49(5):2977-82.

Nieuwenhuijsen MJ, **Donaire-Gonzalez D**, Foraster M, Martinez D, Cisneros A. Using personal sensors to assess the exposome and acute health effects. Int J Environ Res Public Health. 2014;11(8):7805-19.

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C.I.F. G: 59069740 Universitat Ramon Lull Fundació Privada. Rgtre. Fund. Generalitat de Catalunya núm. 472 (28-02-90)

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