Determinants of physical activity behaviour in patients with chronic obstructive pulmonary disease

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To Louis, Rosa, Helene

& Georg

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Vienna, 21 December, 2020

Abstract

Background: Although physical activity is key to improve prognosis in patients with chronic obstructive pulmonary disease (COPD), information to tailor interventions individually is still required. This thesis aims to understand physical activity progression and explore its determinants in COPD patients.

Methods: We used baseline and 12-month data from 643 COPD patients with stable mild-to very severe disease from two European multicentre studies. We assessed: physical activity (Dynaport MoveMonitor), physical activity experience (*Clinical visit-PROactive physical activity in COPD* [C-PPAC]), functional exercise capacity (6-minutes walk distance [6MWD]), as well as sociodemographic, interpersonal, environmental, clinical and psychological variables.

Results: (1) The natural progression in physical activity over time was heterogeneous and three distinct patterns could be identified: *Inactive, Active Improvers* and *Active Decliners*. While *Inactive* patients related to worse scores for clinical COPD characteristics, *Active Improvers* and *Decliners* could not be predicted at baseline; (2) higher population density and long-term NO_2 exposure were associated with lower physical activity, while a steeper slope of the terrain related to better exercise capacity; (3) twelve-month completion of a behavioural physical activity intervention was determined by previous physical activity habits as well as interpersonal and environmental facilitators, while response to the intervention was related to diverse factors associated with motivation to change to an active lifestyle.

Conclusions: This thesis shows that the natural progression of physical activity in COPD patients is heterogeneous and highlights that psychological, interpersonal and environmental factors are important determinants of physical activity behaviour in COPD patients, beyond clinical factors.

Keywords: Chronic obstructive pulmonary disease, physical activity, behaviour, determinants, epidemiology.

Resumen

Antecedentes: Aunque la actividad física es clave para mejorar el pronóstico en pacientes con enfermedad pulmonar obstructiva crónica (EPOC), todavía no se dispone de información que permita adaptar las intervenciones de manera individualizada. El objetivo de la presente tesis es comprender la progresión de la actividad física y explorar sus determinantes en pacientes con EPOC.

Métodos: Utilizamos datos basales y de seguimiento (12 meses) de 643 pacientes con EPOC estable de estadio leve a muy grave, procedentes de dos estudios europeos multicéntricos. Evaluamos: actividad física (Dynaport MoveMonitor), experiencia de actividad física (*Clinical visit-PROactive physical activity in COPD* [C-PPAC]), capacidad funcional de ejercicio (distancia caminada en la prueba de la marcha de 6 minutos [6MWD]) y variables sociodemográficas, interpersonales, ambientales, clínicas y psicológicas.

Resultados: (1) La progresión natural de la actividad física a lo largo del tiempo fue heterogénea y se pudieron identificar tres patrones distintos: *inactivo, activo que aumenta* y *activo que reduce*. Mientras que el patrón de pacientes *inactivo* se relacionaba con peores características clínicas de la EPOC, no se pudo predecir la evolución de los *activos* a *aumentar* o *reducir*; (2) la mayor densidad de población y la exposición a largo plazo al NO_2 se asociaron desfavorablemente con la actividad física, mientras que una mayor pendiente del terreno se relacionó con una mejor capacidad de ejercicio; (3) la compleción a los 12 meses con una intervención de actividad física conductual estuvo determinada por los hábitos de actividad física previos, así como por facilitadores interpersonales y ambientales, mientras que la respuesta a la intervención se relacionó con diversos factores asociados a la motivación para cambiar a un estilo de vida activo.

Conclusiones: Esta tesis muestra que la progresión natural de la actividad física en los pacientes con EPOC es heterogénea y destaca que los factores psicológicos, interpersonales y ambientales son importantes determinantes de la actividad física en los pacientes con EPOC, más allá de los factores clínicos.

Palabras claves: Enfermedad pulmonar obstructiva crónica, actividad física, comportamiento, determinantes, epidemiología.

Resum

Antecedents: Malgrat el paper clau de l’activitat física per millorar el pronòstic en pacients amb malaltia pulmonar obstructiva crònica (MPOC), encara no disposem d’informació que permeti individualitzar les intervencions. L’objectiu d’aquesta tesi és entendre la progressió de l’activitat física i explorar-ne els determinants en pacients amb MPOC.

Mètodes: Vam incloure dades basals i de seguiment (12 mesos) de 643 pacients amb MPOC estable, en estadis lleu a molt greu, procedents de dos estudis europeus multicèntrics. Vam avaluar: l’activitat física (Dynaport MoveMonitor), l’experiència d’activitat física (*Clinical visit-PROactive physical activity in COPD* [C-PPAC], la capacitat d’exercici funcional (distància caminada en la prova de la marxa de 6 minuts [6MWD]) i variables sociodemogràfiques, interpersonals, ambientals, clíniques i psicològiques.

Resultats: (1) La progressió natural de l’activitat física al llarg del temps va ser heterogènia i es van poder identificar tres patrons diferents: *inactiu, actiu que augmenta* y *actiu que redueix*. Mentre que el patró de pacients *inactiu* es relacionava amb pitjors característiques clíniques de la MPOC, no es va poder predir l’evolució dels pacients *actius* a *augmentar* o *reduir*; (2) més densitat de població i més exposició a llarg termini al NO_2 s’associaven de manera inversa amb l’activitat física, mentre que més pendent del terreny es va relacionar amb millor capacitat d’exercici; (3) l’acabament als 12 mesos d’una intervenció d’activitat física conductual va ésser determinat pels hàbits d‘activitat física previs i pels facilitadors interpersonals i ambientals, mentre que la resposta a la intervenció es va relacionar amb diversos factors associats a la motivació per canviar a un estil de vida actiu.

Conclusiones: Aquesta tesi mostra que la progressió natural de l’activitat física en els pacients amb MPOC és heterogènia i destaca que els factors psicològics, interpersonals i ambientals són importants determinants de l’activitat física en els pacients amb MPOC, més enllà dels factors clínics.

Paraules clau: Malaltia pulmonar obstructiva crònica, activitat física, comportament, determinants, epidemiologia.

Preface

This thesis has been written at the Barcelona Institute of Global Health (ISGlobal) between October 2016 and December 2020 and was supervised by Dr. Judith Garcia Aymerich. It is an accumulative thesis, consisting of three scientific articles of which the candidate is the first author. The thesis complies with the procedures and regulations of the Biomedicine PhD Program of the Department of Experimental and Health Sciences of the Universitat Pompeu Fabra.

The thesis has seven main sections, i.e., a general introduction, the rationale of the thesis, its objectives, an overview of the methods, the research results (3 original papers, two of which are published and one is currently in preparation), a discussion of the main findings and final conclusions. The aim of this work was to provide more insight into the determinants of physical activity behaviour in patients with chronic obstructive pulmonary disease (COPD). The work was performed within the context of data from (1) the Urban training study, a randomized controlled trial which assessed a behavioural physical activity intervention in COPD patients and (2) the PROactive initial validation study, a non-interventional cohort study which aimed to develop and validate patient-reported outcome (PRO) instruments to capture the dimensions of physical activity in the daily life of COPD patients. The PhD candidate was responsible for the conceptualization of the work, the statistical analysis and the writing of the manuscripts.

In addition to the work for the thesis, the PhD candidate was actively involved in academic activities. The PhD candidate presented the results of this thesis at international scientific conferences, which merited several awards, and at the local research institute (ISGlobal) and participated in other ongoing research resulting in a co-authored manuscript (a list of the activities is included in the Annexes).

Abbreviations

BMI	body mass index
CAT	COPD assessment test
CCQ	clinical COPD questionnaire
CI	confidence interval
COPD	chronic obstructive pulmonary disease
C-PPAC	clinical visit-PROactive physical activity in COPD
D-PPAC	daily-PROactive physical activity in COPD
FEV_1	forced expiratory volume in 1 second
FFMI	fat free mass index
FVC	forced vital capacity
GOLD	global initiative for chronic obstructive lung disease
HAD-A	hospital anxiety and depression scale – anxiety
HAD-D	hospital anxiety and depression scale – depression
IQR	interquartile range
LABA	long-acting $beta_2$-agonists
LAMA	long-acting anti-muscarinics
L_{den}	day evening night sound level
MET	metabolic equivalent of task
mMRC	modified Medical Research Council dyspnea score
6MWD	6-min walking distance
MVPA	moderate to vigorous physical activity
NO_2	nitrogen dioxide
OR	odds ratio
PM	particulate matter
PRO	patient reported outcome
RRR	relative risk ratio
SD	standard deviation
VMU	vector magnitude unit
WHO	World Health Organization

Content

1. INTRODUCTION

1.1 Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease, and a frequent cause of morbidity and death. It is characterized by a progressive and poorly reversible air flow limitation. Patients mostly suffer from shortness of breath, cough and increased sputum production. The disease is treatable but not curable, high levels of physical activity influence positively the course of the disease.

1.1.1 Global burden of COPD

COPD is one of the most important causes of morbidity and mortality worldwide.[1] According to the Global Burden of Disease Study, COPD accounted for around 55% of all chronic respiratory diseases, the third leading cause of death, in 2017.[2] Although the age-standardized prevalence and death rate of COPD were declining between 1990 and 2015 (by minus 15% and minus 42%, respectively), the absolute numbers were rising due to population growth and ageing: the prevalence of COPD increased by 44% and deaths from COPD increased by 12%, thus affecting more than 174 million patients and causing 3.2 million deaths worldwide in 2015.[1] Importantly, the reported numbers likely capture only a fraction of the true cases as underdiagnosis of COPD is common.[3]

The prevalence of COPD in Spain is also high. According to Episcan II, the prevalence in the general population (aged 40 years or older) was 11.7% in 2017/2018.[4] Underdiagnosis was frequent again with almost 75%.[4] It is suspected that large numbers of cases are missed due to insufficient screening, especially of more vulnerable or difficult to reach populations, such as patients with low socioeconomic status, women and residents of rural areas, or populations not assumed to be at risk (e.g., no history of smoking).[5]

The true burden of COPD for the health system, the individual patients and their families is therefore estimated to be much higher than reported and will likely further increase over the next decades due to population growth, ageing, and continued exposure to multiple risk factors.

1.1.2 Causes and pathomechanism of COPD

COPD was long considered as a disease caused mainly by tobacco smoking which would elicit in susceptible individuals an inflammatory response in airways and alveoli, and induce an accelerated decline of lung function, poorly reversible airflow limitation and chronic respiratory symptoms.[3,6–8] This concept is still accepted but several other causes and a more diverse pathophysiology have now been identified.[3,7,9]

Tobacco smoking is one of the best studied risk factors and remains a major cause of COPD, but not all smokers will develop COPD and a considerable number of COPD patients worldwide are non-smokers which underlines the importance of other factors too.[3,7,9–12] Apart from the genetic susceptibility to tobacco smoke other genetic risk factors have been identified.[3,7] The deficiency of alpha-1 antitrypsin has been widely explored, but other predisposing genes,[13,14] and epigenetic changes related to lung function and inflammatory mechanisms have also been reported. Also other inhaled noxi, such as indoor air pollution from biomass fuel and coal, outdoor air pollution and workplace exposure to fumes or dust have been established as causes of COPD.[1,3,15–18]

These noxious particles can induce tissue damage in the lungs through chronic inflammation and oxidative stress, which involve a wide range of inflammatory cells and mediators.[3,7,19] The lung tissue is infiltrated by neutrophils, macrophages and lymphocytes, as expression of an innate (unspecific) and adaptive (specific) inflammatory response, and inflammatory mucous accumulates in the small airways.[3,7,8] Repair mechanisms lead to remodelling with thickening of the small airways and luminal narrowing.[3,7,8,20] These changes relate to the progression of COPD and the severity of air flow limitation.[3,7,8] The destruction of the small alveoli (emphysema) is another characteristic feature of COPD. Several pathomechanisms, including an imbalance between protease and antiprotease (as in alpha-1 antitrypsin deficiency), a disturbance in lung maintenance,[21] autoimmunity,[22] or abnormal development of the alveoli in early life have been discussed.[23]

The accelerated decline in lung function (forced expiratory volume in 1 second [FEV_1]) often present in COPD has been considered as an indicator of accelerated ageing.[7,24]

However, COPD may also result from abnormal lung development and consequently low FEV_1 in early adulthood, even if the ensuing decline is normal.[3,7,25] Factors which impact lung growth and development during gestation and childhood (such as low birthweight, bodyweight or infant respiratory infection) can therefore also modify the risk for COPD.[3,7,25,26] This results in a heterogeneous spectrum of lung function trajectories and several pathways which may lead to COPD (Figure 1).[3,7,27]

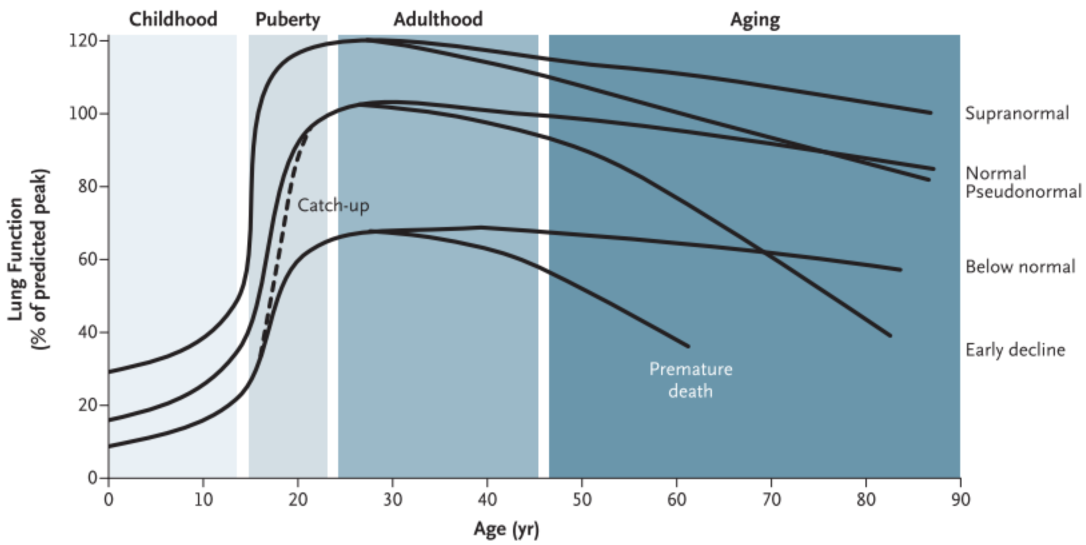

Figure 1. Lung function trajectories during life time, adapted from Agustí and Hogg [7]. Reproduced with permission from the N Engl J Med, 381, Agustí A, Hogg JC., Update on the Pathogenesis of Chronic Obstructive Pulmonary Disease, 1248–1256, doi:10.1056/NEJMra1900475, Copyright © 2019 Massachusetts Medical Society.

COPD is now considered as the result of lifelong gene-environment interactions during lung development and lung ageing, with chronic inflammation as central pathomechanism.[7,8] Importantly, these interactions are not limited to the lungs, but can involve other organs too, thereby contributing to the high prevalence of comorbidities in COPD (Figure 2).[3,7,9] The recognition that COPD is a complex and heterogeneous disease (i.e., that its various components interact dynamically and are not necessarily present in all patients at all moments) has stimulated the search for a more personalized assessment and treatment.[28,29] This has recently led to a focus on the concepts of ‘treatable traits’ and precision medicine, where for each COPD patient his/her individual set of problems is identified and an individualized treatment attempted.[28–30]

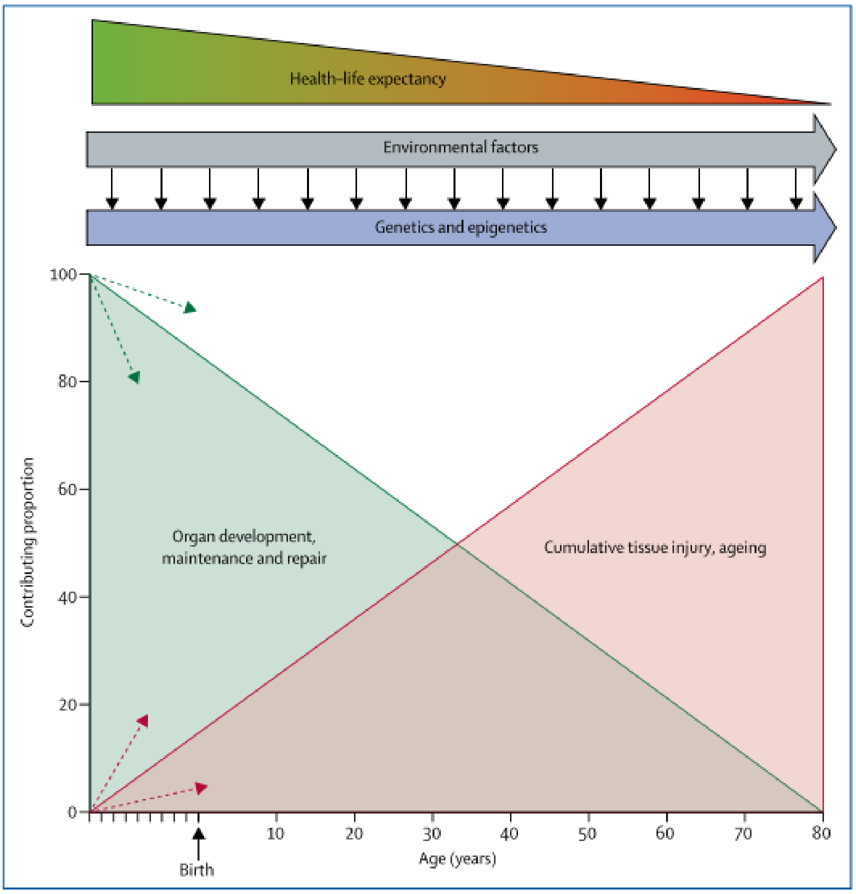

Figure 2. Concept of the interplay between the two major pathogenic mechanisms of COPD and other comorbidities (organ development, maintenance and repair versus cumulative tissue injury and ageing), adapted from Agustí and Faner.[9] Reprinted from the Lancet Respiratory Medicine, 6, Agustí A, Faner R. COPD beyond smoking: new paradigm, novel opportunities, 324–326, doi:10.1016/S2213-2600(18)30060-2, Copyright © 2018, with permission from Elsevier.

1.1.3 Diagnosis and classification

The diagnosis of COPD is established if the post-bronchodilator forced expiratory volume in the first second (FEV_1) to forced vital capacity (FVC) ratio is < 0.70.[31]

GOLD grades

The severity of the air flow limitation is commonly classified into four GOLD (Global Initiative for Chronic Obstructive Lung Disease) grades according to established cut-offs of post-bronchodilator FEV_1 even if the correlation of FEV_1 with symptoms and health status if only weak (Table 1).[3]

Table 1. Classification of air flow limitation severity in patients with COPD ($FEV_1/FVC < 0.70$, based on post-bronchodilator FEV_1).[3]

GOLD grades	**Airflow limitation**	**FEV_1**
GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	Very severe	$FEV_1 < 30\%$ predicted

GOLD groups

The ABCD assessment tool has been proposed to understand better the impact of the disease on the individual COPD patient.[3] This tool assigns the patient to one of four GOLD groups (A, B, C or D) based on the severity of symptoms and his history of exacerbations (Figure 3). Symptoms are assessed as dyspnoea by the modified Medical Research Council dyspnea (mMRC) score, ranging from grade 0 (breathless only with strenuous exercise) to grade 4 (too breathless to leave the house, or breathless when dressing or undressing) or the COPD assessment test (CAT), which measures the health status impairment through a set of eight questions resulting in a score from 0 (no impairment) to 40 (maximal impairment). Moreover, the number of moderate (treated with short acting bronchodilators plus antibiotics and/or oral corticosteroids) and severe (patient visits the emergency room or requires hospitalization) exacerbations is recorded. The ABCD tool is also used to guide the therapy in COPD.

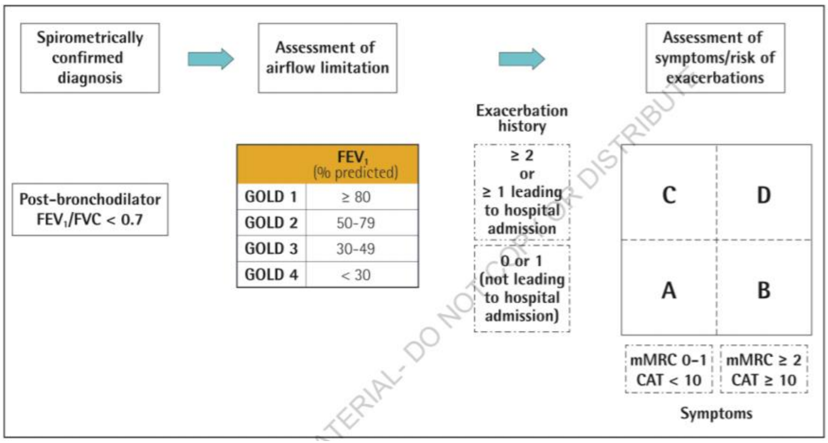

Figure 3. The ABCD assessment tool, adapted from the GOLD 2020 report.[3] Reproduced with permission from Copyright © 2020, Global Initiative for Chronic Obstructive Lung Disease, available from www.goldcopd.org, published in Fontana, WI, USA.

1.1.4 COPD: a clinical syndrome

COPD can manifest with a range of symptoms and associated conditions and is thus best described as a clinical syndrome.[32]

Respiratory manifestations

The structural changes in the lungs (airway wall thickening, luminal narrowing and emphysema) cause an impaired lung function and chronic respiratory symptoms; the patients suffer from an expiratory airflow limitation which is usually progressive and not fully reversible, hyperinflation, cough and dyspnoea.[32]

Mucus production is often increased and mucociliary clearance impaired, and COPD is therefore also termed muco-obstructive disease.[33] The mucus in the small airways can accumulate and enhance airflow obstruction, infection and inflammation.[33]

Exacerbations are common in COPD.[32,33] These are defined as "*acute worsenings of the patient's respiratory condition [...] which require a change in medication*".[34] They often have a bacterial or viral cause but may also be triggered by other factors, such as air pollution. They are often accompanied by a decline in physical activity,[35,36] and are associated with a worse prognosis as they lead to a deterioration of the overall health status, a deline in lung function, and increased mortality.[32]

Comorbidities

COPD patients often suffer from comorbidities which most frequently affect the cardiovascular system (e.g., hypertension or coronary artery disease), the lung (e.g., lung cancer or pulmonary hypertension), the metabolic system (diabetes or hyperlipidemia), the psychological condition (anxiety and depression) and the skeletal system (e.g., osteoporosis, degenerative joint disease and myopathy).[32,37,38] This array of comorbidities has been summarized as comorbidome by Divo et al. (Figure 4).[37]

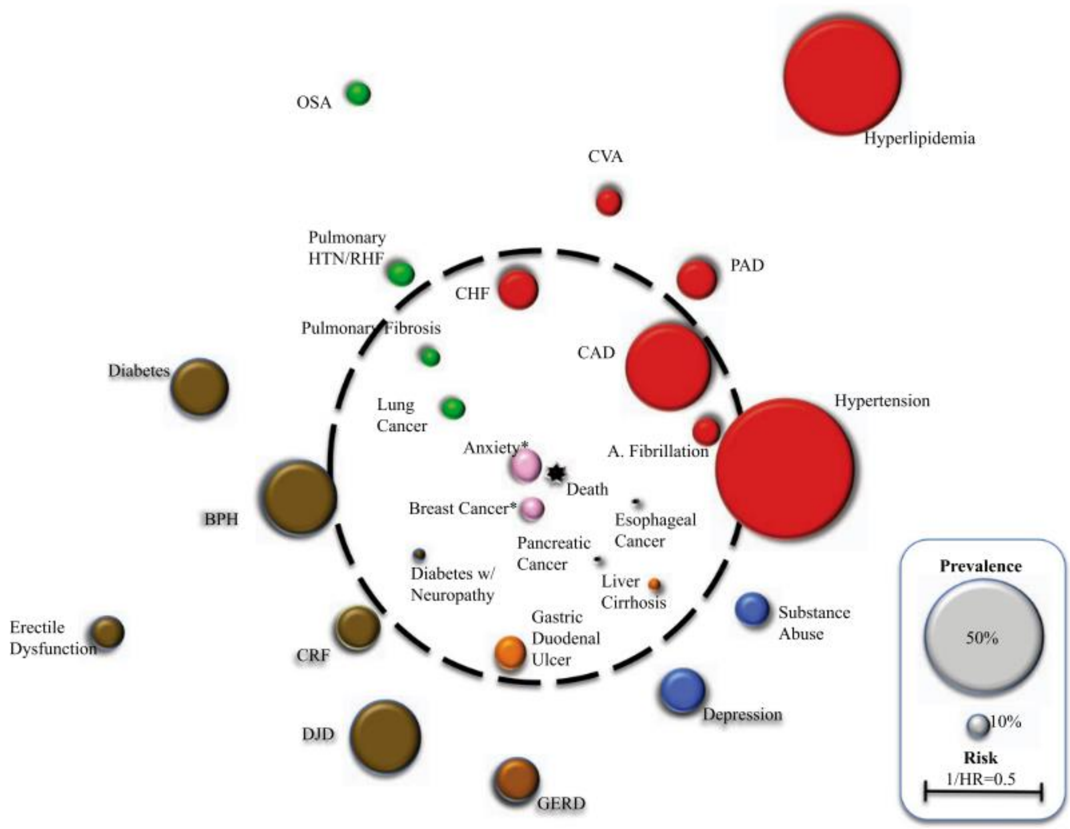

Figure 4: The comorbidome, adapted from Divo et al.[37] Frequent comorbidities (more than 10% prevalence in the BODE cohort) are depicted; the size of the bubble relates to the prevalence of the disease and a shorter distance to the centre indicates higher mortality. A. Fibrillation: atrial fibrillation/ flutter; BPH: benign prostatic hypertrophy; CAD; coronary artery disease; CHF: congestive heart failure; CRF:

chronic renal failure; CVA: cerebrovascular accident; DJD: degenerative joint disease; GERD: gastroesophageal reflux disease; OSA: obstructive sleep apnea; PAD: peripheral artery disease; pulmonary HTN+RHF: pulmonary hypertension and right heart failure. Reprinted with permission from the American Thoracic Society. Copyright © 2020 American Thoracic Society. Divo M, Cote C, De Torres JP, Casanova C, Marin JM, Pinto-Plata V, et al. 2012. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 186:155–161; doi:10.1164/rccm.201201-0034OC. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

Several mechanisms may explain why COPD exhibits an excess risk of concomitant diseases: (1) comorbidities may be caused by a shared risk factor which is potentially harmful to several organs, such as tobacco smoking.[3,24,32] Of note, it was suspected that many risk factors and comorbidities may be connected to COPD by an underlying process of systemic chronic inflammation;[39] (2) the genetic susceptibility which is involved in the pathogenesis of COPD could induce similar changes in several organs (as supported by the '*multi-organ loss of tissue phenotype*' of COPD);[32] (3) factors which impede the development of the lungs may similarly impede the development of other organs, too; in line, adults with low peak lung function in early adulthood seem to have a higher risk for early metabolic and cardiovascular comorbidities and premature death;[7,23] and (4) a process of 'early aging' could not just be involved in the pathogenesis of COPD but of other comorbidities too; multimorbidity occurs 10 to 20 years earlier in patients with than in patients without COPD (even when accounted for smoking) which seems to support this concept.[24]

The concept of comorbidities in COPD is important because, while associated with a worse prognosis, it also offers the opportunity for shared treatment strategies. Life-style modifications, such as smoking cessation or physical activity, can benefit both COPD and the comorbidities.[32,39]

Lifestyle manifestations of COPD: the dyspnoea-physical inactivity vicious circle

As a consequence of their disease, COPD patients tend to decrease physical activity from the early stages of the disease onwards.[40,41] It was hypothesized that patients would lower (often subconsciously) their activity levels in order to avoid exertional dyspnoea, inducing a vicious circle of dyspnoea, deconditioning and physical inactivity.[42]

A recently updated and validated model shows that exercise capacity, which reflects the functional status of the patient, and COPD exacerbations play a more central role in this vicious circle than previously assumed (Figure 5).[43] In addition to the deconditioning due to dyspnoea and inactivity, COPD patients may also exhibit a myopathy due to oxidative stress,[38] which can add to the peripheral muscle dysfunction and contribute to the decrease in physical activity.

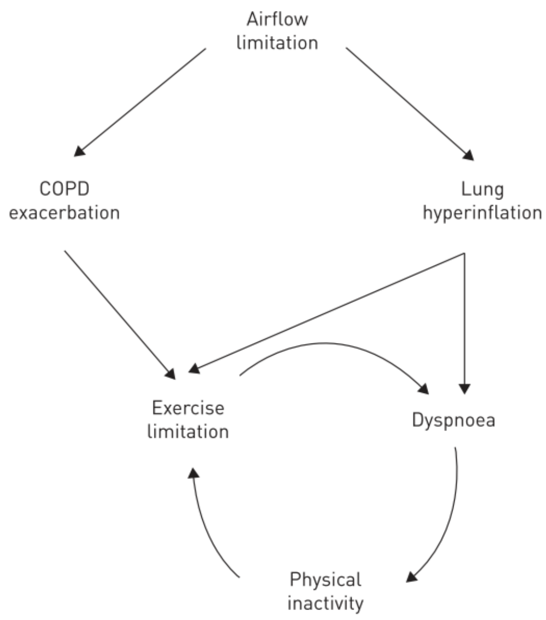

Figure 5. The dyspnoea-physical inactivity vicious circle in COPD patients, adapted from MA Ramon et al.[43] Reproduced with permission from the European Respiratory Society, 52, Ramon MA, Riet G Ter, Carsin AE, Gimeno-Santos E, Agustí A, Antó JM, et al., The dyspnoea–inactivity vicious circle in COPD: Development and external validation of a conceptual model, doi:10.1183/13993003.00079-2018, Copyright © ERS 2020.

1.2 COPD and physical activity

1.2.1 Definition and measurement of physical activity and sedentary behaviour

Physical activity is defined as "*any bodily movement produced by skeletal muscles that results in energy expenditure*".[44] It is the sum of activities during a day and thus includes work related activities, household chores (e.g., cooking, cleaning or gardening), transportation (e.g., walking or cycling), recreational activities and others.[44–46] Exercise is a subcategory of physical activity and typically a planned and structured activity with the aim to improve fitness.[44]

Physical activity is often characterised by frequency, intensity, time and type (*FITT principle*).[47] The 'frequency' refers to the number of individual sessions in a given time interval, 'intensity' to the rate of energy expenditure, 'time' to the duration of an individual session and 'type' to the sort of activity involved.[47,48] The amount of physical activity during a given time interval (e.g., one day) can be derived by multiplying frequency x intensity x time.[49] A common way to express the intensity of an activity is the metabolic equivalent of task (MET). The MET is '*the ratio of the energy expended during an activity to energy expended at rest'*.[50] By convention, the rate of energy expenditure at rest is set at one MET,[50] and the caloric cost of physical activity can be estimated as kilocalories = MET x weight in kilograms x duration in hours.[51] Light physical activity is defined as an absolute intensity of > 1.5 to 2.9 METs (e.g., standing or walking slowly), moderate to vigorous physical activity (MVPA) as ≥ 3.0 to 5.9 METs (rule of thumb: '*can talk but not sing*'; e.g., walking briskly or general gardening), and vigorous intensity as ≥ 6 METs ('*cannot say more than a few words without pausing for a breath'*; e.g., jogging or hiking up-hill).[50,52,53]

To communicate health messages more effectively, and supported by the increasing availability of pedometers and accelerometers, the amount of physical activity is now often expressed in steps/day. A graduated step index has been proposed to conceptualize the amount of physical activity,[45] which ranges from sedentary (<5 000 steps/day) to highly active (≥ 12 500 steps/day) levels (Table 2):

Table 2. Graduated step index, adapted from Tudor-Locke et al.[45]

Daily step count	Activity level
< 5 000 steps/day	Sedentary
5 000 - 7 499 steps/day	Low active
7 500 - 9 999 steps/day	Somewhat active
10 000 - 12 499 steps/day	Active
≥12 500 steps/day	Highly active

WHO recommends for all adults- both, with and without chronic non-communicable comorbidities- aerobic intensity of at least 150 minutes of MVPA per week (30 minutes/day on 5 days of the week, in bouts of at least 10 minutes), or 75 minutes of vigorous intensity per week or a combination of both.[46] The recommended 30 minutes/day in MVPA can be achieved by walking at a cadence of around 100 steps/minute. This adds to about 3000 steps which should be taken in addition to the steps necessary for the common daily requirements to get the desired health benefit.[45]

Finally, sedentary behaviour is defined as a behaviour of low intensity while sitting or lying, corresponding to ≤ 1.5 METs.[54] It typically includes activities such as watching television, reading, or sitting at the computer.[53] Of note, sedentary behaviour is a distinct concept from physical inactivity which results from not meeting the physical activity guidelines.[54,55] Both sedentary behaviour and inactivity must be considered as distinct risk factors for chronic non-communicable diseases and do not necessarily always change in parallel.[54] Indeed, it is possible that patients can be physically very active but still spend large amounts of time in sedentary behaviour.[53,54,56] Despite the growing interest in the topic, there are currently hardly any recommendations available which tackle specifically sedentary behaviour in COPD patients.[57]

Physical activity and sedentary behaviour can be measured using subjective (e.g., questionnaires) or objective (e.g., activity monitors) methods. Questionnaires have the advantage of being inexpensive and easy to use but risk being inaccurate (e.g., limited ability to memorize, difficulty to recall light physical activity).[58,59] They collect information on physical activity in daily life (e.g., walking, climbing stairs, household activities or sport) and are either self-administered or conducted as interview. In general the questionnaires tend to overestimate the activity level.[60] The use of questionnaires to predict the individual physical activity amount must thus be viewed cautiously but they can provide some insight into the patients' view and be helpful when assessing larger patient groups.[58,59]

There is agreement that is more valid to measure the amount of physical activity objectively by using direct methods.[61] This measurement can be challenging in COPD patients though, because these are less active than healthy individuals and the changes in physical activity tend to be more subtle and consequently more difficult to capture correctly.[62–64] Pedometers (step counters) estimate the number of steps in only one vertical plane.[65] They can be useful in healthy, older individuals for assessment and motivation but they are less reliable at slower walking speeds or in gait disorders.[64,66] Accelerometers are more accurate in estimating the physical activity, especially if light and slow.[58] They measure the acceleration of the body in one, two or three axes (uniaxial, biaxial or triaxial monitors).[61] Several devices have been tested and validated in COPD patients such as the Dynaport MoveMonitor (McRoberts BV, The Hague, The Netherlands), the Actigraph (Actigraph, Pensacola, FL, USA) or the SenseWear PRO armband (Body Media, Pittsburgh, PA).[61,67] These are all triaxial devices (SenseWear includes additional sensors for skin temperature etc.) which can provide information on step count, activity time, movement intensity or vector magnitude units (VMUs, indicating acceleration).[67] The time spent in sedentary behaviour (sedentary time) can also be derived from these devices.

1.2.2 Physical fitness and exercise capacity

Physical activity needs to be distinguished from the closely related concept of physical fitness. This refers to the '*ability to carry out daily tasks with vigour and alertness, without undue fatigue and with ample energy'* and is determined by a set of attributes related to health (such as cardiorespiratory endurance, muscular endurance or muscular strength) or skills (athletic abilities).[44]

In patients with COPD, physical fitness is usually conceptualised as functional exercise capacity. Exercise capacity has been found to be moderately to strongly associated with physical activity (r=0.38-0.85).[68] To understand better the association between exercise capacity and physical activity and the resulting physical function, the concept of ‘can do’ vs. ‘do do’ has been introduced recently.[69–71] For this approach COPD patients are distributed across four quadrants by plotting the physical capacity (i.e., exercise capacity, what patients ‘can do’) against the physical activity (what patients ‘do do’) (Figure 6).[70]

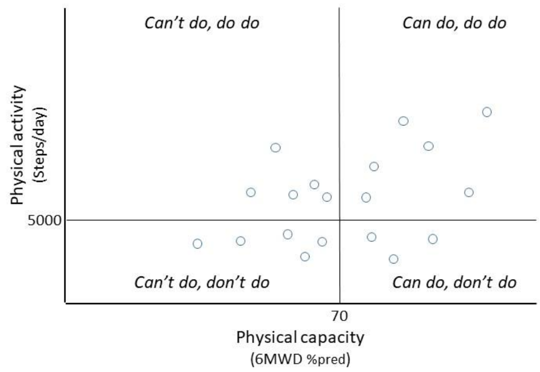

Figure 6. The quadrant concept for physical capacity and physical activity.

The plot illustrates that not all patients who have sufficient exercise capacity are necessarily active (‘can do, don’t do ‘quadrant) while others can be active despite a lack of capacity (‘can’t do, do do’ quadrant) which suggests that other factors may play a role in the physical activity of COPD patients in addition to exercise capacity.[69,70,72]

Functional exercise capacity is often assessed in COPD by the distance walked in a 6-minutes walk test (6MWD), widely applied in clinical practice,[73] and shown to be a key prognostic factor in COPD.[74] For this test, patients are encouraged to walk along a flat corridor (ideally ≥ 30 metres in length) as far as possible in 6 minutes, following standardized conditions.[75,76] The test is usually performed twice with at least a 30-minute rest between and the best 6MWD (in metres) is recorded.[73] The 6MWD can be expressed in metres or as percentage of the predicted value using reference equations.[73]

1.2.3 Physical activity experience

In addition to objective measures of physical activity and functional exercise capacity it is important to understand how physical activity is perceived by the COPD patient. A conceptual framework which aimed to explore the patients' experience with physical activity, identified three main themes.[77] These included the impact of COPD on the amount of physical activity, the symptoms during activity and adaptions necessary to facilitate physical activity.[77] This experience of physical activity can be assessed best with patient reported outcome (PRO) questionnaires. However, such questionnaires alone are not able to capture the full construct of physical activity experience for which the combination with an activity monitor is necessary. To provide such a full picture of all dimensions of physical activity experience in COPD patients the "*PROactive physical activity in COPD*" (PPAC) instruments were developed.[78]

These PPAC instruments are hybrid tools which combine a short patient-reported outcome questionnaire with data from an activity monitor to assess the amount and perceived difficulty of physical activity.[78] Two distinct PPAC instruments were developed, the clinical PPAC instrument (C-PPAC) which contains 14 items and the daily PPAC instrument (D-PPAC) which contains 9 items. Both are reported as amount, difficulty and (combined) total score (ranging from 0 to 100), with lower scores indicating poorer physical activity.

1.2.4 Physical activity levels and changes in COPD patients

COPD patients are typically less active than their peers form the early stages of disease onwards.[40,41,79] Pitta et al. reported that elderly COPD patients were walking less, walking more slowly and standing less, while sitting and lying more when compared to healthy age matched controls.[41] A review of nine studies with 766 participants (including the study by Pitta) found that COPD patients achieved only 57% of the duration, 75% of the intensity and 56% of the activity counts (movements/day) as compared to healthy controls.[40] When considering in more detail the patterns of physical activity in COPD patients, patients of all stages engaged in bouts of MVPA, but patients with severe or very severe disease did fewer and shorter bouts than those with milder disease.[80] If only consecutive minutes were considered, around 25% of patients achieved the recommended ≥ 30 minutes of MVPA per day but if accumulation of bouts of ≥ 10 minutes was taken into account, almost 60% reached this goal.[80] COPD patients are thus less active than their peers but still able to engage in some MVPA; in order to cope with their limitations though, they reorganize their physical activities towards fewer and shorter active units.[80]

In addition to the lower activity levels in COPD patients, physical activity was reported to decline spontaneously by around 400–500 steps/day per year.[81–87] These declines were related to lower levels of lung function,[83,84] acute exacerbations (though evidence was not consistent)[35,36,88], or the seasonality of testing (patients tended to be more active in spring and summer, than in autumn and winter)[85,89]. Importantly, all these studies focused just on the mean annual decline of physical activity and did not take into account a possibly heterogeneous progression. Considering that the nature and progression of COPD are markedly heterogeneous and that distinct lung function trajectories can lead to COPD,[7] it seems plausible that the progression of physical activity is indeed not the same for all COPD patients.

1.2.5 Physical activity as a key prognostic factor in COPD

Physical activity is a key prognostic factor in COPD. First, there is consistent evidence that low physical activity levels[59,62,72,90–96] or a decline in physical activity[97] are associated with an increased risk of hospitalisation; notably, relatively small amounts of physical activity (e.g., walking or cycling 2 hours per week) seem already protective against this risk. Also, it has been shown convincingly in a number of longitudinal studies that low physical activity level[59,72,90,92,93,98–100] or its decline[101] were associated with increased mortality in COPD patients. In line, some longitudinal studies in COPD patients find that a higher physical activity level is associated with an attenuation in lung function decline and symptoms deterioration[102] and improved health-related quality of life.[103] Evidence from cross-sectional studies in COPD patients supports an association between physical activity and other clinically relevant outcomes such as dyspnoea.[72]

Several mechanisms are conceivable how physical activity might influence positively the outcome in COPD patients: (1) physical activity has anti-inflammatory and antioxidant effects[102,104–107] which likely counteract the pro-inflammatory pathomechanism induced by tobacco-smoking and other noxious substances. The findings that higher levels of physical activity were associated with a diminished decline in lung function and a reduced risk for COPD among smokers in the general population support this hypothesis;[102,104] (2) physical activity could exert by its anti-inflammatory and anti-oxidant properties an anti-ageing effect;[19,108] (3) physical activity lowers the risk for the metabolic syndrome[109] and (thereby indirectly and directly) for many other comorbidities in COPD patients. Considering that the comorbidities in COPD patients are associated with a high morbidity and mortality[37] this is prognostically very relevant; finally (4) the reduction of exacerbations associated to higher levels of physical activity could also contribute to the reduced morbidity and mortality.[72,102]

In light of the broad evidence for the benefits of physical activity, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) therefore recommends physical activity for all COPD patients.[110] However, to adequately support physical activity it is important to understand the determinants of physical activity in COPD patients.

1.2.6 Physical activity behaviour in COPD and its determinants

Physical activity is more than just a numerical value, obtained by objective measurements. It is a complex behaviour and a '*life-style choice*'[111] which results from the interplay of a range of individual, societal and environmental factors.

The ecological model of physical activity aims to capture the determinants of physical activity in the general population (Figure 7).[112] It recognizes that physical activity is influenced by several domains, extending from the individual-level (including biological and psychological factors) to the interpersonal (e.g., social relations), the environmental (e.g., built environment), the local policy (e.g., physical activity advocacy) and the global domain (e.g., global media). All these domains are interrelated and exert their effects across the life course of the individuum.

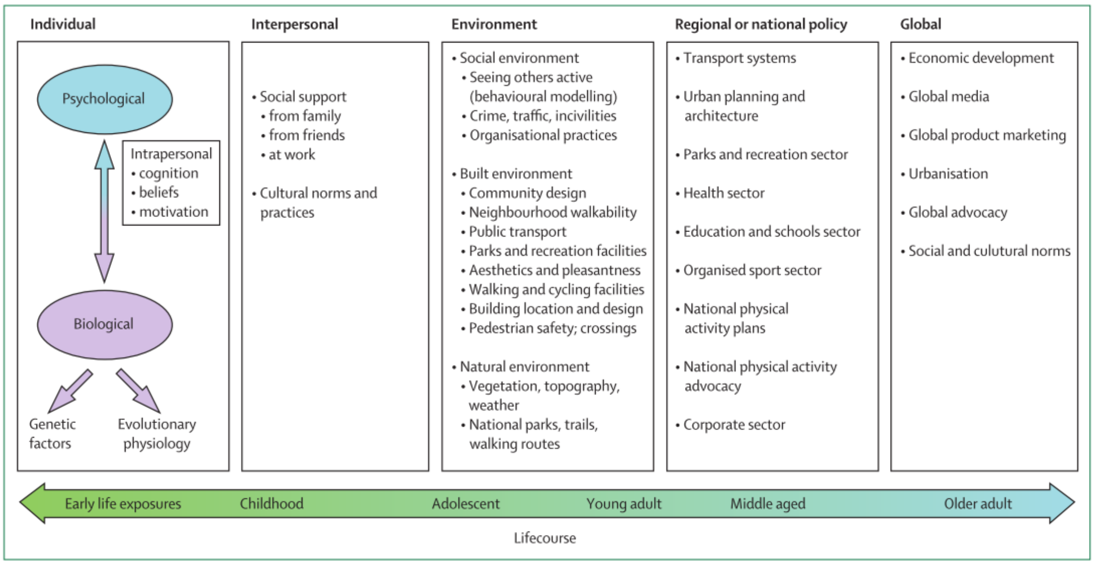

Figure 7. **The ecological model of physical activity**, adapted from Bauman et al.[112] Reprinted from The Lancet, 380, Bauman AE, Reis RS, Sallis JF, Wells JC, F Loos RJ, Martin BW, et al., Correlates of physical activity: why are some people physically active and others not?, 258–271, doi:10.1016/S0140-6736(12)60735-1, Copyright © 2012, with permission from Elsevier.

Importantly though, this model has been developed for the general population. It thus can serve as a valuable guide to explore the determinants of physical activity behaviour in COPD patients, but we need to be cautious that the specific role of some factors (e.g., the environment) may be different in patients who suffer from a chronic disease, such as COPD.

The role of the individual biological and clinical factors in the physical activity of COPD patients have been largely explored (Figure 8).[72] Overall, disease severity was negatively associated with the physical activity level.[113] Specifically factors, such as hyperinflation, exercise capacity, dyspnoea, previous exacerbations, gas exchange, systemic inflammation, quality of life and self-efficacy showed consistent associations with physical activity although it was often difficult to establish firmly the direction of the association due to the cross-sectional design of most studies.[72] Also, many of the common comorbidities in COPD, were negatively associated with physical activity.[59,114,115] Of note the association of isolated lung function impairment with physical activity was relatively weak.[59]

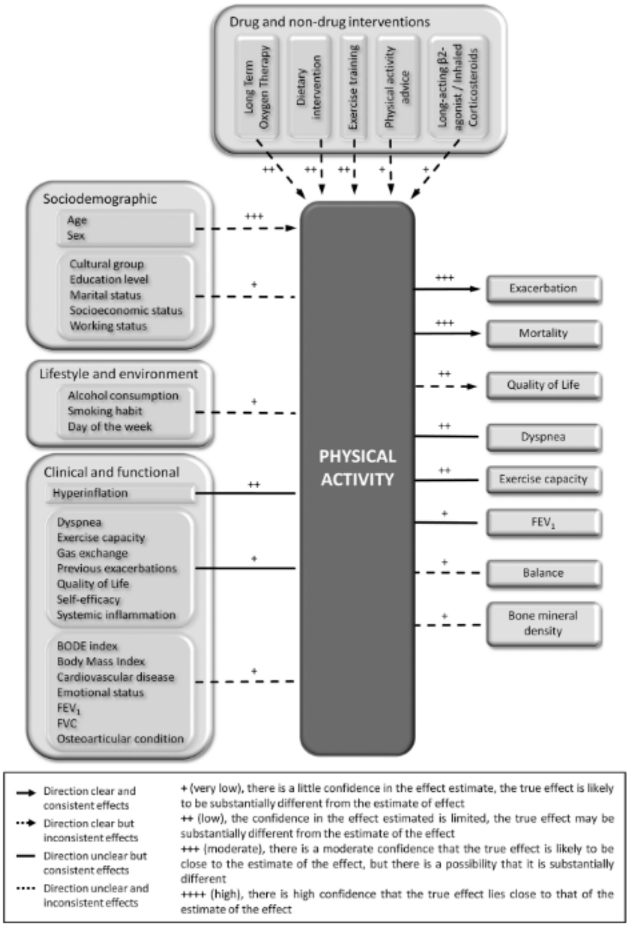

Figure 8. Conceptual model of physical activity in COPD patients, adapted from Gimeno-Santos et al.[72] Reproduced from Thorax, Determinants and outcomes of physical activity in patients with COPD: a systematic review on behalf of PROactive consortium, Gimeno-Santos E, Frei A, Steurer-Stey C, De Batlle J, Rabinovich RA, Raste Y, et al., 69:731–739, doi:10.1136/ thoraxjnl-2013-204763, Copyright © 2014 with permission from BMJ Publishing Group Ltd.

In contrast, information regarding the potential determinants of physical activity beyond the individual clinical domain are scarce. The few available studies point towards the importance of some socio-environmental factors. As regards the interpersonal domain, Arbillaga-Etxarri et al. showed that dog-walking and grandparenting were associated to the amount and intensity of physical activity in COPD patients.[116] Also patients who had a physically active 'loved one' (i.e., the person they were living together) were more active themselves.[117] As concerns the environment, the season of recruitment influenced physical activity; COPD patients were less active in autumn and winter[85,89] and also negatively affected by rainfall[87]. Moreover, air pollution (i.e., high levels of ozone and particulate matter $(PM)_{10}$) were shown to be associated with a reduced step count in COPD patients.[118] However, other environmental factors, such as neighbourhood deprivation, surrounding greenness and proximity to green and blue spaces, were not associated with physical activity which suggests that they could have a less relevant role in COPD patients.[116]

Overall, these studies provide some first insight, but the gaps relating to psychological, interpersonal and environmental factors are still large.

1.2.7 Determinants of change in the physical activity of COPD patients

A considerable number of studies tested interventions to increase physical activity in COPD patients.[119–121] Many of these were short-term interventions which included a pedometer and motivational content, and showed a significant improvement of physical activity at the end of the intervention period.[122] However, the effect of these interventions often waned during the follow-up.[123] It is likely that a long-term change to higher levels of physical activity could be maintained better with a long-term intervention, well embedded into the patients' every-day life. Indeed the Urban Training study, a randomized controlled trial which assessed the long-term effect of a behavioural intervention with urban walking trails, found that patients who were adherent to the intervention walked significantly more than the usual care group at 12 months (adjusted difference +957 steps/day on efficacy analysis).[124] Unfortunately, the optimal timing and use of these interventions are still unclear.[120,125]

More information on the factors which can determine study completion (a prerequisite for a successful study) and a change in the physical activity of COPD patients (the desired outcome) would be important but knowledge of this sort is scarce. Four studies have assessed factors that affected completion and/or response to a physical activity intervention in COPD in post-hoc or secondary analyses. They found overall, that lower baseline physical activity and better functional performance seemed to be related to a better completion and response. Specifically, higher body mass index (BMI), higher isometric quadriceps force and a better health status were associated with study completion.[126] Lower baseline physical activity,[127,128] younger age,[129] less severe disease (lower dyspnea scores, better exercise capacity and mild-to-moderate COPD),[126] and more social support, lack of depression, no necessity for oxygen, and recruitment in spring[128] were significant predictors of a change towards more activity. However, these studies included patients with low exercise capacity (6MWD of around 450m or below) and/or low baseline physical activity, and focused on the typical clinical characteristics of COPD which narrows their practical applicability and does not account for the complexity of the physical activity behaviour.

The consideration of the wider determinants of physical activity in line with the ecological model of physical activity,[112,125] could help to fill some of the knowledge gaps concerning study completion and response and help design more successful physical activity interventions in COPD patients.

2. RATIONALE

To improve the prognosis of COPD patients, it is important to keep these patients active. Physical activity is therefore explicitly recommended for all COPD patients.[3] Driven by the general notion that COPD patients are less active than their peers and further decrease activity over time, a large number of studies have tested interventions to increase physical activity in COPD patients.[86,120] Unfortunately, most of these interventions were only successful at short-term, while the benefit did not persist at long-term.

In order to develop successful interventions with a lasting effect, it may be necessary to overcome a 'one-size-fits-all' approach and tailor the interventions more individually. For such an individualized approach we need a better understanding of how physical activity in COPD patients evolves naturally, and whether the progression really is the same for all patients. In case of potentially distinct trajectories of progression in physical activity it would be important to identify the respective determinants. Moreover, it is essential to know if there are variables, beyond the typical clinical determinants, which can influence the physical activity in COPD patients (e.g., interpersonal or environmental variables). Finally, we need more insight into variables which can possibly determine study completion and response for a given intervention.

Consequently, to promote physical activity and maintain or even increase its levels, more insight into the determinants of physical activity behaviour in COPD patients is strongly needed.

3. OBJECTIVES

The general objective of this thesis is to assess the determinants of physical activity behaviour in COPD patients.

Specifically, the research objectives are:

1. To assess the natural patterns of physical activity progression in COPD patients and explore their potential determinants, based on baseline and 12-month prospective data of 291 patients with stable mild-to-very severe COPD from primary, secondary and tertiary care from five European countries.

2. To assess the role of environmental factors in the physical activity and capacity of COPD patients, based on a cross-sectional sample of 402 patients with stable mild-to-very severe COPD from primary and tertiary care from Catalonia, Spain.

3. To assess the determinants of study completion and response to a 12-month behavioural physical activity intervention in COPD patients, based on baseline and 12-month prospective data of 202 patients with stable mild-to-very severe COPD from primary and tertiary care from Catalonia, Spain.

4. METHODS

The methods for the three objectives of this thesis are presented in detail in the methods sections of the resulting manuscripts. In the following, we give a brief overview of the methods employed.

4.1 Study population and design

For this thesis we used data from the Urban training study[124] and the PROactive validation study.[78]

The **Urban Training study** was a multicentre randomized controlled trial (NCT01897298)[124] that enrolled 407 patients from five Catalan seaside municipalities (Badalona, Barcelona [centre and shore areas], Mataró, Viladecans and Gavà) at primary care centres and tertiary hospitals and randomized patients to the Urban Training behavioural intervention or usual care group between October 2013 and February 2015.

The **PROactive initial validation study** was a non-interventional cohort study (NCT01388218)[78] that enrolled 236 COPD patients from five European cities (Athens/Greece, Edinburgh and London/United Kingdom, Groningen/Netherlands and Leuven/Belgium) at tertiary hospitals, rehabilitation centres and primary care settings between July and November 2011.

Both studies defined COPD according to ATS/ERS (post-bronchodilator forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) ratio <0.70).[31] The studies were approved by all local institutional review boards and written informed consent, including re-use of data for COPD-related research, was obtained from all patients.

For objective 1 (identification of patterns of physical activity progression), we used an observational cohort study design of 12-month follow-up. We included patients from the usual care arm (n = 205) of the Urban Training study and the clinically stable patients (n

= 207) of the PROactive validation study (i.e., patients from both studies had no intervention). Patients were included if they had a valid physical activity measure at baseline and 12-month follow-up (n=291, 71% of total).

For objective 2 (testing the association between environmental variables, and physical activity and capacity), we performed a cross-sectional analysis of baseline pre-randomisation data from the Urban Training study (n=407). For this objective, only data collected at baseline were used and patients were included if they had valid data on physical activity and capacity, and environmental factors (n=402, 99% of total).

For objective 3 (identification of the determinants of study completion and response), we used an observational cohort study design of 12-month follow-up which was based on data of the intervention arm (n=202) from the Urban Training study (i.e., patients who were randomized to the Urban Training trial behavioural physical activity intervention). The determinants of study completion were assessed for all patients of the intervention arm with valid data on physical activity at baseline (n=202), and the determinants of study response were assessed for patients who completed the study and had valid data on physical activity (n=132, 65% of total).

4.2 Physical activity and capacity

Physical activity was measured with the Dynaport MoveMonitor (McRoberts BV, The Hague, The Netherlands)[61,67] for one week at baseline and at 12-month follow-up. In the Urban Training study, patients were wearing the monitor for 24 hours and data during waking hours (from 07:00 h to 22:00 h) were retrieved. In the PROactive study, patients were wearing the device during waking hours only. A valid physical activity measurement was defined as a minimum of three days with at least 8 hours of wearing time within waking hours for both studies;[130] details have been published in the respective studies.[78,124] The Dynaport MoveMonitor provided objective data on daily step count, time spent in physical activity of moderate to vigorous intensity (MVPA, ≥3 METs [metabolic equivalents of tasks] min/day), movement intensity (m/s2) during walking, and sedentary time (sum of lying and sitting time, hours/day).

The physical activity experience was assessed by the Clinical visit-PROactive physical activity in COPD" (C-PPAC) instrument. The C-PPAC combines a short patient-reported outcome questionnaire with data from an activity monitor to assess the perceived amount of physical activity, difficulty with physical activity, and total physical activity experience.[78,131] The three scores range from 0 (worse status) to 100 (better status).

Functional exercise capacity was measured by the 6-minutes walk distance (6MWD) according to published recommendations.[75,76] The 6MWD was measured twice with at least a 30-minute rest between, and the longer of the two distances was used for analysis.

4.3 Potential determinants of physical activity and physical activity change

We obtained baseline data using standardized procedures. These variables were tested for the respective objectives as appropriate: (i) sociodemographic: age, sex, smoking, education and individual socioeconomic status; (ii) interpersonal: living with a partner, working status, grandparenting and dog walking; (iii) environmental: season of recruitment, average yearly rainfall, average land-surface temperature,[132] urban vulnerability index (a measure of socioeconomic status at the census tract level),[133] population density (habitants per square kilometre within the census area),[134] pedestrian street length (sum of pedestrian street length within a 300 metre buffer),[135] slope of terrain (average slope within a 300 metre buffer),[136] road traffic noise (annual average levels of road traffic noise in the nearest street [24h EU indicator L_{den} in dB(A)])[132,137] and annual residential averages of nitrogen dioxide (NO_2) and particulate matter $(PM)_{2.5}$ for the year 2013, assessed using temporally adjusted land-use regression (LUR) models as described previously;[138–141] (iv) clinical: FEV_1 and FVC by forced spirometry post bronchodilator, the COPD assessment test (CAT), the Clinical COPD Questionnaire (CCQ), the modified Medical Research Council dyspnea scale (mMRC), the number of acute COPD exacerbations requiring a hospital admission in the previous 12 months and during follow-up, body mass index (BMI) and fat free mass index (FFMI), comorbidities, pharmacological treatment for COPD, pulmonary rehabilitation at baseline and follow-up, incident diseases during follow-up, and knowledge of baseline physical activity; and (v) psychological: the hospital anxiety (HAD-A) and depression (HAD-D) scores, unwillingness to follow the physical activity intervention,[124] stage of change[142,143] and self-efficacy (from 0 to 10). Full details on study procedures and quality control have been reported previously.[78,124,144]

4.4 Statistical analysis

We used the statistical methods as required for the respective research objectives.

For objective 1, we identified cluster groups (physical activity patterns) using k-means.[145] This data-driven approach allowed us to group patients based on the baseline level, the final level and the change in daily step count. We then built a multivariable multinomial regression model using a generalized linear latent and mixed model with random intercepts for study and city,[146] to assess the determinants of physical activity progression patterns.

For objective 2, we used single- and multi-exposure mixed-effects linear regression models with a random intercept for city, adjusting for confounders to test the association between the environmental variables (population density, pedestrian street length, slope of terrain, road traffic noise, NO_2 and $PM_{2.5}$) and physical activity and capacity (step count, sedentary time, C-PPAC difficulty score and exercise capacity).

For objective 3, we built two distinct multivariable logistic regression models to assess the determinants of study completion and response to the intervention.

We adjusted all analyses for the relevant confounders and considered additional (e.g., stratifications) and sensitivity analyses according to a priori defined statistical analysis plans and as detailed in the respective manuscripts.

5. RESULTS

Paper 1: Koreny M, Demeyer H, Benet M, Arbillaga-Etxarri A, Balcells E, Barberan-Garcia A, Gimeno-Santos E, Hopkinson N, De Jong C, Karlsson N, Louvaris Z, Polkey M, Puhan MA, Rabinovich RA, Rodríguez-Roisin R, Vall-Casas P, Vogiatzis I, Troosters T, Garcia-Aymerich J. Patterns of Physical Activity Progression in Patients With COPD. Arch Bronconeumol; 2020; doi:10.1016/j.arbres.2020.08.00. Online ahead of print.

Paper 2: Koreny M, Bosch de Basea M, Cirach M, Arbillaga-Etxarri A, Barberan-Garcia A, Borrell E, Foraster M, Gimeno-Santos E, Marín A, Vall-Casas P, Vilaró J, Rodriguez-Roisín R, Garcia-Aymerich J. Role of the environment in the physical activity and capacity of patients with chronic obstructive pulmonary disease: a cross-sectional analysis of the Urban Training study in Catalonia. In preparation.

Paper 3: Koreny M, Demeyer H, Arbillaga-Etxarri A, Gimeno-Santos E, Barberan-Garcia A, Benet M, Balcells E, Borrell E, Marin A, Rodríguez Chiaradía DA, Vall-Casas P, Vilaro J, Rodríguez-Roisin R, Garcia-Aymerich J. Determinants of study completion and response to a 12-month physical activity intervention in COPD. PLoS One; 2019; 14:e0217157; doi:10.1183/13993003.congress-2018.oa1987.

5.1 Paper 1

Koreny M, Demeyer H, Benet M, Arbillaga-Etxarri A, Balcells E, Barberan-Garcia A, Gimeno-Santos E, Hopkinson N, De Jong C, Karlsson N, Louvaris Z, Polkey M, Puhan MA, Rabinovich RA, Rodríguez-Roisin R, Vall-Casas P, Vogiatzis I, Troosters T, Garcia-Aymerich J.

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Original article

Patterns of Physical Activity Progression in Patients With COPD

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ABSTRACT

Introduction: Although mean physical activity in COPD patients declines by 400–500 steps/day annually, it is unknown whether the natural progression is the same for all patients. We aimed to identify distinct physical activity progression patterns using a hypothesis-free approach and to assess their determinants.
Methods: We pooled data from two cohorts (usual care arm of Urban Training [NCT01897298] and PROactive initial validation [NCT01388218] studies) measuring physical activity at baseline and 12 months (Dynaport MoveMonitor). We identified clusters (patterns) of physical activity progression (based on levels and changes of steps/day) using k-means, and compared baseline sociodemographic, interpersonal, environmental, clinical and psychological characteristics across patterns.
Results: In 291 COPD patients (mean ± SD 68 ± 8 years, 81% male, FEV_1 59 ± 19%$_{pred}$) we identified three distinct physical activity progression patterns: *Inactive* (n = 173 [59%], baseline: 4621 ± 1757 steps/day, 12-month change (*Δ*): −487 ± 1201 steps/day), *Active Improvers* (n = 49 [17%], baseline: 7727 ± 3275 steps/day, *Δ*: + 3378 ± 2203 steps/day) and *Active Decliners* (*n* = 69 [24%], baseline: 11 267 ± 3009 steps/day, *Δ*: −2217 ± 2085 steps/day). After adjustment in a mixed multinomial logistic regression model using *Active Decliners* as reference pattern, a lower 6-min walking distance (RRR [95% CI] 0.94 [0.90–0.98] per 10 m, *P* = .001) and a higher mMRC dyspnea score (1.71 [1.12–2.60] per 1 point, *P* = .012) were independently related with being *Inactive*. No baseline variable was independently associated with being an *Active Improver*.

Abbreviations: BMI, body mass index; CAT, COPD assessment test; CCQ, clinical COPD questionnaire; CI, confidence interval; COPD, chronic obstructive pulmonary disease; C-PPAC, clinical visit—PROactive physical activity in COPD; FEV1, forced expiratory volume in 1 second; FFMI, fat free mass index; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; HAD-A, hospital anxiety and depression scale – anxiety; HAD-D, hospital anxiety and depression scale – depression; LABA, long-acting $beta_2$-agonists; LAMA, long-acting anti-muscarinics; MET, metabolic equivalent of task; mMRC, modified medical research council dyspnea score; 6MWD, 6-min walking distance; MVPA, moderate to vigorous physical activity; RRR, relative risk ratio; SD, standard deviation.

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Conclusions: The natural progression in physical activity over time in COPD patients is heterogeneous. While *Inactive* patients relate to worse scores for clinical COPD characteristics, *Active Improvers* and *Decliners* cannot be predicted at baseline.

Palabras clave:
EPOC
Actividad física
Patrones de progresión
Análisis de conglomerados
Determinantes

Patrones de progresión de la actividad física en pacientes con EPOC

R E S U M E N

Introducción: Aunque la actividad física en pacientes con EPOC declina una media anual de 400-500 pasos/día, se desconoce si esta progresión es igual en todos los pacientes. Este estudio pretendió identificar los patrones de progresión de la actividad física mediante métodos libres de hipótesis y evaluar sus determinantes.

Métodos: Se estudiaron 291 pacientes con EPOC estable (media ± DE: 68 ± 8 años, 81% hombres, VEMS $59 \pm 19\%_{pred}$) de dos cohortes europeas con actividad física basal y a 12 meses (acelerómetro Dynaport MoveMonitor). Se identificaron conglomerados (patrones) de progresión de actividad física basados en los niveles y cambios de pasos/día usando *k-means*, y se compararon entre patrones las características sociodemográficas, interpersonales, ambientales, clínicas y psicosociales basales.

Resultados: Se identificaron tres patrones: *inactivo* (n = 173 [59%], basal: 4.621 ± 1.757 pasos/día, cambio en 12 meses (Δ): −487 ± 1.201 pasos/día), *activo que aumenta* (n = 49 [17%], basal: 7.727 ± 3.275 pasos/día, Δ: +3.378 ± 2.203 pasos/día) y *activo que reduce* (n = 69 [24%], basal: 11.267 ± 3.009 pasos/día, Δ: −2.217 ± 2.085 pasos/día). La distancia en la prueba de la marcha de 6 minutos (6MWD) y la disnea se asociaron independientemente con ser *inactivo*: RRR [IC 95%] 0,94 [0,90-0,98] por cada 10 m de 6MWD (p = 0,001) y 1,71 [1,12-2,60] por cada punto en la escala mMRC (p = 0,012), respectivamente, en comparación con el patrón *activo que reduce*. No se encontraron variables basales independientemente asociadas con ser *activo que aumenta*.

Conclusiones: La progresión natural de la actividad física en pacientes con EPOC es heterogénea. Mientras que el patrón de pacientes *inactivo* se relaciona con peores características clínicas de EPOC, no se pudo predecir la evolución de los *activos* a *aumentar* o *reducir*.

Introduction

Physical activity is a key prognostic factor in chronic obstructive pulmonary disease (COPD), yet poorly understood. COPD patients are less active than healthy controls from the early stages of disease onwards[1–3] and this reduced activity has been associated with impaired prognosis and accelerated progression of COPD.[4,5] For this reason, several national and international COPD guidelines recommend encouraging patients to maintain a good physical activity level.[6,7]

Despite patients' and health professionals' efforts, physical activity has been shown to exhibit a spontaneous decline of an average of 400–500 steps/day per year in COPD patients.[8–14] Such observed decline has been related, although not consistently, to lower lung function levels,[10,11] the presence of exacerbations[15–17] or the seasonality of testing (e.g., decline observed in patients going from summer to winter).[12,18] Given the heterogeneous nature and progression of COPD,[19] it can be hypothesized that physical activity progression also displays different patterns, not captured by the mean physical activity values. Two previous studies support this hypothesis by showing distinct physical activity trajectories over 9 months after a pulmonary rehabilitation program.[20,21] However, the reported progression in physical activity after rehabilitation programs probably does not reflect how physical activity evolves in the wider COPD population nor in an observational setting, where patients receive a variable combination of pharmacological and non-pharmacological treatments.

We aimed (1) to identify, using a hypothesis-free approach, distinct patterns of natural physical activity progression in COPD patients recruited from diverse settings (primary care, hospital and rehabilitation services) and followed during 12 months; and (2) to assess the baseline sociodemographic, interpersonal, environmental, clinical and psychological determinants for the identified patterns. Better understanding of the natural progression of physical activity, of potential distinct patterns and of their determinants could help to individualize strategies to increase (or prevent a decline in) physical activity.

Methods

Study Design and Patient Population

This was an observational (no intervention) cohort study of 12-month follow-up including patients from: (1) the usual care arm (*n* = 205) from the Urban Training study,[22] that recruited patients from primary care and tertiary hospitals in five Catalan seaside municipalities (Badalona, Barcelona [center and shore areas], Mataró, Viladecans and Gavà); and (2) the clinically stable patients (*n* = 207) from the PROactive validation study,[23] that recruited patients from primary care settings, rehabilitation centers and tertiary hospitals in five European cities (Athens/Greece, Edinburgh and London/United Kingdom, Groningen/Netherlands, and Leuven/Belgium). Both studies defined COPD according to ATS/ERS (post-bronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio <0.70).[24] Patients were included in the present analyses if they had a valid physical activity measure (see below) at baseline and 12-month follow-up.

Both studies were approved by all local institutional review boards and written informed consent, including re-use of data for COPD-related research, was obtained from all patients.

Physical Activity Measurements

Physical activity was objectively measured using the Dynaport MoveMonitor (McRoberts BV, The Hague, The Netherlands)[25] for one week at baseline and follow-up. In Urban Training, patients wore the monitor for 24 h and data during waking hours (from

07:00 h to 22:00 h) were retrieved. In PROactive, patients wore the device during waking hours. A valid physical activity measurement was defined as a minimum of three days with at least 8 h of wearing time within waking hours for both studies[26]; details have been previously published.[22,23] A physical activity report was provided to patients if requested.

We used step count as the primary outcome to define physical activity progression patterns, and time spent in physical activity of moderate to vigorous intensity (MVPA, ≥3 METs [metabolic equivalents of tasks] min/day), movement intensity (m/s^2) during walking, and sedentary time (sum of lying and sitting time, hours/day) as secondary physical activity outcomes to describe patterns. Physical activity experience was assessed by the amount, difficulty and total scores of the Clinical visit-PROactive Physical Activity in COPD (C-PPAC) tool.[23]

Other Measurements

We used variables available from both studies (i.e. exactly the same or equivalent standardized questions and procedures had been used) or variables that were available from one study only but had been related to physical activity or its evolution in the literature: (i) *sociodemographic*: age, sex, smoking history and education; (ii) *interpersonal*: marital status, working status, grandparenting and dog walking; (iii) *environmental*: season of recruitment, average yearly rainfall and urban vulnerability index (a measure of socioeconomic status at the census tract level); (iv) *clinical*: post-bronchodilator FEV_1 and FVC, the 6-min walking distance (6MWD) test, the COPD Assessment test (CAT), the Clinical COPD Questionnaire (CCQ), the modified Medical Research Council dyspnea scale (mMRC), the number of acute COPD exacerbations requiring a hospital admission in the previous 12 months and during follow-up, body mass index (BMI) and fat free mass index (FFMI) by physical examination and bioelectrical impedance, comorbidities from medical records, pharmacological treatment for COPD, pulmonary rehabilitation at baseline and follow-up, incident diseases during follow-up, and knowledge of baseline physical activity (i.e. report on request); and (v) *psychological*: the Hospital Anxiety (HAD-A) and Depression (HAD-D) scores. Full details on study procedures and quality control have been reported previously.[22,23,27]

Statistical Analysis

Sample size calculations, missing data strategy and full statistical analyses are provided in the supplement.

We identified cluster groups (physical activity patterns) using k-means,[28] a hypothesis-free method that allowed grouping patients based on the baseline level, the final level and the change in daily step count. To characterize the patterns, we described physical activity and physical activity experience variables according to the cluster groups and compared baseline to follow-up values by paired *t*-tests.

To assess determinants of physical activity progression patterns, we first compared subjects' characteristics by physical activity patterns and obtained *P*-values from mixed logistic regression models with random intercepts for study and city area to account for possible heterogeneity in unmeasured characteristics related to study and city area. Then we built a multivariable multinomial regression model using the generalized linear latent and mixed model, with also random intercepts for study and city.[29] Model building combined step-forward and backward algorithms and we tested goodness of fit of the final model.

As sensitivity analyses, we (1) repeated cluster analysis separately for Urban Training and PROactive; (2) tested the association between the change in daily step count and the change in wearing time overall and per pattern; and (3) repeated the clustering after excluding patients included in pulmonary rehabilitation programs at baseline and/or during follow-up.

All analyses were conducted using Stata/SE 14.2 (StataCorp, College Station, TX, USA).

Results

From 412 patients at baseline, 291 (71%) completed the follow-up visit and were included in the current analyses (Fig. S1). These patients had a higher proportion of males, better functional status and were more active at baseline than those lost-to follow-up (Table S1). Included patients were 81% male and had a mean age of 68 years, FEV_1 of 59% predicted, 6MWD of 477 m, mMRC dyspnea score of 1.3, and walked 6720 steps/day (Table 1). Compliance with the activity monitor during waking hours was excellent: at baseline median (range) valid days of 7 (3–7) and mean ± SD wearing hours of 14.6 ± 0.5 in Urban Training, and 6 (3–7) days and 14.8 ± 2.2 wearing hours in PROactive; and at follow-up, 7 (4–7) days and 14.6 ± 0.6 wearing hours in Urban Training, and 6 (3–7) days and 14.4 ± 2.2 wearing hours in PROactive.

At the group level, the step count did not change over 12 months. In the hypothesis-free approach, we identified three cluster groups (three distinct physical activity patterns) (Fig. 1, Table S2). A first cluster (*n* = 173 [59%]), labeled *Inactive* pattern due to the low step count, walked at baseline mean ± SD 4621 ± 1757 steps/day and decreased their physical activity by 487 ± 1201 steps/day over 12 months. A second cluster (*n* = 49 [17%]), labeled *Active Improvers*, walked 7727 ± 3275 steps/day at baseline and increased by 3378 ± 2203 steps/day. The third cluster (*n* = 69 [24%]), labeled *Active Decliners*, walked 11,267 ± 3009 steps/day at baseline and decreased by 2217 ± 2085 steps/day. Distribution of

Table 1
Patient Characteristics at Baseline and at 12-month Follow-up for All Patients (n = 291) and by Study Group (Urban Training and PROactive study).

	All Patients *n* = 291 (100%)	Urban Training Study *n* = 148[a] (51%)	PROactive Study *n* = 143[a] (49%)
Sociodemographic			
Age (years)	68 ± 8	69 ± 8	67 ± 8
Sex (men)	237 (81)	130 (88)	107 (75)
Current smoker	52 (18)	30 (20)	22 (15)
Pack-years	58 ± 41	60 ± 45	56 ± 37
Education, high school or higher	168 (58)	49 (33)	119 (83)
Interpersonal			
Living with a partner[b]	216 (74)	124 (84)	92 (65)
Active worker[c]	36 (12)	16 (11)	20 (14)
Grandparenting[d]	67 (45)	67 (45)	–
Dog walking[d]	20 (14)	20 (14)	–

Table 1 (*Continued*)

	All Patients n = 291 (100%)	Urban Training Study n = 148[a] (51%)	PROactive Study n = 143[a] (49%)
Environmental			
Recruitment season			
Spring	35 (12)	35 (24)	0 (0)
Summer	58 (20)	15 (10)	43 (30)
Fall	154 (53)	54 (36)	100 (70)
Winter	44 (15)	44 (30)	0 (0)
Average rainfall (h/day)[e,f]	0.62 (0.30–1.13)	–	0.62 (0.30–1.13)
Urban vulnerability index (from 0 -lowest to 1 – highest)[d,g]	0.637 ± 0.175	0.637 ± 0.175	–
Clinical			
FEV_1 (% predicted)	58.6 ± 19.3	58.2 ± 17.6	59.0 ± 21.0
FEV_1/FVC ratio	0.51 ± 0.13	0.55 ± 0.12	0.48 ± 0.13
Airflow limitation severity (post-bronchodilator FEV_1)			
GOLD 1: Mild ($FEV_1 \geq 80\%$ predicted)	39 (13)	15 (10)	24 (17)
GOLD 2: Moderate ($50\% \leq FEV_1 < 80\%$ predicted)	147 (51)	80 (54)	67 (47)
GOLD 3: Severe ($30\% \leq FEV_1 < 50\%$ predicted)	88 (30)	45 (30)	43 (30)
GOLD 4: Very severe ($FEV_1 < 30\%$ predicted)	17 (6)	8 (6)	9 (6)
6MWD (meters)	477 ± 103	501 ± 83	452 ± 116
CAT score (0–40)	12.9 ± 7.6	12.2 ± 7.6	13.6 ± 7.5
CCQ score (0–6)	1.55 ± 0.98	1.40 ± 0.95	1.70 ± 0.98
C-PPAC amount score (0–100)	69.0 ± 15.8	74.7 ± 14.9	63.8 ± 14.9
C-PPAC difficulty score (0–100)	78.4 ± 14.5	82.7 ± 13.4	74.5 ± 14.5
C-PPAC total score (0–100)	73.7 ± 12.8	78.7 ± 11.5	69.2 ± 12.3
mMRC score (0–4)	1.3 ± 0.9	1.1 ± 0.8	1.5 ± 1.0
Any COPD exacerbation with hospital admission in previous 12 months	34 (12)	12 (8)	22 (15)
BMI (kg/m^2)	27.6 ± 4.6	28.3 ± 4.6	26.8 ± 4.6
FFMI (kg/m^2)	19.0 ± 3.0	19.6 ± 3.2	18.4 ± 2.8
Cardiovascular disease[h]	176 (60)	90 (61)	86 (60)
Ischemic heart disease[h]	29 (10)	13 (9)	16 (11)
Diabetes mellitus[h]	51 (18)	38 (26)	13 (9)
LABA or LAMA, alone	41 (14)	23 (16)	18 (13)
Inhaled corticosteroid with LABA and/or LAMA	179 (62)	80 (54)	99 (71)
Pulmonary rehabilitation at baseline	15 (5)	6 (4)	9 (6)
Knowledge of baseline PA	19 (7)	19 (13)	0 (0)
Psychological			
Anxiety (HAD-A, 0–21)	5 ± 4	5 ± 4	5 ± 4
Depression (HAD-D, 0–21)	4 ± 3	3 ± 3	5 ± 3
Physical activity			
Step count (steps/day)	6720 ± 3667	7783 ± 3847	5619 ± 3121
Time in moderate-to-vigorous physical activity (≥3 METs; min/day)	99.4 ± 45.3	109.1 ± 45.7	89.4 ± 42.8
Intensity during walking (m/s^2)	1.86 ± 0.31	1.88 ± 0.32	1.84 ± 0.29
Sedentary time (h/day)	10.53 ± 1.94	10.43 ± 1.48	10.64 ± 2.31
Wearing time (h/day)	14.73 ± 1.56	14.64 ± 0.54	14.81 ± 2.16
Follow-up data			
Any COPD exacerbation with hospital admission during follow-up	28 (10)	10 (7)	18 (13)
Any incident comorbidity during follow-up[d,i]	34 (23)	34 (23)	–
Pulmonary rehabilitation during follow-up	16 (6)	6 (4)	10 (7)
Wearing time at follow-up (h/day)	14.52 ± 1.63	14.60 ± 0.61	14.43 ± 2.24

Notes: Data are presented as *n* (%), mean ± SD or median (interquartile range).

Abbreviations: FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; 6MWD: 6-min walking distance; CAT: COPD Assessment Test; CCQ: Clinical COPD Questionnaire; C-PPAC: Clinical visit—PROactive Physical Activity in COPD (higher numbers indicate a better score); mMRC: modified Medical Research Council; BMI: body mass index; FFMI: fat free mass index; LABA: long-acting beta$_2$-agonists; LAMA: long-acting anti-muscarinics; HAD-A: Hospital Anxiety and Depression scale – Anxiety; HAD-D: Hospital Anxiety and Depression scale – Depression; MET: metabolic equivalent of task.

[a] Some variables have missing values, as follows. Urban Training: 1 in education, 25 in C-PPAC scores, 1 in any COPD exacerbation with hospital admission in previous 12 months, 18 in FFMI, 2 in HAD anxiety and depression, 5 in any COPD exacerbation with hospital admission during follow-up, 2 in pulmonary rehabilitation during follow-up; PROactive: 1 in living with a partner, 21 in average rainfall, 1 in CAT score, 1 in CCQ score, 6 in C-PPAC scores, 8 in FFMI, 3 in LABA or LAMA, alone, 3 in inhaled corticosteroid with LABA and/or LAMA, 1 in HAD anxiety and depression, 3 in pulmonary rehabilitation during follow-up.

[b] Marital status: living with a partner vs single, widowed or divorced.

[c] Working status: active worker (working full-time or part-time) vs. unemployed, housework or retired.

[d] Only available for Urban Training.

[e] Only available for PROactive.

[f] Average rainfall was calculated as the mean of the measurements at baseline, 6 and 12 months.

[g] The urban vulnerability index is a measure of socioeconomic status at the census tract level that combines demographic, economic, residential and subjective indicators, and ranges from lowest [0] to highest [1] level of neighborhood vulnerability.

[h] ICD10 codes: I00–I99 for cardiovascular diseases; I20–I25 for ischemic heart disease, E14 for diabetes mellitus.

[i] Incident comorbidities included ICD10 codes C00–N99.

MVPA and walking intensity by physical activity pattern followed the same sequence as steps/day, except for walking intensity in *Active Improvers* that did not change. Sedentary time did not change for *Inactive*, decreased for *Active Improvers* and increased moderately for *Active Decliners*. The physical activity experience as expressed by C-PPAC scores did not change for the *Inactive* pattern; the *Active Improvers* increased the C-PPAC scores (i.e., increased amount and reduced difficulty); the *Active Decliners* decreased the

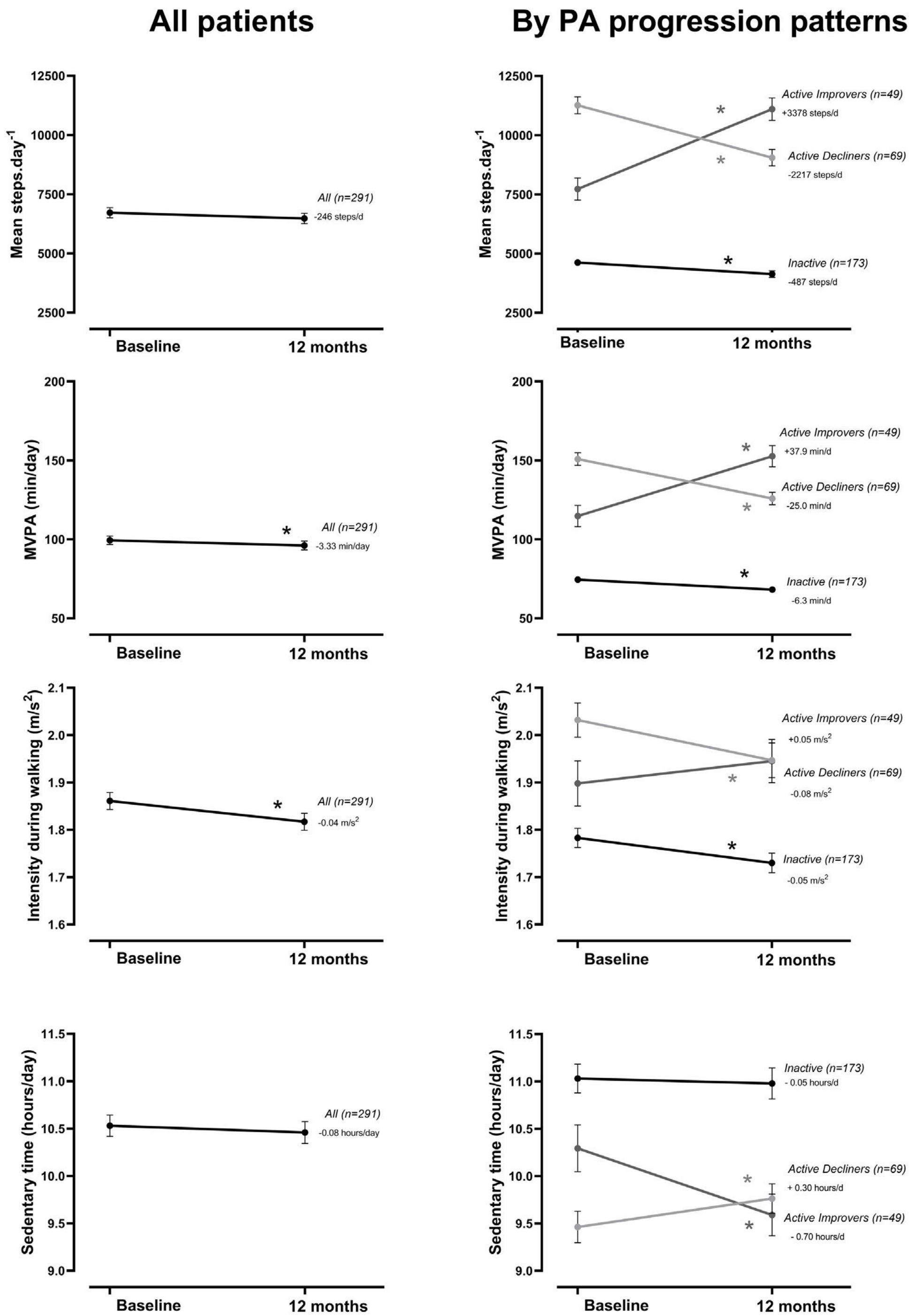

Fig. 1. Physical activity variables at baseline and at 12-month follow-up, overall and by PA progression pattern (*Inactive*, *Active Improvers* and *Active Decliners*). Notes: Data are presented as mean ± SE (specific numbers are presented in Table S2). * *P*-value ≤.05. Abbreviations: MVPA: moderate-to-vigorous physical activity; MET: metabolic equivalent of task.

C-PPAC amount and total scores while the C-PPAC difficulty score did not change (Fig. 2, Table S2).

Patients in the *Inactive* physical activity pattern had a higher degree of education, a smaller proportion was living with a partner or grandparenting, and they presented with a worse general health status, lower lung function, poorer exercise capacity, worse quality of life and higher dyspnea and depression scores than those in the *Active Improvers* or *Decliners* patterns (Table 2). *Active Improvers* and *Decliners* were very similar in their baseline characteristics, except for their daily step count.

In the multivariable multinomial logistic regression model we used *Active Decliners* as the reference pattern to capture both the determinants of being *Inactive* vs *Active* and the determinants of being an *Active Improver* vs *Decliner*. A lower exercise capacity and a higher mMRC dyspnea score were independently related with being *Inactive* whereas no variable was identified as

Table 2
Patient Characteristics by Physical Activity Progression Pattern (*Inactive, Active Improvers* and *Active Decliners*) in 291 COPD Patients.

	Inactive n = 173[a] (59%)	*Active Improvers* n = 49[a] (17%)	*Active Decliners* n = 69[a] (24%)	*P*-Value for *Inactive* vs *Active Improvers* and *Decliners*[b]	*P*-Value for *Active Improvers* vs *Decliners*[b]
Urban training study	59 (34)	39 (80)	50 (72)		
PROactive study	114 (66)	10 (20)	19 (28)		
Sociodemographic					
Age (years)	68 ± 8	69 ± 9	67 ± 7	.282	.079
Sex (men)	137 (79)	41 (84)	59 (86)	.931	.789
Current smoker	33 (19)	5 (10)	14 (20)	.152	.152
Pack-years	60 ± 38	63 ± 52	49 ± 40	.187	.082
Education, high school or higher	124 (72)	20 (42)	24 (35)	.006	.452
Interpersonal					
Living with a partner[c]	115 (66)	42 (88)	59 (86)	.017	.714
Active worker[d]	18 (10)	6 (12)	12 (17)	.088	.454
Grandparenting[e]	20 (34)	21 (54)	26 (52)	.039	.863
Environmental					
Average rainfall (h/day)[f,g]	0.63 (0.33–1.13)	0.90 (0.57–1.47)	0.33 (0.23–1.00)	.877	.329
Urban vulnerability index (from 0 – lowest to 1 – highest)[e,h]	0.646 ± 0.176	0.613 ± 0.200	0.646 ± 0.153	.312	.369
Clinical					
FEV_1 (% predicted)	55.9 ± 19.8	62.9 ± 15.8	62.4 ± 19.5	.001	.875
FEV_1/FVC ratio	0.48 ± 0.14	0.55 ± 0.11	0.55 ± 0.11	.004	.904
6MWD (meters)	446 ± 105	521 ± 90	524 ± 78	<.001	.861
CAT score (0–40)	14.2 ± 7.7	11.5 ± 7.3	10.5 ± 6.6	.002	.435
CCQ score (0–6)	1.74 ± 0.97	1.23 ± 0.91	1.29 ± 0.93	.001	.780
C-PPAC difficulty score (0–100)[i]	74.9 ± 14.7	82.6 ± 13.6	84.8 ± 11.6	<.001	.380
mMRC score (0–4)	1.5 ± 1.0	1.0 ± 0.8	0.9 ± 0.7	<.001	.329
Any COPD exacerbation with hospital admission in previous 12 months	24 (14)	4 (8)	6 (9)	.517	.918
BMI (kg/m^2)	27.6 ± 5.0	27.5 ± 3.9	27.5 ± 4.2	.139	.999
FFMI (kg/m^2)	18.9 ± 3.0	19.3 ± 2.9	19.0 ± 3.1	.650	.591
Cardiovascular disease[j]	109 (63)	28 (57)	39 (57)	.221	.930
Ischemic heart disease[j]	18 (10)	5 (10)	6 (9)	.898	.807
Diabetes mellitus[j]	23 (13)	11 (22)	17 (25)	.412	.786
LABA or LAMA, alone	24 (14)	7 (14)	10 (15)	.796	.949
Inhaled corticosteroid with LABA and/or LAMA	115 (67)	28 (57)	36 (53)	.311	.658
Psychological					
Anxiety (HAD-A, 0–21)	5 ± 4	5 ± 3	5 ± 4	.755	.774
Depression (HAD-D, 0–21)	5 ± 3	3 ± 3	3 ± 3	.009	.992
Follow-up data					
Any COPD exacerbation with hospital admission during follow-up	19 (11)	4 (8)	5 (7)	.759	.846
Any incident comorbidity during follow-up[e,k]	10 (17)	10 (26)	14 (28)	.191	.804

Notes: Data are presented as *n* (%), mean ± SD or median (interquartile range).
Abbreviations: FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; 6MWD: 6-min walking distance; CAT: COPD Assessment Test; CCQ: Clinical COPD Questionnaire; C-PPAC: Clinical visit—PROactive Physical Activity in COPD (higher numbers indicate a better score); mMRC: modified Medical Research Council; BMI: body mass index; FFMI: fat free mass index; LABA: long-acting beta$_2$-agonists; LAMA: long-acting anti-muscarinics; HAD-A: Hospital Anxiety and Depression scale - Anxiety; HAD-D: Hospital Anxiety and Depression scale – Depression.

[a] Some variables have missing values, as follows. *Inactive*: 15 in average rainfall, 1 in CAT total, 1 in CCQ score, 14 in C-PPAC difficulty score, 17 in FFMI, 2 in LABA or LAMA, alone, 2 in inhaled corticosteroid with LABA and/or LAMA, 1 in HAD anxiety and depression, 3 in any COPD exacerbation with hospital admission during follow-up; *Active Improvers*: 1 in education, 1 in living with a partner, 2 in average rainfall, 5 in C-PPAC difficulty score, 4 in FFMI, 1 in HAD anxiety and depression, 1 in any COPD exacerbation with hospital admission during follow-up; *Active Decliners*: 4 in average rainfall, 12 in C-PPAC difficulty score, 1 in any COPD exacerbation with hospital admission in previous 12 months, 5 in FFMI, 1 in LABA or LAMA, alone, 1 in inhaled corticosteroid with LABA and/or LAMA, 1 in HAD anxiety and depression, 1 in any COPD exacerbation with hospital admission during follow-up.

[b] *P*-Value from mixed logistic regression models with random effects for study (UT and PROactive) and city area (Badalona, Barcelona-center, Barcelona-shore, Mataró, Viladecans/Gavà, Athens, Edinburgh, Groningen, Leuven, London).

[c] Marital status: living with a partner vs single, widowed or divorced.

[d] Working status: active worker (working full-time or part-time) vs. unemployed, housework or retired.

[e] Only available for Urban Training.

[f] Only available for PROactive.

[g] Average rainfall was calculated as the mean of the measurements at baseline, 6 and 12 months.

[h] The urban vulnerability index is a measure of socioeconomic status at the census tract level that combines demographic, economic, residential and subjective indicators, and ranges from lowest [0] to highest [1] level of neighborhood vulnerability.

[i] Only C-PPAC difficulty is provided as C-PPAC amount and total score include steps/day which were used for the generation of the PA patterns and therefore cannot be assessed as predictors.

[j] ICD10 codes: I00 to I99 for cardiovascular diseases; I20–I25 for ischemic heart disease, E14 for diabetes mellitus.

[k] Incident comorbidities included ICD10 codes C00–N99.

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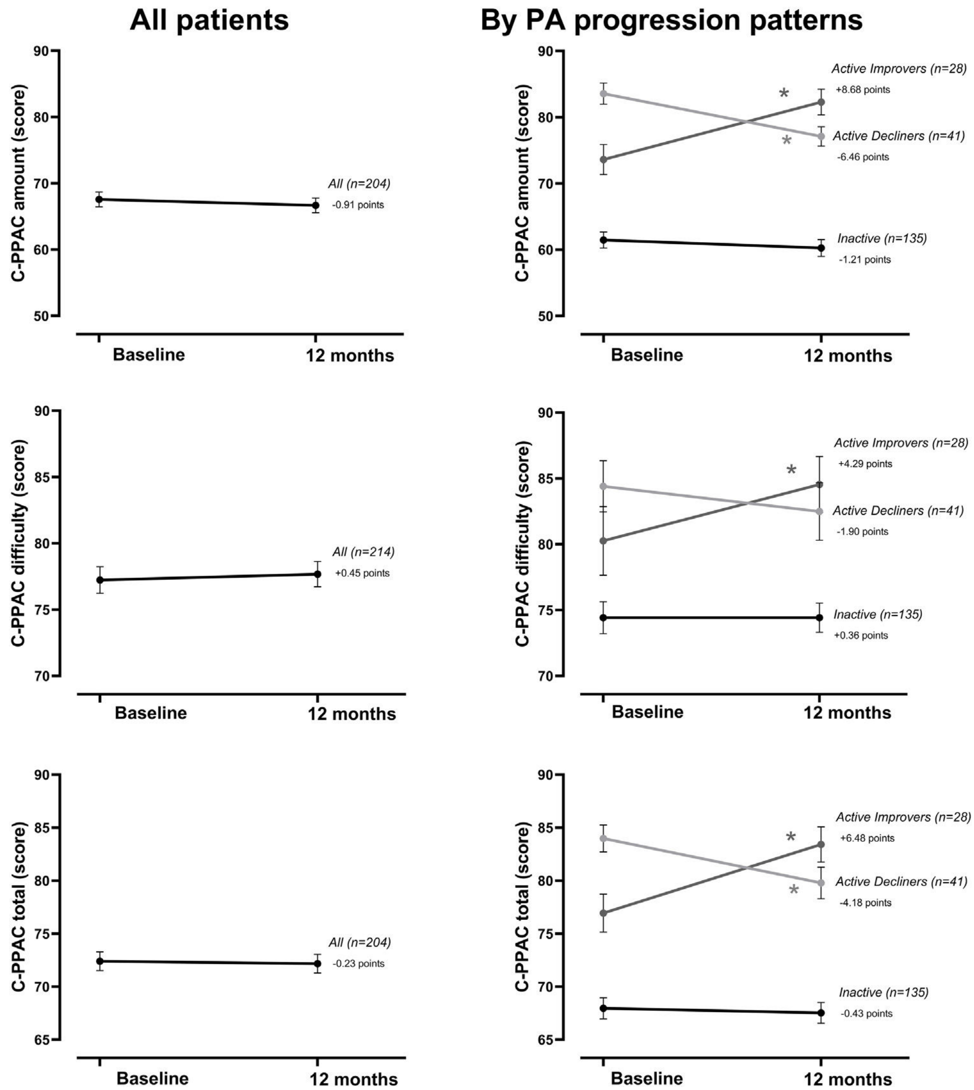

Fig. 2. Physical activity experience variables at baseline and at 12-month follow-up, overall and by PA progression pattern (*Inactive*, *Active Improvers* and *Active Decliners*). Notes: Data are presented as mean ± SE (specific numbers are presented in Table S2). * *P*-value ≤.05. Abbreviations: C-PPAC: Clinical visit—PROactive Physical Activity in COPD (higher numbers indicate a better score). C-PPAC variables have 87 missing values: 38 in *Inactive*, 21 in *Active Improvers*, and 28 in *Active Decliners*.

Table 3
Adjusted Predictive Factors for *Inactive* and *Active Improvers* vs *Active Decliners* in 291 COPD Patients.

	Active Decliners	*Inactive*		*Active Improvers*	
	RRR (95% CI)	RRR (95% CI)	*P*-Value[a]	RRR (95% CI)	*P*-Value[a]
6MWD (per 10 m)	1.00 (ref)	0.94 (0.90–0.98)	.001	1.00 (0.96–1.05)	.868
mMRC score (per 1 point)	1.00 (ref)	1.71 (1.12–2.60)	.012	1.23 (0.73–2.07)	.437

Abbreviations: RRR: relative risk ratio; CI: confidence interval; 6MWD: 6-min walking distance; mMRC: modified Medical Research Council.
[a] *P*-Value from multinomial regression model with random effects for study (UT and PROactive) and city area (Badalona, Barcelona-center, Barcelona-shore, Mataró, Viladecans/Gavà, Athens, Edinburgh, Groningen, Leuven, London).

independently associated with being an *Active Improver* (Table 3). The final model showed good fit. Sensitivity analyses confirmed the results (Tables S3–S5).

Discussion

This study identified, for the first time to our knowledge, the natural progression of physical activity in COPD patients. We used a hypothesis-free approach that allowed the identification of patterns without a priori assumptions about the physical activity changes over time. We found that (1) the natural change in physical activity over time was indeed heterogeneous; (2) the majority of patients (59%) was inactive at baseline and decreased their physical activity level subsequently; (3) among active individuals some increased and some decreased their physical activity level; and (4) although clinical COPD characteristics were related to the physical activity level at baseline they could not predict subsequent physical activity changes.

A first important finding is that physical activity progression in COPD is heterogeneous. In our 12-month study, mean changes in the full group were virtually zero; however when using hypothesis-free clustering methods, we identified one *Inactive* pattern which decreased and two *Active* patterns which increased or decreased physical activity. This observation is in line with previous reports of heterogeneous physical activity progression in patients with rheumatoid arthritis.[30] The average lack of 12-month change in step count differs from previous studies that showed overall a decrease in physical activity.[8,10,11,13] A potential explanation is that most of these studies recruited patients from outpatient or pulmonary clinics, who may have slightly more advanced disease and reduced variability in physical activity and COPD characteristics as compared to our sample including also primary care. Supporting this, the group of patients who started with a lower physical activity (59%) was similar in their baseline characteristics to previous studies and also had a comparable mean decrease of around 500 steps/day.[10,11] Notably, the low overall dyspnea score may have positively influenced the physical activity level of our study population. A second explanation could lie in the high proportion of male subjects and regional differences in physical activity practice (a cohort of patients included in the Mediterranean region[5] had a baseline physical activity comparable to the Urban Training sample). These characteristics of our sample could justify the two patterns with relatively high baseline physical activity and an average small physical activity change.

The second important finding is that there seems to exist a group of COPD patients (our *Active Improvers*) that spontaneously increase their physical activity over time. Of note, such observed increase of >3000 steps/day is remarkably high given that the minimal important difference has been proposed between 600 and 1100 steps/day.[31] There are several possibilities that would explain this observed increase. First, some patients could have been inactive at baseline by chance; however, we tested this option against study records by screening for atypical events and it did not hold true. Second, regression to the mean could account for part of the increase, but in our data regression to the mean was estimated to account for maximal 25% of the effect. Third, changes in daily steps could be due to changes in wearing time, but this was not the case in our study (Table S4). Fourth, patients could have increased their physical activity after participation in rehabilitation programs, but this was dismissed in our analysis (Table S5). Finally, we considered that some patients in the usual care arm of Urban Training could have increased their physical activity due to being enrolled in a physical activity study. However, the proportion of patients from Urban Training was similar between *Active Improvers* and *Active Decliners*. Thus, we suggest that some patients do actually increase their physical activity.

The evolution of other physical activity variables provided complementary information. Time in MVPA and sedentary time (opposite direction) paralleled the progression of step count in all three patterns, supporting previous research that suggested that in COPD patients, physical activity and sedentary time provide information about the same concept.[5] We also investigated the progression of physical activity from the perspective of patients. As expected, C-PPAC amount and total scores followed a trend similar to the objectively measured physical activity, as they include steps/day in their calculation. However, C-PPAC difficulty score remained unchanged in *Inactive* and *Active Decliners* and increased (i.e., less difficulty) in *Active Improvers*, suggesting that the observed increase in amount could be related to experiencing fewer difficulties (less dyspnea for instance[32]) while being active.

Our third main finding is the impossibility to predict the physical activity progression patterns, despite having included sociodemographic, interpersonal, environmental and psychological characteristics in addition to the typical clinical COPD variables. We found a large set of COPD-related, functional characteristics associated with the *Inactive* pattern, in accordance with previous, mainly cross-sectional, literature about the determinants of physical activity levels in COPD.[2,4] Also higher education levels, lower social support (living alone, not taking care of grandchildren) and higher depression scores related to being in the *Inactive* pattern, although none of these factors remained in the multivariable model suggesting they were subject to confounding.

Most tellingly, we did not identify any factors that could predict among *Active* patients, the evolution to *Improvers* or *Decliners*. Surprisingly, the presence of severe exacerbations during follow-up did not play any role. It could be speculated that our harmonized exacerbation data was not detailed enough to distinguish the severity of exacerbations, the length of hospital stay or the time from the last exacerbation to physical activity assessment at follow-up. We also considered the role of incident comorbidities during follow-up, which could have influenced behavior, but they were not significantly different for the three patterns. Pharmacological treatment for COPD was not different across progression patterns discarding any potential role for treatment inappropriateness. Moreover, we did not find an association between the recruitment season and physical activity progression. This is in line with the hypothesis that the recruitment season, although possibly affecting the baseline levels of physical activity,[12,18,33] would not affect the progression pattern during a follow-up of 12 months. Finally, we did not find an effect of accumulated rainfall on physical activity progression, as recently described cross-sectionally in the same PROactive population.[14]

Our study has several implications. It adds to the current knowledge that contrary to the general belief not all patients decline but some patients considerably improve their physical activity, which should be confirmed in future research and shows the importance of including a usual care group in intervention studies. The limitation of traditional clinical COPD characteristics to predict physical activity progression suggests that further research should broaden the view and give more attention to interpersonal and environmental factors potentially related to the individual's motivation. As the optimal timing and use of physical activity interventions to improve physical activity (especially in the long term) is still unclear,[34] understanding the different COPD progression patterns may help to overcome a one-size-fits-all approach and customize physical activity promotion to reflect different physical activity practices and different treatment needs.[35] Finally, our results highlight the limitation of using mean population values in phenomena that are heterogeneous in nature.

A major strength of our study is the inclusion of patients across a broad spectrum of disease severities and physical activity in several European cities. This makes our results applicable (i.e., more representative) to a larger COPD population than a single recruitment setting or severity group. In addition, the inclusion of patients from diverse geographic locations allowed us to indirectly control for residual confounding. Moreover, we included some variables beyond the conventional clinical COPD characteristics.[36] The use of the hypothesis-free clustering approach allowed us to identify patterns of physical activity progression based on the distribution of the data without prior assumptions.

However, we acknowledge some shortcomings. We had a small sample size for some of the hypothesized determinants of physical activity progression patterns, such as dog walking, current pulmonary rehabilitation and knowledge of baseline physical activity, which precluded our ability to test their role. Similarly, we did not collect information on some physical activity barriers (e.g. costs or transportation difficulties), which precluded testing their role on physical activity progression. The drop-out was 29% which is comparable to previous studies[37,38] but the excluded patients had worse functional parameters, and we cannot rule out that they would have presented with a fourth, potentially declining pattern. The two measurement points available for both studies allowed to investigate only linear patterns over time. Having more data points could provide more detailed information on the trajectories. In addition, a longer follow-up would have been desirable, but the 12-month span appears reasonably long to provide this first novel insight into physical activity patterns. Finally, one might argue that pooling of the two studies was not appropriate, although our sensitivity analyses showed similar cluster results and characteristics and it resulted in a broad spectrum of physical activity and COPD severity.

In conclusion, the natural change in physical activity over time in COPD patients is heterogeneous and three distinct patterns of physical activity progression have been identified: a predominant *Inactive* pattern, related to worse scores for clinical COPD characteristics, and two *Active* patterns, *Improvers* and *Decliners*, which cannot be predicted at baseline.

Authors' Contribution

JGA had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. MK, HD and JGA drafted the first version of the manuscript; MK, HD, MB and JGA had full access to the data and were responsible for the statistical analysis; MK, HD, MB, AAE, EB, ABG, EGS, NH, CdJ, NK, ZL, MPo, MPu, RRa, RRo, PVC, IV, TT, JGA contributed to data collection and coordination. All authors (1) provided substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work; (2) drafted or revised the manuscript for important intellectual content; (3) approved the final version; and (4) agreed to be accountable for all aspects of the work.

Ethics Approval

This study was conducted in accordance with the amended Declaration of Helsinki. Both studies were approved by all local institutional review boards and written informed consent, including re-use of data for COPD-related research, was obtained from all patients.

The Urban Training trial was approved by the ethics committees of all participating institutions (Comitè Ètic d'Investigació Clínica Parc de Salut MAR 2011/4291/I, Comitè Ètic d'Investigació Clínica de l'IDIAP Jordi Gol i Gurina P11/116, Comitè Ètic d'Investigació Clínica de l'Hospital Universitari de Bellvitge PR197/11, Comitè Ètic d'Investigació Clínica de l'Hospital Universitari Germans Trias i Pujol AC-12-004, Comitè Ètic d'Investigació Clínica de l'Hospital Clínic de Barcelona 2011/7061, Comitè Ètic d'Investigació Clínica de l'Hospital de Mataró November 23rd, 2011).

The PROactive study was advised and approved by the PROactive ethics and patient advisory boards, and approved by the local ethics committee at each center (Commissie medische ethiek van de universitaire ziekenhuizen KU Leuven (Leuven, S-55919); Medische ethische toetsingscommissie universitair medisch centrum Groningen (Groningen, Metc 2013.362); RES Committee London—South East (London and Edinburgh, 13/LO/1660); Scientific Council of the 'Sotiria' General Hospital for Chest Diseases (Athens, 27852/7-10-13); Kantonale Ethikkommission Zürich and Ethikkommission Nordwest- und Zentralschweiz (Zurich, KEK-ZH-Nr. 2013-0469).

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of Interest

NK is employed by AstraZeneca. MP reports personal fees from Philips, during the conduct of the study. TT reports lecture fees to his institution from Boehringer Ingelheim, Chiesi Belgium and AstraZeneca outside the submitted work. JGA reports payments for consulting and lecture fees to her institution from AstraZeneca and lecture fees from Esteeve, Chiesi and Menarini outside the submitted work. The authors report no other conflict of interest in this work.

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Appendix A. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2020.08.001.

Appendix B. The Urban Training Study Group:

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Appendix C. The PROactive Consortium Members:

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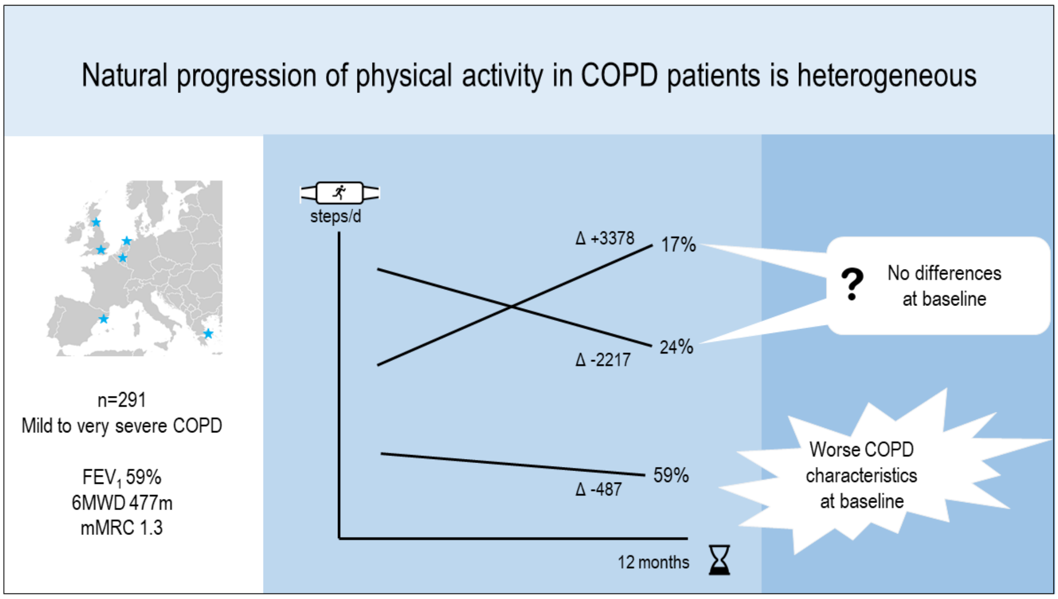
GRAPHICAL ABSTRACT

Patterns of physical activity progression in patients with COPD



SUPPLEMENTARY INFORMATION

Patterns of physical activity progression in patients with COPD

Statistical analysis full version

We compared the baseline characteristics of patients with follow-up vs those lost to follow-up by descriptive statistics and obtained p-values using mixed logistic regression models with random intercepts for study.

We identified cluster groups (physical activity patterns) using k-means (1), a hypothesis-free method that allowed grouping patients based on the baseline level, the final level and the change in daily step count. We used the Calinski-Harabasz stopping rule to decide the number of clusters (2). To characterize the patterns, we described physical activity and physical activity experience variables according to the cluster groups and compared baseline to follow-up values by paired t-tests. Because both studies used the same data collection methods main results are based on the pooled dataset and corrected for study.

To assess determinants of physical activity progression patterns, we first compared subjects' characteristics by physical activity patterns and obtained p-values from mixed logistic regression models with random intercepts for study and city area to account for possible heterogeneity in unmeasured characteristics related to study and city area. Then we built a multivariable multinomial regression model using the generalized linear latent and mixed model, with also random intercepts for study and city (3). Model building combined step-forward and backward algorithms, and determinants were included in the final model if: (i) they related to the outcome with a p-value <0.05; or (ii) they modified (>10% change in regression coefficient) the estimates of the remaining variables in the model (4). We tested goodness of fit of the final model.

We performed the following sensitivity analyses: (1) to investigate a possible difference between the two study samples, cluster analysis and description of resulting patterns was performed separately for both samples; (2) to test whether the observed patterns were due to changes in wearing time, we tested the association between the change in daily step count and the change in wearing time overall and per pattern; (3) to rule out a relevant effect of pulmonary rehabilitation on the physical activity patterns we repeated the clustering after excluding patients included in pulmonary rehabilitation programs at baseline and/or during follow-up.

We estimated that the available sample size (n=291), fixed by the primary objectives of the original studies, was sufficient to identify physical activity patterns using cluster k-means, as our ratio of number of subjects to number of variables (291/3 = 97) was much higher than the 0.01 often used for the same analysis in other contexts (5,6).

Due to the small proportion of missing data (<2% of total data), we used a complete case strategy and reported missing data in the table footnotes.

All analyses were conducted using Stata/SE 14.2 (StataCorp, College Station, TX, USA).

Figure S1 Flow of participants through the study.

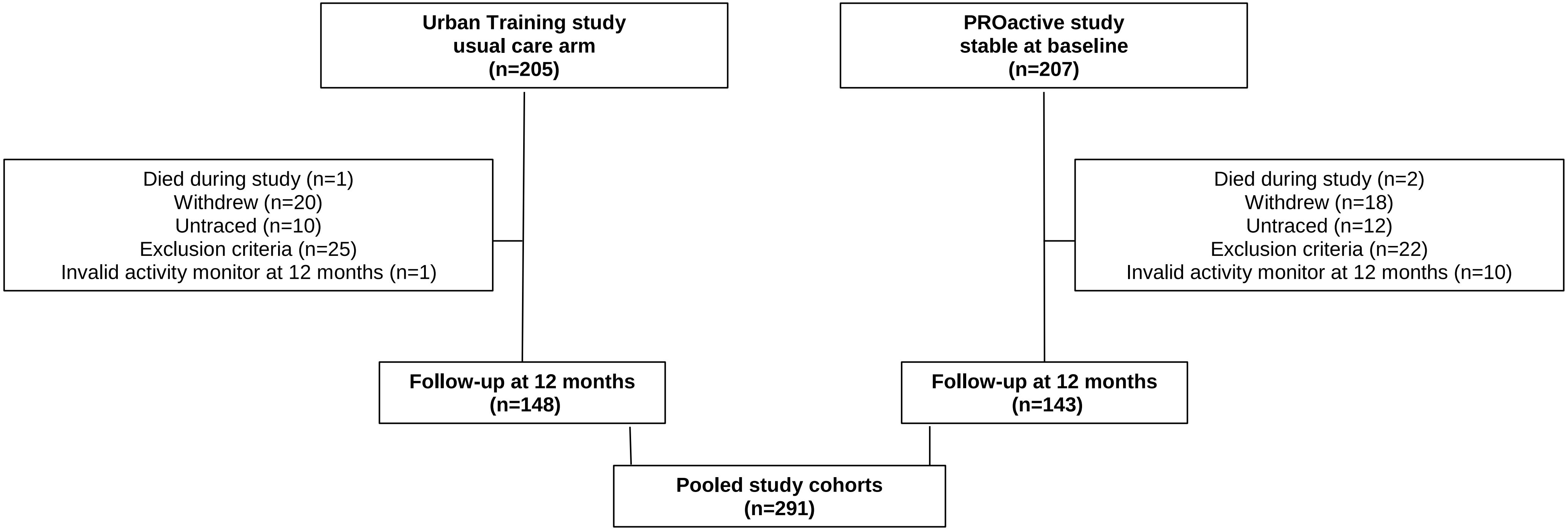


Table S1 Patient characteristics at baseline for all patients (Urban Training and PROactive study, n=412) and for patients with 12-month follow-up vs lost-to follow-up.

	All patients	Follow-up	Lost-to follow-up	p-value[b]
	n = 412 (100%)	n = 291[a] (71%)	n = 121[a] (29%)	
Sociodemographic				
Age (years)	68±8	68±8	68±8	0.745
Sex (men)	316 (77)	237 (81)	79 (65)	**0.001**
Current smoker (yes)	77 (19)	52 (18)	25 (21)	0.508
Pack-years	58±41	58±41	60±41	0.684
Education, high school or higher	236 (57)	168 (58)	68 (56)	0.746
Interpersonal				
Living with a partner[c]	291 (71)	216 (74)	75 (63)	**0.016**
Active worker[d]	47 (11)	36 (12)	11 (9)	0.342
Grandparenting[e]	89 (43)	67 (45)	22 (39)	0.389
Dog walking [e]	26 (13)	20 (14)	6 (11)	0.566
Environmental				
Recruitment season				
Spring	55 (13)	35 (12)	20 (16)	0.161
Summer	82 (20)	58 (20)	24 (20)	
Fall	218 (53)	154 (53)	64 (53)	
Winter	57 (14)	44 (15)	13 (11)	
Urban vulnerability index (from 0 -lowest to 1 –highest)[e,f]	0.642±0.178	0.637±0.175	0.655±0.186	0.514
Clinical				
FEV_1 (% predicted)	57.7±18.9	58.6±19.3	55.6±17.9	0.140
FEV_1/FVC ratio	0.51±0.13	0.51±0.13	0.51±0.13	0.699
Airflow limitation severity (post-bronchodilator FEV_1)				
GOLD 1: Mild ($FEV_1 \geq$ 80% predicted)	52 (13)	39 (13)	13 (11)	0.259
GOLD 2: Moderate (50% $\leq FEV_1 <$ 80% predicted)	207 (50)	147 (51)	60 (50)	
GOLD 3: Severe (30% $\leq FEV_1 <$ 50% predicted)	125 (30)	88 (30)	37 (30)	
GOLD 4: Very Severe (FEV_1 <30% predicted)	28 (7)	17 (6)	11 (9)	
6MWD (meters)	461±109	477±103	421±111	**<0.001**
CAT score (0–40)	13.3±7.5	12.9±7.6	14.2±7.3	0.094
CCQ score (0-6)	1.59±0.98	1.55±0.98	1.69±0.98	0.172
C-PPAC amount score (0-100)	67.8±16.9	69.0±15.8	64.2±19.5	**0.024**
C-PPAC difficulty score (0-100)	77.9±14.9	78.4±14.5	76.3±16.0	0.269
C-PPAC total score (0-100)	72.8±13.6	73.7±12.8	70.3±15.4	**0.044**
mMRC score (0-4)	1.4±1.0	1.3±0.9	1.7±1.1	**<0.001**
Any COPD exacerbation with hospital admission in previous 12 months	49 (12)	34 (12)	15 (13)	0.781
BMI (kg/m^2)	27.7±5.2	27.6±4.6	28.1±6.3	0.306
FFMI (kg/m^2)	18.8±3.2	19.0±3.0	18.4±3.5	0.086
Cardiovascular disease[g]	240 (59)	176 (60)	64 (54)	0.212
Ischemic heart disease[g]	40 (10)	29 (10)	11 (9)	0.823
Diabetes mellitus[g]	73 (18)	51 (18)	22 (18)	0.817
LABA or LAMA, alone	56 (14)	41 (14)	15 (13)	0.686
Inhaled corticosteroid with LABA and/or LAMA	256 (63)	179 (62)	77 (65)	0.557
Pulmonary rehabilitation at baseline	25 (6)	15 (5)	10 (8)	0.233
Knowledge of baseline PA	24 (6)	19 (7)	5 (4)	0.348
Psychological				
Anxiety (HAD-A, 0-21)	5±4	5±4	6±4	0.117
Depression (HAD-D, 0-21)	4±3	4±3	4±4	0.210
Physical activity				
Step count (steps/day)	6415±3678	6720±3667	5682±3613	**0.010**
Time in moderate-to-vigorous physical activity (≥3 METs; min/day)	95.8±45.9	99.4±45.3	87.0±46.2	**0.013**
Intensity during walking (m/s^2)	1.84±0.31	1.86±0.31	1.80±0.30	**0.050**
Sedentary time (h/day)	10.53±1.93	10.53±1.94	10.52±1.92	0.961

Notes: Data are presented as n (%), mean±SD.

[a]Some variables have missing values, as follows. Follow-up: 1 in education, 1 in living with a partner, 1 in CAT total, 1 in CCQ score, 31 in C-PPAC scores, 1 in any COPD exacerbation with hospital admission in previous 12 months, 26 in FFMI, 3 in LABA or LAMA, alone, 3 in inhaled corticosteroid with LABA and/or LAMA, 3 in HAD anxiety and depression; Lost-to follow-up: 1 in living with a partner, 1 in 6MWD, 33 in C-PPAC scores, 3 in any COPD exacerbation with hospital admission in previous 12 months, 5 in FFMI, 2 in ICD10 codes: I00 to I99 for Cardiovascular diseases; I20 to I25 for Ischemic heart disease, E14 for Diabetes mellitus, 3 in LABA or LAMA, alone, 3 in inhaled corticosteroid with LABA and/or LAMA, 1 in HAD depression.

[b]p-value from mixed logistic regression models with random effects for study (Urban Training and PROactive), due to small numbers random effects for city area were not applied.

[c]marital status: living with a partner vs single, widowed or divorced.

[d]working status: active worker (working full-time or part-time) vs. unemployed, housework or retired.

[e]only available for Urban Training.

[f]The urban vulnerability index is a measure of socioeconomic status at the census tract level that combines demographic, economic, residential and subjective indicators, and ranges from lowest [0] to highest [1] level of neighborhood vulnerability.

[g]ICD10 codes: I00 to I99 for cardiovascular diseases; I20 to I25 for ischemic heart disease, E14 for diabetes mellitus.

Abbreviations: FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; 6MWD: 6-min walking distance; CAT: COPD Assessment Test; CCQ: Clinical COPD Questionnaire; C-PPAC: Clinical visit—PROactive Physical Activity in COPD (higher numbers indicate a better score); mMRC: modified Medical Research Council; BMI: body mass index; FFMI: fat free mass index; LABA: long-acting $beta_2$-agonists; LAMA: long-acting anti-muscarinics; HAD-A: Hospital Anxiety and Depression scale - Anxiety; HAD-D: Hospital Anxiety and Depression scale – Depression; MET: metabolic equivalent of task.

Table S2 Physical activity and physical activity experience variables at baseline and at 12-month follow-up, overall and by PA progression pattern (*Inactive*, *Active Improvers* and *Active Decliners*).

	All				***Inactive***				***Active Improvers***				***Active Decliners***			
	n = 291[a]				**n = 173[a] (59%)**				**n = 49[a] (17%)**				**n = 69[a] (24%)**			
	Baseline	**Follow-up**	**Change**	**p-value[b]**	**Baseline**	**Follow-up**	**Change**	**p-value[b]**	**Baseline**	**Follow-up**	**Change**	**p-value[b]**	**Baseline**	**Follow-up**	**Change**	**p-value[b]**
Step count (steps/day)	6720 ±3667	6474 ±3772	-246 ±2420	0.084	4621 ±1757	4134 ±1817	-487 ±1201	**<0.001**	7727 ±3275	11105 ±3330	3378 ±2203	**<0.001**	11267 ±3009	9051 ±2897	-2217 ±2085	**<0.001**
Time in MVPA (≥3 METs; min/day)	99.4 ±45.3	96.1 ±47.5	-3.3 ±29.1	**0.052**	74.5 ±25.9	68.2 ±26.6	-6.3 ±16.7	**<0.001**	114.8 ±47.2	152.7 ±47.1	37.9 ±26.8	**<0.001**	150.9 ±32.3	125.8 ±33.0	-25.0 ±26.0	**<0.001**
Intensity during walking (m/s^2)	1.86 ±0.31	1.82 ±0.31	-0.04 ±0.19	**<0.001**	1.78 ±0.27	1.73 ±0.27	-0.05 ±0.19	**<0.001**	1.90 ±0.34	1.95 ±0.32	0.05 ±0.17	0.062	2.03 ±0.30	1.95 ±0.30	-0.08 ±0.17	**<0.001**
Sedentary time (h/day)	10.53 ±1.94	10.46 ±1.98	-0.08 ±1.82	0.463	11.03 ±2.00	10.98 ±2.15	-0.05 ±2.10	0.744	10.29 ±1.73	9.59 ±1.54	-0.70 ±1.25	**<0.001**	9.46 ±1.39	9.76 ±1.29	0.30 ±1.17	**0.037**
C-PPAC amount score (0-100)	67.6 ±15.9	66.7 ±16.0	-0.9 ±12.7	0.305	61.5 ±14.2	60.3 ±14.7	-1.2 ±12.4	0.255	73.6 ±12.0	82.3 ±10.3	8.7 ±11.2	**<0.001**	83.6 ±10.3	77.1 ±9.4	-6.5 ±11.0	**<0.001**
C-PPAC difficulty score (0-100)	77.2 ±14.3	77.7 ±13.6	0.4 ±10.6	0.547	74.4 ±14.2	74.8 ±13.0	0.4 ±10.0	0.673	80.3 ±13.8	84.5 ±11.3	4.3 ±11.3	**0.054**	84.4 ±12.5	82.5 ±14.0	-1.9 ±11.5	0.295
C-PPAC total score (0-100)	72.4 ±12.6	72.2 ±12.6	-0.2 ±9.2	0.717	68.0 ±11.7	67.5 ±11.5	-0.4 ±8.5	0.562	76.9 ±9.5	83.4 ±8.8	6.5 ±8.0	**<0.001**	84.0 ±8.1	79.8 ±9.6	-4.2 ±9.7	**0.008**
Wearing time (h/day)	14.73 ±1.56	14.52 ±1.63	-0.21 ±1.67	**0.035**	14.68 ±1.72	14.35 ±1.82	-0.33 ±2.01	**0.034**	14.77 ±1.58	15.02 ±1.59	0.25 ±0.77	**0.028**	14.82 ±1.10	14.59 ±0.93	-0.23 ±1.03	0.064

Notes: Data are presented as mean±SD. For C-PPAC variables means and p-values are reported for patients with data at baseline and follow-up.

[a]C-PPAC variables have 87 missing values: 38 in *Inactive*, 21 in *Active Improvers*, and 28 in *Active Decliners*.

[b]paired t-test.

Abbreviations: MVPA: moderate-to-vigorous physical activity; MET: metabolic equivalent of task; C-PPAC: Clinical visit—PROactive Physical Activity in COPD (higher numbers indicate a better score).

Table S3 Step count (mean steps/day) at baseline and at 12-month follow-up as well as selected variables at baseline, by cluster groups (physical activity progression patterns) identified by k-means, performed separately for the Urban Training and the PROactive study.

	Cluster 1					***Cluster 2***					***Cluster 3***				
	n (row%)	**Baseline**	**Follow-up**	**Change**	**p-value[a]**	**n (row%)**	**Baseline**	**Follow-up**	**Change**	**p-value[a]**	**n (row%)**	**Baseline**	**Follow-up**	**Change**	**p-value[a]**
Urban Training															
Step count (steps/day)	**79 (54%)**	6028 ±2176	5125 ±2045	-903 ±1428	**<0.001**	**36 (24%)**	6722 ±2491	10435 ±2293	3713 ±2288	**<0.001**	**33 (22%)**	13144 ±3340	11442 ±3606	-1702 ±2754	**0.001**
Age (years)		69±8					71±9					67±7			
Sex (men)		70 (89)					32 (89)					28 (85)			
FEV_1 (% predicted)		55.2±18.2					62.6±15.5					60.5±17.3			
6MWD (meters)		485±87					519±83					517±68			
mMRC score (0-4)		1.2±0.9					1.1±0.8					0.8±0.7			
PROactive															
Step count (steps/day)	**118 (83%)**	4431 ±1735	4097 ±1891	-334 ±1098	**0.001**	**6 (4%)**	11339 ±1239	14340 ±2593	3001 ±1716	**0.008**	**19 (13%)**	11188 ±1992	8222 ±2685	-2966 ±2166	**<0.001**
Age (years)		68±8					65±9					63±7			
Sex (men)		89 (75)					4 (67)					14 (74)			
FEV_1 (% predicted)		56.8±20.7					68.6±12.1					69.8±21.7			
6MWD (meters)		435±109					520±130					541±110			
mMRC score (0-4)		1.6±1.0					1.0±0.6					1.0±0.8			

Notes: Data are presented as mean±SD.

[a]paired t-test.

Abbreviations: FEV_1: forced expiratory volume in 1 second; 6MWD: 6-min walking distance; mMRC: modified Medical Research Council.

Table S4 Correlation between the change in daily step count and the change in wearing time, overall and by PA progression pattern (*Inactive*, *Active Improvers* and *Active Decliners*).

	n (%)	Pearson correlation coefficient	p-value
All patients	291 (100%)	0.090	0.124
Inactive	173 (59%)	0.002	0.981
Active Improvers	49 (17%)	-0.097	0.508
Active Decliners	69 (24%)	0.162	0.184

Table S5 Step count (mean steps/day) at baseline and at 12-month follow-up, by cluster groups (physical activity progression patterns) identified by k-means, performed separately for all patients (n=291) and excluding patients with rehabilitation (n=270).

	Inactive					***Active Improvers***					***Active Decliners***				
	n (row%)	**Baseline**	**Follow-up**	**Change**	**p-value[b]**	**n (row%)**	**Baseline**	**Follow-up**	**Change**	**p-value[b]**	**n (row%)**	**Baseline**	**Follow-up**	**Change**	**p-value[b]**
Step count (steps/day), all patients	**173 (59%)**	4621 ±1757	4134 ±1817	-487 ±1201	**<0.001**	**49 (17%)**	7727 ±3275	11105 ±3330	3378 ±2203	**<0.001**	**69 (24%)**	11267 ±3009	9051 ±2897	-2217 ±2085	**<0.001**
Step count (steps/day), patients with rehabilitation excluded[a]	**154 (57%)**	4544 ±1763	4003 ±1753	-541 ±1209	**<0.001**	**50 (19%)**	7516 ±3187	10730 ±3345	3213 ±2266	**<0.001**	**66 (24%)**	11206 ±3033	9078 ±2928	-2128 ±1943	**<0.001**

Notes: Data are presented as mean±SD.
[a]patients in pulmonary rehabilitation at baseline and/or follow-up were excluded (n=21).
[b]paired t-test

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5.2 Paper 2

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Role of the environment in the physical activity and capacity of patients with chronic obstructive pulmonary disease: a cross-sectional analysis of the Urban Training study in Catalonia.

In preparation.

Role of the Environment in the Physical Activity and Capacity of Patients with Chronic Obstructive Pulmonary Disease: A Cross-Sectional Analysis of the Urban Training Study in Catalonia

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ABSTRACT

Background: Physical activity and capacity are key prognostic factors in chronic obstructive pulmonary disease (COPD) but their environmental determinants are unknown.

Objectives: To test the association between environmental variables, and physical activity and capacity in COPD.

Methods: We conducted a cross-sectional analysis of baseline data from the multi-centre Urban Training study (NCT01897298) in Catalonia, Spain, in patients with mild-to-very severe COPD. We measured physical activity (step count and sedentary time) by the Dynaport MoveMonitor, difficulty with physical activity by the Clinical visit-PROactive physical activity in COPD (C-PPAC) instrument, and functional exercise capacity by the 6-minutes walk distance (6MWD). We estimated individually (geocoded to the residential address) population density, pedestrian street length, slope of terrain, road traffic noise and annual averages of nitrogen dioxide (NO_2) and particulate matter $(PM)_{2.5}$. We built single- and multi-exposure mixed-effects linear regressions with a random intercept for city, adjusting for confounders.

Results: Patients (n=402, 85% male, mean±SD 69±9 years, FEV_1 57±17 %pred) walked 7538±4050 steps/day, 6MWD was 486±96 metres. Median population density was 31 284 (13 689-45 205) habitants/km^2, slope was 2.0 (1.2-3.5) degrees and annual NO_2 was 43.4 (34.9-48.7) µg/m^3. Higher population density was consistently associated with lower step count, higher sedentary time and worse exercise capacity (e.g., -598 [95% CI -1202, 5] steps/day per IQR, p=0.052 in multi-exposure model); steeper slope with better exercise capacity (16.65 [5.29, 28.01] metres per IQR, p=0.004]; and higher NO_2 with more sedentary time and a lower C-PPAC difficulty score, i.e., more difficulty (-3.67 [-6.26, -1.07] points per IQR, p=0.006). Pedestrian street length was marginally associated with less sedentary time. $PM_{2.5}$ and noise exposure were not associated with physical activity or capacity.

Conclusion: Higher population density and long-term NO_2 exposure are unfavourably associated with physical activity in patients with COPD, while a steeper slope relates to better exercise capacity.

Keywords: built environment, road traffic noise, air pollution, physical activity, exercise capacity, chronic obstructive pulmonary disease

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality worldwide (Soriano et al. 2017). The global burden of disease study estimated that COPD affected more than 174 million patients and caused 3.2 million deaths in 2015 (Soriano et al. 2017). COPD is characterised by a progressive airflow limitation leading to breathlessness that often limits the ability to carry out daily activities, including physical activities. Patients are typically less active than healthy controls from the early stages of the disease onwards (Pitta et al. 2005; Shrikrishna et al. 2012; Van Remoortel et al. 2013). However, physical activity is a key prognostic factor in COPD patients. It is associated with fewer exacerbations of the disease, attenuated disease progression and lower mortality (Demeyer et al. 2019; Gimeno-Santos et al. 2014). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) therefore recommends physical activity for all COPD patients (Singh et al. 2019). To adequately support physical activity in these patients we need to know which factors other than the disease itself influence physical activity.

The ecological model of physical activity (Bauman et al. 2012) suggests that the built environment (e.g., neighbourhood design or walkability) as part of the larger environmental domain, is a determinant of physical activity in the general population. Air pollution and road traffic noise are not explicitly mentioned in this model, but can likely also be attributed to the environmental domain. In line, a range of studies reported that environmental variables were associated with physical activity in the general population (An et al. 2018; Cerin et al. 2020; Ding et al. 2013; Dzhambov et al. 2017; Foraster et al. 2016; Frank et al. 2005; McCormack 2017; Portegijs et al. 2017; Roswall et al. 2017; Witten et al. 2012). It seems plausible that environmental variables play a role in the physical activity of COPD patients too, but evidence is currently limited. To our knowledge no study has assessed the role of the built environment or road traffic noise in the physical activity of COPD patients. One study found that high levels of ozone and particulate matter $(PM)_{10}$ were associated with a reduced step count in patients with COPD (Alahmari et al. 2015). Another study found that urban greenness was not related to physical activity in COPD, leading to the hypothesis that the environment could have a less relevant role in patients with a chronic disease such as COPD, than in the general population (Arbillaga-Etxarri et al. 2017).

The assessment of the role of the environment on physical activity in COPD patients requires a comprehensive approach to physical activity as a behaviour. This ideally covers the traditional objective measures of physical activity as obtained by an activity monitor, such as daily steps or sedentary time, the patient's perception, such as the as difficulty experienced with physical activity (Gimeno-Santos et al. 2015), and the functional exercise capacity that influences how active a patient can be, such as the 6-minutes walk distance (6MWD) (Holland et al. 2015).

We therefore tested the association between environmental variables (measured as population density, pedestrian street length, slope of terrain, road traffic noise, NO_2 and $PM_{2.5}$), and physical activity and capacity (measured as daily step count, sedentary time, difficulty with physical activity and functional exercise capacity) in patients with mild-to-very severe COPD. We anticipate that our results will allow for developing strategies to effectively promote physical activity in COPD patients.

METHODS

Study design and patient population

This is a cross-sectional analysis of baseline pre-randomisation data from the Urban Training study. The Urban Training study was a multi-centre randomized controlled trial (NCT01897298) (Arbillaga-Etxarri et al. 2018) that enrolled 407 patients from five Catalan seaside municipalities (Badalona, Barcelona [centre and shore areas], Mataró, Viladecans and Gavà) at 33 primary care centres and 5 tertiary hospitals and randomized patients to the Urban Training intervention or usual care group between October 2013 and February 2015. All patients had a diagnosis of COPD, according to ATS/ERS (post-bronchodilator forced expiratory volume in 1 second [FEV_1] to forced vital capacity [FVC] ratio <0.70) (Celli et al. 2004). For the present analysis we use the data collected at baseline only and included patients if they had valid data on physical activity and capacity and environmental variables (n=402, 99% of the total).

The study was approved by all local institutional review boards and written informed consent was obtained from all patients.

Physical activity and capacity outcomes

Objective physical activity was measured using the Dynaport MoveMonitor (McRoberts BV, The Hague, The Netherlands) (Rabinovich et al. 2013; Van Remoortel et al. 2012) for one week at study inclusion. Patients wore the monitor for 24 hours and data during waking hours (from 07:00 h to 22:00 h) were retrieved. A valid physical activity measurement was defined as a minimum of three days with at least 8 hours of wearing time within waking hours (Demeyer et al. 2014); details have been previously published (Arbillaga-Etxarri et al. 2018). For the present study, we obtained information on daily step count and sedentary time (sum of lying and sitting time, hours/day).

Perceived difficulty with physical activity was assessed by the clinical "PROactive physical activity in COPD" (C-PPAC) instrument. Briefly, the C-PPAC combines a short patient-reported outcome questionnaire with data from an activity monitor to assess the perceived amount of physical activity, difficulty with physical activity, and total physical activity experience (Garcia-Aymerich et al. 2020; Gimeno-Santos et al. 2015). For the present study, we used the difficulty score, ranging from 0 (worse status, i.e., more difficulty) to 100 (better status, i.e., less difficulty).

Functional exercise capacity was assessed using the six-minute walk test (6MWT) according to published recommendations (Guyatt et al. 1984; Manual de Procedimientos SEPAR, 4), and the six-minute walk distance (6MWD) was determined for each patient. Patients completed two 6MWTs with at least a 30-minute rest between, and the longer of the two distances was used for analysis.

Environmental exposures

We estimated the exposure to environmental variables individually for each patient at his/her geocoded residential address. We obtained population density (habitants per square kilometre within the census area from the Spanish National Statistics Institute for the year 2016 (INE)), pedestrian street length (sum of pedestrian street length within a 300 metre buffer from Navteq (HERE)), slope of terrain from now on 'slope' (average slope within a 300 metre buffer from the topographic map of the Cartographic Institute of Catalonia [digital model elevation 15 metres] (ICGC 2012)), road traffic noise from now on 'noise' (annual average levels of road traffic noise in the nearest street [24h EU indicator L_{den} in dB(A), from the Barcelona's strategic noise map (2012) under EU Directive 2002/49/EC as described previously] (Dadvand et al. 2014b; Mapes estratègics del soroll de Barcelona)) and annual residential averages of nitrogen dioxide (NO_2) and particulate matter $(PM)_{2.5}$ for the year 2013, using temporally adjusted land-use regression (LUR) models as described previously (Beelen et al. 2013; Cyrys et al. 2012; Eeftens et al. 2012a, 2012b).

Other measurements

We obtained at baseline the following data from all patients using standardized procedures: (i) sociodemographic: age, sex, smoking history, education and individual socioeconomic status (based on the employment characteristics and categorized according to the National Statistics Socio-economic Classification); (ii) interpersonal: marital status and working status; (iii) environmental: season of recruitment, land-surface temperature (average temperature within a 50 metre buffer space around the residence, derived from three land-surface temperature maps from the Landsat 5 Thematic Mapper data as described previously (Dadvand et al. 2014b)) and urban vulnerability index (a measure of socioeconomic status at the census tract level) (Atlas de la Vulnerabilidad Urbana. Ministerio de Fomeno. Gobierno de España); (iv) clinical: FEV_1 and FVC by forced spirometry post bronchodilator, the COPD assessment test (CAT) to measure quality of life, the modified Medical Research Council dyspnoea scale (mMRC), the number of acute COPD exacerbations requiring a hospital admission in the previous 12 months, body mass index (BMI) and fat free mass index (FFMI) by physical examination and bioelectrical impedance; and (v) psychological: the hospital anxiety (HAD-A) and depression (HAD-D) scores. Full details on study procedures and quality control have been reported previously (Arbillaga-Etxarri et al. 2016, 2018).

Statistical analysis

Since the sample size was fixed by the main objective of the Urban Training study (Arbillaga-Etxarri et al. 2018), we calculated the statistical power of the available sample (n=402), to test the association between environmental variables and physical activity in COPD patients. Based on own unpublished data about population density in similar studies, previous data about air pollution levels (Rivas et al. 2014) in the same geographic areas, and physical activity levels of COPD patients (Donaire-Gonzalez et al. 2013) from the same geographic areas and similar care settings, 402 patients allow to detect an association of -493 steps per a change of ≈20,000 inhabitants/km^2 in population density (Annegarn et al. 2012; McCormack 2017), and an association of -5.4 steps/day per increase in 1 µg/m^3 in particulate matter (Alahmari et al. 2015) with a statistical power of >99%. Due to the small proportion of missing data (<2% of total data), we used a complete case strategy and reported missing data in the table footnotes.

To test the association between each of the environmental variables (population density, pedestrian street length, slope, noise, NO_2 and $PM_{2.5}$) and physical activity and capacity variables (all normally distributed), we used linear regression models. We first built unadjusted mixed-effects models with a random intercept for city. We then built single-exposure multivariable models, additionally adjusting for age, sex, socioeconomic status and FEV_1, defined a priori as the most compelling confounders based on available literature (see directed acyclic graphs in Supplemental Material, Figures S1 and S2). Other relevant variables which had been included as covariates in the literature previously (e.g., mental health symptoms or dyspnoea) were considered as potential effect modifiers or mediators in our analysis and therefore not included as covariates in main models. Finally, we built a multi-exposure model additionally adjusting for all environmental variables simultaneously to control for mutual residual confounding. We defined a priori a cut off >3 for the variance inflation factor to define collinearity and thus exclude an environmental variable from the model. We tested goodness of fit of the final models.

As sensitivity analyses, (1) we restricted the final models to patients not working actively to test for miss-classification in the exposures (i.e., patients who go to work spend an important part of their time away from their home, thereby reducing the exposure to residential environmental factors) , and (2) we repeated the final models after excluding patients with extreme values (<5th and >95th percentile) in the environmental exposures to test the influence of extreme observations.

All analyses were conducted using Stata/SE 14.2 (StataCorp, College Station, TX, USA).

RESULTS

Of 402 patients included in the present analysis 85% were male, age was mean±standard deviation 69±9 years, FEV_1 was 57±17% predicted and mMRC dyspnoea score was 1.2±0.9 (Table 1). Compliance with the activity monitor was excellent with median (interquartile range) 7 (3 to 7) valid days and 14.6±0.7 wearing hours. The patients walked 7538±4050steps/day, the 6MWD was 486±96 metres (Table 1). There were no differences in physical activity or capacity variables according to season of recruitment. Population density was 31 284 (13 689-45 205) habitants/km^2 within the census area, slope was 2.0 (1.2 to 3.5) degrees within a 300 metre buffer and annual NO_2 was 43.4 (34.9-48.7) µg/m^3 (Table 1).

Higher population density was associated with a lower step count, more sedentary time and reduced exercise capacity, in unadjusted, single- and multi-exposure adjusted models, although in some models the association was only marginally significant (Table 2). We conducted a post hoc analysis stratifying these associations according to the mental health status (separate models for anxiety (HAD-A score </>=11) or depression (HAD-D score </>=11) (Snaith 2003). We found that the results were stronger and statistically significant among COPD patients with anxiety and/or depression symptoms, while they were reduced and lost precision in the COPD patients without mental health symptoms (see Supplemental Material, Table S1).

Steeper slope was consistently associated with an increased exercise capacity but not with the rest of physical activity parameters (Table 2). Pedestrian street length was marginally associated with a lower sedentary time only in multi-exposure analysis (Table 2).

Higher levels of NO_2 were associated with more sedentary time and more perceived difficulty in physical activity (Table 2). In post hoc analysis we included the mMRC dyspnoea score as a covariate to test its potential role as mediator (see directed acyclic graph in Supplemental Material, Figure S1). After the addition of dyspnoea, the association between NO_2 and sedentary time and difficulty with physical activity was attenuated and lost precision (see Supplemental Material, Table S2).

$PM_{2.5}$ and noise were not associated with any physical activity or capacity parameter in this cohort of COPD patients (Table 2).

The sensitivity analyses were in line with the main results. When restricting the adjusted models to patients not working actively, all associations persisted (see Supplemental Material, Table S3). When we excluded extreme values in exposure variables, the associations of slope with exercise capacity and of NO_2 with C-PPAC difficulty score were maintained, and the associations of population density with step count, sedentary time and exercise capacity, and NO_2 with sedentary time lost precision (see Supplemental Material, Table S4).

DISCUSSION

This study found that some environmental variables were associated with physical activity and capacity in COPD patients, specifically: (1) a higher population density was associated with fewer steps, more sedentary time and worse exercise capacity, and this association was stronger in COPD patients with mental health symptoms; (2) a steeper slope was associated with better exercise capacity but not with objective or subjective physical activity parameters; (3) pedestrian street length was marginally associated with less sedentary time; (4) higher long-term NO_2 exposure was associated with more sedentary time and more difficulty with physical activity, and this association could be partly mediated by dyspnoea; and (5) $PM_{2.5}$ and noise exposure were not associated with physical activity or capacity. The findings from our study underline the specific role of some environmental variables in the physical activity and capacity of COPD patients.

Our analysis showed that higher population density was unfavourably associated with step count, sedentary time and exercise capacity in COPD patients. Several previous studies have reported a positive association between higher population density and physical activity of older adults (Corseuil et al. 2016; Hino et al. 2020; Portegijs et al. 2017) and attributed this to a stimulating effect of a more viable neighbourhood (more shops and services, better public transport) (Udell et al. 2014). However, these studies have much lower population density levels than our study (Corseuil et al. 2016; Hino et al. 2020). On the other hand, in a younger Canadian cohort, higher population density was associated with lower time spent in moderate to vigorous physical activity (McCormack 2017). In Chinese seniors residing in Hong Kong, a high residential density (dwellings/km2) seemed to support, but extreme density led to reductions in within-neighbourhood walking (Cerin et al. 2020), which was attributed to the negative effects of concomitantly increased traffic hazards, fumes and noise. We hypothesized that the same mechanism could play a role in our patients, since the median population density for our study population was indeed very high with more than 30.000 habitants/km^2 and Barcelona (where 46% of our patients were recruited) is among the most densely populated cities of Europe (Barcelona, Spain Population (2020) - Population Stat; Barcelona Population 2020 (Demographics, Maps, Graphs)). More pertinently, the negative effect of population density might be stronger in our patients due to the underlying chronic lung disease. Qualitative research found that the embarrassment caused by symptoms such as breathlessness and immobility in public was a personal barrier for physical activity in COPD patients (Kosteli et al. 2017). We thus hypothesized that psychological factors, like fear to attract attention or mood, could have played a role. Indeed, our post hoc analysis stratifying by psychological factors found that the negative effect of population density was much stronger in COPD patients with symptoms of anxiety or depression.

We found that a steeper slope was associated with increased exercise capacity. To the best of our knowledge and despite the clinical relevance of assessing exercise capacity in chronically ill patients, this association has not been directly tested before. Hills are mostly perceived as a barrier to physical activity (Barnett et al. 2017). However, there is some evidence from experimental settings which indicates that downhill walking training can positively affect leg strength and exercise capacity. In healthy, young females a six-week downhill walking training resulted in a significant increase in leg strength (Rodio and Fattorini 2014). In COPD patients undergoing pulmonary rehabilitation, a downhill walking training was associated with a faster rehabilitation progress, less dyspnoea, and a higher percentage of patients who achieved a clinically meaningful improvement in 6MWD as compared to conventional training (Camillo et al. 2020). Authors attributed the positive training effect of downhill walking to the increased eccentric activity in the quadriceps femoris muscle which is necessary for "braking" the individual (Camillo et al. 2015), which could also apply to our study. Of note, the observed association in our study could be translated to an increase of 13.5 metres in the 6MWD per an increase of 2.3 degrees (which corresponds to a very gentle slope (Slope Steepness Index)). This effect appears relevant, given that a change of more than 30 metres is considered as clinically meaningful (Polkey et al. 2013). We therefore argue that COPD patients who live in a hilly neighbourhood may benefit from a "continuous training effect" and that slope has the potential to increase exercise capacity in these patients.

Our results showed that higher NO_2 was associated with more sedentary time and the experience of more difficulty with physical activity. These effects were consistent across different complementary and sensitivity analyses (Table 2 and Supplemental Material, Tables S3 and S4), which reinforces their plausibility. When we excluded subjects with extreme values, only the association between NO2 and difficulty remained statistically significant (Supplemental Material Table S4). We hypothesize that extremely high NO_2 levels may indeed be especially harmful and drive the observed association. Several mechanisms are conceivable about how long-term air pollution in general could influence physical activity and capacity in COPD patients: First, higher levels of air pollution could increase dyspnoea in COPD patients (Schraufnagel et al. 2019). To avoid the feeling of dyspnoea, COPD patients often reduce exertion which leads to deconditioning with a decline in exercise capacity and further dyspnoea (Ramon et al. 2018; Reardon et al. 2006); increased pollution could thus trigger the 'vicious circle of dyspnoea and inactivity' (Ramon et al. 2018; Reardon et al. 2006). While the sample size and lack of repeated measurements precluded a formal mediation analysis, we found that the effect of NO_2 on sedentary time and C-PPAC difficulty score was attenuated when we added the mMRC dyspnoea score to the analysis (Supplemental Material, Table S2, Figure S1), which indirectly supports this hypothesis. Second, patients may be aware of the potential harms associated with air pollution and may therefore avoid to walk in neighbourhoods with more intense traffic. Finally, exacerbations and hospital admissions due to air pollution could lead to a decrease in physical activity and exercise capacity (Alahmari et al. 2014; Demeyer et al. 2018).

Of note, only NO_2 (indicator of traffic related air pollution) was associated with physical activity in our study while $PM_{2.5}$ (indicator of pollution more generally) was not. Whether this was due to the fact that NO_2 levels deviated considerably from the WHO and EU limit of 40 mcg/m^3, that NO_2 could be a surrogate for pollution with other traffic related constituents such as NO_x, O_3 and ammonium nitrate aerosols thereby reflecting a higher true burden (Johannson et al. 2015; Schraufnagel et al. 2019), or that NO_2 exerts a specific (and more harmful) pathomechanism in COPD patients (Dadvand et al. 2014a; Lepeule et al. 2014; Morrow et al. 1992) remains speculative.

Pedestrian street length was in the multi-exposure model inversely associated with sedentary time but the magnitude of the association was very small (around three minutes per IQR change, i.e., 467 metres within a 300 metre buffer). We assume this may rather be explained by the fact that pedestrian street length is inversely related to NO_2 (more pedestrian walkways result in less air pollution) and that the multi-exposure model accounts better for this simultaneous effect. It may seem surprising that our data did not show a stronger association for pedestrian street length. Unfortunately, we did not have any information on additional features (e.g., benches, trees, or shadow/sun) which may have determined how attractive the pedestrian streets were to the individual COPD patient. Moreover, we assume that our COPD patients were limited by their underlying chronic disease to an extent that stimuli to be active (or inactive) had less impact than in the healthy general population in line with the previously observed lack of association between greenness and physical activity in COPD (Arbillaga-Etxarri et al. 2017).

We found no association between noise and any of the physical activity or capacity variables. To our knowledge no study has assessed this association in COPD patients before. A few studies have previously explored this association in the general population and found that noise (Dzhambov et al. 2017; Roswall et al. 2017) and noise annoyance (Foraster et al. 2016) were negatively associated with physical activity and the latter association was reported to be stronger in patients with a chronic disease. Unfortunately, we do not have any information on noise annoyance for the present study. Whether noise levels alone are not sensitive enough to determine an effect on physical activity in COPD patients or whether noise has less impact on COPD patients due to their underlying disease, will need to be addressed in future studies.

Our findings, suggestive of a different role of environmental variables compared to the general population, have implications for research, clinical management and urban health policy. Future research needs to confirm the observed roles of population density, slope, pedestrian streets and NO_2 on physical activity and capacity of COPD, in light of the apparent contradictions with findings in the general population and keeping in mind that heterogeneity due to cultural factors is possible. Research on development of interventions to promote physical activity in COPD patients may need to consider these factors as well. Clinical management of COPD patients may need to (1) address the fear or shame to go out as potential barriers to practice physical activity in COPD patients and especially in those with mental health issues; (2) consider hilly neighbourhoods as facilitators of better exercise capacity which could allow to enrol patients more effectively into a physical activity programme; and (3) advise patients on how to mitigate the effects of traffic related air pollution on respiratory health (e.g., avoid major intersections or rush hour) (Carlsten et al. 2020). Finally, urban health policy must purposely address the role of the environment in the physical activity of patients with an already established chronic disease such as COPD. To promote physical activity in this patient group it will be important to provide a built environment which is adequate for the specific needs (e.g., walkable yet not too crowded) and rigorous control of air pollution.

A strength of our study is the novelty of our research question in COPD patients. We recruited patients with a broad range of COPD severities from several hospital and primary care centres which increases the external validity of our findings. We included a range of objectively measured variables to characterize both the exposures and the outcome thereby reducing information bias. The use of LUR models for air pollution and geocoding of the home address allowed us to assess individual-level exposure and gain further insight into the distinct roles of NO_2 and $PM_{2.5}$. The multi-exposure models allowed us to control for residual confounding by the other environmental variables and to assess the specific effect of one variable within the overall neighbourhood context.

Unfortunately, there are aspects of the environment which we did not capture with this analysis. Variables such as neighbourhood safety, design, land use mix, street connectivity or residential density which may also influence physical activity behaviour (Cerin et al. 2018; Frank et al. 2005; Salvo et al. 2018; Udell et al. 2014) and would be helpful to compare with other studies were not available. Moreover, we do not report other common pollutants such as PM_{10} or O_3; however, we believe that NO_2 and $PM_{2.5}$ capture well traffic related air pollution and urban pollution more generally. Finally, the cross-sectional design limits conclusions on causality and also makes it difficult to rule out self-selection bias concerning the choice of the residential neighbourhood. However, the relatively low socioeconomic status of our sample makes it unlikely that our patients moved due to their COPD.

In conclusion, higher population density and long-term NO_2 exposure are unfavourably associated with physical activity in patients with COPD, while a steeper slope relates to better exercise capacity. These environmental variables should be considered in clinical contacts with patients and when developing urban and transport planning policies that aim to promote physical activity in patients with chronic diseases.

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Table 1. Patient characteristics, physical activity and capacity, and environmental variables in 402 patients with mild-to-very severe COPD.

	All patients (n=402[a])
Patient characteristics	
Sociodemographic	
Age (years)	68.8±8.5
Sex (men)	341 (85)
Current smoker	96 (24)
Pack-years	59.6±41.3
Education, highschool or higher[b]	122 (30)
Socioeconomic status, non-manual skilled or higher[c]	114 (28)
Interpersonal	
Living with a partner[d]	306 (76)
Active worker[e]	48 (12)
Environmental	
Recruitment season	
Spring	100 (25)
Summer	44 (11)
Fall	142 (35)
Winter	116 (29)
Land surface temperature (°C)[f]	24.4 (24.1-24.7)
Urban vulnerability index (from 0 -lowest to 1 –highest)[g]	0.64±0.17
Clinical	
FEV_1 (% predicted)	56.8±17.4
FEV_1/FVC ratio	0.54±0.12
Airflow limitation severity (post-bronchodilator FEV_1)	
GOLD 1: Mild ($FEV_1 \geq 80\%$ predicted)	37 (9)
GOLD 2: Moderate ($50\% \leq FEV_1 < 80\%$ predicted)	215 (54)
GOLD 3: Severe ($30\% \leq FEV_1 < 50\%$ predicted)	120 (30)
GOLD 4: Very Severe ($FEV_1 < 30\%$ predicted)	30 (7)
CAT score (0–40)	12.3±7.2
mMRC score (0-4)	1.2±0.9
Any COPD exacerbation with hospital admission in previous 12 months	23 (6)
BMI (kg/m^2)	28.4±5.0
FFMI (kg/m^2)	19.5±3.2
Psychological	
Anxiety (HAD-A, 0-21)	5.2±4.0
Depression (HAD-D, 0-21)	3.5±3.4
Physical activity and capacity outcome	
Step count (steps/day)	7538±4050
Sedentary time (h/day)	10.4±1.6
C-PPAC difficulty score (0-100)	82.0±14.6
6MWD (meters)	486±96
Environmental exposure	
Population density[h]	31 284 (13 689-45 205)
Pedestrian street length (metres)[i]	242.0 (50.5-516.6)
Slope (degrees)[j]	2.0 (1.2-3.5)
Noise (dB(A))[k]	63 (59-67)
NO_2 (µg/m^3)[l]	43.4 (34.9-48.7)
$PM_{2.5}$ (µg/m^3)[l]	12.6 (10.7-13.8)

Notes: Data are presented as n (%), mean±SD or median (IQR).

[a]Some variables have missing values, as follows: 2 in pack-years, 1 in education, 1 in living with a partner, 11 in any COPD exacerbation with hospital admission in previous 12 months, 38 in FFMI, 2 in HAD anxiety, 4 in HAD depression, 93 in C-PPAC difficulty score, 1 in noise.
[b]Education: highschool or higher vs maximum compulsory school.
[c]Socioeconomic status: non-manual skilled or higher vs manual skilled, partly skilled of unskilled occupations (IIIN, II and I, vs IIIM, IV and V according to the National Statistics Socio-economic Classification).
[d]Marital status: living with a partner vs single, widowed or divorced.
[e]Working status: active worker (working full-time or part-time) vs unemployed, housework or retired.
[f]Average land-surface temperature within a 50 metre buffer space around the residence, derived from three land-surface temperature maps.
[g]The urban vulnerability index as a measure of socioeconomic status at the census tract level that combines demographic, economic, residential and subjective indicators, and ranges from lowest [0] to highest [1] level of neighbourhood vulnerability.
[h]Habitants per square kilometre within the census area.

[i]Sum of pedestrian street length within a 300 metre buffer.
[j]Average slope of terrain within a 300 metre buffer.
[k]Annual average levels of road traffic noise in the nearest street.
[l] Annual residential averages of NO_2 and $PM_{2.5}$.

Abbreviations: BMI: body mass index; CAT: COPD assessment test; C-PPAC: Clinical visit—PROactive Physical Activity in COPD (higher numbers indicate a better score); FEV_1: forced expiratory volume in 1 second; FFMI: fat free mass index; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HAD-A: hospital anxiety and depression scale – Anxiety; HAD-D: hospital anxiety and depression scale – Depression; IQR: interquartile range; L_{den}: day evening night sound level; mMRC: modified Medical Research Council; 6MWD: 6-min walking distance; NO_2: nitrogen dioxide; PM: particulate matter; SD: standard deviation.

Table 2. Associations between the environmental variables and physical activity and capacity variables in 402 patients with mild-to-very severe COPD.

		Steps/day		**Sedentary time (h/day)**		**Difficulty with physical activity (C-PPAC score)**		**6MWD (m)**	
		coef (95% CI)	p	coef (95% CI)	p	coef (95% CI)	p	coef (95% CI)	p
Population density (per IQR, habitants/km^2)[a]	unadjusted	-707 (-1298, -115)	0.019	0.245 (0.013, 0.478)	0.039	0.757 (-1.737, 3.252)	0.552	-14.71 (-28.23, -1.19)	0.033
	single-exposure adjusted	-568 (-1149, 12)	0.055	0.227 (0.007, 0.446)	0.043	0.540 (-1.824, 2.903)	0.655	-9.79 (-21.44, 1.87)	0.100
	multi-exposure adjusted	-598 (-1202, 5)	0.052	0.171 (-0.055, 0.396)	0.138	1.405 (-1.037, 3.847)	0.259	-10.80 (-22.82, 1.23)	0.078
Pedestrian street length (per IQR, metres)[b]	unadjusted	60 (-63, 183)	0.337	-0.042 (-0.094, 0.010)	0.111	-0.234 (-0.760, 0.293)	0.384	0.37 (-2.89, 3.63)	0.824
	single-exposure adjusted	101 (-20, 222)	0.102	-0.035 (-0.083, 0.013)	0.149	-0.156 (-0.643, 0.332)	0.532	0.80 (-1.95, 3.55)	0.569
	multi-exposure adjusted	106 (-29, 240)	0.123	-0.048 (-0.099, 0.002)	0.059	-0.021 (-0.504, 0.462)	0.932	0.21 (-2.47, 2.89)	0.879
Slope (per IQR, degrees)[c]	unadjusted	301 (-187, 790)	0.227	-0.180 (-0.375, 0.014)	0.070	0.829 (-1.500, 3.158)	0.485	16.44 (3.37, 29.52)	0.014
	single-exposure adjusted	61 (-425, 547)	0.807	-0.115 (-0.304, 0.074)	0.232	0.794 (-1.347, 2.934)	0.467	13.47 (2.80, 24.13)	0.013
	multi-exposure adjusted	125 (-445, 695)	0.667	-0.095 (-0.308, 0.118)	0.381	-0.109 (-2.439, 2.220)	0.927	16.65 (5.29, 28.01)	0.004
Noise (per IQR, dB(A))[d]	unadjusted	-353 (-898, 193)	0.205	0.155 (-0.079, 0.390)	0.194	-0.287 (-2.981, 2.406)	0.834	-4.95 (-19.83, 9.92)	0.514
	single-exposure adjusted	-232 (-773, 310)	0.402	0.184 (-0.039, 0.407)	0.106	-0.138 (-2.649, 2.373)	0.914	-3.42 (-15.85, 9.02)	0.590
	multi-exposure adjusted	-60 (-632, 512)	0.838	0.022 (-0.192, 0.236)	0.843	-0.190 (-2.606, 2.225)	0.877	0.34 (-11.06, 11.74)	0.953
NO_2 (per IQR, µg/m^3)[e]	unadjusted	-20 (-568, 527)	0.942	0.233 (0.020, 0.446)	0.032	-2.185 (-4.852, 0.483)	0.108	1.44 (-14.83, 17.71)	0.862
	single-exposure adjusted	43 (-487, 574)	0.873	0.217 (0.019, 0.416)	0.032	-3.408 (-5.513, -1.302)	0.002	-1.02 (-14.26, 12.21)	0.880
	multi-exposure adjusted	128 (-523, 780)	0.699	0.228 (-0.016, 0.471)	0.067	-3.667 (-6.263, -1.071)	0.006	0.21 (-12.76, 13.19)	0.974
$PM_{2.5}$ (per IQR, µg/m^3)[e]	unadjusted	0 (-613, 613)	1.000	0.132 (-0.119, 0.384)	0.302	-0.573 (-3.231, 2.085)	0.672	-1.87 (-17.38, 13.64)	0.813
	single-exposure adjusted	-166 (-771, 438)	0.590	0.131 (-0.101, 0.363)	0.268	-0.018 (-0.050, 0.014)	0.264	-1.48 (-14.60, 11.65)	0.826
	multi-exposure adjusted	-17 (-735, 700)	0.963	-0.048 (-0.317, 0.220)	0.724	0.603 (-2.218, 3.423)	0.675	8.83 (-5.47, 23.13)	0.226

Data are presented as regression coefficients with 95% confidence interval (95% CI) for mixed-effects linear regression models with a random intercept for city. Single-exposure models were adjusted for age, sex, socioeconomic status and %predicted of FEV_1, multi-exposure models were additionally adjusted for all other environmental exposures simultaneously. Models for difficulty with physical activity (C-PPAC score) included 309 patients. All models for noise, including the multi-exposure models, have one subject less due to one missing in noise.

[a]Habitants per square kilometre within the census area.
[b]Sum of pedestrian street length within a 300 metre buffer.
[c]Average slope of terrain within a 300 metre buffer.
[d]Annual average levels of road traffic noise in the nearest street.
[e]Annual residential averages of NO_2 and $PM_{2.5}$.

Abbreviations: C-PPAC: Clinical visit—PROactive Physical Activity in COPD (higher numbers indicate a better score); FEV_1: forced expiratory volume in 1 second; IQR: interquartile range; L_{den}: day evening night sound level; 6MWD: 6-min walking distance; NO_2: nitrogen dioxide; PM: particulate matter.

SUPPLEMENTARY TABLES AND FIGURES

Table S1. Single-exposure adjusted associations between population density and physical activity and capacity, stratified according to the mental health status (anxiety or depression) in patients with mild-to-very severe COPD.

Table S2. Single-exposure adjusted associations between NO_2 and sedentary time and difficulty with physical activity, additionally adjusted for dyspnoea (mMRC score) in 402 patients with mild-to-very severe COPD.

Table S3. Single-exposure adjusted associations between the environmental variables and physical activity and capacity variables, restricted to patients with mild-to-very severe COPD not working actively (n=354).

Table S4. Single-exposure adjusted associations between the environmental variables (5^{th}-95^{th} percentile) and physical activity and capacity variables in patients with mild-to-very severe COPD.

Figure S1. Causal directed acyclic graph to depict the relationship between air pollution ($NO_{2,}$ $PM_{2.5}$), physical activity and capacity (daily step count, sedentary time, difficulty with physical activity, exercise capacity), and potential confounders and mediators, based on the literature (see Methods). U stands for unmeasured common determinants of environmental factors and physical activity and capacity.

Figure S2. Causal directed acyclic graph to depict the relationship between built environment variables and road traffic noise (summarized as environmental factors), physical activity and capacity (daily step count, sedentary time, difficulty with physical activity, exercise capacity), and potential confounders based on the literature (see Methods). U stands for unmeasured common determinants of environmental factors and physical activity and capacity.

Table S1. Single-exposure adjusted associations between population density and physical activity and capacity, stratified according to the mental health status (anxiety or depression) in patients with mild-to-very severe COPD.

		Steps/day		Sedentary time (h/day)		6MWD (m)	
		coef (95% CI)	p	coef (95% CI)	p	coef (95% CI)	p
Population density	no anxiety[c] n=352	-371 (-992, 250)	0.242	0.156 (-0.077, 0.388)	0.190	-6.72 (-19.03, 5.60)	0.285
(per IQR, habitants/km²)[b]	anxiety[c] n=48	-1478 (-3027, 71)	0.061	0.622 (0.008, 1.236)	0.047	-31.10 (-67.56, 5.36)	0.095
	no depression[d] n=379	-358 (-966, 249)	0.248	0.134 (-0.093, 0.361)	0.248	-9.64 (-21.80, 2.52)	0.120
	depression[d] n=19	-2002 (-3308, -695)	0.003	1.013 (0.252, 1.773)	0.009	-29.80 (-74.24, 14.63)	0.189

Notes: Data are presented as regression coefficients with 95% confidence interval (95% CI) for mixed-effects linear regression models with a random intercept for city. Single-exposure models were adjusted for age, sex, socioeconomic status and %predicted of FEV_1.

[a]Mental health status has missing values: 2 in HAD anxiety, 4 in HAD depression
[b]Habitants per square kilometre within the census area.
[c]HAD-A score <11 was defined as ‘no anxiety’, vs HAD-A score ≥11 as ‘anxiety’.
[d]HAD-D score <11 was defined as ‘no depression’, vs HAD-D score ≥11 as ‘depression’.

Abbreviations: FEV_1: forced expiratory volume in 1 second; HAD-A: hospital anxiety score; HAD-D: hospital depression score; IQR: interquartile range; 6MWD: 6-min walking distance.

Table S2. Single-exposure adjusted associations between NO_2 and sedentary time and difficulty with physical activity, additionally adjusted for dyspnoea (mMRC score) in 402 patients with mild-to-very severe COPD.

	Sedentary time (h/day)		**Difficulty with physical activity (C-PPAC score)**	
	coef (95% CI)	p	coef (95% CI)	p
NO_2 (per IQR, μg/m³)[a]	0.167 (-0.030, 0.363)	0.097	-1.574 (-3.342, 0.193)	0.081

Notes: Data are presented as regression coefficients with 95% confidence interval (95% CI) for mixed-effects linear regression models with a random intercept for city. Single-exposure models were adjusted for age, sex, socioeconomic status and %predicted of FEV_1, with additional adjustment for the mMRC score. The model for difficulty with physical activity (C-PPAC score) included 309 patients.

[a] Annual residential averages of NO_2.

Abbreviations: C-PPAC: Clinical visit—PROactive Physical Activity in COPD (higher numbers indicate a better score); FEV_1: forced expiratory volume in 1 second; IQR: interquartile range; NO_2: nitrogen dioxide.

Table S3. Single-exposure adjusted associations between the environmental variables and physical activity and capacity variables, restricted to patients with mild-to-very severe COPD not working actively (n=354).

	Steps/day		**Sedentary time (h/day)**		**Difficulty with physical activity (C-PPAC score)**		**6MWD (m)**	
	coef (95% CI)	p	coef (95% CI)	p	coef (95% CI)	p	coef (95% CI)	p
Population density (per IQR, habitants/km^2)[a]	-686 (-1277,-96)	0.023	0.257 (0.031, 0.483)	0.026	0.798 (-1.701, 3.297)	0.531	-13.90 (-26.44, -1.37)	0.030
Pedestrian street length (per IQR, metres)[b]	38 (-91, 167)	0.563	-0.022 (-0.074, 0.030)	0.407	-0.087 (-0.607, 0.432)	0.742	1.12 (-1.91, 4.16)	0.468
Slope (per IQR, degrees)[c]	248 (-259, 754)	0.338	-0.142 (-0.343, 0.059)	0.165	1.681 (-0.552, 3.915)	0.140	16.42 (5.05, 27.79)	0.005
Noise (per IQR, dB(A))[d]	-302 (-868, 263)	0.295	0.197 (-0.042, 0.436)	0.106	-1.041 (-3.753, 1.671)	0.452	-6.31 (-19.97, 7.35)	0.366
NO_2 (per IQR, μg/m^3)[e]	47 (-497, 590)	0.876	0.239 (0.033, 0.445)	0.023	-3.270 (-5.483, -1.056)	0.004	-2.92 (-16.91, 11.08)	0.683
$PM_{2.5}$ (per IQR, μg/m^3)[e]	-78 (-703, 546)	0.806	0.103 (-0.146, 0.351)	0.417	-2.549 (-5.197, 0.100)	0.059	-5.80 (-20.17, 8.56)	0.428

Notes: Data are presented as regression coefficients with 95% confidence interval (95% CI) for mixed-effects linear regression models with a random intercept for city. Single-exposure models were adjusted for age, sex, socioeconomic status and %predicted of FEV_1. Models for difficulty with physical activity (C-PPAC score) included 272 patients. All models for noise have one subject less due to one missing in noise.

[a]Habitants per square kilometre within the census area.
[b]Sum of pedestrian street length within a 300 metre buffer.
[c]Average slope of terrain within a 300 metre buffer.
[d]Annual average levels of road traffic noise in the nearest street.
[e]Annual residential averages of NO_2 and $PM_{2.5}$.

Abbreviations: C-PPAC: Clinical visit—PROactive Physical Activity in COPD (higher numbers indicate a better score); FEV_1: forced expiratory volume in 1 second; IQR: interquartile range; L_{den}: day evening night sound level; 6MWD: 6-min walking distance; NO_2: nitrogen dioxide; PM: particulate matter.

Table S4. Single-exposure adjusted associations between the environmental variables (5^{th}-95^{th} percentile) and physical activity and capacity variables in patients with mild-to-very severe COPD.

	Steps/day		**Sedentary time (h/day)**		**Difficulty with physical activity (C-PPAC score)**		**6MWD (m)**	
	coef (95% CI)	p	coef (95% CI)	p	coef (95% CI)	p	coef (95% CI)	p
Population density (per IQR, habitants/km^2)[a]	-531 (-1268, 205)	0.158	0.195 (-0.081, 0.471)	0.166	0.536 (-2.224, 3.296)	0.703	2.89 (-11.48, 17.27)	0.693
Pedestrian street length (per IQR, metres)[b]	-71 (-291, 148)	0.523	0.020 (-0.065, 0.105)	0.651	-0.492 (-1.364, 0.381)	0.270	-3.70 (-8.58, 1.19)	0.138
Slope (per IQR, degrees)	-121 (-810, 569)	0.732	-0.074 (-0.338, 0.190)	0.585	0.264 (-2.876, 3.403)	0.869	14.73 (-0.06, 29.52)	0.051
Noise (per IQR, dB(A))[d]	-383 (-990, 225)	0.217	0.224 (-0.026, 0.474)	0.078	-0.254 (-2.961, 2.454)	0.854	-3.97 (-17.73, 9.79)	0.572
NO_2 (per IQR, μg/m^3)[e]	347 (-376, 1070)	0.347	0.074 (-0.216, 0.363)	0.618	-3.808 (-6.817, -0.799)	0.013	-0.98 (-19.56, 17.60)	0.918
$PM_{2.5}$ (per IQR, μg/m^3)[e]	-498 (-1269, 272)	0.205	0.255 (-0.039, 0.548)	0.089	-0.192 (-3.343, 2.959)	0.905	-5.28 (-21.79, 11.23)	0.531

Notes: Data are presented as regression coefficients with 95% confidence interval (95% CI) for mixed-effects linear regression models with a random intercept for city. Single-exposure models were adjusted for age, sex, socioeconomic status and %predicted of FEV_1.

[a]Habitants per square kilometre within the census area.
[b]Sum of pedestrian street length within a 300 metre buffer.
[c]Average slope of terrain within a 300 metre buffer.
[d]Annual average levels of road traffic noise in the nearest street.
[e]Annual residential averages of NO_2 and $PM_{2.5}$.

Abbreviations: C-PPAC: Clinical visit—PROactive Physical Activity in COPD (higher numbers indicate a better score); FEV_1: forced expiratory volume in 1 second; IQR: interquartile range; L_{den}: day evening night sound level; 6MWD: 6-min walking distance; NO_2: nitrogen dioxide; PM: particulate matter.

Figure S1. Causal directed acyclic graph to depict the relationship between air pollution (NO_2, $PM_{2.5}$), physical activity and capacity (daily step count, sedentary time, difficulty with physical activity, exercise capacity), and potential confounders and mediators, based on the literature (see Methods). U stands for unmeasured common determinants of environmental factors and physical activity and capacity.

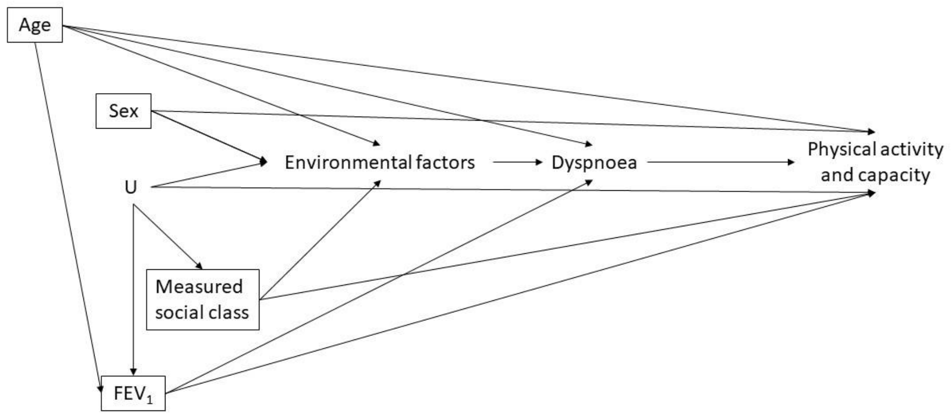
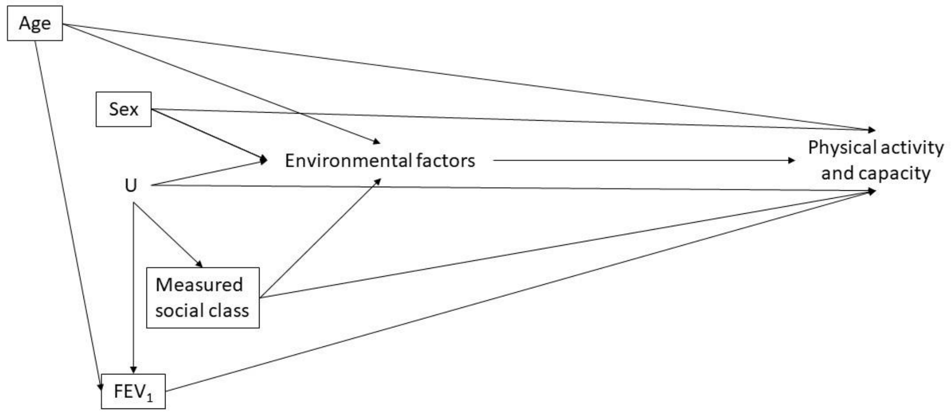


Figure S2. Causal directed acyclic graph to depict the relationship between built environment variables and road traffic noise (summarized as environmental factors), physical activity and capacity (daily step count, sedentary time, difficulty with physical activity, exercise capacity), and potential confounders based on the literature (see Methods). U stands for unmeasured common determinants of environmental factors and physical activity and capacity.



5.3 Paper 3

Koreny M, Demeyer H, Arbillaga-Etxarri A, Gimeno-Santos E, Barberan-Garcia A, Benet M, Balcells E, Borrell E, Marin A, Rodríguez Chiaradía DA, Vall-Casas P, Vilaro J, Rodríguez-Roisin R, Garcia-Aymerich J.

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RESEARCH ARTICLE

Determinants of study completion and response to a 12-month behavioral physical activity intervention in chronic obstructive pulmonary disease: A cohort study

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Data Availability Statement: Data contain potentially identifying variables. For example, built environment variables together with sociodemographics and clinical conditions could allow identification of patients in some geographic areas. Therefore, data cannot be made publicly available according to the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal

Abstract

Objectives

Physical activity is key to improve the prognosis of chronic obstructive pulmonary disease (COPD). To help to tailor future interventions we aimed to identify the baseline characteristics of COPD patients which predict 12-month completion and response to a behavioral physical activity intervention.

Methods

This is a 12-month cohort study of the intervention arm of the Urban Training randomized controlled trial (NCT01897298), an intervention proven to be efficacious to increase physical activity. We considered baseline sociodemographic, interpersonal, environmental, clinical and psychological characteristics as potential determinants of completion and response. We defined completion as attending the 12-month study visit. Among completers, we defined response as increasing physical activity ≥1100 steps/day from baseline to 12 months, measured by accelerometer. We estimated the factors independently for completion and response using multivariable logistic regression models.

data and on the free movement of such data. The corresponding author and the Coordination and Research Management Office of the Projects Unit (research.management@isglobal.org) could provide, upon request, individual participant data that underlie some of the results reported in this article (except variables that may allow identification of patients), after applying necessary measures to guarantee that no individual is identified or identifiable.

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Competing interests: I have read the journal's policy and the authors of this manuscript have the following competing interests: MK: The work was selected for an ERS Grant for Best Abstract in Physiotherapy supported by POWERbreathe. RRR: reports grants and personal fees from Almirall, personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Ferrer Group, grants and personal fees from Menarini, personal fees from Mylan, personal fees from Novartis, personal fees from Pearl Therapeutics, personal fees from Takeda, and personal fees from TEVA during the conduct of the study. He was member of the GOLD Board of Directors (2014-17) and of the Scientific Committee (2014). JGA: JGA's institution has received consulting and lecture fees from

Results

Of a total of 202 patients (m (SD) 69 (9) years, 84% male), 132 (65%) completed the study. Among those, 37 (28%) qualified as responders. Higher numbers of baseline steps/day (OR [95% CI] 1.11 [1.02–1.21] per increase of 1000 steps, p<0.05) and living with a partner (2.77 [1.41–5.48], p<0.01) were related to a higher probability of completion while more neighborhood vulnerability (0.70 [0.57–0.86] per increase of 0.1 units in urban vulnerability index, p<0.01) was related to a lower probability. Among the completers, working (3.14 [1.05–9.33], p<0.05) and having an endocrino-metabolic disease (4.36 [1.49–12.80], p<0.01) were related to a higher probability of response while unwillingness to follow the intervention (0.21 [0.05–0.98], p<0.05) was related to a lower probability.

Conclusions

This study found that 12-month completion of a behavioral physical activity intervention was generally determined by previous physical activity habits as well as interpersonal and environmental physical activity facilitators while response was related to diverse factors thought to modify the individual motivation to change to an active lifestyle.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide [1]. Over the last decades, physical activity has been increasingly recognized as a key factor for COPD for two main reasons. First, higher levels of physical activity practice in daily life have been consistently related to improved prognosis in COPD, specifically to reductions in exacerbations and mortality [2]. Second, in comparison with healthy peers, COPD patients exhibit reduced levels of physical activity already in the early stages [3] and across all other airflow limitation severity stages [4]. As a result, the guidelines for the prevention and management of COPD developed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 include physical activity as a non-pharmacological therapeutic approach that all COPD patients should receive [5].

Recent efforts have succeeded in designing and testing interventions that increased physical activity in COPD patients either at short [6–8] or long-term [9]. However, research is still scarce and there are no clear guidelines on how, when, where or to whom such interventions should be provided [10]. A critical issue is to ensure that a relevant proportion of patients completes the intervention period and responds to the intervention (e.g. with an increase in the targeted outcome above a critical threshold). Unfortunately, research of this kind in physical activity and COPD is scarce. To our knowledge, four studies have assessed factors that affect completion and/or response to a physical activity intervention in COPD in *post hoc* or secondary analyses. Altenburg et al showed that only patients with baseline physical activity <10,000 steps/day maintained a significant long-term effect at 15 months of a 12-week physical activity counselling program [11]. Moy et al found that, among a large number of clinical factors, only age was associated with changes in steps/day at 4 months of an internet-mediated, pedometer-based exercise intervention [12]. Demeyer et al reported that the magnitude of the response to a 12-week semiautomated telecoaching program was higher in patients who exhibited at baseline lower dyspnea scores, better exercise capacity and who suffered from mild-to-moderate COPD [8]. This research also found that study completion was associated with higher body mass index (BMI), higher isometric quadriceps force and a better health status [8]. Finally, AstraZeneca (not related to this study); she has received lecture fees from Esteve and Chiesi (not related to this study). HD, AAE, EGS, ABG, MB, EBa, EBo, AM, DAR, PVC and JV declare that they have no competing interests. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

Kantorowski et al recently found that lower baseline physical activity, social support, lack of depression or oxygen use, and recruitment in spring were significant predictors of a positive change ($\geq$1 step/day) in physical activity after a 12-week pedometer and website intervention (vs pedometer only) [13]. Overall, these studies seem to suggest that lower baseline physical activity and better functional performance relate to a better response and completion.

An important characteristic of the mentioned trials is that they were limited to COPD patients with reduced functional exercise capacity (median 6-min walking distance (6MWD) test $\approx$ 450m [8,11] or below [13]) and/or low baseline physical activity [8,11–13]. Therefore, their results on completion and response to physical activity interventions may not be transferable to other patients. Another shortcoming in previous studies is that they mostly focused on characteristic features of COPD to predict completion and/or response. These characteristics do not reflect the complex interplay of factors affecting physical activity as described by the ecological framework [14].

According to the World Health Organization (WHO) strategy for chronic medical conditions, the outcomes of health promotion and secondary prevention interventions strongly depend on the involvement of patients and their families [15]. Thus, the deployment at the population level of interventions originally assessed at clinical trial level requires a proper assessment of the determinants of completion and response using a broad approach and involving patients across all severity levels as typically found in the community setting.

The aim of our study was to identify which sociodemographic, interpersonal, environmental, clinical, and psychological baseline characteristics were associated with 12-month completion and response to a behavioral physical activity intervention in COPD patients, using data from the intervention arm of the randomized controlled Urban Training trial (NCT01897298) mostly involving COPD patients from primary care. This intervention has previously been reported to be efficacious to increase physical activity in the per protocol population but ineffective in the full population [9], which prompts the need to identify the profile of future completers and/or responders. Ideally, the present results will help to improve clinical guidance on how to tailor behavioral physical activity interventions in COPD patients.

Methods

Design and subjects

We performed a cohort study of 12-month follow-up of the intervention group participating in the Urban Training trial behavioral physical activity intervention in COPD patients. This was a prospective, multicenter, parallel-group, randomized controlled trial, registered at clinicaltrials.gov (NCT01897298) and previously described in detail [9]. In brief, the Urban Training trial recruited 407 patients with a diagnosis of COPD according to the American Thoracic Society and European Respiratory Society (ATS/ERS) recommendations (post- bronchodilator forced expiratory volume in the first second (FEV_1) to forced vital capacity (FVC) ratio $<$0.70) [16] from 33 primary care and 5 tertiary hospitals of five Catalan seaside municipalities between October 2013 and January 2016 and randomized them to the intervention or usual care group. For the present study we included only patients in the intervention arm (n = 202).

The Urban Training trial was approved by the Ethics Committees of all participating institutions (Comitè Ètic d'Investigació Clínica Parc de Salut MAR 2011/4291/I, Comitè Ètic d'Investigació Clínica de l'IDIAP Jordi Gol i Gurina P11/116, Comitè Ètic d'Investigació Clínica de l'Hospital Universitari de Bellvitge PR197/11, Comitè Ètic d'Investigació Clínica de l'Hospital Universitari Germans Trias i Pujol AC-12-004, Comitè Ètic d'Investigació Clínica de l'Hospital Clínic de Barcelona 2011/7061, Comitè Ètic d'Investigació Clínica de l'Hospital de Mataró November 23rd, 2011) and all participants provided written informed consent.

Intervention

The Urban Training intervention included six elements aiming to elicit a behavioral change and to maintain it during the 12 months of the study: (1) a motivational interview [17], following a stage-matched approach [18], with up to four short motivational phone calls during the subsequent 12 months; (2) instructions to walk at least one of the previously validated [19] Urban Training walking trails per day, at least 5 days per week on the appropriate intensity trail with tailored increase of volume and/or intensity over 12 months; (3) a pedometer and a personalised calendar to monitor and note their physical activity and keep motivation; (4) the project website [20] and phone text messages every 2 weeks with educational or motivational messages and the European Lung Foundation information brochure [21]; (5) a guided walking group once per month; and (6) a support phone number available during the 12-month study period.

Procedures

Full details on study procedures and quality control have been reported previously [9,22]. Briefly, we obtained at baseline the following data from all patients using standardized procedures: (i) sociodemographic variables: age, sex, smoking and socioeconomic status; (ii) interpersonal variables: living with a partner (vs single, widowed or divorced), grandparenting and working status (working full-time or part-time vs unemployed, housework or retired); (iii) environmental variables: urban vulnerability index, a measure of socioeconomic status at the census tract level (median area of 0.26 km^2) that combines demographic, economic, residential and subjective indicators, and ranges from 0 (lowest) to 1 (highest level of neighborhood vulnerability) [23], and season of recruitment; (iv) clinical variables: forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) by forced spirometry after bronchodilator, functional exercise capacity measured by the 6-min walking distance (6MWD) test, the modified Medical Research Council dyspnea scale (mMRC), the number of severe COPD exacerbations (defined as requiring a visit to the emergency room or hospital admission) in the 12 months prior to recruitment and during follow-up, body mass index (BMI) and fat free mass index (FFMI) by physical examination and bioelectrical impedance, physician diagnosed comorbidities categorized according to the International Classification of Diseases, Tenth Revision ICD-10 (C00 to D48 for Neoplasm; E00 to E90 for Endocrine, nutritional and metabolic diseases; E10 to E14 for Diabetes mellitus; I00 to I99 for Cardiovascular diseases; I10 to I15 for Hypertension) and physical activity variables: steps/day and time spent on moderate to vigorous physical activity (>3 METs [metabolic equivalents of task]s) measured by the Dynaport accelerometer (McRoberts BV, The Hague, The Netherlands) previously validated for COPD [24,25], defining a valid physical activity measurement as a minimum of 3 days with at least 8 h of wearing time within waking hours [26], and physical activity experience (total and amount and difficulty domains) by the Clinical-PROactive Physical Activity (C-PPAC) tool [27]; and (v) psychological variables: the Hospital Anxiety and Depression scale (HADs), unwillingness to follow the physical activity intervention (i.e. patients who '*spontaneously reported at baseline that they were unwilling to follow any of the instructions*' [9]), stage of change [17,18] and self-efficacy (from 0 to 10).

Study outcomes

We defined study completion as participation in the final visit (12 months after the baseline visit). Among patients who completed the study, we defined intervention response as a positive change in mean daily step count between baseline (visit 2) and 12 months (visit 4) equal or higher than the minimal important difference (MID) [28]. Steps MID in COPD has been estimated to range between 600 and 1100 steps/day [28]; therefore we used a cut-off of ≥1100 vs <1100 steps/day for the main analysis and ≥600 vs <600 steps/day for the secondary analysis.

Statistical analysis

The available sample size (n = 202) was fixed by the primary objectives of the Urban Training study, therefore we calculated the statistical power to answer the current research question. Calculations were performed for a difference in age, FEV_1, FVC, 6MWD, and steps/day at baseline and resulted in a range of statistical power between 93% to 98% for study completion and 79% to 90% for response, using unpaired t-test ($p<0.05$) and assuming a relation of loss-to follow-up to completion and responders to non-responders of 1:2.

We assessed the presence and patterns of missing data. Due to the small proportion of missings (<5% of total data), main analysis was conducted using a complete case strategy and we reported missing data in the Table footnotes. As a sensitivity analysis, to account for the possibility of bias due to missing data, we used multiple imputation (20 imputed datasets) with the method of chained equations [29] assuming the missing-at-random hypothesis (i.e., missingness conditional on measured patients' characteristics [30]). We repeated bivariable and multivariable analysis using the imputed datasets.

To analyze determinants of study completion and response to intervention, we first compared the individual's characteristics (sociodemographic, interpersonal, environmental, clinical and psychological) at baseline between patients lost to follow-up and completers, and between non-responders and responders using unpaired Student's t-test, Wilcoxon rank-sum, Chi square or Fisher's tests, depending on the variable distribution. Second, we built two multivariable logistic regression models (one for study completion and one for response to the intervention) including as exposures all variables that exhibited a p-value <0.2 in the bivariable analysis between lost to follow-up and completers, and non-responders and responders, respectively. Model building combined step-forward and backward algorithms, and covariates were included in the final model if: (i) they related to both the exposure and the outcome in bivariable analysis; (ii) they modified (>10% change in regression coefficient) the estimates of the remaining variables in the multivariable models; or, (iii) there was consistent evidence in the literature of their association with the outcome [31]. To exclude overfitting, we applied the least absolute shrinkage and selection operator (LASSO) approach. We tested goodness of fit of the final models by means of the Hosmer-Lemeshow test, identification of influential observations, and estimation of the specification error. Finally, we tested the discrimination and accuracy to predict the outcome of the final models by calculating the area under the receiver operating characteristic curve (AUROC) and the Brier score, respectively.

We conducted several secondary analyses. First, we used 600 steps (lower limit of steps MID) as a cut-off to define response to the intervention both in bivariable and multivariable analyses. Second, we repeated the final multivariable model for response: (1) including severe acute exacerbations of COPD during follow-up in the multivariable models to test the possibility that this variable affected the risk of being a non-responder; and (2) using time in moderate to vigorous physical activity (categorized according to its median value) instead of steps to define response to the intervention.

All analyses were conducted with Stata 12.0 (StataCorp, College Station, TX, USA).

Results

Patient characteristics

Patient characteristics are shown in Table 1. Patients had a mean (SD) age of 69 (9) years and were mostly male (84%) and living with a partner (72%). Only 14% were active workers and

71% had low socioeconomic status. Patients were mainly in the earlier stages of COPD with a mean FEV_1 56% of predicted and a mean 6MWD of 487m; 29% of patients had an mMRC dyspnea score ≥2, 9% of patients had a severe COPD exacerbation within the previous year and only 6% were participating in a pulmonary rehabilitation program at study inclusion. Patients had a large prevalence of endocrino-metabolic and cardiovascular chronic comorbid conditions and walked more than 7000 steps per day on average. At baseline, 26 patients (13%) reported unwillingness to follow the intervention, 50% of patients were in later phases of stage of change (action, maintaining and finalizing), and self-efficacy was high (median 8 on a scale from 0 to 10).

Determinants of study completion

After 12 months, 70 patients (35%) were lost to follow-up and 132 patients (65%) completed the study (completers) (Fig 1).

Of the broad range of variables assessed at baseline, physical activity levels, marital status, neighborhood vulnerability, unwillingness to follow the intervention and baseline 6MWD were significantly different between patients lost to follow-up and completers (Table 1). In the mutually adjusted logistic regression model, being physically more active (OR [95% CI] 1.11 [1.02–1.21] per increase of 1000 steps, p = 0.012) and living with a partner (2.77 [1.41–5.48], p = 0.003) were independently related to a higher probability of completion while more neighborhood vulnerability (0.70 [0.57–0.86] per increase of 0.1 units in urban vulnerability index, p = 0.001) was related to a lower probability (Table 2).

Determinants of intervention response

Among patients who completed the study, 37 patients (28%) qualified as responders using as threshold 1100 steps/day (Fig 1). The change in steps/day between baseline and 12 months was heterogeneous and ranged between less than minus 10,000 and more than plus 10,000 steps/day following a normal distribution (mean (SD) -67 (3648) steps/day) (Fig 2).

Active working, diagnosis of an endocrino-metabolic disease, unwillingness to follow the physical activity intervention, and FVC at baseline were related to the response to the intervention on bivariable analysis (Table 3).

After mutual adjustment in a multivariable model, being an active worker (3.14 [1.05–9.33], p = 0.040) and having an endocrino-metabolic disease (4.36 [1.49–12.80], p = 0.007) were independently related to a higher probability of response while unwillingness to follow the intervention (0.21 [0.05–0.098], p = 0.047) was related to a lower probability (Table 4).

Models fitting and additional analyses

The LASSO approach confirmed that final models of determinants of completion and response (Tables 2 and 4) were not overadjusted. Goodness of fit tests did not reveal any abnormality. Final models indicated good discrimination, as per AUROC of 0.73 for study completion and 0.71 for intervention response, and accuracy with Brier scores lower than 0.2 in both models. All secondary and sensitivity analyses provided very similar results (Tables A-H in S1 File).

Discussion

This study about the determinants of 12-month completion and response to a behavioral physical activity intervention in COPD patients has found that: (1) being more physically active and living with a partner were positively associated with study completion while living in more

Table 1. Variables related to 12-month completion in COPD patients participating in a behavioral physical activity intervention.

	All patients	Lost to follow-up	Completers	p-value
	n = 202*	n = 70	n = 132	
Sociodemographic				
Age (years), m (SD)	68.8 (9.2)	69.9 (9.3)	68.3 (9.1)	0.229
Sex: male, n (%)	170 (84)	56 (80)	114 (86)	0.239
Smoking status, current, n (%)	56 (28)	22 (31)	34 (26)	0.392
Socioeconomic status, IIIM-IV-V, n (%)	143 (71)	50 (71)	93 (71)	0.948
Interpersonal				
Living with a partner**, n (%)	145 (72)	41 (59)	104 (79)	0.004
Grandparenting, n (%)	68 (34)	21 (31)	47 (36)	0.481
Active workers, n (%)	28 (14)	9 (13)	19 (14)	0.764
Environmental				
Urban vulnerability index (from 0 -lowest to 1 –highest), m (SD)	0.64 (0.17)	0.69 (0.16)	0.61 (0.17)	0.003
Recruitment season				
Spring, n (%)	46 (23)	13 (19)	33 (25)	0.305
Summer, n (%)	22 (11)	11 (16)	11 (8)	
Fall, n (%)	73 (36)	27 (38)	46 (35)	
Winter, n (%)	61 (30)	19 (27)	42 (32)	
Clinical				
FEV_1 (% pred), m (SD)	56.4 (17.1)	57.2 (17.9)	55.9 (16.7)	0.616
FVC (% pred), m (SD)	77.3 (16.8)	76.9 (16.8)	77.5 (16.9)	0.817
6MWD (m), m (SD)	487 (98)	464 (102)	498 (95)	0.018
Moderate to very severe dyspnea (mMRC $\geq$2), n (%)	58 (29)	22 (31)	36 (27)	0.534
Any severe¶ COPD exacerbation in previous 12 months, n (%)	17 (9)	7 (11)	10 (8)	0.591
Any severe¶ COPD exacerbation during follow-up, n (%)	22 (17)	-	22 (17)	-
BMI (kg/m^2), m (SD)	28.5 (5.0)	28.6 (5.1)	28.4 (4.9)	0.812
FFMI, m (SD)	19.6 (3.2)	19.6 (3.5)	19.6 (3.0)	0.978
Neoplasm†, n (%)	24 (12)	5 (8)	19 (15)	0.248
Endocrine, nutritional and metabolic diseases†, n (%)	131 (67)	42 (64)	89 (68)	0.546
Diabetes mellitus†, n (%)	61 (31)	17 (26)	44 (34)	0.262
Cardiovascular disease†, n (%)	124 (63)	43 (65)	81 (62)	0.649
Hypertension†, n (%)	94 (48)	33 (50)	61 (47)	0.649
Steps/day, m (SD)	7488 (4234)	6395 (3315)	8069 (4554)	0.007
Time in moderate to vigorous physical activity (>3 METs; h/day), med (P25-P75)	1.7 (1.2–2.2)	1.6 (1.1–2.0)	1.7 (1.3–2.4)	0.058
Intensity during physical activities (m/s^2), m (SD)	1.029 (0.265)	0.970 (0.229)	1.060 (0.279)	0.020
C-PPAC amount, med (P25-P75)	77 (67–83)	72 (65–83)	77 (67–83)	0.223
C-PPAC difficulty, med (P25-P75)	83 (72–94)	81 (69–94)	86 (75–94)	0.562
C-PPAC score, med (P25-P75)	78 (70–86)	78 (67–84)	78 (72–86)	0.265
Psychological				
Anxiety (HAD-A), m (SD)	5.4 (4.2)	5.6 (4.6)	5.3 (4.0)	0.637
Depression (HAD-D), m (SD)	3.6 (3.7)	3.3 (4.1)	3.8 (3.4)	0.449
Unwillingness to follow the intervention, n (%)	26 (13)	2 (3)	24 (18)	0.002
Stage of change: action, maintaining, finalizing$, n (%)	80 (50)	22 (41)	58 (55)	0.095

(*Continued*)

Table 1. (Continued)

	All patients	Lost to follow-up	Completers	p-value
	n = 202*	n = 70	n = 132	
Self-efficacy‡ (0 to 10), med (P25-P75)	8 (7–10)	9 (7–10)	8 (7–10)	0.920

Data are presented as n (%), mean (SD) or median (P25-P75). FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; 6MWD: 6-min walking distance; mMRC: modified Medical Research Council; BMI: body mass index; FFMI: fat free mass index; MET: metabolic equivalent of task; C-PPAC: Clinical visit—PROactive Physical Activity in COPD; HAD-A: Hospital Anxiety and Depression scale- Anxiety; HAD-D: Hospital Anxiety and Depression scale- Depression.

** Living with a partner vs single, widowed or divorced.

¶ A COPD exacerbation was considered severe if the patient required admission to the hospital or the emergency department.

† ICD10 codes: C00 to D48 for Neoplasm; E00 to E90 for Endocrine, nutritional and metabolic diseases; E10 to E14 for Diabetes mellitus; I00 to I99 for Cardiovascular diseases; I10 to I15 for Hypertension.

§ Stage of change: action, maintaining, finalizing vs pre-contemplation, contemplation, preparation.

‡ Self-efficacy: Sure to go out for a walk every day (0 not sure- 10 completely sure).

* Some variables had missing values. Number of missings for 12-month completion: 1 in socioeconomic status, 1 in marital status, 3 in grandparenting, 3 in urban vulnerability index, 7 for severe COPD exacerbation in previous 12 months, 16 for FFMI, 5 for neoplasm, 5 for endocrine, nutritional and metabolic diseases, 5 for diabetes mellitus, 5 for any cardiovascular disease, 5 for hypertension, 57 for C-PPAC, 1 in depression, 42 in stage of change, 14 in self-efficacy.

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vulnerable neighborhoods was negatively associated; (2) active working and endocrino-metabolic comorbidities were positively associated with intervention response while unwillingness to follow the intervention was negatively associated; (3) most clinical and functional

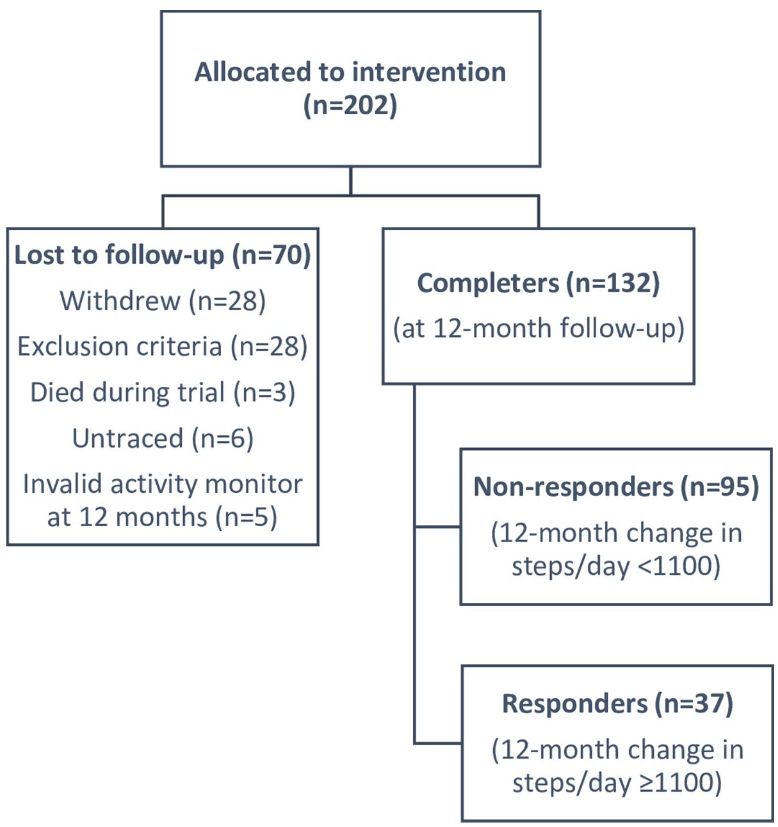

Fig 1. Flow of participants through the study.

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Table 2. Adjusted predictive factors of 12-month completion of a behavioral physical activity intervention in 202 COPD patients.

	OR (95% CI)	p-value
Steps/day (per increase of 1000 steps)	1.11 (1.02–1.21)	0.012
Living with a partner (vs single/ widowed/ divorced)	2.77 (1.41–5.48)	0.003
Urban vulnerability index (per increase of 0.1 units)	0.70 (0.57–0.86)	0.001

OR: odds ratio; CI: confidence interval.

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characteristics of COPD previously reported to be relevant for physical activity and specifically interventions‘ completion or response were not associated with these outcomes in our sample population; and (4) predictors of study completion were different from predictors of intervention response.

Determinants of study completion

Our study shows that patients who were more physically active at baseline were more likely to complete the study. We hypothesize that physically active patients already had established a habit around regular physical activity, which acted as a facilitator for participation so that these patients were willing and able to complete the study. Indeed, continuation of an active lifestyle from the past has been reported as a reason to be physically active in an earlier mixed-methods study which combined qualitative and quantitative approaches [32]. Thus, while some intervention studies have excluded more active patients, our results support the inclusion of all COPD patients, even those already considerably active at baseline, in line with the GOLD strategy to promote physical activity for all patients [5].

Living with a partner or in a less vulnerable neighborhood were further predictors of study completion. The role of interpersonal factors such as social support from family, or environmental factors (e.g. ‘*seeing others active*‘ or ‘*neighborhood walkability*‘), has been recognized within the ecological model of the determinants of physical activity in the general population [14] and is increasingly studied in COPD patients. Being in a supportive relationship was associated with higher levels of physical activity in COPD patients [22,33]. Qualitative studies on barriers to pulmonary rehabilitation have linked living alone to a lack of support, increased challenges to participate, and reduced motivation [34,35]. We anticipate that both living with a partner and living in a less vulnerable neighborhood may facilitate study completion through mechanisms such as social support, behavioral modeling and walkable access to public open spaces [14], thereby lowering mental and physical barriers.

Determinants of intervention response

Being an active worker was related to a higher likelihood of response to the Urban Training intervention. This finding was surprising since one might expect that working actively might hinder a response to the intervention for time constraints. Lack of time has been acknowledged as a barrier to physical activity in the general [36] and in the COPD population [37] and working is often used as excuse not to exercise. Several hypotheses might explain this unexpected association. First, active workers were younger (mean age 59 *vs* 70 years in our sample, $p<0.001$), which could have increased their capacities to engage in the intervention. However, in our study age was not related with response (Table 3). Second, patients who kept working despite their COPD, may have had better overall health conditions than those who were retired (which was supported by higher exercise capacity in this group, median 6MWD 540 vs 508, $p = 0.139$). However, our data does not support a role for exercise capacity in response to the

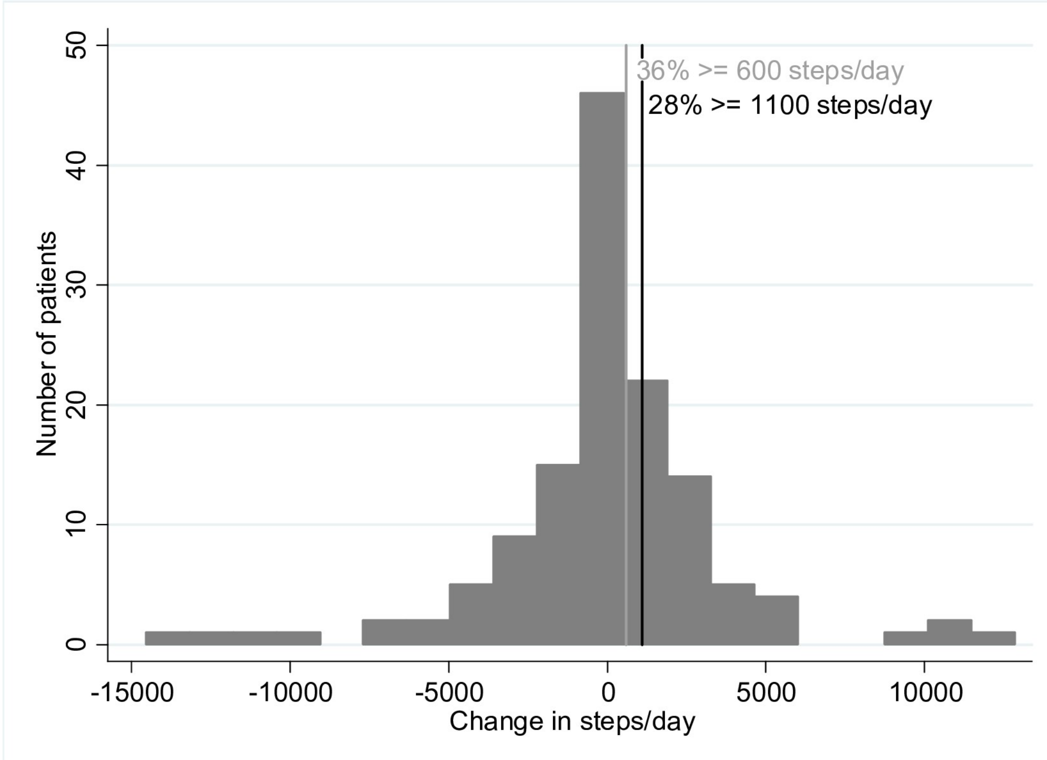

Fig 2. Change in steps/day between baseline and 12-month follow-up after a behavioral physical activity intervention.

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intervention (Table 3). We speculate that active workers may have a more active attitude and higher social support (by work colleagues) to engage in an intervention. They also may have experienced more opportunities to integrate a new physical activity habit into daily life routine and change to a more active life style e.g. switching the commuting mode from private car to walking.

Diagnosis of an endocrino-metabolic comorbidity was also significantly associated with higher likelihood of intervention response, which could seem counterintuitive if patients with concomitant diseases have a poorer health status. In the previous study by Demeyer et al the response to the telecoaching intervention was similar in patients with more than two comorbidities compared to none or one comorbidity [8]. Unfortunately, specific comorbidities were not investigated in that study which precludes direct comparison. Similarly, in the previous study by Moy the number of comorbidities did not predict a change in steps/day at 4 months [12]. Akin to our results, metabolic disease has been reported as an independent predictor for higher response to pulmonary rehabilitation in COPD patients [38]. In our specific sample, endocrino-metabolic comorbidity included mostly a physician diagnosis of diabetes, overweight/obesity and/or hyperlipidemia. However, the small number of cases combined with the high variability in the outcome (response to the intervention) preclude the analysis of the individual effect of each chronic condition. We speculate that the diagnosis of some comorbidities prior to our intervention may have led to the recommendation of increased physical activity in the past. Raised awareness and sensitivity to the topic may in turn have motivated response to the Urban Training intervention.

Spontaneously expressed unwillingness to follow the intervention instructions at baseline was inversely related to the likelihood of response. This is in line with the Urban Training

Table 3. Variables related to 12-month response in COPD patients participating in a behavioral physical activity intervention.

	Non-responders (12-month change in steps/day <1100) n = 95*	Responders (12-month change in steps/day ≥1100) n = 37*	p-value
Sociodemographic			
Age (years), m (SD)	69.2 (8.7)	66.0 (9.7)	0.075
Sex: male, n (%)	85 (89)	29 (78)	0.095
Smoking status, current, n (%)	24 (25)	10 (27)	0.835
Socioeconomic status, IIIM-IV-V, n (%)	66 (70)	27 (73)	0.754
Interpersonal			
Living with a partner**, n (%)	75 (79)	29 (78)	0.943
Grandparenting, n (%)	38 (40)	9 (24)	0.084
Active workers, n (%)	10 (11)	9 (24)	0.043
Environmental			
Urban vulnerability index (from 0 -lowest to 1 –highest), m (SD)	0.60 (0.18)	0.63 (0.15)	0.494
Recruitment season			
Spring, n (%)	24 (25)	9 (24)	0.921
Summer, n (%)	9 (9)	2 (6)	
Fall, n (%)	33 (35)	13 (35)	
Winter, n (%)	29 (31)	13 (35)	
Clinical			
FEV_1 (% pred), m (SD)	54.3 (16.4)	60.1 (17.1)	0.074
FVC (% pred), m (SD)	75.7 (16.3)	82.2 (17.9)	0.048
6MWD (m), m (SD)	493 (97)	512 (90)	0.299
Moderate to very severe dyspnea (mMRC ≥2), n (%)	27 (28)	9 (24)	0.635
Any severe[¶] COPD exacerbation in previous 12 months, n (%)	9 (10)	1 (3)	0.282
Any severe[¶] COPD exacerbation during follow-up, n (%)	13 (14)	9 (26)	0.123
BMI (kg/m^2), m (SD)	28.4 (5.3)	28.4 (4.1)	0.998
FFMI, m (SD)	19.6 (3.3)	19.4 (2.4)	0.690
Neoplasm[†], n (%)	14 (15)	5 (14)	0.902
Endocrine, nutritional and metabolic diseases[†], n (%)	58 (61)	31 (86)	0.006
Diabetes mellitus[†], n (%)	31 (33)	13 (36)	0.707
Cardiovascular disease[†], n (%)	58 (61)	23 (64)	0.765
Hypertension[†], n (%)	41 (43)	20 (56)	0.204
Steps/day, m (SD)	8241 (4824)	7625 (3794)	0.487
Time in moderate to vigorous physical activity (>3 METs; h/day), med (P25-P75)	1.7 (1-3-2.4)	1.8 (1.2–2.4)	0.933
Intensity during physical activities (m/s^2), m (SD)	1.09 (0.31)	1.05 (0.27)	0.431
C-PPAC amount, med (P25-P75)	77 (67–83)	77 (70–91)	0.238
C-PPAC difficulty, med (P25-P75)	86 (75–94)	85 (73–94)	0.908
C-PPAC score, med (P25-P75)	78 (73–86)	83 (68–89)	0.423
Psychological			
Anxiety (HAD-A), m (SD)	5.3 (4.2)	5.4 (3.7)	0.861
Depression (HAD-D), m (SD)	3.8 (3.5)	3.6 (3.3)	0.810
Unwillingness to follow the intervention, n (%)	22 (23)	2 (5)	0.022
Stage of change: action, maintaining, finalizing[$], n (%)	44 (56)	14 (50)	0.559

(*Continued*)

Table 3. (Continued)

	Non-responders (12-month change in steps/day <1100)	Responders (12-month change in steps/day ≥1100)	p-value
	n = 95*	n = 37*	
Self-efficacy‡ (0 to 10), med (P25-P75)	8 (7–10)	8 (6–10)	0.755

Data are presented as n (%), mean (SD) or median (P25-P75). FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; 6MWD: 6-min walking distance; mMRC: modified Medical Research Council; BMI: body mass index; FFMI: fat free mass index; MET: metabolic equivalent of task; C-PPAC: Clinical visit—PROactive Physical Activity in COPD; HAD-A: Hospital Anxiety and Depression scale- Anxiety; HAD-D: Hospital Anxiety and Depression scale- Depression.

** Living with a partner vs single, widowed or divorced.

¶ A COPD exacerbation was considered severe if the patient required admission to the hospital or the emergency department.

† ICD10 codes: C00 to D48 for Neoplasm; E00 to E90 for Endocrine, nutritional and metabolic diseases; E10 to E14 for Diabetes mellitus; I00 to I99 for Cardiovascular diseases; I10 to I15 for Hypertension.

§ Stage of change: action, maintaining, finalizing vs pre-contemplation, contemplation, preparation.

‡ Self-efficacy: Sure to go out for a walk every day (0 not sure- 10 completely sure).

* Some variables had missing values. Number of missings for 12-month response: 1 in socioeconomic status, 1 in grandparenting, 1 in urban vulnerability index, 2 for severe COPD exacerbation in previous 12 months, 5 for severe COPD exacerbation during follow-up, 12 for FFMI, 1 for neoplasm, 1 for endocrine, nutritional and metabolic diseases, 1 for diabetes mellitus, 1 for any cardiovascular disease, 1 for hypertension, 35 for C-PPAC, 1 in depression, 26 in stage of change, 8 in self-efficacy.

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principal paper which observed the intervention to be efficacious to increase physical activity in the *per protocol* population but ineffective in the full population [9]. It also underlines clearly the important role of motivation and a positive mindset towards the physical activity intervention, which have been established previously as important factors for physical activity in qualitative and mixed-methods cross-sectional studies with COPD patients [32,37,39]. Unfortunately, our study did not collect quantitative data on motivation. However, it could be argued that both being an active worker and having a diagnosis of endocrino-metabolic comorbidities essentially also reflect the importance of motivation.

There was a number of variables we had expected to be associated with the intervention response, based on the results of previous studies [8,11,13], on research on physical activity and COPD [2] and on clinical experience. These variables included markers of COPD severity (FEV_1, COPD exacerbations, dyspnea or exercise capacity), psychological factors (depression, anxiety or self-efficacy), the season of inclusion, or the baseline levels of physical activity. Whether their lack of association with intervention response may be due to the fact that other studies recruited patients in more advanced stages of disease needs to be confirmed in further clinical trials.

Implications

Our study has implications for future research, clinical management and public health and policies. First, the response to the Urban Training intervention (defined as an increase of

Table 4. Adjusted predictive factors of 12-month response to a behavioral physical activity intervention in 132 COPD patients.

	OR (95% CI)	p-value
Active workers	3.14 (1.05–9.33)	0.040
Endocrine, nutritional and metabolic diseases†	4.36 (1.49–12.80)	0.007
Unwillingness to follow the intervention	0.21 (0.05–0.98)	0.047

OR: odds ratio; CI: confidence interval.

† ICD10 codes: E00 to E90 for endocrine, nutritional and metabolic diseases.

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≥1100 steps/day after 12 months, according to previously published MID [28]) has been low with 28% which is in line with the telecoaching intervention which observed a 36% response (defined as an increase of > 1000 steps/day) [8]. This reinforces the need to understand which patients would benefit most from the available resources. Second, we may consider excluding patients who reject participation at baseline to contain health service costs and maximize effectiveness, and consider alternative strategies for these patients. Third, physical activity interventions should neither exclude patients with certain chronic conditions nor actively working patients but rather pay special attention to these individuals since they may be particularly motivated and thus respond better. Fourth, the role of baseline levels of physical activity to include or exclude COPD patients into physical activity interventions should be cautiously considered, since existing literature is still unclear and no patient should be left without an intervention potentially efficacious for him/her. Finally, we suggest that screening for interpersonal and environmental factors may help to decide which patients are more likely to succeed in long-term physical activity interventions.

Strengths and limitations

A major strength of our study lies within the fact that the Urban Training intervention was administered to COPD patients from hospital and primary care settings. The findings therefore reflect more closely than previous studies (based on hospitals or rehabilitation settings only) what can be expected when deploying a physical activity intervention at the population level. Moreover, the study design allowed us to assess the determinants of a long-term effect. These are more likely to be the determinants of a real behavior change as compared to the short-term effects shown in literature. Finally, the broad number of variables included in our study reflect well the various domains of the determinants of physical activity within the ecological framework [14].

As potential limitation we have to acknowledge the small sample size that did not allow testing the potential association of some rare factors (e.g. less frequent comorbidities) with completion or response. Although we included a broad range of variables, some variables related to physical activity limitation in COPD patients such as reduced muscle strength or impaired lung volumes were missing. Finally, our study population reflects the behavior of a population from a specific geographic area (i.e. '*elderly inhabitants of Mediterranean cities*' [9]) and included a large proportion of patients with relatively mild-to-moderate stages of disease. Thus, further research is needed to identify determinants of completion and response in patients from other regions or medical settings, as is usually done prior to deployment of any intervention.

Conclusions

Among a broad range of potential predictors of 12-month completion or response to a behavioral physical activity intervention, this study found that completion was generally determined by previous physical activity habits as well as interpersonal and environmental physical activity facilitators while response was related to diverse factors thought to modify the individual motivation to change to an active lifestyle. These results support a look beyond the traditional clinical and functional variables and the consideration of psychological, interpersonal and environmental factors related to habits and motivation to optimize the outcome of physical activity interventions in COPD.

Supporting information

S1 File. Supporting information.
(PDF)

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S1 File. Supporting Information.

Determinants of study completion and response to a 12-month behavioral physical activity intervention in chronic obstructive pulmonary disease: A cohort study

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Tables:

Table A. Variables related to 12-month response to a behavioral physical activity intervention using 600 steps/day as cut-off for response.

Table B. Adjusted predictive factors of 12-month response to a behavioral physical activity intervention using 600 steps/day as cut-off for response.

Table C. Adjusted predictive factors of 12-month response to a behavioral physical activity intervention including exacerbations during follow-up as a covariate.

Table D. Adjusted predictive factors of 12-month response to a behavioral physical activity intervention using change in moderate to vigorous physical activity to define response[#].

Table E. Variables related to 12-month completion in COPD patients participating in a behavioral physical activity intervention using multiple imputation.

Table F. Adjusted predictive factors of 12-month completion of a behavioral physical activity intervention in 202 COPD patients using multiple imputation.

Table G. Variables related to 12-month response in COPD patients participating in a behavioral physical activity intervention using multiple imputation.

Table H. Adjusted predictive factors of 12-month response to a behavioral physical activity intervention in 132 COPD patients using multiple imputation.

Table A. Variables related to 12-month response to a behavioral physical activity intervention using 600 steps/day as cut-off for response.

	Non-responders (12-month change in steps/day <600)	Responders (12-month change in steps/day ≥600)	p-value
	n=85*	n=47*	
Sociodemographic			
Age (years), m (SD)	69.2 (8.3)	66.7 (10.2)	0.138
Sex: male, n (%)	76 (89)	38 (81)	0.170
Smoking status, current, n (%)	21 (25)	13 (28)	0.710
Socioeconomic status, IIIM-IV-V, n (%)	57 (68)	36 (77)	0.290
Interpersonal			
Living with a partner**, n (%)	66 (78)	38 (81)	0.666
Grandparenting, n (%)	36 (43)	11 (23)	0.026
Active workers, n (%)	9 (11)	10 (21)	0.094
Environmental			
Urban vulnerability index (from 0 -lowest to 1 –highest), m (SD)	0.61 (0.18)	0.61 (0.15)	0.853
Recruitment season			
Spring, n (%)	23 (27)	10 (21)	0.773
Summer, n (%)	8 (9)	3 (7)	
Fall, n (%)	29 (34)	17 (36)	
Winter, n (%)	25 (30)	17 (36)	
Clinical			
FEV_1 (% pred), m (SD)	54.4 (16.7)	58.7 (16.6)	0.152
FVC (% pred), m (SD)	76.1 (16.6)	80.1 (17.3)	0.195
6MWD (m), m (SD)	491 (100)	512 (84)	0.240
Moderate to very severe dyspnea (mMRC ≥2), n (%)	25 (29)	11 (23)	0.458
Any severe¶ COPD exacerbation in previous 12 months, n (%)	9 (11)	1 (2)	0.097
Any severe¶ COPD exacerbation during follow-up, n (%)	12 (15)	10 (22)	0.330
BMI (kg/m^2), m (SD)	28.5 (5.4)	28.1 (4.1)	0.669
FFMI, m (SD)	19.7 (3.2)	19.3 (2.8)	0.417
Neoplasm†, n (%)	12 (14)	7 (15)	0.865
Endocrine, nutritional and metabolic diseases†, n (%)	52 (61)	37 (80)	0.024
Diabetes mellitus†, n (%)	29 (34)	15 (33)	0.861
Any cardiovascular disease†, n (%)	52 (61)	29 (63)	0.834
Hypertension†, n (%)	37 (44)	24 (52)	0.344
Steps/day, m (SD)	8397 (4949)	7474 (3709)	0.267
Time in moderate to vigorous physical activity (>3 METs; h/day), med (P25-P75)	1.7 (1.3-2.4)	1.8 (1.2-2.4)	0.938
Intensity during physical activities (m/s^2), m (SD)	1.06 (0.27)	1.06 (0.30)	0.939
C-PPAC amount, med (P25-P75)	77 (63-83)	77 (72-91)	0.194
C-PPAC difficulty, med (P25-P75)	86 (77-94)	83 (73-94)	0.382
C-PPAC score, med (P25-P75)	78 (72-86)	78 (69-89)	0.617
Psychological			
Anxiety (HAD-A), m (SD)	5.3 (4.2)	5.4 (3.8)	0.917
Depression (HAD-D), m (SD)	3.8 (3.5)	3.6 (3.2)	0.718
Unwillingness to follow the intervention, n (%)	21 (25)	3 (6)	0.009
Stage of change: action, maintaining, finalizing§, n (%)	40 (57)	18 (50)	0.484
Self-efficacy‡ (0 to 10), med (P25-P75)	8 (6-10)	9 (7-10)	0.145

Data are presented as n (%), mean (SD) or median (P25-P75). FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; 6MWD: 6-min walking distance; mMRC: modified Medical Research Council; BMI: body mass index; FFMI: fat free mass index; MET: metabolic equivalent of task; C-PPAC: Clinical visit - PROactive Physical Activity in COPD; HAD-A: Hospital Anxiety and Depression scale- Anxiety; HAD-D: Hospital Anxiety and Depression scale- Depression.

** Living with a partner vs single, widowed or divorced.

¶ A COPD exacerbation was considered severe if the patient required admission to the hospital or the emergency department.

† ICD10 codes: C00 to D48 for Neoplasm; E00 to E90 for Endocrine, nutritional and metabolic diseases; E10 to E14 for Diabetes mellitus; I00 to I99 for Cardiovascular diseases; I10 to I15 for Hypertension.

§ Stage of change: action, maintaining, finalizing vs pre-contemplation, contemplation, preparation.

‡ Self-efficacy: Sure to go out for a walk every day (0 not sure- 10 completely sure).

* Some variables had missing values. Number of missings for 12-month response: 1 in socioeconomic status, 1 in grandparenting, 1 in urban vulnerability index, 2 for severe COPD exacerbation in previous 12 months, 5 for severe COPD exacerbation during follow-up, 12 for FFMI, 1 for neoplasm, 1 for endocrine, nutritional and metabolic diseases, 1 for diabetes mellitus, 1 for any cardiovascular disease, 1 for hypertension, 35 for C-PPAC, 1 in depression, 26 in stage of change, 8 in self-efficacy.

Table B. Adjusted predictive factors of 12-month response to a behavioral physical activity intervention <u>using 600 steps/day as cut-off for response.</u>

	OR (95% CI)	p-value
Endocrine, nutritional and metabolic diseases†, n (%)	2.78 (1.17-6.61)	0.021
Active workers, n (%)	2.60 (0.94-7.20)	0.067

OR: odds ratio; CI: confidence interval.

† ICD10 codes: E00 to E90 for endocrine, nutritional and metabolic diseases.

Table C. Adjusted predictive factors of 12-month response to a behavioral physical activity intervention <u>including exacerbations during follow-up as a covariate</u>.

	Main Model OR (95% CI)	p-value	Model with exacerbations OR (95% CI)	p-value
Active workers	3.14 (1.05-9.33)	0.040	2.86 (0.93-8.77)	0.066
Endocrine, nutritional and metabolic diseases[†]	4.36 (1.49-12.80)	0.007	4.45 (1.49-13-29)	0.008
Unwillingness to follow the intervention	0.21 (0.05-0.98)	0.047	0.18 (0.04-0.91)	0.038
Any severe[¶] COPD exacerbation during follow-up	-	-	2.65 (0.92-7.64)	0.071

OR: odds ratio; CI: confidence interval.

[†] ICD10 codes: E00 to E90 for endocrine, nutritional and metabolic diseases.

[¶] A COPD exacerbation was considered severe if the patient required admission to the hospital or the emergency department.

Table D. Adjusted predictive factors of 12-month response to a behavioral physical activity intervention using change in moderate to vigorous physical activity to define response#.

	OR (95% CI)	p-value
Active workers	1.45 (0.52-4.04)	0.474
Endocrine, nutritional and metabolic diseases†	2.31 (1.07-5.01)	0.034
Unwillingness to follow the intervention	0.36 (0.14-0.97)	0.042

OR: odds ratio; CI: confidence interval.

We used the median change of time in moderate to vigorous physical activity (between visit 2 and visit 4) as cut-off to define response to a behavioural physical activity intervention.

† ICD10 codes: E00 to E90 for endocrine, nutritional and metabolic diseases.

Table E. Variables related to 12-month completion in COPD patients participating in a behavioral physical activity intervention using multiple imputation.

	All patients	Lost to follow-up	Completers	p-value
	n=202	n=70	n=132	
Sociodemographic				
Age (years), m (SD)	68.8 (9.2)	69.9 (9.3)	68.3 (9.1)	0.229
Sex: male, n (%)	170 (84)	56 (80)	114 (86)	0.241
Smoking status, current, n (%)	56 (28)	22 (31)	34 (26)	0.392
Socioeconomic status, IIIM-IV-V, n (%)	144 (71)	50 (71)	94 (71)	0.965
Interpersonal				
Living with a partner**, n (%)	145 (72)	41 (59)	104 (79)	0.004
Grandparenting, n (%)	69 (34)	22 (31)	47 (36)	0.482
Active workers, n (%)	28 (14)	9 (13)	19 (14)	0.764
Environmental				
Urban vulnerability index (from 0 -lowest to 1 –highest), m (SD)	0.64 (0.17)	0.69 (0.16)	0.61 (0.17)	0.003
Recruitment season				
Spring, n (%)	46 (23)	13 (19)	33 (25)	0.316
Summer, n (%)	22 (11)	11 (16)	11 (8)	
Fall, n (%)	73 (36)	27 (39)	46 (35)	
Winter, n (%)	61 (30)	19 (27)	42 (32)	
Clinical				
FEV_1 (% pred), m (SD)	56.4 (17.1)	57.2 (17.9)	55.9 (16.7)	0.614
FVC (% pred), m (SD)	77.3 (16.8)	76.9 (16.8)	77.5 (16.9)	0.816
6MWD (m), m (SD)	487 (98)	464 (102)	498 (95)	0.021
Moderate to very severe dyspnea (mMRC ≥2), n (%)	58 (29)	22 (31)	36 (27)	0.535
Any severe¶ COPD exacerbation in previous 12 months, n (%)	19 (10)	9 (13)	10 (8)	0.301
Any severe¶ COPD exacerbation during follow-up, n (%)	22 (17)	-	22 (17)	-
BMI (kg/m^2), m (SD)	28.5 (5.0)	28.6 (5.1)	28.4 (4.9)	0.811
FFMI, m (SD)	19.6 (3.2)	19.4 (3.5)	19.6 (3.1)	0.682
Neoplasm†, n (%)	25 (12)	5 (8)	20 (15)	0.169
Endocrine, nutritional and metabolic diseases†, n (%)	134 (66)	44 (63)	90 (68)	0.522
Diabetes mellitus†, n (%)	63 (31)	18 (26)	44 (34)	0.308
Cardiovascular disease†, n (%)	127 (63)	45 (65)	81 (62)	0.664
Hypertension†, n (%)	96 (48)	35 (50)	62 (47)	0.702
Steps/day, m (SD)	7488 (4234)	6395 (3315)	8069 (4554)	0.009
Time in moderate to vigorous physical activity (>3 METs; h/day), med (P25-P75)	1.7 (1.2-2.2)	1.6 (1.1-2.0)	1.7 (1.3-2.4)	0.025
Intensity during physical activities (m/s^2), m (SD)	1.03 (0.27)	0.97 (0.23)	1.06 (0.28)	0.022
C-PPAC amount, med (P25-P75)	77 (67-83)	72 (67-83)	77 (67-83)	0.406
C-PPAC difficulty, med (P25-P75)	84 (73-94)	84 (71-94)	85 (74-94)	0.924
C-PPAC score, med (P25-P75)	79 (70-86)	79 (69-84)	79 (72-87)	0.456
Psychological				
Anxiety (HAD-A), m (SD)	5.4 (4.2)	5.6 (4.6)	5.3 (4.0)	0.636
Depression (HAD-D), m (SD)	3.6 (3.7)	3.3 (4.1)	3.8 (3.4)	0.435
Unwillingness to follow the intervention, n (%)	26 (13)	2 (3)	24 (18)	0.007
Stage of change: action, maintaining, finalizing§, n (%)	106 (53)	32 (45)	75 (57)	0.136
Self-efficacy‡ (0 to 10), med (P25-P75)	8 (7-10)	8 (6-10)	8 (7-10)	0.444

Data are presented as n (%), mean (SD) or median (P25-P75). FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; 6MWD: 6-min walking distance; mMRC: modified Medical Research Council; BMI: body mass index; FFMI: fat free mass index; MET: metabolic equivalent of task; C-PPAC: Clinical visit - PROactive Physical Activity in COPD; HAD-A: Hospital Anxiety and Depression scale- Anxiety; HAD-D: Hospital Anxiety and Depression scale- Depression.

** Living with a partner vs single, widowed or divorced.

¶ A COPD exacerbation was considered severe if the patient required admission to the hospital or the emergency department.

† ICD10 codes: C00 to D48 for Neoplasm; E00 to E90 for Endocrine, nutritional and metabolic diseases; E10 to E14 for Diabetes mellitus; I00 to I99 for Cardiovascular diseases; I10 to I15 for Hypertension.

§ Stage of change: action, maintaining, finalizing vs pre-contemplation, contemplation, preparation.

‡ Self-efficacy: Sure to go out for a walk every day (0 not sure- 10 completely sure).

Table F. Adjusted predictive factors of 12-month completion of a behavioral physical activity intervention in 202 COPD patients using multiple imputation.

	OR (95% CI)	p-value
Steps/day (per increase of 1000 steps)	1.11 (1.03-1.21)	0.010
Living with a partner (vs single/ widowed/ divorced)	2.67 (1.35-5.23)	0.005
Urban vulnerability index (per increase of 0.1 units)	0.71 (0.58-0.88)	0.001

OR: odds ratio; CI: confidence interval.

Table G. Variables related to 12-month response in COPD patients participating in a behavioral physical activity intervention using multiple imputation.

	Non-responders (12-month change in steps/day <1100)	Responders (12-month change in steps/day ≥1100)	p-value
	n=95	n=37	
Sociodemographic			
Age (years), m (SD)	69.2 (8.7)	66.0 (9.7)	0.077
Sex: male, n (%)	85 (89)	29 (78)	0.102
Smoking status, current, n (%)	24 (25)	10 (27)	0.835
Socioeconomic status, IIIM-IV-V, n (%)	67 (70)	27 (73)	0.772
Interpersonal			
Living with a partner**, n (%)	75 (79)	29 (78)	0.943
Grandparenting, n (%)	38 (40)	9 (24)	0.090
Active workers, n (%)	10 (11)	9 (24)	0.048
Environmental			
Urban vulnerability index (from 0 -lowest to 1 –highest), m (SD)	0.60 (0.18)	0.63 (0.15)	0.515
Recruitment season			
Spring, n (%)	24 (25)	9 (24)	0.873
Summer, n (%)	9 (9)	2 (5)	
Fall, n (%)	33 (35)	13 (35)	
Winter, n (%)	29 (31)	13 (35)	
Clinical			
FEV_1 (% pred), m (SD)	54.3 (16.4)	60.1 (17.1)	0.077
FVC (% pred), m (SD)	75.7 (16.3)	82.2 (17.9)	0.052
6MWD (m), m (SD)	493 (97)	512 (90)	0.299
Moderate to very severe dyspnea (mMRC ≥2), n (%)	27 (28)	9 (24)	0.635
Any severe¶ COPD exacerbation in previous 12 months, n (%)	9 (10)	1 (3)	0.210
Any severe¶ COPD exacerbation during follow-up, n (%)	13 (14)	9 (25)	0.149
BMI (kg/m²), m (SD)	28.4 (5.3)	28.4 (4.1)	0.998
FFMI, m (SD)	19.7 (3.3)	19.5 (2.6)	0.856
Neoplasm†, n (%)	14 (15)	6 (15)	0.929
Endocrine, nutritional and metabolic diseases†, n (%)	58 (61)	32 (86)	0.011
Diabetes mellitus†, n (%)	31 (33)	13 (36)	0.731
Cardiovascular disease†, n (%)	58 (61)	23 (63)	0.806
Hypertension†, n (%)	41 (43)	21 (56)	0.207
Steps/day, m (SD)	8241 (4824)	7625 (3794)	0.484
Time in moderate to vigorous physical activity (>3 METs; h/day), med (P25-P75)	1.7 (1.3-2.4)	1.8 (1.2-2.4)	0.805
Intensity during physical activities (m/s²), m (SD)	1.05 (0.27)	1.09 (0.31)	0.430
C-PPAC amount, med (P25-P75)	77 (65-83)	77 (68-85)	0.347
C-PPAC difficulty, med (P25-P75)	85 (74-94)	84 (73-94)	0.620
C-PPAC score, med (P25-P75)	79 (72-86)	81 (69-89)	0.749
Psychological			
Anxiety (HAD-A), m (SD)	5.3 (4.2)	5.4 (3.7)	0.859
Depression (HAD-D), m (SD)	3.8 (3.5)	3.7 (3.4)	0.859

Unwillingness to follow the intervention, n (%)	22 (23)	2 (5)	0.030
Stage of change: action, maintaining, finalizing§, n (%)	54 (57)	20 (55)	0.836
Self-efficacy‡ (0 to 10), med (P25-P75)	8 (7-10)	8 (6-10)	0.736

Data are presented as n (%), mean (SD) or median (P25-P75). FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; 6MWD: 6-min walking distance; mMRC: modified Medical Research Council; BMI: body mass index; FFMI: fat free mass index; MET: metabolic equivalent of task; C-PPAC: Clinical visit - PROactive Physical Activity in COPD; HAD-A: Hospital Anxiety and Depression scale- Anxiety; HAD-D: Hospital Anxiety and Depression scale- Depression.

** Living with a partner vs single, widowed or divorced.

¶ A COPD exacerbation was considered severe if the patient required admission to the hospital or the emergency department.

† ICD10 codes: C00 to D48 for Neoplasm; E00 to E90 for Endocrine, nutritional and metabolic diseases; E10 to E14 for Diabetes mellitus; I00 to I99 for Cardiovascular diseases; I10 to I15 for Hypertension.

§ Stage of change: action, maintaining, finalizing vs pre-contemplation, contemplation, preparation.

‡ Self-efficacy: Sure to go out for a walk every day (0 not sure- 10 completely sure).

Table H. Adjusted predictive factors of 12-month response to a behavioral physical activity intervention in 132 COPD patients using multiple imputation.

	OR (95% CI)	p-value
Active workers	3.00 (1.01-8.90)	0.048
Endocrine, nutritional and metabolic diseases†	4.19 (1.42-12.32)	0.009
Unwillingness to follow the intervention	0.20 (0.04-0.94)	0.042

OR: odds ratio; CI: confidence interval.

† ICD10 codes: E00 to E90 for endocrine, nutritional and metabolic diseases.

6. DISCUSSION

The results of the three papers, which have been included in the present thesis, have been discussed in detail in the respective paper sections. This discussion intends to complement these previous sections, by identifying the contribution of the individual papers to the aim of the thesis to better characterise ‘the determinants of physical activity behaviour in patients with chronic obstructive pulmonary disease’. This section will therefore expand on the two main findings of this thesis, that (1) the physical activity progression in COPD is heterogeneous, and that (2) psychological, interpersonal and environmental factors are important determinants of physical activity in COPD patients, beyond clinical factors. Moreover, this section aims to identify the implications of our work for future research, clinical management and health policy, and finally will discuss common strengths and limitations.

6.1 The physical activity progression in COPD is heterogeneous

One main finding of this thesis is that the natural progression of physical activity in COPD patients is heterogeneous and specifically that some patients may increase spontaneously their physical activity (*Paper 1*). This finding is important because it questions the common believe that all patients automatically decline in physical activity over time and may help to customize better physical activity interventions. We consider this finding provides three key messages.

First, it may be actually true that some COPD patients increase their physical activity. This group of patients represented 17% of our multi-centre European sample. A spontaneous increase in activity has been also observed in the control groups from some randomized controlled trials which investigated physical activity[123,127,128,147] or pharmacological interventions[148], based on the interpretation of variability measures. It could be argued that some of these patients could have increased physical activity due to being included in an intervention study. However, also some observational studies support the hypothesis that some COPD patients increase physical activity spontaneously.[149,150] Despite the lack of formal description on the proportion of patients increasing physical activity and statistical significance of it, all those previous findings support that the phenomenon may be true.

Second, in our study the mean change of physical activity levels over 12 months was virtually zero, in contrast to previous studies which reported a natural decline in physical activity of around 400 to 500 steps/day per year.[81,83,84,86] Our finding of three distinct patterns of physical activity progression was only possible thanks to the use of a hypothesis-free approach. We are not aware of other similar studies in COPD patients. However, in other contexts it was shown that the physical activity progression can indeed be heterogeneous. In patients with rheumatoid arthritis, three distinct trajectories of physical activity progression (stable high, decreasing and stable low) could be identified over a follow-up of 26 months.[151] Distinct physical activity trajectories have also been reported after pulmonary rehabilitation programmes.[152,153] These studies all aimed to identify distinct trajectories using k-means cluster analysis[151] or latent class growth analysis.[152,153] The results from these authors and our results suggest that for a complex topic such as physical activity behaviour, using the average may not be the best way to summarize information and to explain real-life processes.

Finally, our findings of different patterns of physical activity progression support the notion that the physical activity behaviour is driven by a variety of determinants some of which are not usually considered (see next section). Focusing on the four quadrants plotting ‘can do’ versus ‘do do’ discussed in the introduction, we found a 41% of patients who had the capacity to be active and indeed were active, similar to the reported proportions of 31% and 37% in two previous studies.[70,71] Although the functional exercise capacity in COPD patients is normally declining with the progression of the disease,[154] with the appropriate treatment, such as pulmonary rehabilitation or anti-obstructive therapy to improve dynamic hyperinflation, exercise capacity can improve and enable the patient to be physically more active. Thus, any further research reporting on physical activity changes should also consider the potential role of these interventions, as they become more widely available. Further, other factors are conceivable which could influence changes in physical activity behaviour in patients with sufficient exercise capacity, such as the evolution of a comorbidity, which could cause a decline in physical activity but also motivate a behaviour change (as has been shown for smoking cessation);[155] or retirement, which could imply time to be more active but also loss of necessity (and motivation) to leave the house, the routine of commuting or the support from colleagues. Despite increasing research into the physical activity behaviour of COPD patients, the changes remain often unpredictable. This underlines the need to understand better the determinants of physical activity in COPD patients.

6.2 Psychological, interpersonal and environmental factors are important determinants of physical activity in COPD patients, beyond clinical factors

The second main finding of this thesis is that psychological, interpersonal and environmental factors are determinants of physical activity in COPD patients, beyond clinical factors. This is relevant, because research has commonly focused on the clinical determinants of physical activity in COPD patients, which insufficiently explain the complex physical activity behaviour. The ecological framework of physical activity conceptualizes the complexity of the physical activity behaviour and depicts a broad range of determinants from several interrelated domains (i.e., the individual, the interpersonal, the environmental, the local and the global policy domain) which can determine physical activity.[112] With this thesis we aimed to contribute to this ecological framework and elucidate further the determinants of physical activity behaviour in COPD patients (Figure 8).

The role of the clinical characteristics in COPD patients (corresponding to the biological factors of the individual domain) has been largely explored previously and has been related consistently to the level of physical activity, although the cross-sectional design of most studies limited causal conclusions.[72] Our results support these previous findings; we identified in *Paper 1* lower exercise capacity and increased dyspnoea as predictors of the *Inactive* pattern (i.e., of patients with persistently low physical activity). However, if clinical characteristics were in a range to allow for physical activity and patients were less symptomatic, these characteristics could not explain a change in physical activity, i.e., they could neither predict among *Active* patients who would improve or decline (*Paper 1*), nor they were predictors of study response (*Paper* 3). It could be hypothesized that the determinants of engaging in physical activity, keeping physical activity, reducing physical activity or stopping physical activity are not the same and are not in the same domain. For example, it could be argued that typical COPD symptoms provoke a gradual progression towards lower activity, while a social event (e.g., retirement) can produce a sudden change towards increase (or decrease).[156] Research about other lifestyle behaviours (e.g., smoking) supports this notion.[157,158]

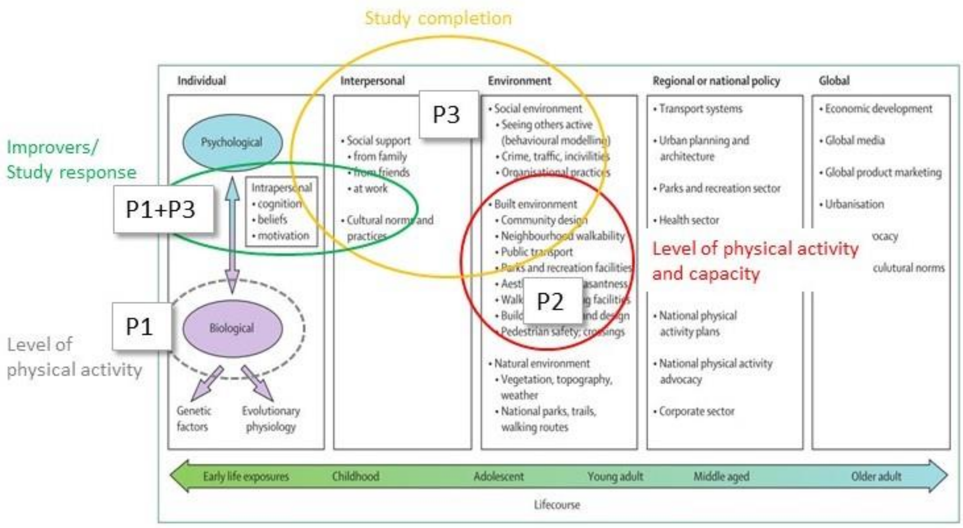

Figure 8. Contribution of this thesis to the ecological framework of physical activity in COPD patients, adapted from Bauman et al 2012.[112] P1: Paper 1, P2: Paper 2; P3: Paper 3. Reprinted from The Lancet, 380, Bauman AE, Reis RS, Sallis JF, Wells JC, F Loos RJ, Martin BW, et al., Correlates of physical activity: why are some people physically active and others not?, 258–271, doi:10.1016/S0140-6736(12)60735-1, Copyright © 2012, with permission from Elsevier.

Our findings from *Papers 1* and *3* suggest that psychological factors are indeed important for a change in physical activity. In *Paper 3* we identified that being an active worker, having an endocrino-metabolic disease and unwillingness to follow the intervention, all associated to individual motivation, were determinants of response to a behavioural physical activity intervention. However, and surprisingly, none of these factors could (in

Paper 1) determine among *Active* patients who would *improve* or *decline*. We assumed that further interpersonal and environmental factors, possibly related to motivation, or self-efficacy which have been identified as individual determinants of physical activity previously[159] may have played an important role in our *Active* patients to stimulate improvement or decline in physical activity. Overall, our findings seem to indicate that motivation and beliefs, and more generally the psychological component of the individual domain are essential for a change in the physical activity behaviour of patients who are clinically fit enough to have the option to be active. This remains an important area for future research.

We further identified a role of social factors (including both interpersonal factors and the social environment) in COPD patients' behaviour. Living with a partner was found a determinant of study completion (*Paper 3*). It has been shown previously that being in a relationship was associated with higher levels of physical activity in COPD patients.[70,160] Also another paper found that patients living with an active partner engaged in higher physical activity.[117] It seems therefore likely that social support from a partner can also make it easier for patients to complete a study program. Physical activity habit was also found a determinant of study completion (*Paper 3*). In our opinion, physical activity habit is not just a marker of less severe disease and fitness but also an indicator of the cultural practices of physical activity. Finally, neighbourhood vulnerability was also related to study completion (*Paper 3*). Neighbourhood vulnerability can actually be seen as barrier (e.g., through crime perception) or enabler (e.g., through more recreation facilities) of study completion. However, we found no evidence that these social factors could predict changes in physical activity behaviour, as they neither played a role as determinants of response in *Paper 3* nor as determinants of being an *Active Improver* or *Decliner* in *Paper 1*. Interestingly, our results of *Paper 2* showed that higher population density, which we also attributed to the social environment, was associated with lower physical activity levels, especially in COPD patients with pre-existing mental health conditions such as anxiety and depression. Altogether, this underscores the importance of social factors, and their interaction with psychological factors as determinants of physical activity behaviour.

We found a role for the natural environment (i.e., slope of the terrain) and the chemical environment (i.e., traffic related air pollution) in the physical activity behaviour (*Paper 2*). Our results showed that steeper slope was associated with better exercise capacity. This could suggest that for patients from a hilly neighbourhood it may be easier to be active. However, better exercise does not necessarily always translate into more physical activity as illustrated by the 'can do – don't do' quadrant of the physical capacity – physical activity concept[69–71] above and is also reflected in our *Paper 1* where we found that exercise capacity could not predict *Active Improvers* and *Decliners*. Our results also showed that higher levels of NO_2 which indicate higher traffic related air pollution were unfavourably associated with physical activity and several mechanisms are conceivable how air pollution could influence physical activity behaviour in COPD patients, such as by triggering the dyspnoea-physical inactivity vicious circle,[42,43] through increased awareness of the harms of air pollution, or due to intercurrent exacerbations or hospital admissions.[35,36] Finally, based on these results it would have been interesting to assess the role of the environment as driver for differences in the progression of physical activity in *Paper 1,* but unfortunately the environmental data was not yet available.

In summary, our research thus provides evidence that factors from the psychological, interpersonal and environmental domains are important for the physical activity behaviour of COPD patients, beyond clinical factors. Interestingly though, the role of the respective factors is not identical: factors related to motivation likely determine the change in physical activity in active patients and the response to a behavioural physical activity intervention; physical activity habits and social factors (including interpersonal factors and the social environment) seem to determine the completion of a physical activity intervention and the level of physical activity; and factors related to the natural environment and air pollution seem to be associated with the level of physical activity and capacity.

6.3 Implications

The results from this thesis have a number of implications for future research, clinical management and health policy. Future observational research around COPD and physical activity should explore the specific importance and interrelatedness of environmental, interpersonal and psychological variables in more detail. Experimental research needs to assess how the knowledge about these factors can be translated into strategies to effectively promote physical activity in COPD patients in a personalized manner (i.e., determine which interventions are most adequate for the patients' respective physical activity patterns). As psychological, interpersonal and environmental factors will likely co-determine how well a behavioural change will be maintained, health care providers should aim to embed physical activity interventions into a framework strongly linked to these domains and specifically consider and discuss with the patients barriers and facilitators in the neighbourhood, support through the partner and the intrinsic and extrinsic motivation to be physically active. Public health policy makers must be aware that neighbourhood vulnerability, some factors of the built environment and traffic related air pollution play a role in the physical activity of patients with a chronic disease, such as COPD; to optimally support physical activity in these patients a concerted action of health policy makers, city and transportation planners with a strong focus on the control of air pollution will be required which will hopefully have synergistic effects and also benefit the wider general public. In line with previous work,[161,162] our results support that the individual physical activity behaviour of COPD patients must be considered within the complex ecological framework and requires coordinated changes across several domains.

6.4 Strengths and limitations

The main strength of this thesis is our broad approach to the determinants and the measurement of physical activity behaviour. We tested as determinants of physical activity a large set of variables across several domains of the ecological framework of physical activity,[112] beyond the typical clinical characteristics, as thoroughly discussed above. Notably, we did not only study determinants of physical activity (as objectively measured via an activity monitor) but also the determinants of intervention completion, of intervention response, of patients' experience with physical activity and of functional exercise capacity. The interpretation of all these factors together allows a better picture on how the (broad) environment affects patients behaviour at a fixed moment of time and over time.

Moreover, the external validity of our work is higher than in many other papers from a comparable geographic setting. Patients in the Urban Training study[124] were recruited from several Catalan hospitals and primary care settings and our results therefore likely reflect better the situation at the population level than previous studies which were often based on hospital or rehabilitation settings alone. In *Paper 1* we pooled the data from the Urban Training[124] with those from the PROactive validation[78] study, thereby including patients across a broad spectrum of disease severities and physical activity in several European cities, which makes the results applicable to an even wider group.

We also need to acknowledge some limitations of this thesis. For some determinants of physical activity we had only a small sample size, which was especially of concern for *Paper 1* due to study pooling; some variables of interest such as dog walking, current pulmonary rehabilitation and the patients' knowledge of baseline physical activity or less frequent comorbidities could therefore not be investigated in *Papers 1* and *3*, respectively. Moreover, the data had been collected for studies with a different research focus, which narrowed the choice of variables; more detailed information related to motivation, the neighbourhood built environment (*Paper 2*) or barriers of physical activity (*Paper 3*) would have been desirable.

7. CONCLUSIONS

This thesis aimed to characterize better the determinants of physical activity behaviour in COPD patients. The results show that the natural progression of physical activity in COPD patients is heterogeneous. Moreover, the results support that psychological, interpersonal and environmental factors are important determinants of physical activity in COPD patients, beyond clinical factors.

Specifically, the conclusions of the three manuscripts included in this thesis are:

1. The natural change in physical activity over time in COPD patients is heterogeneous and three distinct patterns of physical activity progression have been identified: a predominant *Inactive* pattern, related to worse scores for clinical COPD characteristics, and two *Active* patterns, *Improvers* and *Decliners*, which cannot be predicted at baseline.

2. Higher population density and long-term NO_2 exposure are unfavourably associated with physical activity in patients with COPD, while a steeper slope relates to better exercise capacity.

3. Among a broad range of potential predictors of 12-month completion or response to a behavioural physical activity intervention, completion was generally determined by previous physical activity habits as well as interpersonal and environmental physical activity facilitators while response was related to diverse factors thought to modify the individual motivation to change to an active lifestyle.

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ANNEXES

Other co-authored papers

Moitra S, Foraster M, Arbillaga-Etxarri A, Marín A, Barberan-Garcia A, Rodríguez-Chiaradia DA, Balcells E, **Koreny M**, Torán-Monserrat P, Vall-Casas P, Rodríguez-Roisin R, and Garcia-Aymerich J. Role of environment on health-related quality of life in patients with COPD. Submitted

Presentations at international and local conferences

Koreny M et al. Association between air pollution and physical activity in patients with COPD. **Oral presentation at the European Respiratory Society 2020 Virtual International Congress.** September 7th - September 9th , online

Koreny M et al. Physical activity trajectories and their determinants in COPD: A cohort study. **Oral presentation at the European Respiratory Society International Congress.** September 28th – October 2nd, 2019, Madrid, Spain

Koreny M et al. Determinants of study completion and response to a 12-month physical activity intervention in COPD. **Oral presentation at the European Respiratory Society International Congress.** September 16-19th, 2018, Paris, France

Participation in the annual PhD conferences at ISGlobal.

Grants and awards

The abstract 'Physical activity trajectories and their determinants in COPD: A cohort study' was included in the **congress highlights** from the allied respiratory professionals published in ERJ Open Research: Oliveira A, Rutter M, Quijano-Campos JC, et al. ERS International Congress, Madrid, 2019: highlights from the Allied Respiratory Professionals' Assembly. *ERJ Open Res*. 2020;6(1):00034-02020. doi:10.1183/23120541.00034-2020.

ERS Grant for Best Abstract in Physiotherapy supported by POWERbreathe, for the abstract 'Determinants of study completion and response to a 12-month physical activity intervention in COPD' submitted to the European Respiratory Society International Congress. September 16-19th, 2018, Paris, France.

The abstract received also attention in an Editorial published in the Journal of Thoracic Disease: Blonshine J, Cruz J, Sajnic A, De Brandt J. European Respiratory Society International Congress **best abstract preview** from the allied respiratory professionals from assembly 9. In: *Journal of Thoracic Disease*. Vol 10. AME Publishing Company; 2018:S3010-S3016. doi:10.21037/jtd.2018.08.24

For the manuscript 'Determinants of study completion and response to a 12-month behavioural physical activity intervention in chronic obstructive pulmonary disease: A cohort study' (*Paper 1)* the **V Euskadi Physiotherapy Award in the Research category** was awarded to Ane Arbillaga-Etxarri, who was a co-author on this manuscript and who had conducted the Urban Training study.

El Colegio Oficial de Fisioterapeutas del País Vasco entrega los V Premios Euskadi de Fisioterapia

Los galardones reconocen la labor de diferentes profesionales en favor de la fisioterapia durante el último año.

Entre los premios destacan el galardón al fisioterapeuta del año, a la mejor trayectoria en fisioterapia y el reconocimiento a la mejor labor investigadora.

D. Jon Etxeberria Cruz, Delegado Territorial del Departamento de Salud en Gipuzkoa, y Dña. Inmaculada Moro, Subdirectora - Asesora de Enfermería y Fisioterapia de Osakidetza actuaron como maestros de ceremonia.

El Colegio Oficial de Fisioterapeutas del País Vasco (COFPV) celebro el pasado 14 de diciembre la entrega de galardones de los V edición de los Premios Euskadi de Fisioterapia con el objetivo de reconocer la labor de diferentes profesionales en el desarrollo y difusión de esta disciplina sanitaria a lo largo del ejercicio.

Estos premios con seis categorías han sido otorgados por un jurado profesional reunido bajo la presidencia del Colegio Oficial de Fisioterapeutas del País Vasco.

El Premio a la Investigación, uno de los motores imprescindibles para el desarrollo y la consolidación de la Fisioterapia, recayó en Ane Arbillaga por su trabajo "Determinantes de completar y obtener respuesta a una intervención de 12 meses de actividad física en la Enfermedad Pulmonar Obstructiva Crónica: Un estudio de cohorte".

Teaching activities

Instructor for the European Resuscitation Council (ERC) courses, organized by the Vienna Medical Chamber in cooperation with the Vienna Ambulance Service:

ERC–Advanced Life Support Provider Course March 08th – 10th, 2019, Vienna, Austria

ERC–Advanced Life Support Provider Course March 16th – 18th, 2019, Vienna, Austria