

**Effectiveness of an intervention of
urban training in patients with chronic
obstructive pulmonary disease (COPD):
a randomized controlled trial**

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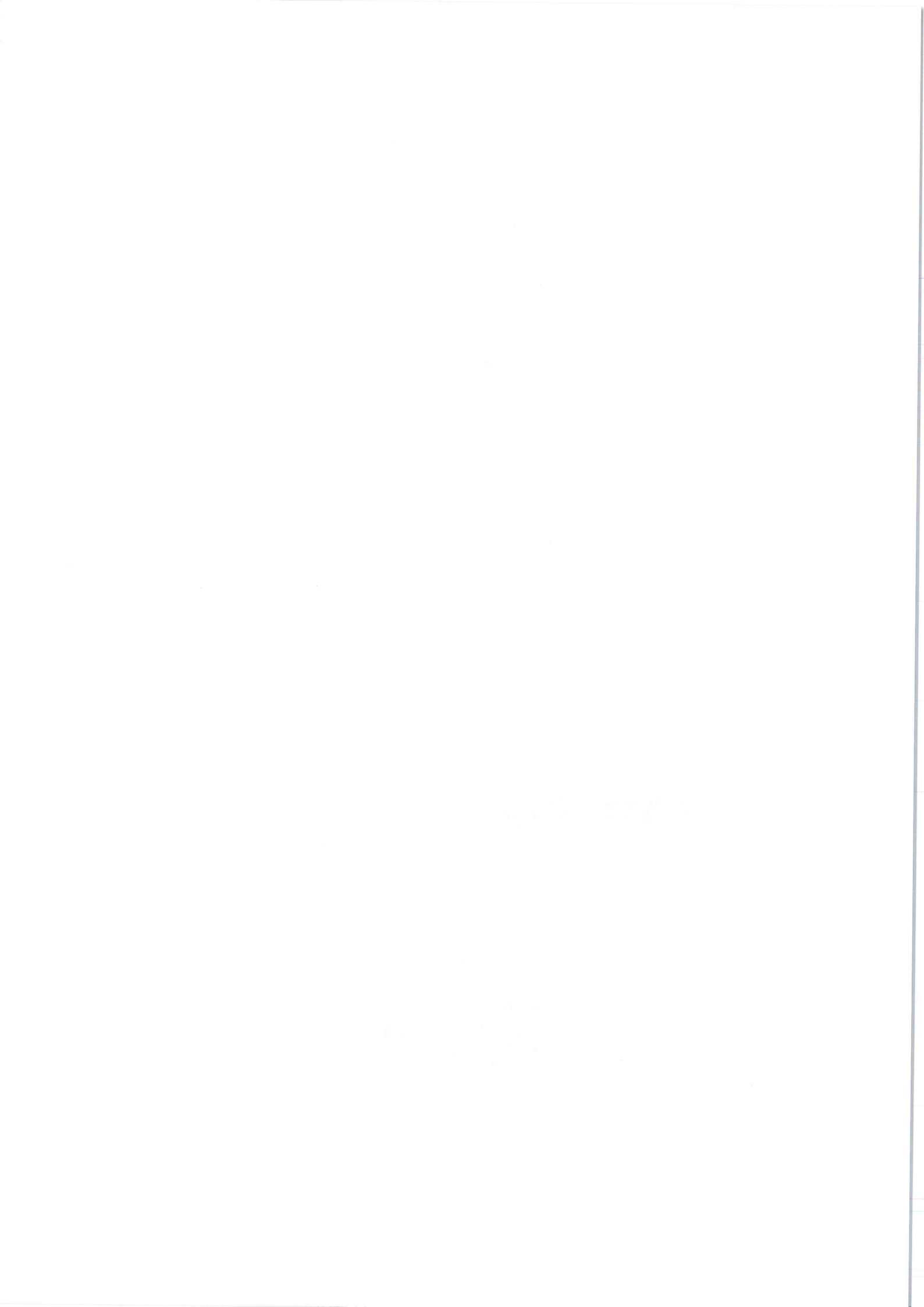
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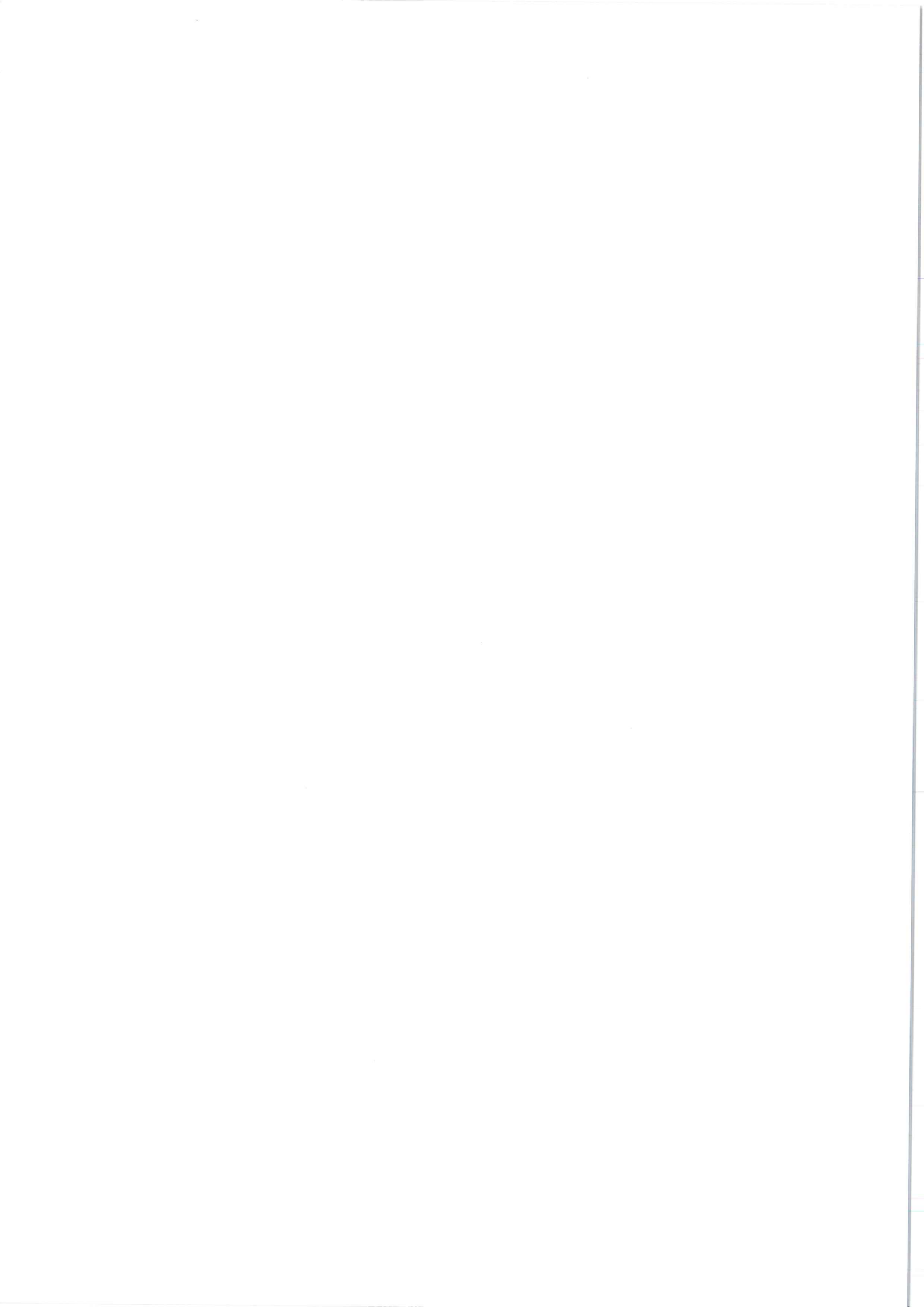
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*"Maite ditut maite geure bazterrak
lanbroak izkutatzen dizkidanean. Zer
izkutatzen duen ez didanean ikusten
uzten orduan hasten bainaiz izkutukoa...
nere baitan pizten diren bazter
miresgarriak ikusten."*

*"M'estimo els nostres racons quan la
boira me'ls amaga. Quan no em deixa
veure què és el que oculta, llavors
començo a descobrir el que està
amagat... aquells racons meravellosos
que comencen a sorgir a dins meu."*

Mikel Laboa



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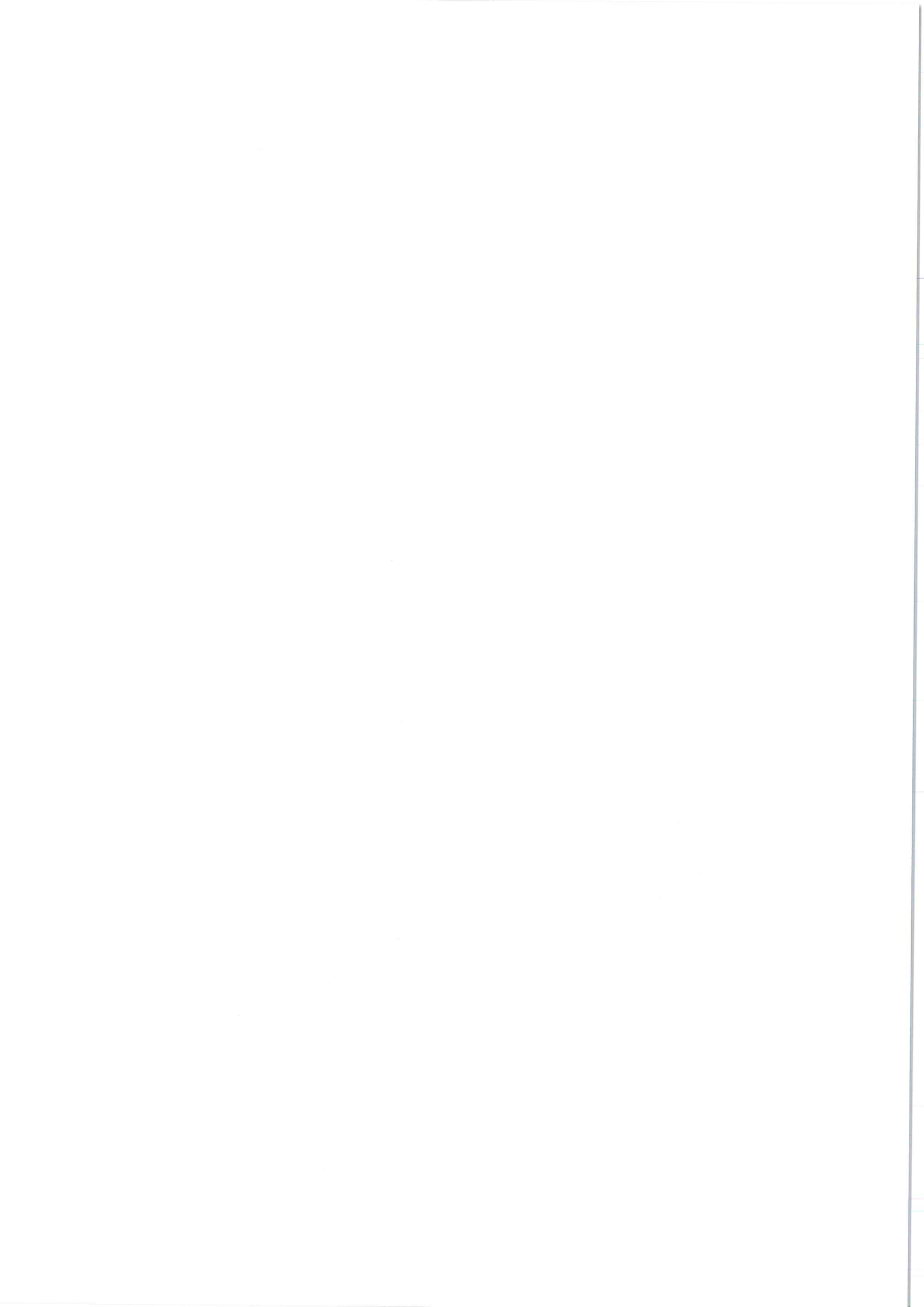
I aprofitant el context, voldria ressaltar el factor humà del CREAL, d'on m'emport grans persones amb mi. Començo doncs amb l'Ignasi, l'autèntic aventurer del CREAL, gràcies per ser com ets. El Martínez, que si tenir-te de "profe" i les classes particulars de Stata van ser un plaer, compartir amb tu les birres fins a límits desconeguts ha estat la hòstia. Al Figuerola, gràcies per fer-me veure que hi ha vida més enllà dels trenta y tantos. I a l'Esther gràcies per la teva naturalesa i autenticitat. Joan Forns, Magda Bosch, Mireia Gascón, Gloria Carrasco i Laia Font, gràcies per la vostra amistat, festes, xerrades, moments i balls. I gràcies també a la Gemma, Ana, Raquel, Anne Elie, Maria, Albert, Carles, i Marcos per l'ambient a la sala i per tots els Ca la Nuris. I al

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ABSTRACT

Background: High levels of physical activity have been related to better prognosis in patients with chronic obstructive pulmonary disease (COPD). However, so far no interventions have proven effective to modify physical activity in COPD. The aims of this thesis are to design, validate and test a novel behavioral intervention (Urban Training) in the community to modify physical activity behavior in COPD patients at the long term.

Methods: We designed and validated walking trails of different intensities in public spaces of five seaside Catalan municipalities using a gas analyzer to measure physiological response to walking trails in 10 COPD patients and 10 healthy subjects. A total of 411 COPD patients recruited from 33 primary care centers and 5 tertiary hospitals were allocated 1:1 to Urban Training intervention or usual care. The intervention used behavioral strategies by combining motivational interviewing, walking trails, pedometers, calendars, website, pamphlets, phone text messages, walking groups and support phone number to increase physical activity. Patients were followed for 12 months.

Results: (1) The physiological response to and energy expenditure on unsupervised walking the Urban Training trails increased according to the predefined trails' intensity and did not change across trails of the same intensity in different public space. (2) The Urban Training intervention improved physical activity after 12 months of follow-up only in patients adherent to the intervention. No effect of the intervention was found in hospital admissions, exercise capacity, body composition, health-related quality of life, anxiety, or depression. (3) Dog walking and grandparenting were associated with a higher amount and intensity of physical activity in COPD patients independent of airflow

limitation and other psychological or biological parameters. Environmental characteristics of green or blue spaces surrounding patients' home were not associated with physical activity.

Conclusions: The present thesis highlights the importance of behavioral strategies and social determinants to design future interventions aiming to enhance physical activity in COPD patients.

Keywords: chronic obstructive pulmonary disease, physical activity, social determinants, intervention, behavioral change, walking trails.

RESUM

Antecedents: Els alts nivells d'activitat física han estat relacionats amb un millor pronòstic en pacients amb malaltia pulmonar obstructiva crònica (MPOC). Però, per ara cap intervenció ha demostrat ser eficaç en modificar l'activitat física en la MPOC. Els objectius d'aquesta tesi són dissenyar, validar i provar una nova intervenció que es centra en el comportament (Entrenament Urbà) i que es dur a terme en la comunitat per modificar al llarg termini l'activitat física en pacients amb MPOC.

Mètodes: Es van dissenyar i validar els circuits de diferents intensitats en diferents espais públics de Catalunya utilitzant un analitzador de gasos per mesurar la resposta fisiològica a caminar en els circuits en 10 pacients amb MPOC i 10 voluntaris sans. Un total de 411 pacients amb MPOC van ser reclutats de 33 centres d'atenció primària i 5 hospitals terciaris. Després van rebre aleatòriament 1:1 la intervenció d'Entrenament Urbà o l'assistència habitual. La intervenció va utilitzar estratègies de comportament combinant entrevistes motivacionals, circuits per a caminar, podòmetres, calendaris, pàgina web, pamflets, missatges de text, grups per a caminar i un número de telèfon per augmentar l'activitat física. Els pacients van ser seguits durant 12 mesos.

Resultats: (1) La resposta fisiològica i la despesa energètica al caminar en els circuits d'Entrenament Urbà van augmentar segons la intensitat predefinida, i no van canviar entre circuits de la mateixa intensitat de diferents espais públics. (2) La intervenció d'Entrenament Urbà va millorar l'activitat física després de 12 mesos de seguiment només en els pacients que van complir amb la intervenció. No es va trobar cap efecte de la intervenció en els ingressos hospitalaris, capacitat d'exercici, composició corporal, qualitat de vida relacionada amb la salut, ansietat, o depressió. (3) Treure el

gos a passejar i cuidar dels néts van mostrar associació amb més quantitat i intensitat d'activitat física en malalts amb MPOC independentment de la limitació al flux aeri i altres paràmetres psicològics i biològics. Les característiques mediambientals dels espais verds o blaus que envolten els domicilis dels pacients no es van associar amb l'activitat física.

Conclusions: La present tesis destaca la importància de les estratègies de comportament i dels determinants socials per dissenyar les intervencions futures per augmentar l'activitat física en pacients amb MPOC.

Paraules clau: Malaltia pulmonar obstructiva crònica, activitat física, determinants socials, intervenció, canvi de comportament, circuits per a caminar.

PREFACE

This thesis was written at the Centre for Research in Environmental Epidemiology (CREAL) between January 2012 and August 2016. The thesis has been directed by Dr. Judith Garcia-Aymerich and consists of a compilation of scientific publications co-authored by the PhD candidate in accordance with the procedures of the Biomedicine PhD program of the Department of Experimental and Health Sciences. The thesis includes an abstract, a general introduction, a rationale, the objectives, the results (3 original scientific papers), a general discussion, and final conclusions.

This thesis was done in the context of the Urban Training project: “Effectiveness of an intervention of urban training in patients with chronic obstructive pulmonary disease (COPD): a randomized controlled trial”, which aims to design, validate and assess the effectiveness of an intervention to improve physical activity in COPD. The PhD candidate was responsible for the design and implementation of the intervention, coordination of the fieldwork and the quality control, the statistical analyses, and writing of the manuscripts.

The PhD candidate has also participated in the project “Elaboration of reference equations for the six-minute walk test and the incremental walking shuttle test in healthy adult Spanish population” and in other studies, all related to physical activity, exercise, physiology and COPD, which have resulted in other manuscripts that the candidate has co-authored during the pre-doctoral period (listed at the end of this thesis). A list of congress contributions is also included.

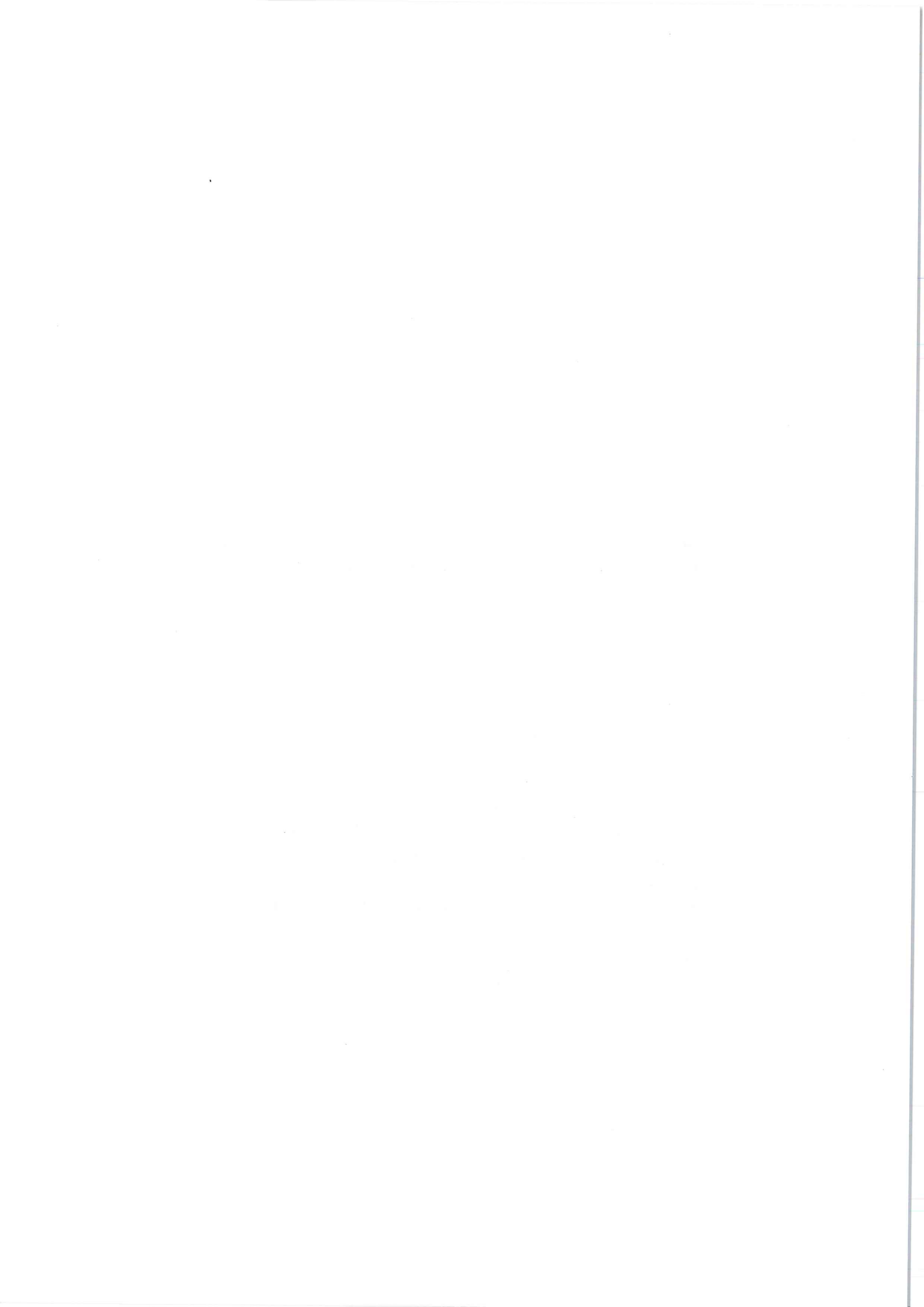


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1-INTRODUCTION

1.1 Chronic Obstructive Pulmonary Disease:

1.1.a Definition and symptoms

Chronic Obstructive Pulmonary Disease (COPD) is a respiratory disease characterized by persistent, progressive, and not fully reversible airflow limitation. It is associated with the inhalation of noxious particles or gases, primarily tobacco and biomass smoking (i.e. cooking and heating with solid fuels) that produces a chronic inflammatory response in the airways (1,2). The airflow limitation is caused by a mixture of fixed narrowing of small airways, lung parenchymal destruction, excessive mucus secretions, and, in many cases, increased airway responsiveness.

The main symptoms of COPD are chronic and progressive dyspnea, cough, and sputum production, although the airflow limitation may develop without the presence of any symptoms (3). Dyspnea is considered the major cause of disability and anxiety associated with the disease. Initially dyspnea appears during exercise, then during activities of daily living, and ultimately even at rest (4).

The progression of COPD is characterized by exacerbations, which are acute events characterized by a worsening of respiratory symptoms that are beyond normal day-to-day variations leading to changes in medication and often require hospitalization (1).

1.1.b Prevalence, morbidity and mortality

Prevalence of COPD is high, increases with age, varies across countries probably due to different cigarettes and biomass smoking patterns, and is more common in men than

in women (1,2). The results of a large epidemiological study conducted in Spain demonstrated an overall prevalence of COPD in the population between 40 and 80 years of age of 10.2% (15.1% in men and 5.6% in women) (5).

The morbidity of COPD is also high and increases with age. COPD represented a 28.2% of hospital discharges for respiratory illnesses in patients between 45 and 85 years in 2013 in Spain (6). The economic costs of COPD are substantial mostly due to the amount of health resources required such as hospital admissions, pulmonary rehabilitation services, ambulatory care, drugs and lost work days.

The mortality from COPD has increased constantly in recent decades and it is estimated that in 2030 COPD will rank as the fourth leading cause of death worldwide (3).

1.1.c Diagnosis and classification

The main criterion to diagnose COPD is a post-bronchodilator forced expiratory volume in the first second to forced vital capacity ratio (FEV_1/FVC) ≤ 0.70 . Four stages have been proposed to classify the severity of airflow limitation, according to the American Thoracic Society, the European Respiratory Society (ATS/ERS), and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (7,8)

Mild: $FEV_1 \geq 80\%$ predicted

Moderate: $50\% \leq FEV_1 < 80\%$ predicted

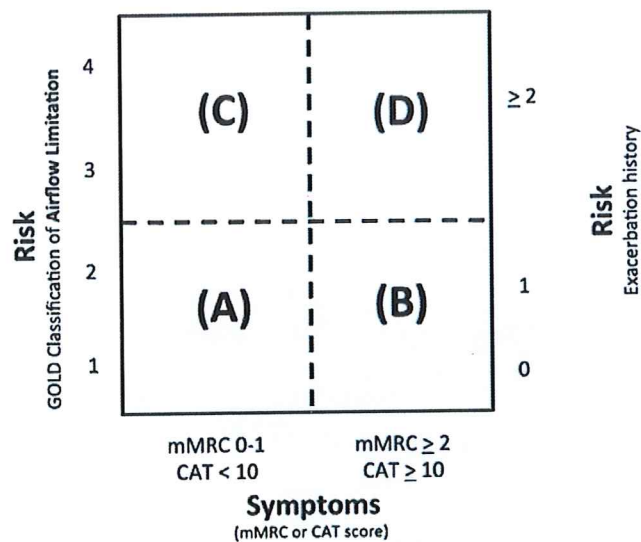
Severe: $30\% \leq FEV_1 < 50\%$ predicted

Very Severe: $FEV_1 < 30\%$ predicted

There are other factors that affect the presentation and evolution of the disease, such as the degree of dyspnea, exercise limitation, and impaired health-related quality of life

(9). Therefore, GOLD proposes a COPD classification based on the level of dyspnea and future risk of exacerbations, in addition to airflow limitation. It consists of 4 groups (A to D) as illustrated in Figure 1.

Figure 1. Combined COPD assessment proposed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Adapted from Vestbo et al (7).



1.1.d Extrapulmonary effects

COPD is currently recognized as a systemic condition due to several extrapulmonary manifestations which are: musculoskeletal wasting, cachexia, cardiovascular disease, depression, osteopenia, and chronic infections (10). They contribute to the disease burden, limit patients' functional capacity, worsening dyspnea, reduce health-related quality of life and increase risk of mortality (2,10,11).

As a consequence of complex interactions between extrapulmonary effects, symptoms, and psychological factors, COPD patients have reduced exercise capacity (12,13) and physical activity (14,15). This process is often called 'the dyspnea inactivity vicious circle' (Figure 2): the dyspnea during daily activities forces the patients to lessen their physical activity level; consequently, patients suffer a physical deconditioning with reduced exercise capacity which, in turn, aggravates dyspnea and other symptoms.

Figure 2. The dyspnea-inactivity vicious circle in patients with COPD adapted from Reardon et al. (14).



Physical inactivity is one of the extrapulmonary consequences of COPD and has a central importance in the above-mentioned vicious circle.

1.2. Physical activity in COPD

1.2.a Definitions

Physical activity is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" (16). In other words, any physical movement that burns kilocalories, whether is walking, gardening or typing a computer, is considered physical activity. It is a complex behavior influenced by factors at different levels, including genetic, social and environmental (17). Physical activity is often confused with other related concepts such as exercise, physical fitness and exercise capacity.

Exercise is defined as "a subcategory of physical activity which is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective." (16). For example, lifting weights in a gym with the explicit goal of maintaining fitness is considered exercise.

Physical fitness is defined as "the ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy leisure-time pursuits and to meet unforeseen emergencies". This is a physiological term that determines the functional capacity and is related to health components. Cardio-respiratory endurance, muscular endurance and strength, body composition, and flexibility are components of physical fitness.

In the context of chronic diseases, a concept very close to physical fitness is exercise capacity. It refers to "the maximum amount of physical exertion that an individual can sustain, operationalized as the maximum work load" that can be achieved during an exercise capacity test (18). It is assessed by means of common procedures carried out in

functional capacity laboratories; the distance walked in 6 minutes walking test is an example of an exercise capacity test.

1.2.b Levels

Several publications have shown that patients with COPD spend less time being active (walking and standing), more time on sedentary positions (sitting and lying) and make lower intensity movements compared to aged-matched healthy peers (19–21). This physical activity reduction appears early in the disease, and is independent of disease severity (22,23), cultural background, and geographical origin of patients (24–27). Besides, a recent study showed that physical activity may decline more in COPD patients than in the healthy elderly (28).

In addition, patients with COPD do not adhere to the physical activity recommendations of the American College of Sports Medicine (ACSM) and the American Heart Association (AHA) (29). In general, a healthy individual is considered physically active if one of the following criteria from the American College of Sports Medicine (ACSM) and the American Heart Association (AHA) is met: 1) 30 min of at least moderate-intensity physical activity on ≥ 5 days every week; or 2) 20 min of vigorous-intensity physical activity on at least 3 days every week. For older adults and the chronically sick population it is accepted that the activities are accumulated in shorter bouts usually lasting 10 min. For example, three bouts of moderate (three times 10 min) or two bouts of vigorous (two times 10 min) physical activity (30). Interestingly, while about 25% of the COPD patients fulfilled the recommendation of engaging in ≥ 30 consecutive minutes of moderate physical activity five or more days per week, this proportion increased to almost

60% when the duration of ≥ 30 min per day was achieved through the accumulation of bouts of ≥ 10 min duration(31).

1.2.c Effects

In the general population, physical inactivity is one of the ten leading causes for the major non-communicable diseases such as cardiovascular diseases, cancer and diabetes. Insufficient physical activity contributes substantially to the global burden of disease, disability and death (32–34), and it is estimated that 6-10% of deaths from the principal non-communicable diseases is due to physical inactivity (35).

In COPD, higher physical activity levels have been related to better prognosis and quality of life, and to reduced risk of hospitalization, exacerbations, and mortality (36–38). In fact, physical activity is the most important independent predictor of all-cause mortality in COPD population (39). Furthermore, evidence shows that lower levels of physical activity are associated with lower exercise capacity and musculoskeletal function, and more systemic inflammation and comorbidities (37,40,41).

1.2.d Determinants

A systematic review of the literature (37) concluded that there is poor evidence about determinants of physical activity in COPD patients. Hyperinflation, exercise capacity, dyspnoea, previous exacerbations, gas exchange, systemic inflammation, quality of life and self-efficacy were consistently related to physical activity, but often based on cross-sectional studies and low-quality evidence (Table 1).

Table 1. Quality of evidence for different determinants (Table 1a and 1b) and outcomes (Table 1c) of physical activity in COPD, as identified in 86 studies. Adapted from Gimeno-Santos E. Thorax 2014.

Table 1 a. Quality of evidence for sociodemographic, lifestyle and environmental determinants of physical activity

Determinant	N studies	Direction established	Control for confounding	Directness	Consistency	Strength	Low precision	Other	Confidence rating
Age	6	na	na	yes	-1 ¹	no	no	no	+++ (moderate)
Alcohol consumption	2	-2 ²	-1 ⁴	yes	-1 ¹	no	-1 ⁶	no	+ (very low)
Cultural group	3	-1 ²	na	-1 ³	-1 ¹	no	no	no	+ (very low)
Day of the week	3	-2 ²	-1 ⁴	yes	-1 ¹	no	no	no	+ (very low)
Education	3	-2 ²	-1 ⁴	yes	-1 ¹	no	no	no	+ (very low)
Marital status	2	-2 ²	-1 ⁴	yes	-1 ¹	no	no	no	+ (very low)
Sex	6	na	na	yes	-1 ¹	no	no	no	+++ (moderate)
Smoking habit	3	-2 ²	-1 ⁴	yes	-1 ¹	no	-1 ⁶	no	+ (very low)
Socioeconomic status	2	-2 ²	-1 ⁵	yes	-1 ¹	no	no	no	+ (very low)
Working status	3	-2 ²	-1 ⁴	yes	-1 ¹	no	no	no	+ (very low)

Table 1 b. Quality of evidence for functional and clinical determinants of physical activity

Determinant	N studies	Direction established	Control for confounding	Directness	Consistency	Strength	Low precision	Other	Confidence rating
BODE index	5	-22	-15	yes	-11	no	no	no	+ (very low)
Body Mass Index	5	-22	-15	yes	-11	no	no	no	+ (very low)
Cardiovascular	2	-22	-15	yes	-11	no	-16	-17	+ (very low)
Dyspnea	7	-22	-15	yes	yes	no	no	no	+ (very low)
Emotional status	2	-22	yes	yes	-11	no	no	no	+ (very low)
Exercise capacity (VO ₂ max, 6MWD)	9	-22	-15	yes	yes	no	no	no	+ (very low)
FEV ₁	14	-12	-15	yes	-11	no	no	no	+ (very low)
FVC	2	-12	yes	yes	-11	no	no	-112	+ (very low)
Gas exchange (DLco)	2	-22	-14	yes	yes	no	no	no	+ (very low)
Gas Exchange (PCO ₂)	2	-22	-14	yes	yes	no	no	no	+ (very low)
Gas Exchange (PO ₂)	2	-22	-14	yes	yes	no	no	no	+ (very low)
Hyperinflation	5	-22	yes	yes	yes	no	no	no	++ (low)
Osteoarticular condition	2	-22	-14	yes	-11	no	-16	no	+ (very low)
Previous exacerbation	3	-12	-14	yes	yes	no	no	-17	+ (very low)
Quality of Life/Health Related Quality of Life	5	-22	-14	yes	yes	no	no	no	+ (very low)
Self-efficacy	2	-22	yes	yes	yes	no	no	-17	+ (very low)
Systemic inflammation	2	-22	-15	yes	yes	no	no	-17	+ (very low)

Table 1c. Quality of evidence for outcomes as a result of different levels of physical activity

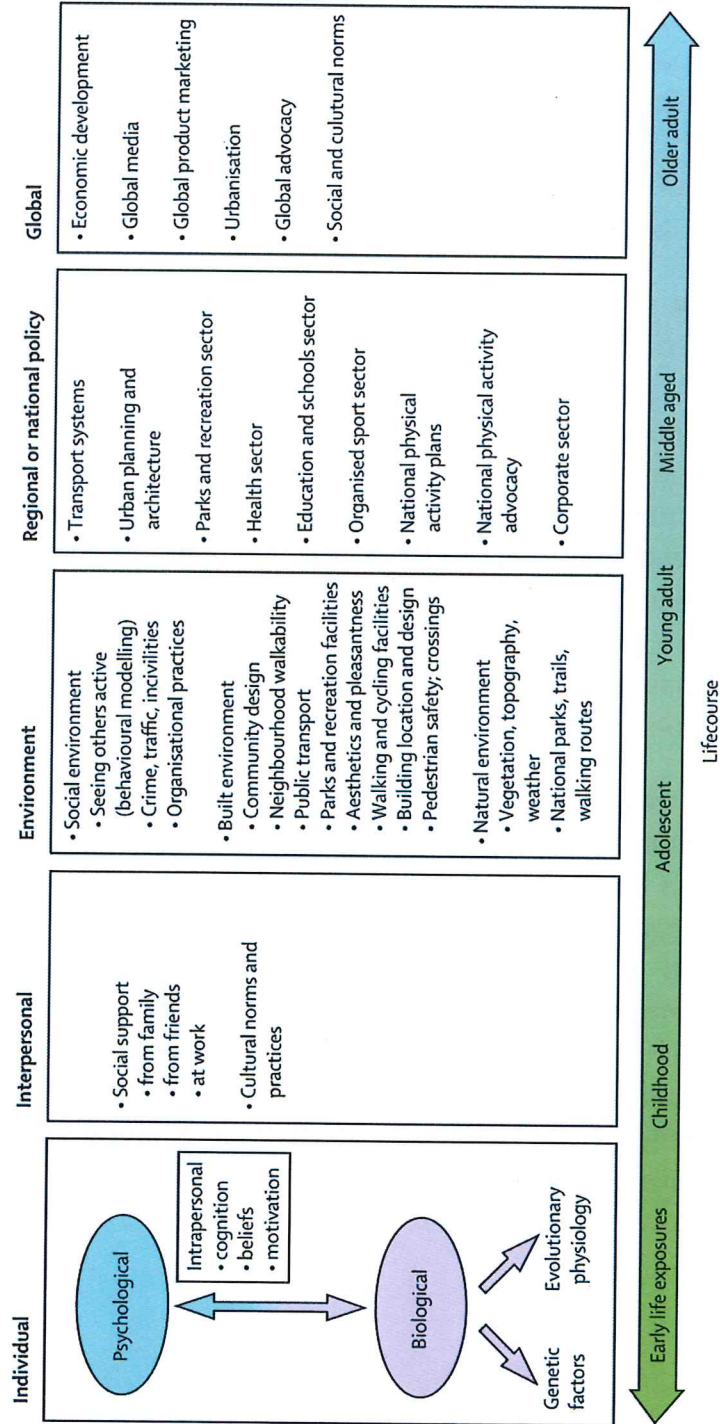
Outcome	N studies	Direction established	Control for confounding	Directness	Consistency	Strength	Low precision	Other	Confidence rating
Balance	2	-12	-18	yes	-11	no	no	-112	+ (very low)
Bone mineral density	2	-22	-18	yes	-11	no	no	-113	+ (very low)
Dyspnea	2	-12	yes	yes	yes	no	no	-113	++ (low)
Exacerbations	8	yes	yes	yes	yes	no	no	-113	+++ (moderate)
Exercise capacity (6MWD)	4	-12	yes	yes	yes	no	no	-113	++ (low)
FEV ₁	2	-22	yes	yes	yes	no	no	-113	+ (very low)
Mortality	7	yes	yes	yes	yes	no	no	-113	+++ (moderate)
Quality of Life / Health-related quality of life	4	yes	yes	yes	-11	no	no	-113	++ (low)

This systematic review also identified that the number of studies investigating the determinants of physical activity in COPD patients is lower than the studies that have tested interventions in this population. It has been hypothesized that this lack of research about determinants is one the reasons for one of the reasons why an intervention in these patients' physical activity has not yet been identified. (42).

Recently, a study followed a cohort of COPD patients and measured every year their levels of physical activity for up to 5 years. In multivariable analysis, determinants that were independently associated with lower levels of physical activity were: lower exercise capacity, older age, active working status, more smoking pack-years, more fatigue, male sex, lower educational levels, not being in fitness programs, more depression, lower lung function, lower overall health status, and more prescription drug use (28). Some of these factors are consistent with previous research while others need replication.

A common limitation to all existing research about determinants of physical activity in COPD patients is that it has been limited to the individual factors' area (biological and psychological). This is in contradiction with the currently accepted socio-ecological models about physical activity determinants in the general population and other chronic diseases. (17,43,44) These models explain physical activity as a result of the effect of psychological, biological, or socio-environmental characteristics, and their interaction, both at the individual and population levels (Figure 3) (17).

Figure 3. Ecological model of the determinants of physical activity from Bauman. The Lancet 2012.



1.2.e Interventions

Physical activity has rarely been included as an outcome of therapeutic trials in COPD. Very recently, a systematic review reported that bronchodilators (mostly tiotropium and indacaterol) had been reported to increase physical activity in 4 out of 6 studies in patients with moderate-to-very severe airflow limitation (45). However, these results should be interpreted cautiously due to the very low quality of the evidence. Other pharmacological COPD treatments have not been tested in relation to physical activity.

Strategies like nutritional supplementation (46) and long-term oxygen therapy (47) have also been explored, but the results are inconsistent and of low to very low quality.

Pulmonary rehabilitation is the most studied intervention to increase physical activity in COPD patients and has been shown to be effective in improving muscle function, reducing dyspnea, and increasing exercise capacity (48). Theoretically, these improvements may allow patients to break with their inactivity vicious circle and become more active. Yet, the translation of the improvements in exercise capacity and symptoms into increments in physical activity levels has no evidence and is controversial (45,49–51). This situation has been attributed to the fact that this intervention, similar to the others previously mentioned, does not primarily aim to modify patients' behavior (48,50–52).

Actually, to achieve the goal of a more active COPD population in the long term, two aspects are essential: 1) improving exercise capacity and limiting symptoms, and 2) generating (and/or sustaining) a behavior change towards an active lifestyle (48,51,53). The first of these goals has been traditionally approached with pulmonary rehabilitation. However, the second is newer and requires knowledge and

expertise from other disciplines. In general, to promote a change in subjects' behavior, different behavioral strategies have been studied in chronically ill patients. Self-monitoring, goal setting, contracting, feedback, administering specific positive consequences by rewards, stimulus control like cues, prompts, or reminders located strategically have been shown to be effective in changing chronic patients' behavior (54,55).

In COPD patients, the study of behavioral strategies has grown only in the last few years. Some interventions have included and combined diverse behavioral strategies such as self-monitoring, self-efficacy, motivation, goal setting, identification of barriers, feedback, and prompts (54). Interestingly, these strategies can be approached with different elements. For instance, motivational interviewing, health coaching and counseling can help with self efficacy, motivation, goals setting and identification of barriers. (56–58); pedometers, diaries and Internet based programs help with feedback and motivation (56,57,59–61); and text message, phone calls, education sessions and informative pamphlets cover reminders and solving problems (58,59,62). Furthermore, some of these studies also included exercise training sessions by pulmonary rehabilitation (57,59), or used the intervention itself to do exercise (56).

In general, most of these studies have been positive in increasing physical activity levels. However, most of them have been limited in time (up to 3 months) so it is unknown if the behavioral change would have been maintained over time (45). Three of these studies followed patients around a year (56,58,62), and only one of them showed a sustained long term (>15 months) increase in physical activity. Yet, this effect was limited to patients who were not sufficiently active (<10000 steps) at baseline (56). Of note, this study had as a main characteristic the combination of elements based on more than one behavioral strategy: lifestyle physical activity

counseling, motivational interviewing, pedometer, and a diary (56).

This last mentioned study is in accordance with the recommendations published recently for future studies aimed at increasing physical activity in COPD patients, which emphasizes the combination of different behavioral strategies besides physical training (53,54,63). Other suggestions are strictly related with behavioral strategy components: inquiring into individuals' motivation, offering education components like counseling or printed material, increasing confidence and self-efficacy, establishing personalized goals, collecting objective physical activity data to provide feedback and adapt goals over time by pedometers, monitoring compliance by diaries, providing the option to contact a health-care professional to overcome barriers, encourage adherence, and resolve doubts (76,83).

Another aspect that should be taken into account is the necessity of showing whether interventions that are effective for the general healthy population can be applicable to patients with the physiological characteristics of COPD (7,64,65). To this effect, these interventions should be tested previously to show if they are suitable, acceptable and understood by the target population. For example, a study offered COPD patients an intervention designed originally for the general healthy population (giving information about 32 local urban walking circuits) after a brief pulmonary rehabilitation program, and it showed an increase in physical activity levels up to 9 months after the program (66). Another study assessed the physiological response to the Nordic Walking exercise modality in COPD, and results suggested that this could be appropriate to enhance community based training programs because it generates higher exercise intensity at the same rate of perceived exertion compared with standard walking (67).

Finally, it is recommended that behavioral interventions are personalized and adapted to patients' capabilities, pleasure, environment characteristics and cultural context (17,51). Interestingly the only intervention that showed a long term improvement in physical activity considered that patients were free to choose the location, type, and time point of the activity (56). Likewise, the scientific literature also suggests that what patients can and want to do should be understood to personalize and integrate the activity fully into patients' common daily lifestyle (42,54,63).

As reviewed above, although the research using new approaches to increase physical activity in COPD patients has increased exponentially, unfortunately, the evidence about which kind of intervention is effective at the long term is still weak and scarce (37,45).

1.3. A new approach to physical activity promotion in COPD patients

1.3.a The potential of socio-environmental factors

In the previous section we have identified that one of the key missing areas in physical activity and COPD research is the investigation of the role of social and environmental characteristics. These are important in the behavior of older population, partly because retirement makes subjects spend a significant part of the day on the vicinity of their home.

The research about how socio-environmental characteristics influence physical activity practice has identified three main dimensions: social inequality, interpersonal relationships, and neighborhood characteristics (68). In patients with COPD, the social inequality dimension has been the most studied, using common measures of socio-economic status (SES) and

socio-demographic determinants, but the results are inconsistent and quality of the evidence is low or very low (28,37).

In contrast with research in the general population, interpersonal relationships and neighborhood characteristics have never been studied in this population. Social interpersonal aspects of neighborhood cohesion (69,70), social participation (71), social contacts (72), talking to neighbors (73), walking the dog (74,75) or grandparenting (76–78) have been related to higher levels of physical activity in middle-aged and older healthy adults. Similarly, neighborhood characteristics such as the proximity and number of green spaces around home (79,80), neighborhood walkability (i.e. how friendly an area is to walk from home to nearby destinations) street connectivity (the number intersections within a neighborhood) (81–85), recreation facilities (86,87), and restricted car access (88) also have been related to higher levels of physical activity in healthy elderly populations. In contrast, traffic, neighborhood deprivation (89,90), high crime levels (84) and bad aesthetics (91) were related negatively.

In future, knowing how these socio-environmental factors may influence physical activity practice in the subjects with COPD will help to design effective interventions in this population.

1.3.b Filling the gaps in physical activity interventions for COPD patients

As reviewed above, the research using new approaches to increase physical activity in COPD patients has increased exponentially. Unfortunately, the evidence of which kind of intervention is effective at the long term is still weak and scarce (37,45). Some issues have been identified in previous

sections that researchers and health professionals should take into account in future research aiming to design interventions:

1. *To focus on generating behavioral change as well as physical training and symptom improvement:*

Any intervention aiming to increase physical activity in COPD patients should both offer physical training and induce behavioral change (92). In this thesis work, we understand that any intervention needs to be designed as an individually tailored intervention to target better each patient abilities and behavior. Different behavioral strategies should form the base of physical activity enhancement, especially self-efficacy and motivation. The identification of barriers and difficulties of daily physical activity also constitute a relevant topic as it offers the opportunity for patients themselves to search for a solution.

2. *To investigate on physical activity determinants beyond the disease's individual patho-physiologic factors:*

The focus of physical activity determinants should be widened. In addition, interventions designed to be carried out in the community, away from hospital and the traditional medical context, go beyond individual patho-physiological determinants as they take into account the potential of socio-environmental factors at every moment.

On the other hand, if public spaces are part of interventions, social-interpersonal aspects and neighborhood characteristics must be analyzed to evaluate the real possibilities that interventions could have to integrate into patients' natural neighborhood and social life.

Likewise, interventions built on activities with direct impact on the interpersonal socialization, such as walking outdoors, could be better integrated with patients' lifestyle.

The importance of environment to promote physical activity is reflected in the World Health Organization recommendation which suggests that urban planning policies should promote an active lifestyle (93,94).

3. To offer common activities fully integrated in patients' lifestyle and adapted to patients:

Some research has suggested that interventions linked to cultural habits may improve adherence (95). For example, Tai chi in Hong Kong, and Nordic Walking in Austria were proposed as alternatives to pulmonary rehabilitation for COPD patients (96–98). These activities are, like walking in the case of Mediterranean cities, common activities fully integrated into the local culture (99,100) and therefore more conducive to facilitate viability and above all, adherence and compliance.

2-RATIONALE

Increasing physical activity of COPD patients has become a key target to improve patients' prognosis. However, research has not yet determined which interventions could modify the physical activity behavior in the long term. Existing interventions are ineffective in modifying physical activity or they only do so at the short term (<3 months).

It is likely that such a lack of effectiveness can be attributed to the poor knowledge about the determinants of physical activity in COPD patients. Also, the understanding of the physical activity behavior has so far been limited to individual patho-physiological factors, without consideration of social or environmental influences.

This doctoral thesis aims to advance the research about physical activity in COPD by setting a broader framework that includes social and environmental dimensions to both the identification of determinants and the design of interventions. The final objective is to test an intervention adapted to the physiological abilities of the patients, as well as to their environment and preferences, in order to generate effect at the long term.

3-OBJECTIVES

3.1. General objectives:

To design a novel behavioral intervention in the community to modify physical activity behavior in COPD patients at the long term, by learning from and overcoming limitations of previous experiences, and to test it in COPD patients from a wide spectrum of severity.

3.2. Specific objectives:

1. To validate the design of Urban Training trails by (i) assessing the physiological response to and the energy expenditure on unsupervised walking trails of different intensities in COPD patients, and (ii) assessing the physiological response to walking trails of the same intensity designed in different spaces in young healthy subjects.
2. To assess the efficacy and effectiveness of the Urban Training intervention in physical activity level after 12 months of follow-up in patients with COPD. Secondary outcomes included hospital admissions for exacerbation, exercise capacity, body composition, health related quality of life, anxiety and depression.
3. To assess the relationship of novel socio-environmental factors (dog walking, grandparenting, neighborhood deprivation, residential surrounding greenness, and residential proximity to green or blue spaces) with the physical activity level of stable mild-to-very severe patients with COPD from five Mediterranean municipalities.

4-RESULTS

4.1. Manuscript 1

Ane Arbillaga-Etxarri, Jaume Torrent-Pallicer, Elena Gimeno-Santos, Anael Barberan-Garcia, Anna Delgado, Eva Balcells, Diego A. Rodríguez, Jordi Vilaró, Pere Vall-Casas, Alfredo Iurtia, Robert Rodriguez-Roisin, Judith Garcia-Aymerich, Urban Training Study Group.

Validation of Walking Trails for the Urban Training™ of Chronic Obstructive Pulmonary Disease Patients.

PLoS One. 2016 Jan 14;11(1):e0146705.

4.2. Manuscript 2

Ane Arbillaga-Etxarri, Elena Gimeno-Santos, Eva Balcells, Anael Barberan-Garcia, Marta Benet, Nuria Celorrio, Anna Delgado, Carme Jané, Alicia Marín, Pilar Ortega, Diego A Rodríguez, Robert Rodriguez-Roisin, Mónica Monteagudo, Nuria Montellà, Laura Muñoz, Pere Toran, Jaume Torrent-Pallicer, Pere Simonet, Carlos Martín-Cantera, Eulàlia Borrell, Pere Vall-Casas, Jordi Vilaró, Judith Garcia-Aymerich.

Effectiveness of an intervention of Urban Training in patients with chronic obstructive pulmonary disease (COPD): a randomized controlled trial

Submitted

4.3. Manuscript 3

Ane Arbillaga-Etxarri, Elena Gimeno-Santos, Anael Barberan-Garcia, Marta Benet, Eulàlia Borrell, Payam Dadvand, Maria Foraster, Alicia Marín, Mónica Monteagudo, Robert Rodriguez-Roisin, Pere Vall-Casas, Jordi Vilaró, Judith Garcia-Aymerich, on behalf of the Urban Training Study Group.

Socio-environmental determinants of physical activity in patients with chronic obstructive pulmonary disease (COPD).

Under second review in Thorax

4.1. Manuscript 1

Validation of Walking Trails for the Urban Training™ of Chronic Obstructive Pulmonary Disease Patients

Arbillaga-Etxarri A, Torrent-Pallicer J, Gimeno-Santos E, Barberan-Garcia A, Delgado A, Balcells E, et al. [Validation of Walking Trails for the Urban Training™ of Chronic Obstructive Pulmonary Disease Patients](#). PLoS One. 2016 Jan 14;11(1):e0146705. DOI: 10.1371/journal.pone.0146705

4.2. Manuscript 2

Effectiveness of an intervention of Urban Training in patients with chronic obstructive pulmonary disease (COPD): a randomized controlled trial

Ane Arbillaga-Etxarri, Elena Gimeno-Santos, Eva Balcells, Anael Barberan-Garcia, Marta Benet, Nuria Celorrio, Anna Delgado, Carme Jané, Alicia Marín, Pilar Ortega, Diego A Rodríguez, Robert Rodriguez-Roisín, Mónica Monteagudo, Nuria Montellà, Laura Muñoz, Pere Toran, Jaume Torrent-Pallicer, Pere Simonet, Carlos Martín-Cantera, Eulàlia Borrell, Pere Vall-Casas, Jordi Vilaró, Judith Garcia-Aymerich.

Submitted

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Urban Training™ is trademark registered in Spain (ref 3502702/9); European trademark registration is in process.

Trial registration: NCT01897298

ABSTRACT

Objective: To assess the efficacy and effectiveness of the Urban Training intervention on physical activity level after 12 months of follow-up in patients with chronic obstructive pulmonary disease (COPD).

Design: Prospective, multicenter, parallel-group, double-blinded, randomized controlled trial.

Setting: 33 primary care centers and 5 tertiary hospitals from five Catalan seaside municipalities: Viladecans, Gavà, Barcelona, Badalona and Mataró, October 2013 to February 2016.

Participants: 411 patients, aged <45 years, with a COPD diagnosis according to spirometric criteria.

Interventions: Participants were allocated using random blocks to Urban Training intervention (n=204) conducted in public spaces which used behavioral strategies by combining motivational interviewing, walking trails, pedometers, calendars, website, pamphlets, phone text messages, walking groups and phone number; or to usual care group (n=207) which consisted of general physical activity recommendation.

Main outcome measures: The primary outcome was the physical activity (steps per day) measured by accelerometer, and the secondary were COPD hospital admissions, exercise capacity, body composition, health-related quality of life, anxiety and depression after follow-up. Modified intention to treat (MITT) and per protocol (PP) analysis were performed, the latter including only patients adherent to their corresponding intervention and adjusted for the determinants of the intervention.

Results: A total of 284 patients completed the 12 months follow-up assessment. In the MITT analysis, there was no difference between groups in the number of steps (7807 steps/day in the usual care vs 7843 in the intervention group, $p=0.943$). However, a large difference was observed in the PP analysis (7807 vs 9100 steps respectively, $p=0.035$). There were no differences in secondary outcomes between groups in either MITT or PP analyses. The number of adverse effects was very similar between groups.

Conclusions: The Urban Training intervention, which combined behavioral strategies and unsupervised physical training in outdoor public spaces, increased physical activity after 12 months of follow-up in adherent patients. No effect of the intervention was found in hospital admissions, exercise capacity, body composition, health-related quality of life, anxiety, or depression.

Abstract word count: 325

Key words: chronic obstructive pulmonary disease, urban training, physical activity, behavioral change, active aging.

INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) are substantially less active than their healthy peers (1,2) as a consequence of COPD-related progressive airflow limitation, decreased exercise capacity, systemic effects, comorbidities and behavioral changes (3–5). In addition, reduced levels of physical activity have been consistently related to worse COPD prognosis in terms of exacerbations, quality of life and mortality (6–8). Therefore, there is a need to define and test interventions that increase physical activity in COPD patients.

Pharmacological therapy and pulmonary rehabilitation are effective to improve muscle function, reduce dyspnea and increase exercise capacity (9–11), which theoretically could result in physical activity increases. However, research so far has not shown that these therapies increase physical activity, which has been attributed to the fact that they do not primarily aim to modify patients' behavior (5,12).

Actually, the effectiveness of an intervention to improve physical activity depends on its capacity to produce behavior changes. To this object, interventions have included and combined diverse behavioral strategies such as self-monitoring, self-efficacy, motivation, goal setting, identification of barriers, feedback, and prompts (13). Interestingly, these strategies can be approached with different elements. For instance, motivational interviewing can help both to identify barriers and setting goals. Similarly, a pedometer may help both self-monitoring and providing feedback. Unfortunately, despite the large body of research showing effectiveness of interventions testing behavioral strategies to change physical activity in chronically ill patients (14), this research in COPD patients has to date been limited. Some studies have tested interventions consisting of motivational interviewing, health coaching, and counseling (15–17); pedometers, diaries and

Internet based programs (15,16,18–21); and text messages, phone calls, education sessions and informative pamphlets (17,18,22). In general, most of these studies have reported positive effects in increasing physical activity levels of COPD patients (23). However, most of them were evaluated only at short term (up to 3 months) (16,18–20,24). Moreover, of the four studies that followed patients more than one year (15,17,21,22), only one of them showed a sustained increase in physical activity, which was limited to patients who were insufficiently active at baseline (<10,000steps/day) (15). Interestingly, this study combined lifestyle physical activity counseling sessions, motivational interviewing, a pedometer and a diary.

Finally, it has been reported that interventions to increase physical activity, in addition to including behavioral strategies, need to be adapted to the local context and use the existing social structures of a community (25). Along these lines, Tai chi has been proposed as potentially successful intervention in some cultures where it is a common activity fully integrated in patients' life (26–28). In Mediterranean cities, where walking is an extended practice well integrated into the daily life routine of the elderly population (29,30), walking in public spaces has been suggested as a feasible and potentially effective strategy to increase physical activity even in COPD patients (31).

We hypothesized that an Urban Training intervention, consisting of motivational interviewing, availability of outdoor trails specifically designed for the exercise training of COPD patients (32), and support (by pedometer, calendar, group sessions, phone calls and text messages) could encourage COPD patients to increase their walking activity and maintain such active behavior at the long term.

The aim of this study was to assess the efficacy and effectiveness of the Urban Training intervention on physical

activity level after 12 months of follow-up in patients with COPD. Secondary outcomes included COPD hospital admissions, exercise capacity, body composition, health-related quality of life, anxiety and depression.

METHODS

Study design

This is a prospective, multicenter, parallel-group, double-blinded, randomized controlled trial registered at the clinicaltrials.gov online database (NCT01897298) and reported according to the 2010 CONSORT statement (33).

Study patients

Patients were recruited from 33 primary care centers and 5 tertiary hospitals from five Catalan (34) seaside municipalities: Viladecans, Gavà, Barcelona, Badalona and Mataró. First, we selected all subjects with a diagnosis of COPD according to the American Thoracic Society and European Respiratory Society (ATS/ERS) criteria (9) who were visited in any of the participating health centers. Exclusion criteria were: age < 45 years, spending > 3 months/year away from their home address, living more than 500 meters from any of the Urban Training trails (32) used for the study, mental disability, severe psychiatric disease, comorbidity limiting survival at one year, or any other severe comorbidity according to medical history. All candidate patients were approached in random order within each municipality (of note, Viladecans and Gavà were grouped because they are conurbated municipalities). Patients were consecutively included until the end of the recruitment period specified for each geographical area. Only clinically stable patients (defined as at least 4 weeks without antibiotics of oral corticosteroids) were included. We finally included a total of 411 COPD patients: 189 from Barcelona, 30 from Badalona, 73 from Mataró, and 119 from Viladecans/Gavà. The study was approved by the Ethics Committee of all participating institutions and all participants provided written informed consent.

Randomization

Randomization sequence was created using Stata 12.0 (StataCorp, College Station, TX, USA) software and was stratified by center with a 1:1 allocation to the Urban Training intervention or usual care groups using random blocks sizes of 6, 8 and 10. Randomization began on October 30, 2013, and final outcome assessments were completed on February 29, 2016.

Interventions

Both groups received the standard pharmacological and/or non-pharmacological treatment for COPD, including pulmonary rehabilitation, to the discretion of their physician and without intervention by the research team.

Usual care

Patients assigned to usual care group received general health counseling and were delivered the European Lung Foundation information pamphlet of "Living an active life with COPD" which includes the recommendation to complete at least 30 minutes of moderate physical activity at least 5 days per week. This recommendation was considered ethically necessary and corresponds to appropriate clinical practice (35).

The Urban Training intervention

Patients assigned to the intervention group received the Urban Training intervention, always proposed as an extra to the physical activities of patients' daily life and in no case as a substitutive activity. The intervention consisted of the following 6 elements (Figure 1):

(1) **Motivational interviewing.** At baseline, a respiratory physiotherapist adequately trained used motivational interviewing techniques centered on empathy, reflective listening, affirmation, and rolling with patients' resistances

(resolve personal difficulties, barriers and limitations) to elicit a behavioral change from patients. Information on the remaining components of the intervention (see below) was provided during this interview, to varying degrees depending on how the conversation progressed. During this 1 hour interview, patients were questioned about their self-efficacy and motivation level in a scale between 0 and 10; and the stage of change (pre-contemplation, contemplation, preparation, action, maintenance and relapse) was identified by the trained physiotherapist. During the follow-up period, the physiotherapist administered additional motivational 5-10 minutes phone calls at different frequencies depending on patients' baseline motivation and self-efficacy levels. Patients with low motivation (score <8) were called at 15, 30, 60 and 180 days; with moderate level (motivational score >8 but self-efficacy <8) at 30, 60 and 180 days; and with high motivation and self-efficacy (both scores >8) at 180 days.

(2) **Urban Training walking trails.** During the motivational interview participants received a dossier containing various maps of walking trails from different areas according to their mobility options and preferences. The design and validation of such walking trails has been previously published (32). [Briefly, we designed walking trails of different intensities (low-green trail, moderate-orange trail or high-red trail) in walkable public spaces (boulevards, beaches and parks) of the five seaside municipalities included in the study by combining urban resources (stairs, ramps and types of surfacing). A validation study showed that the physiological response to and energy expenditure on unsupervised walking these trails increased according to the predefined trails' intensity and did not change across trails of the same intensity in different public spaces.] The physiotherapist provided a complete explanation about trails' characteristics and instructed patients to walk a trail at least 5 days per week on the

appropriate intensity trail (low-green, moderate-orange or high-red) depending on patients' dyspnea and 6-minute walk distance (6MWD). Patients were instructed to increase progressively the volume (number of walks per day on the same trail) and/or the intensity of the trails during the following 12 months according to their symptoms and motivation. The walking pace was recommended to keep a dyspnea Borg scale between 4 and 6 (36). In case of exacerbation or any other health problem, the physiotherapist explained strategies for self-care, and how to adjust exercise as needed during and after these episodes.

(3) **Pedometer and calendar.** During the motivational interviewing, patients were provided a pedometer (Onstep 50 Geonate and Omron) and were trained to wear it all day, and particularly during walks. The pedometer was used to help patients keep track of their physical activity, so they could maintain or increase their daily step number during the 12 months of follow-up. In addition, a calendar also was provided and patients were instructed to note the walk compliance sticking a green, orange or red color sticker (depending on trail intensity) and the number of steps walked every day (according to the pedometer). The calendar was personalized to each patient by including a note about when a change in trails intensity was expected. Calendars also had educational and motivational information.

(4) **Pamphlets, website and phone text messages.** During the interview, patients received the same European Lung Foundation information pamphlet as the usual care group. They were also provided with the link to the project website (<http://www.entrenament-urba.cat/>) which contains information about the research group, project, general counseling about physical activity, links to other relevant websites, group activity schedule and contact phone number. Finally, patients were requested to provide a personal cell

phone number where they would receive phone text messages every 2 weeks with educational or motivational phrases.

(5) **Walking group.** Once per month during the follow-up period patients could join a group for walking a trail accompanied by an experienced physical activity trainer. The schedule of each walking group was provided in calendars, on the website and text messages.

(6) **Phone contact.** Patients were invited to telephone the physiotherapists for any questions related to the intervention or their physical activity practice if needed at any moment during follow-up.

Study procedures

The assessment consisted of 4 visits (Figure 2) carried out by trained technicians. In the 1st visit, all patients answered an interviewer-administered questionnaire, including data on socio-demographic variables, smoking status, dyspnea (by the modified Medical Research Council scale [mMRC]), health-related quality of life and clinical characteristics scored by the Clinical COPD Questionnaire (CCQ) and COPD Assessment Test (CAT), and anxiety and depression symptoms (by the Hospital Anxiety and Depression scale [HAD]). Exercise capacity was assessed by 6-minute walk test (6MWT). Body composition was assessed by weight, height, body mass index (BMI) and the fat free mass index (FFMI) from physical examination and bioelectrical impedance. Finally, lung function was assessed by forced expiratory volume in the first second (FEV₁) and forced vital capacity ratio (FVC) before and after bronchodilator. All tests were determined following standardized methodology.

During the same first visit, patients were provided an accelerometer to measure objectively physical activity. We

used the Dynaport accelerometer (McRoberts BV, The Hague, The Netherlands), previously validated for COPD (37,38). Patients were instructed to wear it for a week on the center of lower back with an elastic strap. A valid physical activity measurement was defined as a minimum of 3 days with at least 8 hours of wearing time (39). Of note, all patients fulfilled this criterion (median wearing days 7, range 4-13; median recording time 15h, range 11.1-15 of 15 h maximum from 7 am to 10 pm).

The second visit was carried out after seven days. Patients delivered the accelerometer and were randomized to the corresponding randomization arm. Physiotherapists provided the corresponding interventions to both groups as detailed above.

After 12 months of follow-up (3rd visit), patients answered questionnaires and performed tests following the same methods used in the 1st visit. The accelerometer was delivered and patients returned it one week later (4th visit). In this case, 3 patients out of 287 (1%) did not fulfill the criterion of wearing time per day and were consequently excluded for important protocol deviation. Among included patients, median wearing days was 7, range 4-7; median recording time 14.8 h, range 10.2-15. During this 4th visit, patients also answered a questionnaire about satisfaction with the study components and potential adverse effects experienced during walking in the previous 12 months.

We also collected the number of hospital admissions for COPD exacerbations in the 12 months prior to the 1st visit, and during the follow-up period from administrative medical records.

Patients, technicians administering questionnaires and performing the tests, and data analysts were kept blinded to

the allocation. The physiotherapists who administered the intervention were aware of the allocated arm.

Quality control consisted of centralized training sessions, rapid support and supervision of all fieldworkers, periodic recording and checking of questionnaires and tests to identify possible deviations from the protocol, double verification of case report forms, the double entry of data, and at least one visit to each of the participating centers during data collection.

Study outcomes

The primary outcome was physical activity using the number of steps per day. Secondary outcomes were hospital admission due to COPD exacerbation, exercise capacity by the 6-minute walk distance, body composition measured as BMI and FFMI, health-related quality of life by the CAT and CCQ total scores, HAD-anxiety score and HAD-depression score.

Statistical Analysis

Based on previous research about distribution of steps per day (primary outcome) in COPD patients and effectiveness of behavioral interventions in the elderly (40), we calculated sample size with the software GRANMO 7.10. The study was powered to detect a difference of 775 steps per day between groups, requiring 142 patients in each group (two-sided $\alpha=0.05$, power 80%, correlation between baseline and final steps ≥ 0.7). Assuming a 30% drop outs rate during follow-up, we planned to recruit 202 participants to each group (404 in total).

The characteristics of the usual care and intervention groups at baseline were reported as mean and SD for normal distributed quantitative variables, median and 25th-75th percentiles for non-normal distributed variables, and number and percentage for qualitative variables. We performed both modified intention to treat (MITT) and per protocol (PP)

analyses. The MITT sample included all randomized patients who completed final visit (see definitions in Supplementary text 1). This group was used to test the effectiveness of the intervention, by comparing primary and secondary outcomes between groups using Student's t, Kruskal Wallis, or Chi^2 , according to the distribution of the outcome variables. Since intention to treat analyses underestimate the treatment effect in presence of non-adherence (41), we pre specified a PP sample including patients who were adherent to their corresponding intervention (Supplementary text 1), which was used for the efficacy analysis. We built linear, Poisson, or negative binomial regression models, depending on the distribution of outcome variables, using intervention arm and variables related to adherence as exposure variables (Supplementary Table 1), since previous literature had shown that this adjustment may reduce the selection bias produced by a differential distribution of the reasons that moved participants to be adherent (41). All analyses were conducted with Stata 14.0 (StataCorp, College Station, TX, USA).

RESULTS

A total of 553 stable COPD patients were assessed for eligibility, and 411 patients were finally included and underwent randomization (Figure 3). During the study period, 127 patients dropped out (58 (28%) in the usual care group, and 69 (33%) in the intervention group). Consequently, 149 in the usual care group and 135 in the intervention group constituted the modified intention to treat population (69% of the initial study population). All patients in the usual care group but only 90 out of 135 in the intervention group reported being adherent to the corresponding intervention and were included in the per protocol analysis.

Patients were mostly male (85%), and had mean (SD) age 69 (8.5) years, mild-to-very severe COPD (FEV_1 56.3 (17.4) % of the predicted value), and preserved exercise capacity (486 (95) m in the 6MWD) (Table 1). They walked more than a mean of 7000 steps per day. Baseline characteristics were similar in the two study groups.

Table 2 shows no difference in the number of steps between groups at 12 months in the MITT analysis (7807 steps/day in the usual care vs 7843 in the intervention group, $p=0.943$), but a large difference in the PP analysis (7807 vs 9100 steps respectively, $p=0.035$). There were no differences in COPD admissions during follow-up, exercise capacity, body composition, quality of life, anxiety, or depression between groups in either MITT or PP analyses.

There were no differences in adverse effects during or after walks between groups (Table 3).

DISCUSSION

This randomized controlled trial showed that the Urban Training intervention is more efficacious than usual care in increasing physical activity after 12 months in patients with COPD, with no safety concerns. However, the intervention was not effective as per the modified intention to treat analysis, suggesting it improves physical activity only in adherent patients. No effect of the intervention was found in hospital admissions, exercise capacity, body composition, health-related quality of life, anxiety, or depression, in either analysis approach.

This intervention increased physical activity in COPD patients after 12 months of follow-up, in a magnitude exceeding the minimal important difference for steps in these patients (42). Positive effects at the long term had only been reported by one previous trial, which showed an increase in physical activity when analysis was restricted to patients insufficiently active (<10000 steps) at baseline (15). In contrast, other behavioural interventions have not achieved long term changes in physical activity (17,22). The fact that motivational interviews, pedometers and diaries/calendars were used in both positive studies and none of the negative ones suggests these could be key elements for the success of the intervention. Indeed, behavioural research has consistently shown that motivation, self-monitoring and feedback are the cornerstone of all behavioral strategies (14,43). In comparison with previous studies, the Urban Training intervention was minimal: the initial interview lasted <1 hour and only a phone call was required during the follow-up period. Despite this, the change in physical activity was maintained 12 months later, while the previous positive trial had required several sessions over few months (15). We hypothesise that the proximity of trails to patients' home

together with the cultural habit of walking in our setting may have contributed to this success. Considered together, these factors make Urban Training an attractive intervention potentially feasible because of its simplicity and reduced burden.

The Urban Training intervention did not improve exercise capacity in the MITT nor the PP analyses. This was unexpected since, based on the physiological response generated when walking the trails during the validation study (32), we hypothesised that the intervention could produce long term effects similar to those of typical exercise training interventions. This discrepancy could be due to the lack of supervision of training intensity (e.g., keeping the pace that generates a dyspnea or fatigue score between 4 and 6 in the Borg scale) during the daily walking in the trails. In addition, possibly as a result of this limitation, the intervention did not modify any of the other secondary outcomes (hospital admissions, body composition, quality of life, anxiety or depression). Another potential explanation for the lack of effects in these outcomes is that our patients already had a relatively good health status as per their values in exercise capacity, quality of life, anxiety or depression; therefore they had little room for improvement. All things considered, our findings suggest that future interventions in the community aiming to increase exercise capacity should include tools, e.g., telemonitoring, that allow supervision of training intensity (44). Alternatively, behavioural interventions aiming to increase physical activity should be accompanied or preceded by effective interventions to increase exercise capacity, such as pulmonary rehabilitation. In short, it seems possible that combining capacity and behavioural approaches will result in multiplicative effects on both parameters (45).

It could be argued that the fact that the intervention is efficacious according to per protocol analysis but not effective

by the intention to treat analysis is a limitation of the current study. Indeed, both approaches were pre specified in our analysis plan given previous reports in the literature about poor adherence to behavioral interventions (15) and the well known argument against ITT analysis that it underestimates intervention effects in situations of non adherence (41). We agree that the per protocol analyses very likely overestimate the potential benefits that would be observed in real life if the Urban Training intervention as currently configured was widely deployed. However, supporting the deployment of a behavioral intervention after its first trial results should not be an objective. Nonetheless, we believe that the Urban Training intervention has high potential for the COPD population. Our findings also suggest that understanding and eventually acting on the determinants of adherence to behavioral interventions is a key step in future COPD research. In our study, only education and baseline exercise capacity were related to intervention adherence, but there is no previous data on this topic to compare with.

Another limitation of the study is the lack of assessments during the follow-up period, which could have been used to give feedback to the patients and would have allowed researchers to distinguish between short and long term effects. Also, the proportion of patients lost to follow-up, very close to that of previous research (15,17,22), could have reduced statistical power and be responsible for the lack of observed intervention effects. However, there were no differences between groups in mean values of most outcomes, indicating that the negative results cannot be attributed to this phenomenon. Finally, given the cultural nature of the behavior under study and its relevant geographic and climatic determinants, our results cannot be extrapolated to countries different in these characteristics.

Strengths of the study are the novelty of the intervention, the large sample size, and the measure of physical activity using an accelerometer. In addition, patients were recruited from primary care and hospitals of several municipalities, with barely any exclusion criteria, which allowed a wide distribution in physical activity, COPD severity and relevant socio-demographic and clinical parameters, and generalizability of our results to the whole COPD population. With regard to the intervention, its simplicity and reduced burden make it possible to adapt it to other populations and/or settings.

CONCLUSION

The Urban Training intervention, which combined behavioral strategies and unsupervised physical training in outdoor public spaces, increased physical activity after 12 months of follow-up in adherent patients. No effect of the intervention was found in hospital admissions, exercise capacity, body composition, health-related quality of life, anxiety, or depression.

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TABLES

Table 1. Baseline characteristics of 411 randomized COPD patients.

	Usual care (n=207)	Urban Training (n=204)
Age (years), m (SD)	69 (8)	69 (9)
Sex: men, n (%)	178 (86)	172 (84)
Smoking status: current, n (%)	42 (20)	57 (28)
Marital status: married, n (%)	166 (80)	146 (72)
Education: secondary or more, n (%)	68 (33)	57 (28)
Socio-economic status (I-III-IV-V), n (%)	148 (72)	144 (71)
Working status: retired or unemployed, n (%)	178 (90)	172 (86)
Dyspnea (mMRC grade, 0-4), med (p25-p75)	1 (1-2)	1 (1-2)
Post-bronchodilator FEV ₁ (% predicted), m (SD)	57 (18)	56 (17)
Post-bronchodilator FEV ₁ /FVC ratio, m (SD)	0.56 (0.1)	0.54 (0.1)
Severity stage, n (%)		
Mild: FEV ₁ /FVC<0.70 and FEV ₁ ≥ 80% of pred.	19 (9)	17 (8)
Moderate: FEV ₁ /FVC<0.70 and FEV ₁ 50-79% of pred.	109 (53)	110 (54)
Severe: FEV ₁ /FVC<0.70 and FEV ₁ 30-49% of pred.	65 (31)	61 (30)
Very severe: FEV ₁ /FVC<0.70 and FEV ₁ <30% of pred.	14 (7)	16 (8)
Combined GOLD classification, n (%)		
A: low risk, low symptoms burden	51 (25)	45 (22)
B: low risk, high symptoms burden	56 (27)	70 (34)
C: high risk, low symptoms burden	31 (15)	24 (12)
D: high risk, high symptoms burden	69 (33)	65 (32)
Steps (num/day), m (SD)	7540 (3871)	7431 (4262)
Any COPD admission*, n (%)	17 (8)	8 (4)
Number of COPD admissions*, (min-p25-med-p75-max)	0-0-0-0-3	0-0-0-0-1
6MWD (meters), m (SD)	485 (93)	487 (98)
BMI (kg/m ²), m (SD)	28.5 (4.9)	28.5 (5.0)
FFMI (Kg), m (SD)	19.6 (3.2)	19.5 (3.2)
CAT score, (0-40), m (SD)	12 (7)	12 (7)
CCQ total score, (0-6), m (SD)	1 (1)	1 (1)
HAD- Anxiety score, (0-21), m (SD)	5 (4)	5.5 (4)
HAD- Depression score, (0-21), m (SD)	3(3)	4 (4)

SD: standard deviation; mMRC: modified medical research council; FEV₁: forced expiratory volume in the first second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; 6MWD: six minute walking distance; BMI: body mass index; FFMI: fat free mass index; CAT: COPD assessment test; CCQ: Clinical COPD Questionnaire; HAD: hospital anxiety and depression scale. Some variables have missing values: 1 in marital status, 1 in education level, 3 in socio-economic status, 13 in working status, 12 in COPD admissions, 53 in FFMI, 2 in CAT and CCQ score, 2 in anxiety and depression HAD score. *Admissions in previous year.

Table 2. Results at 12 months of modified intention to treat and per-protocol analysis.

	Modified intention to treat			Per protocol		
	Usual care (n=149)	Urban Training (n=135)	p-value	Usual care (n=149)	Urban Training (n=90)	Adjusted p-value*
Primary outcome						
Steps (num/day), m (SD)	7807 (3849)	7843 (4700)	0.943	7807 (3849)	9100 (4713)	0.035
Secondary outcomes						
Any COPD admission, n (%)	8 (6)	13 (10)	0.162	8 (6)	7 (8)	0.346
6MWD (meters), m (SD)	492 (90)	485 (107)	0.570	492 (90)	501 (98)	0.465
BMI (kg/m ²), m (SD)	28.3 (4.5)	28.6 (5.2)	0.574	28.3 (4.5)	28.6 (4.5)	0.717
FFMI (Kg/m ²), m (SD)	19.4 (3.0)	19.6 (3.0)	0.741	19.4 (3.0)	19.5 (2.7)	0.827
CAT score, (0-40), m (SD)	11 (7)	11 (7)	0.894	11 (7)	10 (7)	0.433
CCQ total score,(0-6), m (SD)	1 (1)	1 (1)	0.450	1 (1)	1 (1)	0.397
HAD- Anxiety score, (0-21), m (SD)	4 (4)	4 (4)	0.519	4 (4)	4(4)	0.377
HAD- Depression score, (0-21), m (SD)	3 (3)	3 (3)	0.660	3 (3)	3 (3)	0.552

SD: Standard deviation; 6MWD: six minute walking distance. BMI: body mass index; FFMI: Fat Free Mass Index; CAT: COPD assessment test; CCQ: Clinical COPD Questionnaire; HAD: hospital anxiety and depression scale. Number of subjects with missing values in the modified intention to treat analysis: 22 in 6MWD, 17 in BMI, 21 in FFMI, 11 in CAT score, 15 in CCQ score, 16 in anxiety and depression HAD score, 11 in COPD admission and in number of COPD admissions. Number of subjects with missing values in the per protocol analysis: 17 in 6MWD, 11 in BMI, 16 in FFMI, 9 in CAT score, 11 in CCQ score, 12 in anxiety and depression HAD score, 8 in COPD admission and in number of COPD admissions. *p-value of multivariable model adjusted by education and 6MWD at baseline.

Table 3. Adverse effects during or after walks in the modified intention to treat and per protocol populations.

	Modified intention to treat			Per protocol		
	Usual care (n=149)	Urban Training (n=135)	p-value	Usual care (n=149)	Urban Training (n=90)	Adjusted p-value*
Lower-extremity pain, n (%)	40 (30)	39 (32)	0.681	40 (30)	22 (27)	0.577
Lower-extremity muscle pain, n (%)	39 (29)	47 (39)	0.100	39 (29)	33 (40)	0.161
General fatigue, n (%)	62 (46)	56 (46)	0.998	62 (46)	37 (45)	0.889
Dizziness, n (%)	14 (11)	8 (7)	0.276	14 (11)	5 (6)	0.203
Faints, n (%)	2 (2)	0 (0)	0.499	2 (2)	0 (0)	-
Dyspnea, n (%)	49 (37)	46 (38)	0.811	49 (37)	29 (35)	0.925
Chest, n (%)	9 (6)	15 (12)	0.115	9 (6)	9 (11)	0.328
Palpitation, n (%)	23 (16)	22 (18)	0.800	23 (16)	13 (16)	0.898
Falls, n (%)	11 (8)	10 (8)	0.987	11 (8)	7 (8)	0.974
Cold, flu or pneumonia, n (%)	23 (17)	21 (17)	0.968	23 (17)	13 (16)	0.535
Heatstroke or dehydration, n (%)	2 (2)	2 (2)	1.000	2 (2)	1 (1)	0.662

Number of subjects with missing values in the modified intention to treat analysis: 29 in lower-extremity pain, lower-extremity muscle pain, general fatigue, dizziness, faints, dyspnea, falls, cold, flu or pneumonia, and heatstroke or dehydration, 19 for chest and palpitation. Number of subjects with missing values in the per protocol analysis: 22 in lower-extremity pain, lower-extremity muscle pain, general fatigue, dizziness, faints, dyspnea, falls, cold, flu or pneumonia, and heatstroke or dehydration, 15 for chest and palpitation. *p-value of multivariable model adjusted by education and 6MWD at baseline.

FIGURES

Figure 1. The Urban Training intervention elements.

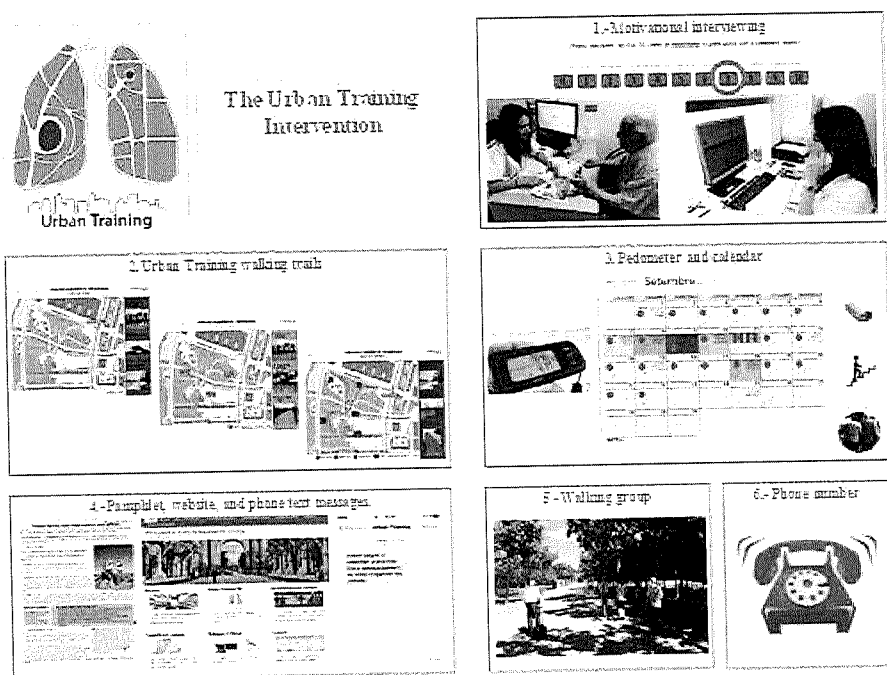


Figure 2. Study visits and assessments.

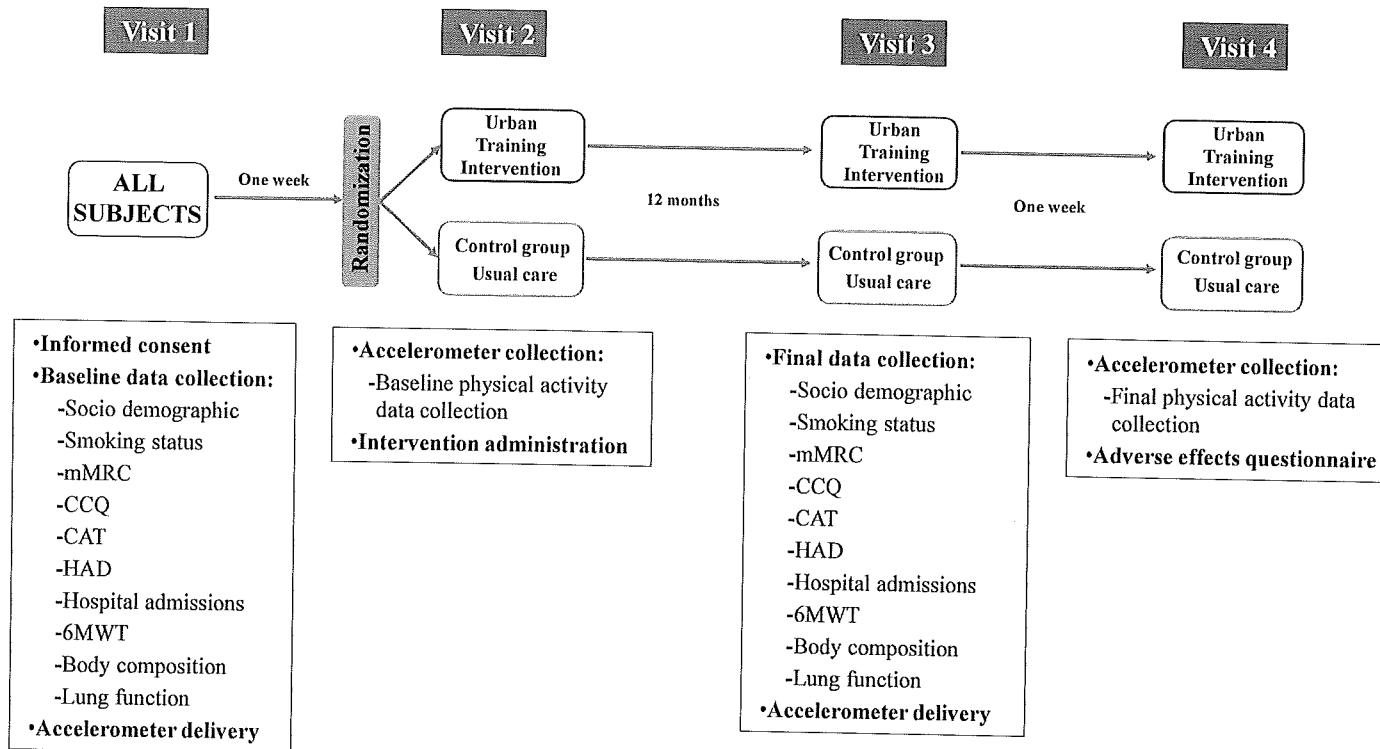
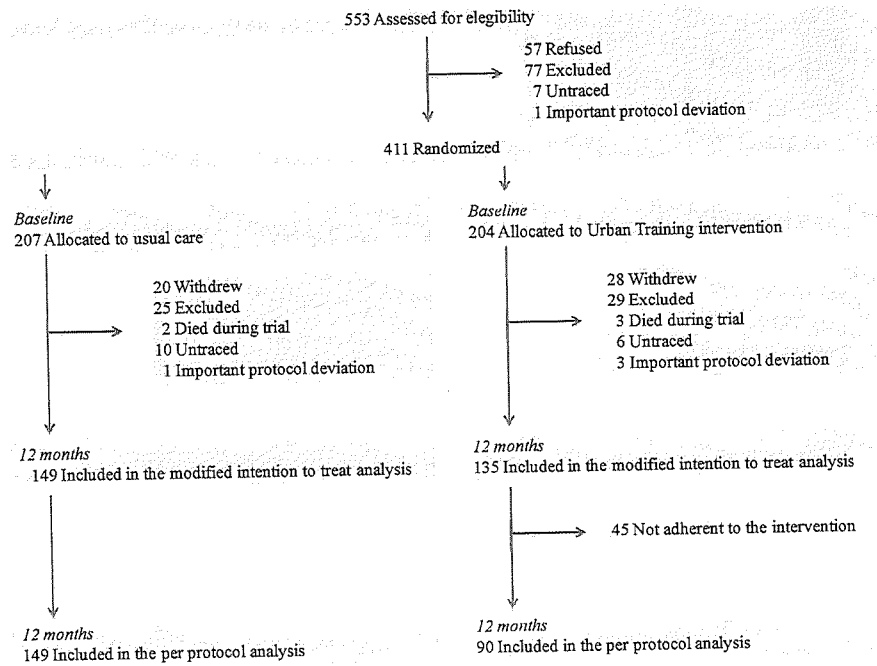


Figure 3. Flow diagram of the progress through the phases of the trial.



SUPPLEMENTARY DATA

Supplementary text 1. Definition of samples for analysis

Exclusions from the **modified intention to treat** analysis:

- Patients withdrawn or lost to follow-up before or at the 12 months visit
- Patients who died during the 12 months follow-up period
- Patients who, after being initially classified as eligible, present an exclusion criteria during follow-up
- Patients who are unable to record physical activity or do it for a minimum of 3 days a minimum of 8 hours per day (classified as “important protocol deviation”)

Additional exclusions from the **per protocol** analysis:

- Patients who are not adherent to the intervention they were allocated to.

Definition of **adherence** to the intervention:

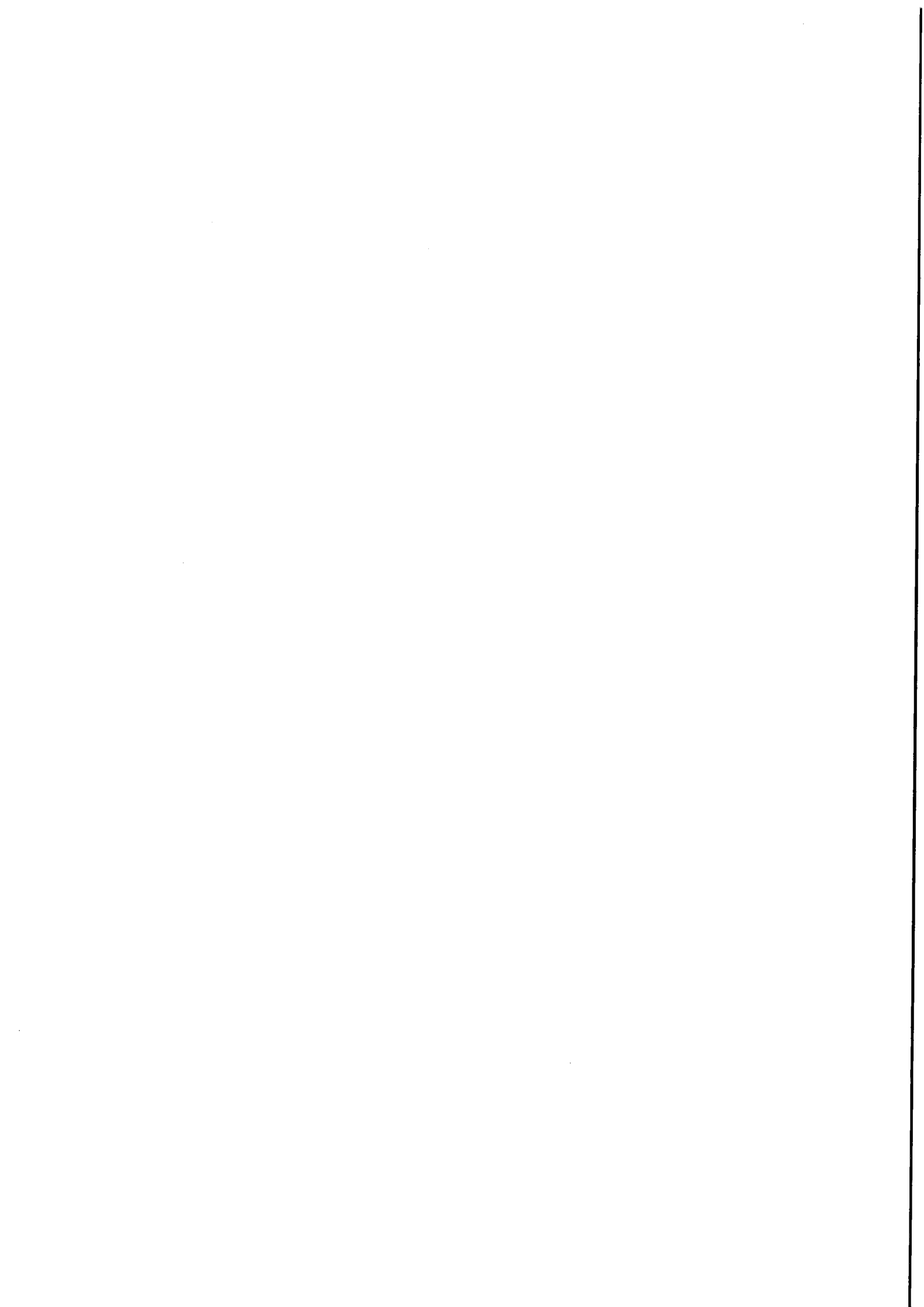
- Patients who report being adherent to the instructions they received by the physiotherapist at baseline
AND
- For patients allocated to the intervention (Urban Training) arm, patients who filled a minimum of 6 months in the calendar

Otherwise patients are classified as not adherent.

Supplementary Table 1. Baseline characteristics according to adherence to Urban Training intervention

	Not Adherent (n=45)	Adherent (n=90)	p-value
Age (years), m (SD)	68 (9)	69 (9)	0.421
Sex: men, n (%)	40 (90)	77 (86)	0.591
Smoking status: current, n (%)	13 (29)	21 (23)	0.483
Pack-years, m (SD)	59 (33)	56 (37)	0.657
Marital status: married, n (%)	34 (76)	71 (79)	0.661
Education: secondary or more, n (%)	16 (36)	20 (22)	0.099
Socio-economic status (I-III-IV-V), n (%)	30 (68)	65 (72)	0.629
Working status: retired or unemployed, n (%)	39 (87)	74 (85)	0.803
Dyspnea (mMRC grade, 0-4), med (p25-p75)	1 (1-2)	1 (0-1)	0.137
Post-bronchodilator FEV ₁ (% predicted), m (SD)	52 (18)	57 (16)	0.070
Post-bronchodilator FEV ₁ /FVC ratio, m (SD)	0.51 (0.1)	0.55 (0.1)	0.100
Steps (num/day), m (SD)	7141 (5370)	8318 (4175)	0.164
Any COPD admission*, n (%)	4 (9)	3 (3)	0.170
6MWD (meters), m (SD)	473 (111)	509 (83)	0.037
BMI (kg/m ²), m (SD)	28.6 (5.8)	28.3 (4.4)	0.693
FFMI (Kg), m (SD)	19.5 (3.7)	19.5 (2.7)	0.915
CAT score, (0-40), m (SD)	13.4 (7.3)	11.9 (6.7)	0.224
CCQ total score,(0-6), m (SD)	1.6 (1.0)	1.3 (1.0)	0.100
HAD- Anxiety score, (0-21), m (SD)	5.5 (4.0)	5.2 (4.0)	0.670
HAD- Depression score, (0-21), m (SD)	4.3 (3.6)	3.5 (3.3)	0.192

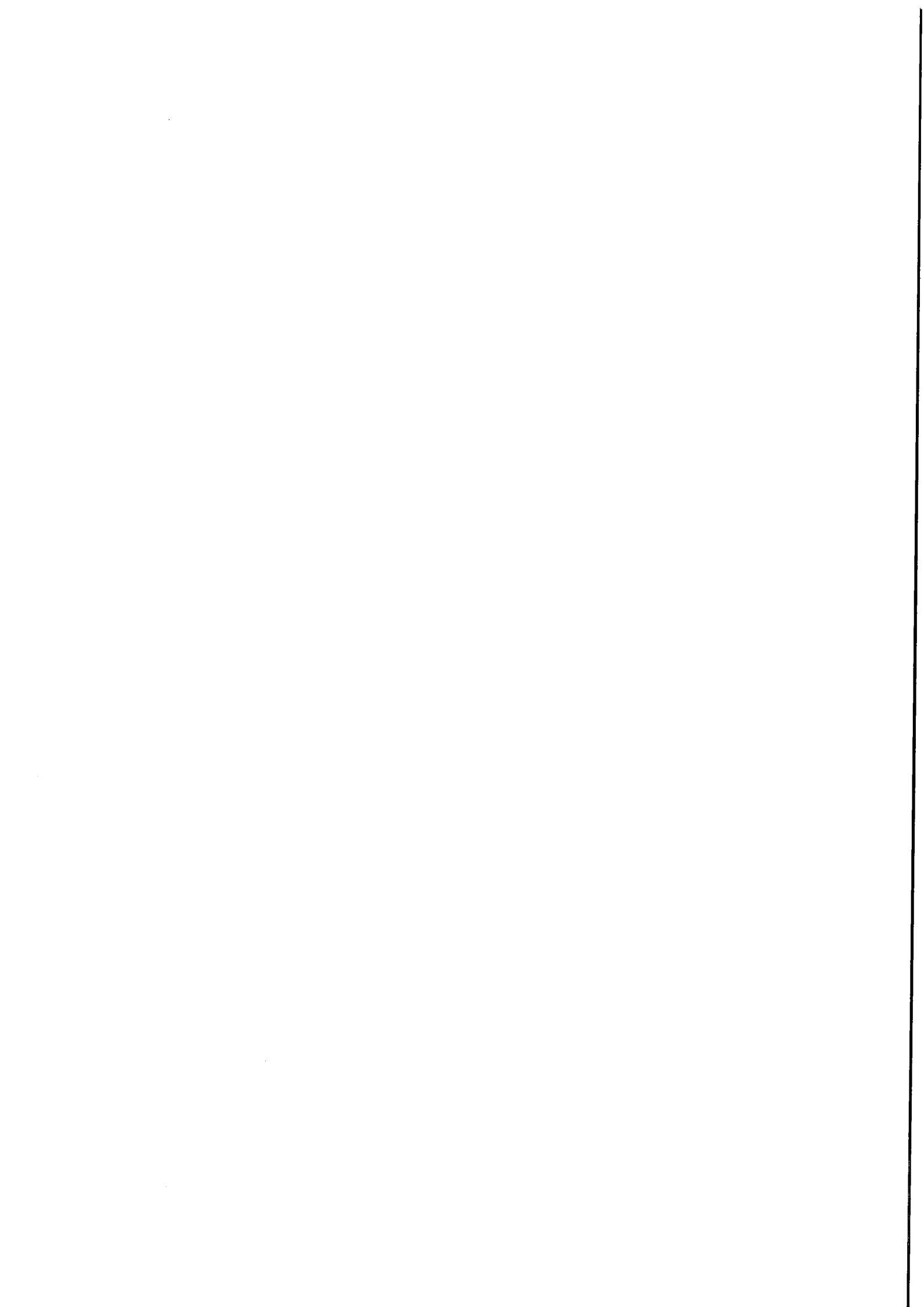
SD: Standard deviation; mMRC: modified medical research council; FEV₁: forced expiratory volume in the first second; FVC: forced vital capacity; 6MWD: six minute walking distance; BMI: body mass index; FFMI: fat free mass index; CAT: COPD assessment test; CCQ: Clinical COPD Questionnaire; HAD: hospital anxiety and depression scale. Some variables have missing values: 1 in pack-years, 1 in socio-economic status, 3 in working status, 3 in COPD admissions, 18 in FFMI, 2 in CCQ score, 2 in anxiety and depression HAD score.



4.3. Manuscript 3

Socio-environmental determinants of physical activity in patients with chronic obstructive pulmonary disease (COPD)

Arbillaga-Etxarri A, Gimeno-Santos E, Barberan-Garcia A, Benet M, Borrell E, Dadvand P, et al. [Socio-environmental correlates of physical activity in patients with chronic obstructive pulmonary disease \(COPD\)](#). Thorax. 2017 Sep;72(9):796–802. DOI: 10.1136/thoraxjnl-2016-209209



5-GENERAL DISCUSSION

The results of the three manuscripts have been discussed in depth in the corresponding section of each article. This section first expands upon previous discussions, second, considers the weaknesses and strengths of the present work, and, finally, reflects on the impacts of this thesis on clinical practice and also future research.

5.1. Social determinants, interpersonal relationships and the necessity to go beyond

During the motivational interviewing, we detected that social aspects had an important role into COPD patients' behavior. This was supported by the finding in the third manuscript where walking the dog and grandparenting were related to higher levels of physical activity. This is a novel information not usually taken into account in COPD management and which emphasizes the importance of considering other behavior components such as the interaction between the individual factors and the social interpersonal milieu (101).

The results of the third manuscript give some information about factors included in the wide spectrum of the socio-ecological model mentioned in the introduction. In other populations, the research in this topic is more advanced, and this has opened new ways to manage different behaviors in a diverse range of populations and settings (102,103). For example, it is known that childhood obesity has a multi-factorial nature, where several components impact on students' weight (families, school, social support, etc.). In this way, interventions based on the socio-ecological model (community-based participatory, multi-component and multi-setting) have been effective in sustainably decreasing

childhood overweight and obesity (104,105). This kind of interventions are becoming more frequent, and offer a promising new alternative in improving lifestyle behaviors. (106)

As evidenced by this thesis, in COPD the knowledge about physical activity determinants beyond patho-physiological dimension is very limited. Thus, considering how evidence has developed with other populations, in COPD, this would be the first gap that future research may fill.

5.2. Physical activity as a complex behavior

The fact that only 67% of patients allocated to the Urban Training intervention reported having been adherent to it raises some questions about what determines patients' adherence. Indeed, engaging or maintaining a health behavior is not an easy task. Therefore, interventions undertaken to promote healthy behaviors imply a wide scope of complexity (107). In other words, a complex behavior needs a complex intervention, and this is defined as a combination of at least two interacting components such as procedures (e.g., integrated care pathway), behavior strategies (e.g., self-efficacy), or products (e.g., medicines) (108,109). In this context, the complex interventions in smoking cessation that combined behavioral support and pharmacotherapy have shown to be effective (110,111). Similarly, in adults with type 2 diabetes, applying behavioral strategies increased physical activity and produced clinically significant improvements in long-term glucose control (112).

On the other hand, the implementation of a complex intervention into every day clinical practice and policy is another gap that should be filled (109). Researchers, health-care professionals and health service managers often

question how best to implement complex interventions in clinical practice (113,114). This is because the implementation of a complex intervention is very difficult within a context of work overload, and with lack of time, training, and knowledge about how people can be influenced from the socio-ecological perspective using behavioral strategies (106,115).

Indeed, the Urban Training was designed as a simple and practical intervention to be implemented easily in primary care centers and hospital by pulmonologists, family physicians, physiotherapists and nurses. However, results of this thesis and current research suggest that researchers as well as health professionals that implement physical activity interventions should have the appropriate training in behavior strategies (106,115).

5.3. Weaknesses

Although the limitations of the studies that are part of the thesis are detailed in each article, certain limitations of this thesis deserve to be highlighted. A previous pilot study with a smaller number of patients may have helped to identify adherent patients as well as intervention's design errors. Due to time constraints, it was impossible to apply the knowledge extracted from the novel socio-environmental determinants to improve the design of Urban Training intervention. In addition, the results showed in this thesis may not be applicable in other countries because natural environmental factors' such as extreme hot or cold temperatures, and high altitudes influence on physical activity in COPD patients (52). And finally, considering the evidence about the air pollution effects, Urban Training intervention could have considered including advice and education about the risks of air pollutant exposures during outdoor exercise (116,117).

5.4. Strengths

The physiological response assessment by indirect calorimetry, the satellite images to record the greenness, the objective physical activity measurement by accelerometers, the large number of variables analyzed, the representative and broad sample of patients, and the design of a multicenter randomized clinical trial with a long term follow-up (12 months) are clear strengths of the research included in this doctoral thesis.

The novelty of the intervention as well as the study of the novel determinants of physical activity also should be mentioned. Moreover, to complement this approach, qualitative research, which consists of personal interviews and focus groups, is being undertaken at the present. However, due to time constraints, the results are not yet available. In future, this will further develop the knowledge about socio-environmental determinants from other perspective.

Urban Training was a multi-disciplinary project, where health-care professionals (physiotherapist, nurses, pulmonologists, and epidemiologist) and architects, urban planners, environmental technicians, statisticians, and sport scientists were involved.

Finally, this thesis provides novel clinical applicability information about physical activity patterns and interventions in COPD patients.

5.5. Clinical implications for future research and clinical practice

The results of the present study should be taken into account for further research, specifically, to study the complex spectrum of physical activity determinants and also to design future interventions to modify physical activity behavior in COPD patients.

As discussed in the second and third manuscript, understanding the determinants of physical activity beyond the patho-physiological dimension in COPD is essential to design future interventions and to guide clinical practice. To this effect, more well conducted observational studies are needed, preferably longitudinal studies and clinical trials (37).

The first manuscript also highlights the necessity of testing the different components that form an intervention. Indeed, the second manuscript and previous literature showed that the combination of pedometers, motivational interviewing and calendars/diaries (56) have the ability to modify physical activity at long term. Yet, when Urban Training trails were designed, a specific study was needed to test their ability to produce a change in exercise capacity due to their novelty. After their implementation, we concluded that the use of walking trails in the community aiming to increase exercise capacity needs to be complemented by new technology such as telemedicine, so future research may help in this line.

In addition, this second manuscript shows that adherence to the intervention was relatively low. Urban training showed a similar adherence value to that the other study with positive long term effects on physical activity (67% in Urban Training vs 70% in Altenburg et al. (56)). Nevertheless, the highest adherence value was showed by the approach that combined behavioral strategies (goal setting, feedback, educational and

motivational content), and an online community forum (83%) (118), but this intervention was efficacious only at 4 months. Therefore, research may focus on the adherence determinants to improve the design of future interventions.

Logically, further research is needed to identify how the Urban Training can be adapted and implemented in countries with other cultural, social, geographical and weather characteristic, and to analyze the cost-effectiveness.

6-CONCLUSIONS

1. The physiological response to and the energy expenditure on unsupervised walking on Urban Training trails increased according to the predefined trails' intensity and did not change across trails of the same intensity and different public space.
2. The Urban Training intervention, which combined behavioral strategies and unsupervised physical training in the community, improved physical activity after 12 months of follow-up only in patients adherent to the intervention. No effect of the intervention was found in hospital admissions, exercise capacity, body composition, health related quality of life, anxiety, or depression.
3. Dog walking and grandparenting are associated with a higher amount and intensity of physical activity in patients with COPD.

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ANNEXES

Other research activities and scientific contributions

Ongoing research activities

The PhD candidate is working on a qualitative study to understand the barriers and facilitators of physical activity in COPD patients from Mediterranean areas. This study will complement the quantitative approach to the social and environmental determinants of physical activity reported in the third paper of this thesis. Data collection is in process and the manuscript is expected for January 2017.

Published manuscripts

During the thesis period, the PhD candidate has participated in other studies that complement the thesis research.

- Barberan-Garcia A, Rodríguez DA, Blanco I, Gea J, Torralba Y, **Arbillaga-Etxarri A**, Barberà JA, Vilaró J, Roca J, Orozco-Levi M. Non-anaemic iron deficiency impairs response to pulmonary rehabilitation in COPD. *Respirology*. 2015 Oct;20(7):1089-95.
- Barberan-Garcia A, **Arbillaga-Etxarri A**, Gimeno-Santos E, Rodríguez DA, Torralba Y, Roca J, Vilaró J. Nordic walking enhances oxygen uptake without increasing the rate of perceived exertion in patients with chronic obstructive pulmonary disease. *Respiration*. 2015;89(3):221-5.
- Rodríguez DA, **Arbillaga A**, Barberan-Garcia A, Ramirez-Sarmiento A, Torralba Y, Vilaró J, Gimeno-

Santos E, Gea J, Orozco-Levi M, Roca J, Marco E. Effects of interval and continuous exercise training on autonomic cardiac function in COPD patients. Clin Respir J. 2016 Jan;10(1):83-9.

Participation in national and international congresses

The PhD candidate has participated in different congresses with the following contributions:

- Poster discussion: *Social and environmental determinants of physical activity in patients with chronic obstructive pulmonary disease (COPD)*. ERS Congress, London, 2016.
- Oral communication: *Determinantes sociales y ambientales de la práctica de actividad física en pacientes con enfermedad pulmonar obstructiva crónica*. Congreso Nacional SEPAR, Granada, 2016.
- Poster discussion: *Reference equations for 6-minute walk test in Spanish population*. ERS Congress, Amsterdam, 2015.
- Poster discussion: *Reference equations for incremental shuttle walk test in Spanish population*. ERS Congress, Amsterdam, 2015.
- Poster discussion: *Validation of urban trails for COPD patients*. ERS Congress, Munich, 2014.
- Oral communication: *Validación de circuitos para el entrenamiento urbano en pacientes con EPOC*. Symposium EPOC, Barcelona, 2014.

- Poster discussion: *Diseño de circuitos para el entrenamiento urbano en pacientes con enfermedad pulmonar obstructiva crónica*. Congreso Nacional SEPAR, Barcelona, 2013.
- Poster discussion: *Autonomic cardiac dysfunction in COPD: The role of 6MWT*. ERS Congress, Viena, 2012.
- Thematic poster: *Recuperación de la frecuencia cardíaca después de la prueba de 6 minutos en pacientes con enfermedad pulmonar obstructiva crónica*. Congreso Nacional SEPAR, Madrid, 2012.
- Poster discussion: *Usabilidad de un dispositivo móvil como soporte de la actividad física*. Congreso Nacional SEPAR, Madrid, 2012.