Physical Activity as a crucial Patient-Reported Outcome in Chronic Obstructive Pulmonary Disease

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“Was mich nicht umbringt, macht mich stärker“

“What does not kill me, makes me stronger”

Friedrich Nietzsche

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Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is a treatable and preventable lung disease with extra-pulmonary effects contributing to morbidity and mortality. Physical inactivity is a hallmark of COPD, which relates to outcomes relevant for patients and healthcare providers. Despite its importance, no patient reported outcome (PRO) instrument exists that captures physical activity in a way that it maximally reflects the experience of patients with COPD. The main aim of this thesis was to understand what physical activity in patients with COPD is, which are the causes and effects of physical (in)activity in this condition, and how to measure it.

Methods: In the context of the European Commission-funded PROactive project (www.proactivecopd.com) we performed two systematic reviews focused on physical activity in COPD conducted through searches in four databases (Medline, Embase, CINAHL and PsycINFO). We also conducted a six-week, randomized, two-way cross-over, multi-centre study assessing physical activity with the PROactive draft questionnaires (Daily and Clinical visit versions) and two previously validated activity monitors. Item reduction to derive the final PROactive instruments followed an iterative process including classical and Rasch model analyses, and incorporated input both from patients and clinical experts.

Results: (1) We identified only 2 manuscripts providing a concept and a conceptual framework of physical activity in patients with COPD. (2) None of the 104 PRO instruments to measure physical activity in COPD were based on a conceptual framework of physical activity. (3) Physical activity levels in COPD are consistently associated with important outcomes such as mortality and exacerbations, but there is poor evidence about determinants (including interventions) of physical activity. (4) The concept of physical activity in COPD has 2 domains: 'amount of' and 'difficulty with' physical activity. (5) The Daily and Clinical visit 'PROactive Physical Activity in COPD' instruments are hybrid tools combining a short PRO questionnaire and two activity monitor variables, that provide simple, valid and reliable measures of physical activity in patients with COPD.

Conclusions: In the present thesis we highlight the importance of the presence of a conceptual framework that defines the concept to be measured, both for research and clinical practice. Also, there is a need for increasing the knowledge about the determinants and outcomes of physical activity in COPD, not only for the development of interventions, but also for guiding the clinical practice and COPD recommendations.

Keywords: chronic obstructive pulmonary disease, physical activity, patient-reported outcome instrument, activity monitor, conceptual framework, conceptual model.

Resum

Antecedents: la Malaltia Pulmonar Obstructiva Crònica (MPOC) és una malaltia respiratòria tractable i prevenible amb efectes extrapulmonars que contribueixen a la seva morbiditat i mortalitat. La inactivitat física és un aspecte clau en la MPOC que es relaciona amb esdeveniments de salut rellevants tant per als pacients com per als proveïdors de salut. Malgrat la importància de l'activitat física, no existeix cap instrument de resultats percebuts pels pacients (*patient-reported outcomes – PRO*) que capturi l'activitat física reflectint al màxim l'experiència dels pacients amb MPOC. L'objectiu principal d'aquesta tesi és comprendre què és l'activitat física en els pacients amb MPOC, quines són les causes i els efectes de la (in)activitat física en aquesta condició, i com mesurar-la.

Mètodes: En el context del projecte PROactive, finançat per la Comissió Europea (www.proactivecopd.com), es van realitzar dues revisions sistemàtiques centrades en l'activitat física en la MPOC, mitjançant cerques en quatre bases de dades (Medline, Embase, CINAHL i PsycINFO). També es va portar a terme un estudi multicèntric aleatori creuat de dues vies, de sis setmanes de duració, per l'avaluació de l'activitat física amb els esborranys dels qüestionaris PROactive (en les seves versions Diària i Visita clínica) i dos monitors d'activitat prèviament validats. La reducció d'ítems per derivar els instruments PROactive finals va seguir un procés iteratiu, incloent anàlisis clàssiques i models de Rasch, i també va incorporar informació obtinguda directament dels pacients i d'experts clínics.

Resultats: (1) Es van identificar només 2 manuscrits que proporcionessin un concepte i marc conceptual sobre l'activitat física en pacients amb MPOC. (2) Cap dels 104 instruments PROs per mesurar activitat física en la MPOC es van basar en un marc conceptual sobre activitat física. (3) Els nivells d'activitat física en la MPOC s'associen de manera consistent amb resultats rellevants com la mortalitat i les exacerbacions, menter que l'evidència sobre els determinants de l'activitat física (incloent intervencions) és pobra. (4) El concepte d'activitat física en la MPOC té 2 dominis: 'quantitat de' i 'dificultat amb' activitat física. (5) Les versions Diària i Visita clínica dels instruments 'PROactive d'Activitat Física en la MPOC' són eines híbrides que combinen un breu PRO qüestionari i dues variables del monitor d'activitat física, i que proporcionen mesures simples, vàlides i fiables d'activitat física en pacients amb MPOC.

Conclusions: En la present tesi es destaquen la importància de la presència d'un marc conceptual que defineixi el concepte a mesurar, tant per a la investigació com per a la pràctica clínica. A més, és necessari augmentar el coneixement dels determinants i els efectes de l'activitat física en la MPOC, no només per al desenvolupament d'intervencions, sinó també per guiar la pràctica clínica i les recomanacions en la MPOC.

Paraules clau: malaltia pulmonar obstructiva crònica, activitat física, resultats percebuts pels pacients, monitor activitat física, marc conceptual, model conceptual.

Preface

This thesis was written at Centre for Research in Environmental Epidemiology (CREAL) between January 2010 and July 2014, including a short-term research stay (from January to March 2010) at Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA. The thesis has been directed by Dr. Judith Garcia-Aymerich and Dr. Milo A. Puhan and consists of a compilation of scientific publications co-authored by the PhD candidate according to 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, final conclusions, and future research plans.

This thesis was done in the context of the European Commission-funded PROactive project (www.proactivecopd.com), which aims to develop and validate patient-reported outcome (PRO) instruments that capture the dimensions of physical activity in daily life relevant to patients with chronic obstructive pulmonary disease (COPD). The PhD candidate was responsible for the coordination of the systematic reviews, for the quality control of the fieldwork, for the statistical analyses and writing of the manuscripts.

Apart from the work done for the present thesis, the PhD candidate has also been principal investigator of the multicenter project: "*Elaboration of reference equations for the six-minute walk test and the incremental walking shuttle test in healthy adult Spanish population*" funded by the Pneumology and Thoracic Surgery Spanish Society (SEPAR, 269/2010) and by the Pneumology Catalan Society (SOCAP, 2010). The PhD candidate has written the protocol, has coordinated the project and the data collection, has performed the analysis and is responsible of the manuscripts elaboration.

The PhD candidate has also participated in other ongoing research projects, all related to physical activity and COPD management or prognosis, which have resulted in several manuscripts that the candidate has co-authored during the pre-doctoral period (listed at the end of this thesis as an appendix). A list of congress contributions is also included.

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1 INTRODUCTION

1.1 Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is a disease characterized by persistent, and usually progressive, not fully reversible airflow limitation due to the susceptibility of the individual to noxious particles or gases that produce a chronic inflammatory response in the airways (1, 2). The airflow limitation in COPD is caused by a mixture of small airway disease, parenchymal destruction, and, in many cases, increased airways responsiveness. COPD is a common preventable and treatable disease with some significant extrapulmonary effects that contribute to the disease burden of individual patients (1). COPD prevalence, morbidity and mortality varies across countries and increases with age (1, 2). In 2030, COPD is projected to rank as the fourth leading causes of death and it is the only disease where mortality has increased constantly in past decades (3). COPD is associated with a significant and increasing socioeconomic burden (1).

COPD is currently recognized as a systemic condition due to its impact on other organs (4). Extrapulmonary (or systemic) manifestations are common in patients with COPD, such as skeletal muscle wasting, cachexia, cardiovascular disease, depression, osteopenia, and chronic infections, that can produce a limited functional capacity, worsening dyspnoea, reduced health-related quality of life and increased risk of mortality (2, 4, 5). Another extrapulmonary manifestation of COPD, also mediated through the respiratory impairment and dyspnea and fatigue symptoms, is the reduction of usual physical activity (4, 6, 7). This situation is known as the ‘dyspnea-inactivity vicious circle’ (or ‘dyspnea spiral’) (Figure 1) where COPD patients, who suffer from dyspnea during activities, decrease their daily levels of physical activity to reduce dyspnea. Patients adopt a more sedentary lifestyle and experience physical deconditioning, which in turn perpetuates the aggravation of dyspnea and other symptoms (6). Progressively, this vicious circle negatively impacts on health-related quality of life.

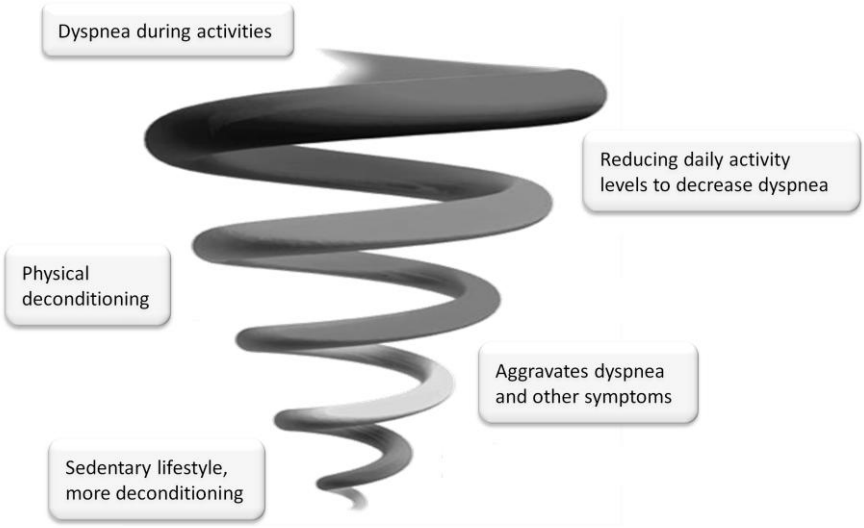

Figure 1. The dyspnea-inactivity vicious circle (*dyspnea spiral*) in patients with COPD.
Adapted from Reardon J *et al.* (6).

1.2 Physical Activity

1.2.a The concept of physical activity

Physical activity has become a key topic in public health because a reduced level of physical activity is a well-known risk factor for many disorders and chronic diseases (8–15), and a sedentary lifestyle is common around the world (16). Physical inactivity is one of the leading causes for the major non-communicable diseases and contributes substantially to the global burden of disease, disability and death (16–18). It is estimated that 6-10% of deaths from the principal non-communicable diseases is due to physical inactivity (8). The recommendations in older adults from the American College of Sports Medicine (ACSM) and the American Heart Association (AHA) to promote and maintain health consider a minimum of 30 minutes per day on 5 days per week of moderate-intensity aerobic physical activity, or a minimum of 20 minutes per day on 3 days per week of vigorous-intensity aerobic activity (19). Recently, some benefits in all-cause and all-cancer mortality has been associated to 15 min/day or 90 min/week of brisk walking (20), half of the ACSM/AHA recommendations.

Frequently, the terms physical activity, physical fitness and exercise are used as synonyms and interchangeably, although they describe different

concepts (21). **Physical activity** is defined as ‘any bodily movement produced by skeletal muscles that results in energy expenditure’. Since physical activity is a complex behaviour due to the multidimensionality of the concept (22), it is challenging to measure because it can be considered in different ways as for example leisure and occupation activities, sedentary activities, or high intensity activities; and it implies other variables such as psychological, physiological or functional characteristics of the individual.

Exercise is defined as ‘a subcategory of physical activity that is planned, structured, and repetitive and has as a purpose the improvement or maintenance of physical fitness components’. Hence, tasks regularly performed and planned to develop muscular strength or to "burn up" calories are considered exercise.

Physical fitness is defined as ‘a set of attributes that people have or achieve that relates to the ability to perform physical activity’. The health-related factors of physical fitness include cardiorespiratory endurance, muscular endurance, muscular strength, body composition, and flexibility. Hence, physical fitness determines the functional capacity of an individual, defined as the maximal performance potential and limited by disease-related impairments (23). In comparison with physical activity, the components of physical fitness are easier to assess and the procedures available are commonly used based on laboratory, epidemiologic and self-assessment objectives.

Physical activity, physical fitness and exercise are concepts strongly related among them but they need to be distinguished both in the clinical practice and in research, and therefore measured with specific tests for each one.

1.2.b Physical activity in COPD

A substantial amount of research about physical activity in COPD patients has been published recently. Many studies have demonstrated that patients with COPD have reduced **levels** of physical activity compared to their healthy pairs, irrespective of the tool for assessing physical activity, cultural background, and the geographical origin of the subjects (24–33). Existing data show that that time spent walking and movement intensity of patients are significantly lower compared to aged-matched healthy subjects (24, 26, 28, 34, 35). Furthermore, patients with COPD do not follow the ACSM/AHA recommendations of physical activity (36, 37).

One of the first studies that assessed compliance with current recommendations showed that only 26% of patients with moderate COPD were able to reach at least 30 consecutive minutes of moderate intensity physical activity on at least 5 days per week. However this increased to 50% of adherence when the 30 minutes were split in bouts of minimum 10 minutes (37). In general, COPD patients spend more time in sitting and lying positions than walking and standing (24, 35, 38). Interestingly, patients with severe to very severe COPD seem to adapt to the physiological limitations by performing physical activities in fewer and shorter bouts than patients with mild to moderate disease (37).

A couple of recent reviews, one from an expert perspective (39) and a systematic review of the literature (40), identified a large amount of **correlates** of physical activity in patients with COPD. For example, lower levels of physical activity in COPD have been associated with higher airway obstruction and systemic inflammation, more dyspnea and comorbidities, lower exercise capacity, and poorer muscle function and health-related quality of life (Figure 2) (39, 40). Most of the studies cited in the reviews showed associations but they did not allow ascertaining whether the identified correlates were cause or consequence of the physical inactivity in these patients. In large part, this was due to the cross-sectional design of most of the studies, but also partly due to a lack of clarity in the research questions.

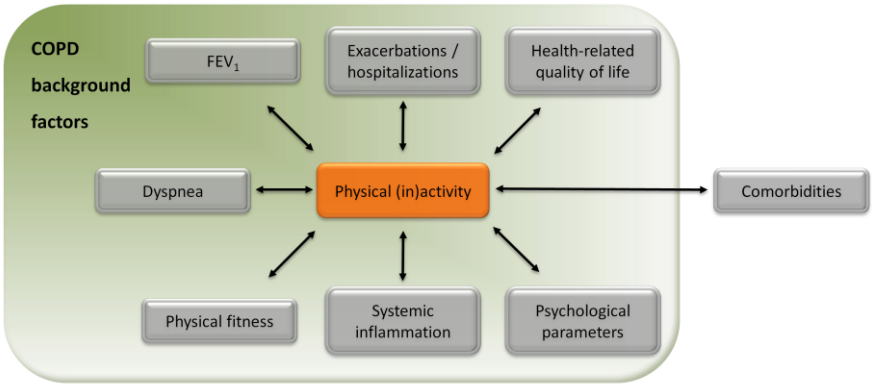

Figure 2. Theoretical framework of correlates of physical activity in patients with COPD. These relationships are embedded in background factors related to COPD such as age, smoking status, genes, medications, among others. The comorbidities (the presence of diseases other then COPD) may also influence physical activity. Adapted from Hartman J *et al.* (39) and Bossenbroek L *et al.* (40).

Regarding the **effects** of physical activity in COPD, several clinical and epidemiological studies have shown that reduced levels of physical activity are related to increased risks of hospitalization and readmission in the following year, and of all-cause and respiratory mortality, in comparison to patients who had a more active life style (41–43). Even so, these evidence needs to improve and expand to other effects because is still limited to hospitalizations and mortality outcomes. Also, the methodology of the studies is questionable since the cross-sectional design is the most frequent, combined with some prospective and retrospectives studies, and the measurement of physical activity is mainly by questionnaire which is known to produce misclassification (39, 40).

Based on the limited but existing evidence, it seems clear that physical activity has an impact on the disease and it seems it is important for patients with COPD. An exploratory study identified two interrelated domains that 'really mattered to patients': (i) physical activities (subdivided into walking, driving a car, and household activities), and (ii) social interactions (44). The large multinational PERCEIVE study showed that in a cohort with more than 1000 patients, 54% of the subjects reported that they were not able to complete the activities they liked to do due to their COPD (45). Thus, the view has grown that physical activity is not only relevant for its "objective" effects, but also that it matters to patients, and so their perceptions and experiences need to be considered.

As a result of the abovenoted, the interest of the assessment of daily physical activity in patients with COPD has increased in the last years, and the body of literature has grown considerably (46). Even the Global initiative for Chronic Obstructive Lung Disease (GOLD) in its 2011 version recommended to maintain regular physical activity for all patients with stable COPD (1). However, in the absence of clear information on which are causes or consequences of physical activity in COPD, or the type of activity that improves the evolution, is impossible to make specific recommendations. Furthermore, so far the interventions to promote physical activity in COPD patients have not proven effective, which could be partly attributable to the limitations of existing observational research (39, 47).

1.2.c Assessment of physical activity in COPD

Physical activity can be measured using different approaches, usually divided into indirect (questionnaires) and direct (activity monitors). So far, patient-reported outcomes (PRO) questionnaires have been the most commonly used method to assess physical activity in patients with COPD.

But there is a clear trend to use more objective measures such as the activity monitors (pedometers and accelerometers). The selection of one or another method requires consideration of the strengths (e.g. accuracy) and limitations (e.g. feasibility, cost) of each one and the objectives and purposes of the measurement (48).

PRO questionnaires of physical activity in COPD

The PRO questionnaires are frequently used in epidemiological studies and clinical trials because they are easy to administer and cheaper than other methods (46, 49). Also, PRO instruments may capture patient lifestyle information and related limitations that may not be identified by objective assessments such as activity monitors (50). Many PROs capture different aspects of physical activity such as amount, type, duration, intensity, symptom experience, and performance of 'activities of daily living' (46, 50, 51).

The selection of a suitable PRO questionnaire to measure physical activity requires that the specific questionnaire fits the study aim based on the construct that is being measured, it is properly developed and has strong psychometric properties. Other criteria include the recall period, its format, interpretability and ease of use (51, 52), availability of a culturally validated version, the time required for questionnaire (self-)administration, and the ability to compare outcome levels across studies (51). In the specific case of patients with COPD, other criteria should be considered such as the validation of the questionnaire in the target population, or the inclusion of information on low-intensity activities (46, 51).

Besides the above-mentioned criteria, it is important to notice that questionnaires have some general limitations or disadvantages such as the tendency to provide wishful or socially acceptable answers, and the presence of a recall bias (49, 51, 53). Also, an inappropriate recall period may produce variability in the responses, increase the recall bias and reduce content validity (54, 55). However, there is no consensus on what the most appropriate recall period is (52), and, in the case of PRO questionnaires on physical activity, it varies from 'today' to 'past year'. Very short recall periods (i.e. today) may underestimate physical activity due to day-to-day fluctuation of the concept of the interest. On the other hand, too long recall intervals (i.e. past month or past year) may either over- or underestimate the physical activity performed due to recall bias.

Two recent systematic reviews have assessed all available PRO instruments to measure physical activity in the elderly or chronically ill patients including COPD patients (50, 56) and, from the 104

questionnaires identified, 15 were specifically developed for use in patients with COPD (50). However, these PRO instruments have some critical limitations such as a lack of definition of the instruments' aims or important concepts relating to symptoms and limitations, lack of patients or experts involvement, or absence of rigor in assessing their content validity, among others (50, 56). Also, one of the reviews reports that there is no agreement in the appropriated recall period for measuring physical activity in these patients, with great heterogeneity in the recall period among existing instruments (50). All these issues may produce measurement error leading to serious concerns about validity, which in turn would increase the risk for false-negative associations in epidemiological studies and in clinical trials evaluating interventions. Therefore, there is a need of properly developed and validated PROs to measure physical activity in COPD patients.

Activity monitors

Activity monitors are instruments for detecting body movement and to objectively quantify and monitor free-living daily physical activity, both at an individual and a population level. The activity monitors currently used in chronic disease populations could be classified in three classes: pedometers, accelerometers and integrated multisensor systems (46, 49, 57). For the purpose of this thesis, this section is focused primarily on accelerometers.

Accelerometers are small, lightweight, portable and little intrusive, and many models and brands are available. These technologically more sophisticated electronic portable devices detect the body's acceleration using piezoelectric accelerometers. They have the ability to capture both quantity and intensity of physical activity. The interest in the use of accelerometers has increased in recent years as they provide objective data of physical activity that cannot be obtained by questionnaires. They are worn on the waist but also on the arm, wrist, ankle, or even on a shoe. Accelerometers can detect acceleration in one, two, or three axes (uni-, bi, or triaxial accelerometers, respectively) based on how many planes (dimensions) detect the movements. These monitors are able to measure and accumulate data continuously over time and they quantify activity counts, vector magnitude units, time spent, number of steps, and estimate energy expenditure (46, 49). Sometimes accelerometers are combined with other physiological sensors (such as heart rate or skin resistance) with the objective of increasing their accuracy to estimate daily physical activity and energy expenditure (58, 59).

The validity of different activity monitors to assess physical activity in patients with COPD has been the subject of many investigations in recent years (38, 46, 49, 58, 60–62). Important conclusions from these studies are that triaxial accelerometers are more sensitive and valid than the uniaxial devices since they have greater agreement with reference standards such as indirect calorimetry (57) or with measures of energy expenditure such as doubly labeled water method (62). In COPD, some activity monitors have been identified superior than others in all criteria including patient compliance and preferences (61, 62). These monitors, all triaxial accelerometers, are: the DynaPort MiniMod (McRoberts, The Hague, the Netherlands), the ActiGraph GT3X (ActiGraph, Pensacola, FL), and the SenseWear Armband (SMT Medical, Würzburg, Germany).

However, accelerometers also have some limitations. The variability in the output from different accelerometers limits the comparability of the data (63, 64) and requires technical expertise and specialized software (49). In addition, these devices may be sensitive to vibrational artefacts, for example, recording vibration related to being in a motor vehicle (65). Most accelerometers are not sensitive enough to detect changes in physical activity in slowly moving subjects and, for example, they tend to underestimate the number of steps for walking at low speeds which may limit its accuracy in patients with severe-to-very severe COPD (61, 66). A limitation of motion sensors worn on the waist, hip or ankle is that activities of the upper extremities of the body will not measured. Also, activities other than walking such as riding a bicycle or swimming are not well captured by some accelerometers (46, 49). Finally, another limitation from the activity monitors is the inability to obtain information from the patient's perspective which is, based on qualitative research, known to be relevant to the regular physical activity practice and should be considered for measuring physical activity both in clinical and research practice (47, 67, 68). Finally, another concern about activity monitors is compliance by subjects, which should be maximized both by study design and device characteristics (46). Even so, accelerometers are considered the standard for assessing physical activity levels and are often used to validate the much simpler, less expensive methods such as pedometers or physical activity questionnaires.

1.3 Patient-Reported Outcomes (PRO)

1.3.a Definition of a PRO and a PRO instrument

A PRO is a "direct self-report of patients' perception of their health and illness experiences without any interpretation from anyone else", as defined by regulatory authorities such as the Food and Drug Administration (FDA) (55). The information obtained is unavailable from other sources. The assessment may include symptoms, health-related quality of life, perceptions or satisfaction with treatment and care received, that other assessments would not identify (54, 69). This definition includes both the concept to be measured and the instrument developed or used to measure it. In the context of this thesis, we use the term ***PRO*** to define *the concept of interest*, and ***PRO instrument*** (or PRO questionnaire) to define *the tool that aims to measure the concept*.

1.3.b From the conceptual framework to the conceptual and the end-point models

The FDA, which provides the guidance for the PRO instrument development, defines the PRO concept as 'the specific goal of measurement'. So, the complexity of the PRO instrument depends on the complexity of the concept that will be measured. Due to this, prior to developing a PRO instrument, one should develop a conceptual framework of the PRO concept, which defines the main concept, the domains, and subdomains of interest (55).

A **conceptual framework** explicitly defines the PRO concept (aimed to be measured by the PRO instrument) in a diagram that presents a description of the relationships between items, domains (subconcepts), and concepts measured and the scores derived (55, 69) (Figure 3). The conceptual framework should arise from literature review, expert opinion, and patients (55). According to FDA guidance, the development of PRO questionnaires should be based on an adequate and well predefined (or hypothetical) conceptual framework that will allow to redefine and modify both the instrument and the conceptual framework during the iterative process for the PRO development (Figure 4) (55, 69). In the absence of a conceptual framework, it is not clear what exactly a PRO instrument is measuring (55).

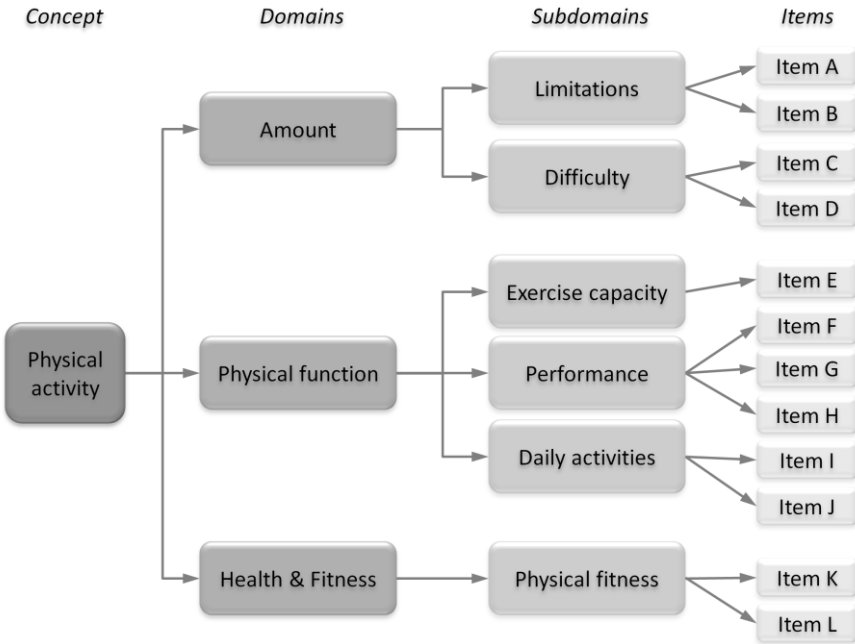

Figure 3. Example of conceptual framework for physical activity.

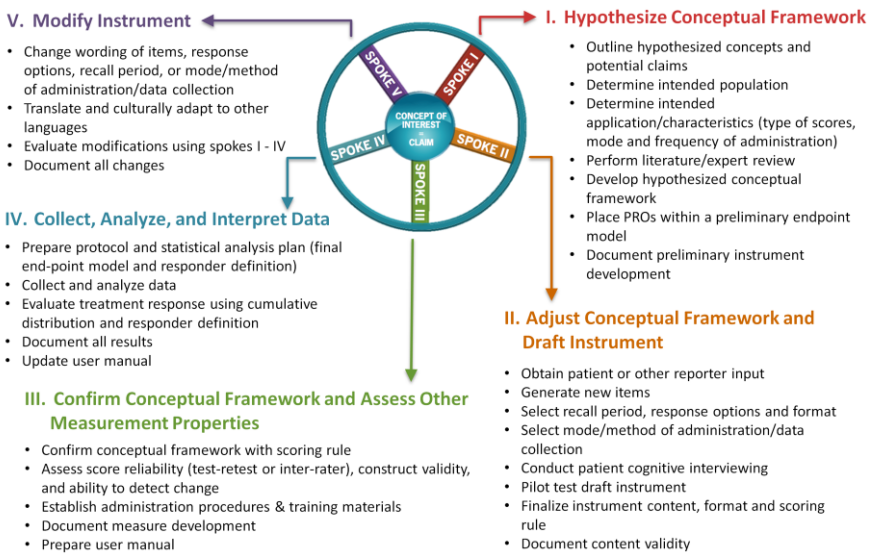

Figure 4. Iterative process used in developing a PRO instrument. Adapted from US Department of Health and Human Services Food and Drug Administration (55) (www.fda.gov)

A **conceptual model** describes the relationship and directionality among the PRO concept and its correlates. Given that a PRO questionnaire should capture the concept it is supposed to measure, a solid basis for their development and selection is needed. In other words, a conceptual model should provide the rationale for the concepts being to be measured, the population of interest, and for the actual questions, and provides an evidence base for developing end-point models for specific trials (Figure 5) (69).

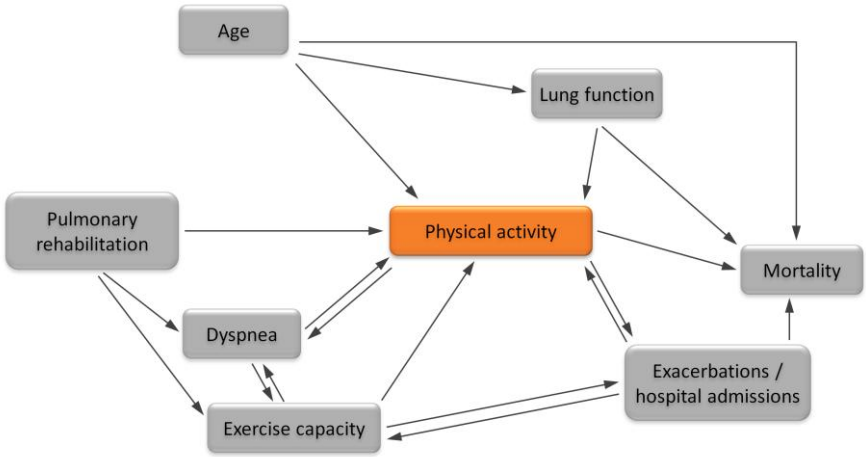

Figure 5. Example of conceptual model for physical activity in patients with COPD.

Finally, the **end-point model** describes the relationship among the subset of variables included in the conceptual model that are relevant for a specific research study, as primary, secondary or exploratory outcomes, or other relevant variables. The end-point model helps the study to use the PRO instruments according its aims (55) (Figure 6).

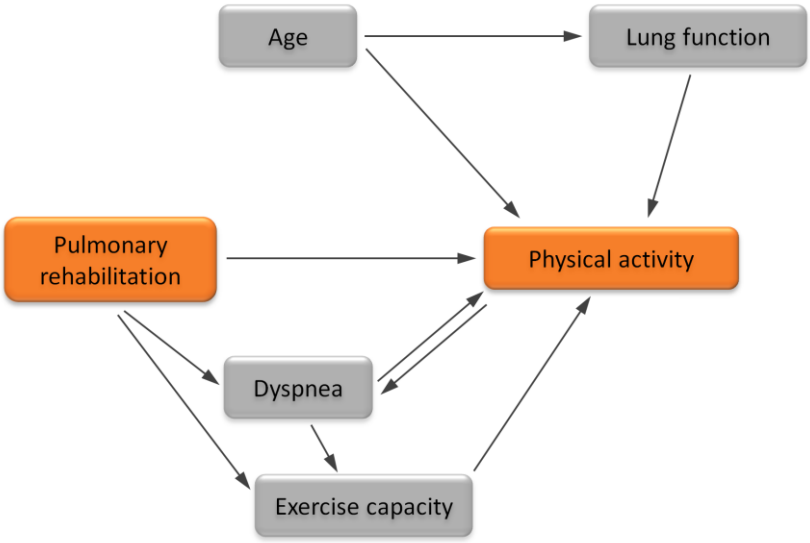

Figure 6. Example of the end-point model of a study aiming to assess the effectiveness of pulmonary rehabilitation on physical activity changes in patients with COPD.

1.3.c PRO instrument development

The interest but also the pressure to develop robust and valid PRO instruments has increased in recent years (70) and several guidelines are available (55, 71). Briefly, the key steps for developing a PRO instrument should cover the following: to investigate the already existing measures developed on the same topic, to have a theoretical conceptual framework to be based on, to specify the target population, and to perform qualitative research as well as rigorous psychometric testing (70, 72, 73).

The first step requires that the researchers verify, not only whether available measures exist, but also if they meet their specific research objectives and if the psychometric and validity evidence is enough to select that existing PRO instrument (72).

The existence (or development) of a PRO conceptual framework guides the construct selection, item development, and psychometric testing when a new PRO instrument is developed (55, 69, 72).

The qualitative research (i.e. cognitive debriefings and focus groups) allows identifying experiences and perceptions of the target population

that need to be addressed during the development of the PRO instrument together with input from experts in the field.

Finally, rigorous psychometric testing needs to be followed (70, 74). Traditional approaches (e.g., classic test theory) are combined with more recently developed approaches (e.g. structural equation models and item response theory) to test important properties of PRO instruments such as reliability and validity (70).

2 RATIONALE

The literature review of the introduction shows that physical inactivity is a hallmark of COPD, which relates to outcomes relevant for patients and healthcare providers. Improvement of physical activity in patients with COPD may decrease symptoms, exacerbations, the progression of the disease and early death and may reduce the economical burden.

Despite the significance of physical activity, no PRO instrument exists to capture the experience of physical activity for patients with COPD. There is a need to develop and validate a PRO instrument investigating all relevant dimensions of physical activity and following a rigorous methodology in concordance with the state-of-the-art and the current guidelines on PRO development. We hypothesized that the PRO instrument should have two versions, one to cover the day-to-day recall and centred in research purposes, and another covering seven-days recall more focused for clinical practice.

The availability of a valid instrument to measure physical activity would leverage important clinical and epidemiological research in COPD because it would allow identification of important determinants of physical activity and testing the effects of drug- and non-drug treatments.

3 OBJECTIVES

3.1 General objective

- To understand what physical activity in patients with COPD means, what the causes and effects of physical (in)activity in these patients are and how to measure physical activity in patients with COPD in a valid and reliable way.

3.2 Specific objectives

- To identify available conceptual frameworks of physical activity in COPD.
- To identify and summarize studies assessing associations between physical activity and its determinants and/or outcomes in patients with COPD.
- To build a conceptual model of physical activity in COPD based on the current evidence.
- To develop and validate two versions of a PRO instrument, to cover both the day-to-day and a seven-days recall, that capture the dimensions of physical activity relevant to patients with COPD.

4 RESULTS

Manuscript 1

Gimeno-Santos E, Frei A, Dobbels F, Rüdell K, Puhan MA, Garcia-Aymerich J, on behalf of PROactive consortium.

Validity of instruments to measure physical activity may be questionable due to a lack of conceptual frameworks: a systematic review.

Health Qual Life Outcomes 2011; 9: 86-99

Impact Factor: 2,112

Manuscript 2

Gimeno-Santos E, Frei A, Steurer-Stey C, de Batlle J, Rabinovich RA, Raste Y, Hopkinson NS, Polkey MI, van Remoortel H, Troosters T, Kulich K, Karlsson N, Puhan MA, Garcia-Aymerich J, on behalf of PROactive consortium.

Determinants and outcomes of physical activity in patients with COPD: a systematic review.

Thorax 2014; 69(8): 731-739

Impact Factor: 8,376

Manuscript 3

Gimeno-Santos E, Raste Y, Demeyer H, Louvaris Z, de Jong C, Rabinovich RA, Hopkinson NS, Polkey MI, Vogiatzis I, Tabberer M, Dobbels F, Ivanoff1 N, de Boer WI, van der Molen T, Kulich K, Serra I, Basagaña X, Troosters T, Puhan M, Karlsson N, Garcia-Aymerich J, on behalf of PROactive consortium.

The PROactive instruments to measure physical activity in COPD: item reduction and initial validation.

Submitted to *European Respiratory Journal*

4.1 Manuscript 1

Validity of instruments to measure physical activity may be questionable due to a lack of conceptual frameworks: a systematic review

Gimeno-Santos E, Frei A, Dobbels F, Rüdell K, Puhan MA, Garcia-Aymerich J, on behalf of PROactive consortium

Health Qual Life Outcomes 2011; 9: 86-99

Gimeno-Santos E, Frei A, Dobbels F, Rüdell K, Puhan MA, Garcia-Aymerich J; PROactive consortium. Validity of instruments to measure physical activity may be questionable due to a lack of conceptual frameworks: a systematic review. Health Qual Life Outcomes. 2011 Oct 3;9:86.
doi: 10.1186/1477-7525-9-86

4.2 Manuscript 2

Determinants and outcomes of physical activity in patients with COPD: a systematic review

Gimeno-Santos E, Frei A, Steurer-Stey C, de Batlle J, Rabinovich RA, Raste Y, Hopkinson NS, Polkey MI, van Remoortel H, Troosters T, Kulich K, Karlsson N, Puhan MA, Garcia-Aymerich J, on behalf of PROactive consortium

Thorax 2014; 69(8): 731-739

Gimeno-Santos E, Frei A, Steurer-Stey C, de Batlle J, Rabinovich RA, Raste Y,Hopkinson NS, Polkey MI, van Remoortel H, Troosters T, Kulich K, Karlsson N,Puhan MA, Garcia-Aymerich J; PROactive consortium. Determinants and outcomes of physical activity in patients with COPD: a systematic review. Thorax. 2014 Aug;69(8):731-9. doi: 10.1136/thoraxjnl-2013-204763. Epub 2014 Feb 20. Review.
Erratum in: Thorax. 2014 Sep;69(9):810. multiple investigator names added.
Supplementary data

4.3 Manuscript 3

The PROactive instruments to measure physical activity in COPD: item reduction and initial validation

Gimeno-Santos E, Raste Y, Demeyer H, Louvaris Z, de Jong C, Rabinovich RA, Hopkinson NS, Polkey MI, Vogiatzis I, Tabberer M, Dobbels F, Ivanoff N, de Boer WI, van der Molen T, Kulich K, Serra I, Basagaña X, Troosters T, Puhan M, Karlsson N, Garcia-Aymerich J, on behalf of PROactive consortium

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doi: 10.1183/09031936.00183014
Online data supplement

5 GENERAL DISCUSSION

This general discussion complements the discussion sections included in each manuscript of this thesis with the aim to provide a broader and more integrated interpretation of the topic and the project. This section expands upon previous discussions on: (i) what physical activity for patients with COPD means, and specifically how physical activity is defined as a concept; (ii) what we know about the determinants of the physical activity and about the effects of the existing interventions to enhance physical activity in this condition; and (iii) which approaches and recommendations, both for future research and clinical practice, should be encouraged in order to advance the knowledge and implementation of physical activity measurement and/or interventions in patients with COPD.

5.1 Physical activity in COPD as a concept

So far, the both the concept and the assessment of physical activity have been focused on *the amount* of physical activity performed during a period of time. The measurement of *amount of physical activity* allows detecting levels, types and/or patterns of physical activity. However, and as a part of the PROactive project, our group identified that patients with COPD define physical activity differently, as suggested earlier (68). One of the aims of the PROactive study was to design a conceptual framework of physical activity in COPD patients using qualitative research, including patients' interview, focus groups and experts' opinion (68). The results showed that the concept 'physical activity in COPD' has three different themes: (i) amount of physical activity, (ii) symptoms experienced during physical activity, and (iii) need for physical adaptations (68). This conceptual framework was the basis for the development and validation of the 'PROactive Physical Activity in COPD (PPAC) instruments' presented in this thesis (see Manuscript 3). Actually, the items (we further tested) were generated during such qualitative research and refined in cognitive debriefings. In the process of validation (see Manuscript 3), this conceptual framework has been tested, so the concept 'physical activity in COPD' has two domains clearly defined and independent between them: 'amount' of physical activity, and 'difficulty' during physical activity. Hence, it seems that previous research, clinical approach or even health policies, that limited physical activity in patients with COPD only to its amount, are, at minimum, incomplete, and probably wrong. We propose that from now

on, both in research and in clinical practice, the whole concept of physical activity in patients with COPD, including its both domains, should be used.

The lack of a conceptual framework of physical activity in patients with COPD, identified early in this thesis work (see Manuscript 1 of this thesis), further supports this claim. The fact that researchers have been using up to 104 PRO questionnaires without a clear definition on the concept to measure and its potential domains and subdomains is a serious major concern which, at least, implies: (i) a misleading approach for grouping and scoring items into domains; (ii) an impairment in the quality of psychometric measurement model; and (iii) a wrong interpretation of the scores (55, 69). Unfortunately, it is likely that this situation is not limited to physical activity or to COPD research (22), but that probably many other PRO concepts are still not well defined prior to the development of instruments.

5.2 Determinants and interventions of physical activity in patients with COPD

One of the objectives of this thesis was to assess the associations between physical activity and its determinants, including the effects of treatments. At this moment, we can affirm that the knowledge about which are the determinants of physical activity in COPD is still scarce because, despite the large amount of research, evidence is of very poor quality (see Manuscript 2 of this thesis). This has also been proposed to be the case for the determinants of physical (in)activity in the general population (75). It is important to notice that the results about interventions (both pharmacological and non-pharmacological) aiming to improve the levels of physical activity in COPD are not that promising yet, because the effects are very inconsistent and the quality of the evidence is, again, low (see Manuscript 2). The later is very important because the initiatives to promote and increase physical activity in COPD are growing despite the current evidence is not enough (in quantity nor quality) to guide appropriate design of such programs.

Besides the traditional measurement error in physical activity questionnaires as potential responsible of null (or false negative) results, already discussed in the introduction, we believe that part of the problem with previous trials comes back to the loose definition of physical activity in COPD (see Manuscript 1). To use an example, most exercise training programs have been proven ineffective to increase physical activity in COPD patients, *when physical activity was defined uniquely as amount*

(see Manuscript 2). Most likely, results of such studies would change if the difficulty domain was also incorporated. Thus, results of previous research may have been biased (wrongly interpreted) because the main concept was not well defined (in most of the cases was not defined at all), and consequently it was not adequately assessed.

Defining physical activity with its two domains, it is likely that some interventions increase amount, others decrease difficulty, and maybe others change both domains. The same may happen when studying the determinants of physical activity, and as that should be considered in the future. It could be plausibly hypothesised, that the physiological determinants may be more related to the difficulty domain, and the psychological and environmental determinants might be more related to the amount domain.

5.3 Recommendations for future research and clinical practice related to physical activity in COPD patients

From the work in this thesis, there are two messages that seem key to improve both further research and clinical practice: (i) the design of studies and (ii) the concept of physical activity in COPD.

First, because understanding the determinants and the outcomes of physical activity in COPD is essential, not only for the development of interventions, but also for guiding the clinical practice and COPD recommendations, a major hurdle of existing research is the predominance of cross-sectional studies. As discussed in Manuscript 2, such design challenged the interpretation of the evidence because associations could not be interpreted in terms of causal effects, neither for determinants nor for outcomes. Nevertheless, the cross-sectional design has some advantages because it is useful for hypothesis testing, and allows assessing associations between variables at low cost, which provides evidence base for further longitudinal studies and clinical trials (75). Therefore, we strongly argue in favour of longitudinal studies when research focuses in variables already identified as potential determinants and/or outcomes in cross-sectional studies; the perpetuation of data "suggesting correlates" of physical activity is a waste of time, money and an unnecessary burden to patients. With regard to the design of clinical trials, we identified a surprisingly large proportion of non-controlled or non-

randomised studies. Again, this is a relevant limitation to overcome in future research.

As stated previously, two domains explained the concept of physical activity in patients with COPD: amount and difficulty (see Manuscript 3). We propose to consider the latter, together with amount, in the assessment of physical activity in patients with COPD, independently of whether the evaluation has clinical or research purposes. For research purposes, its inclusion may help to better understand which determinants related to difficulty on performance activity may modify the habit or routine in the patients.

In the clinical context, the anamnesis with a patient with COPD should routinely include a friendly discussion covering how much activity patients perform in their daily life (*amount*) and whether this is enough or not to benefit from physical activity, as well as how patients perceive their physical activity practice in relation to (internal or external) limitations (*difficulty*). Only then, the role of the health professional when advising on physical activity can effectively help the patients to identify how they can adapt their daily symptoms or other limitations towards a more active lifestyle.

6 CONCLUSIONS

Overall, the results presented in this thesis increase the knowledge about what physical activity is and how to measure it in patients with COPD. More in detail, the following conclusions result from this thesis:

1. None of the currently available PROs for measuring physical activity in patients with COPD follows the guidance on the development and validation of PROs, essentially because none of them are based on a conceptual framework with physical activity as a main concept. There is the need to develop specific conceptual frameworks for appropriate development of new PRO instruments.
2. The knowledge about the determinants of physical activity in patients with COPD is still scarce because reported associations cannot be interpreted as causal effects due to the lack of control for confounders and the cross-sectional design of most the studies. In contrast, the evidence about some outcomes of physical activity in COPD, such as on mortality and COPD exacerbations, is consistent and based on longitudinal studies of good quality.
3. The evidence of the effect of the interventions on physical activity levels in COPD patients is inconsistent and with low-to-very low quality. A well-defined end-point model in a specific clinical trial will help to choose the most appropriate PRO instrument for measuring physical activity.
4. The concept 'physical activity in COPD' has two domains: 'amount of' and 'difficulty with' physical activity, that are complementary and non interchangeable.
5. The Daily and Clinical visit 'PROactive Physical Activity in COPD' instruments are hybrid tools combining a short PRO questionnaire and two activity monitor variables, that provide simple, valid and reliable measures of physical activity in patients with COPD.

7 FUTURE RESEARCH PLANS

The validation of the Daily and Clinical visit 'PROactive Physical Activity in COPD' (PPAC) instruments is not yet complete and the PhD candidate is (and will be) participating in studies answering the following research questions:

- To investigate the responsiveness of the PPAC to several drug and non-drug (tele-coaching) interventions, all compared to usual care, in stable COPD.
- To further validate the PPAC with respect to validity and reliability in a larger number of languages, geographic areas, and a wider severity of COPD patients.

Also in the frame of the PROactive project, the PhD candidate will be leading or participating in the following analyses:

- Validation of the conceptual model of physical activity (defined with PROs) in COPD patients.
- Assessment of the physical activity pattern before and after (weeks, 6-m, 12-m) an exacerbation period.
- Assessment of the effect of sleep activity (assessed with Actigraph) at baseline on the number of COPD exacerbations during follow-up.
- Assessment of the long-term effect of physical activity on mortality in COPD patients.

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Annexes

List of manuscripts co-authored by the PhD candidate about exercise, physical activity and COPD

- Blanco I, **Gimeno E**, Munoz PA, Pizarro S, Rodriguez-Roisin R, Roca J, Barbera JA. Effects of Sildenafil in hemodynamic and gas exchange in patients with COPD and pulmonary hypertension. Am J Respir Crit Care Med 2010; 181:270-8.
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- Watz H, Pitta F, Rochester CL, Garcia-Aymerich J, [...], **Gimeno-Santos E**, [...], and Spruit MA; Rehabilitation & Chronic Care Task Force. An Official ERS Statement on Physical Activity in Chronic Obstructive Pulmonary Disease. Eur Respir J *Accepted on July 29th, 2014*.

Congress contribution

- Thematic Poster: *"Do we know what physical activity means in COPD? A systematic review*". European Respiratory Society (ERS) 2010 Annual Congress, Barcelona, Spain.
- Thematic Poster: *"Validity of instruments to measure physical activity may be questionable due to a lack of conceptual frameworks: a systematic review*". International Society for Environmental Epidemiology (ISEE) 2010 Congress, Barcelona, Spain.
- Thematic Poster: *"Estudios de validación de monitores de actividad física en comparación con calorimetría indirecta: revisión sistemática".* Congreso Nacional 2012 de la Sociedad Española de Neumología y Cirugía Torácica (SEPAR), Madrid, Spain.
- Poster Discussion: *"Validez de seis monitores de actividad física en epoc: comparación con la calorimetría indirecta"*. Congreso Nacional 2012 de la SEPAR, Madrid, Spain.
- Poster Discussion: *"Marcos conceptuales de actividad física en la enfermedad pulmonar obstructiva crónica: revisión sistemática"*. Congreso Nacional 2012 de la SEPAR, Madrid, Spain.
- Thematic Poster: *"Determinants and outcomes of physical activity in patients with COPD"*. ERS 2013 Annual Congress, Barcelona, Spain.
- Thematic Poster: *"Patient reported outcomes for the measurement of physical activity in COPD patients. The PROactive tools"*. ERS 2013 Annual Congress, Barcelona, Spain.
- Poster Discussion: *"Determinantes y efectos de la actividad física en pacientes con enfermedad pulmonar obstructiva crónica (EPOC)"*. Congreso Nacional 2013 de la SEPAR, Barcelona, Spain. Award: "Best communication of the Nurse and Physiotherapy Group".