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Assessing Physical Activity and Physical Capacity in Subjects with Chronic Obstructive Pulmonary Disease

MIKAEL ANDERSSON

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Abstract

Andersson, M. 2014. Assessing Physical Activity and Physical Capacity in Subjects with Chronic Obstructive Pulmonary Disease. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 982. 64 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-554-8905-2.

The overall aim of this thesis was to assess measurement properties of methods suitable for screening or monitoring of physical capacity and physical activity in subjects with chronic obstructive pulmonary disease (COPD), and to explore factors associated with physical activity levels.

Methods: Four observational studies were conducted. Participants in studies I-III (sample sizes) (n=49, n=15, n=73) were recruited from specialist clinics, and in study IV from a population-based cohort (COPD n=470 and Non-COPD n=659). Psychometric properties of methods assessing physical capacity (study I) and physical activity (study II) were investigated in laboratory settings. Daily physical activity and clinical characteristics were assessed with objective methods (study III) and with subjective methods (study IV).

Results: Physical capacity as measured by walking speed during a 30-metre walk test displayed high test-retest correlations (ICC>0.87) and small measurement error. The accuracy for step count and body positions differed between activity monitors and direct observations. In study III 92% of subjects had an activity level below what is recommended in guidelines. Forty five percent of subjects' activity could be accounted for by clinical characteristics with lung function (22.5%), walking speed (10.1%), quadriceps strength (7.0%) and fat-free mass index (3.0%) being significant predictors. In study IV, low physical activity was significantly more prevalent in COPD subjects from GOLD grade ≥II than among Non-COPD subjects (22.4 vs. 14.6%, p = 0.016). The strongest factors associated with low activity in COPD subjects were a history of heart disease, OR (CI 95%) 2.11 (1.10-4.08) and fatigue, OR 2.33 (1.31-4.13) while obesity was the only significant factor in Non-COPD subjects, OR 2.26 (1.17-4.35).

Conclusion: The 30 meter walk test and activity monitors are useful when assessing physical capacity and physical activity, respectively in patients with COPD. Impaired physical activity in severe COPD is related to low lung function, low walking speed, low muscle strength and altered body composition, whereas comorbidities and fatigue are linked to insufficient physical activity in patients with moderately severe COPD.

Keywords: COPD, chronic obstructive pulmonary disease, physical activity, measurement properties, reliability, accuracy, validity, sedentary behavior, activity monitor, questionnaire, anthropometrics, comorbidity, fatigue

Mikael Andersson, Department of Neuroscience, Physiotheraphy, Box 593, Uppsala University, SE-75124 Uppsala, Sweden.

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“If it can't be expressed in figures, it is not science; it is opinion”

Robert A. Heinlein

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Andersson M, Moberg L, Svantesson U, Sundbom A, Johansson H, Emtner M. (2011) Measuring walking speed in COPD: test-retest reliability of the 30-metre walk test and comparison with the 6-minute walk test. *Primary Care Respiratory Journal*, 20(4):434–40.

II Andersson M, Janson C, Emtner M. (2014) Accuracy of three activity monitors in patients with chronic obstructive pulmonary disease - A comparison with video recordings. *COPD [accepted for publication]*.

III Andersson M, Slinde F, Grönberg AM, Svantesson U, Janson C, Emtner M. (2013) Physical activity level and its clinical correlates in chronic obstructive pulmonary disease: a cross-sectional study. *Respiratory Research,* 1 (14) 128.

IV Andersson M, Stridsman C, Rönmark E, Lindberg A, Emtner, M. (2014) Physical activity and fatigue in subjects with COPD – A population-based study *[in manuscript]*.

Contents

Abbreviations

6MWT	6-Minute Walk Test
30mWT	30-metre Walk Test
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
GOLD	The Global initiative for Obstructive Lung Disease
EE	Energy Expenditure
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
FFM	Fat-Free Mass
FFMI	Fat-Free Mass Index
ICC	Intraclass Correlation Coefficient
ISWT	Incremental Shuttle Walk Test
IPAQ	International Physical Activity Questionnaire
mMRC	Modified Medical Research Council
OLIN	Obstructive Lung disease In Northern Sweden
RMR	Resting Metabolic Rate
SEM	Standard Error of Measurement

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease, characterized by non-reversible airflow obstruction (1). COPD is a leading cause of morbidity and mortality, and was ranked as the third leading cause of death in the world 2010 (2). The prevalence of COPD is estimated to be about 9-10% from the age of 40 (3) and the disease has implications reaching far beyond the lungs and airways. The fact that the condition is chronic means that treatment is directed towards symptom relief, halting progression and minimizing the impact on daily life. Although the condition in chronic, there are many possibilities for treatment, and the condition is not to be seen as static.

Definition of COPD

The current updated report from the Global initiative for Obstructive Lung Disease (GOLD) defines COPD as follows: *"COPD, a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory response in the airways and lungs to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients"* (1).

Pathology

The primary cause of COPD is inhalation of particles (usually tobacco smoke) that gives rise to an inflammatory response in the lung parenchyma and small airways. The inflammation leads to mucosal hyper secretion (4), remodeling of small airways (5), increased airway resistance, loss of alveolar detachments and decreased elastic properties of the lung (5). Primary smoking is the dominant risk factor for developing disease, but exposure to secondary smoke is also associated with COPD (6). In developing countries noxious particles can be

Altered mechanical properties of the lungs, increased dead space ventilation, increased ventilatory demands, deconditioning and peripheral muscle dysfunction (7), contributes to the ventilatory limitations in subjects(8). The

inability to rapidly expire air leads to incomplete emptying of the lungs, particularly during exercise (9). In flow limited subjects, increasing expiratory effort beyond a critical point only contributes to further worsening of the flow limitation (8) and increased sensations of dyspnea relating to a discrepancy between inspiratory muscle effort and ventilatory output (10).

Indicators of COPD

Key indicators of COPD include: progressive and persistent dyspnea, chronic cough, chronic sputum production, and a history of exposure to risk factors, particularly tobacco smoke (1). If one or several of the indicators are present, spirometry should be performed to confirm or refute the diagnosis of COPD. A post bronchodilator value for the ratio of forced expiratory volume in one second (FEV_1) by the Forced Vital Capacity (FVC) below 0.7 indicates an obstructive spirometric pattern (1).

If airway obstruction is confirmed, subject's post bronchodilator FEV_1 expressed percent of predicted values can be used to grade the severity of airway obstruction according to the system proposed by GOLD (1) (table 1).

Table 1. Grading of airflow obstruction according to GOLD.

All values are intended as post-bronchodilator FEV_1 in patients with a ratio of $FEV_1/FVC < 0.70$:		
GOLD I	Mild	$FEV_1 \geq 80\%$ predicted
GOLD II	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD III	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD IV	Very Severe	$FEV_1 < 30\%$ predicted

FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; GOLD = the Global initiative for Chronic Obstructive Lung Disease

An exacerbation of COPD is defined as a worsening of the patient's respiratory symptoms that is beyond normal day-day variations and leads to a change in medication. By combining lung function measurements, symptoms and exacerbation history, assessment of risk of future exacerbations is possible and now recommended as a complement to the spirometric classification (1).

Characteristics of COPD

Cardinal symptoms of COPD are dyspnea and fatigue, often leading to limitations in daily life (11). Co-morbid conditions contribute to the over-all burden in the individual patient and cardiovascular, metabolic, musculoskel-

etal dysfunction, systemic inflammation and osteoporosis are commonly reported comorbid conditions (12)(13).

The complexity of the disease has been suggested to form a "vicious cycle" (14) where the pulmonary manifestations interact in a complex manner to impact patient's health status and health related quality of life through deconditioning, activity limitations and symptoms of dyspnea and anxiety (figure 1). The complexity strongly supports the need for an integrated treatment that extends beyond pharmacological alternatives.

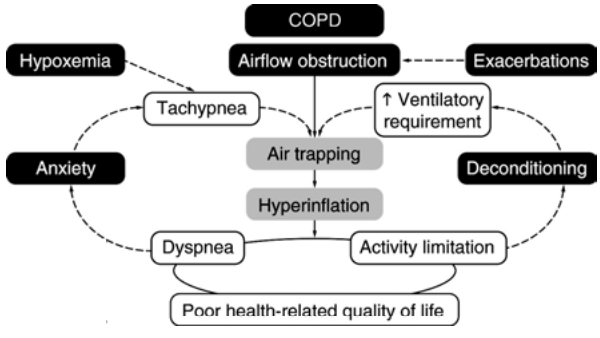


Figure 1. The vicious cycle of symptoms and physical inactivity in COPD.
Troosters *et al. Respiratory Research* 2013 **14**:115 (15)

Treatment of COPD

Treatment can be divided into two main directions; pharmacological and non-pharmacological treatment, which are often combined.

The goal of pharmacological therapy is to reduce symptoms frequency and severity of exacerbations as well as to improve health status and exercise tolerance (1). The greatest potential for impacting the progression of COPD is smoking cessation in subjects who are active smokers (16). The damage that has been inflicted to the lung parenchyma and airways it is not recovered, but the rate of the decline in lung function is reverted to the expected age-related decline seen in non-smokers. The pharmacological treatment is directed towards respiratory symptoms; bronchodilators ($Beta_2$-agonists and anticholinergics) are prescribed as regular and relief treatment, and in addition inhaled corticosteroids are indicated in patients at higher risk of exacerbations.

The term non-pharmacological treatment is usually synonymous with pulmonary rehabilitation. Pulmonary rehabilitation is described as an integrated care model which has been proposed to "*be an integral part of the clinical management of all patients with chronic respiratory disease, ad-*

dressing their functional and/or physiologic deficits"(17). Key parts of the pulmonary rehabilitation include physical exercise, nutritional counseling and patient education, with the aim of improving patients' participation in everyday activities and reducing activity limitations (1)

The limitations in activity becomes evident when comparing physical activity patterns in subjects with COPD to that of healthy subjects: In COPD, more time is spent in sedentary behaviors (sitting and lying) and less time walking and standing up (18)(19)(20). Regular physical activity is reported to be preventive for a number of health conditions; diabetes, cancer, cardiovascular disease, hypertension, depression, osteoporosis and obesity (21). This indicates that the lower activity levels observed in COPD could place these subjects at risk for several other conditions. The severity of low physical activity was highlighted in the 2009 report from the World Health Organization (WHO) on the burden of disease and mortality attributable to various risk factors. The WHO concludes that physical inactivity constitutes the fourth leading risk factor for global mortality (22). Support for the need of extra vigilance in regards to activity levels in COPD comes from cross-sectional data comparing physical activity in healthy with that of subjects with chronic diseases (23). Insufficient physical activity was common in healthy (60%), but significantly more prevalent in rheumatoid arthritis (74%) and diabetes mellitus (72%) and particularly in COPD (82%). From a health care perspective, physical activity (and inactivity) should be seen as a modifiable risk factor in the population, and of particular importance in a sedentary population such as COPD.

Physical activity –definition of terms and public recommendations

Physical activity is defined as "Any bodily movement produced by skeletal muscles that result in energy expenditure" (24). This is distinctly separate, although related, to the concept of **physical fitness** which is defined as "a set of attributes people have or achieve that relates to the ability to perform activities". If activities are "planned, structured, repetitive and purposive in the sense that improvement or maintenance of one or more components of physical fitness is the objective" it is labeled **exercise.** The health-related components of physical fitness (considered equivalent to the term **physical capacity** used in this thesis) can be further subdivided into cardio-respiratory endurance, muscular endurance, muscular strength, body composition and flexibility (24). The complete assessment and description of subjects' physical activity or exercise habits would need to include information on four more dimensions: *i*) **frequency***,* the number of time the activity/event has oc-

curred, *ii*) **duration**, time invested in a single bout of activity, *iii*) **intensity**, the physiological effort associated with performing it, *iv*) the **type** of activity performed (25). The **volume** indicates the total amount activity accumulated in a specific time period and is the result of the frequency, duration and intensity of the performed activities.

The recommended amount of weekly physical activity for individuals aged 65 years and above, or individuals with chronic non-communicable conditions, is to achieve a weekly volume of at least 150 minutes of moderate intensity aerobic physical activity, accumulated in bouts of a minimum 10 minute duration, *or* by performing higher intensity activities for a shorter total duration (75 minutes) *or* any combination of the above (22). In addition to aerobic activities, muscle-strengthening exercises should be performed two times per week according to the same guidelines. The recommendations recognizes that in elderly subjects or those with chronic conditions affecting their ability to perform activities, smaller volumes of activity is probably still beneficial and should be encouraged. Furthermore, the intensity of activities should be interpreted relative to the fitness level of the individual.

As reflected in the definition of physical activity, a key construct relating to physical activity is movement. Movement can be expressed in terms of behaviors individuals exhibit (active or sedentary), or by their resulting physiological attributes (energy expenditure, increased/decreased fitness) (26) (figure 2). The separation of behavioral aspects of movement from the associated physiological attributes is necessary as a guide in selecting the appropriate type of measurement tool for the quantification of the aspect of interest.

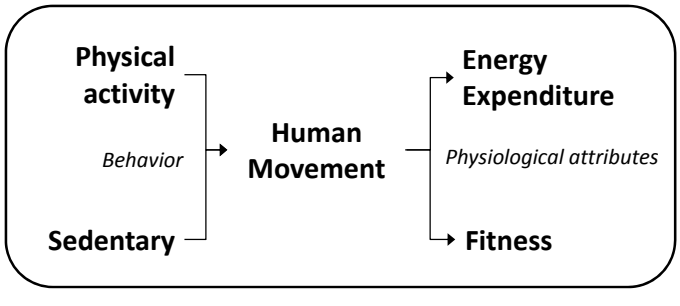


Figure 2. Graphical representation of the relationships between the behavioral aspects of human movement and the related physiological attributes. Inspired by the framework by Pettee Gabriel, Morrow and Woolsey (26).

The term **physical inactivity** can be used to describe the state of subjects not reaching the recommended level of activity, whereas sedentary is considered as a separate entity. **Sedentary behavior** has been defined as "activities that do not increase energy expenditure substantially above the resting level and

includes activities such as sleeping, sitting, lying down (27). Sedentary behavior has been linked to increased risk for metabolic syndrome and mortality, effects that are present even if the recommended physical activity level is achieved (28)(29). However, whether these observations on sedentary behaviors and their associated risks are valid for subjects with COPD is not yet established.

Clear evidence of positive health outcomes from physical activity (21)(30), and emerging evidence of detrimental effects from sedentary behaviors (31) highlights the need for reliable and valid methods for quantifying all aspects of human movement.

Methods for quantifying physical activity

Two principal methods can be applied for quantifying the behaviors of physical activity and sedentary behavior as well as the physiological attributes; objective and subjective methods (32).

Objective methods

There are several methods that are considered "objective" in the sense that the data collected is not dependent on subject's report and recall of events. The type of objective method to utilize depends on aspects such as economical, practical (need of specialist personnel) or availability, but should primarily be guided by the research question at hand (25). Different methods are needed for capturing behavioral aspects of movement than the physiological attributes resulting from the behavior (figure 2).

To estimate energy expenditure (EE), a physiological attribute, in daily life the doubly labeled water technique can be applied (33)**.** The technique is limited by very high costs associated with the analysis, and by the fact that the only outcome consists of the total energy expended. No data on type, intensity, duration or frequency can be derived. To achieve greater level of details on both the behavioral and the physiological attributes of subject's movement in daily life, different types of activity monitors can be utilized. These are devices worn on the body to register movement (acceleration). The simplest form of device is pedometers, a spring-loaded devices that measures vertical movement of the body and translates this into steps·unit time^{-1} (e.g. per day). More sophisticated motion sensors, accelerometers, register both the rate and magnitude of movement (34). These devices register accelerations (gravitational forces) in one, two or three planes depending on the type of accelerometer used.

A subdivision of accelerometers can be made with regard to the primary outcome they provide; EE-devices, or body-positional devices (35). The EE-types record raw acceleration data (counts) and averages these counts over a specific time frame (epoch). The outcome is an estimate of the time spent at different intensity levels (moderate, vigorous or sedentary) and often step

count is reported as a measure of ambulatory activity. The body-positional device either attempts to determine the body position through an algorithm that assesses the accelerometer signal, or uses inclinometers to track the position of the device (and thereby the body segment by which it is attached). Other approaches such as integrating physiologic sensors to improve the estimated energy expenditure are also available (36).

The accuracy of activity monitors has been shown to be negatively affected in subjects with slow movement patterns, such as COPD (37).

Subjective methods

If data is collected based on patients recollection of events the method is said to be subjective. To assess physical activity (or sedentary) behaviors by subjective methods, questionnaires, recall forms or record/log books of activity can be utilized (32). Typically questionnaires are designed to collect data on the four dimensions relating to the activity behavior; frequency, intensity, type and duration. With these data, physiological attributes relating from the reported activity can be estimated using standard tables of energy expenditure for various types of activities (38). Advantages of subjective measures compared to objective methods are low costs and ease of administration which makes it a feasible method for large scale, epidemiological studies (39). Drawbacks include uncertainty of subjects to recall activities, and concerns regarding the construct validity in many of the questionnaires have been raised (40). Some types of activities, such as eating behaviors are often underreported, whereas physical activity is over reported (41).

Reliability and validity of assessment methods

Reliability of assessment methods

All performance based tests are affected by several sources of error contributing to variability in the measurement, including learning effects, motivational aspects and the biological variability in human performance. In measurement theory, the score of an individual is only an *observed score*. This means that inherent in every observed score is both the *true score* and some degree of *error*. In the 6-minute walk tests, an increase in the distance walked between two test occasions, attributed two a learning effect, ranges between 0-17% (42). To separate variability in scores due to different sources of error, reliability studies must be conducted for the specific instrument and population for which it is to be applied. The information can then be used to assess whether differences in performance are due to a real treatment effect or possibly be accounted for by measurement error.

Reliability is a term describing the consistency or reproducibility of measurements across different occasion, or to assess the consistency between different raters (43). There are several ways in which reliability could be

evaluated, and several statistical methods can be applied (44). One of the most common analyses is assessing same individuals at two occasions, separated by a short time frame and analyzing the agreement between them, *test-retest reliability*. The Intraclass Correlation Coefficients (ICC) are often applied, but should be complemented by methods analyzing the differences between tests (45)(43). The time between occasions in a test-retest study should be long enough to avoid fatigue from the first test to affect the latter, but short enough to avoid the underlying construct to change.

Validity of assessment methods

Validity pertains to the question of whether an instrument measures what it is intended to measure (46). If a new method is introduced to complement or replace and established one, the criterion validity of the new method should be addressed. This is achieved by comparing the new instrument with a well established method (the criterion) for the area of interest using correlation analysis. The type of criterion chosen should be based on the construct of interest.

Recommendation on how to perform and report validation studies on activity monitors are to compare several different activity monitors against a specific criterion in the same study (47). In this way criterion validity can be assessed for each activity monitor, and by comparing the agreement between monitors against the criterion the concurrent/convergent validity can also be assessed. Most studies examining the validity of activity monitors have been in healthy young subjects with only limited evidence in disabled populations (48). The various ways that different activity monitors processes, filters and analyzes the accelerometer signal means that although identical outputs are reported by different activity monitors, equivalency cannot be assumed if validation studies in the intended population are not available (47).

Physical activity in COPD

When assessed by objective methods, the physical activity level in subjects with COPD is low compared to healthy controls (18)(19)(20)(49)(50). The consequences of low physical activity can be severe in COPD, as indicated by a longitudinal population-based study; among subjects reporting some degree of physical activity (low, moderate or high), the risks of both hospital admission and all-cause mortality were decreased (51). The authors also observed that this protective effect of at least some regular physical activity persisted when reanalyzing groups stratified by age, disease severity and history of heart disease. In active smokers moderate (≥2h/week) to high (≥4h/week) amounts of light activity has been associated with a reduction in lung function decline and seem to protect against the development of COPD (52). Pitta et. al showed, using activity monitors, that patients with low activ-

ity (time spend walking) were more likely to have been admitted for exacerbations the proceeding year, and to be admitted during the year following the current exacerbation (53). Low activity levels among subjects with COPD are associated with worse health related quality of life (23), and increased activity levels are associated with improved quality of life (54). Some caution is needed in the interpretation of the latter studies since the physical activity was assessed with subjective methods.

The traditional pulmonary rehabilitation efforts have been targeting the physical capacity dimension, assuming that improvements in capacity will spill over to activity, but also by the associations between impaired in physical capacity and increased mortality.

Physical capacity in COPD

Systemic effects of COPD are observed in several aspects of physical capacity; altered body composition, muscle dysfunction and impaired exercise capacity are frequently observed and associated with increased mortality.

The impact of weight change, as measured by reduction in body mass index (BMI) on mortality was investigated in the population-based Copenhagen City Heart Study (55). Increased risk of mortality was observed for weight loss of >3 units of BMI in both COPD and non-COPD, whereas weight gain was associated with mortality in non-COPD only (55). The association between mortality and BMI has been described as U-shaped in the general population with the least risk attributable to subjects of normal weight (BMI 20.0-29.9 kg/m^2) and higher risks at both the low and high end of the BMI continuum (56). In COPD, low weight (BMI<20) has been associated with increased risk of mortality (57). Since BMI does not take into account the distribution of weight loss in the different body compartments, the risks associated with loss of fat-free mass (FFM) has been investigated (58). Vestbo et al. observed that despite having a BMI in the normal range, 26% of subjects had a FFM below the 10^{th} percentile of a healthy population. The authors concluded that both BMI and FFM was predictors of mortality, but that FFM was an independent predictor even in cases of normal BMI, therefore contributing complementary information in clinical practice. Since the main proportion of FFM is muscle mass, an impaired body composition could be expected to have implications for functional performance and exercise capacity.

Reduced maximal quadriceps strength has been shown to be linked to impaired exercise capacity when assessed by a field walk test, whereas the maximal exercise capacity mainly was associated with lung function (59). The impairment in muscle function can be complex as both the maximal strength and endurance capacity can be affected. When comparing both these aspects in a sample of subjects with COPD and elderly controls, both maxi-

mal strength and endurance were reduced in COPD (60). Coronell et al. observed that reduced endurance was independent of physical activity and present already in mild airway obstruction. They also noted that impaired endurance could not be predicted based on their subjects maximal strength measurements.

In assessing whether functional capacity is impaired the use of exercise tests have been recommended as a global sign of the integrated response of the involved systems (61). The type of test to conduct in clinical setting is often dictated by practical issues of having access to the necessary equipment and limited time at hand (62). This has lead to the development of several field tests of exercise capacity, and in COPD most have been targeting walking performance. Walking has usually been assessed by the maximal distance covered in fixed time (6 or 12 minutes) (42)(63), or by the distance walked at a constant (64) or incremental speed (65). A reduced walking distance in COPD has been shown to be a better indicator of progression of disease than lung function (66), and distance walked in a 6MWT has been recommended as an outcome in clinical trials (42), useful for predicting mortality (67), exacerbations (68), and as an outcome of pulmonary rehabilitation (69).

When assessing the complex picture of impairments reported in COPD, clearly no test of function is likely to be able to capture the full range of possible impairments. The degree of airway obstruction is not likely to reliably reflect body composition, symptoms and subjects performance. In an attempt to improve the predictive capabilities of physical capacity measures, Celli et al. derived a composite index of several known risk factors; BMI, airway Obstruction, Dyspnea and Exercise capacity (BODE-index)(70). They demonstrated that the predictive capabilities were improved when assessed as a composite score than as individual predictors in their sample, indicating the need of comprehensive assessment of patients.

Rationale for this thesis

Although several field exercise tests have been developed and proven successful in identifying individuals at risk of exacerbations and mortality (66), the time required to perform them as well as the strain placed on patients makes implement into clinical practice challenging. Low levels of activity in daily life is a risk factor for exacerbations (53) and mortality (51). New objective assessment methods could prove useful for exploring both sedentary behaviors as well as supplying detailed information on physical activity behaviors in COPD if their validity for behavioral aspects proves adequate. The identification of factors distinguishing subjects suitable for pulmonary rehabilitation is still highly relevant given the positive effects thereof.

Aims

The overall aim of this thesis was to assess measurement properties of methods suitable for screening or monitoring of physical capacity and physical activity levels in subjects with chronic obstructive pulmonary disease, and to explore factors associated with daily physical activity levels.

The specific aims of the studies included in this thesis were:

To examine test-retest reliability of the 30-metre walk test in subjects with COPD and to compare the 30-metre walk test with the 6-minute walk test (*Study I*).

To assess the accuracy and equivalency of three activity monitors regarding steps, body position and their ability to differentiate between periods of physical activity and inactivity in subjects with moderate to very severe COPD (*Study II*).

To explore the clinical characteristics of physical activity in subjects with moderate to very severe COPD, with special emphasis on variables that are amendable through rehabilitation efforts (*Study III*).

To assess physical activity levels in a population-based sample of subjects with and without COPD, and to investigate which factors that would be associated with low physical activity in these groups *(Study IV)*.

Methods

Design and ethics

The thesis consists of four observational studies, based on four samples (table 2). Participants in all studies were given verbal and written information about the aim, methods and procedures of the specific study and gave their informed consent to participate. All studies were approved by the respective regional ethical review board (EPN); **studies I** and **III** were approved by the EPN in Gothenburg (D-nr: 408-05), and **study II** by the EPN in Uppsala (D-nr: 2009/093). **Study IV** was approved by the Regional Ethics Committee at University Hospital of Northern Sweden and Umeå University.

Participants and procedures

All participants in **studies I** and **III** had diagnose of COPD and were recruited by convenience sampling from the pulmonary units at Uppsala University Hospital, Uppsala and/or Sahlgrenska University Hospital, Gothenburg. Participants in **study II** were recruited from the pulmonary unit at Uppsala University Hospital. **Study IV** was based on an outpatient sample from the population based Obstructive Lung disease In Northern Sweden (OLIN) COPD study cohort, consisting of subjects with and without COPD. Sample characteristics are presented in table 3. In **studies I-III** treatment with long term oxygen therapy was an exclusion criterion. In **study II** a $FEV_1 > 80$ percent of predicted was also applied as exclusion criteria. In **study III** other conditions known to affect muscular tissue or performance (such as chronic heart failure, renal failure, rheumatic disease, diabetes or severe arthritis) were grounds for exclusion.

Table 2. Overview of study designs, sample sizes, inclusion criteria and procedures of the studies included in the thesis.

	Study I	Study II	Study III	Study IV
Design	Observational (Descriptive, correlative)	Observational (Descriptive)	Observational (Descriptive, correlative)	Observational (Cross-sectional cohort)
Inclusion criteria	• $FEV_1/FVC < 0.70$ • Ability to perform walk tests	• $FEV_1/FVC < 0.70$ • Stable condition	• FEV_1/FVC of 2 SR below reference population • ≥ 10 pack years • Stable disease	• $FEV_1/FVC < 0.70$ • Complete IPAQ
Sample size, (n)	49	15	73	1129
Type of data collected	Functional performance Lung function	Physical activity Video observation Lung function	Objectively assessed physical activity Functional performance Detailed anthropometrics Blood samples Lung function	Questionnaires (physical activity, fatigue) Structured interview Lung function
Main analysis strategy	Bland-Altman SEM ICC	Bland-Altman Friedmans ANOVA ICC	Multiple linear regression	Binary logistic regression

1 pack year = 20 cigarettes/day x 365; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; SR = standardized residuals; IPAQ = International physical activity questionnaire; SEM = standard error of measurement; ICC = intraclass correlation coefficient; Bland-Altman = mean vs. difference analysis with accompanying graphical presentation

Table 3. Overview of the sample characteristics for studies included in the thesis. Numbers are mean and standard deviations or proportions if not otherwise stated.

	Study I	**Study II**	**Study III**	**Study IV**	
Characteristic	(n = 49)	(n = 15)	(n = 73)	(n = 470 COPD)	(659 Non-COPD)
Age (years)	67 ± 8	64 ± 6	65 ± 7	68 ± 10	67 ± 10
Gender, male/female (n)	16/31	7/8	28/44	257/213	359/300
BMI (kg/m^2)	25 ± 6	21 ± 3	24 ± 4.7	27 ± 4	28 ± 4
FEV_1 (L)	1.20 ± 0.49	1.13 ± 0.39	1.11 ± 0.43	2.26 ± 0.52	2.75 ± 0.76
FEV1 % pred. (%)	46 ± 17	37 ± 12	43 ± 15	82 ± 18	104 ± 16
(F)VC (L)	2.77 ± 0.85	2.97 ± 0.81	2.61 ± 0.80	3.48 ± 1.02	3.51 ± 0.96
FVC % pred. (%)	83 ± 22	77 ± 21	83 ± 20	105 ± 19	110 ± 18
GOLD grade I/II/III/IV (n)	1 / 19 / 18 / 9	0 / 3 / 8 / 4	1/18/37/16	309/148/11/2	n/a
Current smokers (%)	17%	*38**	28%	25%	8%

*= pack years (1 pack year = 20 cigarettes/day x 365); n/a = not applicable; FEV_1 % pred. = forced expiratory volume in one second; FVC = forced vital capacity; FEV_1 % pred. = FEV1 in percent of predicted value; FVC % pred. = FVC in percent of predicted value.

Study I

A total of 49 subjects were recruited, 25 in Uppsala and 24 in Gothenburg. Potential subjects were identified from patient registries and study representatives contacted them by telephone to inform about the purpose of the study and to assess eligibility against inclusion criteria. Subjects were consecutively invited to two clinical visits. At the first visit inclusion criteria was confirmed and four walk tests were performed; two 30-metre walk tests and two six minute walk tests. At the second visit, approximately seven days later and at the same time of day, a retest of the 30mWT was conducted.

Study II

Seventeen subjects were approached and 15 accepted participation. The same physiotherapist (MA) was responsible for screening of subjects and recruitment to the study. Subjects were consecutively included until the target sample size of 15 had been reached. At the clinical visit, subjects performed a structured protocol of 53 minutes comprised of different activities mimicking daily life of subjects with COPD. When performing the protocol subjects wore all three activity monitors simultaneously while being video recorded. After completion of the protocol measurements, subjects were asked to simultaneously wear all three monitors during one day at home.

Study III

Seventy-three subjects were recruited from the pulmonary unit at Sahlgrenska University Hospital in Gothenburg, Sweden. Eligible subjects matching the inclusion criteria were contacted by telephone. Subjects who gave their oral consent were sent detailed information on the study by post and the first of three clinical visits were scheduled. At the first visit a spirometry was performed, each subject´s resting metabolic rate was measured and blood-samples were drawn. At the second visit, walk tests were performed and anthropometrics measured. At the end of the visit subjects were fitted with the activity monitor and given instruction and information regarding its application and use. The instruction to subjects was to wear the monitor for seven days and then return it by prepaid mail.

Study IV

Participants consisted of subjects from the OLIN COPD study in the county of Norrbotten, Sweden. The OLIN COPD cohort was formed from previous population-based OLIN cohorts that were re-invited for clinical visits including lung function measurements between years 2002-2004. Subjects with a

ratio of FEV_1/FVC ratio < 0.70 (n = 993) were defined as cases with COPD, and from the same population a similar age and gender-matched control group was formed by subjects with a FEV_1/FVC > 0.70 (n = 993). These groups formed the OLIN COPD study which has been invited for yearly examinations since 2005.

In **study IV** all subjects in the OLIN COPD cohort that attended the clinical visit in 2008 were eligible for participation. Inclusion criteria were: complete data on the International Physical Activity Questionnaire (IPAQ), and having performed spirometry assessments. Subjects were grouped into COPD and Non-COPD based on the spirometry performed at the clinical visit 2008.

Data collection

Lung function

If no recent spirometry data measurements (within six months) were available in patient´s records, dynamic spirometry was performed to ascertain inclusion criteria of the respective study. Spirometry was performed according to guidelines (71) and reference values were applied to assess disease severity. Reference values of the European Community for Coal and Steel (72) were used in **studies I-III** and in **study IV** reference values by Berglund were applied (73).

Definition of chronic airway obstruction*:* A fixed ratio of FEV_1/ (F)VC < 0.70 was used in studies I, II and IV. In study III a ratio of > 2 standardized residuals below the reference population was used.

Grading of airway obstruction: Based on a subject´s FEV_1 in percent of predicted value, the four-grade spirometric classification proposed by the GOLD committee was applied (74) ($FEV_1 \geq 80$ % predicted = GOLD I, FEV_1 79-50 % predicted = GOLD II, FEV_1 49-30 % predicted = GOLD III, $FEV_1 < 30$ % predicted = GOLD IV).

Symptoms

Dyspnea (Studies I, III, IV)

The modified Medical Research Council dyspnea scale (mMRC) (75) was used to assess dyspnea. The scale is a five item self-complete adjectival scale ranging from 0: "*I only get breathless with strenuous exercise*" to 4: "*I am too breathless to leave the house or I am breathless when dressing*". The maximum score is 4, indicating the worst dyspnea.

Fatigue (Study IV)

The Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT-F) was used (76). FACIT-F is a 13-item self-reported Likert scale

with five options per item. Questions relate to both the intensity and impact of fatigue during the last seven days and scored on as follows: (score) *Not at all (0), A little bit (1), somewhat (2), Quite a bit (3), Very much (4)*. Maximum score is 52 indicating less fatigue, which is achieved by reversing scores for negatively phrased questions. A difference of 3-4 points has been reported as the minimal important difference (77).

Definition of clinically significant fatigue: In study IV a score ≥3 points below the median person of the Non-COPD group was considered indicative of clinically significant fatigue.

Anthropometrics

Body weight and height (studies I, II, III, IV)

A wall-mounted stadiometer was used to measure a subject's height (cm), and body weight was measured to the nearest 0.1 kg. BMI was calculated as bodyweight/body height squared (kg/m^2).

Fat-free mass (study III)

Dual-energy x-ray absorptiometry (DEXA) (Lunar Prodigy, GE Healthcare, United Kingdom) was used to measure body composition in **study III**. Fat-free mass (FFM) was measured in grams and normalized to the subject´s height into a fat-free mass index (FFMI). FFMI was calculated as FFM-weight/body height squared (kg/m^2).

Definition of FFM-depletion*:* FFM depletion was defined as a FFMI ≤ 15 for women or ≤ 16 for men, as proposed by Vermeeren et al. (78).

Definition of sarcopenia: Sarcopenia was defined as a lean appendicular mass, corrected for height squared, of two standard deviations below the mean of a healthy young reference group in combination with usual walking speed < 1.0m/s and/or low muscle strength (79).

Functional performance

Walking speed (Studies I, III)

The 30-metre walk test (30mWT) was used to assess the time needed to cover a 30-metre distance at two walking speeds: *self-selected* and *maximal speed.* The outcome of the test is the time(s) needed to cover the 30-metre distance, from which the mean self-selected and maximal speeds (m/s) are derived.

Definition of slow walking: In study III a self-selected walking speed of 1.0 m/s was used as a cut-off for normal walking speed (80). Reference values for walking speed from Bohannon et al. were applied in study I (81).

Walking distance (Study I, II, III)

The six-minute walk test (82) (6MWT) was used to measure the maximal distance covered in six minutes when walking at a self-selected speed. The

test was performed in a quiet, 30 metre corridor and standardized according to guidelines (42). The outcome of the test is distance (m) covered in six minutes. Reference values for walking distance from Enright and Sherrill were applied in study I (83).

Muscle strength (study III)

The maximal knee-extensor strength was measured by isometric dynamometry using the *SteveStrong dynamometer* (SteveStrong HB, Gothenburg, Sweden). The outcome used was the maximal strength (N) obtained from either leg.

Definition of quadriceps weakness: Muscle weakness was defined as a maximal quadriceps strength ≥ *1.645* standardized residuals below the reference population (84).

Physical activity – objectively assessed

Accelerometry was used in **study II**. The accelerometers included were: the DynaPort ADL-monitor (McRoberts, The Hague, Netherlands), the DynaPort MiniMod (McRoberts, The Hague, Netherlands) and the BodyMedia SenseWear Armband, pro3 (SenseWear, BodyMedia, Pittsburg, USA). Monitor accuracy was assessed for the following indices of physical activity: *step count, body positions and pattern of energy expenditure rates*. Physical activity level was dichotomized based on daily step count from one day of measurement in the subject´s home setting as active (≥ 4580/day) or inactive (<4580/day) (85).

In **study III**, the ActiReg activity monitor (Premed AS, Oslo, Norway) was used. The main outcome is energy expenditure calculated using the ActiCalc software (Premed AS, Oslo, Norway). By incorporating a subject´s resting metabolic rate, the relationship of the total energy expenditure and resting energy expenditure can be expressed as a ratio; the physical activity level (PAL) (86).

Definition of activity levels: Subjects mean PAL value from seven days of measurement was used to categorize their lifestyle as; very inactive (PAL<1.40), lightly active (PAL 1.40-1.69), active or moderately active (PAL 1.70-1.99) or vigorously active (PAL 2.00-2-40)(86).

Physical activity – self-reported

The International Physical Activity Questionnaire (IPAQ) (87), specifically the culturally adapted short version (88), was used in **study IV** to assess habitual physical activity levels. The outcomes from IPAQ is expressed categorically as *low, moderate* or *high* physical activity level*,* alternatively expressed as a body weight adjusted estimate of total weekly activity, MET-minutes performed at health enhancing levels (at least moderate intensity) (89).

Definition of low physical activity: In **study IV** subjects not reporting weekly physical activity equivalent to at least 30 minutes of moderate activity or walking on five days or more, were categorized in the IPAQ low category (89).

Resting metabolic rate

In **study III** resting metabolic rate (RMR) was measured using a ventilated hood system (Deltatrac II, Datex, Helsinki, Finland). Measurements were performed after overnight fast (12h) with subjects well rested, in the supine position and in a temperature-neutral environment. The mean energy expenditure rate from the last 25 minutes of a 30-minute measuring period was used to determine the RMR.

Systemic inflammation (study III)

In **study III** venous blood samples were used to assess systemic inflammation. Blood samples were drawn after overnight fast (12h). Systemic inflammation was assessed by C-reactive protein (CRP) and conducted according to standardized procedures at the Department of Clinical Chemistry, Sahlgrenska University hospital, Gothenburg.

Structured interview questionnaire (study IV)

In **study IV** a structured interview questionnaire was used to collect data on subject characteristics, medication, respiratory symptoms and comorbidity. The questionnaire has been used in previous studies (90)(91).

Statistical methods and data management

All statistical analyses were performed using IBM SPSS Statistics (IBM Corporation, New York, United States) versions 17, 19, 21 or 22. An overview of analysis methods are presented in table 4. Missing values in studies I, II and IV were treated by pairwise deletion. In study III the multiple imputation technique was used to impute missing values for independent variables in the regression model. Statistical significance was declared at $p < 0.05$ in all studies.

Table 4. Data analysis methods in studies I-IV.

Methods	Study I	Study II	Study III	Study IV
Descriptive analyses				
- Median and/or range	X	X	X	X
- Interquartile range		X	X	X
- Numbers and frequencies	X	X	X	X
- Mean and standard deviation	X		X	X
Inferential analyses				
- Paired t-test	X	X		
- Mann-Whitney U test	X		X	X
- Wilcoxon Signed rank test	X	X		
- Kruskal-Wallis test			X	X
- Analysis of variance	X			
- Friedman´s ANOVA		X		
- Spearman´s correlation coefficient for ranked data	X	X	X	
- Pearson´s product moment correlation coefficient	X		X	
- Linear regression	X		X	
- Logistic regression				X
Psychometric analyses				
- Intra class correlation coefficient	X	X		
- Standard error of measurement	X			
- Bland-Altman analysis	X	X		

The analysis strategy was based on the type of data collected (categorical or continuous) and the distribution of collected data. For methods assuming normal distribution, normality was assessed graphically using histograms and through tests of normality (Kolmogrov-Smirnov test and Shapiro-Wilk test). Non-normally distributed variables and categorical data were analyzed by non-parametric methods or transformed to normalize the data.

Psychometric analyses

In **study I** *absolute reliability and agreement* in walking speed and walking distance was assessed using the method proposed by Bland and Altman with accompanying graphical presentation (45) and by the SEM method. *Relative reliability* was assessed using correlation analysis ($ICC_{2.1}$).

In **study II** the correlation between the step count from the three activity monitors and manually counted steps from video recordings was analyzed by $ICC_{2.1}$ and complemented by the Bland-Altman method to allow for assessment of accuracy/agreement. Differences between devices in step count during specific walking tasks of the protocol as well as time spent in different body positions were analyzed by Friedman's ANOVA.

Multivariate analyses

In **study III** the explanatory capabilities of a set of objectively measured variables (not reported by subjects) on variations of physical activity levels were assessed by hierarchical linear regression. PAL measured by activity

monitor was used as the dependent variable. Age, gender, FEV_1 in percent predicted, self-selected walking speed, quadriceps strength, FFMI and CRP were included as independent variables. Assumptions for regression (linearity, presence of outliers and/or multicollinearity between independent variables) were assessed by scatter plots, standardized residuals (<3) Cook's distance (<1) variance inflation factor (<10) respectively. Two cases were identified as potential outliers but retained as they were deemed as true extremes of the population, not resulting from selection bias or faulty measurements.

In **study IV** variables associated with a low physical activity level were explored using binomial logistic regression. The two levels of the dependent variable were based on having a low physical activity level or not in the IPAQ questionnaire. Age, gender, FEV_1 in percent of predicted value, BMI, history of heart disease, smoking status and clinically significant fatigue were chosen as covariates. The same model was fitted separately on subjects with COPD and those without COPD. Assumptions were assessed by Cook's distance (< 1) and standardized residuals (<3).

In both **study III** and **study IV** independent variables were selected based on prior knowledge and/or for exploratory reasons.

Results

Study I

Both the self-selected and maximal speeds were lower than reference populations and decreased in comparable degree to the walking distance (table 5).

Table 5. Walking speeds and distance at the two test occasions. Percent predicted values are not reported in the published paper.

Test	Test 1	% Pred.	Test 2	% Pred.
ss-30mWT, (m/s) (n=47)	1.14 ± 0.20	87 ± 15	1.15 ± 0.18	88 ± 14
ms-30mWT, (m/s) (n=47)	1.55 ± 0.28	83 ± 17	1.60 ± 0.30	85 ± 17
6MWT, (m) (n=35)	413 ± 99	85 ± 22	435 ± 104	89 ± 23

% Pred. = Compared to reference values based Bohannon et al (81) for walking speed and Enright and Sherrill for walking distance (83); ss-30mWT=self-selected speed from the 30-metre walk test; ms-30mWT=maximal speed from the 30-m walk test; 6MWT=six-minute walk test

In both self-selected and maximal speeds measurement error was small (SEM % 5.9 and 4.4 respectively) and comparable to that of the 6MWT (SEM % 4.7) (table 6). In the maximal speed 30mWT a small bias of 0.05 m/s (p=0.04) between test occasions was identified. High correlation coefficients between the 30mWTs and the best 6MWT (all $ICC_{2.1}$> 0.70), indicated good criterion validity of the 30mWT for measuring functional performance.

Table 6. Reliability of the 30mWT and 6MWT

Test	$ICC_{2.1}$ (95 % CI)	*d* (95 % CI)	SEM	SEM %
ss-30mWT (n=47)	0.87 (0.78 to 0.93)	0.01 (-0.04 to 0.01)	0.07	5.9
ms-30mWT (n=47)	0.93 (0.87 to 0.97)	0.04 (-0.07 to -0.02)	0.07	4.4
6MWT (n=35)	0.94 (0.75 to 0.98)	22.0 (12.5 to 32.0)	20.01	4.7

ss-30mWT=self-selected speed from the 30-metre walk test; ms-30mWT=maximal speed from the 30-m walk test; 6MWT=six-minute walk test; $ICC_{2.1}$=intraclass correlation coefficient; SEM=standard error of measurement; SEM %=Standard error of measurement expressed as a percentage.

Study II

Step count and body positions

Manually counted steps from the video observations were median (IQR) 1824 (252) and the corresponding data from the activity monitors were: ADL-monitor = 1700 (398), MiniMod = 1799 (290) and SenseWear Armband = 1269 (570).

Compared to video recordings, the MiniMod underestimated time in locomotion (77 %, p=0.001) and overestimated time in sitting (121 %, p=0.001) whereas the ADL-monitor overestimated time standing (114 %, p=0.004) and underestimated time in locomotion (92 %, p=0.001). The SenseWear Armband did not recognize any body position. Details on time spent in different body positions are presented in table 7.

Physical activity level during one day of home measurement

Step count captured from the MiniMod was 3364 (2851- 5101) and from the SenseWear Armband 2489 (2873-4694) and the difference was not statistically significant (p=0.427) (figure 3).

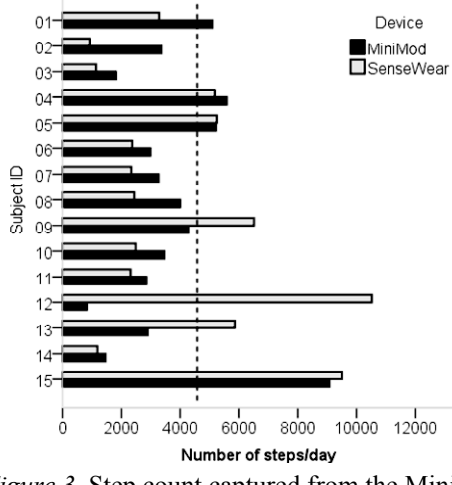
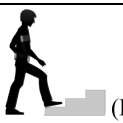


Figure 3. Step count captured from the MiniMod and SenseWear Armband during one day of home measurements. The dotted line represents the cut-off (4580 steps) associated with severe physical inactivity (85).

Table 7. Step count and time in different body positions captured on video and from activity monitors. Values are medians (1st-3rd quartiles).

	Type of walking activity performed (steps)				Body position (seconds)		
Device	 (A)	 (B)	 (C)	 (D)	 (E)	 (F)	 (G)
Video	597 (574-641)	417 (376-424)	511 (468-543)	288 (258-315)	352 (333-374)	1109 (1077-1137)	347 (335-367)*
ADL-monitor	583 (505-639)	393 (420-312)	480 (414-552)	258 (207-310)	360 (330-360)†	1080 (1020-1080)*†	420 (360-420)
MiniMod	594 (561-594)	419 (424-365)	509 (469-542)	264 (254-300)	363 (360-365)	1334 (1257-1621)	283 (154-351)
SenseWear	524 (406-600)*ǂ	63 (0-220)*ǂ§	434 (358-506)*ǂ	223 (163-270)*ǂ	*Not detected*	*n/a*	n/a

Sample size: Video n = 15, ADL-monitor n = 13, MiniMod n = 15, SenseWear n = 14. n/a = not applicable. A= walking slow and fast on the level; B = walking with rollator; C= walking with backpack; D= walking intermittent and stair climbing; E= lying; F=sitting; G=standing. * = $p<0.05$ for difference to video: ǂ= $p<0.01$ for difference to MiniMod: §= $p<0.01$ for difference to ADL-monitor: †< 0.05 compared to video.

Study III

Physical activity level

The majority of subjects (92 %) were *very inactive or sedentary*, four subjects were *active or moderately active* and two subjects were classified as *vigorously active.*

Factors associated with varying physical activity levels

FEV_1 accounted for the largest proportion (22.5 %) of the explained variability in PAL when adjusting for age and gender. Self-selected walking speed added further improvements to the model (10.1 %) as did quadriceps strength (7.0 %) and FFMI (3 %). No significant contribution to the model was seen for age, gender or CRP when adjusting for previous variables entered.

The fit of the final model was $R^2 = 0.45$ ($p<0.001$) (figure 4).

By further analyzing the modifiable variables that contributed to the model, 30 subjects (41.7 %) had an abnormally low walking speed, 15 (20.8 %) had quadriceps weakness and 35 (48.6 %) were FFM-depleted (figure 5).

Additional analysis not included in the publication:
Sarcopenia with reduced mobility was present in 13 (18 %) of subjects.

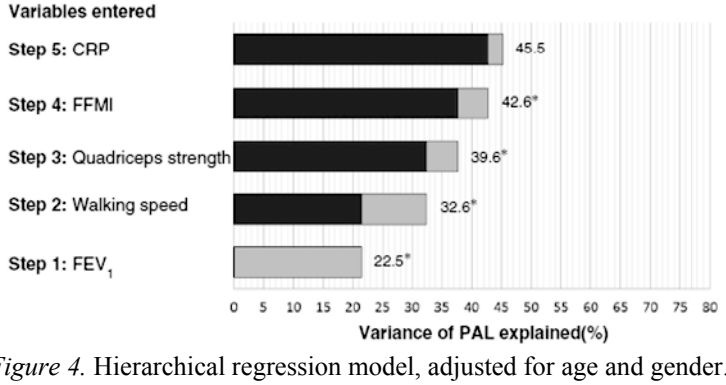


Figure 4. Hierarchical regression model, adjusted for age and gender. Light grey color represents proportion of variance gained at current step of the evolving model. Values outside is the total variance explained at current step; asterisk denotes a significant contribution to the model.

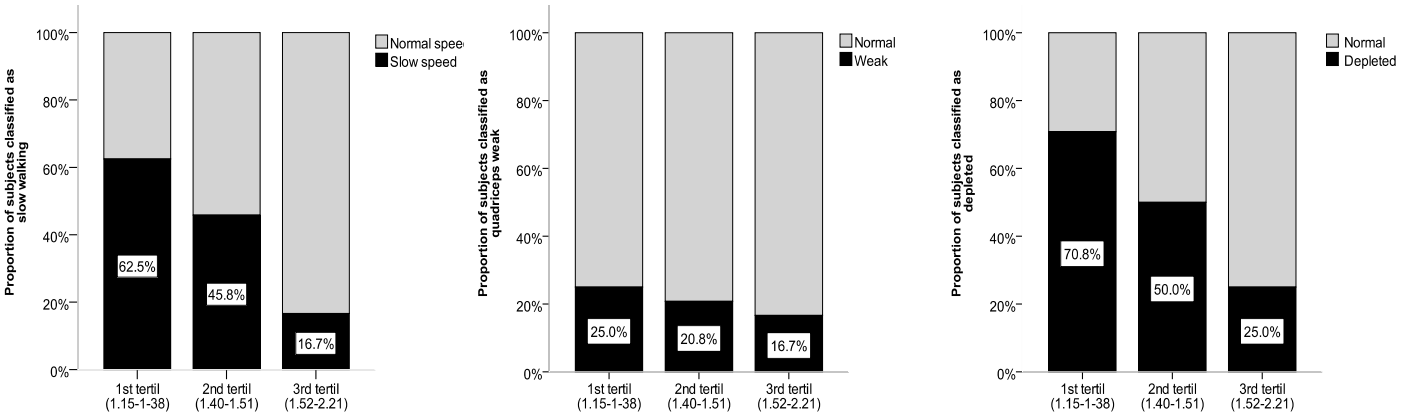


Figure 5. Distribution of subjects classified as abnormal according to clinical cut-offs for walking speed, muscle strength and fat-free mass. Y-axis shows the proportion of subjects in each tertile of physical activity level (PAL).1st tertile indicates the least physically active, 3rd tertile the most active, (n= 24 in all tertiles of activity).

Study IV

Physical activity levels

Equal proportions (14.6 %) of subjects in Non-COPD and GOLD I were categorized as having *low physical activity level.* The proportion in IPAQ category *low* was increased from GOLD II (20.3 %) compared to Non-COPD (p=0.016) (figure 6).

In COPD 77.2 % of the total physical activity reported was accumulated from walking compared to 59.8 % in Non-COPD (figure 6).

Factors associated with low physical activity

- In subjects without COPD *low* physical activity was associated with obesity, OR 2.26 (1.17-4.35)
- In subjects with COPD, age, OR (1.12-2.06), a history of heart disease, OR 2.11 (1.10-4.08) and reporting clinically significant fatigue, OR 2.33 (1.33-4.13) were associated (table 8).

Table 8. Multivariate analysis of associations with low physical activity in non-COPD and COPD respectively. Numbers are odds ratios (OR) with upper and lower 95 % confidence interval (95 % CI).

	Non-COPD (n =607)		**COPD (n = 435)**	
Variables included	*OR*	*95 % CI*	*OR*	*95 % CI*
Age per 10 years	1.29	0.99 - 1.67	1.52	1.12 – 2.06
Gender (female = 1)	0.92	0.57 – 1.49	1.22	0.69 – 2.14
FEV_1 per 10 %	0.94	0.80 – 1.10	0.90	0.77 – 1.05
Normal weight	1.00		1.00	
Underweight	0.91	0.18 – 4.47	0.21	0.02 – 2.08
Overweight	0.87	0.47 – 1.60	1.15	0.63 – 2.12
Obesity	2.26	1.17 – 4.35	0.44	0.18 – 1.07
Heart disease	0.89	0.47 – 1.66	2.11	1.10 – 4.08
Non-smoker	1.00		1.00	
Ex-smoker	0.76	0.46 – 1.26	0.85	0.41 – 1.75
Current smoker	1.21	0.51 – 2.89	1.62	0.72 – 3.65
Clinically significant fatigue (yes = 1)	1.28	0.79 – 2.07	2.33	1.31 – 4.13

Underweight = BMI < 20, Normal weight = BMI 20.0 -24.99, Overweight = BMI 25.0-29.99, Obesity = BMI >30; Missing data for FACIT-F in 87 cases (Non-COPD = 52, COPD = 35).

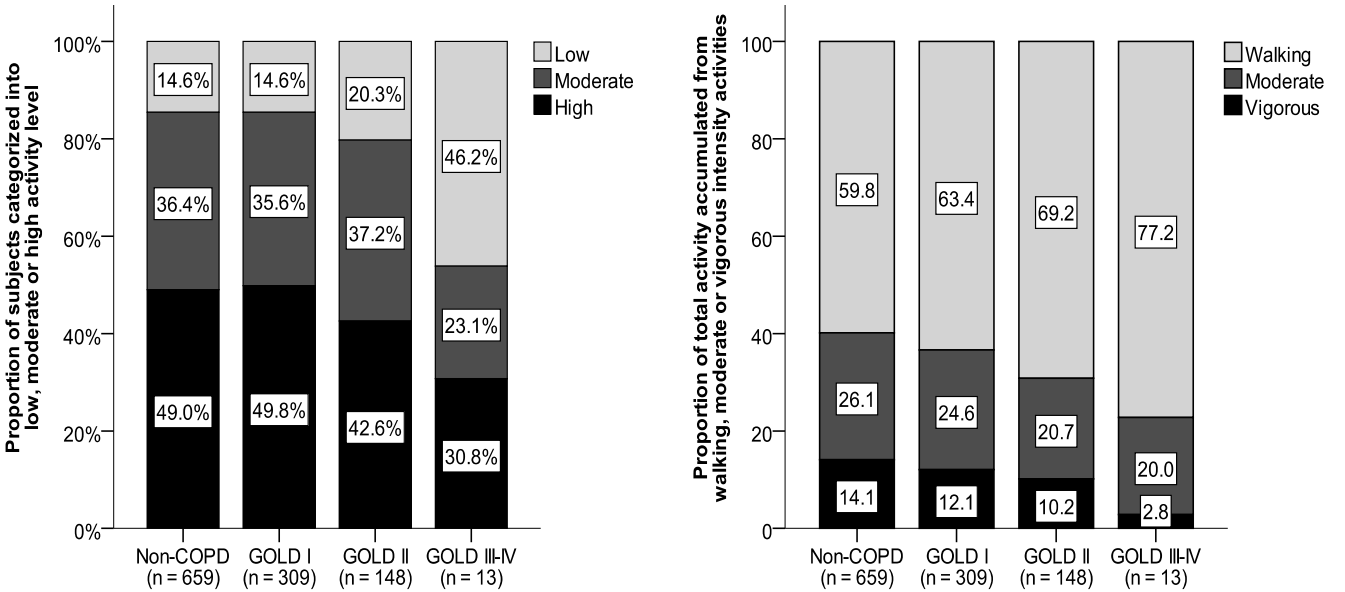


Figure 6. *X*-axis represents groups of varying lung function and y-axis represents proportions in each category of lung function: Left panel displays proportions of subjects categorized as *low, moderate*, or *high* physical activity level; right panel represents proportions of the total weekly physical activity accumulated from *walking, moderate* and *vigorous* activities. GOLD = Global initiative for Obstructive Lung Disease

Discussion

Physical capacity

How to assess walking performance

Our group was among the first to study walking performance in COPD from the aspect of walking speed. Previously, most studies assessed walking performance based on distance walked in a fixed time, such as in 2, 6 or 12-minutes (82) or in tests of fixed or incremental speed, as in the endurance shuttle walk tests (92) or incremental shuttle walk test (ISWT) (93).

The reliability of the 30mWT was comparable to the reliability of the 6MWT, as indicated by high correlation coefficients and low measurement errors. As we had expected, the physiological demands were much lower during the shorter walk test, whereas the 6MWT resulted in significantly more dyspnea and exertion.

A method suitable for clinical use should ideally be quick to complete, require little or none additional resources, give meaningful and easily interpretable information, and have little patient recovery time (62). A short test of walking speed seems to fit this description well. Since 2011, other groups have published data on walking speed in COPD (94)(95)(96)(97)

In a similar study design as ours, Kon et al. investigated the test-retest reliability of the 4-metre walk test and compared it with the ISWT (94). The 4-meter walk test was performed essentially in the same way as the 30mWT, but speed was measured over four meters. The authors reported very high test-retest coefficients, $r = 0.99$ and very similar associations to the comparison test ($r_s = 0.78$). The higher correlations and subsequently also smaller measurement errors of the 4mWT, SEM% =1.8, might be accounted for by shorter test-retest interval (24-38h) or that a shorter distance might not allow subjects to alter their speed during the performance of the test, thereby decreasing variability.

What does walking speed reflect?

In COPD a 6-minute walk distance less than 350 m has been reported to predict mortality (98) and a walking distance less than 357m constitutes an increased risk of hospitalizations due to exacerbations (68). Although capable of supplying valuable information, the 6MWT is still not considered as

practical for clinical use because of the time needed to perform it, especially if a practice walk is performed, and the stress placed on subjects (62). By converting the 6MWD into 6-minute walking speed (distance in meters/360 seconds) the results are strikingly close to the walking speed cut-off value of 1.0m/s showed to be clinically meaningful as predictors of mortality in the elderly (99). Therefore it seems reasonable to assume that subjects with COPD having a walking speed <1.0 m/s should be a cause for concerns in clinical practice as it could, by proxy, be predictive of mortality. By applying this cut-off value of 1.0m/s for self-selected speed in study III we observed that among the lowest tertile of physical activity, 65% were "slow walkers", identifying them as being at increased risk of mortality and exacerbations.

By applying a cut-off value of 0.80m/s Kon et al. reported that slow walking subjects had substantial deficits in health status, as measured by St George´s Respiratory Questionnaire, compared to those with preserved walk speed (94). As both health-status and physical activity seem impaired among the slowest moving subjects, walking speed could be useful as an important clinical marker of systemic effects of COPD.

The high correlation coefficients observed between the 30mWT and 6MWT as well as between the 4-m walk test and ISWT indicate that all these field test, although different in appearance and complexity, might be assessing a common underlying cause/construct.

A physiological model explaining impaired walking performance might be found in the concept of c*ritical power. Critical power* is a term describing the speed which one can endure almost indefinitely, that is by titrating work rate to remain below the ventilatory threshold (100). In subjects without lung disease, neither young nor old exceed the ventilatory threshold when walking at self-selected speeds (101). The same was observed in an study on subjects with COPD: that the speed chosen in the final three minutes of a 6MWT was highly correlated to subject's *critical walk speed* (the maximal sustainable walking speed without exceeding the ventilatory threshold) (95). Remarkably stable walking speeds across all minutes of a 6MWT has been reported (97). Both the endurance time and the speed of walking has been shown to be responsive to pulmonary rehabilitation (96).

If applying a walk test to screen for increased risk of morbidity and mortality, then a short test of walking speed could potentially be equally useful as the longer 6MWT, but much more easily implemented into clinical practice. It should be recognized that the shorter test does not reveal any underlying physiological explanation to the impaired exercise capacity, such as oxygen desaturation, for which a longer test such as the 6MWT would be preferable, or a test of higher intensity such as the ISWT.

Physical activity levels and associated factors in COPD

Factors associated to activity levels in a selected sample

In the studies included in the thesis we have used both objective methods and subjective methods to assess the activity levels of our samples, and the methods have yielded substantially different results. When assessments were performed with an activity monitor, less than 10% of subjects were classified as sufficiently active. Although activity levels were generally low in the sample, some distinct patterns emerged. In the multivariate model, lung function in combination with walking speed emerged as the two variables most strongly associated with daily activity, alongside muscle strength and FFMI. A surprisingly large proportion of subjects was FFM-depleted and categorized as having a slow walking speed. It is likely that the subgroup of participants (18%) that showed a combination of both low FFM and impaired function, i.e. sarcopenia, would be of extra concern. Although these impairments were affecting mainly subjects in the lowest two tertiles of activity, these observations should not be interpreted as evidence for a causal chain between these impairments of capacity and a low physical activity, since the cross-sectional design of the study does not permit such a conclusion. However, sarcopenia could potentially be a determinant of physical activity, but that needs to be investigated in future studies of longitudinal design.

The need for studies of longitudinal design was recently highlighted in a systematic review where the evidence for determinants of activity as well as outcomes of activity were summarized (102). The authors concluded that the only two areas currently supported by moderately strong evidence as being outcomes of activity, were mortality and exacerbations. Furthermore, concluded that although many high quality cross-sectional studies have been performed, and potential determinants identified, the lack of longitudinal data makes any assumptions of causality invalid.

Factors associated to activity levels in a population-based sample

To our knowledge, we are the first study reporting on the relationship between physical activity and symptoms of fatigue in subjects with COPD. In our study, fatigue and a history of heart disease were associated with not reporting the recommended level of physical activity. This would identify these subjects as suitable for pulmonary rehabilitation, based solely on not achieving the recommended level of activity. This is supported by results from recent studies showing that subject with cardiovascular comorbidities (103) and subject with fatigue show (104) improvements in exercise capacity following pulmonary rehabilitation.

Our results highlight the importance of having accurate methods for quantifying walking behavior, especially in more severe COPD. If an intervention for increased physical activity behavior was to be implemented, clearly, methods able to accurately reflect changes in the activity most often performed would be desirable.

The IPAQ instrument is constructed so that only activities of at least moderate intensity is reported, corresponding to the recommended intensity for health enhancing physical activity (22). Using objective methods, subjects with COPD has been reported to move slower than healthy elderly controls (19), but the opposite has also been observed (18). Both situations could contribute to a non-differential miss-classification of subjects with COPD. If they were walking slower it could mean that they are more likely to achieve the minimum bout-length of 10 minutes, albeit at lower intensity than intended, on the other hand they were walking at higher intensities it would likely provoke symptoms of dyspnea and thereby fulfilling the criterion of vigorous intensity stated in the IPAQ:"*activities that take hard physical effort and make you breathe much harder than normal*". However, this misclassification would contribute to subjects being classified as more active than intended. The latter scenario is not likely to have impacted results in any substantial way given that the proportion of total activity reported in the vigorous category only constitutes less than 3 % of the total volume of physical activity. Whether walking actually constitutes a moderate activity in COPD has been investigated with activity monitors, by assessing the proportion of total time spent walking with the proportion of that time which corresponded to at least moderate intensity (105). The majority (82%) of subjects did accumulate 30 minutes of walking, but only 23% of total walking time was at moderate intensity. However, as stated in the guidelines, the intensity levels should be relative to the subject's fitness level, which an activity monitor is not capable of taking into account. The information from an activity monitor should therefore ideally, be combined with some measure of perceived exertion related to the performing of the activity.

The activity levels in study IV, although seemingly high, are in line with the 12-country reliability study of the IPAQ questionnaire, where 82% were reported as sufficiently active (87). Identical levels of activity existed between non-COPD and subjects with mild airway obstruction, and reduced activity levels were present from GOLD II. This is corroboratory of results from smaller samples assessed by objective methods (106)(107)(108). A PAL < 1.40 has been reported as the strongest predictor of 4 year mortality in subjects with COPD (109). Using subjective methods for assessing physical activity is still the most feasible option for large studies due to the costs and complexity of the objective methods.

Objective measures of activity and sedentary behaviors

The public recommendations for older adults state that 30 minutes of daily moderate intensity activity on five days of the week, accumulated in bouts of at least 10 minutes duration should be performed (22)(30). Furthermore, the health enhancing activities are to be accumulated *over and above* the light intensity activities performed as part of daily life. To ascertain whether recommended levels are met, the objective methods have a clear advantage in the details they are capable of capturing.

We hypothesized that activity monitors would not be equivalent in their ability to accurately capture physical activity in subjects with severe COPD. Problems for the early activity monitors in accurately detecting steps in slow moving subjects were reported (37).This was based on the fact that a multitude of different monitors were being applied in research, but the validity was not rigorously investigated. The new technology has great promise, theoretically, to be able to capture both physical activity behavior and sedentary behaviors of subjects.

By designing a study on the accuracy and equivalency of three activity monitors used in the field of COPD research, we were able to identify some weak spots of monitors which, if not taken into account, might bias results from a study of the most disabled and those using walking aids. The differences highlighted in study II were, we believe, primarily due to the placement of the respective device. An arm mounted monitor cannot reliably be used to assess physical activity in the form of step count if the subject is using a rollator, nor can time standing up be accurately captured from a device mounted at the lower back, if transitions between postures are not accompanied with a period of steps taken.

As a separate part of study II, we included one day of home measurements of subjects' activity levels. Although this did not allow for a comparison of monitors against a gold standard, the monitors could be compared against each other. If the pattern established under laboratory settings, a consistent underestimation of steps from the SenseWear Armband, would be mirrored in the free living data. Due to the small number of subjects in the study, it was possible to analyze data ongoing and wherever unsuspected discrepancies between monitors emerged, subjects was asked to recall what he/she had been doing at the time of the day. As confirmed in the laboratory setting, rollator use severely underestimates step count from the SenseWear Armband in home setting (ID 2), vibrations from a motorcycle caused the opposite error with increased step count from the SenseWear Armband (ID 13), and as could be expected, some subjects will not be compliant with wearing the devices (ID 12). The in step count from the SenseWear armband would however only affect the step count, not the energy expenditure estimates, since they rely on the added information from the physiological sen-

sors. It would however mean that detailed information on ambulatory activity in subjects using a rollator would be lost.

From study III we clearly see that few subjects are truly active in accordance with public guidelines. The ActiReg monitor used in study III falls somewhere between a EE-device and a body positional device, according to the classification by Granat (35). The ActiReg uses information on body positions and positional changes which is then used to estimate the energy expenditure (110). The monitors used in study II would have allowed us to assess the activity and sedentary behavior of the sedentary subjects in study III in greater detail. Patterns of sedentary behaviors or physical activity that can be identified through the real time activity monitoring could be used in forming individualized activity plans for subjects, if these aspects are adequately captured by the monitor. However, with support from the data in study II, some caution in the interpretation of the outcomes related to behavioral aspects is warranted.

We deliberately constructed a test protocol to be challenging to the particular monitors included in the study, and the results clearly show that the activities that were anticipated to be problematic for the monitors were confirmed as sources of error in the analysis.

One challenge in activity monitoring is deciding on whether or not to strictly apply the 10-minute bout criteria stipulated in the activity guidelines. From a physiological standpoint, a subject walking for nine minutes who is forced to stop for one minute is likely to obtain positive health aspects even if the 10-minute bout is interrupted. This means that although the activity monitor itself is objective in the collection of data, subjective judgment will be involved even in this process. The implication in regards to whether public guidelines are met will be very much impacted by this decision (111)(112). Hagströmer et al. reported that although more than 50% of subjects reached the recommended amount of weekly activity, only 1% had accumulated it according to the stipulated minimum bout of 10 minutes. This was later confirmed in a population-based sample from the United States where less than 5 % of adults achieved the recommended level when an 8-10 minute bout criteria was applied (112).

Method discussion

In studies I-III convenience sampling was used to identify potential subjects. Although more susceptible to introducing selection bias, the method was deemed as appropriate for the following reasons: In study I we had no prior knowledge regarding the 30mWT and how it would perform in subjects with varying disease severity and opted for a wider criteria to gain this knowledge. In study II the goal was to have a majority of subjects with severe disease, as these were expected to walk slower and pose greater challenges to the monitors (19). Regarding sample selection in study III subjects

with many of the common comorbid conditions (heart failure, diabetes) were purposely excluded. This was done to better be able to study the specific effects from COPD on physical activity levels, body composition and performance. Had we included many of the comorbid conditions present with COPD, the observed associations would have been expected to be stronger. These data are therefore likely conservative, but of the generalizability of the estimated associations should nonetheless be viewed in light of the sample used.

Study IV was based on subjects from an ongoing study cohort of subjects with and without COPD, originally recruited from representative samples of the population. However, a healthy survivor effect cannot be excluded in the COPD group, meaning that the subjects with better health are remaining in the study whereas those with more severe disease subjects drop out. In addition, because the categorization into COPD and Non-COPD were made solely on spirometric criteria using the fixed ratio of FEV_1/FVC, some misclassification may have occurred as a result (113). It is likely that symptomatic smokers in the Non-COPD group might be more limited than asymptomatic subjects defined as GOLD I.

Clinical application and future perspectives

To the clinician: we have shown that a test assessing walking speed in subjects with moderate to severe COPD is both tolerable to subjects, and feasible for a clinical settings. If given the chance to add two complementary objective assessments to your spirometry of moderate to severe COPD patients, walking speed and body composition should be prioritized. In less severe airway obstruction comorbid conditions and symptoms of fatigue should not be overlooked.

To the researcher: the importance of impaired walking speed and altered body composition as possible determinants of insufficient physical activity needs to be addressed longitudinally.

Conclusions

The 30-metre walk test is reliable in subjects with moderate and severe COPD. The walking speed in the 30-metre walk test is highly correlated to the distance walked in the 6-minute walk test.

Activity monitors are not equivalent in their abilities to detect steps and time in varying body positions among subjects with moderate to very severe COPD, but they display similar capabilities in capturing patterns of energy expenditure.

In addition to lung function, walking speed and muscle strength are important correlates of physical activity in subjects with moderate to very severe COPD. Further explorations of the longitudinal effects of the factors characterizing the most inactive subjects are warranted.

Physical activity levels are reduced in subjects with moderate to severe COPD. The factors associated with not reaching health-enhancing levels of physical activity in subjects with COPD were a history of heart disease and symptoms of fatigue, whereas in subjects without COPD obesity was the only associated factor.

Swedish summary

Kroniskt obstruktiv lungsjukdom (KOL) är en långsamt progredierande inflammatorisk lungsjukdom. Den största riskfaktorn för KOL är rökning, men andra faktorer kan inverka. Tillståndet är vanligt och år 2010 beräknades den vara den tredje vanligaste dödsorsaken i världen.

Vi behöver fler metoder som kan hjälpa oss att identifiera personer som skulle dra nytta av rehabiliteringsinsatser, för hjälp finns, men vi behöver bli bättre på att kunna identifiera de personer som har störst behov.

Syfte

Det övergripande syftet med avhandlingen var att undersöka metoder som kunde vara användbara för att upptäcka och följa påverkan av sjukdomen, samt även att studera vilken koppling som finns mellan fysisk aktivitet och eventuell andra faktorer som är påverkade vid sjukdomen.

Delarbete I

Det första delarbetet undersöker tillförlitligheten (reliabiliteten) i två tester av fysisk prestationsförmåga. Vi ville studera ett nytt test som inte använts inom detta område förut, 30-meters gångtest, och jämföra resultatet med ett väletablerat test, 6-minuters gångtest. Vi lät 49 personer med KOL genomför två upprepningar av respektive test och jämförde sedan i) hur överensstämmelsen mellan testtillfällen för respektive test var, ii) hur påverkade personerna blev av att genomföra de olika testerna. Resultatet visade att överensstämmelsen mellan testtillfällen var hög (Korrelationskoefficienter ≥ 0.87 för alla jämförelser) samt att graden av mätfel var jämförbar mellan de olika typerna av test. Deltagarna var betydligt mer påverkade efter genomförandet av 6-minuters gångtest än 30-meters gångtest. Slutsatsen från delarbete I var att tillförlitligheten i 30-meters gångtest är god, och att det genom sin ringa påverkan på deltagarna skulle lämpa sig väl för användande i vården.

Delarbete II

Genom så kallade aktivitetsmätare kan man få en detaljerad bild av hur fysiskt aktiva personer är i sitt dagliga liv. Detta är apparater som fästs på

kroppen och som registrerar hur mycket och hur intensivt personen rör sig. Vi undersökte tre olika aktivitetsmätare (DynaPort MiniMod, DynaPort ADL-monitor, SenseWear Armband) avseende deras förmåga att korrekt registrera antalet steg och tid i olika kroppspositioner som våra deltagare utförde i ett standardiserat försök. Vid försöket fick 15 personer med svår KOL bära alla tre aktivitetsmätare samtidigt medan de utförde olika ett antal olika moment som efterliknar aktiviteter i vardagen. Alla försök videofilmades och överrensstämmelsen mellan mätarnas uppgifter och videofilmen analyserades. Resultatet visade att mätarna inte var likvärdiga i förmågan att korrekt identifiera steg och tid i kroppspositioner. Slutsatsen från arbetet var att valet av aktivitetsmätare behöver göras med vägledning av exakt vilken aspekt av aktivitet man önskar studera eftersom de visade sig vara olika bra på att mäta olika aspekter av aktivitetsbeteenden.

Delarbete III

Här studerade vi deltagares fysiska aktivitet med hjälp av en aktivitetsmätare samt undersökte deras fysiska prestationsförmåga och eventuell påverkan av sjukdomen, förutom lungfunktion, på ett flertal sätt: gångförmåga, muskelstyrka, kroppssammansättning och inflammationsmarkörer i blodet. De 72 deltagarna fick bära aktivitetsmätare under sju dagar. Vi analyserade hur den fysiska aktiviteten varierade i gruppen samt huruvida de olika markörerna för systemisk påverkan kunde förklara varför personerna hade olika grader av aktivitet. Resultatet visade att gruppen i stort var inaktiv, 92 % nådde inte upp till en aktivitetsnivå som är rekommenderad för bibehållande av hälsa. Vi fann att variationer i aktivitet till ca hälften (45 %) kunde förklaras av att man uppvisade olika grader av systemisk påverkan i testerna. De starkaste sambanden till aktivitet sågs för lungfunktion, gångförmåga, muskelstyrka och kroppssammansättning. Kön, ålder eller inflammatorisk aktivitet spelade inte roll. Slutsatsen blev att lungfunktion kan förklara en del av daglig aktivitet, men att även gångförmåga och muskelstyrka är starkt kopplat till aktivitetsnivån. Huruvida de karakteristika som utmärkte de mest inaktiva personerna innebär en särskild risk är något som behöver studeras i framtida studier.

Delarbete IV

I detta arbete undersökte vi deltagarnas aktivitetsnivåer genom ett frågeformulär. Även här studerade vi ett antal andra faktorer och huruvida de var kopplade till att inte uppnå rekommenderad grad av aktivitet. För att besvara dessa frågor inkluderades en grupp personer med KOL (470 stycken) och en grupp personer utan lungfunktionsnedsättning (569 stycken). Alla personer besvarade frågeformulär om sin fysiska aktivitetsnivå och sin förekomst av symptomet utmattning (fatigue). Dessutom besvarade deltagarna frågor om

andningsrelaterade symptom, förekomst av andra sjukdomar, rökvanor samt registrerade uppgifter om deras kroppssammansättning (BMI). Resultatet visade att majoriteten i båda grupper uppnådde rekommenderad nivå för fysisk aktivitet (83 % vid KOL och 85 % hos de utan KOL). I gruppen med KOL ökade andelen personer som inte uppnådde rekommenderad aktivitetsnivå i svårare grader av lungfunktionsnedsättning. Vi analyserade även sambandet mellan en låg aktivitetsnivå och ett antal olika faktorer (ålder, kön, lungfunktion, BMI, hjärtsjukdom, rökvanor, upplevd utmattning). Effekten av dessa faktorer undersöktes i var grupp för sig. I gruppen med KOL var de starkaste sambanden, uttryckt som Oddskvoter (95 % konfidensintervall), för tidigare förekomst av hjärtsjukdom, OR 2.11 (1.10–4.08), samt upplevd utmattning, OR 2.33 (1.31–4.13), medan hos gruppen utan KOL var förekomst av fetma (BMI >30) den enda signifikanta faktorn, OR 2.26 (1.17–4.35). Slutsatsen från arbetet var att hos personer med KOL föreligger en sänkt aktivitetsnivå från grad II, och att faktorerna som är kopplade till att inte uppnå rekommenderad aktivitetsnivå är olika vid KOL jämför med personer utan KOL. Att registrera upplevd utmattning och förekomst av hjärtsjukdom hos personer med KOL skulle kunna vara användbart i arbetet med att identifiera vilka som bör erbjudas rehabilitering.

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