

# **ASSESSMENT OF PHYSICAL ACTIVITY IN COPD PATIENTS IN THE STABLE STATE AND DURING EXACERBATION AND RECOVERY**

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# DECLARATION

I, Ayedh D. AlAhmari confirm this thesis is the result of my own work and was carried out at Respiratory Medicine department, University College London and Royal Free Hampstead hospital NHS Trust. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature \_\_\_\_\_

Data 05/09/2016

# **ABSTRACT**

## **INTRODUCTION**

Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality worldwide. It is mainly caused by long-term inhalation of smoke particles.

## **AIMS**

This thesis aims to describe physical activity in COPD patients in the stable state, during exacerbation and subsequent recovery, and the factors which influence these phases especially those that are environmental.

## **METHODS**

Physical capacity and activity was assessed with a variety of methods and devices. I chose to use a six minute walking distance test and an accelerometer (SenseWear) device which estimates energy expenditure. A number of clinical factors were also assessed at the stable, exacerbation and recovery states through use of questionnaires (COPD assessment test, Hospital Anxiety and Depression Scale and Functional Assessment of Chronic Illness Therapy-Fatigue Scale). To prospectively collect data leading up to an exacerbation I used a pedometer which was validated against the SenseWear device and manual counting. Patients recorded their step counts on a total of 16,478 days- an average of 267 days per patient (range 29-658)-

when stable, at exacerbation presentation (day 0) and at recovery visits (days 3, 7 and 14 days thereafter). At the same time, patients recorded any increase over usual stable symptoms per day, time spent outdoors and Peak Expiratory Flow (PEF).

## **RESULTS**

The 73 COPD patients (70% male) had a mean ( $\pm$ SD) age 71.1 ( $\pm$ 8.7) years and FEV1 52.9 (16.5) % predicted. Results showed that daily step count in community treated exacerbations returns to pre-exacerbation levels within 3–4 days, with those patients experiencing the greatest reduction in step count taking longer to recover, and patients suffering frequent exacerbations experiencing a faster decline in activity. I also observed that patient activity in the stable state was inversely associated with high levels of atmospheric pollution. Moreover patient activity was markedly lower during the weekends and during cold weather.

At exacerbation, changes in exercise capacity, muscle strength and energy expenditure were related to disease severity, changes in the perception of fatigue and exacerbation frequency. The results also indicated that prior pulmonary rehabilitation may have a lasting benefit in mitigating this reduction in physical activity, and that possibly change in physical activity is associated with changes in systemic inflammatory markers at exacerbation.



## **CONCLUSIONS**

Maintenance of physical activity is important in COPD. Strategies that encourage activity when patients are unwell (such as personalised early Pulmonary rehapilation) or unwilling to take exercise (such as during the winter or weekends) need to be devised to prevent de-conditioning at these times. Physical activity and exercise capacity are reduced during COPD exacerbation recovery and may be linked to increased systemic inflammation and fatigue. Frequent exacerbators should be particularly targeted for exercise programs. Schemes to reduce levels of atmospheric pollution should be further encouraged.

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# CONTRIBUTION

This thesis covered many topics and without the help of others it would not have been possible to complete. I saw the patients in clinic, instructed the patients in the use of the pedometry and made all the clinic based measurements of physical activity and capacity. I also analysed all the results with the exception of the statistical analysis of large data sets (chapters 4 and 5) for which I am grateful for the help of Dr. Gavin Donaldson.

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# ABBREVIATIONS

<b>6MWT/D</b>	Six Minute Walking Test/Distance
<b>ATS</b>	The American Thoracic Society
<b>BDI/TDI</b>	The Baseline and Transition Dyspnoea Indices
<b>BMI</b>	Body Mass Index
<b>D<sub>Lco</sub></b>	Diffusing Capacity for Carbon Monoxide
<b>CAT</b>	COPD Assessment Test
<b>CO<sub>2</sub></b>	Carbon Dioxide
<b>COPD</b>	Chronic Obstructive Pulmonary Disease
<b>CRP</b>	C-Reactive Protein
<b>CT</b>	Computed Tomography
<b>CXCL1</b>	C-X-C Motif Ligand 1
<b>CXCL8</b>	C-X-C Motif Ligand 8
<b>DLW</b>	Doubly Labelled Water
<b>EADL</b>	Extended Activity of Daily Living
<b>EE</b>	Energy Expenditure
<b>EU</b>	The European Union
<b>FACIT-F</b>	Functional Assessment of Chronic Illness Therapy–Fatigue
<b>FEV1</b>	Forced Expiratory Volume in 1 Second
<b>Ft</b>	Feet
<b>FVC</b>	Forced Vital Capacity
<b>g/l</b>	Gram/Litre
<b>GOLD</b>	Global Initiative for Chronic Obstructive Lung Disease
<b>GRO-α</b>	Growth Related Oncogene-Alpha

<b>HADS</b>	The Hospital Anxiety and Depression Scale
<b>HRCT</b>	High Resolution Computed Tomography
<b>HRQL</b>	Health Related Quality of Life
<b>ICS</b>	Inhaled Corticosteroid
<b>I.V</b>	Intravenous Therapy
<b>IL-6</b>	Interleukins-6
<b>IL-8</b>	Interleukin-8
<b>IQR</b>	Inter Quartile Range
<b>Kcal</b>	Kilocalories
<b>kg/m<sup>2</sup></b>	Kilogram Per Square Meter
<b>KJ</b>	Kilojoules
<b>Km</b>	Kilometres
<b>LABAs</b>	Long-Acting Beta (2)-Agonists
<b>LBP</b>	Lipopolysaccharide Binding Protein
<b>LCADL</b>	The London Chest Activity of Daily Living Scale
<b>m</b>	Meter
<b>MCP-1</b>	Monocyte Chemoattractant Protein-1
<b>MET</b>	Metabolic Equivalent Rate
<b>METs</b>	Metabolic Equivalents
<b>MRC</b>	Medical Research Council
<b>MRI</b>	Magnetic Resonance Imaging
<b>NHANES III</b>	The Third National Health and Nutrition Examination Survey
<b>NHS</b>	The National Health Service
<b>NICE</b>	The National Institute for Health and Clinical Excellence

<b>NIH</b>	The National Institutes of Health
<b>NO<sub>2</sub></b>	Nitrogen Dioxide
<b>O<sub>2</sub></b>	Oxygen
<b>O<sub>3</sub></b>	Ozone
<b>°C</b>	Celsius
<b>PEF</b>	Peak Expiratory Flow
<b>PEFR</b>	Peak Expiratory Flow Rate
<b>PFT</b>	pulmonary Function Testing
<b>PM<sub>10</sub></b>	Particulate Matter <10 Microns in Diameter
<b>PR</b>	Pulmonary Rehabilitation
<b>QMVC</b>	Quadriceps Maximal Voluntary Contraction
<b>REE</b>	Resting Energy Expenditure
<b>SABA</b>	Short acting Beta Agonists
<b>SAMA</b>	Short-Acting Antimuscarinic Antagonists
<b>SD</b>	The Standard Deviation
<b>SEM</b>	Standard Error of The Mean
<b>SGRQ</b>	The St. George's Respiratory Questionnaire
<b>SO<sub>2</sub></b>	Sulphur Dioxide
<b>SWT</b>	Shuttle Walk Test
<b>TNF</b>	Tumour Necrosis Factor
<b>TNF-a</b>	Tumour Necrosis Factor Fibrinogen Leucocytes
<b>UK</b>	The United Kingdom
<b>USA</b>	The United States of America
<b>VO<sub>2</sub> Max</b>	Maximal Oxygen Consumption
<b>µg/m<sup>3</sup></b>	Micrograms Per Meter of Air

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# 1

## INTRODUCTION

This introduction describes the diagnosis of chronic obstructive pulmonary disease (COPD), its management and definition and the treatment of exacerbations.

It also serves to review the current literature on physical activity and capacity, describing the relevant outcome measures, their implementation and limitations. The aims and objectives of the study are outlined.

## 1.1 CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is a significant cause of morbidity and mortality globally. It describes the irreversible and progressive decline of lung function that leads to reduced airflow into the lungs. COPD contributes a significant burden of illness and generates high healthcare costs (7). Worldwide, COPD is ranked as the third greatest cause of death (8). COPD has been defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) committee as *“a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.”* ([www.goldcopd.org](http://www.goldcopd.org)).

There are two major components of COPD: chronic bronchitis and emphysema. Chronic bronchitis is defined as *“the presence of cough and sputum production for at*

*least three months for two consecutive years”* and emphysema is defined as *“enlargement of the airspace and destruction of the alveoli”* (9). COPD can be described as a long-latency illness in that it develops over a few years after initial causative agent exposure (10). Active smoking still remains a major risk factor although other factors are now being identified. These include air pollution and occupational factors (11). People exposed to these risk factors do not always develop COPD but may experience respiratory symptoms. These include chronic bronchitis and sub-clinical airway obstruction, and consequently the condition is difficult to identify during its early phases. Many people are not diagnosed until the later stages of the disease when breathlessness and impairment of daily activity cause them to seek medical advice (12). COPD speeds up the ageing process in the lungs. Therefore, the earlier individuals are treated and diagnosed, the more likely a positive outcome (13).

## **1.2 EPIDEMIOLOGY**

In the UK, COPD is one of the leading causes of death and the second most common reason for emergency hospital admission. It is estimated to be responsible for almost 5 per cent of all fatalities and statistics show that approximately 3 million people in the UK have COPD (14). Estimates of its prevalence varies between 1 and 4 percent of the UK populace, primarily affecting those over 35 years old (14).

It is also the most expensive inpatient condition handled by the NHS (14). Over £800 million is spent by the NHS on COPD each year. It is responsible for more than 24

million lost work days annually (14). COPD brings a considerable financial and societal cost, and as such warrants considerable research attention.

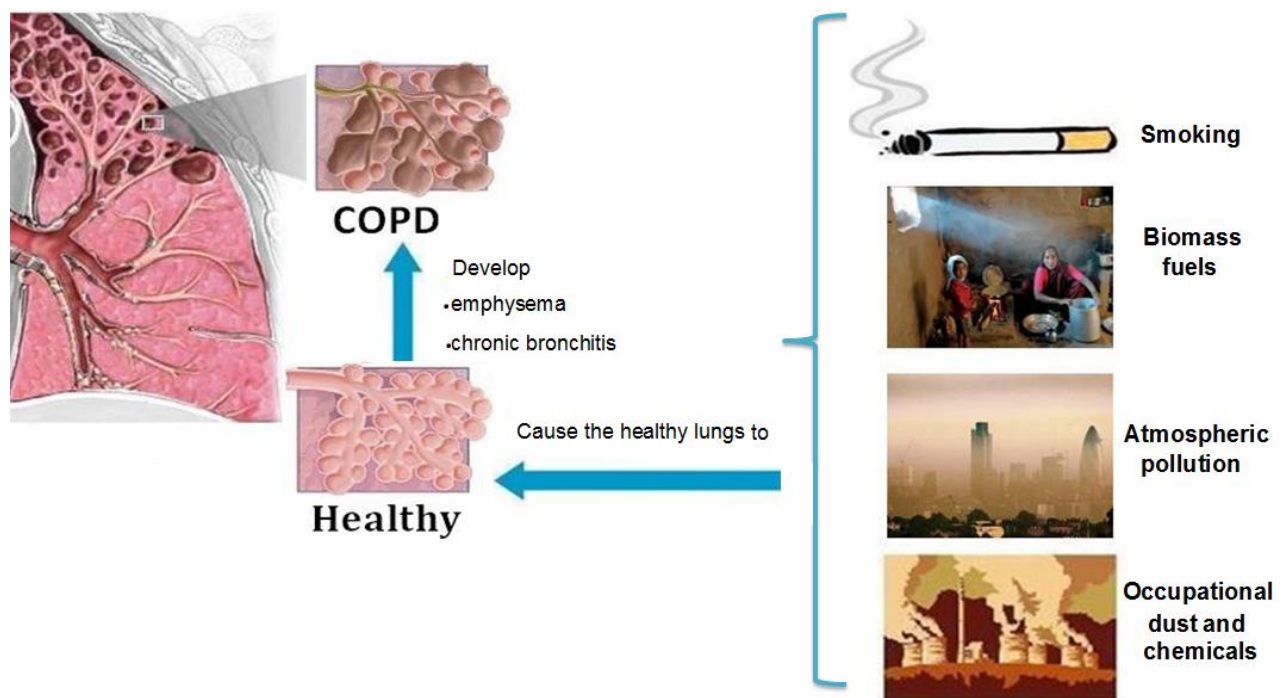
Dyspnoea (breathlessness) is the principal symptom of COPD and presents the biggest challenge to patient welfare. This is normally a result of weakened pulmonary mechanics (10). Even after lung transplantation, exercise performance tends to remain substantially lower than that of age-matched controls. This raises the possibility that lungs alone are not responsible for breathlessness (15). Pulmonary function is interrelated with muscle strength. Muscle weakness, conversely, is a characteristic of COPD that plays a critical part in reducing a patient's exercise capacity (16). COPD dyspnoea occurs during exercise or even at rest in more severe cases (17). The cause of this dyspnoea is lung hyperinflation due to the early collapse of airways during expiration. This, in turn, is because the volume of surrounding tissue supporting the airway has been reduced following tissue destruction. Airflow limitation caused by blockage of the airways by mucus is also involved (18).

### **1.3 AETIOLOGY**

The causes of COPD vary with respect to geographical areas. For instance, in high- and middle-income countries, tobacco smoking is the highest risk factor (19), but in low-income economies, exposure to indoor pollution such as biomass fuel used in cooking and heating is also an important cause of the disease (20). Other than smoke, COPD is associated with fumes and dust and exposure to certain forms of



dust and chemicals in the workplace such as grains, cadmium, coal, and isocyanates, which may lead to development of COPD even in non-smokers (20-22) (Figure 1). Air pollution also causes an abnormal inflammatory response, which may lead to parenchymal tissue destruction and loss of elastic recoil (emphysema) (23).



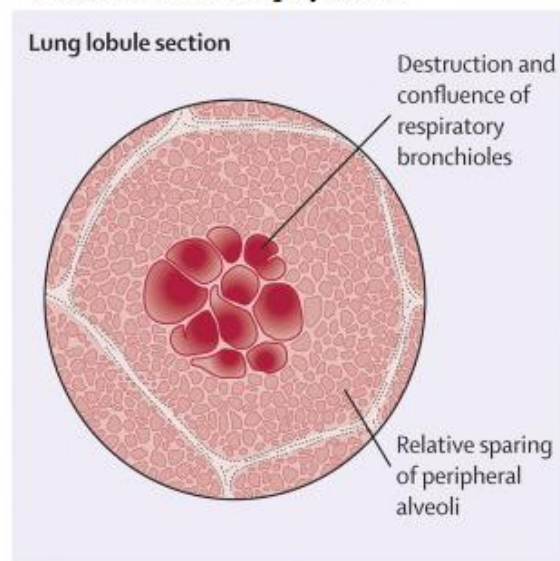
**Figure 1:** Smoking cigarettes, biomass fuels, atmospheric pollution and occupational dust and chemicals cause healthy lungs to develop emphysema, with destruction of the alveoli and airways blocked with mucus. (Copyright ©ADAM.inc)

COPD develops at different rates in different people who are exposed to comparable amounts of similar pollutants (24). Studies show that nitrosative and oxidative stress prompted by cigarette smoke contributes to the corticosteroid resistance found in COPD (1). According to Hansel and Barnes, oxidative stress might play a key factor in exacerbations by increasing the inflammatory response and might inhibit the anti-inflammatory effects of corticosteroids, even at high doses (1). Genetic and epidemiologic evidence indicate that the ability of an individual to defend themselves against cigarette smoke-induced oxidative stress via up-regulation of the lung antioxidant defences is critical. This means that oxidative stress is an important event in COPD pathogenesis (25). Despite this understanding of the basic mechanisms involved in COPD there is no new or effective disease modifying therapy for this irreversible disease.

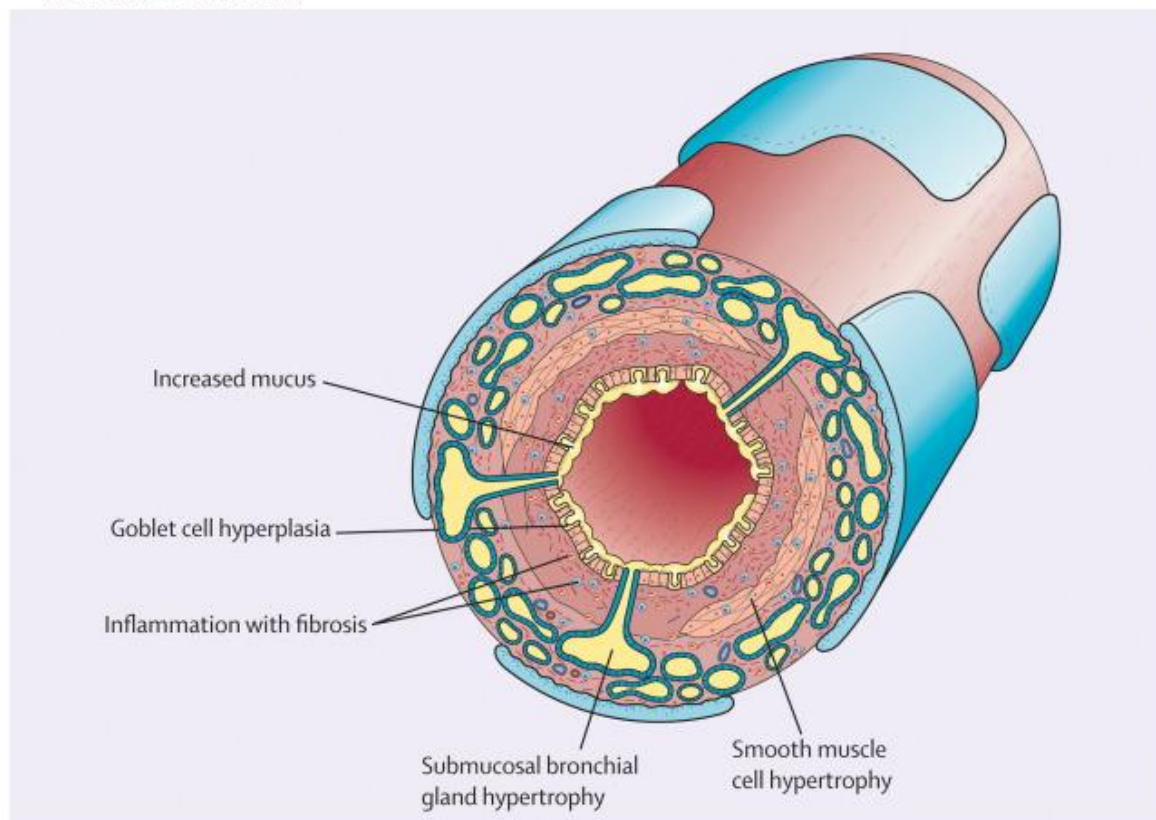
## **1.4 PATHOPHYSIOLOGY**

Figure 2A shows features of emphysema and figure 2B shows the large thickening of the subepithelial basement membrane, hyperplasia of the subepithelial seromucinous glands, bronchial wall fibrosis, and goblet cell hyperplasia (chronic bronchitis) (26). This inflammatory damage overwhelms normal defence mechanisms and results in small-airway fibrosis and air trapping

### A. Centrilobular emphysema



### B. Chronic bronchitis



**Figure 2:** Pathology of COPD. **A)** Centrilobular emphysema. **B)** Chronic bronchitis

(1). Copyright © 2009 Elsevier Ltd

Exposure to specific risk factors causes hypertrophy of mucous glands and mucus hypersecretion, which can lead to bacterial infection and ciliary loss (27, 28). Similarly, exposure of the lung to noxious particles or gases stimulates an inflammatory response, whereby the lungs are infiltrated by neutrophils, macrophages and lymphocytes (9, 29). In COPD patients, destructive mediators and pro-inflammatory cytokines are released by immune cells, resulting in inflammation (30). Chronic inflammation leads to permanent structural change in the airway, such as alveolar destruction and epithelial hyperplasia, which is considered the third component of a vicious cycle (31)

Another important part of the vicious cycle is the systemic component which involves the priming of circulating inflammatory cells, tissue hypoxia, skeletal muscle dysfunction and weight loss (32). In particular, skeletal muscle dysfunction limits patient exercise capacity and activity, and leads to muscle malfunction (33). A number of pharmacological therapies (e.g. bronchodilators) (32), and non-pharmacological therapies (e.g. pulmonary rehabilitation), play an important role in the treatment and breaking of the vicious cycle of COPD (6).

## **1.5 DIAGNOSIS OF COPD**

COPD diagnosis is based on both patients' history of exposure to risk factors and the presence of airflow limitation. People with persistent cough and sputum production and a history of exposure to risk factors are usually tested for airflow limitation even in the absence of dyspnoea (4).

A diagnosis of COPD normally requires a history of smoking or particulate exposure as well as lower respiratory tract symptoms of breathlessness, cough, wheezing and/or sputum production. The diagnosis is confirmed by spirometric tests that measure the amount of forcibly exhaled air in the first second of exhalation (FEV<sub>1</sub>) and forced vital capacity (FVC). COPD is diagnosed as an FEV<sub>1</sub>/FVC ratio <0.70 and its severity is based on FEV<sub>1</sub> as a percentage of the normal FEV<sub>1</sub> in healthy people matched for gender, age, height and ethnicity. There are four grades of COPD severity as defined by the GOLD (Table 1) (34).

	FEV <sub>1</sub> /FVC	FEV <sub>1</sub> predicted
Grade 1: Mild	<0.70	≥80% predicted
Grade 2: Moderate	<0.70	50%≤FEV <sub>1</sub> <80% predicted
Grade 3: Severe	<0.70	30%≤FEV <sub>1</sub> <50% predicted
Grade 4: Very severe	<0.70	<30% predicted

**Table 1:** COPD severity grades

Spirometry is essential for COPD diagnosis. The process is easily performed in a hospital setting or by formal pulmonary function testing (PFT) in laboratories. Measurement of the diffusing capacity for carbon monoxide (DL<sub>CO</sub>) is another test that assesses the ability of the lungs to exchange gases and is useful in the diagnose of emphysema where lung volumes may appear normal. DL<sub>CO</sub> can be measured by one of two methods; both of these methods utilise carbon monoxide.

They are known as the single-breath and breath-hold techniques (35). Lung volume and ventilation tests are also important for diagnosing and differentiating between obstructive and restrictive disease. These tests can also be used to assess response to therapy (e.g. bronchodilators) and assess air trapping in the lung (36). Pulmonary function tests also include metabolic measurements which help to assess patient nutritional management by indirectly estimating resting energy expenditure (REE) (37).

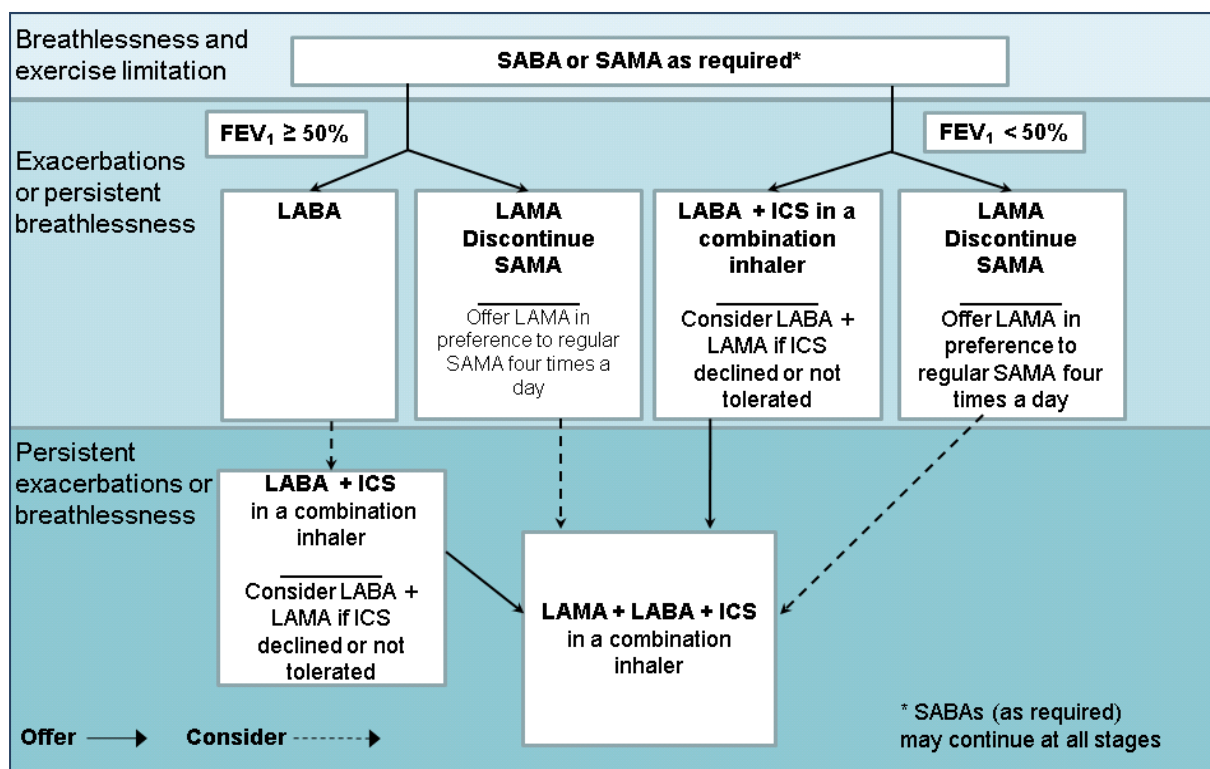
A normal chest X-ray does not exclude the diagnosis of COPD. Typical radiological findings include hyperinflation, escalation in retrosternal airspace on the lateral view, tubular heart, parenchymal hyperlucencies, and flattening of the diaphragm (38). In addition, a chest X-ray could be beneficial in excluding other related conditions such as heart failure, lung fibrosis and bronchiectasis. Although chest-computed tomography (CT) is not usually recommended, high-resolution CT (HRCT) can be used to confirm the diagnosis or to exclude related conditions such as lung fibrosis and bronchiectasis, and also to diagnose emphysema (39). When surgical procedures such as lung volume reduction or bullectomy are considered, HRCT is a critical requirement. Arterial blood gas analysis can offer the most convincing clues about the acuteness and severity of COPD exacerbation. In exercise tolerance testing, the ability of the patient's heart and lungs to provide oxygen and remove carbon dioxide is quantified (40).

## 1.6 CLINICAL MANAGEMENT OF STABLE COPD

Management of stable COPD is characterised by a stepwise increase in treatment. This depends on disease severity. Health education plays a critical role in enhancing skills and ability to cope with COPD (34). The National Institute for Health and Clinical Excellence (NICE) has recommended strategies for managing COPD based on airflow limitation and symptom severity. Pharmacological therapy starts with inhaled therapy including bronchodilators, both short-acting and long-acting beta2 agonists and muscarinic antagonists for relief of dyspnoea (41). As the disease worsens, additional therapy includes inhaled corticosteroids that have an anti-inflammatory action. Oral therapy includes corticosteroids, theophylline, and mucolytic and antibiotic therapy (2). However, there is controversy over the benefits of inhaled corticosteroids. Non-pharmacological therapy includes smoking cessation, which is a crucial element in COPD management to prevent an accelerated loss of lung function (42). Pulmonary rehabilitation (PR) is also very beneficial and safe, as discussed further below. In the later stages of the disease, if required, the patient may be prescribed long-term oxygen therapy or nutritional supplements and those with upper lobe emphysema may undergo lung-volume reduction surgery (LVRS) (4). Lung transplantation, LVRS and bullectomy are considered only to treat patients with advanced stage of the disease and for patients are unresponsive to medical therapy (2).

According to the NICE 2010 guidelines, there are several forms of inhaled combination therapy such as inhaled short-acting antimuscarinic antagonists (SAMA) (43). However, long-acting beta 2-agonists (LABAs) are the most effective first-line

bronchodilators in the management of stable COPD patients (Figure 3) (2). LABA therapy provides substantial benefits to patients such as improvement of symptoms and exacerbations; as it improves lung function, and reduces the frequency of exacerbations and the need for oral corticosteroid therapy (44). An added advantage of inhaled combination therapy is the possibility of one agent enhancing the function of the other (45). As COPD increases in severity, patients usually become hypoxaemic. In addition, some COPD patients could become transiently hypoxaemic after exercise and oxygen is used to enhance exercise capacity and to decrease disability (46). Oxygen can also be used to provide symptomatic relief in instances of breathlessness (47).



**Figure 3:** COPD inhalation therapy (The National Institute for Health and Clinical Excellence, clinical guideline (2)). Inhaled Corticosteroid (ICS), Short Acting Beta Agonists (SABA), as inhaled Short-Acting Anti-Muscarinic antagonists (SAMA), and Long-Acting Beta 2-Agonists (LABAs).



## 1.7 COPD EXACERBATIONS

### 1.7.1 Definitions and Symptoms

Exacerbations of the respiratory symptoms that require medical intervention are critical clinical events in COPD (48). Most exacerbations are due to infections but pollution may also play a role. However, over a third of severe exacerbations have no known cause (4).

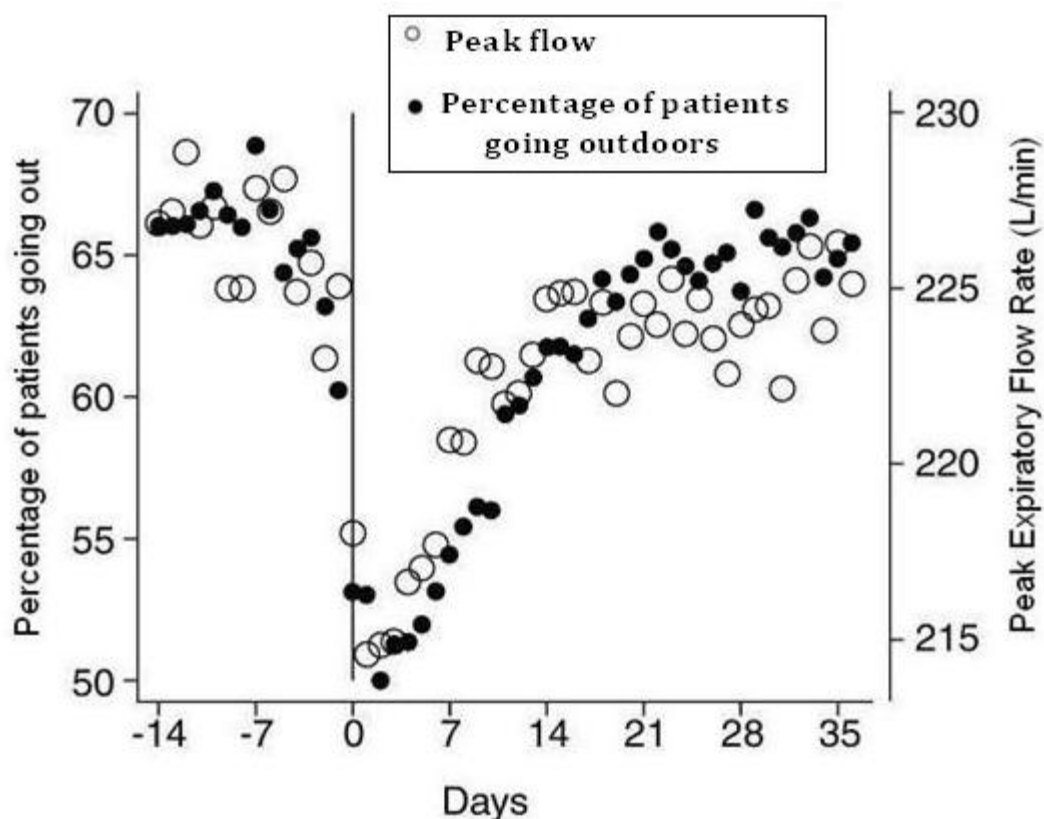
There is no generally agreed definition for COPD exacerbations. COPD exacerbations have been defined by respiratory symptoms and medication prescription or by symptoms alone, and (in some studies) by hospital admission. A standard definition might help guide decisions to treat, and help in research/ clinical trial design. Burge and colleague suggested the definition should not imply aetiology and severity (49). However, some studies used this definitions for exacerbation “a worsening of respiratory symptoms, which required treatment with oral corticosteroids or antibiotics or both”(50). Rodrigues-Roisin et al defined exacerbations as “a sustained worsening of the patient’s condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD” (51). However, both of these definitions required healthcare access where treatment can be given. On other hand, other epidemiological, clinical and pharmacological studies have assessed change in respiratory symptoms and defined exacerbations as an “Increase for two consecutive days in respiratory symptoms, with at least one major symptom “dyspnoea, sputum purulence or sputum volume) plus another major or

minor symptom (wheeze, cold, sore throat, and cough" (52). (modified from Anthonisen and coworkers, and used consistently in all London COPD cohort studies (53-56)). However, this requires daily symptom monitoring; therefore other interventional studies commonly define an exacerbation as health-care utilisation that typically involves the prescription of systemic therapy such as antibiotics and steroids, or hospitalisation (57). It is worth noting that exacerbation symptoms differ between individuals (58) and patients may also describe general malaise and fatigue which are non-specific symptoms of exacerbations.

These episodes of worsening respiratory symptoms are common and lead to substantial morbidity and mortality (59). Exacerbations are also characterised by deterioration of physiological variables such as lung function ( $FEV_1$ ), peak expiratory flow rate (PEFR) and physical activity (time outdoors) (3).

COPD patients with severe exacerbations are markedly inactive during and after hospitalisation (60) and skeletal muscle weakness has been associated with an exacerbation compared with stable COPD patients and healthy people (61). Efforts to enhance physical activity should be among the aims of disease management during and following a COPD exacerbation to prevent complications of inactivity, such as skeletal muscle dysfunction and reductions in quality of life (61, 62). According to Donaldson and colleagues, patients experience a significant decline in the amount of time spent outdoors during exacerbations compared with pre-exacerbation levels (3). They show the time course for 136 COPD patients during 51 days, which was included the percentage of time spent outdoor, together with

changes in PEF. In addition, there was significantly reduced in outdoor time between baseline and onset exacerbation ( $p=0.021$ ) and also reduced when comparing baseline with post exacerbation period ( $p=0.024$ ) (Figure 4) (3).



**Figure 4:** Percentage of patients going outside and changes in PEF rate. This figure illustrates the time course over exacerbations which show the percentage of patients going outdoors (white circles) and changes in PEF rate for the same patients (black circles). Exacerbation onset (Day 0) and baseline is considered to be the week from day -14 to -7 (3).

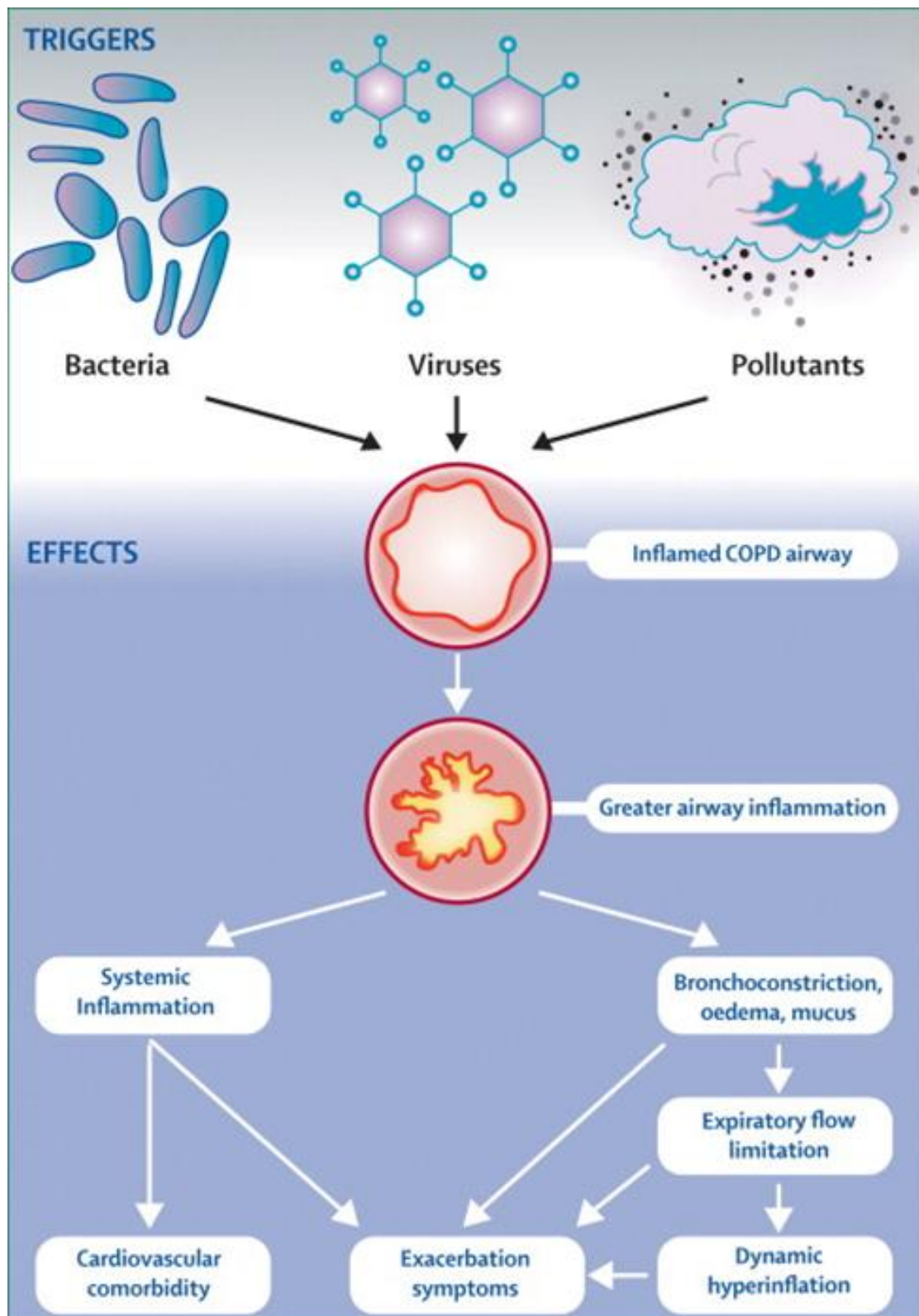
### 1.7.2 Exacerbation Aetiology

Exacerbations of COPD are caused by intricate interactions between the patient, environmental pollution, viruses, and bacteria (Figure 5). These are thought to escalate the inflammatory problem, particularly in the lower airways. This overpowers host defensive anti-inflammatory mechanisms, resulting in tissue damage.

According to published data, 50–70% of exacerbations are caused by respiratory infections (63), 10% are caused by environmental pollution, and approximately 30% have an unknown aetiology (64). The relationship between bacteria and COPD is well-recognised (65). In most cases, bacteria are isolated from the sputum of a stable patient, and from lower airway samples obtained with a protected brush. This has revealed that approximately one third of patients are colonised by bacteria at any given time (66). There are various mechanisms by which bacteria have been shown to mediate COPD symptoms. For example, strains of *H influenzae*, *S pneumoniae*, and *P aeruginosa* cause a hypersecretion of mucus in vitro. In addition, *H influenzae* and *P aeruginosa* inhibit the frequency of ciliary beating (67) .

In a comparison of patients during stable COPD versus during exacerbations of COPD, it has shown that there is a significantly higher prevalence of the airway bacteria *H influenzae*, *S pneumoniae* and *M catarrhalis* in patients undergoing an exacerbation (57.7% vs 26.9% prevalence,  $p = 0.001$ ) (55) . Furthermore, the study

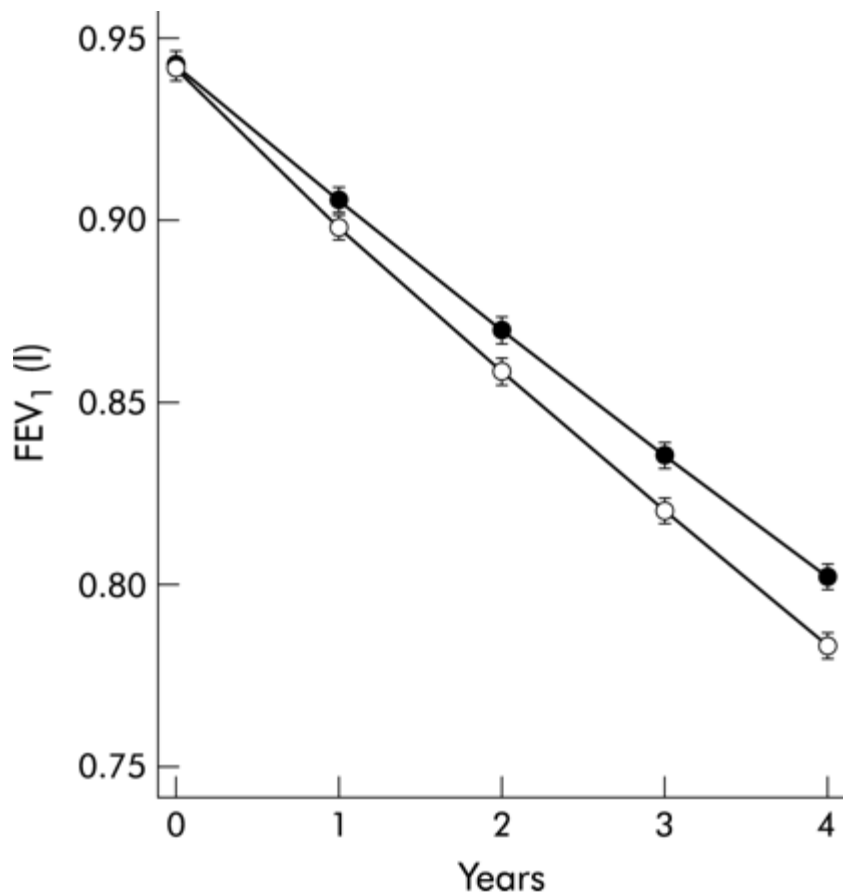
also illustrated that in patients who had these airway bacteria at both stable and exacerbated states, there was a significant 20-fold increase in mean bacterial load at exacerbation ( $10^{8.5}$  vs  $10^{7.2}$  colony forming units/ml;  $p= 0.011$ ) (55).



**Figure 5:** Triggers (bacteria, viruses and pollutants) of COPD exacerbations with increased airway and systemic inflammation leading to increased exacerbation symptoms (4).

### **1.7.3. COPD Exacerbation Frequency Status**

Frequent COPD exacerbators are generally considered as those patients who have two or more exacerbations per year, whereas those who have under two exacerbations per year are termed infrequent exacerbators. Patients with more frequent exacerbations have poorer health-related quality of life (68) and higher mortality (69). Donaldson and colleagues showed that the percentage decline in FEV<sub>1</sub> in patients with frequent exacerbations was 4.22 %/year compared to 3.59 %/year in patients with infrequent exacerbations. Also, patients with infrequent exacerbations decline by 25.3 ml/year compared to frequent 46.1 (p<0.001) (Figure 6) (5). In addition, frequent exacerbators ( $\geq 2.47$  exacerbations per year) had a greater decline in time outdoors (4.2 minute/day as recorded on diary cards) when compared to 1.2 minute/day infrequent exacerbators (p=0.011) (3)



**Figure 6:** Changes in Forced Expiratory Volume in 1 second during 4 years. A black circle shows infrequent exacerbations and white circles show frequent exacerbations. For those with infrequent exacerbations, FEV<sub>1</sub> dropped by 25.3 ml/year, whereas there was a 46.1 ml/year drop in those with frequent exacerbations ( $p < 0.001$ )(5).

The heterogeneity of COPD exacerbations mirrors their reliance on a complicated spectrum of interrelated factors. Therefore, the vulnerability to exacerbations and the foundation of a frequent exacerbator is most likely to be multifactorial. Classifying the contributory factors, such as the airway microbiome, the background airway inflammation, and the patient's immunological responses, could offer potential



targets in the attempt to change a patient's exacerbation frequency phenotype (70, 71). Airways of frequent exacerbators are more inflamed and are characterised by higher levels of interleukins (IL)-6 and (IL)-8 even when in a stable state (72). Furthermore, the trajectory of frequent exacerbators' inflammation has been demonstrated to be worse and with higher levels of plasma fibrinogen and IL-6, that increase most quickly over time. During the exacerbation recovery periods, these patients have increased sputum IL-6 and C-reactive protein serum (CRP) (73), which makes persistent post-exacerbation inflammation a more likely result of recurrent exacerbation.

#### **1.7.4. Clinical Management of Exacerbation**

Pharmacological management of a COPD exacerbation can include advice to increase use of salbutamol (a short-acting beta<sub>2</sub> agonist) and/or prescription of oral corticosteroids and/or antibiotics if the sputum becomes purulent (2).

Short-acting beta 2-agonists like salbutamol (albuterol) assist in opening narrowed airways (74). Long-acting bronchodilators can be used as well. They help in relieving airway constriction and help stop bronchospasm. Antibiotics are often administered when an infection of the lungs is recognised (74). Expectorants, on the other hand, are used to assist in loosening and expelling mucus secretions. Oral steroids are often used to treat an exacerbation with high doses administered intravenously or orally(4). Typically, oral prednisone is used to treat exacerbations in the UK. In emergency treatment oxygen therapy is used (4, 75).

Clinical trials have not revealed a benefit for mechanical percussion (chest therapy), although one of them demonstrated a substantial fall in FEV<sub>1</sub> (76). It is important to carry an initial hospital assessment in order to confirm diagnosis and to dismiss uncompensated respiratory acidosis (76). The use of mucolytics has been studied extensively; however, these treatments have been shown not to speed up FEV<sub>1</sub> recovery during exacerbation. It has been shown, however, that the use of mucolytics improves symptoms (77). Because frequent COPD exacerbations deteriorate a patient's health status, and may hasten failure in pulmonary function, treatment to diminish the frequency of the exacerbations is crucial (78).

Non-pharmacological management of a COPD exacerbation includes patient education, such as checking for the correct use of spacer devices and inhaler technique. If hospitalised and in respiratory failure, the patient may need oxygen therapy, non-invasive mechanical ventilation if hypercapnic, and in the most serious cases invasive mechanical ventilation may be required (79).

Pulmonary rehabilitation is not commonly considered part of COPD exacerbation management, although some studies have shown positive results of starting rehabilitation early post-exacerbation (80) as discussed further below.

## **1.8 SYSTEMIC INFLAMMATORY RESPONSE IN COPD**

The pathogenesis of COPD has not been completely elucidated, although immunopathological mechanisms with crucial roles for macrophages and neutrophils in the

mechanism of the development of the disease have been shown (81). The presence of inflammatory mediators and proteins such as IL-6, TNF-alpha, leptin, etc., have been shown in COPD (81), however, the absence of a correlation between the concentration of systemic and pulmonary cytokines necessitates further research to understand the exact mechanism of inflammation (82). Aging, hypoxia and hyperinflation due to smoking, pollution, etc., have shown to increase IL-6 and TNF-alpha levels initiating systemic inflammation (82). The study of Hurst et al., (83) showed a positive correlation between upper and lower airway inflammation owing to the development of the postnasal drip and bacterial load in the nasal area shown by the presence of the neutrophil attractant IL-8 protein and colonization of bacteria in the lower airway, although the exact mechanism remains unknown (83).

An easily measured systemic inflammatory marker is CRP. Previous studies in healthy people have shown significantly reduced CRP levels in exercising compared with non-exercising people (84-86). In COPD patients, CRP is raised and patients have impaired exercise performance and decreased daily activity (30, 87). CRP is one of the markers which has been shown to be increased in COPD patients compared with a healthy control group. As reported by a systematic review the mean difference between COPD patients and healthy people was 1.86mg/l (95% CI 0.75 to 2.97 mg/l) (88).

Several researchers have documented increased levels of neutrophil chemotactic factors in COPD patients. In sputum specimens, growth related oncogene-alpha (GRO- $\alpha$ ) and monocyte chemoattractant protein (MCP)-1 have been shown to be significantly increased in patients with COPD when compared to healthy people

(smokers and non-smokers) (89). Recent studies have shown that levels of cytokines remain relatively high in COPD patients (90). In lung tissue and bronchoalveolar lavage specimens of COPD patients, high levels of chemotactic factors have been discovered suggesting that anti-chemotaxis agents could be a therapeutic strategy in the treatment of COPD. Various cytokines are responsible for the stimulation of leukocyte chemotaxis through interacting mechanisms. A developing theory concerning increased levels of cytokines in COPD states that these factors have direct roles in airway remodelling and in lung injury. A study using transgenic mice has shown interesting effects of cytokines in lungs. Interleukin 13 (IL-13) was shown to escalate the expression of matrix metalloproteinases, which may change the lung's protease-antiprotease balance (91).

Fibrinogen has been shown to increase in COPD patients compared with healthy individuals (92). It is a soluble plasma glycoprotein primarily produced in the liver and is converted by thrombin into fibrin during blood coagulation (93). Fibrinogen levels show a clear correlation with COPD mortality (94). The normal levels of fibrinogen in the blood are between 1.5 and 3.5 g/l (93), and the level increases during acute phases such as COPD exacerbation events, in response to raised IL-6 levels (95, 96).

## **1.9 AIR POLLUTION IN GENERAL AND SPECIFICALLY IN LONDON**

Air pollution may be summarized as the presence of various harmful substances, particulate and non-particulate matter in air from different sources, both outdoor and

indoor that hampers the health, welfare, and functioning of the biological entities of the environment, both plant and animal (97). The increasing quantities of harmful gases such as SO<sub>2</sub>, NO<sub>2</sub>, CO and others constitute the major pollutants that are released by the emissions of transport, industries, and domestic and commercial sources of fuel heating systems (97). The quality of air in developed countries including London has deteriorated immensely compared to rural environment owing the advancement of technology and development that has resulted in increasing levels of air pollution, with a considerable rise of fatal health conditions of the respiratory system such as COPD, lung cancer, etc., leading to increased number of death every year (98) making it necessary to adopt suitable measures to control emissions.

Information concerning how the climate and atmospheric pollutants alter physical activity in COPD patients is particularly valuable for determining how physical activity might be encouraged. In particular, examining adherence to rehabilitation programmes would be beneficial.

### **1.9.1 Effect of Air Pollution on Normal Subjects and COPD Patients**

Evidence shows that atmospheric pollution is a cause of COPD exacerbations (99). When pollutants come into direct contact with respiratory epithelium, they activate an inflammatory cascade, which causes damage to tissue. Different studies have documented the relationship between particulate matter such as ozone (O<sub>3</sub>), sulphur dioxide (SO<sub>2</sub>) and NO<sub>2</sub> and respiratory inflammation (100, 101). COPD patients show greater sensitivity to air pollution particles than normal subjects. One study found

that the deposition of particles in the lungs evokes low-grade alveolar inflammation that results in COPD exacerbations (100). In a study by Gong and colleagues on the association between particulate matter (PM) and exposure and COPD exacerbations, a statistically significant fall in maximal mid-expiratory flow and saturation of arterial O<sub>2</sub> were reported (102). The decrements were higher for normal subjects than for COPD patients. These disparate responses to air pollutants and increased sensitivity have several explanations, including the association between PM levels with other constituents of air pollution which could be responsible for the observed effects (103). Pollution episodes may also reduce activity as PM <10 microns in diameter (PM<sub>10</sub>) in London increases symptoms of dyspnoea in COPD patients independently of other pollutants (104). PM<sub>10</sub> and traffic density also reduce pulmonary function in COPD patients (105). In addition, traffic-related air pollution exposure has been shown to be positively associated with first hospital admission for COPD (106).

## **1.10 PSYCHOMETRIC AND HEALTH STATUS IN COPD PATIENTS**

### **1.10.1 COPD Anxiety and Depression**

The Hospital Anxiety and Depression Scale (HADS) is a psychometric questionnaire with 14 items. This questionnaire reflects anxiety and depression in COPD patients; the minimum clinically important difference is 1.5, or a 20% change from baseline score (107). Van Ede and colleagues showed that the prevalence of depression ranges from 7% to 42% In COPD patients, and that this was four times greater than that found in healthy subjects. Also, the prevalence of anxiety was 15% when compared to a prevalence of 6% in healthy control subjects ( $p < 0.001$ ) (108, 109).

### 1.10.2 COPD Health Status

A COPD assessment test (CAT) and SGRQ questionnaire are used to assess health status in COPD patients.

The SGRQ is a 50-item questionnaire with 76 weighted responses and has three component scores: activity, symptoms and impacts, as well as a total score. This scale is commonly used to assess health status in COPD patients. The questionnaire has been validated with activity measurements in COPD patients with tools and measurement values such as 6MWD, dyspnoea and FEV<sub>1</sub> % predicted (110). The minimal clinically important difference in SGRQ has been estimated to be four units (111)

The CAT is an eight-item questionnaire designed to assess patient health status and was developed for clinical use. The CAT questionnaire provides clinicians and patients with a simple and reliable measure of overall COPD-related health status for the assessment and long-term follow-up of individual patients. The CAT score rises by 5 units (12% of a 40 point scale,  $p > 0.0001$ ) from the stable state in COPD patients ( $n=229$ ) to exacerbation ( $n=67$ ) (112). Patients with infrequent exacerbations show a significantly lower score at baseline ( $24.1 \pm 7.3$ ) compared with those with frequent exacerbations ( $19.4 \pm 6.8$ ,  $p < 0.001$ ) (54). The CAT questionnaire has been validated and shown to provide reproducible results. Furthermore, in the same study has been shown high correlation with SGRQ ( $r = 0.8$ ) (112).

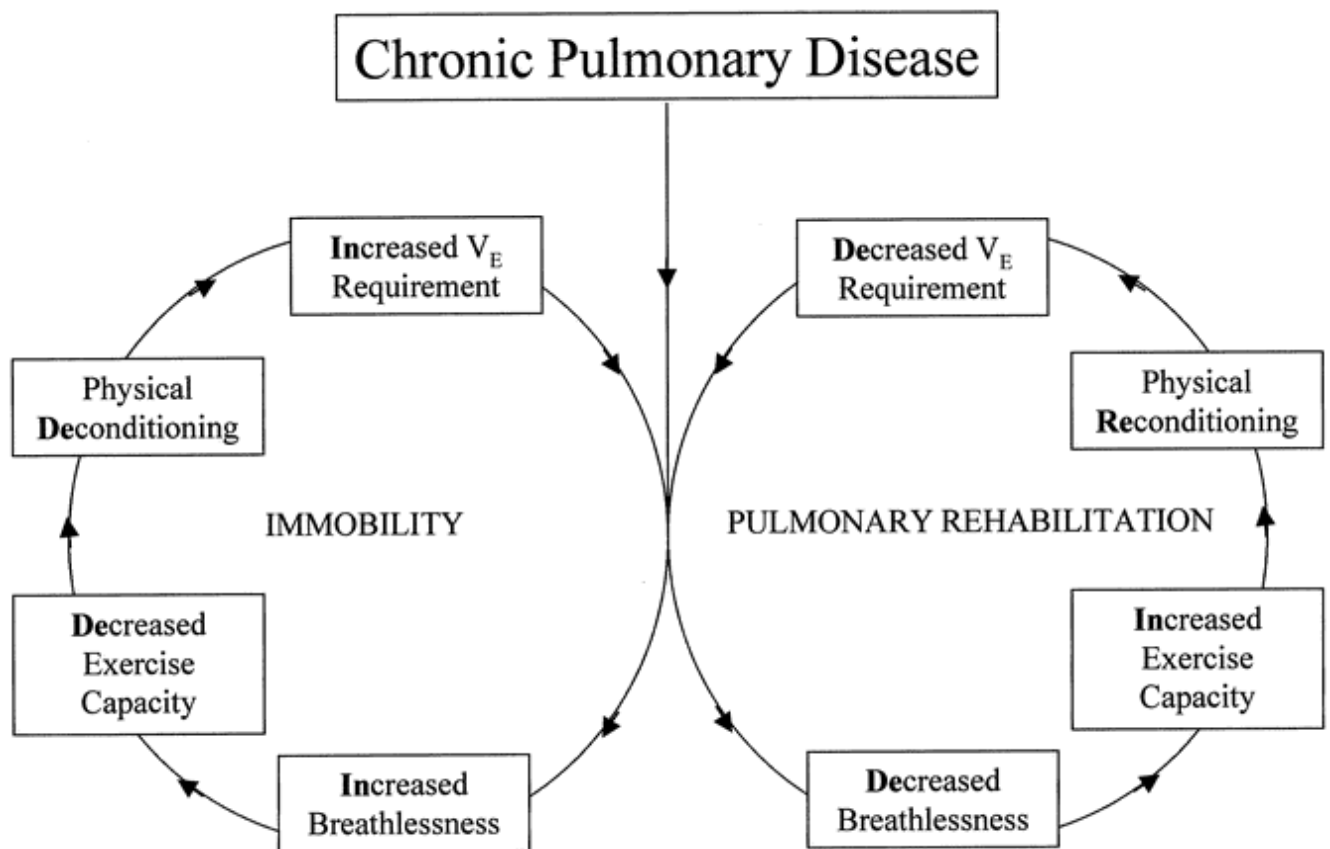
## **1.11 PULMONARY REHABILITATION**

### **1.11.1 Pulmonary Rehabilitation in Stable COPD**

Pulmonary rehabilitation (PR) is a hospital or community programme designed to help patients with chronic lung disease. The programme usually consists of physical exercise and an educational element. The exercise element comprises aerobic training of the lower limbs and may include upper limb exercise and strength building (113). The patient and their family or carer may also be informed of breathing strategies and receive psychological and nutritional counselling. The delivery of PR should involve a multi-disciplinary team including specialist physiotherapists, nurses, doctors, occupational therapists, psychologists and nutritionists (114, 115).

PR should be considered for all COPD patients who have shown persistent symptoms or restricted activity and for those who are incapable of adjusting to the illness notwithstanding minimal medical management. The benefits of PR include improved functional exercise capacity, improved health status, reduced dyspnoea and a trend towards fewer hospital admissions and bed days (2) (Figure 7).





**Figure 7:** COPD vicious cycle of disabling symptoms. The cycle leads to worsening symptoms, physical inactivity, deconditioning, and exercise limitation(6).

The benefits from PR can be attained irrespective of sex, age, smoking status or lung function (99). Recent evidence has shown that PR is associated with reduced healthcare costs (116). PR can be conducted in different structured programmes, which may have an impact on the level or the duration of long-term benefits (99).

COPD patients can be referred by physicians to specialized pulmonary rehabilitation clinics to undergo a few weeks of physical training and education but poor uptake and a failure to continue exercising limits the effectiveness of this intervention. There

is a need therefore to understand the barriers to participation and sustained behaviour change (117).

### **1.11.2 Pulmonary Rehabilitation Post-Exacerbation**

Most studies of PR in COPD have excluded patients with exacerbation due to concerns that early PR post-exacerbation may pose safety concerns (80). In addition, during exacerbation, increased muscle weakness (60) and persistent systemic inflammation may occur. These may confound the outcome measures normally used to assess PR such as exercise tolerance and quality of life (118).

In the UK, one-third of COPD patients admitted to hospital are readmitted within 90 days due to exacerbation (119). A PR programme delivered shortly after COPD exacerbation showed decreased re-admission rates in the following three months (120). Early post-exacerbation PR has also been shown to significantly improve exercise capacity, skeletal muscle strength, dyspnoea, quality of life and prevention of muscle atrophy (118, 119). However, Greening and colleagues showed that early PR during hospitalisation post-exacerbation did not improve patients' physical activity over 12 months post examination; also the same study showed that early PR did not reduce hospital re-admissions and mortality was higher in patients receiving early PR compared to usual treatment (121).

The time to start PR post-exacerbation has not been defined (116). Two studies which started PR within four to eight days of admission showed a reduction in the number of hospital admissions (87) and improved exercise capacity (122). Also, when PR was started within 10 days of hospital discharge there was improved exercise capacity and health status (123). Monitoring physical activity and exercise capacity post-exacerbation may help to identify the optimal time to start PR post-exacerbation.

Since PR programmes are focused on educating the patient to make lifestyle changes including increasing physical activity, seeking care at the earliest onset of exacerbation signs and quitting smoking, one advantage of PR following exacerbation of COPD could be associated with the readiness of the patient to change after an acute distress episode (116). Furthermore, COPD patients who participate in PR programmes receive continuity of care with regard to improving proper medication use and attention to crucial symptoms. However, attending PR programmes following acute exacerbation may be affected by severely reduced endurance, which necessitates slower exercise progression and a longer rehabilitation process (116). PR is ideal for patients who have persistent symptoms and a drop in functional status or health status. The improvement in health for COPD patients post-exacerbation is not necessarily associated with improvements in exercise tolerance (124).

### **1.11.3 Limitations of Previous Early PR Studies**

There are a number of limitations in previous studies examining early PR. As previously mentioned, rehabilitation was started on different days post-exacerbation onset (99). A number of studies did not show whether exacerbations had affected the outcomes they used to assess the benefit of PR (120, 123). Some studies relied on patient-reported outcomes and did not include an objective measure of physical activity such as accelerometry or pedometry. The results from previous studies may have been affected by recurrent exacerbations that follow from an index exacerbation and would have altered the schedule of PR (120).

## **1.12 EXERCISING MUSCLE**

### **1.12.1 Regulation of Oxygen Delivery to Exercising Muscle**

Uptake of oxygen ( $O_2$ ) and the regional distribution of blood flow within exercising muscles are not homogeneous (125). However, it is evident that there is an increase of blood flow in active muscles relative to those that are not involved in the specific form of exercise. Even in muscle groups that are taking part in the exercise, the increase in blood flow is not uniform (125). These disparities in blood flow and  $O_2$  distribution are associated with the composition of the muscle fibre type and the muscle tissue's recruitment patterns (126). Different studies have shown that the  $O_2$  consumption rate is higher in the highly oxidative soleus muscle than in inactive muscles. There has been debate about the mechanism regulating  $O_2$  delivery to exercising muscles. There are those who favour the idea that the dynamics of  $VO_2$

adjustment during exercise are responsible whereas others suggest that overall O<sub>2</sub> delivery to muscle fibres is the limiting factor (127, 128).

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### **1.12.2 Exercise Limitation in COPD: the Role of Peripheral Skeletal Muscle**

There is substantial peripheral skeletal muscle dysfunction in COPD patients (10, 129), marked by an earlier onset of muscle exhaustion (post-exercise quadriceps strength lower than that pre-exercise) (129) and a reduction in quadriceps endurance (130). Deconditioning or the presence of a specific myopathy may both play a role (10, 131), the latter perhaps driven by changes in the type of muscle fibre, reduced oxidative enzyme capacity and modified cellular bioenergetics, and reduced capillarity (132).

Recent studies have proposed other factors including exposure to systemic corticosteroids (133), systemic inflammation (134), hypoxia (135) malnutrition (136) and cachexia (137) as possible causes of peripheral muscle disease.

Cachexia is characterised by a loss of muscle tissue over fat, unresponsiveness to nutritional intervention (138, 139), along with increased protein breakdown (140). Loss of muscle mass in COPD patients is related to weaker peripheral muscles (10) and poorer quality of life (15) and increased mortality (141). The precise cause and the mechanism of cachexia in COPD are still unknown. However, evidence points to the involvement of pathological changes within intracellular mechanisms involved with the maintenance of muscle mass. Some of the potential factors that could

trigger these mechanism changes in COPD are myostatin, oxidative stress and inflammation (142).

### **1.12.3 Exercise Training in COPD**

Exercise training is an important aspect of PR and enhances the exercise capacity (degree, maximal work and endurance) of COPD patients despite an irreversible aberration in lung function (143). Evidence has shown that exercise training enhances exercise tolerance for COPD patients over and above the benefits provided by maximising medical therapy (144). There are a number of factors attributable to exercise intolerance in COPD patients, with airway obstruction recognised as playing a major role in the impairment. A reduction in FEV<sub>1</sub> on its own does not appear to cause a reduction in exercise capacity. This suggests that other factors are involved. Possible candidates could be pulmonary circulation abnormalities, reduced lung gas exchange, reduced performance of respiratory muscles, variations in the extent of hyperinflation, impaired right and left ventricular function, and decreased blood oxygen carrying capacity (145). In addition, skeletal muscle dysfunction, nutritional impairment and psychological factors could be involved (146).

The type and intensity of training for COPD patients is the subject of debate. Although all types of training are likely to enhance exercise performance, various outcomes can be expected with respect to whether the patient is undergoing aerobic endurance or strength training, high or low intensity training, or upper limb and/or

respiratory muscle training (116). There is no single exercise programme which can be regarded as ideal for all patients. However, the exercise programme needs to be customised in order to meet the patient's goals with the resources available (147).

There are a number of strategies that can be used to optimise the benefits of exercise training for specific COPD patients including supplemental O<sub>2</sub> and non-invasive assisted ventilation (148). In addition, nutritional support could be an essential additional intervention for improving exercise performance (149).

In normal individuals, vigorous exercise causes the exercising muscle to develop contractile fatigue. This fatigue causes the force produced by the muscle for a particular neural input to decrease (131). However, when COPD patients exercise, they become breathless. This may cause them to stop exercising even before the exercising muscle can develop fatigue (150). On average, quadriceps muscle biopsies in COPD patients reveal a lower proportion of type I fibres and a higher proportion of type II fibres relative to normal individuals. Type I fibres are slow-twitch fibres which are characterised by slight tension and resistance to fatigue. On the other hand, type II fibres are fast-twitch, develop high tensions and are vulnerable to fatigue (151).

### **1.13 PHYSICAL ACTIVITY**

Physical activity is defined as '*any bodily movement produced by skeletal muscles that results in energy expenditure (EE)*' (152). It is greater than that which is

expended at rest (maintaining body temperature and the function of the heart, lungs, nervous system and other body organs) (resting metabolic rate). Physical exercise is different from physical activity, which is defined as “*any planned, structured and repetitive bodily movement*” (152).

In daily life, physical activity can be categorised as occupational, conditioning, household, sports or other activities. Physical fitness is defined as “The ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy leisure-time pursuits and to meet unforeseen emergencies” (152). The amount of energy necessary to carry out an activity is quantified in kilojoules (KJ) or kilocalories (Kcal), but KJ is preferred over Kcal. Traditionally, Kcal has been used as a measure of heat. When stated as a rate, the quantity of energy used by an individual takes the form of a continuous variable (152). The total caloric expenditure that is associated with a physical activity can be determined from the amount of muscle mass which produces body movements and the duration, intensity and the frequency of muscle contractions (153).

### **1.13.1 Physical Activity in COPD Patients**

Physical activity is important in the everyday life of the entire populace. Its intensity and amount are crucial because of its close correlation with health, and inverse correlation with loss of life and disability (154, 155). In the recent past, physical activity assessment has attracted much interest, especially in vulnerable populations like COPD patients. This group of patients require a lot of care and monitor closely to face this chronic illness. Maintenance of physical activity can substantially reduce



age-related mortality (156) but it is particularly important for patients with COPD since those who continue to exercise have less dyspnoea, fewer hospital admissions for COPD and reduced mortality. Growing concern about physical inactivity in COPD patients has led to global efforts to address the problem, as physical inactivity is a leading predictor of death in COPD (157). It is critical that patients are given personalised PR programmes of support and encouragement. Behavioural modification, as well as pharmacotherapy, is also an important step in assisting patients to lead more proactive lives (158).

Physical activity has both physiological and psychological benefits particularly in reducing coronary heart disease and depression, which are more prevalent in COPD (159, 160). PR involving an exercise programme tailored to the individual is very successful at improving activity-related outcomes in COPD particularly after exacerbation (116) .

### **1.13.2 Physical Activity in COPD Patients at Exacerbation**

Previous studies have shown that COPD patients are less active and less likely to go outside during exacerbations compared to a stable state (3). Inactivity during hospitalised exacerbations leads to reduced walking and physical activity (60). There was also a significant reduction in quadriceps muscle strength during exacerbation after admission to hospital compared with stable COPD patients and healthy people (61). Physical activity has been assessed in hospitalised patients with an activity

monitor device (DynaPort, McRoberts BV, the Hague, the Netherlands) which patients wore for 12 hours on day 1 and day 7 of hospitalisation and after one month of discharge. This study showed that patients with exacerbations exhibited severely reduced physical activity during and after hospitalisation compared to one month after discharge (60).

### **1.13.3. Assessment of Physical Activity**

Subjective methods are practical in that they offer patients the chance to gain insights into their performance in everyday functional and living activities. Specially designed diaries and questionnaires help to evaluate patients' perceptions on their capacity to undertake daily tasks. However, these self-reported surveys are not always accurate (155). Objective methods such as motion sensors on the other hand offer more reliable information. As a type of motions sensor, accelerometers detect body acceleration as a marker of movement and thus of energy expenditure (155). Pedometers also detect movement but tend to underestimate the amount of physical activity, especially during slow walking. Pedometers do not provide data on physical activity patterns or the time spent on various physical activities (161).

The assessment and quantification of a patient's physical activities in daily life can be undertaken with one of the following methods: direct observation, physical activity questionnaires (self-report), diary card, quantification of EE and motion sensors (discussed below) (60).

These methods are characterised by a number of problems; for instance, direct observation is not only time-consuming but is also intrusive. Self-report questionnaires and diaries depend on memory, which makes them imprecise, particularly amongst the elderly, and they are time-consuming for participants (155). The radioisotope approach is an expensive methodology and is technologically complicated, e.g. it uses doubly labelled water or indirect calorimetry. Doubly labelled water is a non-invasive method which calculates as oxygen-18 is lost as  $H_2O$  and  $CO_2$ , and deuterium only as  $H_2O$ . The difference in loss is thus an index of  $CO_2$  production, and thus energy expenditure (especially if respiratory exchange ratio/respiratory quotient are known). Indirect calorimetry assesses activity by measuring  $O_2$  consumption and  $CO_2$  production (162). Moreover, heart rate monitoring is both expensive and inexact for use with COPD patients who have a heart rate that varies due to medication and other causes unconnected with physical activity (163).

Three important factors must be considered when one examines the accuracy and precision of any measuring method: validity, responsiveness, and reliability. A key aspect of validity is the method's reproducibility. However, reliability is a prerequisite for validity. Responsiveness refers to the measuring instrument's ability to identify change over time (164).

#### **1.12.3.1. Direct Observation**

This method records and counts patients' activities performed on videotape. It is an accurate technique for monitoring a patient's daily activity. The disadvantages of this

technique are that it is time-consuming, expensive, and demanding (155). It is also not feasible for a large number of patients because of the length of time required to investigate COPD exacerbations prospectively.

#### **1.13.3.2 Questionnaires**

Questionnaires are widely used to assess daily physical activity. This method has advantages in that it is inexpensive and suitable for use in large populations. The disadvantage of questionnaires is that they depend on the recall and accurate reporting of information by the patient. Differences in outcomes may be seen depending on the patient's characteristics, age, and culture (155).

#### **1.13.3.3. Diary Cards**

The diary card is a daily record sheet given to patients to record certain variables and is submitted or posted to the hospital clinic every month. This method can be used to assess patients over a long period; it is inexpensive and easily understood by patients. It also has disadvantages; for example, patients can underestimate or overestimate values, or inaccurately recall information, which could be an important limitation in older patients (155).

#### **1.13.3.4. Activity Monitors**

Activity monitoring instruments are devices used to detect body movement and quantify physical activity over a period of time. Two types of these monitors are accelerometers (Energy Expenditure (EE)) and pedometers (steps).

Energy Expenditure is widely used to assess physical activity. The gold-standard methods for measuring EE are doubly labelled water and indirect calorimetry, as explained previously.

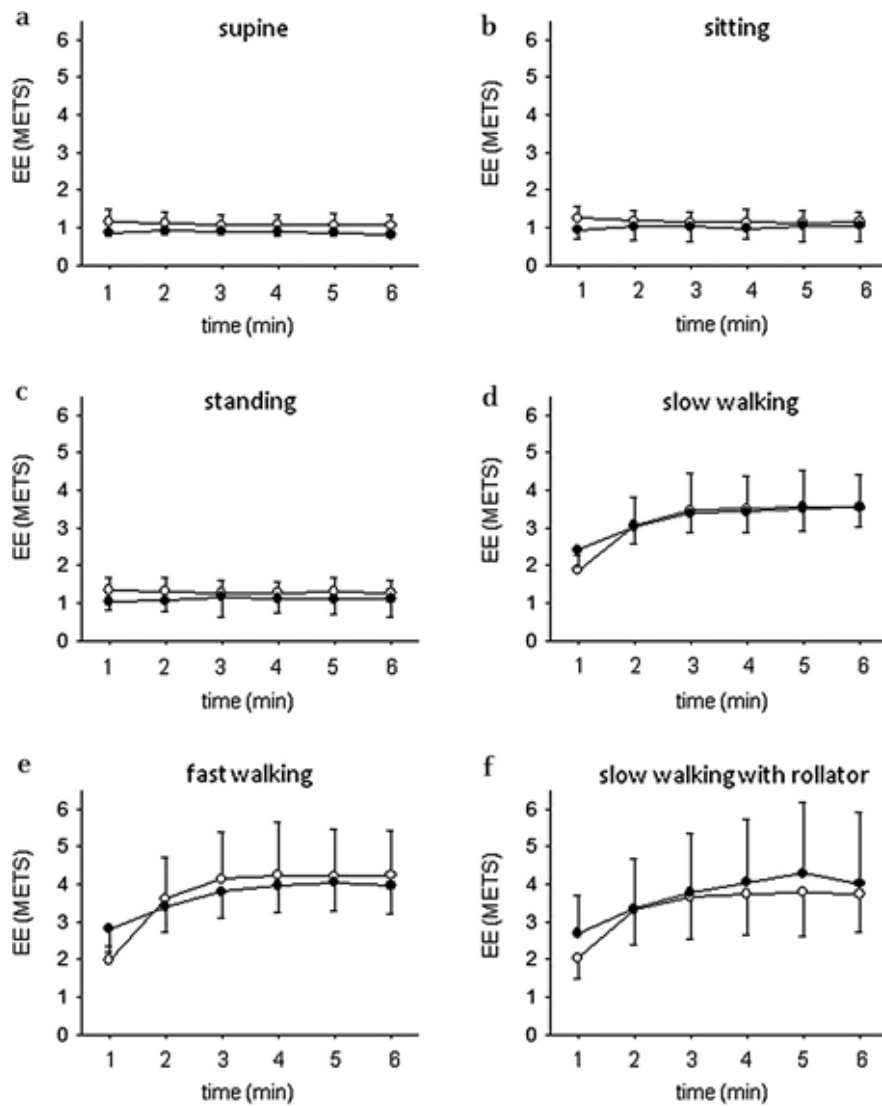
##### ***Accelerometers (energy expenditure)***

Accelerometer devices are considered a good way to monitor patient's physical activity. Accelerometers are electronic devices which can assess the intensity and quantity of body movement, level of physical activity, and EE based on body acceleration measurements (155).

##### **SenseWear Armband 7.0**

The SenseWear system comprises the system display device, SenseWear software and the SenseWear armband. The armband is utilised to monitor some diseases (metabolic disease), and help during diagnostic tests and studies such as nutritional diagnostics, cardiac and pulmonary studies, paediatrics, internal medicine and sleep screening (165, 166). Generally, it is used to monitor energy and caloric

consumption, physical activity and patient movement. This versatile monitor is worn by patients on the left triceps in a comfortable position such that it does not affect daily activities. The SenseWear system is utilised by researchers and clinicians and has been scientifically authenticated, featured in numerous peer-reviewed texts (165). SenseWear systems devices can be used to record and store data whilst the patient is away from the clinic. Hill et al used SenseWear and indirect calorimetry to determine average energy expenditure per minute for 26 COPD patients undertaking different tasks. They concluded that SenseWear was a useful device for estimating EE in patients with COPD who walk without a rollator (Figure 8) (165). The SenseWear device is a well-tolerated device in patients with COPD (165). It was found to make reproducible measurements and detect small but important changes (32, 165).



**Figure 8:** The energy expenditure (Metabolic Equivalents (MET)) measured every minute over all activities on day one of validation study (stable patients). Data comprise the mean and SD. Open circles: indirect calorimetry data; Closed circles: SenseWear armband (165).

Many types of accelerometers have been used to assess physical activity. The SenseWear device is light and costs £5000 for one piece of software and five

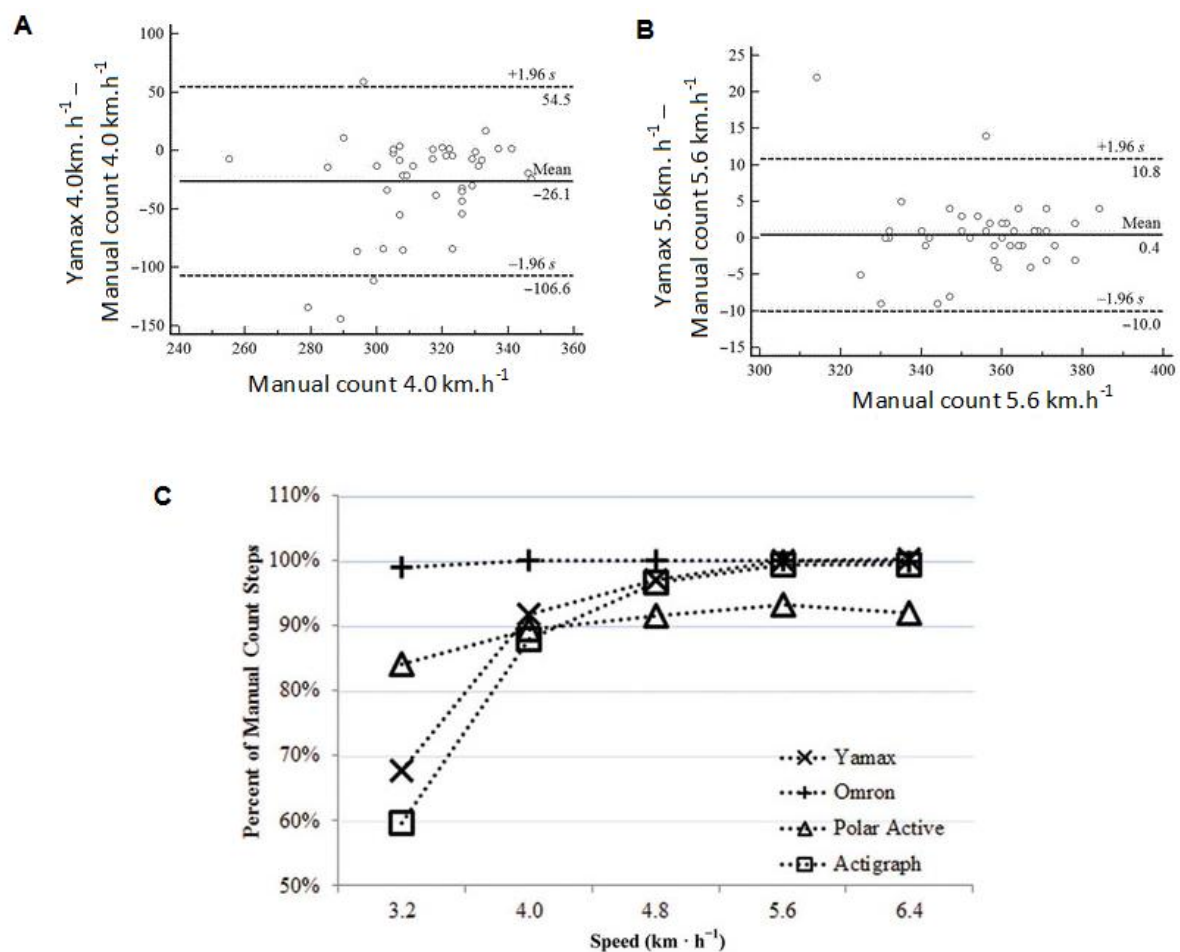
armbands, i.e. approximately £1000 per armband. Other instruments are available, such as the RT3 (StayHealthy Inc., Monrovia, CA, USA) and DynaPort (McRoberts BV, the Hague, the Netherlands) accelerometers. There have been some issues with the RT3 in detecting non-human movements, such as registering bumpy car rides as physical activity (167). The DynaPort (McRoberts BV, the Hague, the Netherlands) accelerometer is one of the most accurate instruments, but is too large for patients and difficult to tolerate for days. In addition, each device costs £4900, which is considerably more than the SenseWear armband (155).

## **Pedometer**

A pedometer counts each step a person takes by detecting the motion of the person's hips. The Yamax Digi-walker SW-200 uses a spring-suspended horizontal lever arm that moves up and down in response to the hip's vertical accelerations. This movement opens and closes an electrical circuit; the lever arm makes electrical contact and a step is registered. This pedometer has consistently been shown to be among the most accurate pedometers and is suitable for use by normal, overweight and moderately obese people (168). It has also been shown to be one of the most accurate step counters in a controlled laboratory setting (169). It is sufficiently inexpensive and thus can be used in a large cohort study and the model used in this study has been shown to be accurate within  $\pm 3\%$  of the actual steps taken 95% of the time (170). Also, this pedometer has been tested on the 4.88-km pavement course and measured the number of steps to within 1% of the actual steps (171). This pedometer has been tested on different surfaces and showed in general that



the effect of walking surface (track versus sidewalk) on pedometer recordings was not significant. Lee and colleagues studied 43 individuals, who wore activity monitors whilst walking at different speeds on a treadmill. Steps counted by these devices were compared to the visual step count (Figure 9A and B). They concluded that the Yamax pedometer was both reliable and valid in measuring step count (Figure 9 C). There is one potential disadvantage in that it can underestimate the number of steps taken by people walking very slowly ( $2.0 \text{ mph}$  ( $0.9 \text{ m} \cdot \text{min}^{-1}$ ))(171).



**Figure 9:** Bland-Altman plots of agreement in step counted between the Yamax pedometer and visual step count during treadmill walking speeds of (A). 4.0 and (B). 5.6 km.h<sup>-1</sup>. (C) Comparing daily activity monitors on treadmill walking at different speeds.

## **1.14 ESTIMATE EXERCISE CAPACITY AND MUSCLE STRENGTH IN COPD**

Exercise capacity is defined as the maximum amount of physical exertion that can be sustained by a patient (172). The measurement of exercise capacity demands that maximal exertion be prolonged in order to have a stable effect on both the circulation and the pattern of patient response (173, 174). The measurement of exercise capacity requires a complete and accurate history, which includes detailed and quantitative information concerning the intensity and duration of maximal effort and the features of the limiting symptoms.

In an interview assessment, patients are requested to describe their observations relative to a recent period of physical activity. Laboratory measurements use a performance index where maximal exercise performance is characterised with respect to duration and intensity of effort. The resulting values and the associated limiting symptoms are then compared with historical estimates (175).

The evaluation of muscle strength during rehabilitation could help identify muscle weakness and allow for targeted training programmes and mechanisms for monitoring progress. There are different techniques for measuring muscle strength in COPD. A dynamometer can be used to assess isometric, dynamic or isokinetic muscle strength, and can be applied to COPD patients (176). Both CT and magnetic resonance imaging (MRI) can be used to measure muscle mass (176). Other techniques can also assess body composition- including assessment of skinfold

thickness, underwater weighing, and use of dual-energy x-ray absorptiometry (DEXA).

#### **1.14.1 Six-Minute Walking Distance**

The Six-Minute Walk Distance (6MWD) test was initially introduced to assess exercise tolerance in people with heart and respiratory problems (88). It is widely used to assess exercise capacity in patients with COPD. However, performing the test can be difficult for those patients who are severely physically impaired. It can be used for measuring response to medical intervention in patients with severe to moderate lung and heart disease. It can also be used in conjunction with degree of obstruction ( $FEV_1$ ), the body mass index (BMI) and the dyspnea (MRC) scale to predict mortality (27). COPD patient mortality is evaluated not only by GOLD stages which is, based on the degree of obstruction ( $FEV_1$ ) (42), but also by using exercise capacity (6MWD), BMI and the dyspnea (MRC) scale to calculate the BODE index. The BODE index is a multidimensional grading system that predictor of the risk of death from respiratory causes. Celli and colleagues validated the BODE index within 625 COPD patients and found that the BODE index it is better than  $FEV_1$  for in predicting that risk of mortality. This index is graded from low mortality risk to high mortality risk (0-10) (27).

The 6MWD is a validated tool to follow progression and help determine outcomes. Walking fewer than 350m is associated with increased mortality, as reported in one study in the USA (177). However, patients who walk more than 350m in the 6MWD

have a relatively good prognosis and may not necessarily need to be followed or observed as closely, as reported in the USA, but this can change if warranted (177). The 6MWD minimal clinically important difference (MCID) is  $26 \pm 2$  metres (178). Also, MCID defined as “the smallest difference in score in the domain of interest that patients perceive as beneficial and that would mandate, in the absence of troublesome side effects and excessive costs, a change in the patient’s management”(179)

The American Thoracic Society (ATS) provides practical guidelines for the 6MWD (88). There is no practice test before the 6MWD, which is a particular advantage in COPD patients who are reluctant to take the test at exacerbation. In 2001, Solway and colleagues conducted a systematic review and compared the 6MWD, 2MWD, 12MWD, the Self-Paced Walk Test and the Shuttle Walk Test. They found that the 6MWD was better tolerated by patients, easier to administer, and more reflective of activities of daily living than the other tests (180). It was also correlated with the ability to perform sustained exercise such as walking (181). The disadvantage of a time- and self-limited test is that patients may tend to select a relatively comfortable speed and may not stress themselves by undertaking maximum effort (161)

The 6MWD must be conducted indoors, where there is a flat, straight, long and enclosed hard surface hallway that is rarely travelled. Conclusively, the test is a suitable measure of functional capability for individuals with fairly severe impairment (88).

#### **1.14.2. Quadriceps measurements (quadriceps maximal voluntary contraction force)**

Quadriceps muscle strength is a critical predictor of the functional abilities of a COPD patient. Assessment of muscle function entails the quantification of the force of maximum voluntary contraction. The contraction of the quadriceps muscle is measured with a muscle-testing chair called Cybex Norm dynamometer (Cybex, division of Lumex, Inc., Ronkonkoma, New York, USA) (182). The use of Cybex Norm has been shown to be effective in COPD patients. Magnetic stimulators can also be used to assess quadriceps force and fatigue. This is achieved by stimulating the nerve endings at the motor end plate region. When large pad electrodes are used, 30 to 50% of the whole muscle is activated and useful information is produced with minimal discomfort to the patient. However, the high costs of the measurement instruments are a major disadvantage of this technique (183).

Baarends and colleague shows that fat-free mass (FFM) significantly contributes to a disturbed peak exercise capacity in COPD patients (185). Tissue weakening is a key determinant of exercise capacity and health-related quality of life (HRQL) free of dyspnoea. Early research studies on quadriceps tissues have shown a reduced proportion of type I fibers and an increase in the proportion of type II fibers as compared to control group (normal individuals)(186-189). Consequently, Muscles myopathy is considered a feature of COPD. Histological examination of biopsy tissues taken from quadriceps shows a reduction in oxidative enzymes (190) and change to fatigable type II fibers. So this leads to anaerobic metabolism at lower work rate than in normal people (184). Lactic acid produced by anaerobic

metabolism is then buffered by bicarbonate to yield CO<sub>2</sub> (191). In addition, two studies showed that C-X-C motif ligand 1 (CXCL1) levels were inversely correlated with quadriceps strength during exacerbation recovery visits in a hospital (61, 191). Decramer and colleagues have shown the consequences of corticosteroid use in COPD patients and related it to steroid myopathy (133, 192).

# 2

## **HYPOTHESIS AND AIMS**

**This thesis tests the hypothesis that physical activity is reduced during COPD exacerbation recovery, and that a number of other factors, especially environmental and inflammatory factors, may affect physical activity in COPD.**

## 2.1. The aims of this thesis

- To evaluate prospectively daily step count in COPD patients with a simple pedometer, before and during the onset of an exacerbation. To evaluate recovery in physical activity post-exacerbation and its return to stable state.
- To evaluate the longitudinal trend of daily activity in patients with a history of frequent and infrequent exacerbations.
- To examine the effect of weather variables and air pollutants on daily step-count and hours spent outdoors, peak expiratory flow, worsening dyspnoea and health-related quality of life of stable patients with moderate to severe COPD.
- To investigate whether acute changes in physical capacity (6MWD, and quadriceps strength) and activity (energy expenditure and daily step-count) in naturally acquired, outpatient-treated exacerbations are associated with changes in systemic inflammatory markers and fatigue levels. To determine which falls in exercise capacity and physical activity at exacerbation are associated with disease severity, frequent exacerbations or prior pulmonary rehabilitation (PR) attendance. Such information could aid the choice and targeting of interventions.



- To determine whether step counts measured by a pedometer (Yamax Digi-Walker SW-200) are correlated with other measures of physical activity and whether the device can be used to assess COPD patients.

# 3

# METHODS

### **3.1 LONDON COPD COHORT**

The London COPD cohort is a group of approximately 200 COPD patients under longitudinal observation at the Centre for Respiratory Medicine, University College London. This cohort was started in 1995 for the prospective investigation of COPD exacerbations. Patients complete daily diary cards, are seen in clinic every three months and annually undergo a comprehensive medical review when stable. Patients are also seen at the onset of exacerbation and 3, 7 and 14 days post-onset. Patients who withdraw or die are replaced on a rolling basis. This cohort was designed to study the aetiology and pathophysiology of COPD exacerbations. The criteria for inclusion of patients to this cohort include an  $FEV_1/FVC < 0.7$ ; and  $FEV_1\%$  predicted  $\leq$  less than 80%; plus, a history of respiratory symptoms and plausible causative factor, usually tobacco smoking. Patients are categorised as mild, moderate, severe or very severe according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification (34).

Patients with other primary respiratory diseases or those who are unable to complete daily diary cards are excluded. For the studies described in this thesis, patients were also excluded if they used a walking support (cane or frame), were confined to a wheelchair or used ambulatory oxygen cylinders.

Some patients had been recruited prior to the start of this study, and thus patient characteristics in the stable state were those recorded as close as possible to the

start of this doctoral work in 2011 either at annual reviews or, for replacement patients, at recruitment.

At recruitment, age, gender, chronic respiratory symptoms (including cough, sputum production and nasal symptoms), smoking history, comorbidities and influenza vaccination were noted. Also, social and family histories were recorded, as were occupational history and number of people living in the patient's home. Every new recruit is asked to recall the number of courses of antibiotics and/or oral steroids which have been administered in the last year for the treatment of a COPD exacerbation.

FEV<sub>1</sub> and FVC were measured with a Vitalograph Gold Standard spirometer (Vitalograph Ltd, Maids Moreton, UK). Height and weight were measured with electronic scales and height stick. Patients were asked to perform the six-minute walking test and quadriceps muscle test. Patients also completed the Functional Assessment of Chronic Illness Therapy (FACIT-F), St George's Respiratory Questionnaire (SGRQ), Hospital Anxiety and Depression Scale (HADS), London Chest Activity of Daily Living (LCADL), and COPD Assessment Test (CAT) (Appendix A).

### **3.2 ETHICS**

The study was approved by the London-Hampstead Research Ethics Committee and all patients gave written informed consent (REC 09/H0720/8).

### **3.3 DAILY MONITORING**

Patients were monitored on a daily basis with a diary card (Figure 10). The diary card had space for a month of entries on a sheet of A4 paper; three to four months' worth of entries were given to each patient and collected at their three-monthly clinic visits. For this study, 73 patients were asked to wear a pedometer (Yamax Digi-Walker SW-200) at the waist on the left-hand side (193, 194) and record their daily step-count on the diary cards. The characteristics of the 73 COPD patients are shown in Table 2. After recording daily Peak Expiratory flow and noting respiratory symptoms, the patients were instructed to record on the diary card their estimate of the time that you were out of your own home on the previous day.

	<b>73 COPD patients</b>		<b>Remaining 126 COPD patients in the Cohort</b>		<b>P-value</b>
	<b>Mean</b>	<b>(±SD)</b>	<b>Mean</b>	<b>(±SD)</b>	
<b>Age (years)</b>	71.1	(±8.7)	70.2	(±8.8)	0.51
<b>FEV<sub>1</sub> (l)</b>	1.31	(±0.5)	1.40	(±0.5)	0.25
<b>FEV<sub>1</sub> (% predicted)</b>	52.9	(±16.5)	56.2	(±16.1)	0.22
<b>FVC (l)</b>	2.79	(±0.9)	2.76	(±0.9)	0.83
<b>FEV<sub>1</sub>/FVC (%)</b>	47.8	(±12.6)	50.7	(±12.3)	0.11
<b>BMI (kg/m<sup>2</sup>)</b>	26.8	(±5.6)	27.0	(±5.1)	
	<b>Median</b>	<b>( IQR)</b>	<b>Median</b>	<b>(IQR)</b>	
<b>Exacerbations/year</b>	2	(1.0-3.0)	1.4	(0.7-3.0)	0.40
	<b>%</b>				
<b>Sex (Males)</b>	69.9		62.6		0.36
<b>Chronic bronchitis</b>	54.3		54.5		0.98
<b>Smoking at-recruitment</b>	35.6		32.0		0.77

**Table 2:** Characteristics of the 73 COPD patients in the study and 126 COPD patients in the cohort not recruited to the study.

Patients were educated to use diary cards at the recruitment visit and re-educated as needed when visiting the clinic. The diary cards also have instructions and contact numbers on the back of every card (Figure 11). On enrolment to the COPD cohort, the research team ask patients to report exacerbations and attend the clinic if possible at the exacerbation onset.

NAME	Nov. 2012												NEXT APPOINTMENT / / 11 am
	WORSENING SYMPTOMS? CALL US												
Study Number													
THE LONDON COPD STUDY													
DATE	1th	2Fr	3Sa	4Su	5Mo	6Tu	7We	8Th	9Fr	10Sa	11Su		
Peak Flow %	240/97%	260/96%	240/96%	260/96%	250/98%	250/97%	250/98%	250/98%	250/97%	250/97%	250/98%		
CHANGE in Symptoms													
CHANGE in Treatment	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON		
Hours out of the home	6	8	7	4	6	5	5	10	5	6	5		
Number of Steps	3809	2976	3296	3261	2896	3206	2682	4981	370	3121	3390		
DATE	12Mo	13Tu	14We	15Th	16Fr	17Su	18Su	19Mo	20Tu	21We	22Th		
Peak Flow %	245/97%	245/98%	245/98%	250/98%	250/98%	240/97%	250/98%	250/99%	250/98%	250/98%	250/98%		
CHANGE in Symptoms													
CHANGE in Treatment	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON		
Hours out of the home	5	6	6	6	7	6	6	7	5	6	5		
Number of Steps	3162	3093	3203	3201	3630	4631	2236	2915	3207	3639	3372		
DATE	23Fr	24Sa	25Su	26Mo	27Tu	28We	29Th	30Fr					
Peak Flow %	250/98%	250/97%	250/97%	240/96%	240/96%	250/97%	240/98%	250/97%					
CHANGE in Symptoms													
CHANGE in Treatment	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON	MEDS VIA SIMON					
Hours out of the home	5	4 1/2	4	5	5	6	5	8					
Number of Steps	4105	3301	3267	3449	2814	3787	4270	6700					

EX-11/11/12 to 11/11/12

**Figure 10:** London COPD cohort diary card. Red circle shows the exacerbation event. The card includes daily peak flow, change in symptoms, changes in treatment, hours out of the home and number of steps.



## Instructions for filling in the DIARY CARDS

### EVERY DAY...

1. After taking morning medications record the best of 3 attempts at the PEAK FLOW blowing test in the box on the sheet.
2. Please record any **WORSENING** of symptoms **ABOVE YOUR USUAL** daily level. The symptoms we are interested in are listed below, just put the appropriate letter in the box on the sheet. Continue recording until the symptom has gone away or got back to the level you consider 'normal'.

Letter	Symptom
A	increased BREATHLESSNESS.
B1	increased SPUTUM COLOUR.
B2	increased SPUTUM AMOUNT.
C	a COLD (such as a runny or blocked nose).
D	increased WHEEZE or CHEST TIGHTNESS.
E1	SORE THROAT.
E2	increased COUGH.
F	FEVER.

If you experience a worsening in any of these symptoms please phone us to arrange an assessment visit, and do this **BEFORE** starting any antibiotic or steroid tablets. The phone number is  
**07762 038662.**

Anant or Alex will have the phone and we can usually arrange to see you later the same day or the following morning.

Please phone if you are not sure what to write down or you have any questions.

3. Please record any **CHANGE** to your usual treatment for as many days as it applies. Again, just put the appropriate letter in the box on the sheet.

Letter	Treatment
H	I am in Hospital.
I	I am taking more than usual <b>INHALED STEROID</b> (red / brown/purple)
R	I needed to take extra <b>RELIEVER</b> (blue / green / grey / nebuliser). <b>HOW MANY PUFFS?</b> Write, eg 'R3' for 3 puffs, 'R2' for 2 etc
S	I am taking <b>STEROID</b> (Prednisolone) <b>TABLETS</b> . <b>HOW MANY TABLETS?</b> Write, eg 'S6' for 6 tablets, 'S5' for 5 etc
X	I am taking <b>ANTIBIOTIC TABLETS</b> . <b>PLEASE RECORD WHICH</b> (write the name on the diary card).

- 4- Please estimate the time that you were out of your own home on the previous day.

### 5- Pedometer

- Attach the pedometer to your belt, beltless, slacks, skirts or training suits bottoms using the clip.
- To open the pedometer hold it upright; grasp the top of the clip with one hand. Use the other hand to push the projecting portion of the case body between the sides of the clip away from the clip, thus opening the case.
- After you have written down the number from the pedometer on this sheet, press the yellow button to reset the pedometer.

**Figure 11: Diary card instruction sheet.**

### **3.4 EXACERBATIONS AND STABLE STATE**

An exacerbation was defined as an increase for two consecutive days in respiratory symptoms, with at least one major symptom (dyspnoea, sputum purulence or sputum volume) plus another major or minor symptom (wheeze, cold, sore throat, and cough). Five consecutive symptom-free days were required before identification of the next exacerbation. Symptoms were disregarded in identification of exacerbation onset if recorded continuously in the preceding five days. If earlier diary card data was unavailable due to recent recruitment (n=3 patients) then the number of exacerbations was based on patient recall or hospital admission record data (195). Symptom counts were obtained by summing each increased respiratory symptom recorded on diary cards per day.

Patients were considered to be stable (non-exacerbating) 30 days after the onset of an exacerbation and at least 14 days after ending treatment (oral corticosteroids and/antibiotics).

#### **3.4.1 Exacerbation Frequency**

Patients were divided into two groups based on the number of exacerbations in the 12 months preceding the start of the study: If earlier diary card data were unavailable because of recent recruitment then the number of exacerbations was based on patient recall and from the letter received from patient's GP. Those with two or more

exacerbations per year were called frequent exacerbators and those with no or one exacerbation per year were called infrequent exacerbators (5).

For this research, data from patients who experienced multiple exacerbations were averaged to avoid bias through repeated measures. However, I analysed exacerbations as individual events when investigating whether the characteristics of exacerbations (respiratory symptoms, treatment, and change in step count) influenced fall in activity or recovery.

### **3.5 MEASUREMENTS AT BASELINE AND EXACERBATION**

All questionnaires, 6MWD and blood samples were prospectively collected from patients at baseline (3-month intervals), from 2011 to September 2013. For this study, a non-exacerbation associated measurement, nearest in time to the start of the exacerbation was used as baseline result to compared to the exacerbation. These baseline measurements were generally collected either at an annual review or a recruitment visit. For chapter 7, some baseline data may have been collected a year prior to an exacerbation but it is not possible to predict when an exacerbation will occur and it was felt that repeated testing every 3 monthly would be too burdensome.

Changes at exacerbations in symptom count and hours spent outdoors were assessed by comparison of the average over a seven-day baseline period which started two weeks before onset with the average over a seven-day exacerbation period starting on the day of onset. Recovery in symptoms was determined as the day preceding two days with no recorded increased symptoms.

Changes at exacerbations in daily step count, symptom count, PEF and hours spent outdoors were assessed by comparison of the average value over a seven-day baseline period which started two weeks before onset with the average value over a seven-day exacerbation period starting on the day of exacerbation onset. Recovery was determined as the day after exacerbation onset when a three-day moving average of a parameter matched or exceeded its baseline value. The baseline was determined as the average daily step count over a 7 day period which started 2 weeks before the onset of the exacerbations. A moving average was used to avoid false early recoveries when step count or lung function improved for just a single day but then remained below baseline for a few more days (196).

Patients were asked to call a 24-hour phone line to arrange an appointment if their symptoms deteriorated. Most patients were seen within two days of the onset of symptoms. Exacerbations were defined as a worsening of respiratory symptoms not treatment. Generally, patients who attend our clinic do not go to their GP for an exacerbation as we provide transport and speedy appointments and appropriate treatment.

The patients were seen in clinic before treatment (day 0) and on days 3, 7, and 14 after treatment. This timing was chosen to capture both the early, rapid phase of recovery and include a measurement. We conducted the 6MWD at all visits except day 0; questionnaires were completed, blood was taken, and pulmonary function tests were performed at every visit. In addition, symptoms were assessed over a week, from three days before to three days after the date of the 6MWD.

Quadriceps muscle test and 6MWD were not conducted on the day of reporting exacerbation to avoid any harm to patients on that day. Energy expenditure and daily steps were continuously assessed with an accelerometer and a pedometer for two weeks. Also, patients wore the SenseWear and pedometer for 14 days starting from day 0 on the left side of the body, from waking until they went to bed at night, taking them off before sleeping or having a shower.

### **3.6 STUDY DESIGN**

## **BASELINE**

6MWD /SenseWear armband (SWA) /Pedometer  
Measuring Peripheral Muscle Strength  
CAT/ Diary Card /HADS/LCADL/SGRQ  
Lung Function Test / CRP

## **EXACERBATION ONSET**

Instruct patient on use SWA + handling instruction sheet  
Patients wear the SWA and pedometers for 14 days from this day  
Measuring Peripheral Muscle Strength  
CAT/ Diary Card/ HADS  
Lung Function / CRP

## **Recovery visits (days 3, 7,14)**

6MWD / SWA / Pedometer  
Measuring Peripheral Muscle Strength  
CAT/ Diary Card /HADS  
Lung Function /CRP

## **Day 14**

Downloading the activity data from SenseWear

### **3.7 QUESTIONNAIRES**

In this study, I decided to use five validated questionnaires: 1) LCADL, 2) SGRQ, 3) HADS, 4) CAT and 5) FACIT-Fatigue.

#### **3.7.1 London Chest Activity of Daily Living scale (LCADL)**

The LCADL investigates the level of disability induced by dyspnoea. The questionnaire asks about breathlessness associated with 15 common activities and is subdivided into four areas: self-care, domestic, physical and leisure activities. LCADL was used to assess COPD routine activity on a Likert scale of zero to five, with low scores reflecting low physical activity and high scores reflecting patients' ability to undertake daily activity (9). The maximum score was 75 points (Appendix A).

#### **3.7.2 St George's Respiratory Questionnaire (SGRQ)**

The SGRQ is a questionnaire designed to assess health impairment in patients with COPD. It is a 50-item questionnaire with 76 weighted responses and has three component scores: activity, symptoms and impacts, as well as a total score. The maximum score is 100 points and high scores indicate poor health status (197) (Appendix A). The SGRQ score can be calculated per component and total score. The first step to calculate score is summed the weights for all positive responses items. Then, the second steps is deducted the weights for missed items from

maximum weight for each component or for the total score. Then calculate the SGRQ score for each component or total score by using this equation:

$$=100 \times \frac{\text{Summed weights from positive items in that component (all components)}}{\text{Sum of weights for all items in that component (all components)}}$$

The maximum possible weights for symptoms component are 662.5, activity is 1209.1 and impacts is 2117.8 and total weight for all component is 3989.4 (197)

### **3.7.3 Hospital Anxiety and Depression Scale (HADS)**

The HADS is a 14-item questionnaire divided into two domains. The response to each question is measured on a scale of zero to three. The maximum total score is 21 points for anxiety and 21 points for depression. If the total score for both is less than or equal to seven it indicates normal levels, a score between 8 and 10 indicates borderline abnormal anxiety and depression, and a score from 11 to 21 is considered abnormal (15) (Appendix A).

### **3.7.4 COPD Assessment Test**

The CAT is a valid questionnaire and includes eight items. The CAT score is designed to assess COPD patient health status. The response to each question is measured on a scale of zero to five and the maximum total score is 40 points. High scores indicate poor health status (54) (Appendix A).



### 3.7.5 Functional Assessment of Chronic Illness Therapy–Fatigue

The FACIT-F is a fatigue scale and it has been validated with COPD (198). This questionnaire contains 13 items which measure a patient's fatigue during daily activity. The FACIT-F is measured in four points: four indicates no fatigue at all and zero extreme fatigue, and the total score is 52, (Appendix A).

### 3.8 BODE INDEX SCORES

The BODE (Table 3) index score combines four important variables in one score. BODE refers to (B) body mass index; (O) the degree of airflow obstruction measured by FEV1 predicted; (D) dyspnoea assessed by (MRC) scale; and (E) exercise capacity (6MWD). The BODE index ranges from zero to 10. A higher score indicates a higher risk of death (27).

	0	1	2	3
FEV1% pred	≥65	50-64	36-49	≤35
6MWD (m)	≥350	250-349	150-249	≤149
MMRC	0-1	2	3	4
BMI (kg.m <sup>-2</sup> )	>21	≤21		

**Table 3:** Scoring the BODE index (total BODE 0 to 10 based on patients results)

### **3.9 MEDICAL RESEARCH COUNCIL (MRC)**

The MRC dyspnoea score was used as a measure of the degree of perceived breathlessness which is associated with level of disability (199) Patients choose one of the 5 following statements which best describes them:

- Grade 1, "I only get breathless with strenuous exercise"
- Grade 2, "I get short of breath when hurrying on the level or up a slight hill"
- Grade 3, "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"
- Grade 4, "I stop for breath after walking 100 yards or after a few minutes on the level";
- Grade 5, "I am too breathless to leave the house or am breathless when washing or dressing".

### **3.10 TEMPERATURE AND POLLUTION DATA**

Daily data for atmospheric PM<sub>10</sub> (particulate matter of 10 microns diameter) and Ozone (O<sub>3</sub>) were obtained for Bloomsbury Square, Central London from the Air Quality Information Archive database (<http://www.airquality.co.uk>). Data from the archive is reported as µg/m<sup>3</sup>. The conversion factor of ozone is 1 ppb = 1.9957 µg/m<sup>3</sup>

at 20°C and 1013 millibar atmospheric pressure. In London, one monitoring was more centrally located (Hackney) but it did not record data on PM10.

Climatic data were the average of hourly readings over 24 hours at London Heathrow Airport obtained from the British Atmospheric Data Centre ([www.badc.nerc.ac.uk](http://www.badc.nerc.ac.uk)). A dry day was zero precipitation defined by means of a tilting siphon rain gauge that produces an autographic record of rainfall accumulation to an accuracy of 0.1mm. A sunny day was when sunlight for a minimum of 0.1 hours was of such intensity that a Campbell-Stokes recorder would, after the rays were focused, scorch thick card. The patients lived on average 7.29 km (SD 4.72) from the Bloomsbury Square site.

### **3.11 ACTIVITY MONITORS**

#### **3.11.1 Pedometer**

A Yamax Digi-walker SW-200 pedometer was used to count the number of steps taken per day (Figure 12). Patients were instructed to wear the device on the left side of the body all the time, except when sleeping or showering. Pedometer placement was standardised by placing it on the belt or waistband, in the midline of the thigh, consistent with the manufacturer's recommendation and with studies conducted previously (193, 194). Patients recorded daily step counts on daily diary cards. This pedometer has been shown to measure steps accurately in free-living

individuals (194) and in normal and moderately obese patients (200) and has detected differences in physical activity of COPD patients from day to day.

A pedometer counts each step a person takes by detecting the motion of the person's hips. The Yamax Digi-walker SW-200 uses a spring-suspended horizontal lever arm that moves up and down in response to the hip's vertical accelerations. This movement opens and closes an electrical circuit; the lever arm makes an electrical contact and a step is registered.

Patients could not be supervised with the pedometer so data collected over the initial seven days were discarded to avoid any learning effects. Only patients who had recorded more than 35 days of pedometry data were included in this analysis.

All hundred ninety-nine patients in our rolling cohort were considered for participation in this study. Twenty-four patients were not eligible as they used a walking support (cane or frame), were confined to a wheel chair or used ambulatory oxygen cylinders; 30 refused. I eventually provided pedometers to 145 patients. Data were successfully acquired from only seventy three patients (table 2) due to the following reasons a) Twenty one patients once issued refused to use the pedometer b) Nineteen patients lost their pedometers c) Twenty three patients recorded less than 35 days of data whilst stable and d) Nine pedometers broke (e.g. loss battery and disappear number from screen). Patients are lost to follow-up for a variety of reasons (other medical problems, re-location, reluctance to travel to far, and frailty of

themselves or illness of a partner). Whether the loss causes a systemic bias is unknown and difficult to assess

### Instructions for using the pedometer (in the back of diary card)

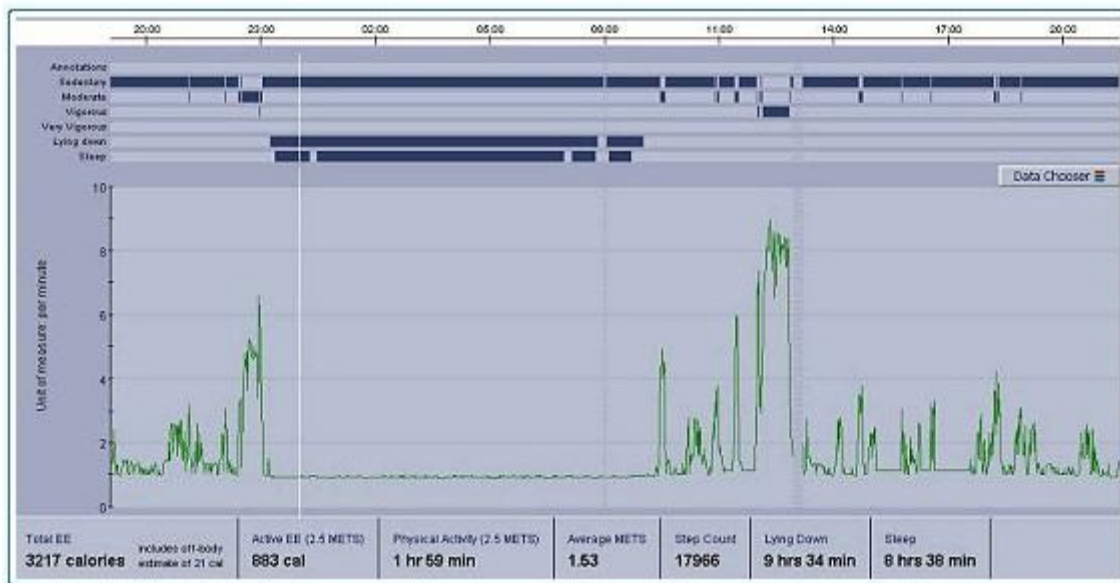
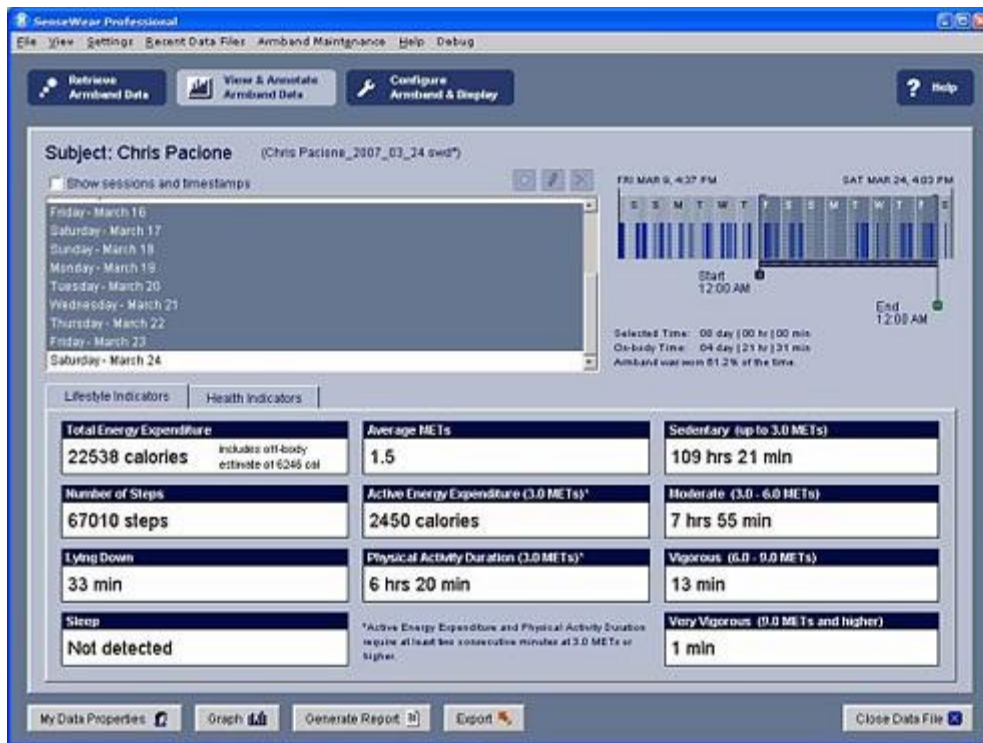
- Attach the pedometer to your belt, beltless slacks, skirts or training suit bottoms using the clip.
- To open the pedometer hold it upright; grasp the top of the clip with one hand. Use the other hand to push the projecting portion of the case body between the sides of the clip away from the clip, thus opening the case.
- After you have written down the number from the pedometer on this sheet, press the yellow button to reset the pedometer.



**Figure 12:** Pedometer (YamaxDigi-Walker SW-200).

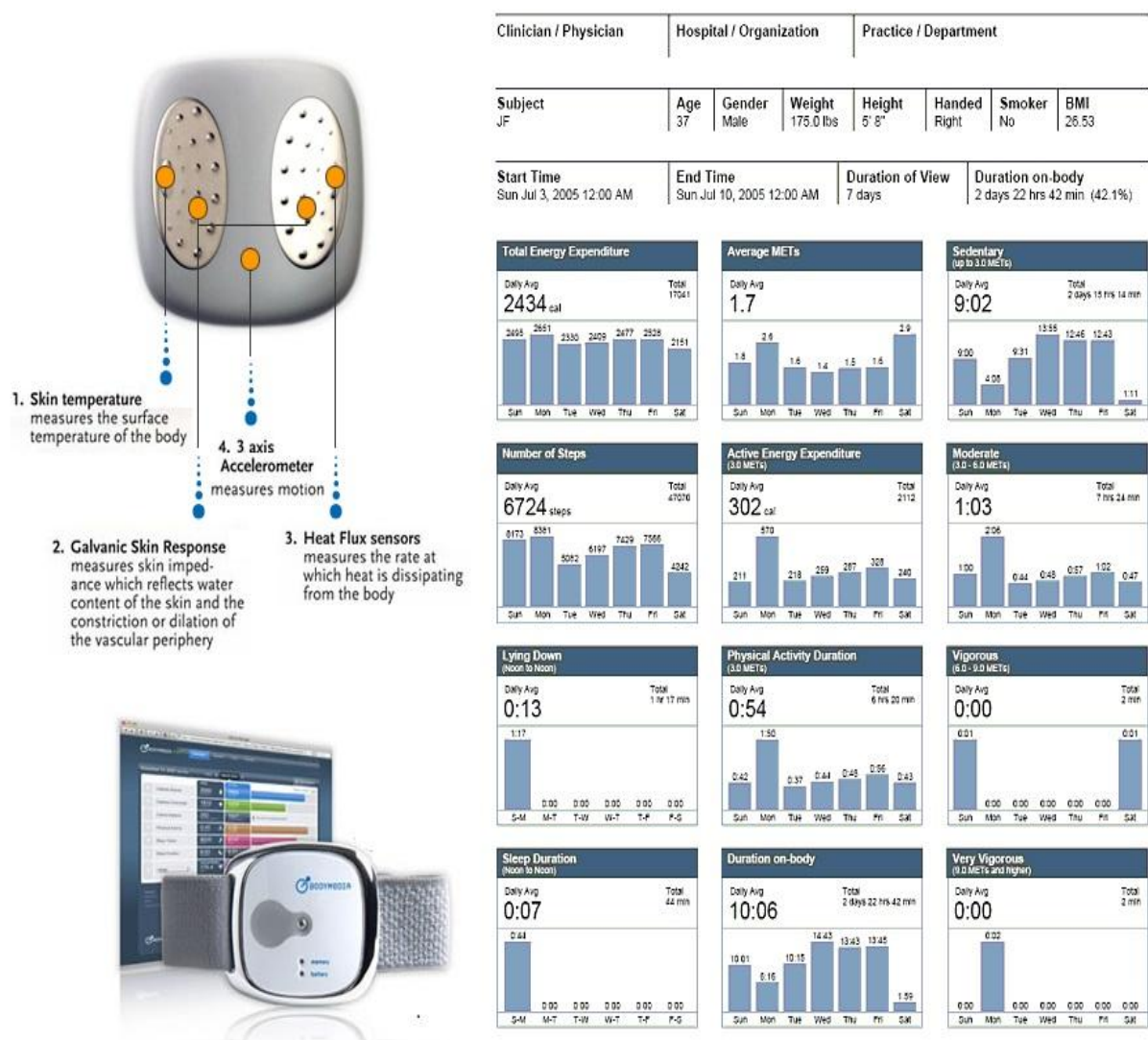
### **3.11.2 SenseWear armband**

The SenseWear device is a body monitor with multisensing capabilities, and it contains an accelerometer that detects motion and can count steps, as well as an electrical circuit to measure the electrical conductivity of the skin and an electronic thermometer to measure skin temperature (Figure 13). Software and calibration of the device against calorimetry enables automated monitoring of energy expenditure and daily activity (201).



**Figure 13:** The data collected by SenseWear and computer software.

The patient wears the SenseWear on the left triceps, a position that is very comfortable and does not hinder usual life activities. This position allows constant recording of total energy expenditure (EE), EE above 2.5 METs and activity duration at various EE levels (sedentary, moderate, vigorous and very vigorous) per second (Figure 14). When fully charged, it can be used for up to seven days. Before distribution to new users, the armband is cleaned and disinfected.



**Figure 14:** The SenseWear structures.



## **The SenseWear Instructions**

This instruction was given to the patients to remind them how to use the SenseWear at home.

- 1- Be sure the upper arm is clean, dry and free of lotion/oil then slide the armband onto your left arm.
- 2- Adjust the strap so that it fits comfortably, and then secure the Velcro pull-tab. Ensure that the sensors on the underside of the armband maintain continuous contact with your skin and that the armband does not slide off your arm.
- 3- Do not secure the strap too tightly. You should be able to place two fingers beneath the strap.
- 4- Wait for the armband to automatically power on. This may take up to 10 minutes. Activation is indicated by a series of audio tones.
- 5- Wear it when you wake up until you go to bed. Please remove it before you have a shower or bath and do not wear it until your body is completely dry.
- 6- Try to clean it at the end of the day to avoid irritation.
- 7- If you regularly do exercises or any other activities (walking, running, jogging etc...) press the armband button before and after activities to highlight your activities in the software.
- 8- Plug in the charger when you take it off, to charge overnight.

### **3.12 SIX-MINUTE WALKING DISTANCE**

The 6MWD test is a measure of functional capability for individuals with fairly severe impairment. This individualised test examines patients' submaximal functioning level. The majority of the participants in the test are unable to reach the maximum exercise level and are, therefore, allowed to rest and stop during the assessment.

The test measures the total distance a subject is able to walk in six minutes under standardised conditions (88). The patients walked along a 30-metre track. They were instructed to walk as fast as possible and warned that they would get out of breath or become exhausted. They were permitted to slow down, stop or rest as necessary. At the beginning and end of the test, heart rate and oxygen saturation were recorded (Appendix B). The patients were also asked to assess their dyspnoea and fatigue at the start and end of the test using a Borg Scale (Table4).

<b>SCALE</b>	<b>SEVERITY</b>
<b>0</b>	<b>No Breathlessness At All</b>
<b>0.5</b>	<b>Very Very Slight (Just Noticeable)</b>
<b>1</b>	<b>Very Slight</b>
<b>2</b>	<b>Slight Breathlessness</b>
<b>3</b>	<b>Moderate</b>
<b>4</b>	<b>Somewhat Severe</b>
<b>5</b>	<b>Severe Breathlessness</b>
<b>6</b>	
<b>7</b>	<b>Very Severe Breathlessness</b>
<b>8</b>	
<b>9</b>	
<b>10</b>	<b>Very Very Severe (Maximal)</b>

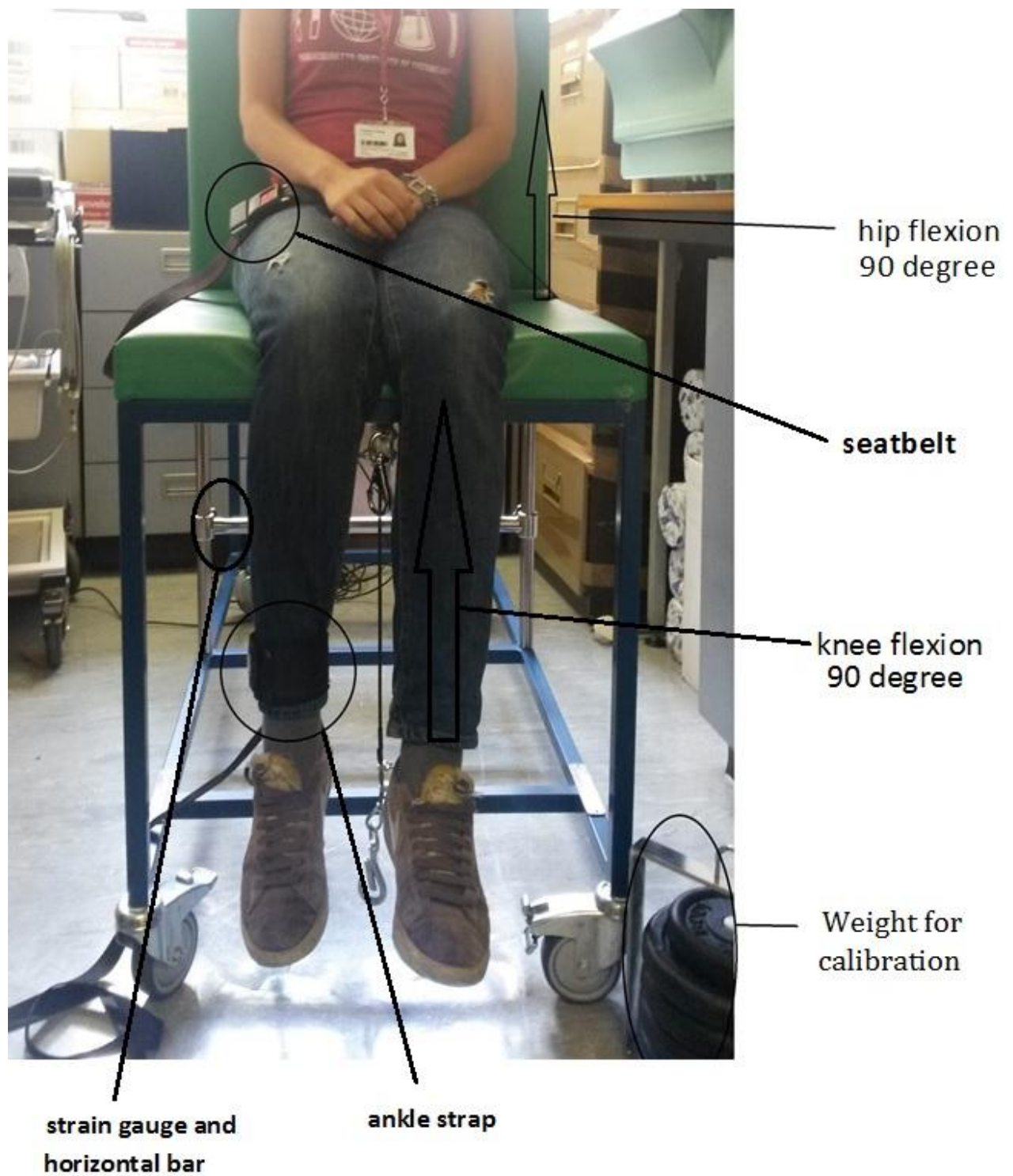
**Table 4:** Borg Scale used to assess fatigue and dyspnoea

An absolute contra-indication for the test was unstable angina or a myocardial Infarction during the previous month. The American Thoracic Society (ATS) provides practical guidelines for the 6MWD (88). There was no practice test for COPD patients reluctant to take the test at exacerbation and it was considered unlikely they would undertake both a practice walk and a test. The 6MWD was undertaken indoors along flat, straight, long and hard surface hospital corridors when few people were about (88).

### **3.13 QUADRICEPS MAXIMAL VOLUNTARY CONTRACTION TEST**

Quadriceps maximal voluntary contraction (QMVC) was measured with the method described previously by Edwards (202). The equipment used to measure QMVC included a chair with a seatbelt, strain gauge (Strainstall, Cowes, UK), ankle strap and horizontal bar (Figure 15). Patients were excluded if they were experiencing any neuromuscular or musculoskeletal problems, which included: spinal problems, primary muscle disease, mononeuropathy or polyneuropathy, osteoarthritis co-existent, neuromuscular junction, peripheral vascular disease and stroke affecting the legs.

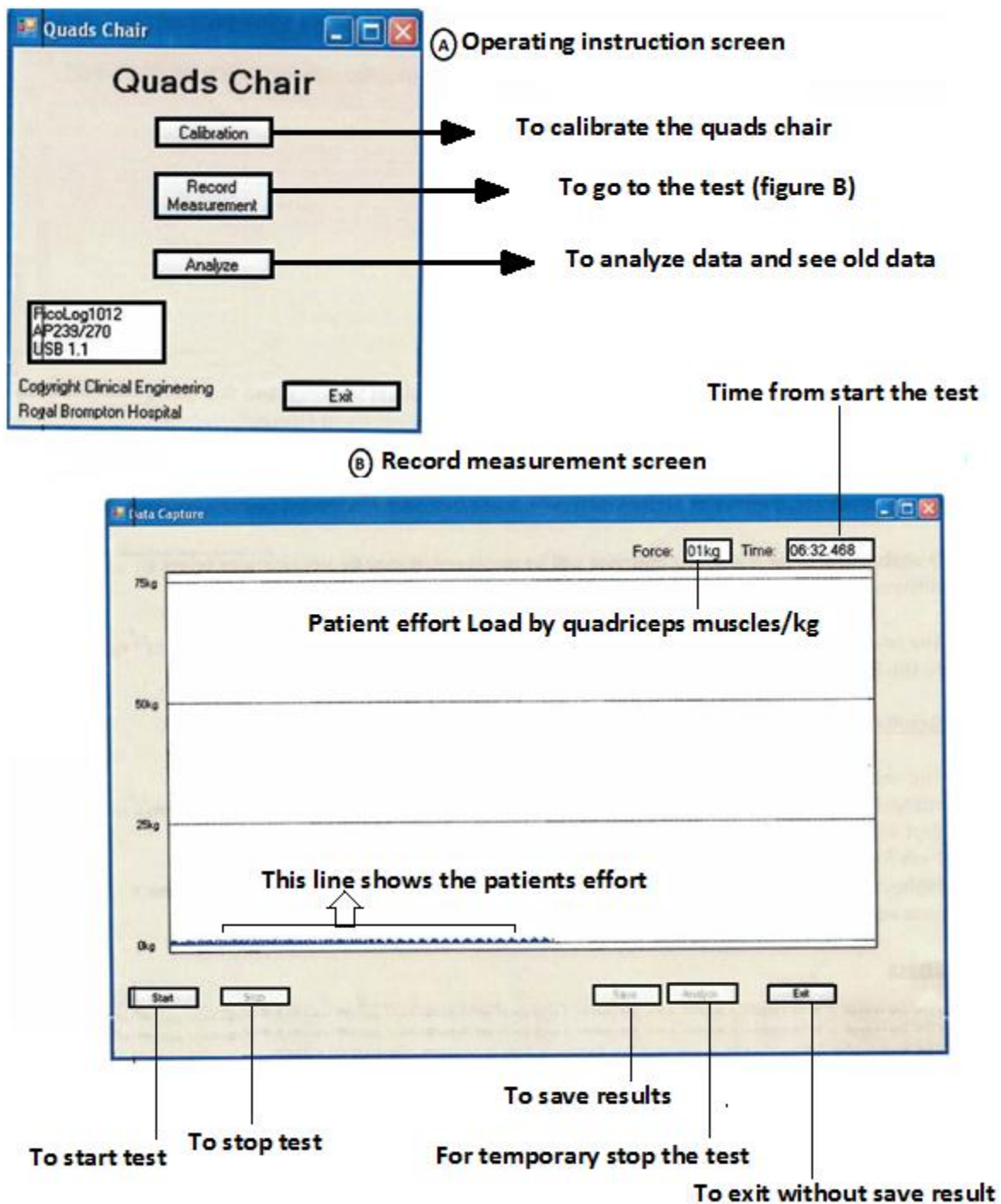
I assessed the patient's right leg but patients could choose to use their left leg if they wished. However, all subsequent tests on the same patient were performed on the same leg to ensure consistency and reproducibility (Appendix B).



**Figure 15:** Quadriceps maximal voluntary contraction test structures

### **3.13.1 Quadriceps maximal voluntary contraction test instructions**

The quads chair calibrated every time it was connected to the computer software (Figure 16A and 16B). Patients were seated in the chair with knee and hip flexion of 90 degrees and a seatbelt secured across the hips. The strain gauge was connected to a horizontal bar on the back of the quads chair. An inextensible strap was placed around the ankle, which connected to the strain gauge on the back of the chair. The ankle strap was positioned perpendicular to both the ankle and strain gauge. Patients were asked to put their hands/arms on top of their thighs, and asked not to lift their buttocks off the chair or arch their back. Patients warmed up prior to any recordings with four contractions at about 50% of maximal effort and four at approximately 75% of maximal effort. During the test, patients received oral encouragement. Patients were then asked to contract their quadriceps and push against the strap for at least one second. Six separate readings of QMVC were made and the maximum reading recorded. Patients rested for at least 20 seconds between attempts (Figure 16B).



**Figure 16:** A) The quadriceps chair calibration and analysis screen and B) Screen-grab of quadriceps measurement screen

### **3.14 SERUM C-REACTIVE PROTEIN (CRP) AND FIBRINOGEN MEASUREMENTS**

When patients attended for a baseline, exacerbation onset or exacerbation recovery visits, venous blood was collected from an arm vein. These samples were sent directly to the Clinical Biochemistry Department at the Royal Free Hospital for CRP and fibrinogen measurement.

Serum C-reactive protein was measured with a Modular Analytics E 170 Module (Roche, Burgess Hill, UK) and plasma fibrinogen by the Clauss method (IL ACL Top Coagulation Analyzer, Lexington, MA).



# 4

## QUANTIFYING PHYSICAL ACTIVITY VIA PEDOMETRY IN COPD PATIENTS

This chapter explored whether step counts measured by a pedometer (Yamax Digi-Walker SW-200) were sufficiently correlated with other measures of physical activity prospectively to allow the device to be used reliably in COPD patients. The data were presented at meeting of the British Thoracic Society (BTS) in 2012, *as attached in Appendix C*

## 4.1 INTRODUCTION

Physical activity is important in everyday life for the entire populace. Its intensity and amount are crucial because of its close correlation with health, mortality, disability and physical activity intensity (154, 155).

The instruments for determining the level of activity include self-report questionnaires and motion sensors such as accelerometers and pedometers. Self-reporting is subject to recall bias and may not produce accurate information. As such, it should be used with caution when assessing the intensity, duration and frequency of daily physical activity. This technique is mainly applicable for group estimates rather than individual estimates (155).

More reliable and detailed individualised data on walking and other physical activities can be obtained using motion sensors (155). While the motion sensors produce accurate information on the body movement, they are ineffective in estimating the energy expenditure. A multi-sensor armband has dual functionality recording both the body movement and energy expenditure (140).

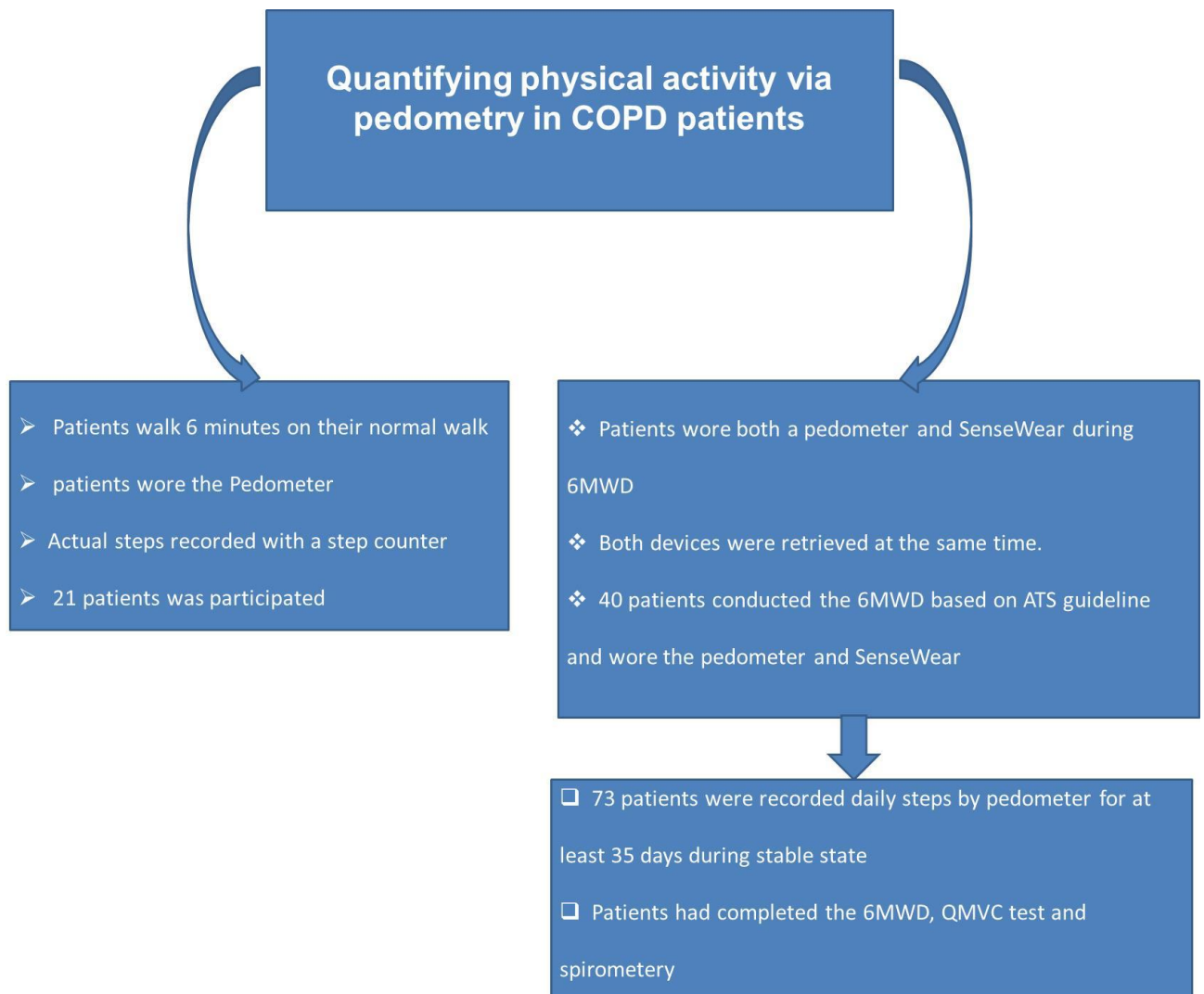
An extensive literature exists on the assessment of exercise capacity using the 6MWD test and incremental Shuttle Walk Tests. It remains unclear if improving exercise capacity translates into greater daily physical activity. Intuitively the latter may be more important for patients but its measurement is more difficult as patients

need to be monitored throughout the day. Pedometers are cheap and simple for the patient to use, but there are few data to support their use in COPD patients (155).

## 4.2 AIMS

- To assess how steps counted by pedometer (Yamax Digi-Walker SW-200) corresponded to actual steps walked and steps counted by SenseWear armbands (SenseWear, BodyMedia, Pittsburgh, PA).
- To evaluate the relationship of average steps for 28 days with exercise capacity, quadriceps muscles strength and disease severity

## 4.3 METHODS



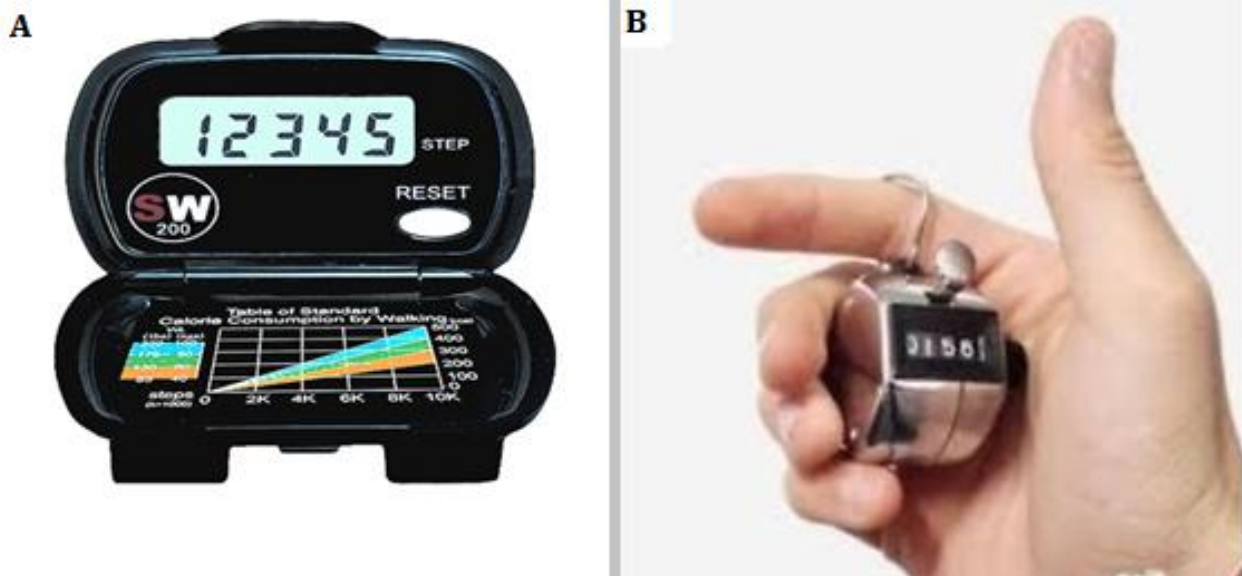
## **Statistical Analysis**

Data were analysed with SPSS (IPM SPSS Statistics 21). Normally distributed data were expressed as mean and standard deviation ( $\pm$ SD) and skewed data as median and interquartile range (IQR). Comparisons were made by paired Student t test or Wilcoxon signed-rank test. Multiple linear regression models were used to analyses the relationship between number of steps against other variables such as FEV1% predicted, 6MWD and QMVC.

## 4.4 RESULTS

In total, 73 patients were studied. They had moderate to very severe COPD (Table 2). Between 8 April 2011 and 30 November 2012, the patients recorded diary card data and wore the pedometer.

Actual steps were counted by step counters (Tally Counter Hand Held Clicker 4 Digit Chrome Palm Golf People Counting Club) (Figure 17).

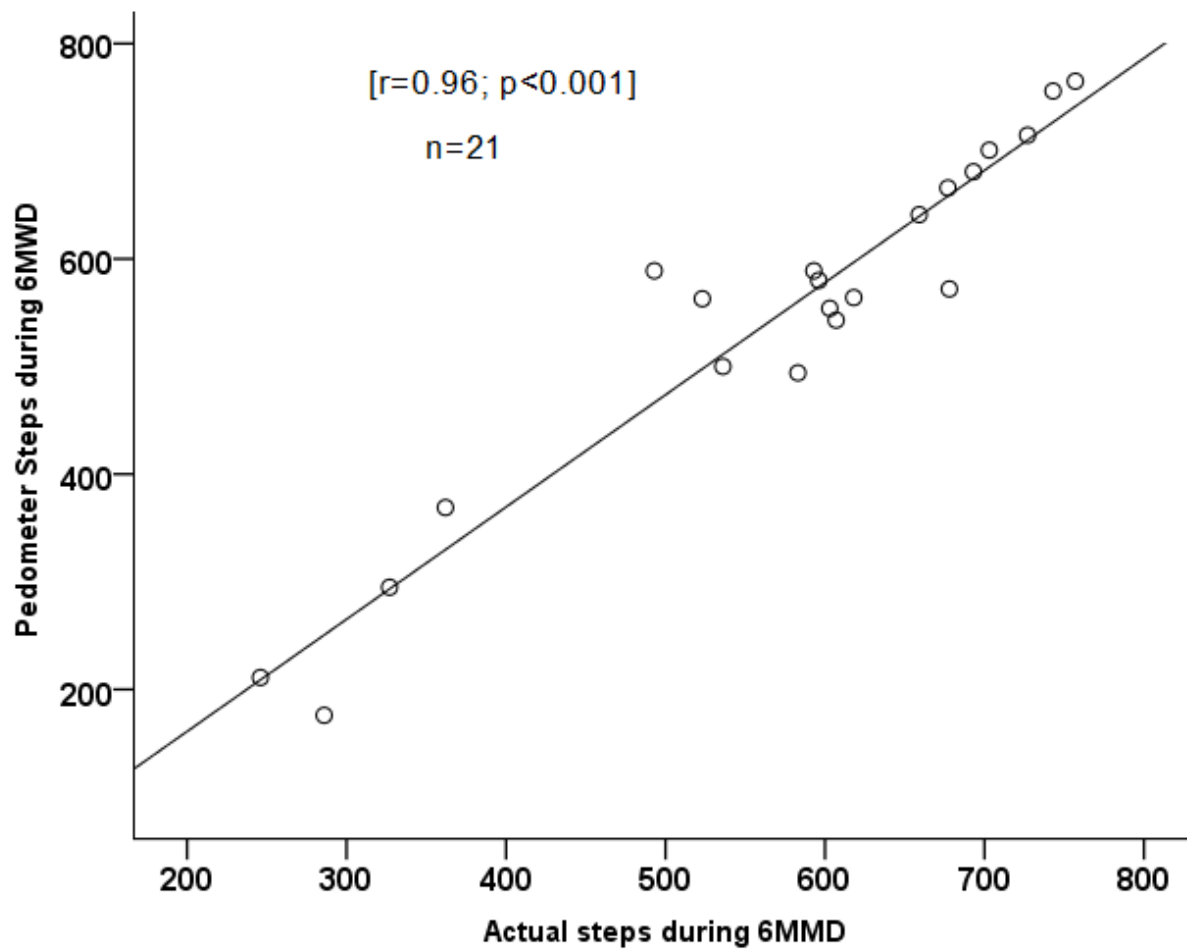


**Figure 17:** A) pedometer (Yamax Digi-walker SW-200). B) Step counters (Tally Counter Hand Held Clicker 4 Digit Chrome Palm Golf People Counting Club)

### **Pedometer with actual steps during 6 minutes walking**

Twenty one stable COPD patients had a mean ( $\pm$ SD) age 70.3 (8.7) years and FEV1 51.0% predicted ( $\pm$ 14.1); male gender 67%. Those group characteristics did not differ from those of the cohort from which they were drawn. Figure 18 shows high

correlation between steps counted by pedometer (Yamax Digi-walker SW-200) and actual steps during 6 minutes walking distance [ $r=0.96$ ;  $p<0.001$ ].

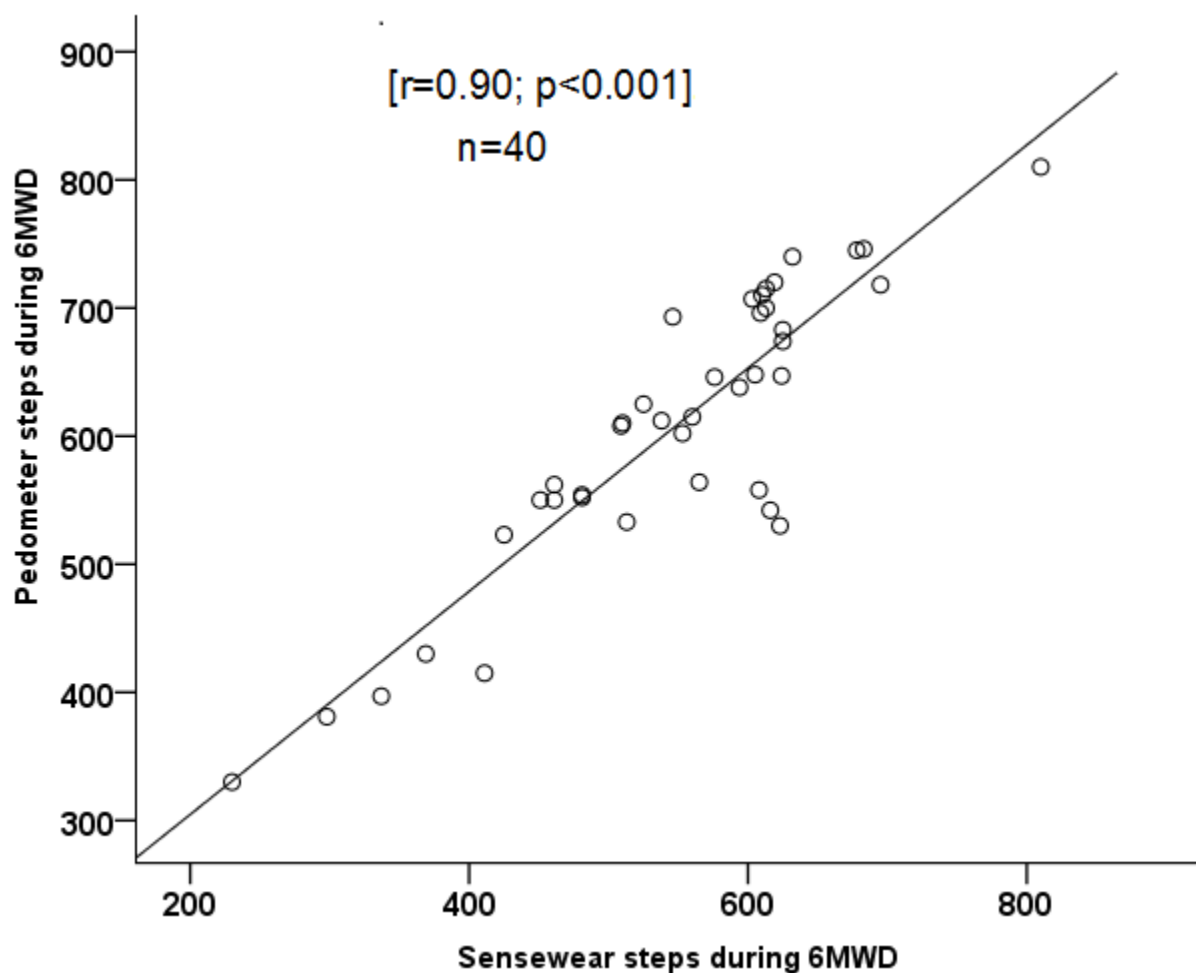


**Figure 18:** The relationship between steps counted by pedometer (Yamax Digi-walker SW-200) and actual steps.



## Pedometer validation with steps counted by SenseWear armband during 6MWD

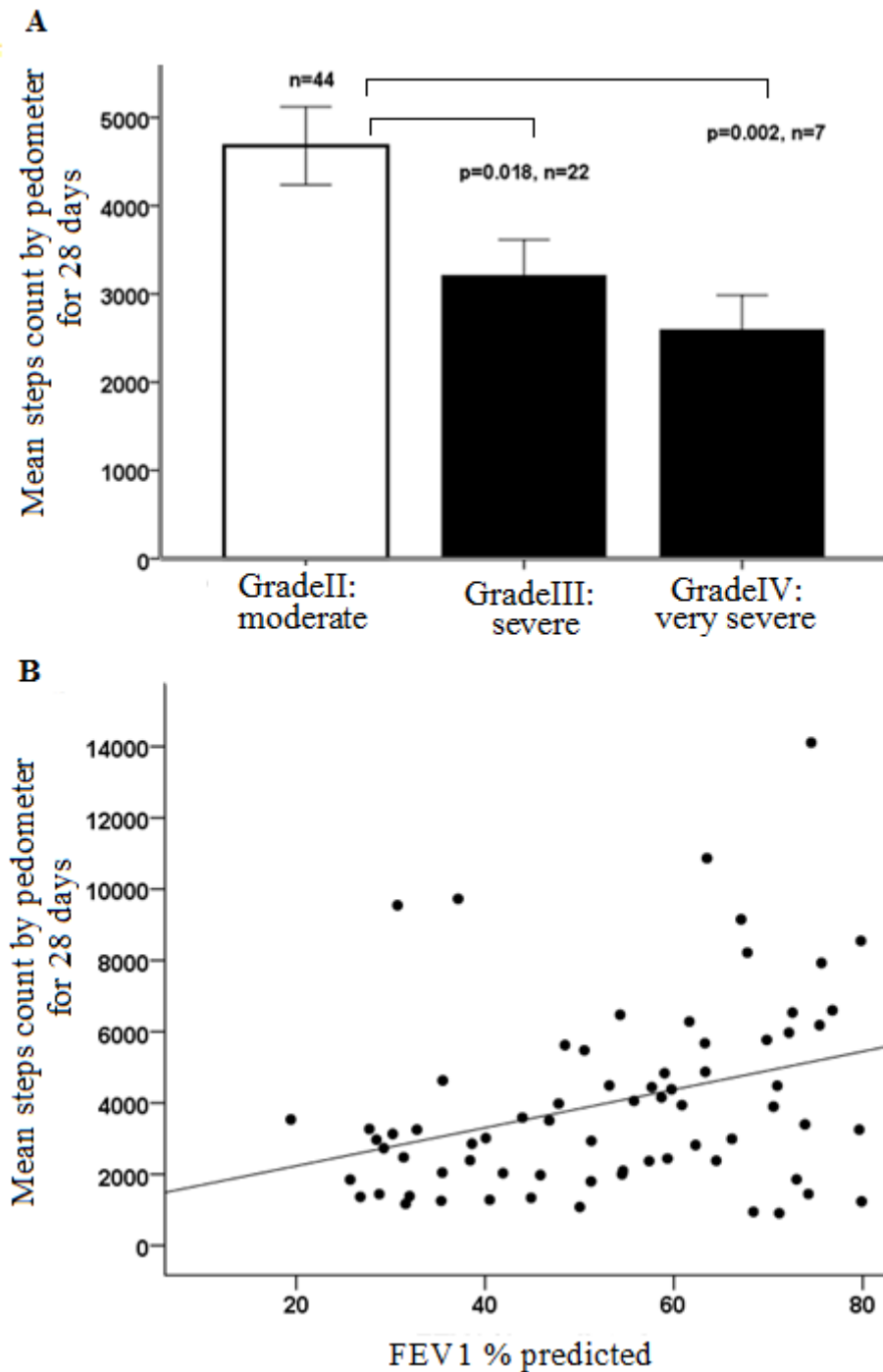
Forty COPD patients completed the 6MWD and wore on their left hand side a SenseWear armband and a pedometer. There was a high relationship between number of steps counted by SenseWear and pedometer [ $r=0.90$ ;  $p<0.001$ ] (Figure19).



**Figure 19:** The relationship between steps counted by pedometer (Yamax Digi-walker SW-200) and steps counted by SenseWear armband (SenseWear, BodyMedia, Pittsburgh, PA).

## **COPD GOLD stages**

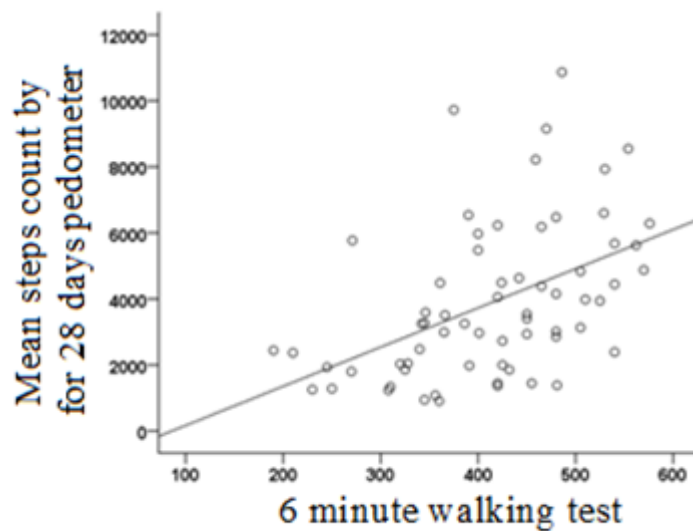
Figure 20A shows that the average number of steps was significantly different between COPD patients with different GOLD stage disease. Mean steps for patients with moderate COPD were 4678 (SE 442) steps per day. This was significantly higher by 1659 steps per day than the average 3204 (SE 410) steps per day [ $p=0.018$ ] in severe patients. Furthermore, step count was significantly lower in very severe patients by 2233 steps per day, which averaged 2590 (SE 395) steps per day compared to moderate COPD 4678 (SE 442) steps per day [ $p=0.002$ ]. No statistically significant differences were seen between patients with severe and very severe disease. Figure 20B depicts the relationship between disease severity and average steps counted for 28 days [ $r=-0.302$ ;  $p=0.009$ ].



**Figure 20:** A) average steps/day count for 28 days for 73 COPD patients. From left to right, average steps for 44 moderate COPD patients, 22 severe patients and 7 very severe patients. B) Correlation between activity (pedometer steps/day) and FEV1% predicted.

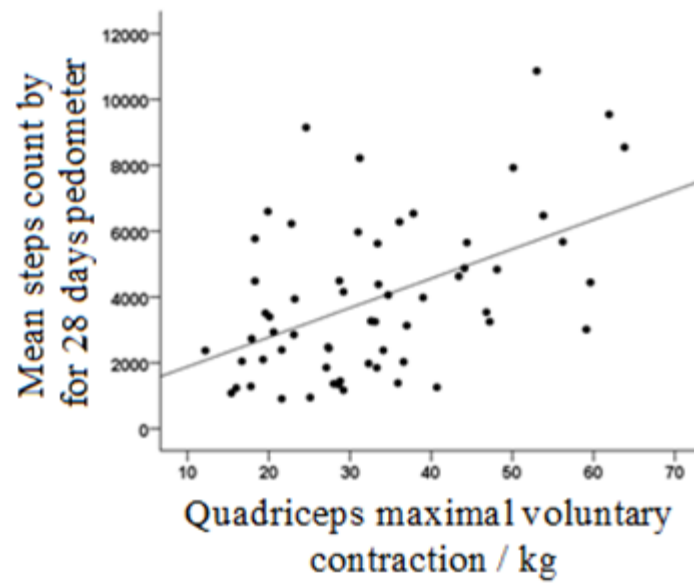
## Daily steps with 6MWD and quadriceps muscles

Figure 21 shows that patients with greater 6MWD distance took on average a greater number of steps per day over the 28 days following the test [ $\rho=-0.54$ ;  $p<0.001$ ].



**Figure 21:** Scatterplot between 6MWD and number of steps

Stronger quadriceps muscles were related to higher daily step counts [ $\rho=0.44$ ;  $p<0.001$ ] (Figure 22).



**Figure 22:** Scatterplot between QMVC and number of steps.

## 4.5 DISCUSSIONS

This chapter showed the accuracy of the pedometer against actual number of steps counted during the 6MWD. In the second part compared step number counted by pedometer against step number counted by the SenseWear armband during 6MWD. Both results suggest that the pedometer is an accurate device for assessing daily steps. The last section of the results showed that daily step counts measured by a pedometer over 28 days correlated well with objective tests of physical capacity, disease severity, and quadriceps muscle strength.

Previous studies (for example, that of Pitta and colleagues) (60) have monitored patient activity for just one day every week during exacerbation recovery (for two weeks) and one day at baseline (60). Other studies have used clinic tests requiring personnel to assess physical capacity (6MWD, Shuttle Test) (203) or questionnaires to monitor patient activity (204). However, these methods are not suitable for objective monitoring patient activity on a daily basis during an exacerbation when activity levels may change rapidly as the patient recovers. According to weekly activity reports, in the general population both men and women tended to be more active in the summer than in the winter (205). However, the weather varies from one day to another and this may change activity on a daily basis. In addition, patients need to monitor their health closely in order to understand their daily activity and what could affect it. Further work is required to show how COPD patients spend their day, and to ascertain why some patients are more active than others.

Skeletal muscle dysfunction and wasting is an important extra-pulmonary manifestation of COPD, particularly in severe disease. Over time, muscle weakening affects a patient's exercise capacity and they may complain of breathlessness and fatigue with minimum activity.

The pedometer used in the current studies has consistently been shown to be among the most accurate pedometers available and is suitable for use with normal, overweight and moderately obese people (168, 194). It has also been shown to be one of the most accurate step counters in a controlled laboratory setting (169). The pedometer is relatively inexpensive to use in a large cohort study and the model used in this study has been shown to be accurate within  $\pm 3\%$  of the actual steps taken 95% of the time (170). Also, this pedometer has been tested on a 4.88-km sidewalk course and measured the number of steps to within 1% of the actual number of steps taken (171).

Exercise capacity and physical activity can be assessed with walking tests or questionnaires, or with expensive accelerometer-based monitoring devices that require regular clinic visits to download data. However, these approaches are not well-suited to capturing activity prospectively during an exacerbation in a large observational cohort, as patients need to be monitored continuously over many months before attending clinic in order to capture the prodrome and early stages of these events. Some studies have also reported that pedometers underestimate step counts in people who walk very slowly (171), but I found strong correlations between the step counts with this pedometer and actual steps and steps counted by SenseWear during 6MWD for patients of different ages, speed level and disease

severity. The assessment of COPD daily activity is important because these data can provide insight into COPD patients' goals and motivation to improve their activity or stop daily activity getting worse. We suggest that using a pedometer could be the best way currently to assess activity at home or outdoors in a wide range of COPD patients (205).



## **4.6. CONCLUSIONS**

Daily step counts measured by a pedometer averaged over one month correlated well with objective tests of physical capacity disease severity, and quadriceps muscle strength. Pedometry is a simple, cheap method for quantifying daily physical activity in COPD patients over a long period of time and during exacerbations in a large observational cohort.

# 5

## **DAILY ACTIVITY DURING STABILITY AND EXACERBATION OF COPD**

This chapter assesses the impact of exacerbation on COPD patient's daily steps. The data have been published in *BMC Pulmonary Medicine* (206), as attached in Appendix C and was previously presented at a meeting of European Respiratory Society (ERS) 2013.

## 5.1 INTRODUCTION

COPD is a respiratory system disease that also causes skeletal muscle dysfunction and reduction in patient activity. Physical activities are all the body movements that are produced by skeletal muscles and are associated with energy consumption (207). The decline in physical activity seen in COPD patients is itself associated with worsening deterioration in lung functions, more frequent hospitalization, and increased mortality rates (60, 207). Physical activity limitation is not well documented. Therefore, it is important to study the relationship between inactivity and mortality in chronic conditions such as COPD (208).

According to Singh & Morgan, levels of higher level physical activity (e.g. brisk walking) reduce sharply in COPD exacerbation but recovers rapidly afterwards (209). For example, the outcomes of the study by Pitta and colleague showed that time spent standing and walking reduced in the first and second weeks of hospitalisation (60). Additionally, the study participants reported that the amount of time they devoted to the above activities increased after one month. Therefore, dyspnea and fatigue during exacerbation can affect a patient's level of activity.

Patients treated in the community for an exacerbation are not actively encouraged to maintain their physical activity during exacerbation recovery. Possibly, information is lacking concerning the extent that physical activity decreases during these non-

hospitalized events. These data would be needed for determining the sample size required for a clinical trial of early PR in community treated exacerbations.

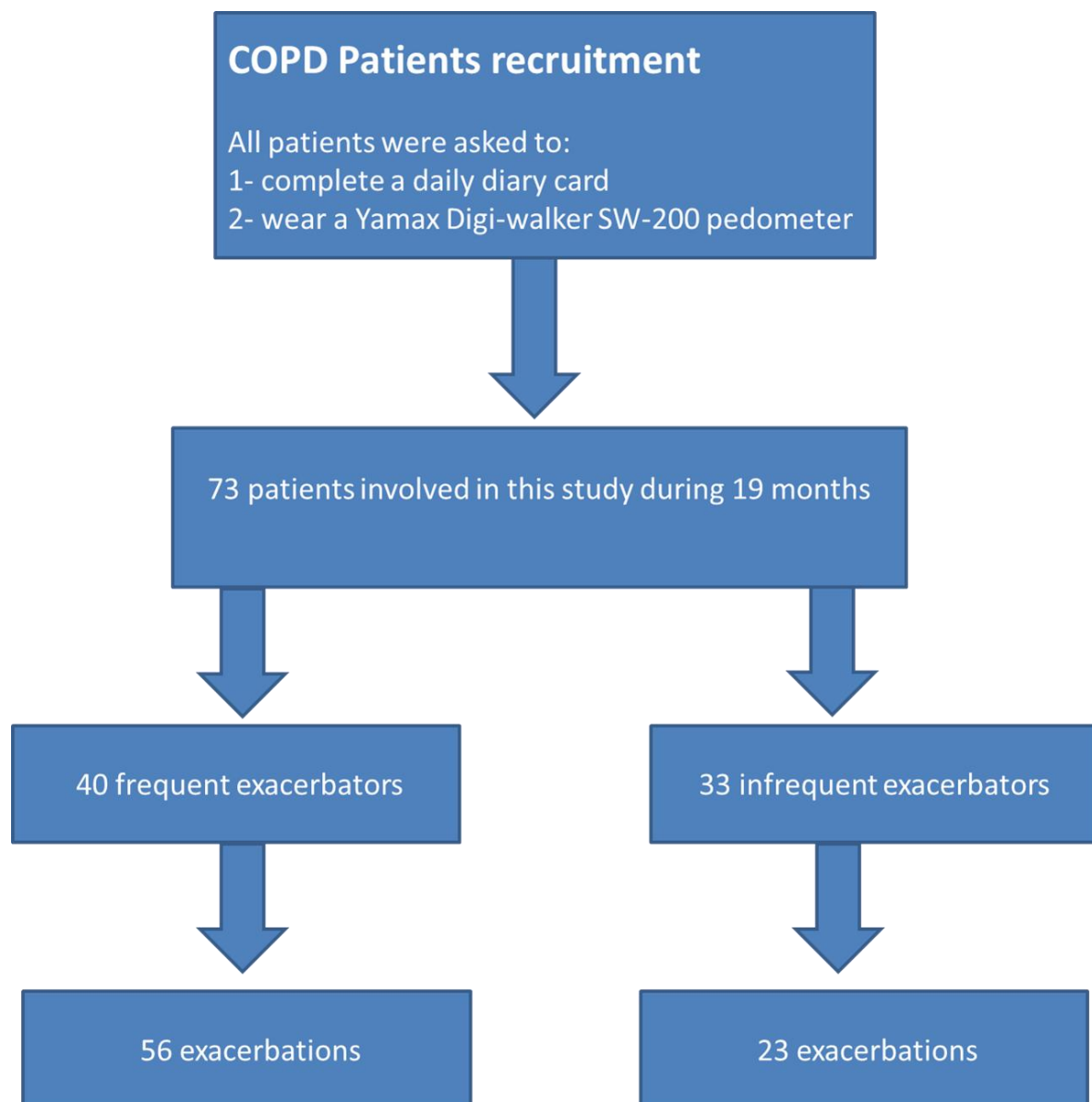
It is also crucial to assess physical activity when examining the effect of exacerbation since baseline activities vary with time and season. However, accelerometers can be expensive and demand that the patient takes frequent trips to the clinic to download the data. Therefore, such devices are unsuitable for continuous use and for conditions that require capturing of relatively rare events like exacerbations. Pedometers are alternative devices, which are cheap and straightforward to use, but have not been certified for use in COPD patients.

## 5.2 AIMS

- To prospectively evaluate daily step-count determined with a simple pedometer, before and during the onset and recovery of an exacerbation
- To evaluated the longitudinal trend of daily activity in patients with a history of frequent and infrequent exacerbations.

## 5.3 METHODS

Seventy-three COPD patients participated in this study. There were no significant differences in the patient characteristics between patients involved in this study and 126 patients excluded for reasons mentioned in the main methods (table 2). The diagram below shows the study protocol.



## Statistical Analysis

Data were analysed with STATA 8.2 (Stata Corporation, College Station, TX) and PASW statistics V.21 (SPSS Inc.). Normally distributed data are reported as a mean and standard deviation (SD) or standard error of the mean (SEM) and skewed data reported with a median and inter quartile range (IQR). Comparisons were made by paired Student t test or Wilcoxon signed-rank test as appropriate. Stable mean daily step count and other patient characteristics were related with a Pearson correlation or Spearman rank correlation. Random effect linear regression models were used to assess annual decline in daily stable step count and whether the decline was faster in frequent than infrequent exacerbators. A stable step count was defined as outside a period starting 2 weeks before and ending 2 weeks after an exacerbation. Data from patients who experienced multiple exacerbations were averaged to avoid bias through repeated measures. However, I analysed exacerbations as individual events when investigating whether the characteristics of exacerbations (respiratory symptoms, treatment, change in step count) was associated with a fall in activity or recovery. The level of significance was set at  $p < 0.05$ .

## 5.4 RESULTS

Patients recorded daily pedometry data for a minimum of 35 days with the initial 7 days considered as training and discarded for the purposes of analysis. The study took place over 19 months between April 2011 and November 2012. Seventy-three COPD patients had moderate to very severe COPD (Table 2).

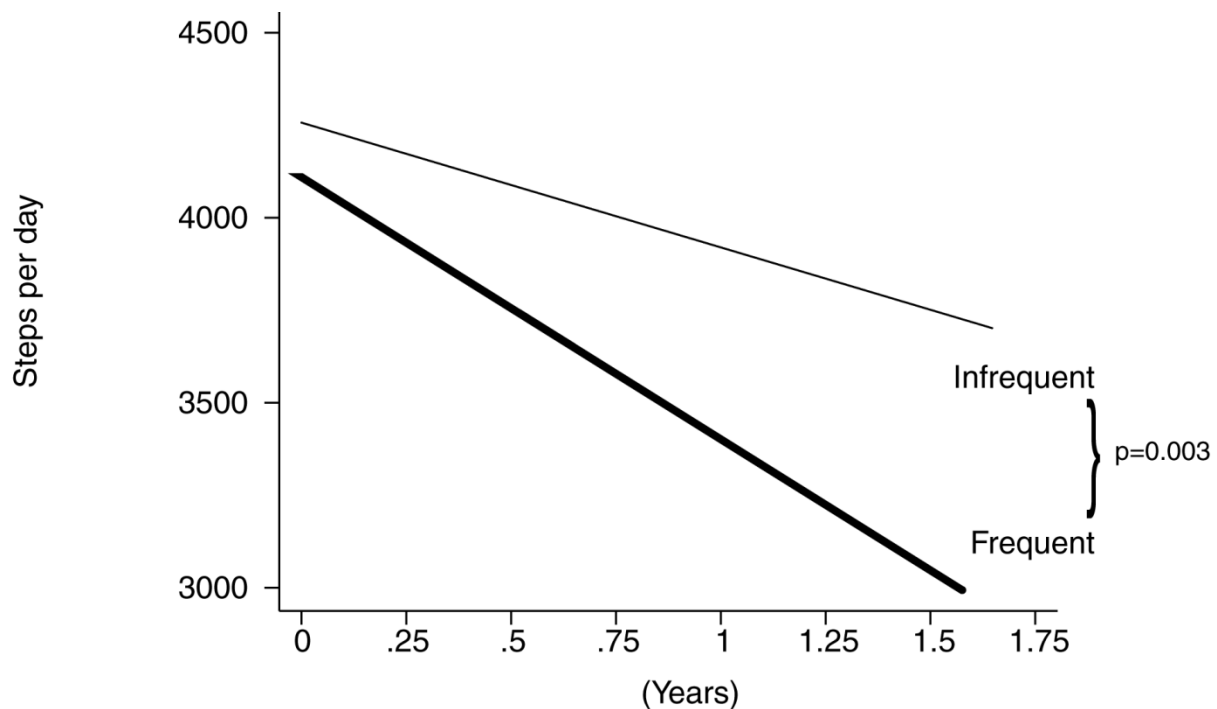
### **Decline of daily step-count between patients with frequent and infrequent exacerbations**

Daily step-count was recorded in the stable state on 14,653 days (median 169 days per patient; IQR 113-285; range 29 - 488) and for 2508 days with exacerbation (median 21 days per patient; IQR 0-57; range 0-239). Separately, daily step-count fell in the 33 infrequent exacerbators by 338 steps/year [95% CI: -504 to -170] compared to 708 steps/year [95% CI: -867 to -549] in the 40 frequent exacerbators (both  $p < 0.001$ ) (Table 5). The annual decline in daily step-count was significantly faster in the frequent exacerbators ( $p = 0.003$ ; see figure 23).



	<b>40: frequent exacerbations</b>		<b>33: infrequent exacerbations</b>	
	<b>Mean</b>	<b>(±SD)</b>	<b>Mean</b>	<b>(±SD)</b>
<b>Age (years)</b>	71.1	(±8.7)	71.1	(±8.6)
<b>FEV<sub>1</sub> (l)</b>	1.30	(±0.5)	1.32	(±0.5)
<b>FEV<sub>1</sub> (% predicted)</b>	51.7	(±15.2)	54.3	(±18.1)
<b>FVC (l)</b>	2.78	(±0.9)	2.81	(±0.8)
<b>FEV<sub>1</sub>/FVC (%)</b>	47.6	(±11.9)	48.0	(±13.5)
<b>BMI (kg/m<sup>2</sup>)</b>	26.9	(±5.6)	26.5	(±5.5)
	<b>Median</b>	<b>(IQR)</b>	<b>Median</b>	<b>(IQR)</b>
<b>Exacerbations/year</b>	3	(2.0-4.0)	1	(0.0-1.0)
<b>Sex (Males)</b>	70.0		69.7	
<b>Smoking at recruitment</b>	40.0		30.3	

**Table 5:** Patient characteristics in both patients group (frequent and infrequent exacerbations)



**Figure 23:** Daily step-count of 33 infrequent (number of days with data=6878) and 40 frequent (number of days with data=7775) exacerbators; predicted values obtained from the random effects, linear regression model (test of interaction,  $p=0.003$ ). Time 0 corresponds to the start of the study.

### Time course of daily step-count at COPD exacerbation

Thirty seven patients experienced 79 exacerbations and the characteristics of these patients are reported on table 6. The median time since the last exacerbation was 85.5 days (IQR 42-193). The shortest interval was 15 days. There was no record of a preceding exacerbation for 7 exacerbations as these patients had been recently recruited. There were no significant differences in patient characteristics between these 37 patients and the 36 who did not experience an exacerbation except a higher FVC (L) table 6.

	<b>Mean</b>	<b>(<math>\pm</math>SD)</b>
<b>Age (years)</b>	70.4	( $\pm$ 7.9)
<b>FEV<sub>1</sub> (l)</b>	1.4	( $\pm$ 0.5)
<b>FEV<sub>1</sub> (% predicted)</b>	52.1	( $\pm$ 15.7)
<b>FVC (l)</b>	3.0	( $\pm$ 0.8)
<b>FEV<sub>1</sub>/FVC (%)</b>	46.2	( $\pm$ 13.3)
<b>BMI (kg/m<sup>2</sup>)</b>	27.3	( $\pm$ 6.0)
	<b>Median</b>	<b>( IQR)</b>
<b>Exacerbations per year</b>	3	(1-3)
	<b>%</b>	
<b>Sex (Males)</b>	78.4	
<b>Smoking at recruitment</b>	32.4	

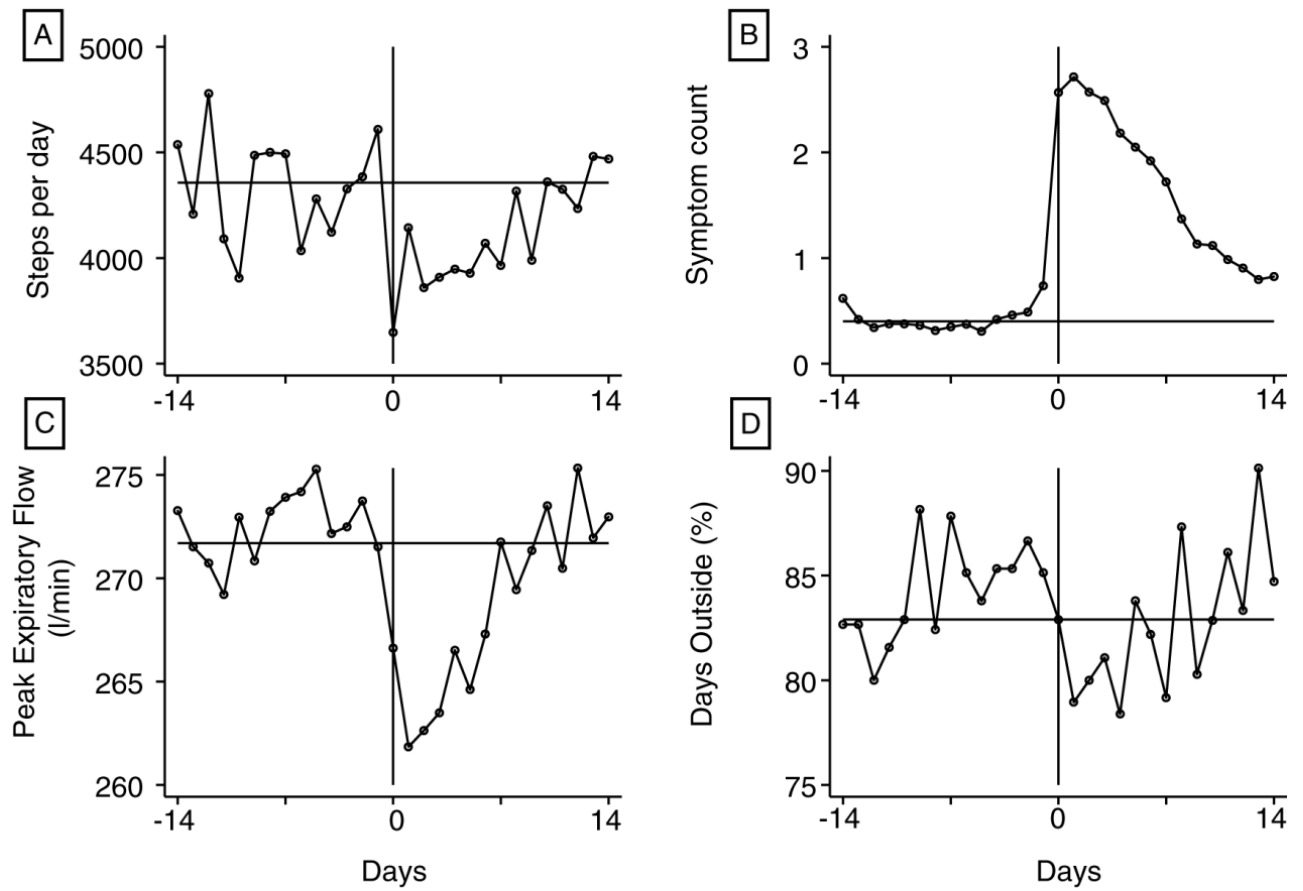
**Table 6:** Characteristics of the 37 COPD patients in whom pedometry data were recorded during one or more exacerbation

Table 7 shows that daily step-count, symptoms count rises and PEF fell significantly at exacerbation but not hours spent outdoors or whether the patient went out or not. Daily step-count took a median 3.5 (IQR 1-8) days to return to baseline levels (see figure 24A). Symptom count rose and took 11 (IQR 8-17) days to resolve (Figure 24B) and PEF (Figure 24C) took a median 4 (0-15) days to return to normal. Hours spent outdoors per day returned to baseline levels within 1.4 (IQR 0.3-5.3) days

(Figure 24D). Step count recovered significantly earlier than did symptoms ( $p<0.001$ ) but not PEF ( $p=0.33$ ) or hours spent outdoors ( $p=0.18$ ).

	Stable	Exacerbation	Difference	p-value
<b>Daily step-counts (step/day)</b>	4154( $\pm 2586$ )	3673( $\pm 2258$ )	-480( $\pm 1408$ )	0.045
<b>Symptom count</b>	0.4( $\pm 0.7$ )	2.4( $\pm 1.0$ )	1.9( $\pm 1.3$ )	<0.001
<b>Peak Expiratory Flow (L/Min)</b>	273 ( $\pm 109$ )	266 ( $\pm 108$ )	-7( $\pm 13$ )	0.005
<b>Time outdoors (hours/day)</b>	3.4 ( $\pm 1.8$ )	3.2( $\pm 1.8$ )	-0.1( $\pm 1.1$ )	0.51
<b>Percentage of days on which patient went outdoors (%)</b>	84.4 (24.2)	79.6 (26.1)	-4.8( $\pm 18$ )	0.13

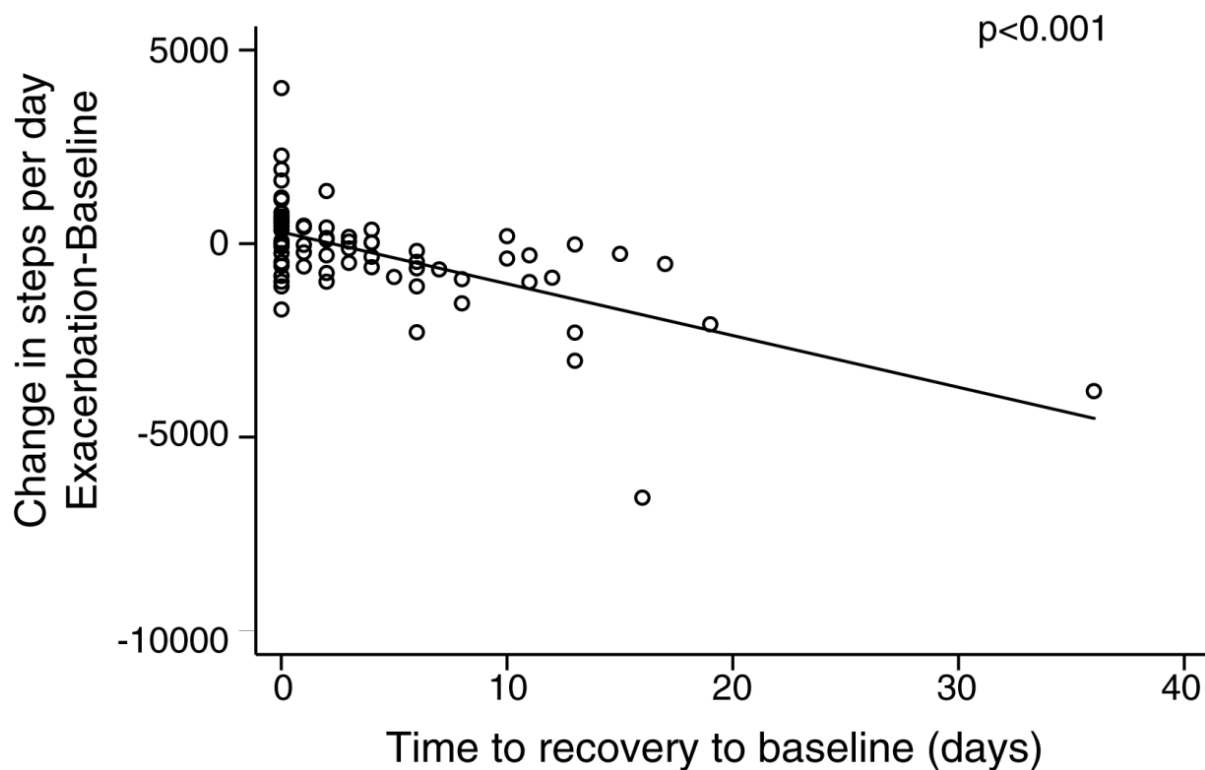
**Table 7:** Comparison between baseline and first 7 days of exacerbation (mean $\pm$ SD)



**Figure 24:** Time courses of daily step, symptoms, peak expiratory flow and time spent outside. These are mean of data on consecutive days from -14 to +14 days before and after 79 exacerbations.

## **The relationship between fall in daily steps and respiratory symptoms and activity recovery**

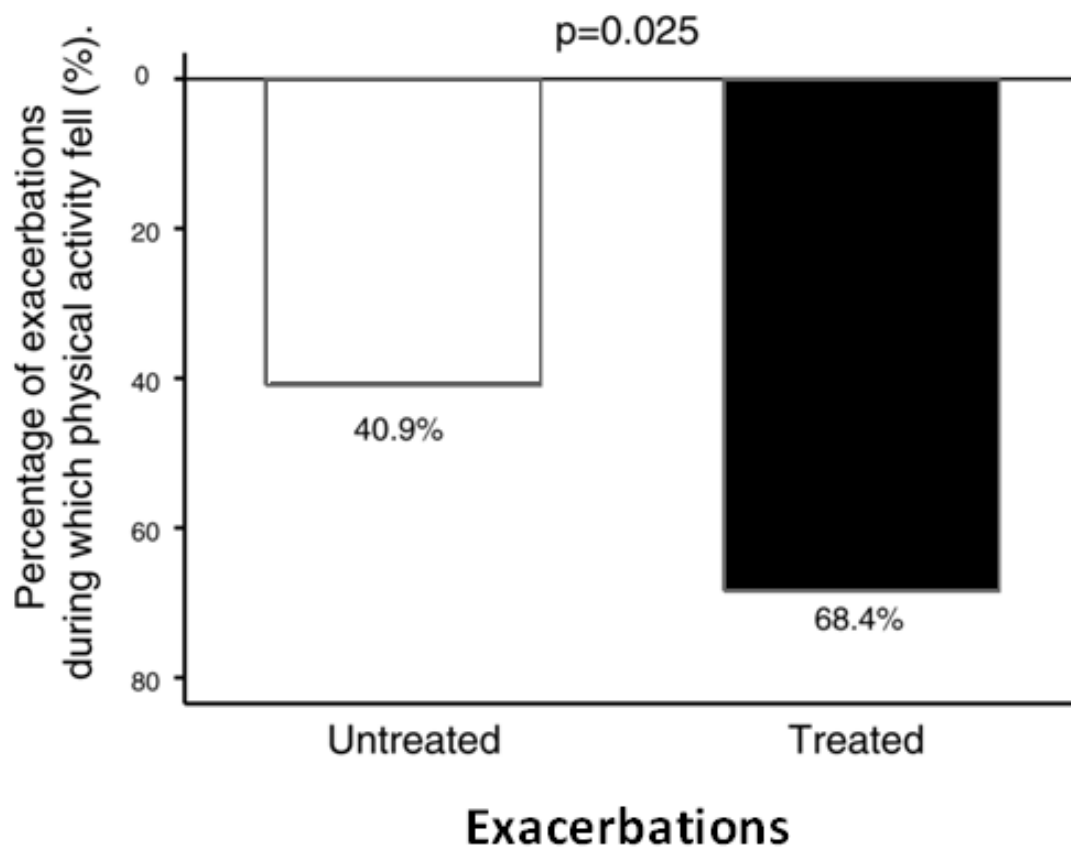
Prevalence of major symptoms during 79 exacerbations was reported as 83.5% for dyspnoea, 43.0% for sputum purulence and 67.1% for increased in sputum volume. Also minor symptoms were reported as 43.0% for cold, 49.4 for wheezing and 21.5% for sore throat and 54.4% for cough. There was no relationship between symptoms and fall in daily step count at exacerbation or recovery in steps count, with one exception: the fall in step count was related to the presence of sore throat ( $p=0.037$ ). Those with the largest falls in daily step count took longer to recover to baseline ( $\rho=-0.56$ ;  $p<0.001$ , Figure 25). ( $p=0.037$ ).



**Figure 25:** Change in daily steps between baseline and exacerbation against time to recovery to baseline; 79 exacerbations ( $p<0.001$ ).

### Activity and treatment

The 37 COPD patients (28 male) had 79 exacerbations. Twenty-two exacerbations were untreated and showed faster daily activity recovery (median 0 days (IQR 0-3)) than treated exacerbations (3 days (IQR 0 – 6)) ( $p=0.030$ ). However, 57 exacerbations were treated in the COPD clinic (11 antibiotics only; 7 oral corticosteroids only; 39 both antibiotics and oral steroids). Figure 26 shows that 68.4% of treated exacerbations were associated with a fall in daily step count between baseline and exacerbation compared to only 40.9% for untreated exacerbations ( $p=0.025$ ).



**Figure 26:** The percentage of treated and untreated exacerbatons during which daily activity fell between baseline (average days -14 to -8) and exacerbation (average days 0 to 6). (A lower daily step count than the pre-exacerbation baseline step count).



## 5.5 DISCUSSION

The objective of the current study was to examine the fall and recovery in daily walking activity for ambulatory patients (COPD) with non-hospitalized exacerbations. Daily step count reduced by 480 steps per day during each exacerbation, and took a median of 3.5 days for step count to recover to baseline levels. Also, the daily step count reduced faster in patients who had frequent exacerbations. Additionally, exacerbations linked with a fall in the daily step had a higher probability of patients attending clinic and they received treatment.

Previous work on activity during exacerbation recovery has been mainly based on the study of hospitalised COPD patients. Pitta and colleagues saw improvements in time spent walking in hospital compared to one month after discharge, but they observed no difference between day 2 and day 7 (60). Borges and coworkers reported that daily step count examined using the tri-axial accelerometer increased from 602 step/day on the 2<sup>nd</sup> day of hospitalisation to 3,575 steps/day at one month post discharge ( $p < 0.001$ ) amongst 32 consecutively-studied patients (211). However, exacerbations leading to hospitalization may be associated with different behavioral responses than those managed in the community because hospitalized patients may rest in bed for lengthy periods and fail to maintain their normal activities. Additionally, such studies fail to collect data before the start of exacerbation.

It is likely that severity of the severity of the respiratory symptoms during the later stages of recovery is not sufficient to inhibit activity. This was demonstrated by a

past study that examined 1465 exacerbations and reported that patients have a lower probability of moving out of their homes during exacerbation (3). A similar trend was observed in the current study, but it was not statistically significant because a low number of patients were reviewed. It was noted that the time spent walking indoors and outdoors was constant compared to baseline data. Therefore, it can be concluded that patients having exacerbation walked more slowly or used transport while they were outside their home. Accelerometers can be used to examine the nature and amount of exercise taken.

I found that a larger reduction in daily step count during exacerbation was associated with an extended time before activity returned to normal. Previous studies have shown that pulmonary rehabilitation programs started initiated early post-exacerbation show a benefit compared to usual care (87, 118, 122, 123, 214, 215) possibly by avoiding muscle deconditioning through inactivity during bed-rest (62). But Eaton and colleagues reported there being no substantial impact on acute care utilization, though it was considered feasible and safe. Treated exacerbations took more time to recover than untreated exacerbations. Additionally, it was unclear why patients report some exacerbations and not others. Further, about 50% of exacerbations are unreported as they found these exacerbations from patient's diary card (212, 213).

The outcomes of the current research study are that patients who experienced frequent exacerbations have twice as fast an annual decline in daily step-count than patients with infrequent exacerbations. Frequent exacerbations are associated with reduced FEV1 (5) and increased systemic and airway inflammation (3, 216) and a higher likelihood of suffering depression (160) and fatigue (217) with patients becoming housebound faster. The precise mechanism of activity decline is unclear but it is possible that prolonged recovery or non-recovery after an exacerbation may contribute to this decline. Also, fatigue, depression, and anxiety are linked to exacerbations and could limit activity. The above could be seen in patients having frequent exacerbations since they have relatively extended hospital admissions, but hospital admission was not incorporated into the research study.

A notable strength of this research study is that it maintained daily examination of patients to get reference activity intensity before start of the exacerbation. Reference data gathered from exacerbation is not acceptable since the daily step count reduces with time and changes with the season (213). But the study failed to consider and incorporate mild patients, patients using walking supports, or ambulatory oxygen having GOLD stage 1 COPD. However, outcomes from the current study can be applied to the community nursed exacerbations and hence a larger of COPD patients in the community.

## **5.6 CONCLUSIONS**

Pedometers may be a useful way to prospectively monitor and quantify physical activity during COPD exacerbations. Physical activity reduces during exacerbations and recovers with 3-4 days post-exacerbation. Frequent COPD exacerbators have an accelerated decline in physical activity compared to infrequent exacerbators. Reduction in daily activity is greater in those who report exacerbations and seek additional therapy. Non-hospitalised COPD exacerbations are also associated with reduced activity.

# 6

## **INFLUENCE OF WEATHER AND ATMOSPHERIC POLLUTION ON PHYSICAL ACTIVITY IN PATIENTS WITH COPD**

This chapter examines the association of climatic variables and air pollutants with daily step count and hours spent outdoors, peak expiratory flow, worsening dyspnoea and health-related quality of life. The data have been published in *Respiratory Research Journal*:13 June 2015, as attached in Appendix C (218). The data have also been presented at a meeting of the American Thoracic Societies 2014 (appendix C),

## 6.1 INTRODUCTION

There is growing evidence showing the effect of particulate air pollution on the increase in severity of respiratory diseases, as well as the increase in the number of deaths resulting from respiratory and cardiovascular diseases (100). This has led to the decision by the United Kingdom government to use the evidence of health issues related to air pollution to develop exposure limits of air pollution in relation to human health. Consequently, effective measures to mitigate the effects of air pollution may reducing exposure limits of air pollution while at the same time minimizing pollution levels (100, 219). The Committee on the Medical Aspects of Air Pollution (COMEAP) recommended in 2011 the establishment of air quality alert systems that assist in providing essential information that aids in advising the public to reduce exposure to air pollutants (220-222). As a result, the systems help in reducing adverse effects of air pollution while at the same time helping health service providers to develop systems that reduce symptoms associated with effects of air pollution.

Increased air pollution levels have been linked to the increase in severity of COPD and its development. Studies have shown that increased air pollution recorded over the past years have been accompanied by increased emergency department attendances and hospital admissions (223). This is evident by the data collected in the 1950s and 1960s which demonstrated that exacerbation in symptoms associated with COPD rose as the pollution index increased over similar period (224).

It is, however, important to note that the results that have been collected vary depending on individuals. The differences have been attributed to the susceptibility of individuals to air pollution, as well as the type of pollution mixtures that vary depending on the regions affected with this environmental issue (224). Furthermore, air pollution has been linked to the increase in cases of COPD (106). Pollution may also reduce activity and previously reported that particulate matter <10 microns in diameter ( $PM_{10}$ ) in London increases symptoms of dyspnoea in COPD patients (104) and reduce pulmonary function (105). Research studies have shown air pollution leading to enhanced impairment of the function of lungs which in turn leads to increased establishment of clinical features associated with COPD (19).

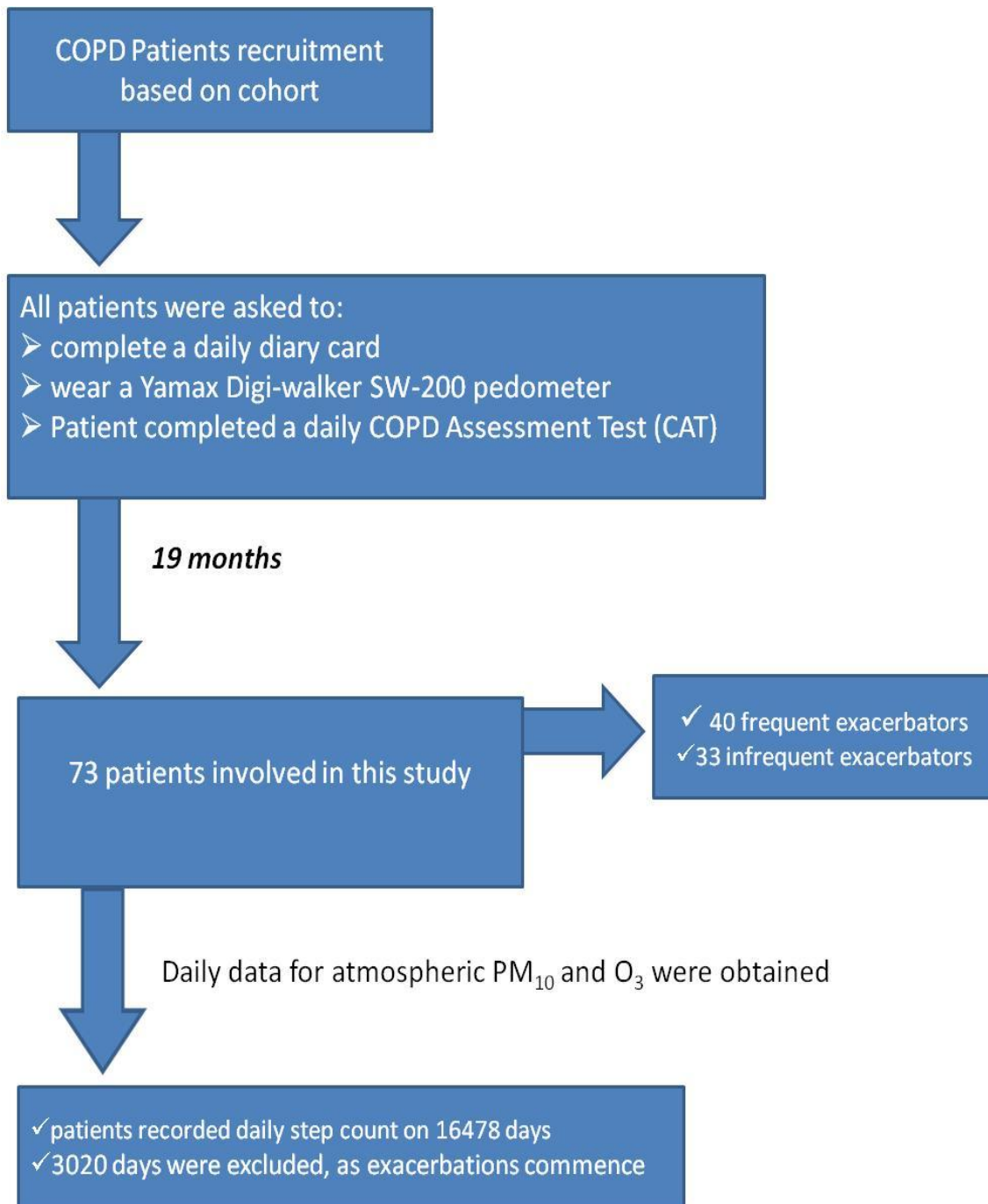
The interest in the perceived correlation between air pollution and COPD has led to need to assess physical activity in older people (156, 225). However, the effect of weather changes on physical activity of patients suffering from COPD has not been established. Air pollution has been found to be associated with reductions in the activity of patients with COPD, especially when particulate matter exceeds the diameter of 10 microns. This has been reported in London where patients suffering from COPD depicted reduction in pulmonary function (105), as well as enhanced symptoms of dyspnoea (104). Furthermore, it has been established that there is a positive correlation between traffic-associated air pollution and first admissions of patients suffering from COPD (106). It was explained in chapter five that there is a positive link between reduction in physical activity and increase in severity of COPD symptoms (226). I intend to discuss the data collected in patients who reported stability in their clinical functioning in this chapter.

## **6.2 AIMS**

To examine the effect of weather variables and air pollutants on daily step and hours spent outdoors, peak expiratory flow, worsening dyspnoea and health-related quality of life of stable patients with moderate to severe COPD



### 6.3. METHODS



## **Statistical methods**

Patient characteristics are summarised as appropriate by a mean and standard deviations or standard errors, or a median and inter-quartile ranges, or as a percentage.

### ***Unadjusted analysis***

Generalised estimating equations (GEE) were used to model the association of weather and pollution with daily step count, PEF, CAT scores (assuming their Gaussian distribution), time (hours) outdoors (as Poisson distributed: used to model the number of events occurring within a given time interval) or worsened dyspnoea (with a Bernoulli distribution: is discrete distribution with two possible outcomes; either success( $n=1$ ) or failure ( $n=0$ )) on days with temperatures  $\leq 22.5$  °C as average of hourly readings. It was an a priori decision that a cut-off would be necessary as relatively hot weather can reduce time spent outdoors (227). To identify the inflexion in the relationship between activity and temperature we plotted mean daily step count against temperature in 0.25 °C intervals. After inspection, a cut-off of 22.5 °C was chosen as daily step count was highest at this temperature and decreased with temperatures below or above 22.5 °C this average of hourly reading. The GEE models took into account variations between individuals and repeated measures within the same individual. Robust estimates of the variance were made and therefore it was not assumed that my estimate of the correlation structure as independent was correct.

Comparisons between daily step count of a sunny compared to a dull day, or a dry versus rainy day were made by paired t-test, after first obtaining the average for each patient under the various conditions.

Analysis of variance (ANOVA) was used to determine the effect of day of the week on daily step count, hours outdoors, O<sub>3</sub> and PM<sub>10</sub>. Post-hoc comparisons were made between Sunday and Saturday, and between Saturday and Friday.

### ***Adjusted analysis***

GEE regression models were used to assess the association of climate and pollution with daily step count and the other outcome measures. These models included a linear term to adjust for age related decline, sine and cosine terms with periods of 12, 6 and 4 months to allow for seasonal changes, and a variable for day of week with Monday as the first day of the week. All models included daily temperature, wind speed, rainfall, hours of sunshine and day-length as independent variables. Only two important pollutants were examined (PM<sub>10</sub> and O<sub>3</sub>) so as not to dilute effects with multiple atmospheric pollutants. Data were unlogged as the overall R-squared for daily step count against temperature was higher un-lagged than with 1 days lag. The analysis was repeated using data collected during weekdays only (Monday-Friday) and during weekends (Saturday and Sunday) since activity was markedly dissimilar in these periods. The analysis was also repeated with an auto-regressive term (the previous day value of the dependent variable) in the model to adjust for

autocorrelation in the dependent variable. I also repeated the analysis of daily step count and the pollutants with time outdoors included as an independent variable.

***Distance to pollution monitoring site.***

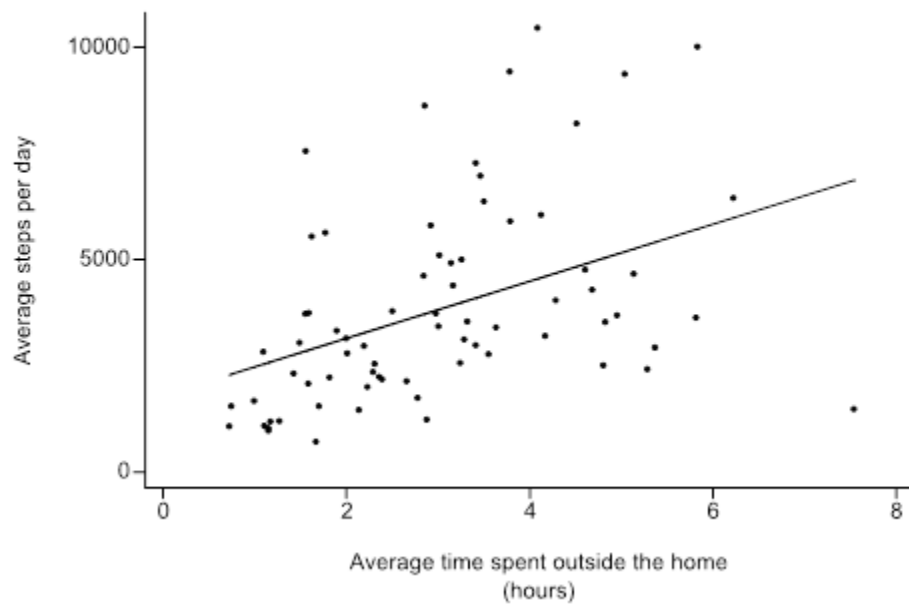
Distances to Bloomsbury Square were calculated by Pythagoras theorem using the Northings and Eastings (in metres) for the centre of each patient's post-code.

## 6.4 RESULTS

The 73 COPD patients (51 male, 22 female) studied had moderate to very severe COPD (Table 2). The patients recorded daily step count on 16,478 days with an average per patient of 267 days (range 29-658). Of these, 3020 days were excluded, as exacerbations commenced either two weeks before or after.

The patients lived on average 7.29 km (SD 4.72) from the Bloomsbury Square site. Of the 73 patients, 61 lived North of the site and 66 lived East.

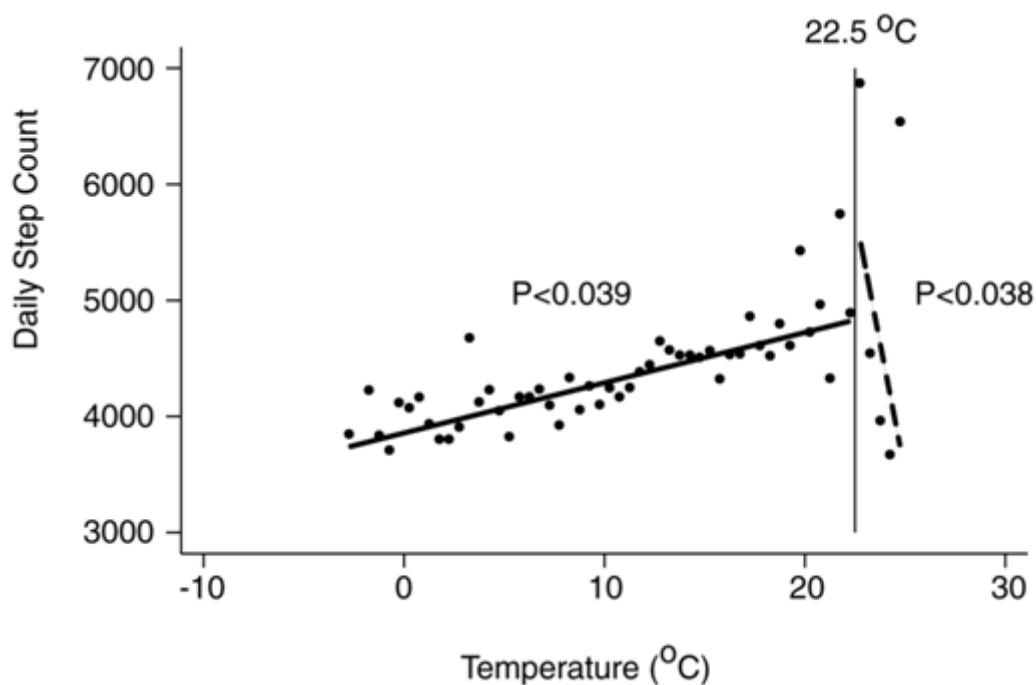
The stable state dataset consisted of an average of 225 days of pedometry readings per patient (SD 139; range 29-578); 459 days of PEFr readings per patient (SD 139; range 124-768); 463 days per patient of whether or not dyspnoea was worse than usual (SD 138; range 124-680) and 70 days with a CAT score per patient (SD 87; range 0-356). During the week, the mean of each patient's average time outside the home per day was 3.05 hours (SD 1.51; range 0.52 to 7.3 hours). Over the whole week, there was a strong relationship between the average number of steps per day and the average time spent outdoors (regression coefficient =671 steps per day per hour outdoors; intercept = 1804 steps per day;  $p=0.001$ ; see figure 27).



**Figure 27:** Relationship between the average steps per day for each patient and the average hours spent outside the home during the whole week.

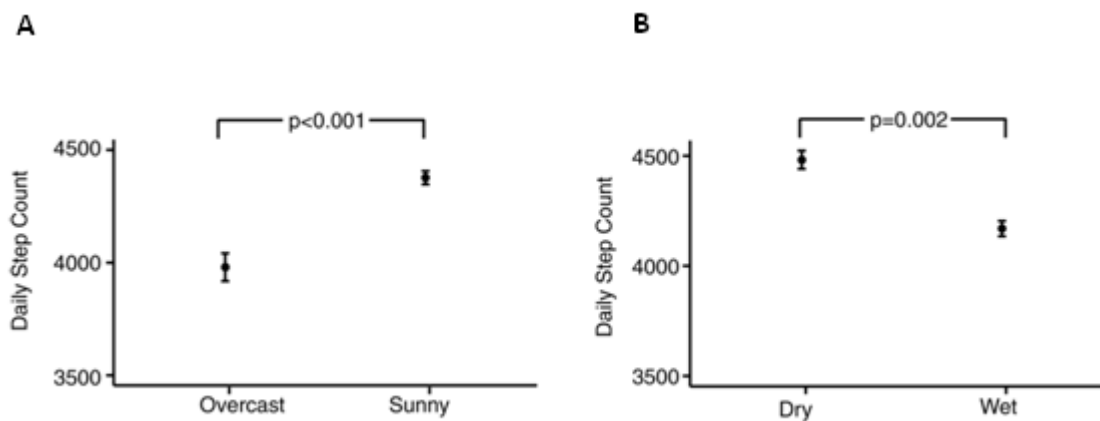
### Unadjusted analysis

Warmer weather was associated with increased daily step count (Figure 28). A 1 °C rise in temperature increased the count by 43 steps per day per °C (95% CI 2.14 to 84.4;  $p=0.039$ ). However, when the temperatures exceeded 22.5 °C, patient activity appeared to decrease and steps per day fell by -891 per 1 °C rise (95% CI -1735 to -47;  $p=0.038$ ).



**Figure 28:** Relationship between daily step count and daily temperature; data are averaged in 1 °C intervals.

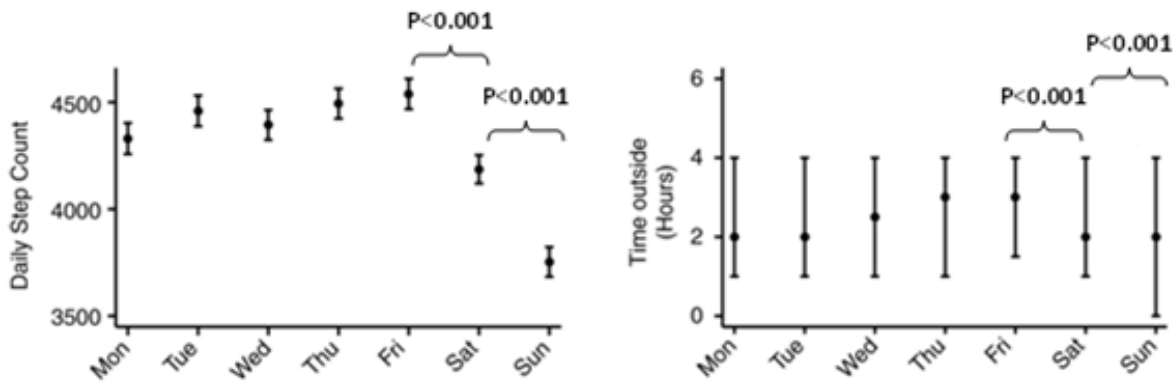
Physical activity was higher on days with sunshine or without rain (Figure 29). The mean of patient's average step count on sunny days was 3938 per day (SD 2447) compared to 3596 per day (SD 2260) on overcast days (paired t-test;  $p<0.0010$ ). Similarly, on dry days the mean of each patient's average step count was 3999 per day (SD 2507) compared to 3771 per day (SD 2349) on days with rain ( $p<0.0001$ ).



**Figure 29:** (A) Daily step count on overcast versus sunny days. (B) Daily step count on dry versus wet days. Data are means  $\pm$  standard errors of the average for each patient; p-values by paired t-test.

The day of week effected both daily step count and hours outside. A post-hoc analysis of variance showed that daily step count was 434 steps per day lower on Sunday than Saturday ( $p<0.001$ ) and 353 steps per day lower on Saturday than Friday ( $p<0.001$ ). Similarly, time outdoors was 0.55 hours lower on a Sunday compared to Saturday ( $p<0.001$ ) and by 0.09 hours lower on Saturday compared to Friday ( $p<0.001$ ) (Figure 30).





**Figure 30:** Daily step count and time outside during the week in COPD patients; data are means  $\pm$  standard errors for daily step count; median  $\pm$  inter-quartile range for hours outside; p-values from a post-hoc analysis of variance and wilcoxon rank-sum test respectively.

### Adjusted analysis

Table 8 shows results from the GEE models with daily step count data recorded during either (a) the whole week and (b) over Monday to Friday (weekdays). Daily step count increased significantly with warmer, sunny weather and fell with wet weather. Over the whole week, higher  $O_3$  levels were associated with decreased activity ( $p=0.005$ ) but not with  $PM_{10}$  ( $p=0.112$ ). Conversely, over just weekdays,  $PM_{10}$  was associated with reduced activity ( $p=0.018$ ) but not  $O_3$  ( $p=0.239$ ). There were no significant seasonal effects (sine and cosine terms) with temperature included in the model. With inclusion of an autoregressive term, over the whole week, rise in  $O_3$  was still associated with reduced daily step count ( $p=0.008$ ) and rise in  $PM_{10}$  also significantly and independently associated with reduced daily step count

( $p=0.047$ ). Inclusion of time outdoors as an independent variable in the regression model, eliminated the effect of  $O_3$  on daily step count over the whole week (regression coefficient = -3.9; 95% CI -8.8 to 0.9;  $p=0.113$ ) and similarly between step count and  $PM_{10}$  over weekdays only (regression coefficient = -4.4; 95% CI -10.4 to 1.5;  $p=0.147$ ).

	Over full week			Weekdays only		
	Regression Coefficient	95% CI	p-value	Regression Coefficient	95% CI	p-value
Temperature ( $^{\circ}C$ )	37.7	14.1 to 61.4	0.002	36.5	9.6 to 63.4	0.008
Sunshine (% day)	4.7	2.8 to 6.7	<0.001	4.0	1.8 to 6.2	<0.001
Rainfall (mm)	-16.8	-27.1 to -6.6	0.001	-15.3	-26.4 to -4.2	0.007
Wind speed (m/s)	-17.2	-37.6 to 3.2	0.099	-43.8	-66.2 to -21.5	<0.001
$PM_{10}$ ( $\mu g/m^3$ )	-5.4	-12.2 to 1.3	0.112	-7.8	-14.2 to -1.3	0.018
$O_3$ ( $\mu g/m^3$ )	-8.0	-13.5 to -2.4	0.005	-3.5	-9.4 to 2.4	0.239

**Table 8:** Relationship between daily step count and environmental factors (climate, pollutants and weekday) over the full week, and during weekdays only; allowance was made for season, linear trend and day-length (data for these variables not shown).

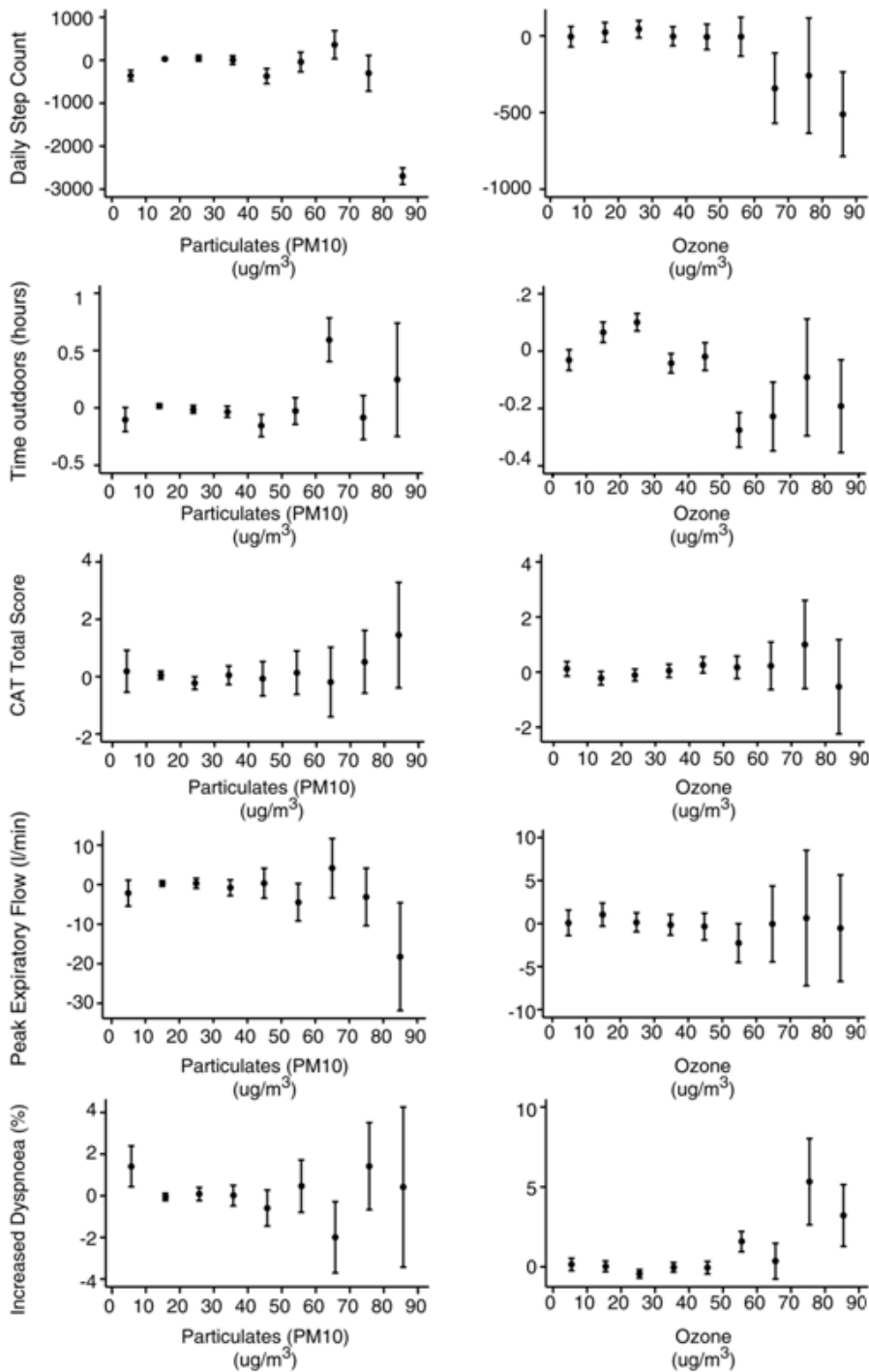
Table 9 shows only the effects of the two pollutants ( $PM_{10}$  and  $O_3$ ) on the various outcome measures over the whole week; weekdays and over the weekend.

	Effect of 1 $\mu\text{g}/\text{m}^3$ PM <sub>10</sub>			Effect of 1 $\mu\text{g}/\text{m}^3$ O <sub>3</sub>			
	Regression Coefficient	95% CI	p-value	Regression Coefficient	95% CI	p-value	
Step count	-5.4	-12.2 to 1.3	0.112	-8.0	-13.5 to -2.4	0.005	Over the full week including Saturday and Sunday
Hours outdoors	$2.3 \times 10^{-3}$	$-6.5 \times 10^{-3}$ to $1.8 \times 10^{-3}$	0.275	$-9.9 \times 10^{-3}$	$-14.2 \times 10^{-3}$ to $-5.6 \times 10^{-3}$	<0.001	
CAT score	$9.8 \times 10^{-3}$	$-19.6 \times 10^{-3}$ to $39.1 \times 10^{-3}$	0.515	$16.0 \times 10^{-3}$	$-14.0 \times 10^{-3}$ to $45.9 \times 10^{-3}$	0.296	
PEFR	-0.077	-0.17 to 0.018	0.110	-0.089	-0.18 to 0.001	0.054	
Dyspnoea	$-0.41 \times 10^{-3}$	$-8.0 \times 10^{-3}$ to $7.1 \times 10^{-3}$	0.915	$6.6 \times 10^{-3}$	$1.3 \times 10^{-3}$ to $12.0 \times 10^{-3}$	0.015	
Step count	-7.8	-14.2 to -1.3	0.018	-3.5	-9.44 to 2.35	0.239	Over weekdays (Monday to Friday)
Hours outdoors	$-2.5 \times 10^{-3}$	$-6.5 \times 10^{-3}$ to $1.4 \times 10^{-3}$	0.217	$-7.2 \times 10^{-3}$	$-11.6 \times 10^{-3}$ to $-2.9 \times 10^{-3}$	0.001	
CAT score	0.005	-0.02 to 0.03	0.749	0.02	-0.015 to 0.053	0.267	
PEFR	-0.09	-0.18 to 0.002	0.056	-0.11	-0.23 to -0.005	0.040	
Dyspnoea	$0.3 \times 10^{-3}$	$-8.0 \times 10^{-3}$ to $8.7 \times 10^{-3}$	0.941	$7.1 \times 10^{-3}$	$-1.3 \times 10^{-3}$ to $13.0 \times 10^{-3}$	0.017	
Step count	-2.58	-15.97 to 10.8	0.705	-10.7	-20.4 to -0.89	0.032	Over the weekend only Saturday and Sunday
Hours outdoors	$-2.6 \times 10^{-3}$	$-10.2 \times 10^{-3}$ to $-5.0 \times 10^{-3}$	0.502	$-13.1 \times 10^{-3}$	$-19.7 \times 10^{-3}$ to $-6.5 \times 10^{-3}$	<0.001	
CAT score	0.027	0.011 to 0.065	0.157	-0.006	-0.030 to 0.043	0.717	
PEFR	-0.047	-0.20 to 0.11	0.554	0.04	-0.13 to 0.056	0.441	
Dyspnoea	$3.81 \times 10^{-3}$	$-16.1 \times 10^{-3}$ to $8.45 \times 10^{-3}$	0.542	$-4.27 \times 10^{-3}$	$5.32 \times 10^{-3}$ to $1.38 \times 10^{-3}$	0.383	

**Table 9:** Relationship between pollutants (PM<sub>10</sub> and O<sub>3</sub>) and daily steps count, hours spent outdoors, health status (CAT score), PEFR, dyspnoea, **over the whole week; weekdays and the weekend;** with allowance for season, linear trend, day-length, temperature, sunshine, rain and wind.

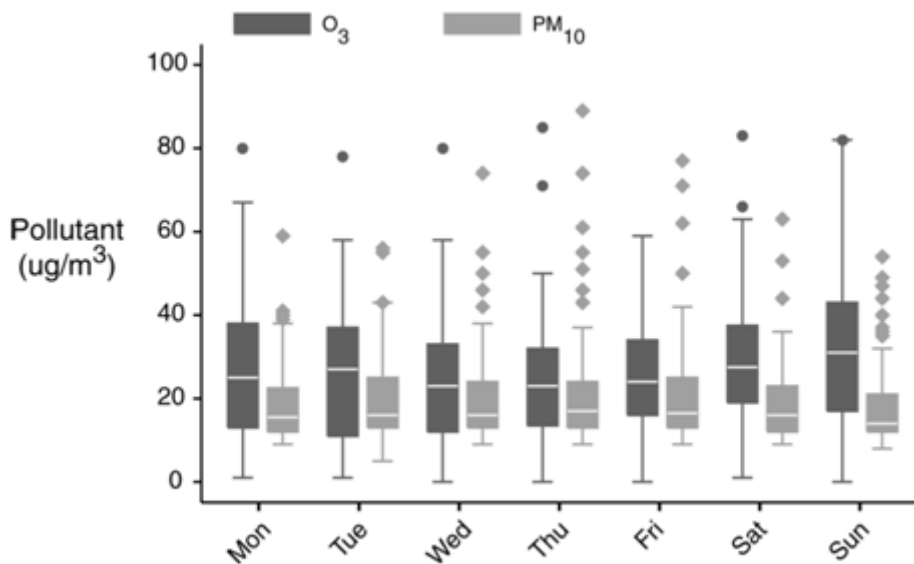
Time spent outdoors fell with higher  $O_3$  levels ( $p < 0.001$ ) for data collected over the whole week, just weekdays ( $p = 0.001$ ) and at weekends ( $p < 0.001$ ).  $PM_{10}$  show no effects on time spent outdoors on either whole week ( $p = 0.275$ ) or weekdays ( $p = 0.217$ ) or weekends ( $p = 0.502$ ). Dyspnoea increased and PEF fell with higher levels of  $O_3$  over the whole week ( $p = 0.015$  and  $p = 0.054$  respectively) and for weekdays only ( $p = 0.017$  and  $p = 0.040$  respectively) but not at weekends. No effects of  $PM_{10}$  were observed on daily dyspnoea or PEF. No effects of either pollution were seen on daily CAT score.

Figure 31 shows the residuals after fitting the climatic and other variables plotted against  $PM_{10}$  and  $O_3$ . The plots show little effect of the pollutants on daily step count, time outdoors, PEF and dyspnoea until they exceed around  $60-70 \mu g/m^3$ . CAT score appears unrelated throughout the range of pollutants.



**Figure 31:** Residuals from a GEE model that included temperature, wind speed, rainfall, hours of sunshine, day length, season and linear trend, plotted against daily PM<sub>10</sub> and Ozone (O<sub>3</sub>) levels; data are averaged over 10  $\mu\text{g}/\text{m}^3$  intervals; bars as  $\pm$  standard error.

Figure 32 shows that O<sub>3</sub> concentration was higher by 4.6 µg/m<sup>3</sup> (p=<0.001) and PM<sub>10</sub> levels 1.73 µg/m<sup>3</sup> lower during the weekend but this increased in PM<sub>10</sub> was not reached the significance level (p=0.057)



**Figure 32:** PM<sub>10</sub> and O<sub>3</sub> concentrations during the week between 7<sup>th</sup> April 2011 and 31 March 2013

## 6.5. DISCUSSION

In this chapter, the effect of atmospheric pollutants, meteorological factors, and day of the week factors on patients with COPD is discussed. The weekends were deliberately left out in the study as the physical activity of participants is not significantly affected due the fact that weekends are the period of rest. It was established that the participants would depict reduced activity during rainy, overcast, and cold days but would like to walk more during sunny, warm, and dry days. Previous studies have shown that healthy individuals tend to avoid engaging in physical activity during winter and colder seasons while, on the other hand, increasing their physical activity during sunny days (228). For instance, COPD patients have shown seasonal variation in their physical activity (229). However, in this study, I try to explore further the fact that patients tend to vary their physical activity depending on the meteorological conditions rather than the seasons as has been explained in previous studies.

The findings which I discuss in this chapter takes into consideration the importance of incorporating the fact that COPD patients are forced to reduce their exercise as a result of the limitation of airflow caused by their conditions. Any further reductions of activity due to the weather or day-of-the-week may worsen muscular de-conditioning which is common in inactive COPD patients. Muscle weakness and feelings of frailty may make the patients feel unable to leave their homes and once this behaviour is established may prove difficult to reverse. It might in part explain why health related quality of life is poorer in winter than spring or summer (230) and measures of anxiety and depression higher in winter (231).

Additionally, the findings which I will discuss in this chapter are important because I am trying to show for the first time positive correlation between air pollution and physical activity which was made possible by carefully choosing participants with air-flow limitation, thus making it possible to easily determine effects of air pollution on their physical activity.

At the highest levels, O<sub>3</sub> was associated with reduced daily step count and time outdoors. The regression models which I used in the analysis showed that there was disappearance of the effects when the period that was spent outside was included in the study. For instance, when the number of steps/day was considered in relation to period spent outside, the dependent variable represented walking speeds when the adjustment of time was made. It suggests that possibly air pollution influences the time spent outdoors but not walking speed when outside, however, as no direct measurements were made, this idea needs further investigation.

My research findings suggest mechanisms by which outdoor atmospheric pollution may reduce outdoor physical activity. As shows previously by Tremblay et al which was determined that atmospheric pollution such as O<sub>3</sub> that exceeded 200 ppb affected peak expiratory flow of elite cyclists during maximal exercise (232). However, this may lead to problems at low levels (233). Furthermore, I established that increased levels of O<sub>3</sub> were associate with reduced PEF during weekdays ( $p=0.040$ ). However, it was found out that the results were insignificant over the whole week ( $p=0.054$ ). Kakinoki and colleague shows that atmospheric pollutants led to harmful effects on airways, including airway ciliary activity reduction (234), inflammation of pulmonary system (235, 236), airway oxidative stress (237),



and enhanced bronchial reactivity (238). Additionally, blood pressure and heart rate were affected while there reports of mitochondrial damage when the patients are exposed to O<sub>3</sub> (239). It has, however, not been established that the patients were informed on the anatomic and systemic effects of atmospheric pollution. Additionally, increased O<sub>3</sub> were positively correlated with increased dyspnoea. However, the relationship between higher O<sub>3</sub> and CAT quality of life scores was not established in the study. The study did not determine the motive of patients avoiding to go out during higher levels of pollution. Limited evidence show that patients may be avoiding to go out when they get news alert from advisory systems regarding increased air pollutants (240). O<sub>3</sub> is mainly emitted from motor vehicle exhaust fumes, and it is a colorless and odorless gas making it difficult to be detected (240).

In London, a pollution haze can be seen on some days (241) but the patients might not live on hills or in high-rise buildings where these observations can easily be made. It has been found out that increased levels of O<sub>3</sub> happen during hot weather when patients tend to avoid exercising. Based on this observation, it was prudent that I deliberately dismissed the data I collected when the mean temperature for the day and night exceed 22.5°C, thus this was not included in my analysis. It is important that further studies are done to determine if and how COPD patients can detect increased atmospheric pollution.

A number of limitations for this study have been noted. First, physical activity intensity was not determined. This was attributed to the fact that I was not able to use accelerometers which require weekly and bimonthly visits to hospitals to allow downloading of data. Consequently, this was not possible with the long-term study that I carried out. Secondly,

inaccuracy of pedometers, especially in patients with slow walking pace, has been reported. Thus, this would lead to a consistent bias in particular patients, and as a consequence patient's response to weather or pollution could not be easily established. Thirdly, the group was not able to comprehensively collect pedometry data as in the case of dyspnoea and PEF data. This is attributed to the failure of some patients to wear the allocated pedometer on particular days. Additionally, I do not know whether patients are currently in employment or participating in full-time voluntary work. Also, there were instances of the loss and breakage of pedometers during washing. Such challenges were difficult to address as replacement was only possible during clinic visits which was required after three months. Fourthly, a number of patients were excluded from the study when periods of exacerbation were not factored in the study leading to negligible data. Such patients exhibited frequent exacerbations, and their collected data was not included in the study. Fifthly, adverse weather conditions like ice and snow on the ground which might limit excursions outdoors by patients so as to avoid risks of slipping were not considered. Neither was there any consideration as to wind-chill effects as clothing and exposure to wind was unknown. Sixthly, it was not possible to assess pollution exposure of each individual forcing us to use the data collected Bloomsbury monitoring site and make the assumption that the data related to the exposure experienced by each patient. This assumption may not be valid and patients may experience greater or less pollution exposure. Seventhly, the definition of a rainy day could have included both day time and night-time rainfall. Night-time rainfall may have had less influence on patient's activity as they would be unlikely to go outside at this time even if the weather had been good. Lastly, difficulty to define a time period over which the influence of rain and sun should be assessed that would not be open to criticism. It is quite likely that 6 minutes does not constitute what the average person would consider sunny. Also, I defined a sunny day as the minimum

measurable unit of sunshine but such an unlikely that such a brief period would influence outdoor activity

Previous research findings have shown that the data that was collected at the Bloomsbury site were well correlated with the pollution levels experienced at suburban sites (242), as well as in other regions of London (243). However, collected outcome data for each participant as the semi-individual design which I employed has been validated to be used in air pollution studies (244). I deliberately analyze weekends and weekdays data separately and the data for the whole week. This was to avoid analyzing data for the day-of-the-week which could have been large, and thus confounding the results. It has been found out that  $O_3$  are higher during the weekends in most countries (245-247). On the other hand,  $PM_{10}$  is higher during weekdays (245). This was clearly depicted in London, and the considerations of these factors in my analysis assisted in reducing statistical power. As a consequence, the failure to report consistent effects during weekends and weekdays could be attributed to this development.

## 6.6. CONCLUSIONS

The study findings that I have discussed in this chapter have far reaching implications. First, the findings could help healthcare providers to inform COPD patients to embrace physical activity as this is a basis for pulmonary rehabilitation which would in turn make patients to be tolerant, enhance quality of life, and mitigate breathlessness effects. Secondly, providers would be able to use the findings to develop rehabilitation policies that would be implemented during cold weather to reduce inactivity which has been found to be elevated during cold conditions. Thirdly, patients should be encouraged to perform exercises during the weekends as the findings show that COPD patients tend to take less physical activity during such days. Lastly, it has been established that higher levels of atmospheric pollution are associated with differences in daily activity of COPD patients. Thus, it is imperative that public health bodies should be encouraged to come up with measures to curb atmospheric pollution. Further studies with personal pollution monitors are required to confirm these findings.

# 7

## **DETERMINANTS OF THE REDUCTION IN PHYSICAL ACTIVITY AND CAPACITY WITH COPD EXACERBATIONS**

This chapter assesses the reduction in physical activity, capacity and muscles at COPD Exacerbations and related to inflammations level. Some of the findings of this study have been previously reported in abstract form (appendix C). The data will be published in *European Respiratory Journal (ERJ)*:28 April 2016 (in press).

## 7.1 INTRODUCTION

Muscle disuse is a common feature in COPD patients, and inactivity, chronic inflammation, hypoxia, coexisting heart disease, malnutrition, and use of corticosteroids are the most likely mechanisms involved in exercise intolerance (137). External factors, such as ageing and comorbidity, can hinder the ability to describe the association between lung weakness and changes in peripheral muscles in patients with COPD (248).

The aetiology and natural history of limb muscle dysfunction is probably multifactorial with significant inter-individual variation. Deconditioning due to low habitual physical activity is thought to be the key driver of muscle dysfunction but other disease related factors such as systemic inflammation have been proposed as additional factors in some patients(249). Pulmonary inflammation and bacterial colonisation have been shown to be closely related,(250) but whether systemic inflammation, when present, is driven by pulmonary inflammation or bacterial colonisation is unknown.

A reduction in skeletal muscle strength in patients at exacerbation of COPD has been demonstrated in several studies. For instance, Spruit and colleagues found a marked reduction of skeletal muscle strength in patients with exacerbation of COPD as compared to stable patients (60). They also found a significant reduction in quadricep muscle force after hospitalization that improved three months after the patients were discharged (60). Muscle weakness is multi-factorial and includes administration of steroids, and modification of metabolism, nutrition prolonged inflammation and high oxidative stress (61). The weakness of

muscles affects the capacity to exercise, reduces quality of life and increases mortality rate (251).

Lacasse and colleagues showed that regular activity and exercise may be considered a therapeutic intervention with several benefits, for example defence against COPD (115). Skeletal muscles can be considered as an endocrine organ as cytokines and other peptides that are released from muscle fiber and they exert paracrine autocrine or endocrine effects. These proteins are termed “myokines” (252). A well-known myokine is the gp130 receptor cytokine interleukin-6. This marker increases up to 100 fold in the bloodstream after 30 min of physical exercise (252). There is an intriguing possibility that the IL-6 response may be a signal indicating that muscle glycogen stores are reaching critically low levels and that the active muscles' reliance on blood glucose as a source of energy is on the increase (253). Patients who joined cardiac rehabilitation for three months have been shown to have a significant reduction in CRP (40%) when compared to a non-training group (19% reduction) (254). Also, the majority of studies suggest that activity and exercise programs are associated with a reduction in level of CRP (255).

Skeletal muscle weakness has been shown to be an important predictor of exercise limitation in COPD (256). Muscle weakness at exacerbation has been attributed to hypoxia inhibiting muscle protein synthesis and activating muscle proteolysis, oxidative stress, up-regulation of apoptosis, enhanced systemic inflammation or result from treatment with oral corticosteroids (257). The inflammatory cytokine, interleukin-6 (IL-6) increases in both airway sputum and blood at exacerbation (72, 258). Infusion of IL-6 into rats causes skeletal muscle atrophy

(259, 260). No study has yet examined the relationship between systemic inflammatory markers and exercise capacity or physical activity during the very early phases of an exacerbation.



## 7.2 AIMS

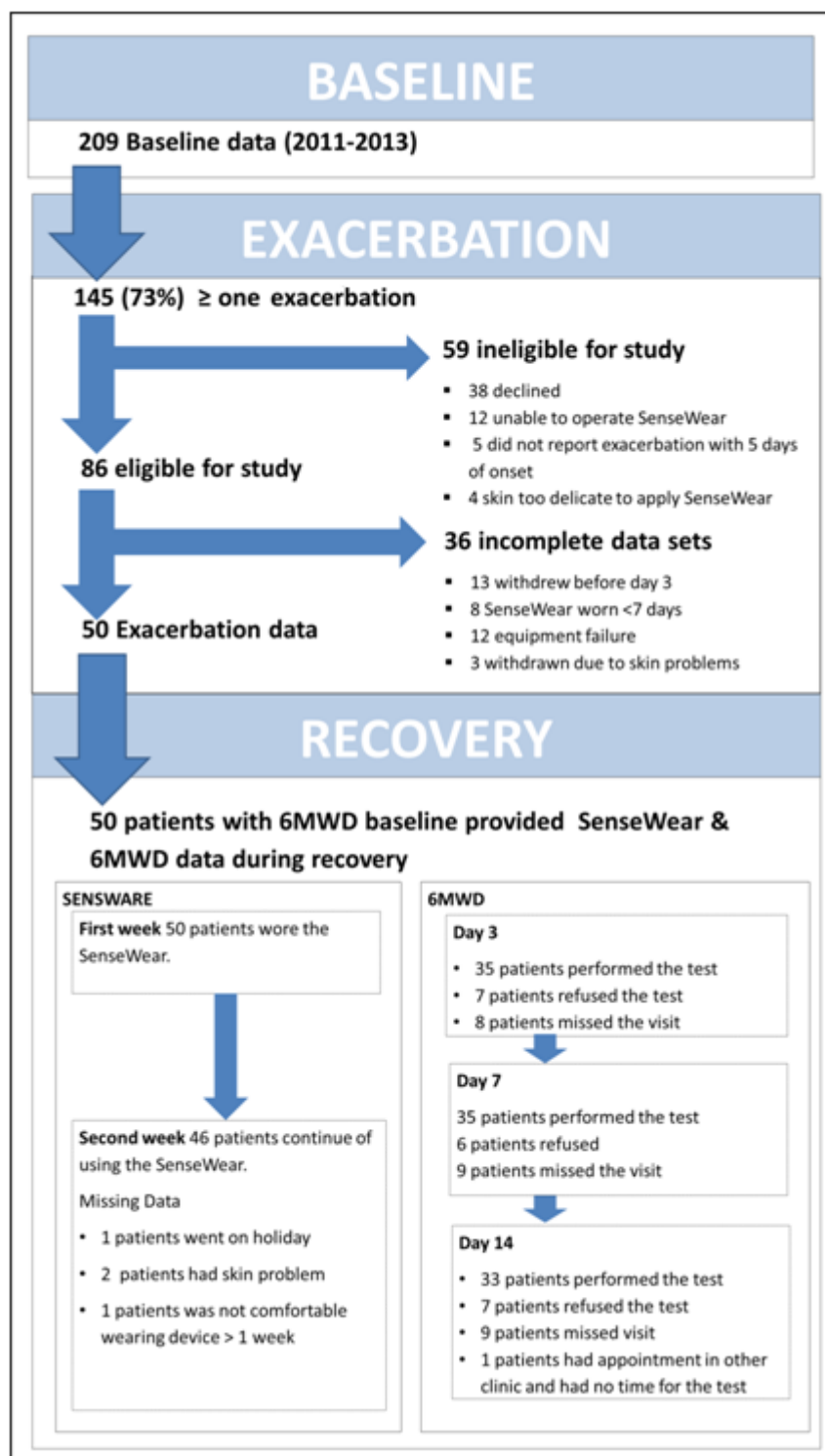
- To investigate whether acute changes in exercise capacity and quadriceps strength and physical activity (energy expenditure and daily step count) during naturally acquired, outpatient treated exacerbations are associated with changes in systemic inflammatory markers and fatigue levels.
- To examine whether falls in exercise capacity and physical activity at exacerbation were associated with disease severity, frequent exacerbations or prior pulmonary rehabilitation attendance. Such information could aid the choice and targeting of interventions.

## 7.3 METHODS

### *Protocol 1*

Fifty patients were asked to wear a SenseWear armband 7.0 (Bodymedia Inc, Pittsburgh, USA) over their left tricep continuously for 14 days from the day of reporting exacerbation to the clinic for except whilst washing or sleeping. The device measured indirectly energy expenditure and has been validated for use in COPD patients (140). Data collected on days with incomplete recording (day 0 and day 14) were excluded. Patients also undertook a 6MWD test on days 3, 7 and 14. Due to changes in 6MWD over time, only data from patients with an exacerbation and baseline measured in the same 12 months period were analysed. See consort diagram 1.

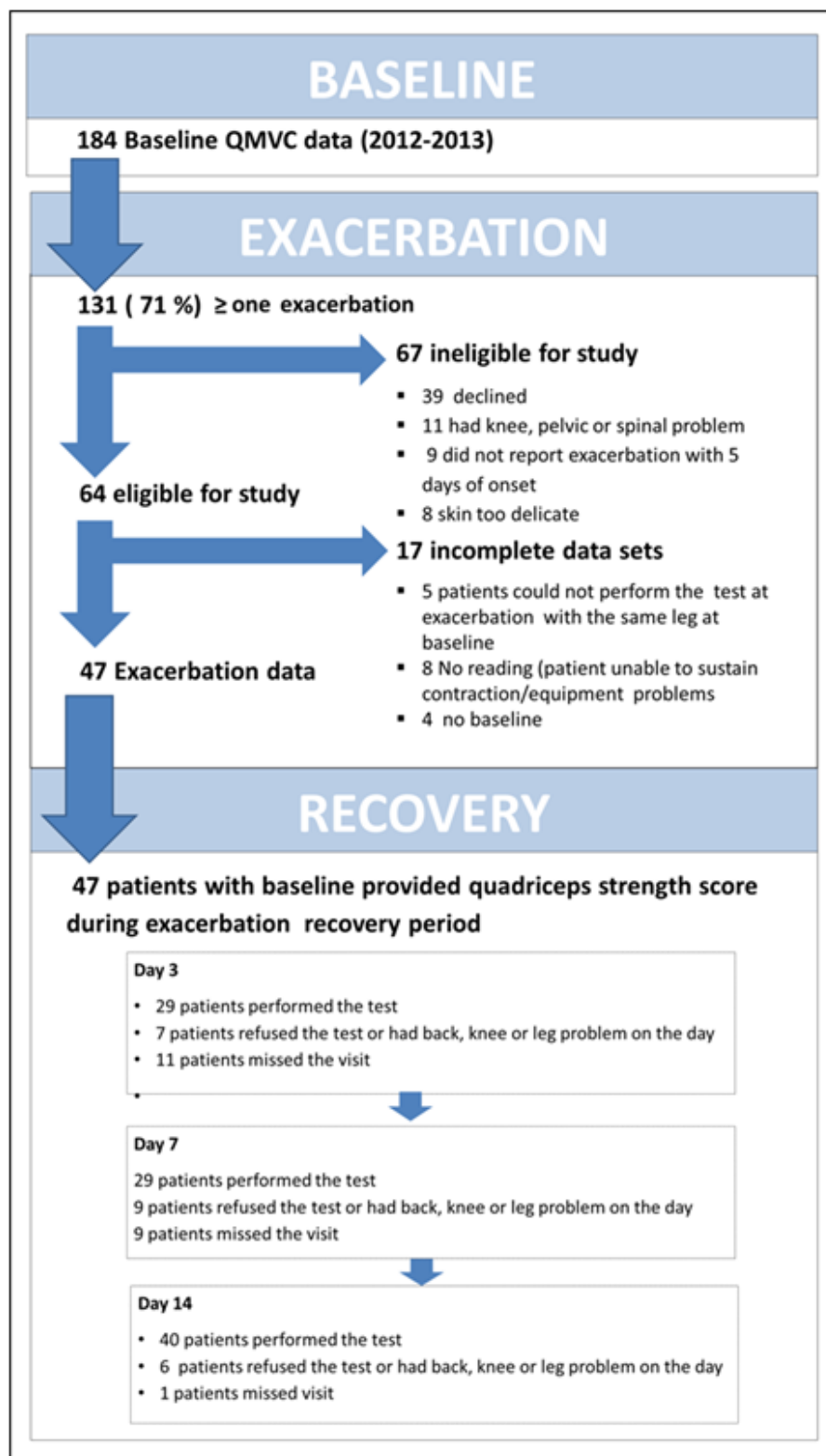
**Diagram 1 (protocol 1)**



## ***Protocol 2***

Forty-seven patients underwent QMVC testing on days 3, 7, 14 post exacerbations previously described by Edwards (202). The equipment used included a chair with seatbelt, strain gauge, ankle strap and horizontal bar. Data were collected during different exacerbations to those in protocol 1 but 19 patients undertook both protocols. Exacerbation and baseline data were collected in the same year. See consort diagram 2.

**Diagram 2 (protocol 2)**



## **Statistical analysis**

All data were analysed with SPSS (IPM SPSS statistical 22). Normally distributed data are reported as a mean and standard deviation (SD) or standard error of the mean (SEM) and skewed data reported with a median and inter quartile range (IQR). Data recorded at baseline and during recovery were compared by paired Student t-test and Wilcoxon rank-sum test. The relationship between changes in 6MWD, QMVC, FACIT-F, and CRP between baseline and exacerbation were examined by Pearson correlation (r) or Spearman rank correlation (rho). Significant was taken as a p-value <0.05.

## 7.4 RESULTS

Table 10 shows the characteristics of the 50 COPD patients who wore the SenseWear armband (Protocol 1) and a subset of 44 patients who agreed to a 6MWD test during exacerbation visits.

Table 10 also describes the 47 patients whose QMVC was measured (Protocol 2).

	<b>SenseWear armband (50 patients)</b>	<b>6MWD (44 patients)</b>	<b>Quadriceps muscles test (47 patients)</b>
	<i>Mean (±SD)</i>	<i>Mean (±SD)</i>	<i>Mean (±SD)</i>
<b>Age (years)</b>	72.9 (±8.2)	73.3 (±8.3)	72.4 (±7.8)
<b>FEV<sub>1</sub> (% predicted)</b>	50.7 (±15.1)	50.9 (±15.8)	50.1 (±17.2)
<b>FEV<sub>1</sub> (l)</b>	1.36 (±0.6)	1.33 (±0.6)	2.24 (±0.5)
<b>FVC (l)</b>	2.78(±0.9)	2.71 (±0.9)	2.81 (±1.0)
<b>FEV<sub>1</sub>/FVC (%)</b>	48.8 (±13.2)	49.2 (±13.6)	45.2 (±13.6)
<b>BMI (kg/m<sup>2</sup>)</b>	26.6 (±5.6)	26.6 (±5.6)	25.9 (±5.6)
<b>6MWD (meter)</b>	414 (±111)	414 (±111)	426 (±104)
	<i>Median (IQR)</i>	<i>Median (IQR)</i>	<i>Median (IQR)</i>
<b>Exacerbations/year</b>	2 (1.0-4.0)	2(1.0-4.0)	3 (2.0-4.0)
	%		
<b>Sex (Males)</b>	72	70	60
<b>Smoking at recruitment</b>	30	27	32
<b>GOLD (stages 1&amp;2)</b>	45	43	55
<b>GOLD (stages 3 &amp; 4)</b>	55	57	42
<b>Attended PR</b>	60	64	62

**Table 10:** Characteristics of patients participating in protocol 1 and protocol 2



## Changes in activity at exacerbation

Figure 33A shows that the mean duration of energy expenditure above 2.5 METs was greater during week 1 [(2.18 hours/day (SEM 0.23)) than during week 2 (1.98 hours/day (SEM 0.22));  $p=0.009$ ,  $n=46$ ]. Time spent lying down either sleeping or resting was not significantly different in week 1 (10.93 hours/day (SEM 0.24)) compared to week 2 (11.35 hours/day (SEM 0.26));  $p=0.158$ ,  $n=46$  (Figure 33B). Four patients did not complete week 2.

Figure 33C shows that prior to the exacerbation (baseline), the median 6MWD was 422 m (IQR 335-502) but fell to 373 m (IQR 262-450) by day 3;  $p=0.001$ , paired ( $n=35$ ). Improvements in 6MWD were seen between day 3 and day 7, rising in paired data from 373 m (262-450) to 415 m (285-480);  $p<0.001$ ;  $n=33$ , but 6MWD was still below baseline on day 14, 422 m (335-502) compared to baseline values that had a median of 435 m (285-480) respectively;  $p=0.021$ ,  $n=33$ .

## Changes in QMVC at exacerbation

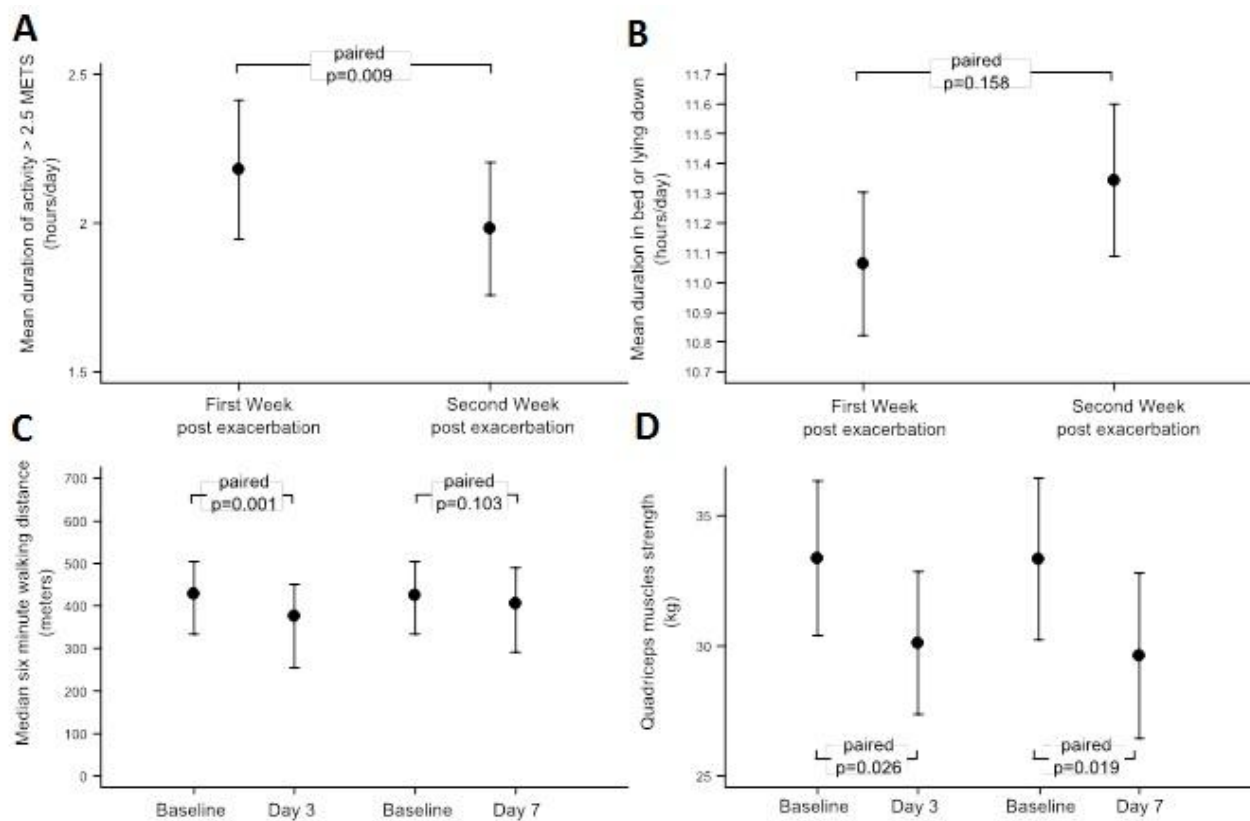
QMVC mean was 32.6 kg (SEM  $\pm 2.7$ ) at baseline but fell to 29.7 kg ( $\pm 2.5$ ) by day 3;  $p=0.026$ , paired ( $n=29$ ). Also, QMVC was still less than baseline on day 7, 29.1 kg ( $\pm 2.8$ ) compared with 32.2 kg ( $\pm 2.7$ );  $p=0.019$ ;  $n=29$ . However, by day 14, QMVC had returned to baseline levels, 32.7 kg ( $\pm 2.0$ ) compared to 32.6 kg ( $\pm 2.1$ ) respectively;  $p=0.931$ ;  $n=40$  (Figure 33D).

## **Changes in fatigue and depression at exacerbation**

Fatigue levels were worse at exacerbation presentation (day 0) compared to the baseline, 31 (SEM  $\pm 1.7$ ) vs. 36 ( $\pm 1.5$ );  $p < 0.001$ ;  $n = 39$  and on day 3, 35 ( $\pm 1.5$ ) compared with 37 ( $\pm 1.4$ );  $p = 0.037$ ;  $n = 36$ . Depression levels also were higher on day 0 compared to baseline 5 (IQR 2-7) compared with 4 (2-6);  $p = 0.024$ ,  $n = 31$  but had returned to pre-exacerbation levels by day 3, 4 (2-7) compared with day 0, 4 (2-6);  $p = 0.316$ ;  $n = 28$ .

## **Changes in systemic inflammation at exacerbation**

Systemic inflammation also rose at exacerbation with CRP increasing from 3.0 mg/l (IQR 1.0-8.5) at baseline to 8.0 (3.0–37.0) mg/l ( $p < 0.001$ ,  $n = 42$  at exacerbation presentation (day 0). It remained elevated relative to baseline on day 3 [5.0 (2.0–13.5) mg/l vs 3.0 (1.0-8.5) mg/l;  $p < 0.027$ ,  $n = 34$ ] but had fallen significantly from peak levels on day 0 to day 7, [47 (8.0-37.0)mg/l to 3.0 (1.0-7.0) mg/l;  $p < 0.001$ ,  $n = 43$ ] (Normal CRP range between 0-10 mg/l).



**Figure 33:** A) Duration of light activity in week 1 and week 2 post-exacerbation. B) Duration of time in bed at night and sleep or lying down during the day C) 6MWD at baseline and during exacerbation recovery. D) Maximal voluntary quadriceps contraction at baseline and during exacerbation recovery. Bars for exercise duration (A), time in bed and lying down (B) and quadriceps strength (D) are SE, and inter-quartile ranges for 6MWD (C).

## **Determinants of changes in physical activity**

### **Frequent vs. infrequent exacerbators**

I found that patients with infrequent exacerbations ( $\leq 2$  per year) had a smaller reduction in the duration of light activity compared to patients with frequent exacerbations (0.10 hours/day (SEM 0.09)) vs (0.40 (0.11)) hours/day respectively;  $p=0.048$ ,  $n=46$  (Figure 34A). There were no differences between frequent and infrequent exacerbators in the change in 6MWD or quadriceps strength between baseline and day 3 (Figure 34B, 34C).

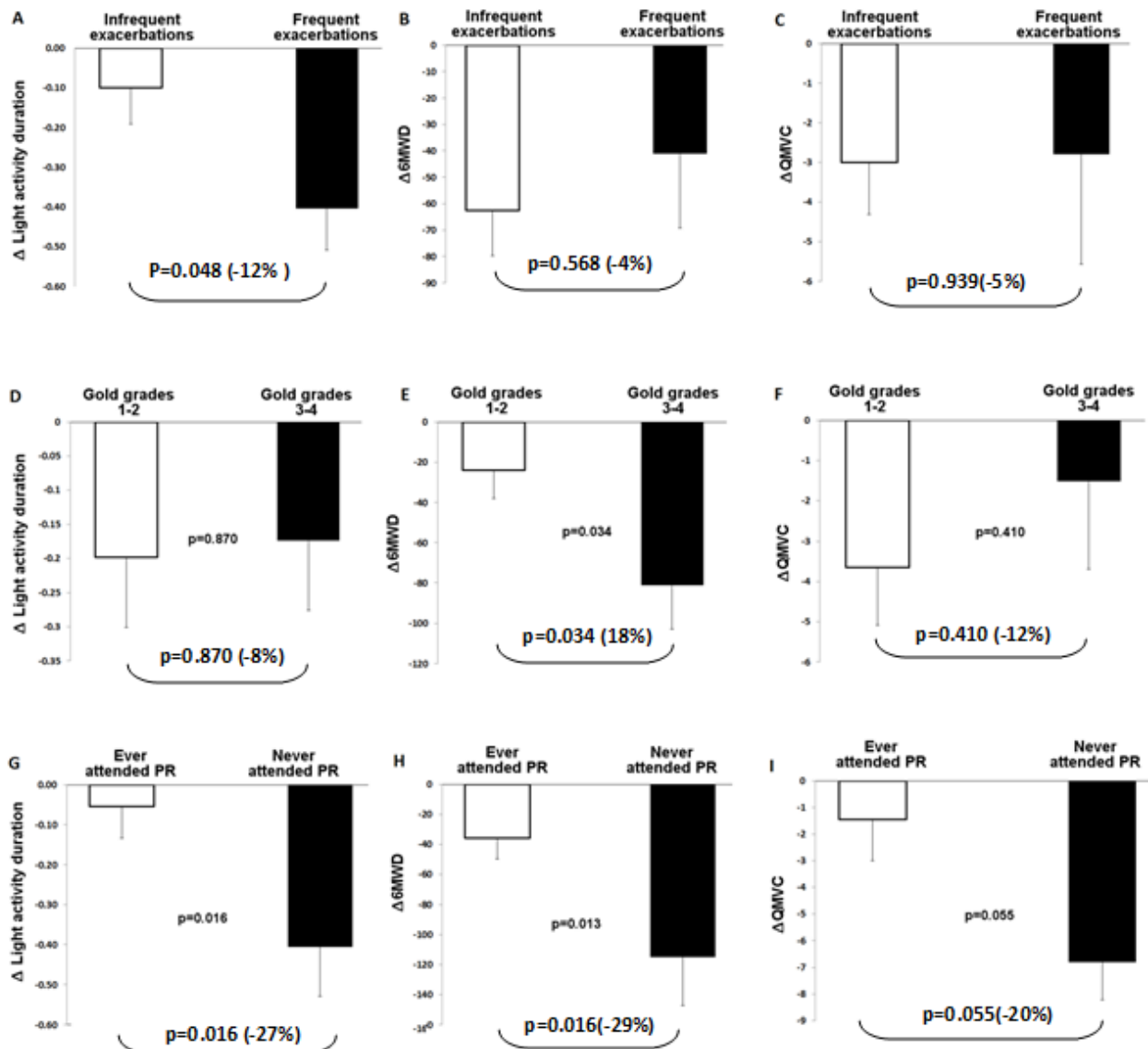
### **Disease severity**

There were no differences in light energy expenditure or quadriceps strength between mild/moderate GOLD stages and severe/very severe GOLD stages. However, the reduction in 6MWD between baseline and day 0 was significantly greater in patients with severe/very severe disease compared to mild/moderate GOLD stage patients. -81.2 m (SEM 21.9) vs -24.1 m (13.8) respectively; [ $p=0.034$ ] (Figure 34E).

### **Pulmonary rehabilitation attendance**

Patients who had attended PR had a smaller fall (week 2 – week 1) in the daily duration of light activity of only -0.06 hours/day (SEM 0.07) compared to patients who had never undertaken PR whose activity fell by -0.41 (0.12) hours/day;  $p=0.016$  (Figure 34G). Similarly, there was a smaller change in 6MWD in patients who had attended PR compared to those

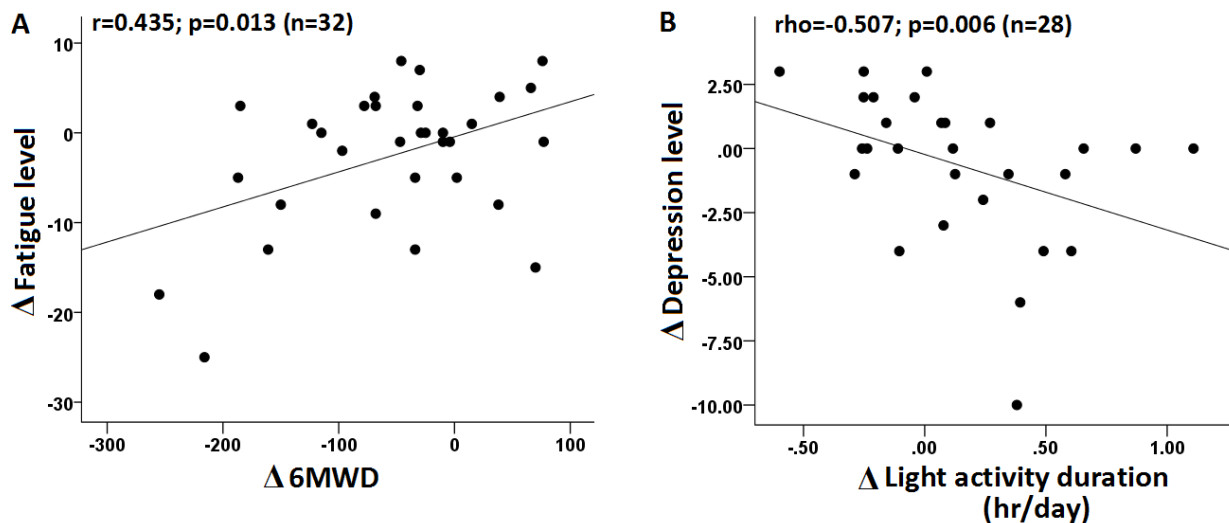
who had not undertaken PR, -35.0 m (14.1) and -114.9 m (32.2) respectively; [p=0.013] (Figure 34H). There was also a smaller fall in quadriceps muscles strength compared to patients who had attended PR [-1.5 kg (1.5) and -6.8 kg (1.4); p=0.055] (Figure 34C).



**Figure 34:** Decrease in light activity duration, 6MWD and quadriceps muscles at exacerbation relative to baseline values according to previous history of frequent versus infrequent exacerbations (A-C), COPD GOLD grade severity (D-F) and if subject has never or ever previously attended a pulmonary rehabilitation course (G-I)

## Relationship between changes in daily activity fatigue and exercise capacity

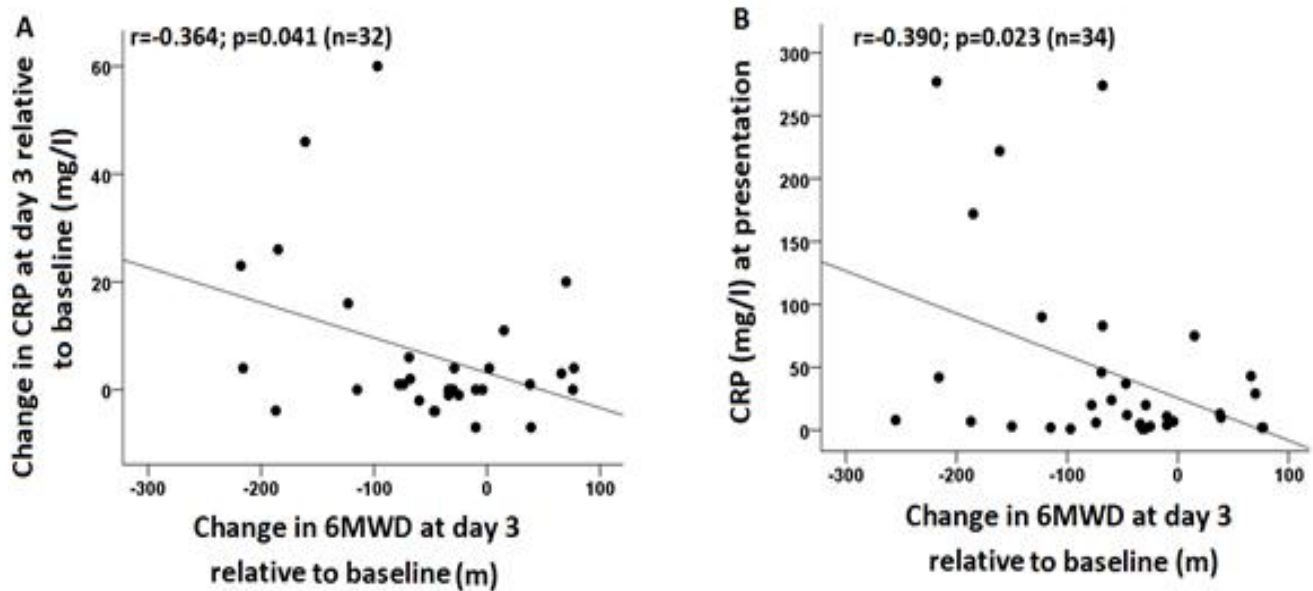
Increasing levels of fatigue (a fall in FACIT-F score) were associated with a greater reduction in 6MWD between baseline and day 3 [Figure 35A;  $r=0.435$ ;  $p=0.013$ ]. This questionnaire had two questions about daily activity and I showed correlations between FACIT-F score and 6MWT. Removing individual questions on physical activity will affect the questionnaire validity and therefore there is the possibility of confounding between the two measures. Figure 35B Higher depression scores were associated with larger falls in light energy expenditure between the first week and second week [ $\rho=-0.507$ ;  $p=0.006$ ;  $n=28$ ]. There was no relationship between changes in the duration of light energy expenditure and changes in fatigue [ $r=0.15$ ;  $p=0.441$ ].



**Figure 35:** Changes in fatigue and 6MWD between baseline and day 3 post-exacerbation and B) changes in depression and light activity duration.

## Changes in systemic inflammation and exercise capacity at exacerbation

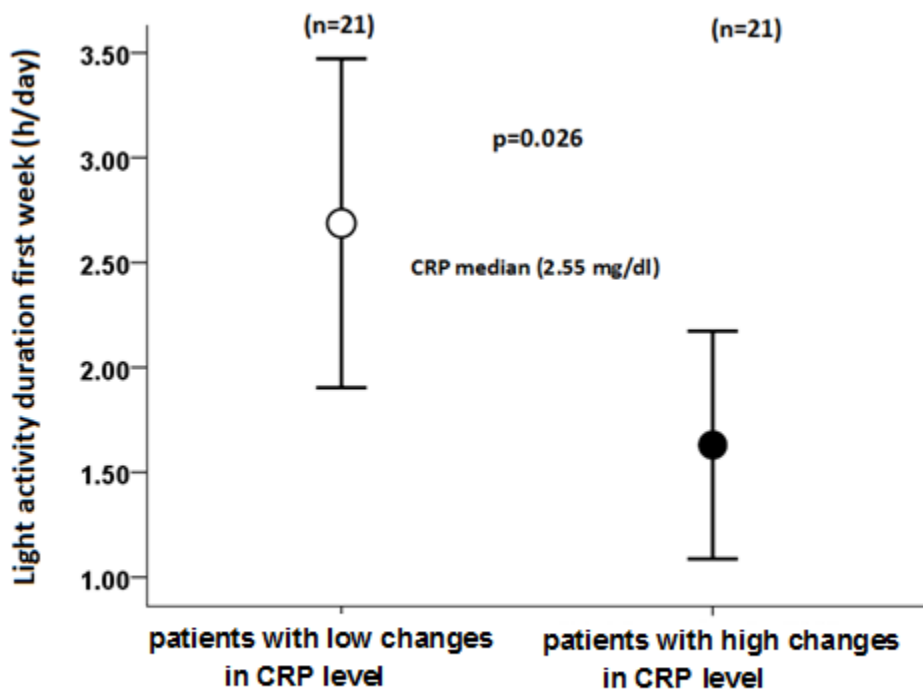
Larger falls in 6MWD between baseline and day 3 were seen in patients with the greatest rises in CRP,  $r=-0.364$ ;  $p=0.041$ ;  $n=32$  (Figure 36A). Patients with high CRP levels at exacerbation presentation had larger falls in 6MWD between day 3 and baseline [ $r=-0.390$ ;  $p=0.023$ ;  $n=34$ ] (Figure 36B).



**Figure 36:** The CRP changes and relationship to 6MWD at A) day 3 visit, and B) exacerbation presentation visit



Patients with a CRP above the group median ( $>2.55$  mg/dl) on the day of exacerbation presentation had a significant lower duration of light activity at the first week post exacerbation than those below ((mean  $\pm$  sem)  $1.63 \pm 0.26$  vs  $2.69 \pm 0.37$  hour/day respectively;  $p=0.026$ ) Figure 37.



**Figure 37:** The difference in light activity duration between patients with low vs high changes in CRP level ( $\leq 2.55$  vs  $>2.55$  mg/dl) from baseline to exacerbation presentation visit (day 0).

## 7.5 DISCUSSION

This study showed that exercise capacity, muscle strength and time spent in “light” activity with energy expenditure ( $>2.5$  METS) is reduced during community treated exacerbations of COPD. Also, for the first time, observed reduction in exercise capacity at exacerbation was associated with an increase in systemic inflammation (CRP) levels and related to changes in the perception of fatigue. Indeed, I found that changes in the duration of “light” energy expenditure during exacerbation recovery were related to increases in depression levels. An additional finding was that patients who had attended pulmonary rehabilitation had a smaller decrease at exacerbation in exercise capacity and light activity.

Skeletal muscle dysfunction and wasting is one of the most important extra-pulmonary manifestations of COPD. Much of the evidence concerning a possible link between systemic inflammation and reduced physical activity is based on statistical associations in cross-sectional studies which may have been confounded by disease severity and exacerbation frequency (261-263). Evidence from patients hospitalized for an acute exacerbation can be difficult to interpret as bed-rest in healthy people will also decrease exercise capacity (264, 265). My study examined moderate exacerbations during which patients were at liberty to engage in their normal daily activities. This category of exacerbation comprises the majority of events that involve health-care resources. My objective was therefore to examine changes in physical activity and systemic inflammation before and after a moderate exacerbation.

This study showed a significant association between the rise in CRP at exacerbation and the decrease in 6MWD between baseline and 3 days post-presentation. CRP may not have a direct effect on muscle but its rise at exacerbation will be correlated with increases in other acute-phase proteins such as interleukin-1 $\beta$ , tumor necrosis factor (TNF)- $\alpha$  and  $\alpha$ 1-antichymotrypsin (ACP). Chronic treatment with TNF- $\alpha$  or IL-1 in rats decreases muscle protein content (266) possibly through interference with myoblast differentiation (267) and high levels of ACP are associated with loss of hand grip strength (268). Sputum levels of TNF- $\alpha$  and serum levels of ACP increase at exacerbation (269, 270).

Increased systemic inflammation at exacerbation is unlikely to be solely responsible for reduced physical activity during these events, especially given that the rises in CRP were modest, although it is known that viraemia is associated with transient myalgia and measurable respiratory muscle weakness (84). I observed that falls in exercise capacity at exacerbation were larger in severe/very severe GOLD grade COPD patients. In healthy individuals, muscle fatigue limits exercise capacity but in COPD patients breathlessness may cause patients to stop exercising before fatigue is noticeable (150). The role of breathlessness is supported by studies which show physical activity related to lung hyperinflation (271) which is an important determinant of breathlessness. I observed a 5 unit increase in fatigue with exacerbation which is consistent, but smaller, than the 8.3 unit increase previously reported (217). One explanation for this inconsistency is that patients volunteering to undergo exercise testing at exacerbation may not experience large increases in fatigue.

In this study, frequent exacerbations were a patient phenotype associated with a greater reduction at exacerbation in the duration of light energy expenditure. Donaldson et al previously reported that patients with frequent exacerbations experience a significantly faster decline in both the amount of time they spend outside the home (3). Thus, this group of patients appears at greatest risk of exercise impairment. Patients with frequent exacerbations have higher modified Medical Research Council dyspnoea scores (70) and thus may be more likely to experience levels of exacerbation-related breathlessness that are sufficient to limit activity. Also in this study observed that increases in depression scores between week 2 and week 1 correlated with reduced energy expenditure in week 2 compared to week 1. Higher depression scores are seen in patients who spend less time outdoors (160).

In those patients who had attended at some time a course of pulmonary rehabilitation, reductions at exacerbation in the duration of “light” energy expenditure and 6MWD were significantly smaller than those who had not attended a course. The effect on QMVC was not significant ( $p=0.055$ ) but the direction and consistency with all three different outcome measures was noteworthy. During pulmonary rehabilitation, patients are educated about their disease and undergo exercise training to improve muscle strength and desensitize themselves to dyspnoea (272, 273). I believe this is the first time shown that changes in patients physical activity at exacerbation related positively to pulmonary rehabilitation and it is worthy of prospective investigation as this finding may encourage patient to undertake programs.

A limitation of the study is that I did not include COPD patients using ambulatory oxygen or walking supports, and my results should not be extrapolated to these patient groups. It was difficult sometimes to persuade patients with an exacerbation to undertake exertional activity and thus data were missing at various time points. Eaton and colleagues have also noticed this reluctance to engage in exercise at exacerbation with only 97 of 228 (42%) eligible patients agreed to participate in a randomized, controlled trial of early pulmonary rehabilitation at exacerbation (274). I cannot rule out bias because patients who refused to be tested may have been the more disabled patients and thus my data may have underestimated the true effect. Another limitation is that it was not feasible with a limited number of SenseWear devices to prospectively collect stable data over 7 days and to ask the patient to make as a special journey to return the device.

This study showed that a high CRP at exacerbation presentation was associated with reduced exercise capacity (6MWD). This might prove to be a useful indicator of those patients who should be targeted at exacerbation for extra encouragement to keep active whilst suffering an exacerbation and receiving treatment at home.

## **7.6 CONCLUSIONS**

In summary, my findings suggest that a greater rise in systemic inflammation at exacerbation is associated with a larger reduction in exercise capacity which is associated with increases in symptoms of depression and fatigue. Decreases in exercise capacity and physical activity at exacerbation are greater in those with more severe disease and those with a history of frequent exacerbations. It is possible that prior pulmonary rehabilitation may protect against loss of exercise capacity and physical activity at exacerbation

# 8

## **CONCLUSIONS AND SUGGESTIONS FOR FUTURE STUDIES**

## 8.1 CONCLUSIONS

Each chapter has its own discussion and conclusion, but in general terms, this thesis shows that moderate, community-treated exacerbations have a measurable but brief impact on the physical activity of COPD patients. This is important as COPD patients will likely experience a number of moderate exacerbations before they are hospitalized for a severe exacerbation. Thus, the descent into inactivity related to exacerbations starts early in the course of disease and activity related interventions should be targeted to begin at an early stage. More research into the consequences of inactivity at moderate exacerbations is needed, in addition to hospital based studies on COPD patients.

Pulmonary rehabilitation improves exercise tolerance (116), which means that patients should be continually encouraged to increase their physical activity. In this study, I observed that patients who had undergone pulmonary rehabilitation had a smaller reduction in daily activity and quadriceps muscle strength than patients who had not undergone rehabilitation, which suggests that it may confer a hitherto unexplored longer-term benefit. It is also important as attempts to encourage activity during the early stages of exacerbation recovery to prevent de-conditioning have not been successful because of non-participation and early withdrawal.

Pharmacological interventions that hasten exacerbation recovery would be beneficial to patients in a number of ways, particularly by reducing symptom burden and extending the time to the next event. Such interventions would also allow patients to return to normal activity and thus are urgently needed.



It was observed that frequent exacerbators have acceleration in the age-related decline in daily activity. This group of patients may benefit most from continued exercising and pulmonary rehabilitation. This is supported by the finding that they had a greater reduction in the duration of light activity compared with patients with infrequent exacerbations. Impairment of daily activity may be one of the factors prompting patients to report exacerbations to their physician for treatment. The causes of unreported exacerbations are not well understood, and their relationship with impairment of daily activity requires further investigation.

During cold and overcast and rainy days, unlike warm, sunny and dry days, inactivity is greatest. Indoor exercise classes could be promoted during the wintertime. At the weekends, it was observed that the activity of patients was reduced compared with the rest of the week. Pulmonary Rehabilitation at the weekend is unlikely to be a priority for the NHS but patients could be educated to increase activity at the weekend or at least be warned that this is an important time for exercise. I found evidence that COPD patients' daily activity is reduced when levels of atmospheric pollution are high. Schemes to reduce the level of atmospheric pollution or prevent very high peaks should be put in place so that COPD patients are not imprisoned in their homes.

Exacerbations are inflammatory events (4). I observed a relationship between increased systemic inflammation and reduced physical activity at exacerbation. The data are not proof of causation but do not contradict the hypothesis that reducing inflammation may improve physical performance.

Agreement was shown between the steps counted by pedometer and the actual steps obtained when a walking test was performed. Pedometry is a simple, affordable and

increasingly fashionable method for monitoring daily physical activity. Studies are required to test whether giving patients such devices encourages them to exercise more.

## **Main findings**

- Simple, cheap pedometers can be used to monitor patients' everyday activities during exacerbations treated in the community.
- Over a one-month period, average daily step count correlates moderately well with objective tests of exercise capacity, and of quadriceps muscle strength.
- Moderately severe COPD exacerbation reduced physical activity with patients recovering within three-four days.
- Frequent exacerbations accelerate the reduction over time in a patient's physical activity.
- COPD patient are most inactive during the winter, and pulmonary rehabilitation interventions that reduce inactivity could be implemented within this period.
- Physical activity also diminishes during weekends. Patients should therefore be encouraged to sustain physical activity on weekends.
- Less physical activity in COPD patients is associated with atmospheric pollution. Public health initiatives that seek to minimize air pollution need to be emphasized.

- Patients who have had pulmonary rehabilitation classes had smaller reductions in physical activity at exacerbation and smaller rises in systemic inflammatory markers. These associations should be treated cautiously but merit further investigation.

## 8.2 SUGGESTIONS FOR FUTURE WORK

1- COPD patients experience progressive decline in pulmonary function and daily activity and get worse acutely at exacerbation. Further work is needed to validate the newer range of devices currently available to assess this, such as wristband pedometers. These devices are popular with younger members of the public but utility in elderly COPD patients' needs to be investigated.

2- Chronic obstructive pulmonary disease is characterised by breathlessness and reduced daily activity which worsens acutely at exacerbation. In this thesis I showed that prior pulmonary rehabilitation within on average two years was associated with less loss of exercise capacity and physical activity at exacerbation. It would be worth examining this finding in a prospective study in which prior pulmonary rehabilitation attendance in the same year of exacerbation is related to the change in physical activity, exercise capacity and muscle strength between stable and exacerbation recovery visits.

3- The skeletal muscles of patients with COPD have increased expression of TNF, CRP, IL-6 and other inflammatory cytokines and compared with normal individual. These are factors which may contribute to muscle wasting and dysfunction. In previous studies it has been shown that inflammation is linked to muscle weakness (145, 261, 262), while others studies showed that muscles weakness related to fatigue (275). However, interventional experiments are needed to examine the relationship between pro and anti-inflammatory mediators, fatigue and physical activity.

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# **APPENDICES**

**APPENDIX A: QUESTIONNAIRES**

**APPENDIX B: 6MWD and QMVC forms**

**APPENDIX C: PUBLICATIONS**

## APPENDIX (A)

## Department of Academic Respiratory Medicine

Name		Cohort No.		Date	
Exacerbation		2W		5W	Baseline

## FACIT-Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

		Not at all	A little bit	Some- what	Quite a bit	Very much
Hi7	I feel fatigued.....	0	1	2	3	4
Hi 12	I feel weak all over .....	0	1	2	3	4
An1	I feel listless ("washed out") .....	0	1	2	3	4
An2	I feel tired.....	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired.....	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired.....	0	1	2	3	4
An5	I have energy.....	0	1	2	3	4
An7	I am able to do my usual activities .....	0	1	2	3	4
An8	I need to sleep during the day .....	0	1	2	3	4
An 12	I am too tired to eat.....	0	1	2	3	4
An 14	I need help doing my usual activities .....	0	1	2	3	4
An 15	I am frustrated by being too tired to do the things I want to do.....	0	1	2	3	4
An 16	I have to limit my social activity because I am tired .....	0	1	2	3	4

My appetite has been reduced	0	1	2	3	4
------------------------------	---	---	---	---	---

NAME \_\_\_\_\_

DATE \_\_\_\_/\_\_\_\_/\_\_\_\_

**Hospital Anxiety and Depression Scale (HADS)**

<b>I feel tense or 'wound up':</b>	<b>A</b>	<b>I feel as if I am slowed down:</b>	<b>D</b>
Most of the time	3	Nearly all of the time	3
A lot of the time	2	Very often	2
Time to time, occasionally	1	Sometimes	1
Not at all	0	Not at all	0
<b>I still enjoy the things I used to enjoy:</b>	<b>D</b>	<b>I get a sort of frightened feeling like 'butterflies in the stomach':</b>	<b>A</b>
Definitely as much	0	Not at all	0
Not quite so much	1	Occasionally	1
Only a little	2	Quite often	2
Not at all	3	Very often	3
<b>I get a sort of frightened feeling like something awful is about to happen:</b>	<b>A</b>	<b>I have lost interest in my appearance:</b>	<b>D</b>
Very definitely and quite badly	3	Definitely	3
Yes, but not too badly	2	I don't take as much care as I should	2
A little, but it doesn't worry me	1	I may not take quite as much care	1
Not at all	0	I take just as much care as ever	0
<b>I can laugh and see the funny side of things:</b>	<b>D</b>	<b>I feel restless as if I have to be on the move:</b>	<b>A</b>
As much as I always could	0	Very much indeed	3
Not quite so much now	1	Quite a lot	2
Definitely not so much now	2	Not very much	1
Not at all	3	Not at all	0
<b>Worrying thoughts go through my mind:</b>	<b>A</b>	<b>I look forward with enjoyment to things:</b>	<b>D</b>
A great deal of the time	3	A much as I ever did	0
A lot of the time	2	Rather less than I used to	1
From time to time but not too often	1	Definitely less than I used to	3
Only occasionally	0	Hardly at all	2
<b>I feel cheerful:</b>	<b>D</b>	<b>I get sudden feelings of panic:</b>	<b>A</b>
Not at all	3	Very often indeed	3
Not often	2	Quite often	2
Sometimes	1	Not very often	1
Most of the time	0	Not at all	0
<b>I can sit at ease and feel relaxed:</b>	<b>A</b>	<b>I can enjoy a good book or radio or TV programme:</b>	<b>D</b>
Definitely	0	Often	0
Usually	1	Sometimes	1
Not often	2	Not often	2
Not at all	3	Very seldom	3

Questions relating to anxiety are indicated by an 'A' while those relating to depression are shown by a 'D'. Scores of 0-7 in respective subscales are considered normal, with 8-10 borderline and 11 or over indicating clinical 'caseness'

## ST. GEORGE'S RESPIRATORY QUESTIONNAIRE ORIGINAL ENGLISH VERSION

### ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

*This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.*

*Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.*

*Before completing the rest of the questionnaire:*

*Please tick in one box to show how you describe your current health:*

Very good	Good	Fair	Poor	Very poor
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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UK/ English (original) version

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## St. George's Respiratory Questionnaire

### PART 1

**Questions about how much chest trouble you have had over the past 3 months.**

Please tick (✓) one box for each question:

	most days a week	several days a week	a few days a month	only with chest infections	not at all
1. Over the past 3 months, I have coughed:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Over the past 3 months, I have brought up phlegm (sputum):	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Over the past 3 months, I have had shortness of breath:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Over the past 3 months, I have had attacks of wheezing:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. During the past 3 months how many severe or very unpleasant attacks of chest trouble have you had?	Please tick (✓) one:				
	more than 3 attacks <input type="checkbox"/>				
	3 attacks <input type="checkbox"/>				
	2 attacks <input type="checkbox"/>				
	1 attack <input type="checkbox"/>				
	no attacks <input type="checkbox"/>				
6. How long did the worst attack of chest trouble last? (Go to question 7 if you had no severe attacks)	Please tick (✓) one:				
	a week or more <input type="checkbox"/>				
	3 or more days <input type="checkbox"/>				
	1 or 2 days <input type="checkbox"/>				
	less than a day <input type="checkbox"/>				
7. Over the past 3 months, in an average week, how many good days (with little chest trouble) have you had?	Please tick (✓) one:				
	No good days <input type="checkbox"/>				
	1 or 2 good days <input type="checkbox"/>				
	3 or 4 good days <input type="checkbox"/>				
	nearly every day is good <input type="checkbox"/>				
	every day is good <input type="checkbox"/>				
8. If you have a wheeze, is it worse in the morning?	Please tick (✓) one:				
	No <input type="checkbox"/>				
	Yes <input type="checkbox"/>				

## St. George's Respiratory Questionnaire PART 2

### Section 1

How would you describe your chest condition?

Please tick (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problem ☐

If you have ever had paid employment.

Please tick (✓) *one*:

- My chest trouble made me stop work altogether ☐
- My chest trouble interferes with my work or made me change my work ☐
- My chest trouble does not affect my work ☐

### Section 2

**Questions about what activities usually make you feel breathless these days.**

Please tick (✓) in *each box* that applies to you ***these days***:

	True	False
Sitting or lying still	<input type="checkbox"/>	<input type="checkbox"/>
Getting washed or dressed	<input type="checkbox"/>	<input type="checkbox"/>
Walking around the home	<input type="checkbox"/>	<input type="checkbox"/>
Walking outside on the level	<input type="checkbox"/>	<input type="checkbox"/>
Walking up a flight of stairs	<input type="checkbox"/>	<input type="checkbox"/>
Walking up hills	<input type="checkbox"/>	<input type="checkbox"/>
Playing sports or games	<input type="checkbox"/>	<input type="checkbox"/>



## St. George's Respiratory Questionnaire PART 2

### Section 3

***Some more questions about your cough and breathlessness these days.***

Please tick (✓) in ***each box*** that applies to you ***these days***:

	True	False
My cough hurts	<input type="checkbox"/>	<input type="checkbox"/>
My cough makes me tired	<input type="checkbox"/>	<input type="checkbox"/>
I am breathless when I talk	<input type="checkbox"/>	<input type="checkbox"/>
I am breathless when I bend over	<input type="checkbox"/>	<input type="checkbox"/>
My cough or breathing disturbs my sleep	<input type="checkbox"/>	<input type="checkbox"/>
I get exhausted easily	<input type="checkbox"/>	<input type="checkbox"/>

### Section 4

***Questions about other effects that your chest trouble may have on you these days.***

Please tick (✓) in ***each box*** that applies to you ***these days***:

	True	False
My cough or breathing is embarrassing in public	<input type="checkbox"/>	<input type="checkbox"/>
My chest trouble is a nuisance to my family, friends or neighbours	<input type="checkbox"/>	<input type="checkbox"/>
I get afraid or panic when I cannot get my breath	<input type="checkbox"/>	<input type="checkbox"/>
I feel that I am not in control of my chest problem	<input type="checkbox"/>	<input type="checkbox"/>
I do not expect my chest to get any better	<input type="checkbox"/>	<input type="checkbox"/>
I have become frail or an invalid because of my chest	<input type="checkbox"/>	<input type="checkbox"/>
Exercise is not safe for me	<input type="checkbox"/>	<input type="checkbox"/>
Everything seems too much of an effort	<input type="checkbox"/>	<input type="checkbox"/>

### Section 5

***Questions about your medication, if you are receiving no medication go straight to section 6.***

Please tick (✓) in ***each box*** that applies to you ***these days***:

	True	False
My medication does not help me very much	<input type="checkbox"/>	<input type="checkbox"/>
I get embarrassed using my medication in public	<input type="checkbox"/>	<input type="checkbox"/>
I have unpleasant side effects from my medication	<input type="checkbox"/>	<input type="checkbox"/>
My medication interferes with my life a lot	<input type="checkbox"/>	<input type="checkbox"/>

## St. George's Respiratory Questionnaire PART 2

### Section 6

*These are questions about how your activities might be affected by your breathing.*

Please tick (✓) in *each box* that applies to you *because of your breathing*:

	True	False
I take a long time to get washed or dressed	<input type="checkbox"/>	<input type="checkbox"/>
I cannot take a bath or shower, or I take a long time	<input type="checkbox"/>	<input type="checkbox"/>
I walk slower than other people, or I stop for rests	<input type="checkbox"/>	<input type="checkbox"/>
Jobs such as housework take a long time, or I have to stop for rests	<input type="checkbox"/>	<input type="checkbox"/>
If I walk up one flight of stairs, I have to go slowly or stop	<input type="checkbox"/>	<input type="checkbox"/>
If I hurry or walk fast, I have to stop or slow down	<input type="checkbox"/>	<input type="checkbox"/>
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	<input type="checkbox"/>	<input type="checkbox"/>
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	<input type="checkbox"/>	<input type="checkbox"/>
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	<input type="checkbox"/>	<input type="checkbox"/>

### Section 7

*We would like to know how your chest usually affects your daily life.*

Please tick (✓) in *each box* that applies to you *because of your chest trouble*:

	True	False
I cannot play sports or games	<input type="checkbox"/>	<input type="checkbox"/>
I cannot go out for entertainment or recreation	<input type="checkbox"/>	<input type="checkbox"/>
I cannot go out of the house to do the shopping	<input type="checkbox"/>	<input type="checkbox"/>
I cannot do housework	<input type="checkbox"/>	<input type="checkbox"/>
I cannot move far from my bed or chair	<input type="checkbox"/>	<input type="checkbox"/>

## St. George's Respiratory Questionnaire

***Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):***

Going for walks or walking the dog  
Doing things at home or in the garden  
Sexual intercourse  
Going out to church, pub, club or place of entertainment  
Going out in bad weather or into smoky rooms  
Visiting family or friends or playing with children

Please write in any other important activities that your chest trouble may stop you doing:

.....  
.....  
.....  
.....

Now would you tick in the box (one only) which you think best describes how your chest affects you:

- It does not stop me doing anything I would like to do ☐  
It stops me doing one or two things I would like to do ☐  
It stops me doing most of the things I would like to do ☐  
It stops me doing everything I would like to do ☐

***Thank you for filling in this questionnaire. Before you finish would you please check to see that you have answered all the questions.***

Your name:

Today's date:



## How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

**Examples** I am very happy 0 **X** 1 2 3 4 5 I am very sad

		SCORE	
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	
		<b>TOTAL SCORE</b>	

COPD Assessment Test and the CAT logo is a trade mark of the GlaxoSmithKline group of companies.  
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Last Updated: February 24, 2012

## **APPENDIX B**

LONDON COPD STUDY COPDMAP STUDY		Muscle Assessments				
Name		Cohort No			Date	
Visit Type	A/R		3-month Baseline		6-month Baseline	
	Exacerbation		Post exacerbation 2W		Post exacerbation 6W	

<b>Muscle Strength Assessment (QMVC) done?</b>		Yes		No		Contra- indications	
Leg (circle)	R/L	No. attempts					
Reading 1	Reading 2	Reading 3	Reading 4	Reading 5	Reading 6	Best	

## **6MWT Worksheet**

Patient name: \_\_\_\_\_ Patient ID# \_\_\_\_\_

Date: \_\_\_\_\_

Medications taken before the test (dose and time): \_\_\_\_\_

---

Supplemental oxygen during the test: No Yes

flow \_\_\_\_\_ L/min, type \_\_\_\_\_

---

	Pre-Test	End of Test
Time	____:____	____:____
Heart Rate	_____	_____
Dyspnea	_____	_____ (Borg scale)
Fatigue	_____	_____ (Borg scale)
SpO2	_____ %	_____ %

Did the patient complete the six minute walk? Yes No

If No please circle the primary reason the subject did not complete the test

Breathlessness chest pain Dizziness General fatigue  
Leg fatigue Test was contraindicated per ATS guideline

Other , Please specify \_\_\_\_\_

---

Number of laps: \_\_\_\_\_ (X60meters)+ final partial lap: \_\_\_\_\_ meters

=Total distance walked in 6 minutes: \_\_\_\_\_ meters \_\_\_\_\_

---

## **APPENDIX (C)**

### **1) Publications Arising from this Thesis**

**Ayedh D Alahmari**, Anant RC Patel, Beverly S Kowlessar, Alex J Mackay, Richa Singh, Jadwiga A Wedzicha, Gavin C Donaldson. Daily activity during stability and exacerbation of Chronic Obstructive Pulmonary Disease. *BMC Pulmonary Medicine* 2014, 14:98  
doi:10.1186/1471-2466-14-98

**Ayedh D Alahmari**, Alex J Mackay, Anant RC Patel, Beverly S Kowlessar, Richa Singh, Simon E Brill, James P Allinson, Jadwiga A Wedzicha, Gavin C Donaldson. Influence of weather and atmospheric pollution on physical activity in patients with COPD. *Respiratory Research* 2015, 16:71 doi:10.1186/s12931-015-0229-z. Published: 13 June 2015.

**Ayedh D Alahmari**, Beverly S Kowlessar, Anant RC Patel, Alex J Mackay, Richa Singh, Simon E Brill, James P Allinson, M. Polkey, Jadwiga A Wedzicha, Gavin C Donaldson. Determinants of the reduction in physical activity and capacity with COPD exacerbations. (*under review "ERJ"*)

Bethan L Barker, Richa Singh, Umme Kolsum, Karen Edwards, **Ayedh Alahmari**, Maria Shelley, Joanne Finch, Leena George, Ruth Tal-Singer, Christopher Newby, Adam J Webb, Nicholas S Hopkinson, Gavin Donaldson, Mike I Polkey, Dave Singh, Jadwiga A Wedzicha, Michael C Steiner, Christopher E Brightling. Sputum bacterial load is associated with reduced quadriceps strength in chronic obstructive pulmonary disease. (*under review "Thoracic journal"*)



RESEARCH ARTICLE

Open Access

# Daily activity during stability and exacerbation of chronic obstructive pulmonary disease

Ayedh D Alahmari\*, Anant RC Patel, Beverly S Kowlessar, Alex J Mackay, Richa Singh, Jadwiga A Wedzicha and Gavin C Donaldson

## Abstract

**Background:** During most COPD exacerbations, patients continue to live in the community but there is little information on changes in activity during exacerbations due to the difficulties of obtaining recent, prospective baseline data.

**Methods:** Patients recorded on daily diary cards any worsening in respiratory symptoms, peak expiratory flow (PEF) and the number of steps taken per day measured with a Yamax Digi-walker pedometer. Exacerbations were defined by increased respiratory symptoms and the number of exacerbations experienced in the 12 months preceding the recording of daily step count used to divide patients into frequent ( $\geq 2$ /year) or infrequent exacerbators.

**Results:** The 73 COPD patients (88% male) had a mean ( $\pm$ SD) age 71( $\pm$ 8) years and FEV<sub>1</sub> 53( $\pm$ 16)% predicted. They recorded pedometer data on a median 198 days (IQR 134–353). At exacerbation onset, symptom count rose by 1.9( $\pm$ 1.3) and PEF fell by 7( $\pm$ 13) l/min. Mean daily step count fell from 4154( $\pm$ 2586) steps/day during a preceding baseline week to 3673( $\pm$ 2258) step/day during the initial 7 days of exacerbation ( $p = 0.045$ ). Patients with larger falls in activity at exacerbation took longer to recover to stable level ( $\rho = -0.56$ ;  $p < 0.001$ ). Recovery in daily step count was faster (median 3.5 days) than for exacerbation symptoms (median 11 days;  $p < 0.001$ ). Recovery in step count was also faster in untreated compared to treated exacerbation ( $p = 0.030$ ). Daily step count fell faster over time in the 40 frequent exacerbators, by 708 steps/year, compared to 338 steps/year in 33 infrequent exacerbators ( $p = 0.002$ ).

**Conclusions:** COPD exacerbations reduced physical activity and frequent exacerbations accelerate decline in activity over time.

**Keywords:** COPD, Exacerbation, Daily step-count, Physical activity, Daily monitoring

## Background

Chronic obstructive pulmonary disease (COPD) is a global cause of morbidity and mortality and an impairment of health status [1]. Patients with COPD experience episodes of acute worsening of respiratory symptoms termed exacerbations, often triggered by infections [1]. Frequent exacerbations are a stable feature of the disease [2] and have important impacts, such as, accelerating decline in lung function, reducing quality of life and impose higher health care utilization and costs [3–5]. Respiratory symptoms following an exacerbation can take a number of weeks to return to baseline [6]. COPD

patients are less likely to go outside during an exacerbation [7]. Also, patients with frequent exacerbations experience a significant faster decline in the amount of time spent outdoors [7]. Depression is a significant comorbid condition in COPD patients [8] and associated with increased risk of exacerbation and hospitalisation [9].

COPD although primarily affecting the respiratory system is known to have extra pulmonary effects such reduced patient activity and skeletal muscle dysfunction. Studies using accelerometers have shown that activity declines at exacerbation especially in hospitalized patients in comparison to a month later [10,11] and over time [12]. Low levels of physical activity assessed with a multisensory arm-band (SenseWear) is strongly associated with all-cause mortality in patients with COPD

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[13] and data from an ankle-worn accelerator independently predicts exacerbation frequency [14].

Most clinical trials of early post-exacerbation pulmonary rehabilitation (PR) trials have shown significant improvement in exercise capacity, skeletal muscle strength, dyspnoea, quality of life and prevent de-conditioning [15-17]. Despite this evidence, patients treated in the community for an exacerbation are not actively encouraged to maintain their physical activity during exacerbation recovery. Possibly, information is lacking concerning the extent that physical activity decreases during these non-hospitalized events. These data would be needed for determining the sample size required for a clinical trial of early PR in community treated exacerbations.

Prospective monitoring of physical activity is necessary for quantifying the effects of exacerbation on activity as baseline measurements falls over time and may vary with season. Accelerometer-based monitoring devices are expensive and require regular clinic visits to download the data and are therefore not ideal for the long-term use required to prospectively capture relatively rare events such as exacerbations. Accelerometers may slightly underestimate step count at the slow walking speeds expected in COPD patients [18]. Pedometers are cheap and simple to use, but there is little published data to support their use in COPD patients. The aims of this study were to prospectively evaluate daily step-count determined with a simple pedometer, before and during the onset and recovery of an exacerbation. We have also evaluated the longitudinal trend of daily activity in patients with a history of frequent and infrequent exacerbations.

## Methods

### Patient recruitment and characteristics

Seventy three patients were recruited from the London COPD cohort. These patients recorded daily pedometry data for a minimum of 35 days with the initial 7 days considered as training and discarded for the purposes of analysis. The study took place over 19 months between April 2011 and November 2012.

All 199 patients in our rolling cohort were considered for participation in this study. 24 patients were not eligible as they used a walking support (cane or frame), were confined to a wheel chair or used ambulatory oxygen cylinders; 30 refused. We eventually provided pedometers to 145 patients. Data was successfully acquired from only 73 patients due to the following reasons a) 21 patients once issued refused to use the pedometer b) 19 patients lost their pedometers c) 23 patients recorded less than 35 days of data whilst stable d) 9 pedometers malfunctioned.

COPD was defined as a post-bronchodilator forced expiratory volume in one second ( $FEV_1$ ) to forced vital capacity (FVC) ratio below 0.70 and  $FEV_1$  expressed as a

percentage of predicted  $FEV_1$  of less than 80%. Patients were categorised as moderate, severe or very severe according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification [19]. Patients with a history of another significant respiratory disease or considered unable to complete daily diary cards excluded [4]. Patients were recruited when clinically stable, at least six weeks after their last exacerbation.

At recruitment, age, gender, chronic respiratory symptoms and smoking history were noted, and height and weight measured.  $FEV_1$  and FVC were measured with a Vitalograph Gold Standard spirometer (Vitalograph Ltd, Maids Moreton, UK).

### Daily monitoring

All patients were asked to complete a daily diary card on which they recorded their morning post-medication peak expiratory flow (PEF) measured with a mini-Wright peak-flow meter (Clement-Clarke International Ltd, Harlow, UK). They also recorded any worsening in their respiratory symptoms above normal and the number of hours spent outside their home.

Patients were also instructed to wear a Yamax Digi-walker SW-200 pedometer on the left side of their body [20,21] all the time, except when sleeping or showering. Pedometer placement was standardized by placing it on the belt or waistband, in the midline of the thigh, consistent with the manufacturer's recommendation [22]. This pedometer has been shown to accurately measure steps in free-living individuals [22] and in normal and moderately obese patients and [23] detected differences in physical activity of COPD patients recorded their daily step count on the diary cards.

### Exacerbation definition

An exacerbation was defined as an increase for two consecutive days in respiratory symptoms, with at least one major symptom (dyspnoea, sputum purulence or sputum volume) plus either another major or a minor symptom (wheeze, cold, sore throat, and cough) [6]. Five consecutive symptom free days were required before identification of the next exacerbation. Symptoms were disregarded in identifying exacerbation onset if recorded continuously in the preceding 5 days [24]. A small proportion of exacerbations for which no diary-card symptoms had been recorded by questioning the patient at clinic visits about any recent prescriptions [24]. Symptom counts were obtained by summing each increased respiratory symptom recorded on diary cards per day.

Patients were then divided into two groups, based on the number of exacerbations in the 12 months preceding the start of the study, those with 2 or more exacerbations per year were called frequent exacerbators and



those with 0 or 1 exacerbation per year called infrequent exacerbators [25].

Changes at exacerbations in daily step-count, symptoms count, PEF and hours spent outdoors were assessed by comparison of the average value over a 7 day baseline period which started 2 weeks before onset with the average value over a 7 days exacerbation period starting on the day of exacerbation onset. Recovery was determined as the day after exacerbation onset when a 3 day moving average of a parameter matched or exceeded its baseline value. A moving average was used to avoid false early recoveries when step count or lung function improved for just a single day, but then remained below baseline for a few more days [6].

#### Ethics

The study was approved by the London-Hampstead research ethics committee and all patients gave written informed consent (REC 09/H0720/8). The current study is entirely novel and has not been reported before except in abstract form (*European Respiratory Society Annual Congress 2013, Barcelona, Spain 7–11 September*).

#### Statistical analysis

Data were analyzed with STATA 8.2 (Stata Corporation, College Station, TX) and PASW statistics V.21 (SPSS Inc.). Normally distributed data are reported as a mean and standard deviation (SD) or standard error of the mean (SEM) and skewed data reported with a median and inter quartile range (IQR). Comparisons were made by paired Student t test or Wilcoxon signed-rank test as appropriate. Stable mean daily step count and other patient characteristics were related with a Pearson correlation or Spearman rank correlation. Random effect linear regression models

were used to assess annual decline in daily stable step count and whether the decline was faster in frequent than infrequent exacerbators. A stable step count was defined as outside a period starting 2 weeks before and ending 2 weeks after an exacerbation. Data from patients who experienced multiple exacerbations were averaged to avoid bias through repeated measures. However, we analyzed exacerbations as individual events when investigating whether the characteristics of exacerbations (respiratory symptoms, treatment, change in step count) was associated with a fall in activity or recovery. Significant was taken as  $p < 0.05$ .

#### Results

The 73 COPD patients (51 male, 22 female) studied had moderate to very severe COPD (Table 1). Between 8<sup>th</sup> April 2011 and 30<sup>th</sup> November 2012, daily step count was recorded on 17,161 days with a median of 198 days per a patient (IQR 134–353; range 29 to 540) days per patient. There were no significant differences in the patient characteristics between the 73 patients involved in this study and 126 patients excluded for reasons mentioned in the methods (Table 1).

#### Decline of daily step-count between patients with frequent and infrequent exacerbations

Daily step-count was recorded in the stable state on 14,653 days (median 169 days per patient; IQR 113–285; range 29–488) and for 2508 days with exacerbation (median 21 days per patient; IQR 0–57; range 0–239). Separately, daily step-count fell in the 33 infrequent exacerbators by 338 steps/year [95% CI: –504 to –170] compared to 708 steps/year [95% CI: –867 to –549] in the 40 frequent exacerbators (both  $p < 0.001$ ). The annual

**Table 1 Characteristics of the 73 COPD patients in the study and 126 COPD patients in the Cohort not recruited to the study**

	73 COPD patients		Remaining 126 COPD patients in the Cohort		P-value
	Mean	(±SD)	Mean	(±SD)	
Age (years)	71.1	(±8.7)	70.2	(±8.8)	0.51
FEV <sub>1</sub> (l)	1.31	(±0.5)	1.40	(±0.5)	0.25
FEV <sub>1</sub> (% predicted)	52.9	(±16.5)	56.2	(±16.1)	0.22
FVC (l)	2.79	(±0.9)	2.76	(±0.9)	0.83
FEV <sub>1</sub> /FVC (%)	47.8	(±12.6)	50.7	(±12.3)	0.11
BMI (kg/m <sup>2</sup> )	26.8	(±5.6)	27.0	(±5.1)	
	Median	(IQR)	Median	(IQR)	
Exacerbations/year	2	(1.0–3.0)	1.4	(0.7–3.0)	0.40
%					
Sex (males)	69.9		62.6		0.36
Chronic bronchitis	54.3		54.5		0.98
Smoking at recruitment	35.6		32.0		0.77

SD=Standard Deviation, IQR=Inter-quartile range.

decline in daily step-count was significantly faster in the frequent exacerbators ( $p = 0.002$ ; see Figure 1).

#### Time course of daily step-count at COPD exacerbation

Thirty seven patients experienced 79 exacerbations and the characteristics of these patients are reported as additional file table (see Additional file 1: Table S1). The median time since the last exacerbation was 85.5 days (IQR 42–193). The shortest interval was 15 days. There was no record of a preceding exacerbation for 7 exacerbations as these patients had been recently recruited. There were no significant differences in patient characteristics between these 37 patients and the 36 who did not experience an exacerbation except a higher FVC (L).

Table 2 shows that daily step-count, symptoms count and PEF fell significantly at exacerbation but not hours spent outdoors or whether the patient went out or not. Daily step-count took a median 3.5 (IQR 1–8) days to return to baseline levels (see Figure 2A). Symptom count rose and took 11 (IQR 8–17) days to resolve (Figure 2B) and PEF (Figure 2C) took a median 4 (0–15) days to return to normal. Hours spent outdoors per day returned to baseline levels within 1.4 (IQR 0.3–5.3) days (Figure 2D). Recovery in step count was significantly earlier than symptoms ( $p < 0.001$ ) but not PEF ( $p = 0.33$ ) or hours spent outdoors ( $p = 0.18$ ).

#### The relationship between fall in daily steps-count and respiratory symptoms and activity recovery

For the 79 exacerbations, those with the largest falls in daily step count took longer to recover to baseline ( $\rho = -0.56$ ;  $p < 0.001$ , Figure 3). During the 79 exacerbations, symptoms of dyspnoea were reported in 83.5%, sputum

purulence in 43.0% and increase sputum volume in 67.1% as major symptoms. Minor symptoms of cold were reported in 43.0%, wheezing in 49.4%, sore throat in 21.5% and cough in 54.4%. No relationship was seen between symptoms and fall in daily step count at exacerbation or recovery in steps count with one exception the fall in step count and symptoms of a sore throat ( $p = 0.037$ ).

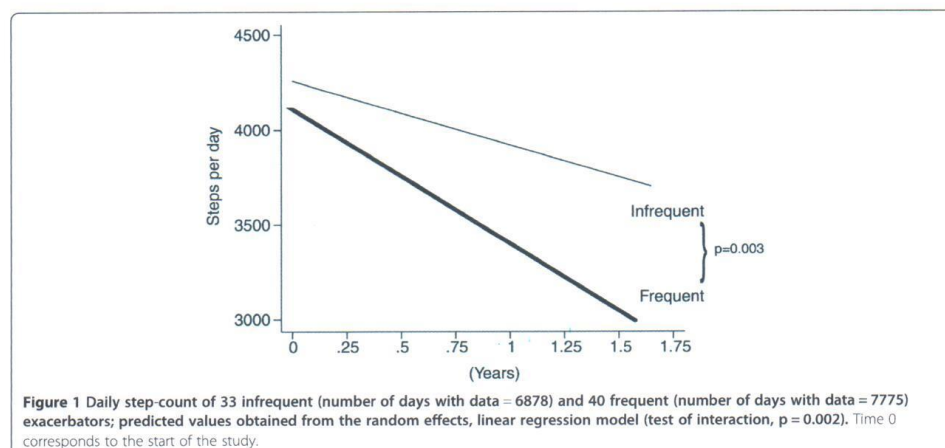
#### Activity and treatment

Fifty-seven exacerbations (11 antibiotics only; 7 oral corticosteroids only; 39 both antibiotics and oral steroids) were treated in the COPD clinic and 22 were untreated. Untreated exacerbations showed faster activity recovery (median 0 days (IQR 0–3)) than treated exacerbations (3 days (IQR 0–6)) ( $p = 0.030$ ). Figure 4 shows that only 40.9% of untreated exacerbations were associated with a fall in daily step count between baseline and exacerbation compared to 68.4% for treated exacerbations ( $p = 0.025$ ).

#### Discussion

This is the first and largest study to report fall and recovery in daily walking activity using pedometry in ambulatory COPD patients during non-hospitalized exacerbations. We found that daily step count fell by 480 steps per day during exacerbation and recovery took a median 3.5 days. Over time, daily step count fell faster in patients with frequent exacerbations. We also observed that exacerbations associated with a fall in daily step count were more likely to be reported and received treatment.

Previous work on activity during exacerbation recovery has been mainly based on the study of hospitalised COPD patients. Pitta and colleagues saw improvements



**Table 2 Comparison between baseline and first 7 days of exacerbation (mean  $\pm$  SD)**

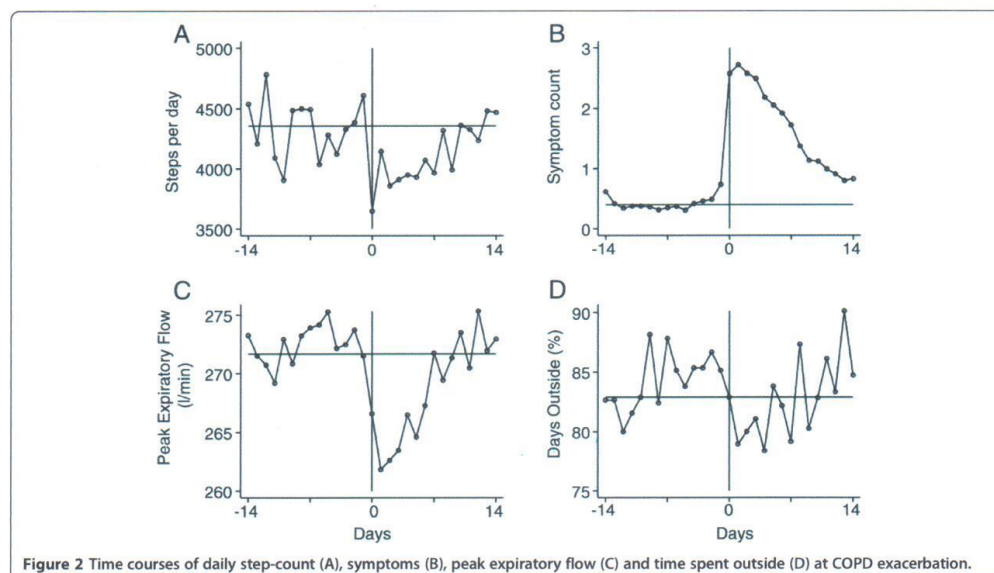
	Stable	Exacerbation	Difference	p-value
Daily step-counts (step/day)	4154 ( $\pm$ 2586)	3673 ( $\pm$ 2258)	-480 ( $\pm$ 1408)	0.045
Symptom count	0.4 ( $\pm$ 0.7)	2.4 ( $\pm$ 1.0)	1.9 ( $\pm$ 1.3)	<0.001
Peak Expiratory Flow (L/Min)	273 ( $\pm$ 109)	266 ( $\pm$ 108)	-7 ( $\pm$ 13)	0.005
Time outdoors (hours/day)	3.4 ( $\pm$ 1.8)	3.2 ( $\pm$ 1.8)	-0.1 ( $\pm$ 1.1)	0.51
Percentage of days on which patient went outdoors (%)	84.4 (24.2)	79.6 (26.1)	-4.8 ( $\pm$ 18)	0.13

in time spent walking in hospital compared to one month after discharge, but they observed no difference between day 2 and day 7 [11]. Borges and colleagues have shown that daily step count assessed with a tri-axial accelerometer increased from 602 steps/day on the 2<sup>nd</sup> day of hospitalisation to 3,575 steps/day at one month post discharge ( $p < 0.001$ ) in 32 patients [10]. However, activity monitoring during exacerbations that required hospitalisations may not reflect patient behaviour during exacerbations taking place in the community as hospitalised patients are likely to stay in bed for prolonged periods and not undertake their usual activities. Furthermore, these hospital based studies did not collect data prior to the onset of the exacerbation. In a recently published small study, Ehsan reported on activity levels in 17 patients who had just 27 symptom-define (EXACT) exacerbation in the community [12] but daily data was lacking.

In this study we found that respiratory symptoms took longer than daily step-count or time outdoors to return to baseline values. The reasons for an earlier recovery in

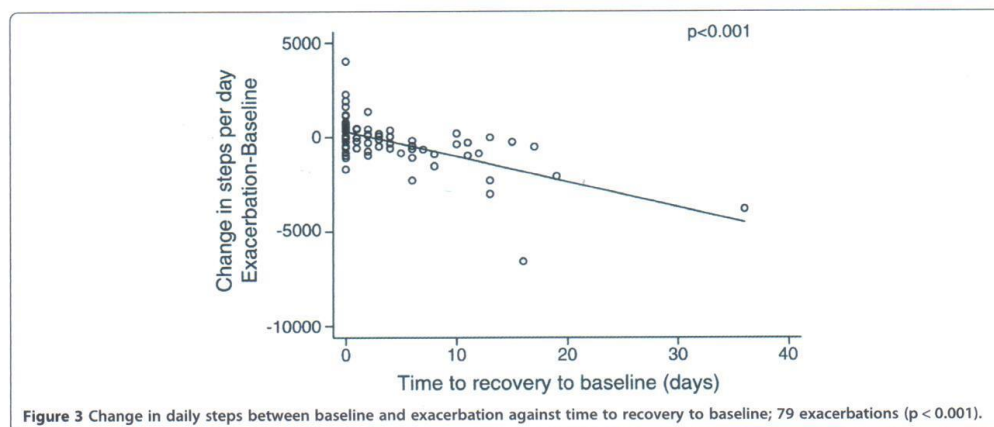
activity are unclear, but may be due to the need to go out of the home for social reasons or shopping, perhaps to return to work or a desire to exercise after a period of being housebound. It is also possible that the severity of the respiratory symptoms during the later stages of recovery is not sufficient to inhibit activity. In a previous study, on 1465 exacerbations, we reported that patients are significantly less likely to leave their home during an exacerbation [7]. In this study, we observed a similar trend, but it did not reach statistical significance due to the smaller patient numbers studied. As daily step count fell but hours outdoors was unchanged relative to the baseline, it might be that patients with an exacerbation used transport or walked more slowly when outside the home. The actual intensity and nature of exercise undertaken is a question that can only be addressed by more sophisticated accelerometer devices.

The present study shows that the larger the fall in the daily step count at exacerbation the longer it takes activity to return to normal. This suggests that COPD patients



**Figure 2** Time courses of daily step-count (A), symptoms (B), peak expiratory flow (C) and time spent outside (D) at COPD exacerbation.



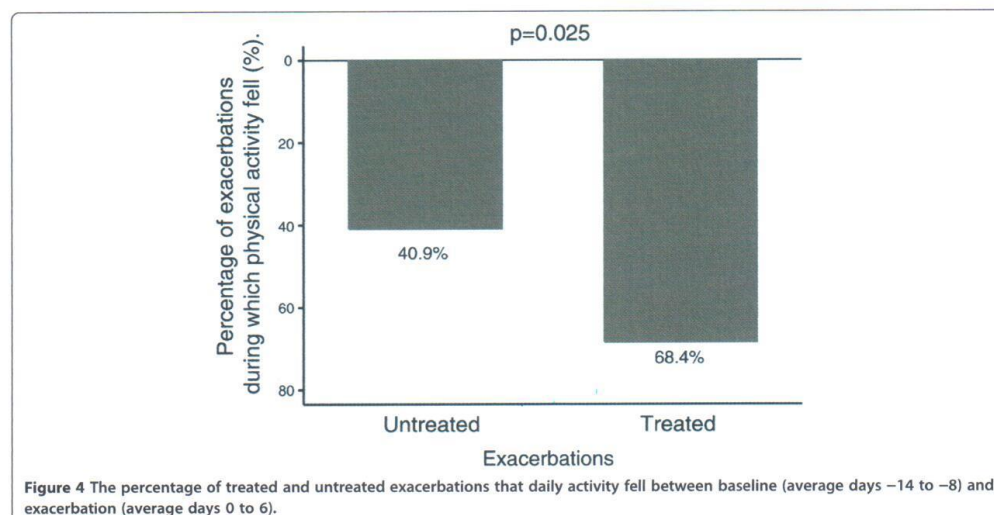


should be encouraged to keep active during the early stages of exacerbation since activity will return to normal faster. Pulmonary rehabilitation programmes initiated early post-exacerbation show a benefit compared to usual care [15-17,26-28] possibly by avoiding muscle deconditioning through inactivity during bed-rest [29]. However, in the largest study to date, Eaton and colleagues found no significant effect on acute health-care utilization, although it was found to be safe and feasible [30].

Treated exacerbations were slower to recovery compared to untreated exacerbations though our previous work has suggested there is little difference in respiratory symptoms between treated and untreated events [4]. The

reasons why patients report some exacerbations to a health care professional and not others have been unclear and approximately 50% of exacerbations are unreported [4,31]. Our findings suggest that impairment of daily activity may be a key factor in patients seeking additional therapy for their exacerbation.

This study has shown for the first time that patients who experienced frequent exacerbations have twice as fast an annual decline in daily step-count than patients with infrequent exacerbations. Frequent exacerbations are known to accelerate both decline in  $FEV_1$  [25] and rise in airway and systemic inflammation [3,32] with patients becoming housebound faster [7], and more likely



to suffer from depression [33] and fatigue [34]. The precise mechanism of activity decline is unclear but it is possible that prolonged recovery or non-recovery after an exacerbation may contribute to this decline. In addition, anxiety, depression and fatigue are associated with exacerbations and any discourage patients from maintaining activity. This may be particularly marked in more severe patients with frequent exacerbations as they have significantly more and longer hospital admissions, though hospital admissions were not a subject for this study. Cote and colleagues found a reduction in exercise capacity after an exacerbation, with a 72 m decline (20%) in 6MWD [35].

An important strength of the study was the prospective daily monitoring of COPD patients to capture a baseline activity level just before the exacerbation event started. Baseline data collected away from the exacerbation may not be valid as daily step count declines over time and varies with seasonal changes [14]. Daily monitoring is also essential when investigating exacerbation where symptoms recovery to normal in a few days. One limitation of the study is that we did not include patients using ambulatory oxygen or walking supports or mild patients with GOLD stage 1 COPD and our results should not be extrapolated to these patient groups. However an important feature of this study is that exacerbations treated in the community were included and this makes the data applicable to the majority of exacerbations experienced by COPD patients.

## Conclusions

Pedometer measurements can be used to track daily activity easily during COPD exacerbations that do not require hospital admission. We have shown that exacerbations reduce physical activity with patients recovering within a 3 to 4 day period. Frequent exacerbations also hasten a decline in activity over time and potentially this patient group would benefit from greater encouragement to continue exercising. Our results also show that daily activity is a major drive for patients reporting exacerbation events and seeking additional therapy. Thus, non-hospitalized COPD exacerbations are key events that not only cause symptomatic deterioration but also impair the patients' activity.

## Additional file

**Additional file 1:** Characteristics of the 37 COPD patients in whom pedometer data was recorded during at least one exacerbation.

## Abbreviations

COPD: Chronic Obstructive Pulmonary Disease; PEF: Peak expiratory flow; PR: Pulmonary rehabilitation; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; GOLD: Global initiative for chronic obstructive

lung disease; SEM: Standard error of the mean; IQR: Inter quartile range; SD: Standard deviation.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contribution

AA, JW, GD designed the study and analyzed the data; AA, AP, BK, AM, RS, saw patients in clinic and collected data; AA, AP, BK, AM, RS, JW and GD contributed to interpretation and drafting the manuscript for important intellectual content. All authors read and approved the final manuscript.

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# Influence of weather and atmospheric pollution on physical activity in patients with COPD

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## Abstract

**Rationale:** Information concerning how climate and atmospheric pollutants affects physical activity in COPD patients is lacking and might be valuable in determining when physical activity should be encouraged.

**Methods:** Seventy-three stable COPD patients recorded on daily diary cards worsening of respiratory symptoms, peak expiratory flow rate, hours spent outside the home and the number of steps taken per day. Pedometry data was recorded on 16,478 days, an average of 267 days per patient (range 29-658). Daily data for atmospheric PM<sub>10</sub> and ozone (O<sub>3</sub>) were obtained for Bloomsbury Square, Central London from the Air Quality Information Archive databases. Daily weather data were obtained for London Heathrow from the British Atmospheric Data Archive.

**Results:** Colder weather below 22.5 °C, reduced daily step count by 43.3 steps day per °C (95 % CI 2.14 to 84.4;  $p = 0.039$ ) and activity was lower on rainy than dry days ( $p = 0.002$ ) and on overcast compared to sunny days ( $p < 0.001$ ). Daily step count was 434 steps per day lower on Sunday than Saturday ( $p < 0.001$ ) and 353 steps per day lower on Saturday than Friday ( $p < 0.001$ ). After allowance for these effects, higher O<sub>3</sub> levels decreased activity during the whole week (-8 steps/ug/m<sup>3</sup>;  $p = 0.005$ ) and at weekends (-7.8 steps/ug/m<sup>3</sup>;  $p = 0.032$ ). Whilst, during the week PM<sub>10</sub> reduced activity ( $p = 0.018$ ) but not during the weekend.

**Conclusions:** Inactivity of COPD patients is greatest on cold, wet and overcast days and at the weekends. This study also provides evidence of an independent effect of atmospheric pollution at high levels.

**Keywords:** COPD, Atmospheric pollution, Weather, Daily step-count, Physical activity, Daily monitoring

## Introduction

Chronic obstructive pulmonary disease (COPD) causes much morbidity and reduces quality of life [1]. The disease is projected to become the fourth leading cause of death worldwide by 2030 [2]. COPD involves airflow obstruction that results in dyspnoea which is associated with reduced daily activity and increased muscle weakness [3].

Patients with COPD experience episodes of acute worsening of in their respiratory symptoms termed exacerbations that are often triggered by respiratory infection [1, 4]. Frequent exacerbations have an accelerated decline in lung function [5] and an increase rise in airway and systemic inflammation [6, 7]. Patients with frequent

exacerbations patients also becoming housebound faster [8] and have greater perception of fatigue [9] which might explain why this group suffers more from depression [10]. We have previously reported that physical activity is reduced during a COPD exacerbation [11]. In this study, we report only on data collected when the patients were clinically stable.

A few studies have examined activity in older people [12, 13] but we are unaware of any studies that have specifically examined the impact of daily weather on physical activity in patients with COPD.

Pollution may also reduce activity and we have previously reported that particulate matter <10 µm in diameter (PM<sub>10</sub>) in London increases symptoms of dyspnoea in COPD patients [14] and reduce pulmonary function [15]. Traffic-related air pollution exposure has also been shown

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to be positively associated with first hospital admission for COPD [16].

Maintenance of physical activity can substantially reduce age-related mortality [12] but it is particularly important for patients with COPD since those who continued to exercise have less dyspnoea, fewer hospital admissions for COPD and reduced mortality. Indeed, COPD patients can be referred by physicians to specialized pulmonary rehabilitation clinics to undergo a few weeks of physical training and education but poor participation and a failure to continue exercising limits the effectiveness of this intervention. There is a need therefore to understand the barriers to participation and sustained behaviour change [17]. In this study, we examine for the first time in patients with COPD how the weather and atmospheric pollution levels affect physical activity.

## Methods

### Patient recruitment

The London COPD cohort is a group of approximately 200 COPD patients under longitudinal observation at the Centre for Respiratory Medicine, University College London. This cohort was started in 1995 for the prospective investigation of COPD exacerbations. Patients who withdraw or die are replaced on a rolling basis. COPD is defined as a Forced Expiratory Volume in 1 s ( $FEV_1$ )  $\leq 80\%$  of a normal value predicted from age, height, and sex and a  $FEV_1$ /Forced Vital Capacity (FVC) ratio  $< 0.7$ . Patients enrolled in the cohort complete daily diary cards and are seen in clinic every 3 months if stable and annually undergo a comprehensive medical review. Patients were also seen at exacerbation and most were prescribed oral corticosteroids and/or antibiotics. Patients with any other primary respiratory diseases or who are unable or unwilling to complete daily diary cards were excluded.

In April 2011, there were 199 patients enrolled in the London COPD cohort. 24 patients were ineligible as they used a walking support (cane or frame) or were confined to a wheel chair or used ambulatory oxygen cylinders and 30 refused. We eventually provided pedometers to 145 patients. Data was successfully acquired from only 73 patients for the following reasons a) 21 patients once issued refused to use the pedometer, b) 19 patients lost their pedometers, c) 23 patients recorded less than 35 days of data whilst stable due to repeated exacerbation and, d) 9 pedometers malfunctioned. The study ended in March 2013.

A full medical and smoking history was taken and measurements of  $FEV_1$  and FVC made with a Vitalograph Gold Standard spirometer (Vitalograph Ltd, Maids Moreton, UK). Body mass index (BMI) was calculated from height and weight.

### Monitoring

Patients were educated to use diary cards at the recruitment visit and re-educated as needed when visiting the clinic. The diary cards also have instructions (how to fill the card and how use the pedometer) and contact numbers on the back of every card. All patients kept a daily diary card on which they recorded any worsening in their respiratory symptoms, the number of hours spent outside their home and their daily peak expiratory flow (PEF) measured with a mini-Wright meter (Clement-Clark International, Harlow, UK) once a day at morning. Patients were instructed to wear a pedometer (Yamax Digi-Walker SW-200) on left side of body all the time, except when sleeping or showering. Patients recorded daily step counts on written daily diary cards. This pedometer has been shown to accurately measure steps in free-living individuals [18, 19] and in normal and moderately obese patients and [20] detected differences in physical activity of COPD patients [21]. Patient also completed a daily COPD Assessment Test (CAT) questionnaire after first being trained in clinic. Pedometry data collected over the initial 7 days were discarded to avoid any learning effects and only patients who had recorded more than 35 days of data were included in this analysis.

### Exacerbations

Exacerbations were identified according to our usual criteria of increases in any two major symptoms (dyspnoea, sputum volume or sputum purulence) or one major and one minor symptom (nasal congestion, wheeze, cough, sore throat) over two consecutive days [22]. Data recorded two weeks either side of the onset of an exacerbation were excluded from the analysis.

### Ethics

The study was approved by the London-Hampstead research ethics committee and all patients gave written informed consent (REC 09/H0720/8).

### Temperature and pollution data

Daily data for atmospheric  $PM_{10}$  and ozone ( $O_3$ ) were obtained for Bloomsbury Square, Central London from the Air Quality Information Archive databases (<http://www.airquality.co.uk>). Data from the archive is reported as  $\mu g/m^3$ . The conversion factor of ozone is 1 ppb =  $1.9957 \mu g/m^3$  at  $20^\circ C$  and 1013 millibar atmospheric pressure. We did not use data from the monitoring site in Hackney that would be closer to our patients because it did not record data on  $PM_{10}$  which we have previously shown to increase dyspnoea [14].

Weather data was the average of hourly readings over 24 h at Heathrow Airport and obtained from the British Atmospheric Data Centre ([www.badc.nerc.ac.uk](http://www.badc.nerc.ac.uk)). A dry day was defined as zero precipitation [23] and a sunny



**Table 1** Characteristics of the 73 COPD patients in the study and 126 COPD patients in the London COPD Cohort not recruited to the study

	Recruited COPD patients (n = 73)	Not recruited COPD patients (n = 126)	P-value
	Mean ( $\pm$ SD)	Mean ( $\pm$ SD)	
Age (years)	71.1 ( $\pm$ 8.7)	70.2 ( $\pm$ 8.8)	0.51
FEV <sub>1</sub> (l)	1.31 ( $\pm$ 0.5)	1.40 ( $\pm$ 0.5)	0.25
FEV <sub>1</sub> (% predicted)	52.9 ( $\pm$ 16.5)	56.2 ( $\pm$ 16.1)	0.22
FVC (l)	2.79 ( $\pm$ 0.9)	2.76 ( $\pm$ 0.9)	0.83
FEV <sub>1</sub> /FVC (%)	47.8 ( $\pm$ 12.6)	50.7 ( $\pm$ 12.3)	0.11
BMI (kg/m <sup>2</sup> )	26.8 ( $\pm$ 5.6)	27.0 ( $\pm$ 5.1)	
	Median (IQR)	Median (IQR)	
Exacerbations/year	2% (1.0-3.0)	1.4 (0.7-3.0)	0.40
Sex (Males)	69.9	62.6	0.36
Chronic bronchitis	54.3	54.5	0.98
Smoking at recruitment	35.6	32.0	0.77

day arbitrarily defined as a day when the sun shone for a minimum 0.1 h or more.

#### Statistical methods

Patient characteristics are summarised as appropriate by a mean and standard deviations or standard errors, or a median and inter-quartile ranges, or as a percentage.

#### Unadjusted analysis

Generalised estimating equations (GEE) were used to model the effects of weather and pollution on daily step count, PEF, CAT scores (assuming their Gaussian distribution), time (hours) outdoors (as Poisson distributed) or worsened dyspnoea (with a Bernoulli distribution) on days with temperatures  $\leq 22.5$  °C. It was an a priori

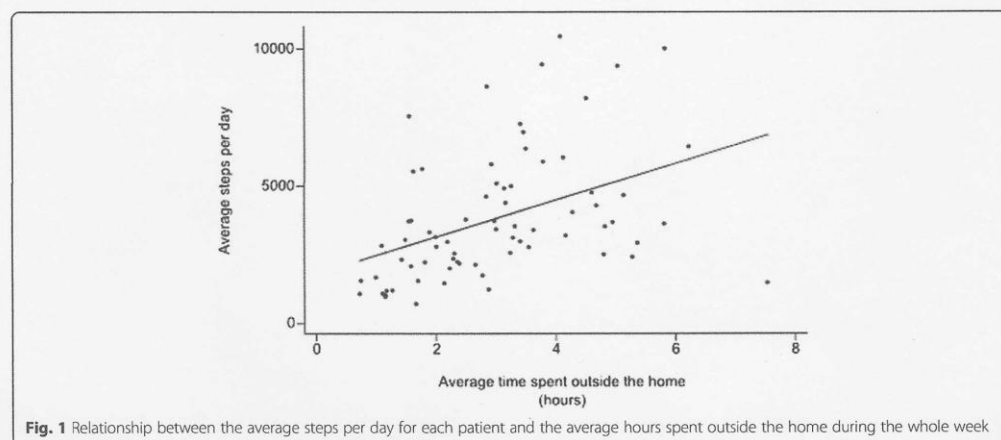
decision that a cut-off would be necessary as relatively hot weather can reduce time spent outdoors [24]. To identify the inflexion in the relationship between activity and temperature we plotted mean daily step count against temperature in 0.25 °C intervals. After inspection, a cut-off of 22.5 °C was chosen as daily step count was highest at this temperature and decreased with temperatures below or above 22.5 °C. GEE models were used to examine our panel data as they correct the standard errors and p-values for the various regression coefficients for the correlation structure between the repeated measurements on the same patient. We used the xtgee command in Stata with the robust option as this would produce valid standard errors even if our assumption of an independent correlation structure was incorrect.

Comparisons between daily step count of a sunny compared to a dull day, or a dry versus rainy day were made by paired *t*-test, after first obtaining the average for each patient under the various conditions.

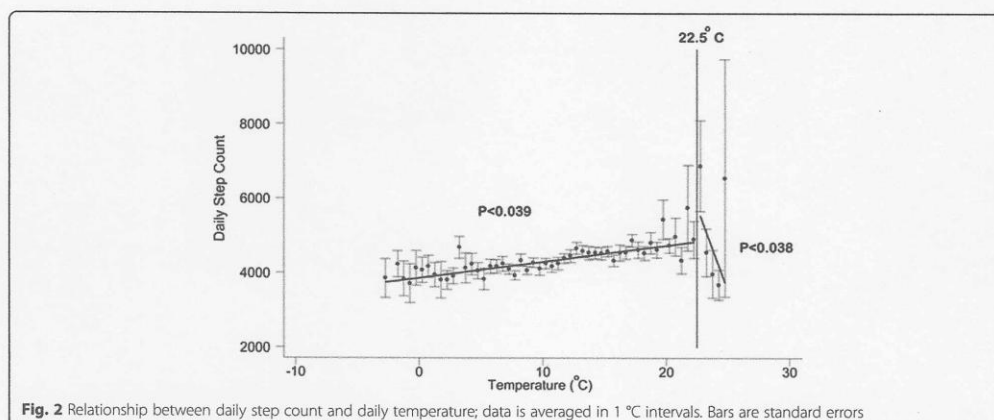
Analysis of variance (ANOVA) was used to determine the effect of day of the week on daily step count, hours outdoors, O<sub>3</sub> and PM<sub>10</sub>. Post-hoc comparisons were made between Sunday and Saturday, and between Saturday and Friday.

#### Adjusted analysis

GEE regression models were used to assess the independent effects of climate and pollution on daily step count and the other outcome measures. These models included a linear term to adjust for age related decline, sine and cosine terms with periods of 12, 6 and 4 months to allow for seasonal changes, and a variable for day of week with Monday as the first day of the week. The covariates also included daily temperature, wind speed, rainfall, hours of



**Fig. 1** Relationship between the average steps per day for each patient and the average hours spent outside the home during the whole week



**Fig. 2** Relationship between daily step count and daily temperature; data is averaged in 1 °C intervals. Bars are standard errors

sunshine and day-length,  $PM_{10}$  and  $O_3$  as independent variables. We did not examine any lagged effects of climate or pollution. The analysis was repeated using data collected during week-days only (Monday-Friday) and during week-ends (Saturday and Sunday) since activity was markedly dissimilar in these periods. The analysis was also repeated with an auto-regressive term (the previous day value of the dependent variable) in the model to adjust for autocorrelation in the dependent variable. We also repeated the analysis of daily step count and the pollutants with time outdoors included as an independent variable.

#### Distance to pollution monitoring site

The coordinates of Bloomsbury Squares and the patient's home (defined as the centre of their post-code) were obtained from the National Statistics postcode directory database. The straight-line distance between the two sets of coordinates was calculated by Pythagoras' theorem.

## Results

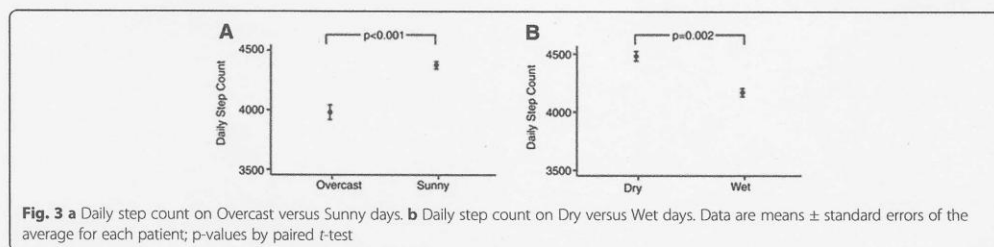
### Patient characteristics

The 73 COPD patients (51 Male, 22 Female) studied had moderate to very severe COPD (Table 1). There were no significant differences in the patient characteristics between the 73 patients involved in this study and 126

patients excluded for reasons described in the methods. The patients recorded daily step count on 16,478 days with an average per patient of 267 days (range 29-658). Of these, 3020 days were excluded, as exacerbations commenced either two weeks before or after.

The patients lived on average 7.39 km (SD 4.70) from the Bloomsbury Square site. Of the 73 patients, 59 lived north-east, 7 north-west, 2 south-east and 5 south-west of Bloomsbury.

The average of 225 days of pedometry readings per patient (SD 139; range 29-578); 459 days of PEFR readings per patient (SD 139; range 124-768); 463 days per patient of whether or not dyspnoea was worse than usual (SD 138; range 124-680) and 70 days with a CAT score per patient (SD 87; range 0-356). During the week, when patients might be at work, the mean of each patient's average time outside the home per day was 3.05 h (SD 1.51; range 0.52 to 7.3 h). Over the whole week, there was a strong relationship between the average number of steps per day and the average time spent outdoors (regression coefficient = 671 steps per day per hour outdoors; intercept = 1804 steps per day;  $p = 0.001$ ; see Fig. 1).



**Fig. 3 a** Daily step count on Overcast versus Sunny days. **b** Daily step count on Dry versus Wet days. Data are means  $\pm$  standard errors of the average for each patient; p-values by paired t-test



**Table 2** Relationship between daily step count and environmental factors (climate, pollutants and weekday) over the full week, and during weekdays only; allowance was made for season, linear trend and day-length (data for these variables not shown)

	Over full week			Weekdays only		
	Regression coefficient	95 % CI	p-value	Regression coefficient	95 % CI	p-value
Temperature (°C)	37.7	14.1 to 61.4	0.002	36.5	9.6 to 63.4	0.008
Sunshine (% day)	4.7	2.8 to 6.7	<0.001	4.0	1.8 to 6.2	<0.001
Rainfall (mm)	-16.8	-27.1 to -6.6	0.001	-15.3	-26.4 to -4.2	0.007
Wind speed (m/s)	-17.2	-37.6 to 3.2	0.099	-43.8	-66.2 to -21.5	<0.001
PM <sub>10</sub> (µg/m <sup>3</sup> )	-5.4	-12.2 to 1.3	0.112	-7.8	-14.2 to -1.3	0.018
O <sub>3</sub> (µg/m <sup>3</sup> )	-8.0	-13.5 to -2.4	0.005	-3.5	-9.4 to 2.4	0.239

**Unadjusted analysis**

Warmer weather was associated with increased daily step count (Fig. 2). A 1 °C rise in temperature increased the count by 43 steps per day per °C (95 % CI 2.14 to 84.4;  $p = 0.039$ ). However, when the temperatures exceeded 22.5 °C, patient activity appeared to decrease and steps per day fell by -891 per 1 °C rise (95 % CI -1735 to -47;  $p = 0.038$ ).

Physical activity was higher on days with sunshine or without rain (Fig. 3). The mean of patient's average step count on sunny days was 3938 per day (SD 2447) compared to 3596 per day (SD 2260) on overcast days (paired  $t$ -test;  $p < 0.0010$ ). Similarly, on dry days the mean of each patient's average step count was 3999 per day (SD 2507) compared to 3771 per day (SD 2349) on days with rain ( $p < 0.0001$ ).

The day of week effected both daily step count and hours outside. A post-hoc analysis of variance showed that daily step count was 434 steps per day lower on Sunday than Saturday ( $p < 0.001$ ) and 353 steps per day lower on Saturday than Friday ( $p < 0.001$ ). Similarly, time outdoors was 0.55 h lower on a Sunday compared to Saturday ( $p < 0.001$ ) and by 0.09 h lower on Saturday compared to Friday ( $p < 0.001$ ) (see Additional file 1: Figure S1).

**Adjusted analysis**

Table 2 shows results from the GEE models with daily step count data recorded during either (a) the whole week and (b) over Monday to Friday (weekdays). Daily

step count increased significantly with warmer, sunny weather and fell with wet weather. Over the whole week, higher O<sub>3</sub> levels were associated with decreased activity ( $p = 0.005$ ) but not with PM<sub>10</sub> ( $p = 0.112$ ). Conversely, over just weekdays, PM<sub>10</sub> was associated with reduced activity ( $p = 0.018$ ) but not O<sub>3</sub> ( $p = 0.239$ ). There were no significant seasonal effects (sine and cosine terms) with temperature included in the model. With inclusion of an autoregressive term, over the whole week, rise in O<sub>3</sub> was still associated with reduced daily step count ( $p = 0.008$ ) and rise in PM<sub>10</sub> also significantly and independently associated with reduced daily step count ( $p = 0.047$ ). Inclusion of time outdoors as an independent variable in the regression model, eliminated the effect of O<sub>3</sub> on daily step count over the whole week (regression coefficient = -3.9; 95 % CI -8.8 to 0.9;  $p = 0.113$ ) and similarly between step count and PM<sub>10</sub> over weekdays only (regression coefficient = -4.4; 95 % CI -10.4 to 1.5;  $p = 0.147$ ).

Table 3 shows only the effects of the two pollutants (PM<sub>10</sub> and O<sub>3</sub>) on the various outcome measures over the whole week (Table 3); over week-days (see Additional file 1: Table S1) and over the week-end (see Additional file 1: Table S2).

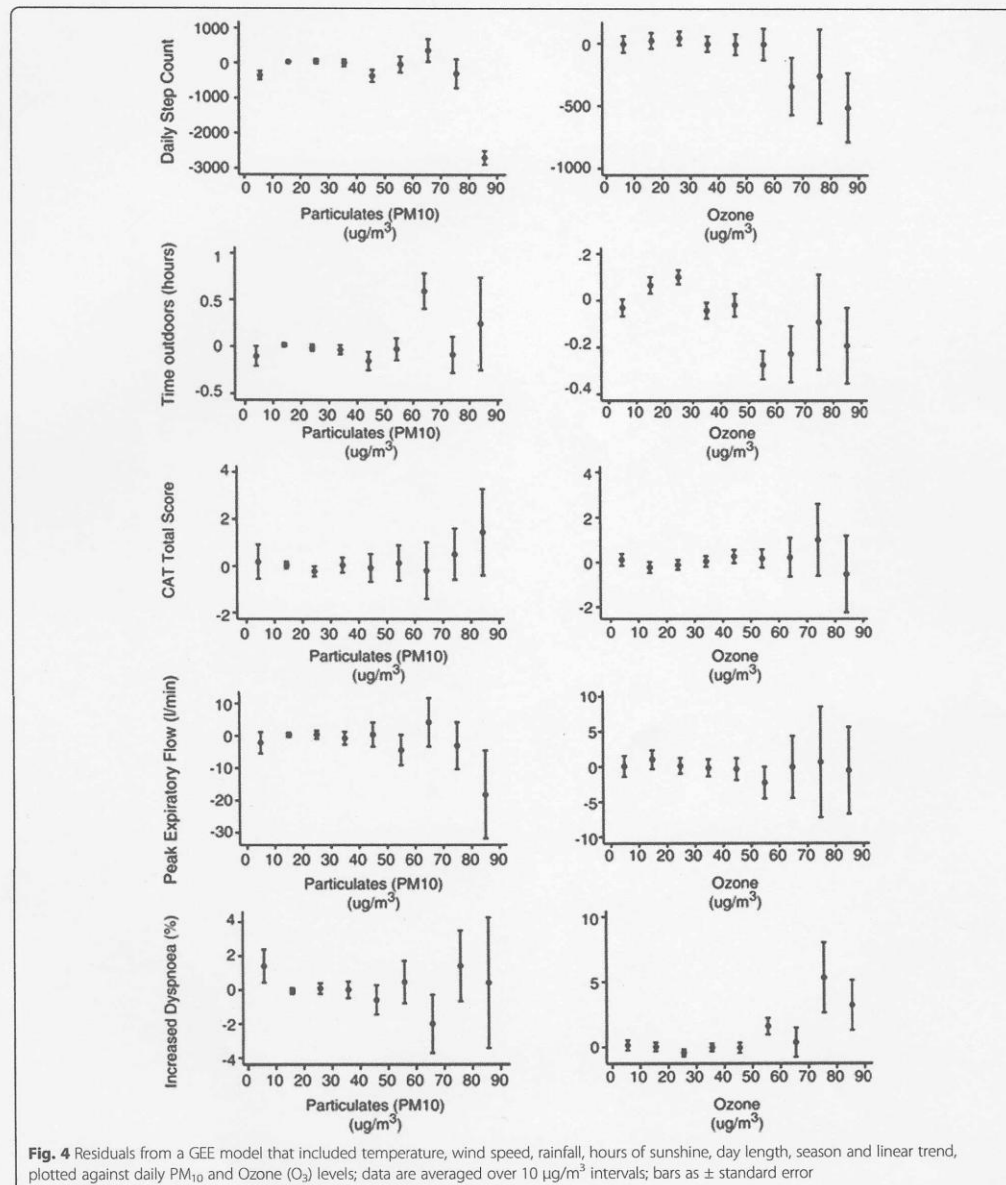
Time spent outdoors fell with higher O<sub>3</sub> levels ( $p < 0.001$ ) for data collected over the whole week, just weekdays ( $p = 0.001$ ) and at weekends ( $p < 0.001$ ). PM<sub>10</sub> show no effects on time spent outdoors on either whole week ( $p = 0.275$ ) or weekdays ( $p = 0.217$ ) or weekends ( $p = 0.502$ ). Dyspnoea increased and PEF fell with higher levels

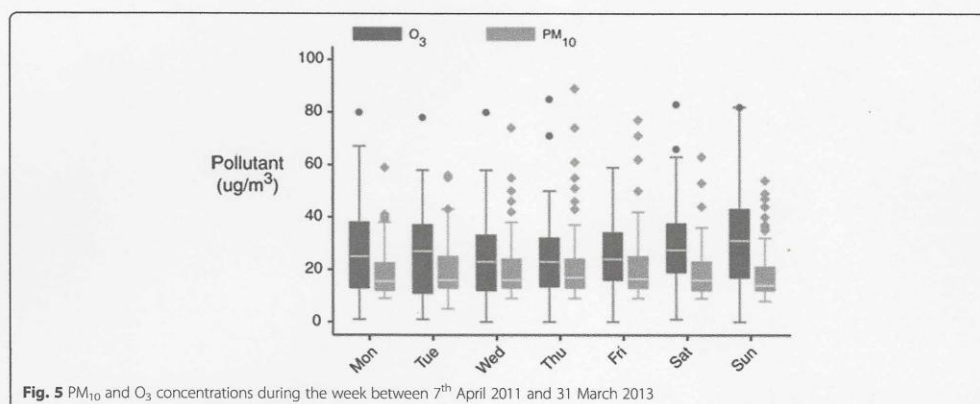
**Table 3** Relationship between pollutants (PM<sub>10</sub> and O<sub>3</sub>) and Daily steps count, hours spent outdoors, health status (CAT score), PEFR, dyspnoea, over the full week including Saturday and Sunday; with allowance for season, linear trend, day-length, temperature, sunshine, rain and wind

	Effect of 1 µg/m <sup>3</sup> PM <sub>10</sub>			Effect of 1 µg/m <sup>3</sup> O <sub>3</sub>		
	Regression coefficient	95 % CI	p-value	Regression coefficient	95 % CI	p-value
Step count	-5.4	-12.2 to 1.3	0.112	-8.0	-13.5 to -2.4	0.005
Hours outdoors	$2.3 \times 10^{-3}$	$-6.5 \times 10^{-3}$ to $1.8 \times 10^{-3}$	0.275	$-9.9 \times 10^{-3}$	$-14.2 \times 10^{-3}$ to $-5.6 \times 10^{-3}$	<0.001
CAT score	$9.8 \times 10^{-3}$	$-19.6 \times 10^{-3}$ to $39.1 \times 10^{-3}$	0.515	$16.0 \times 10^{-3}$	$-14.0 \times 10^{-3}$ to $45.9 \times 10^{-3}$	0.296
PEFR	-0.077	-0.17 to 0.018	0.110	-0.089	-0.18 to 0.001	0.054
Dyspnoea	$-0.41 \times 10^{-3}$	$-8.0 \times 10^{-3}$ to $7.1 \times 10^{-3}$	0.915	$6.6 \times 10^{-3}$	$1.3 \times 10^{-3}$ to $12.0 \times 10^{-3}$	0.015

of  $O_3$  over the whole week ( $p = 0.015$  and  $p = 0.054$  respectively) and for weekdays only ( $p = 0.017$  and  $p = 0.040$  respectively) but not at weekends. No effects of  $PM_{10}$  were observed on daily dyspnoea or PEF. No effects of either pollution were seen on daily CAT score.

Figure 4 shows the residuals after fitting the climatic and other variables plotted against  $PM_{10}$  and  $O_3$ . The plots show little effect of the pollutants on daily step count, time outdoors, PEF and dyspnoea until they





**Fig. 5** PM<sub>10</sub> and O<sub>3</sub> concentrations during the week between 7<sup>th</sup> April 2011 and 31 March 2013

exceed around 60–70  $\mu\text{g}/\text{m}^3$ . CAT score appears unrelated throughout the range of pollutants.

Figure 5 shows that O<sub>3</sub> concentration was significantly higher by 4.6  $\mu\text{g}/\text{m}^3$  and PM<sub>10</sub> levels 1.73  $\mu\text{g}/\text{m}^3$  lower during the weekend ( $p < 0.001$  and  $p = 0.057$  respectively).

### Discussion

This study shows that day-of-the-week, meteorological factors and for the first time that high levels of atmospheric pollutants affect physical activity in COPD patients. The reduction in activity at weekends was not unexpected as this is typically a period of rest. Days that were warm, dry and sunny appeared to encourage patients to go outside and walk more, whereas cold, rainy and overcast days reduced activity. A number of studies have observed that physical activity decreases in healthy adults during the colder, shorter winter months or increases on longer, sunny days [25]. Indeed, some studies have shown seasonal variation in activity in COPD patients [26–28] and is reduced at weekends compared to weekdays [29, 30] but we extend these findings by showing that activity is primarily related to meteorological conditions irrespective of the season.

Our findings are important because COPD patients already have a reduced exercise capacity due to their air-flow limitation. Any further reductions of activity due to the weather or day-of-the-week may worsen muscular de-conditioning which is common in inactive COPD patients. Muscle weakness and feelings of frailty may make the patients feel unable to leave their homes and once this behaviour is established may prove difficult to reverse. It might in part explain why health related quality of life is poorer in winter than spring or summer [31] and measures of anxiety and depression higher in winter [32]. The findings are also important because for the

first time we show an effect of atmospheric pollution on physical activity which was only possible because we studied a group whose air-flow limitation is sufficient to make such effects apparent.

There are mechanisms by which outdoor atmospheric pollution might cause patients to be less active when outdoors. O<sub>3</sub> above 200 ppb can affect peak expiratory flow in elite cyclists during maximal exercise [33] but may not cause problems at low levels [34]. We found that PEF was also reduced only at high levels of O<sub>3</sub> during the weekdays ( $p = 0.040$ ) though it just failed to reach significance over the whole week ( $p = 0.054$ ). Atmospheric pollutants can also produce harmful effects on the airways, such as pulmonary and systemic inflammation [35, 36], reduction in airway ciliary activity [37], increases in bronchial reactivity [38] and airway oxidative stress [39]. Exposure to O<sub>3</sub> can also significantly increase heart rate and blood pressure, as well as causing mitochondrial damage [40]. However, whether patients are aware of these systemic and anatomic effects is not clear. We found that dyspnoea increased with higher O<sub>3</sub> levels but did not find any effect on the CAT quality of life score. Some patients may not have gone outdoors when the pollution levels were high but it is not obvious how the patients knew not to go out. There is little evidence that people alter their behaviour in response to pollutant alerts in the news or from other advisory systems [41]. O<sub>3</sub> is a colourless, odourless, gas which cannot be seen or smelt but its precursors are mainly motor vehicle exhaust fumes might be detected [41]. In London, a pollution haze can be seen on some days [42] but the patients might not live on hills or in high-rise buildings where these observations can easily be made. High levels of O<sub>3</sub> are known to be associated with hot weather which might discourage patients from taking exercise. However, we excluded from the analysis the hottest days



with mean temperatures over night and day exceeding 22.5 °C. Further studies are needed to determine if and how COPD patients can detect increased atmospheric pollution.

The limitations of this study should be discussed. We were not able to assess the intensity of the physical activity. This can be measured with accelerometers but would require weekly or fortnightly clinic visits by patients to download data which was not practical in this long term study. Pedometers can be inaccurate in slow walking individuals but this would be a consistent bias in a given patient and thus unlikely to alter how they respond to changes in pollution or the weather. Another limitation was that we did not collect pedometry data as fully as the PEF or dyspnoea data and we have no control group. Some patients did not wear their pedometer every day, some were lost and/or broken when inadvertently washed and a replacement only possible at their 3 monthly clinic visit. Some patients were excluded because too little data remained after excluding periods of exacerbation. These excluded patients may well have been frequent exacerbators, and thus our findings might not necessarily apply to this group though the exacerbation frequency in the studied group was similar to the 126 patients not included. We have also not examined other weather conditions such as snow or ice, when the risk of slipping might discourage excursions outdoors. It was not practical to monitor the pollution and climate exposure of each individual and thus we assumed that the pollution levels at the monitoring site in Bloomsbury and weather measured at Heathrow were indicative of that experienced by the patient. Previous studies have shown the data at Bloomsbury is correlated with outer suburban sites [43] and similar in temporal evolution to other sites in London [44]. Although, we did not use personal pollution monitors we did collect individual outcome data – and this semi-individual design is considered valid for air pollution studies [45]. In our analysis, we felt it necessary to analyse separately weekdays and weekends as well as the whole week because the “day-of-the-week” effect was very large and may have confounded the results. In many countries,  $O_3$  is significantly higher at weekends compared to weekdays [46–48] whereas  $PM_{10}$  is higher at weekdays [46]. We found similar effects in London. By analysing the data in this way, we reduced the statistical power and this could explain the absence of consistent effects during both weekdays and weekends.

## Conclusions

There are a number of important implications to this work. Patients with COPD should be encouraged to increase physical activity as pulmonary rehabilitation reduces breathlessness, improves quality of life and exercise

tolerance. Inactivity is greatest during cold weather and perhaps pulmonary rehabilitation programmes should be targeted in the winter to limit this inactivity. Activity is also reduced at weekends and patient education should encourage patients to maintain activity on these days. This study provides evidence of an effect on the daily activity of COPD patients of atmospheric pollution at higher levels and public health schemes to reduce levels of atmospheric pollution should be further encouraged.

## Additional file

**Additional file 1: Influence of weather and atmospheric pollution on physical activity in patients with COPD.**

## Abbreviations

COPD: Chronic obstructive pulmonary disease; PEF: Peak expiratory flow; PR: Pulmonary rehabilitation; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity;  $PM_{10}$ : Particulate matter <10  $\mu m$  in diameter; BMI: Body mass index; CAT: COPD assessment test;  $O_3$ : Ozone; GEE: Generalised estimating equations; ANOVA: Analysis of variance; GOLD: Global initiative for chronic obstructive lung disease; SEM: Standard error of the mean; IQR: Inter quartile range; SD: standard deviation.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

AA, JW, GD designed the study and analysed the data; AA, AM, AP, BK, RS, SB, JA saw patients in clinic and collected data; AA, AM, AP, BK, RS, SB, JA, JW and GD contributed to interpretation and drafting the manuscript for important intellectual content. All authors read and approved the final manuscript. COPD: Epidemiology.

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## Abstracts arising from this Thesis

- 1) **AD Alahmari**, BS Kowlessar, ARC Patel, AJ Mackay, R Singh, SE Brill, JP Allinson, JA Wedzicha, GC Donaldson . Determinants of the reduction in physical activity and capacity with COPD exacerbations. 2015 American Thoracic Society, Denver, Colorado, USA.
- 2) **AD Alahmari**, BS Kowlessar, ARC Patel, AJ Mackay, R Singh, SE Brill, JP Allinson, JA Wedzicha, GC Donaldson . Exercise capacity and systemic inflammatory changes during stability and exacerbation recovery in COPD patients. 2015 American Thoracic Society, Denver, Colorado, USA.
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