FALLS IN PEOPLE WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE: RISK FACTORS, INCIDENCE AND IMPACT ON HEALTH RELATED QUALITY OF LIFE

by

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Abstract

Introduction

People with chronic conditions show increased susceptibility to falls, however, little is known about the risk factors, incidence and impact of falls on people with chronic obstructive pulmonary disease (COPD).

Purposes

The purposes of this thesis were to:

1) provide a theoretical framework for identifying risk factors for falls in COPD.

2) compare physical risk factors for falls in people with COPD and healthy people and;

3) determine risk factors, incidence and impact of falls on health related quality of life (HRQoL) in COPD.

Methods

The first study (Chapter 2) was a literature review for identifying risk factors for falls in COPD. The second study (Chapters 3-6) was a cross sectional design that compared 21 people with COPD and 21 healthy participants. We investigated: 1) thigh muscle strength, cross sectional area (CSA) and quality; 2) functional performance, including the Self-Selected Gait-Speed, Stair Climbing Power, Repetitive Sit-To-Stand, Timed Up-and-Go and Six-Minute Walk tests; 3) postural control using the Sensory Organization Test. The third study (Chapter 7) was a 6-month prospective survey study that investigated fall incidence and HRQoL as reflected by the Health Survey Short Form (SF-36) and the Chronic Respiratory Questionnaire (CRQ) in 101 people with COPD.
Results

Chapter 2: Risk factors for falls are present in COPD. Chapter 3-6: People with COPD showed deficits in knee extensors muscle strength ($p<0.016$), CSA ($p=0.008$) and quality ($p=0.003$) as well as knee flexors concentric strength ($p=0.024$) and quality ($p=0.005$). Functional performance ($p<0.002$) and postural control ($p=0.014$) were reduced in people with COPD. Chapter 7: People with COPD showed an incidence rate of 0.1 falls per person-month (95% CI: 0.06 to 0.14). Fallers showed lower scores in the baseline physical domains of HRQoL. Falls appeared to lower the dyspnea domain of the CRQ ($p=0.017$). Predictors of falls in COPD were: the number of previous falls (OR=7.36), coronary heart disease (OR=7.07), female gender (OR=3.73) and age (OR=1.09).

Conclusions

Risk factors and incidence of falls are increased in people with COPD and can result in significant deterioration of HRQoL related to dyspnea. Fall prevention strategies in people with COPD are recommended.
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List of Abbreviations

ADLs: Activities of daily living
AP: Anterior-posterior
ATS: American Thoracic Society
BMI: Body mass index
CCHS: Canadian community health survey
CI: Confidence interval
COG: Center of gravity
COPD: Chronic obstructive pulmonary disease
CRQ: Chronic respiratory questionnaire
CSA: Cross sectional area
CT: Computerized tomography
DEXA: Dual-energy x-ray absorptiometry
ERS: European Respiratory Society
FEV₁: Forced expiratory volume in the 1st second
FVC: Forced vital capacity
GOLD: Global initiative for obstructive lung disease
HRQoL: Health related quality of life
HU: Hounsfield units
ICC: Intraclass correlation coefficient
IF: Intramuscular fat
IR: Incidence rate
MRI: Magnetic resonance imaging
N: Newton
NIH: National Institute of Health
O₂: Oxygen
OR: Odds ratio
P₂₅: 25th percentile
P₇₅: 75th percentile
PASE: Physical activity scale of the elderly
POH: Postural orthostatic hypotension
QoL: Quality of life
RSTS: Repetitive sit-to-stand
RT: Resting twitch
RR: Risk ratio
SCPT: Stair climbing power test
SD: Standard deviation
SF-36: Health survey short form
SOT: Sensory organization test
SPECT: Single photon emission computed tomography
SPSS: Statistical package for the social sciences
SSGS: Self-selected gait speed
ST: Superimposed twitch
SWT: Shuttle-walk test
PT: Potentiated twitch
**TUG**: Timed up-and-go
**WHO**: World Health Organization
**6MWT**: Six-minute walk test
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I would also like to dedicate this thesis to my parents. I wish I could give my children half the love and education you have given me. I have been very lucky to have your support all these years. Thank you. I love you too.

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Co-Authorship Statement

Published papers

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Contribution: 80% - Marc Roig and Dr Reid provided study concept and design, study coordination, data analysis and manuscript preparation. Dr Reid was the key editor on this manuscript. Drs Eng, MacIntyre and Road provided support at all steps of the research process and critically reviewed the manuscript before submission.

Submitted papers

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Contribution: 80% - Marc Roig and Dr Reid provided study concept and design, study coordination, data analysis and manuscript preparation. Dr Reid was the key editor on this manuscript. Drs Eng, MacIntyre and Road provided support at all steps of the research process and critically reviewed the manuscript before submission.

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Chapter One: Statement of the Problem

1.1 Introduction

1.1.1 Definition of COPD

Chronic obstructive pulmonary disease (COPD) is defined as “a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases”.1 The two most common manifestations of COPD are chronic bronchitis and emphysema. Chronic bronchitis is characterized by the obstruction of small airways due to inflammation and hypersecretion of mucus while emphysema is characterized by enlargement of air spaces, destruction of the lung parenchyma, increased lung compliance and obstruction of small airways. Both manifestations can be accompanied by lung fibrosis and bronchospasm.2 Although people with COPD tend to show a tendency towards either chronic bronchitis or emphysema, most patients present with some degree of both processes.

1.1.2 Epidemiology of COPD

1.1.2.1 Prevalence of COPD Worldwide

In 2002, the World Health Organization (WHO) estimated that COPD was the fifth leading single cause of death worldwide. It is expected that mortality from COPD will continue to increase by more than 30% in the next 10 years, such that it will become the third leading single cause of death by 2020.3 In 2007, approximately 210 million people were diagnosed with COPD worldwide.3 It is
estimated that, globally, the prevalence of COPD is 11.6/1000 men and 8.77/1000 women, however, due to the increasing rates of smoking among women, COPD rates are currently rising much faster in this latter population.³ Although the overall prevalence and associated socio-economic impact of this respiratory disease is expected to increase worldwide, the local incidence of COPD varies substantially between different countries.⁴

1.1.2.2 Prevalence of COPD in Canada

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading single cause of death in Canada and it is projected that it will be the third cause of death for both males and females by 2020.⁵ While estimates of the specific prevalence of COPD vary depending on the diagnostic criteria and measurement methods applied,⁶ estimates in a 2005 report state that between 1.6% and 11.8% of the adult population of Canada suffers from COPD.⁷ The breadth of this range is multifactorial, stemming, in part, from the disparity in prevalence reports between Canadian provinces and the uncertainty surrounding the frequency of undiagnosed cases. In 2005, for example, 4.4% (3.9% of men and 4.8% of women) of adults over the age of 34 surveyed in the Canadian Community Health Survey (CCHS) reported that they had been diagnosed with COPD by a physician while estimates for Canadian aboriginal people living off reserve in Canada suggests that 7.9% of this population has COPD. Further, while it is estimated that there are more than 1.6 million people in Canada
diagnosed with COPD, the actual number might be double after considering the people with COPD that remain undiagnosed.\textsuperscript{5}

### 1.1.3 Aetiology of COPD

The mechanisms underlying the development of COPD are complex and determined by the action of a number of various risk factors acting either alone or synergistically. The most important of these is cigarette smoking, ranking as the leading cause of COPD. However, a significant proportion of smokers (~40%) never develop COPD and more than 25% of COPD related mortality occurs in non-smokers.\textsuperscript{8} Thus, other factors must play a role in the development of the disease. Indeed, the WHO estimates that 400,000 COPD related deaths per year arise from exposure to air pollution from biomass fuels – a risk factor especially prominent in developing countries with rising levels of industrialization.\textsuperscript{3} Occupational exposures,\textsuperscript{9} respiratory infections,\textsuperscript{10} bronchial hyper-responsiveness\textsuperscript{6} and genetic alterations such as $\alpha$-1 antitrypsin deficiency\textsuperscript{11} are other important risk factors predisposing people to COPD.

### 1.1.4 Natural History and Characteristics of COPD

The presentation, development and course of COPD can not easily be reconciled into a single, typical pattern.\textsuperscript{12} This discordance might be due to the multi-systemic nature of the disease, the different levels of exposure, the partial reversibility of the symptoms and the diversity of genetic predispositions to COPD. While the specific onset of the disease is difficult to pinpoint, it is
generally agreed that COPD typically begins following prolonged exposure to a noxious agent (e.g., tobacco, air pollution). In response to these toxic offences, the respiratory system initiates a cascade of events including inflammation of the respiratory airways, increased mucus production and an overall reduction in elasticity of the pulmonary parenchyma. All of these changes increase the resistance to air flow and produce a progressive reduction in respiratory capacity. This ventilatory impairment is further aggravated by symptoms such as exertional dyspnea, coughing and wheezing. Although the severity of these symptoms typically increases as the disease advances, COPD is characterized by episodic exacerbations that augment the magnitude of these symptoms and negatively impact the course of the disease.

1.1.5 Systemic Effects of COPD

Chronic obstructive pulmonary disease (COPD) is associated with a multitude of non-respiratory systemic effects that may contribute to disease severity in individual patients. These effects include, but are not limited to, skeletal muscle dysfunction, systemic inflammation, nutritional abnormalities and weight loss. Cardiovascular problems, neurological impairments and metabolic alterations are also commonly associated with COPD. Due to the progressive nature of COPD, both disease-specific and age-related factors likely contribute to the functional limitations encountered among people with COPD.
Exertional dyspnea, the most common and disabling symptom of COPD, is characterized by the rapid onset of breathlessness and fatigue even during light activities of daily living (ADLs). In order to minimize the effects of this respiratory distress, patients with COPD tend to reduce their physical activity, thus leading to progressive deconditioning, further impairing their overall physical wellness. In some cases, extreme deconditioning, further leads to the patient becoming confined to bed or at home. This, in turn, is thought to affect social participation and, over the long term, to produce isolation and depression. With disease progression, systemic effects become increasingly evident and burdensome. In addition, end-stage COPD individuals are often affected by other age related co-morbidities that themselves compromise their health status, reduce their functional independence and increase the risk of mobility accidents such as falls.

1.1.6 Falls in COPD

Falls are a notable health problem with devastating consequences for older adults. With a strong tendency to engender devastating consequences, including reduced functional capacity, morbidity and mortality, falls have a significant economic impact on health and social systems alike. Falls are incriminated as the most common cause of injury and mortality among seniors. In 2004, for example, falls were identified as the leading cause of injury-related hospitalizations and deaths among seniors in Canada. It is estimated that 30% to 50% of people aged 65 years old or older fall at least once a year. The
estimates of falls prevalence, however, vary considerably with the individuals’ age, the definition of a fall and the methods used for recording fall events.\textsuperscript{29} Of interest for the purposes of this thesis, people with chronic conditions tend toward a greater susceptibility for falls.\textsuperscript{30} Intrinsic risk factors for falls commonly associated with chronic conditions include, for example, aspects related to physical deconditioning such as lower limb muscle weakness as well as deficits in mobility and postural control.\textsuperscript{27,28} Other predisposing risk factors for falls that are commonly reported in people with chronic conditions include the use of multiple medications\textsuperscript{31-33} and associated comorbidities such as depression.\textsuperscript{34}

A cursory analysis of the pathophysiological features of COPD suggests that people with COPD harbor many of the fall risk factors identified in older individuals, including, for example, muscle weakness,\textsuperscript{35} medications,\textsuperscript{36} depression,\textsuperscript{25} and polyneuropathy.\textsuperscript{19-21} It is reasonable to speculate, therefore, that people with COPD might be at higher risk of experiencing frequent falls compared to their healthy peers. However, whether disease-specific risk factors for falls exist in COPD or whether generic risk factors for falls and incidence of falls are increased in people with COPD compared to age-matched healthy individuals is currently unknown. More importantly still, the impact of falls on the quality of life (QoL) of these individuals has not yet been investigated.
1.1.7 Quality of Life (QoL) and Health Related Quality of Life (HRQoL) in COPD

1.1.7.1 Definition of QoL and HRQoL

Quality of Life (QoL) is defined as “a holistic and self-determined evaluation of satisfaction with issues important to the person”.\textsuperscript{37} Since QoL is considered a multidimensional and dynamic construct\textsuperscript{38} and its conceptualization may differ substantially depending on subjective experiences,\textsuperscript{39} the term health related quality of life (HRQoL) has emerged in the literature. Health related quality of life (HRQoL) represents a much narrower concept that refers specifically to the physical, psychological and social domains of health care that are unique to each individual.\textsuperscript{40} In other words, “HRQoL measures the impact of the disease on ADLs and the individual’s sense of well-being”.\textsuperscript{24} Even though the use of HRQoL measurements may help clinicians and researchers evaluate the impact of rehabilitation on different aspects of patients’ health status and overall well-being, methods of evaluation and their underlying rationale differ considerably.

1.1.7.2 Impact of COPD on QoL and HRQoL

There exist only a few comparative observational studies that have analyzed HRQoL in people with COPD compared to either healthy individuals or people with other chronic disorders.\textsuperscript{41} Similarly, relatively little attention has been given to the burden of COPD on family members and caregivers’ HRQoL.\textsuperscript{42} There are, however, a great number of studies which have introduced HRQoL
measurements to evaluate the effect of specific interventions (e.g., medications, exercise) on the overall health status of people with COPD. In order to fully appreciate the many aspects influencing HRQoL in people with COPD, the reader of this thesis is encouraged to review the personal testimony of a person with COPD. This personalized account describes in detail the impact of this disease on the different dimensions of HRQoL (e.g., physical, psychological, social).

People with COPD suffer from profound physical limitations secondary to the rapid onset of exertional dyspnea during ADLs. Numerous studies have shown that the prevalence of psychological alterations such as depression or anxiety is likely to be high among these individuals. Although little research, to date, has systematically investigated the social functioning of these individuals, it is widely assumed that their poor physical status as well as their psychological alterations limit their capacity to engage in social activities. In summary, COPD, similar to many other chronic diseases, is believed to have a profound multidimensional impact on HRQoL of people suffering from this disease.

1.1.7.3 Justification for Inclusion of HRQoL Assessment in COPD

There are several advantages in measuring HRQoL in people with COPD, making it a useful tool in the overall assessment of this population. First, the measurement of HRQoL in COPD is based on the outcomes model, which in contrast to the biomedical model, is more appropriate for the
assessment of individuals with chronic conditions. While the biomedical model links benefit to changes among the diagnostic criteria of a disease, the outcomes model places great value on the patient’s own testimony, HRQoL, and their life expectancy. Since people with chronic conditions such as COPD usually have to live with the disease indefinitely, the patient-focused perspective of the outcomes model is appealing in its ability to monitor overall progressive impact of the disease on these patients’ HRQoL.

Second, HRQoL can serve as a measurement to discriminate between people with different health statuses. Indeed, when differentiating between people with COPD based on their HRQoL, some studies have reported that the stage of the disease, categorized as the level of pulmonary impairment, does not reliably correlate with the individual’s self-perceived health status, suggesting that traditional diagnostic tools based exclusively on physiological parameters (e.g., pulmonary function tests) fail to detect some variables relevant to influencing HRQoL in these people. Health-related quality of life (HRQoL) measurements have also been used to assess changes in health status following a specific treatment (evaluative measurement) to determine whether these changes are clinically meaningful. For example, recent studies assessing pharmacological interventions have shown these interventions to increase perceived HRQoL in people with COPD.
Third, the use of HRQoL measures improves the capacity of patients to express what is relevant to them, thus facilitating effective communication between them and their care providers. Effective communication is especially important to ensure the early detection of COPD and to target effective therapies that will help mitigate the symptoms experienced by these individuals. In addition, effective communication improves the capacity of researchers to identify the impact of specific aspects of the disease on the patients’ HRQoL and thus improve shared clinical decision-making between clinicians and patients.

1.2 Rationale of the Thesis

The specific risk factors for falls, the incidence of falls and the impact of falls on HRQoL in people with COPD are currently unknown. Recent research underscores the importance of identifying risk factors for falls in order to design effective preventive strategies.\textsuperscript{53} Risk factors for falls that are typically targeted in rehabilitation include measures of muscle strength and mass, functional performance and postural control. If people with COPD have an increased risk for falls, these measures would be expected to be impaired in comparison to healthy people. Furthermore, since measures of muscle and functional performance,\textsuperscript{54} as well as postural control,\textsuperscript{55} are correlated in older adults, it is of paramount importance to determine whether these associations are also common in people with COPD compared to healthy counterparts. Such measures might be used to detect early signs of decreased mobility and also be used as responsive measures, before and after training interventions, to enhance
mobility and reduce fall risk in people with COPD.

The study of the risk factors for falls in people with COPD, however, lacks clinical relevance if these individuals do not show increased susceptibility to falls. Since falls are increased in patients with chronic conditions, it is expected that fall incidence in people with COPD is also high. In view of the association between risk factors for falling and HRQoL, it is also expected that an increased fall incidence might also have negative effects on the HRQoL of people with COPD. Hence, ascertaining the risk factors for falls, the incidence of falls and potential associations between falls and HRQoL might be critical in determining the clinical relevance of preventing falls in people with COPD.

1.3 Objectives and Hypotheses of the Thesis

An overview of the studies, objectives, hypotheses and outcomes of this thesis are outlined in Figure 1.1. The content of this thesis is organized into three major studies with three main objectives. The specific objectives and hypotheses of each study are outlined below.

1.3.1 Study I: Falls in People with COPD: A Call for Further Research (Chapter 2).

Objective 1: to provide a theoretical framework for identifying potential risk factors that could increase fall incidence among people with COPD.
Hypothesis 1: Well-established risk factors for falls identified in older people will be common in people with COPD.

1.3.2 Study II: Risk Factors for Falls in People with COPD (Chapters 3-6).

Objective 2: to determine if there are differences in measures of knee extensors and flexors muscle strength (torque), cross sectional area (CSA) and quality (i.e., intramuscular fat) and functional performance between 21 people with COPD and 21 healthy control subjects matched for age, gender and body mass (Chapters 3 and 4).

Hypothesis 2: People with COPD will show greater deficits in measures of knee extensors and flexors muscle torque, CSA and quality (i.e., intramuscular fat), as well as functional performance, compared to healthy control subjects.

Objective 3: to determine differences in the associations between measures of muscle and functional performance in people with COPD and healthy control subjects matched for age, gender and body mass (Chapters 3 and 4).

Hypothesis 3: Measures of knee extensors muscle torque, CSA and quality will be associated with measures of functional performance in people with COPD and healthy control subjects.

Objective 4: to determine if there are differences in muscle activation of knee extensors between 12 people with COPD and 13 healthy control subjects (Chapter 5).

Hypothesis 4: Muscle activation will be reduced in people with COPD compared to healthy control subjects.
Objective 5: to determine if there are differences in postural control between 20 people with COPD and 20 healthy control subjects matched for age, gender and body mass (Chapter 6).

Hypothesis 5: People with COPD will show greater deficits in postural control compared to healthy control subjects.

1.3.3 Study III: Fall Incidence and Impact on HRQoL in People with COPD (Chapter 7).

Objective 6: to investigate fall incidence, risk factors and impact of falls on HRQoL in 101 people with COPD during 6 months.

Hypothesis 6: People with COPD will show a high incidence of falls and fallers will have decreased scores in measures of HRQoL compared to non-fallers after the 6-month period.
Figure 1.1 Schematic view of overall objectives, hypotheses and outcomes of the studies of the thesis.

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Chapter Two: Falls in People with COPD: A Call for Further Research.¹

2.1 Introduction

Chronic obstructive pulmonary disease (COPD) is a respiratory disease characterized by progressive, partially reversible airflow limitation, which results from an emphysematous destruction of the lung parenchyma and increased airway resistance due to inflammation, bronchospasm and increased mucous production. Despite being formerly considered a disease affecting the lungs, it is now well recognized that people living with COPD also suffer from many non-respiratory manifestations including skeletal muscle dysfunction, systemic inflammation, nutritional depletion and malnutrition.¹⁻⁴ Cardiovascular problems (e.g., coronary heart disease),⁵ neurological impairments (e.g., polyneuropathy),⁶⁻⁸ and metabolic disorders (e.g., osteoporosis)⁹ are also commonly associated with COPD as are psychological alterations such as depression and anxiety.¹⁰⁻¹³ While the presentation, development and manifestations of COPD are highly variable from patient to patient, the severity of the disease typically progresses as the patient ages.¹⁴ As such, age-related physiological changes and co-morbidities can compound the pathophysiological challenges generally observed in people with COPD.

¹ A version of this chapter has been published. Roig M, Eng JJ, Road JD, Reid WD. Falls in people with chronic obstructive pulmonary disease: a call for further research. Respiratory Medicine 2009;103:1257-69.
Falls, which are common among older people, can have devastating effects on overall function, health related quality of life (HRQoL) and life expectancy. Although chronic conditions have been commonly associated with a higher risk for falling, the potential implications of both respiratory and non-respiratory manifestations of COPD on the fall risk of these individuals have not been systematically examined. Furthermore, studies specifically analyzing the incidence of falls among people with COPD are lacking. To date, only one fall-risk study has included people diagnosed with COPD. In this large cross-sectional retrospective study (4050 older women), a linear trend of increasing fall risk with increasing number of chronic diseases was found (OR=1.37; 95% CI: 1.25 to 1.49). More importantly, COPD was found to be one of the leading conditions associated with number of falls, second only to osteoarthritis. Because this study did not specifically include neurological conditions commonly associated with high prevalence of falls such as stroke or Parkinson’s disease, whether people with COPD have an increased risk for falling compared to these patients is currently unknown.

Recent research has highlighted the importance of identifying risk factors for falls in order to enhance prevention. Given the scarcity of studies specifically assessing contributing factors for falls in people with COPD, this review aims to provide a theoretical framework to identify potential risk factors that could increase fall incidence among these individuals. We report the pathophysiological manifestations (i.e., respiratory and non-respiratory) commonly observed in
COPD and well-established risk factors for falls to study any potential association. In an attempt to evaluate the relevance of independent risk factors for falls in COPD, the evidence behind each risk factor will be categorized into three different levels: established, possible and theoretical. The number of studies and their methodological quality will determine the level of evidence. The clinical relevance of this review lies in identifying specific risk factors for falls in people with COPD, which may facilitate the design of appropriate rehabilitation strategies to prevent falls.

### 2.2 Risk Factors for Falls

To analyze the different aspects that can increase fall occurrence in people with COPD, we propose the use of a framework (Figure 2.1) that includes intrinsic and precipitating factors for falls. Intrinsic factors include those related to the physical and psychological status of the individual: muscle weakness, gait, balance, visual deficits, use of an assistive device, impaired activities of daily living (ADLs), depression and cognitive impairments. Medications are also considered an intrinsic factor due to their inextricable impact on the physical and psychological well-being of the individual. In addition, nutritional depletion and malnutrition, which are common in people with COPD, are also included as potential intrinsic factors. Precipitating factors are acute episodes (e.g., syncope and postural hypotension) that might increase the risk for falls. Exacerbations and dyspnea, which are common in COPD, are also included as potential precipitating factors. Although falls can also be affected by extrinsic factors such
as environmental hazards (e.g., stairs and poor lighting), this framework only analyzes intrinsic and precipitating factors that may increase fall risk in people with COPD. Due to the ensuing multitude of possible risk factors for falls in COPD, the proposed framework outlines potential interactions among these factors (Figure 2.1). This framework may prove useful to identify potential risk factors for falls in both clinical practice and research.

2.2.1 Intrinsic Factors

2.2.1.1 Muscle Weakness

Clinical trials\textsuperscript{25,26} and systematic reviews\textsuperscript{27} have shown strong correlations between fall incidence and lower limb muscle weakness. Muscle strength is thought to be an essential factor in maintaining postural control and minimizing postural sway,\textsuperscript{28,29} both of which are important in preventing older people from falling.\textsuperscript{23} Muscle power, which appears to be more closely related to postural control (e.g., single-leg stand and postural sway)\textsuperscript{30} and functional performance (e.g., stair climbing and comfortable gait speed)\textsuperscript{31-34} than muscle strength, might be even more important to prevent falls.\textsuperscript{35,36}

Muscle strength and endurance are reduced in people with COPD compared to healthy controls. Lower limb muscles, which are actively involved in fall avoidance strategies, are preferentially impaired in these individuals.\textsuperscript{37} For example, Mathur et al., found that a group of people with moderate to severe COPD (FEV\textsubscript{1}=51 ± 17% predicted) had reduced volume (~25%), strength
(~25%), and increased intramuscular fat (~35%) of the thigh muscles, when compared to a healthy control group matched for age, gender and body mass. All these factors (i.e., reduced muscle volume, strength and increased intramuscular fat) have been associated with an increased loss of function and mobility in older adults.

Muscle endurance is reduced in people with COPD compared to healthy controls. For example, one study assessed muscle endurance through a protocol in which participants had to perform 100 sub-maximal knee extensions. While the control group was able to complete the protocol (i.e., 100 sub-maximal knee extensions), a large percentage (~43%) of people with COPD were not able to do so. Reduced muscle endurance in COPD is important because it reflects increased muscle fatigability, which has been associated with impaired postural control assessed by single-leg stand in young adults. At the functional level, muscle activation measured with magnetic stimulation has been found to be significantly lower in people with severe COPD (FEV₁=29 ± 9% predicted) compared to controls (89 ± 20% versus 109 ± 6%; p<0.01). Other common structural muscle abnormalities in COPD also include muscle fibre atrophy (most notably in fast twitch type II fibres), reduced capillary density, mitochondrial dysfunction and a lower proportion of oxidative enzymes. Taken together these abnormalities indicate an overall decline in both the contractile and oxidative capacity of lower limb muscles in people with COPD.
Muscle power, defined as the product of force and velocity of muscle contraction, has not been investigated in people with COPD. However, given that strength and power are so highly correlated,\(^4\) it is unlikely that people with COPD, with compromised muscle strength, could have normal values of muscle power. The preferential atrophy of fast twitch type II fibres in the lower limb muscles of these individuals\(^4\) is indicative of decreased ability to perform activities involving fast and powerful muscle contractions.\(^5\) Given the importance of muscle function in the prevention of falls, it is possible that the reductions of muscle strength, and presumably power, in people with COPD could predispose this population to fall (\textit{Table 2.1}).

\textbf{2.2.1.2 Gait Deficits}

Since falls are reported to occur mainly during walking activities,\(^5\)\(^,\)\(^6\) it is not surprising that gait deficits had been associated with disability and falls in older adults.\(^5\)\(^,\)\(^3\) Gait deficits have been commonly assessed both quantitatively (e.g., speed and distance) and qualitatively (e.g., gait variability and instability). Quantitatively, gait speed has usually been assessed by measuring the time required to walk a number of meters (5-8 m) either at comfortable (self-selected) or fast gait speeds.\(^5\)\(^4\) Lowered comfortable gait speed ($<1\text{m}\cdot\text{s}^{-1}$) measured over an 8 m walkway, has been found to be strongly associated with an increased risk for falls (RR=5.4; 95% CI: 2.0 to 14.3) in seniors aged 75 years old and older.\(^5\)\(^5\) Consistent with reduced gait speed, the time required to walk 400m has also
shown to be significantly larger in a group of fallers compared to non-fallers (338 ± 65.8s vs. 330.5 ± 60s; p<0.05).\textsuperscript{56}

Only a few studies have reported gait speed impairments in people with COPD. For example, Butcher et al.,\textsuperscript{57} reported that fast gait speeds measured over a 6 m walkway were significantly lower (~28\%) in oxygen-dependent people with COPD (FEV\textsubscript{1}=29.9 ± 3.7\% predicted) compared to a healthy control group. Although the values obtained by this group of people with COPD (1.53 ± 0.11m·s\textsuperscript{-1}) are well above the threshold for fall risk established in older adults (<1m·s\textsuperscript{-1}),\textsuperscript{55} it should be taken into account that in this study,\textsuperscript{57} gait speed tests were performed at fast, not comfortable gait speeds. Average values of fast gait speed for healthy elderly (<60 years) range from 0.84 m·s\textsuperscript{-1} to 2.1 m·s\textsuperscript{-1}.\textsuperscript{54} Since normative data on comfortable gait speed in people with COPD are not yet available, more studies are required to establish average measures of gait speed and specific values prognostic of an increased fall risk in COPD.

Another quantitative approach commonly used to evaluate gait deficits consists of measuring walking distance. Although walking distance is intrinsically related to gait speed and stride length,\textsuperscript{58} the association between reduced walking distance and increased fall risk in older adults has not been directly investigated. Depending on the level of impairment, walking distance tests such as the six-minute walk test (6MWT) or the shuttle walk test (SWT) provide good estimates of endurance/aerobic capacity\textsuperscript{59} and overall functional performance.\textsuperscript{60}
For example, walking distance in the 6MWT has been correlated to peak oxygen consumption ($r=0.63$ to $0.79$) in people with COPD$^{61}$ and measures of muscle function commonly associated with increased fall risk such as strength ($R^2=0.38$) and peak power ($R^2=0.48$) of lower limbs in older adults.$^{62}$ Given these associations, it is likely that shorter walking distance might be correlated to increased fall risk.

Unlike gait speed, shorter walking distance has been extensively reported in people with COPD.$^{63}$ For example, people with end-stage emphysema have shown a lower 6MWT walking distance (235.1 ± 92 m)$^{64}$ compared to reference data (~535 m) from healthy older adults (~61 years).$^{65}$ While these studies indicate that gait impairments are not uncommon in people with COPD, and therefore, that increased fall risk associated with gait deficits might be possible (Table 2.1), qualitative studies$^{58}$ assessing gait kinematics (e.g., variability and instability) associated with fall risk in these individuals are lacking.

### 2.2.1.3 Balance Deficits

Postural control is mainly determined by the interaction of three major sensory systems: vestibular, somatosensory and visual.$^{66,67}$ Postural control is critical in preventing older people from falling.$^{20}$ A recent meta-analysis of 16 controlled studies ranked balance disorders as the second most important individual risk factor for falling following lower limb muscle weakness.$^{68}$ Not
surprisingly, balance training has shown to be effective in lowering fall risk in this population.\textsuperscript{69}

Unlike walking distance and muscle strength, postural control has not been extensively investigated in COPD. A prospective cohort study investigating postural control in people with COPD (FEV\textsubscript{1}=62 $\pm$ 23\% predicted) found a significantly reduced performance (9\%; \(p<0.0017\)) in the Functional Reach Test when the COPD group (\(n=1202\)) was compared with the control group (\(n=302\)).\textsuperscript{63} The Functional Reach Test is a clinical measure of balance that measures how far a subject can reach forward beyond arm’s length using a fixed base of support (i.e., feet on the floor) without losing balance.\textsuperscript{70} Another study showed significantly lower scores in the Community Balance and Mobility Scale in two groups of people with moderate (FEV\textsubscript{1}=45.7 $\pm$ 3.7\% predicted) and severe (FEV\textsubscript{1}=29.9 $\pm$ 3.7\% predicted) COPD compared to a healthy control group.\textsuperscript{57} However, differences among groups in postural sway measured through dynamic posturography were not significant. Chang and colleagues investigated standing postural sway before and after a sub-maximal exercise task (6MWT) in a group of 19 people (69 $\pm$ 9 years) with COPD (FEV\textsubscript{1}=46\% predicted).\textsuperscript{71} Postural sway was significantly increased after the 6MWT, which suggests that, as shown in other studies with healthy individuals,\textsuperscript{43,44} fatigue may worsen postural control in people with COPD. More importantly, when compared to a fall-risk study that used similar balance tests in 156 older adults (76.5 $\pm$ 5.1 years),\textsuperscript{72} Chang et al., found that the values of lateral postural sway measured at baseline in the COPD
group were similar to those with a history of falls. In spite of the small number of studies assessing postural control in COPD, these preliminary results suggest that increased fall risk secondary to balance deficits in these individuals may be present (Table 2.1).

The underlying mechanisms for the increased postural sway observed in people with COPD are currently unknown. Although vestibular deficits are unlikely, somatosensory deficits could contribute to impaired balance in this group. For example, studies evaluating polyneuropathy in people with COPD have shown that the presence of nerve conduction abnormalities is not uncommon, especially in the most disabled individuals. Appenzeller et al., reported reduced peroneal nerve conduction velocity in people with severe COPD. Another study revealed electrophysiological disturbances in the motor and sensory nerves of 23 people with severe COPD (FEV₁ < 50% predicted). In a more recent study, 5 out of 30 people with moderate COPD (FEV₁ < 80% predicted) showed signs of axonal neuropathy (smaller amplitude potentials, increased latency, decreased conduction velocity) compared to an age-matched group but these anomalies were only significant in the afferent nerves of the most impaired patients. Interestingly, the majority of studies assessing nerve conduction in COPD show that polyneuropathy affects preferentially the sensory nerves of the lower limbs.
Polyneuropathy has a profound impact on the somatosensory system and people with polyneuropathy show deficits in postural control as assessed by single-leg stance,\textsuperscript{76} gait (i.e., speed, kinematics and efficiency),\textsuperscript{77} lower limb muscle function (i.e., peak velocity and strength),\textsuperscript{78} in addition to a high prevalence of falls.\textsuperscript{79,80} Unfortunately, to date no studies have specifically examined the prevalence of polyneuropathy in a large cohort of people with COPD. Moreover, the impact that polyneuropathy may have on proprioception, reaction time, muscle activation and postural control in people with COPD is unknown.

\subsection*{2.2.1.4 Visual Deficits}

Visual deficits have been associated with an increased risk for falling in older adults.\textsuperscript{81,82} For example, in a large prospective cohort study with 2002 older women, Coleman et al., reported that the odds of experiencing a fall were approximately two times greater for those with loss of vision.\textsuperscript{83} In other studies, the relative fall risk in people with visual deficits compared to people without visual problems has been estimated to be 1.45; 95\% CI: 1.08 to 1.94.\textsuperscript{84} Associations between impaired vision and falls might be mediated by the role that visual inputs, particularly stereopsis and contrast sensitivity, play in the stabilization of posture.\textsuperscript{81,85} This is especially relevant in older people who are more dependent on vision to maintain a standing posture.\textsuperscript{86}
There are no studies reporting on the prevalence of visual impairments in people with COPD. Several studies, however, have found strong dose-dependent associations between inhaled corticosteroid use and risk of cataracts\textsuperscript{87-89} as well as associations between oral corticosteroids and risk of glaucoma.\textsuperscript{90} Cataracts and glaucoma reduce visual acuity, impair postural control, and have been associated with an increased rate of falls.\textsuperscript{91,92} Since inhaled corticosteroids are frequently prescribed in people with COPD,\textsuperscript{93} the deleterious effects these medications can have on visual function and falls should not be underestimated. Smoking has also been correlated with an increased risk of cataracts, particularly nuclear cataracts.\textsuperscript{94} Although the associations of corticosteroids and smoking with cataracts and glaucoma are well established, there are no studies analyzing the prevalence of either corticosteroid or smoking induced visual deficits in a large cohort of patients with COPD. Similarly, there are no studies exploring associations between visual deficits and risk for falls in people with COPD. Likewise, the potential role that visual deficits have as a risk factor for falls in people with COPD is only theoretical (Table 2.1).

\textbf{2.2.1.5 Nutritional Depletion and Malnutrition}

Nutritional depletion, which is common among people with COPD,\textsuperscript{95,96} is characterized by body weight loss, in particular, muscle mass.\textsuperscript{97} The loss of muscle mass in people with COPD has been associated with increased mortality,\textsuperscript{98} impaired muscle function,\textsuperscript{99,100} reduced exercise capacity\textsuperscript{101} and poorer HRQoL.\textsuperscript{102} Even though there are no studies reporting on the association
between nutritional depletion and risk for falls, leg muscle mass assessed by
dual-energy X-ray absorptiometry (DEXA) has been found to be significantly
lower (p<0.01) in a group of older adults fallers compared to non-fallers.\textsuperscript{56} The
deleterious consequences of muscle depletion on function and mobility are well
established.\textsuperscript{40}

Malnutrition is not uncommon in people with COPD. For example, recent
studies have reported that people with COPD show low levels of circulating
vitamin D.\textsuperscript{103,104} Vitamin D deficiency is important because it has been associated
with an increased risk for falling.\textsuperscript{105} The physiological mechanisms underlying this
correlation are possibly related to the role that vitamin D plays in muscle
function.\textsuperscript{106} In support of this, vitamin D supplementation has shown to be
effective in improving neuromuscular function and postural control in older
adults.\textsuperscript{107,108} and higher vitamin D serum levels (25-hydroxyvitamine D) have
been correlated with increased lung function in a large (n=14091) cohort study.\textsuperscript{109}
Whether vitamin D supplementation improves respiratory function or reduces the
incidence of falls in people with COPD is yet to be determined, however, the low
levels of circulating vitamin D and the high prevalence of osteoporosis among
people with COPD\textsuperscript{110} provide some indication that vitamin D supplementation
might be beneficial. Although the effects that nutritional depletion and
malnutrition have on the risk for falls in people with COPD are uncertain, the
evidence of decreased muscle mass and nutritional deficits in COPD is strong.
Due to the well established association between muscle mass and strength,\textsuperscript{111} as
well as the impact of muscle weakness on the risk for falls,\textsuperscript{27} it is possible that nutritional depletion may contribute as a risk factor for falls in COPD (Table 2.1).

\textbf{2.2.1.6 Use of an Assistive Device}

The use of an assistive device has been associated with an increased risk for falling (OR=2.6; 1.2 to 4.6).\textsuperscript{20} The reasons why people that use an assistive device fall more frequently are unclear and it is possible that the use of these devices could simply reflect impaired mobility, gait and balance, all of which have been associated with increased fall risk.\textsuperscript{20,68} The use an of assistive device may also reflect fear of falling, which is thought to impact on the physical performance and mobility of older adults.\textsuperscript{112} Some people with COPD that are oxygen dependent use portable oxygen tanks to reduce breathlessness. However, these devices have now become so portable and small that they do not seem to interfere with the normal mobility of these individuals. In addition, some people with severe COPD use wheel-walkers and scooters to facilitate mobility, however, it is unclear whether the use of these devices is more frequent in this group than in older adults. There are no studies indicating that the use of any assistive device in people with COPD could increase the risk for falling (Table 2.1).

\textbf{2.2.1.7 Impaired Activities of Daily Living (ADLs)}

Impaired ADLs have been associated with an increased risk for falling in older adults (OR=2.3; 95\% CI: 1.5 to 3.1).\textsuperscript{20,23} However, the order of causation of
impaired ADLs and falls is uncertain. Impaired ADLs are normally accompanied by reduced mobility and poor physical performance, both of which have been associated with increased risk for falling in older adults.\textsuperscript{113} On the other hand, injurious falls are sometimes followed by a period of immobilization, which has detrimental effects on mobility, physical conditioning and ADLs. Numerous studies employing different quantification methods have confirmed that people with COPD have impaired ADLs compared to healthy individuals. For example, Pitta et al., used triaxial accelerometers to evaluate physical activity levels in 50 people with moderate to severe COPD (FEV\textsubscript{1}=43 \pm 18\% predicted) compared to 25 healthy controls.\textsuperscript{114} Compared to the control group, people with COPD showed significantly lower levels of physical activity (i.e., lower walking/standing time and higher sitting/lying time) and movement intensity (during walking). Similar findings have been obtained in several other studies using either motion sensors or physical activity questionnaires.\textsuperscript{115,116} Therefore, impaired performance of ADLs in people with COPD is well-established (Table 2.1).

2.2.1.8 Depression and Cognitive Impairments

A recent study has reported that depression is associated with the number of falls in older adults.\textsuperscript{23} Although depression and falls share common risk factors (e.g., impaired ADLs and impaired cognitive function),\textsuperscript{117} the underlying mechanisms governing this association and the order of causation are unclear. A potential explanation might be that the use of antidepressant medications can have deleterious effects on the physical status of people with depression.\textsuperscript{118}
Others have suggested that depression may result in inattention to potential environmental hazards.\textsuperscript{20}

Chronic obstructive pulmonary disease has recently been associated with a number of psychiatric disorders,\textsuperscript{119} including depression and anxiety.\textsuperscript{120,121} Two reviews have reported on the prevalence of depression and anxiety in COPD, which could affect between 2\%-57\% and 2\%-51\% of these people respectively.\textsuperscript{122,123} Compared to control subjects,\textsuperscript{12} this high prevalence of depression may suggest that people with COPD have an increased risk for falling (\textit{Table 2.1}). However, there are no studies assessing associations between depression and fall occurrence in people with COPD. Furthermore, although medications commonly prescribed for anxiety disorders (e.g., benzodiazepines and neuroleptics) have been associated with an increased risk for falls,\textsuperscript{118} the potential association between anxiety and falls has not yet been determined.

Cognitive impairments have been identified as an important factor of increased fall risk in older adults. For example, a 2 year prospective study showed that people with dementia fell four times per year,\textsuperscript{124} which is a much higher rate than commonly reported rates from older community-dwelling adults.\textsuperscript{125} Another prospective study with 336 old adults (\textgreater75 years) showed that people with cognitive impairments fell 5 times more often (OR=5; 95\% CI: 1.8 to 13.7) than people without cognitive impairments.\textsuperscript{125} The major involvement of associative cortical areas in the integration of sensory and executive tasks\textsuperscript{126}
may explain the link between reduced cognitive capacity and increased risk for falls. For example, a recent cross-sectional study found significantly increased postural sway and lower performance of executive functions (i.e., set shifting, updating and response inhibition) in people with mild cognitive impairment compared with people without cognitive deficits.\textsuperscript{127}

Several studies have reported that cognitive impairments are not uncommon among people with COPD, especially in those with hypoxemia and hypercapnia.\textsuperscript{128} For example a clinical study showed that 42\% of hypoxemic people with COPD (PaO\(_2\) 51mmHg) had severe cognitive impairments, assessed through neuropsychological tests, compared with only 14\% of controls.\textsuperscript{129} These seminal findings have been recently confirmed with more advanced brain imaging techniques. For example, compared to healthy and non-hypoxemic people with COPD, hypoxemic people with COPD have shown reduced brain perfusion in both anterior and sub-cortical areas of the dominant hemisphere evaluated through single photon emission computerized tomography (SPECT).\textsuperscript{130} More importantly, such changes in brain perfusion have been correlated to poorer performance in neuropsychological tests in people with COPD.\textsuperscript{131} Even though these studies suggest that cognitive impairment is not rare in people with COPD, the exact prevalence of cognitive impairments and their effects on fall risk in COPD are currently unknown (Table 2.1).
2.2.1.9 Medications

Numerous studies have shown that certain types of medications are associated with increased frequency of falls in older people. In a systematic review, Leipzig and colleagues found that cardiac and psychotropic drugs increased the risk for falls with OR ranging from 0.9 to 1.6 and 1.5 to 1.7 respectively.132,133 Similar findings have been replicated in other studies investigating the action of central nervous system medications (e.g., narcotics and antidepressants) on the risk for falls and fractures in older women.118 For example, Tinetti and colleagues found that sedative medications (i.e., benzodiazepines, phenothiazines and antidepressants) significantly increased the risk for falls in older people (OR=28.3; 95% CI: 3.4 to 39.4).125 The number of medications has also been independently correlated to impaired postural control assessed by a composite of balance measures (i.e., side by side balance, sternal nudge, tandem stand, one leg standing balance).134

Medications commonly used in the management of COPD include: bronchodilators (anticholinergics, \( \beta_2 \)-agonists, methylxanthines), oral and inhaled corticosteroids, and theophylline. Other less frequent pharmacologic treatments include: vaccines, mucolytics, antitussives, \( \alpha \)-1 antitrypsin augmentation therapy, antioxidants, immunoregulators, vasodilators, narcotics, and antibiotics in cases of acute infection.135 While some of these medications may have adverse side effects including dizziness, postural hypotension, altered vision and long-term cognitive changes that might theoretically increase the risk for falling24 the
frequency and severity of these side effects and any impact they may have on fall risk in people with COPD is still to be elucidated.

Two types of medications commonly used in COPD warrant special attention for their potential adverse effects on fall risk: corticosteroids and psychotropics. Corticosteroid use in people with COPD has been estimated to be ~61.5% and ~8.3% for inhaled and oral corticosteroids respectively. In spite of their known benefits, these medications have several detrimental side effects that can potentially increase the risk for falling. Side effects of corticosteroid use include steroid induced myopathy, hyperglycemia, hypertension, loss of bone mineral density, glaucoma and cataracts. Some of these side effects have been specifically observed in people with lung disease. For example, Nava et al. reported muscle weakness after 5 days of treatment with high dosage (12mg·kg⁻¹) of methylprednisolone in patients with acute lung rejection. Although not all studies have observed such decline in muscle function, the detrimental effects of corticosteroids, in particular oral corticosteroids, on both respiratory and peripheral muscle function in people with COPD are well established.

Long term use of corticosteroids in people with COPD has also been associated with metabolic disorders such as osteoporosis and osteopenia and a subsequent increased risk of bone fracture in some, but not all, studies. The severity of side effects such as muscle weakness, risk of fracture and visual deficits appears to be related to the dose, duration, and type of administration.
(i.e., oral corticosteroids produce more side effects).\textsuperscript{89,135,144,145} Differences in these parameters might well explain conflicting results among studies. Given the deleterious effects that visual impairments,\textsuperscript{81,82} and muscle weakness,\textsuperscript{25,26} have in the risk for falling, the use of corticosteroids in patients with COPD needs to be weighed against the potential risks.\textsuperscript{146}

Because people with COPD experience many psychological effects such as depression, anxiety and sleep disorders,\textsuperscript{119} the use of psychotropic medications including antidepressants and benzodiazepines is conceivably high among these patients. Anxylitics, narcotics and antidepressants have been associated with an increased risk for falling in several studies.\textsuperscript{16,118} The underlying mechanisms explaining the association between the use of these medications and increased fall risk might be related to commonly reported side effects such as dizziness, fatigue, daytime sleepiness, slowed postural reflexes, postural hypotension and impaired postural control.\textsuperscript{147} Since no specific studies have quantified the exact prevalence of use of these substances in people with COPD, the importance that these medications may exert on their risk for falling in these subjects remains unknown (Table 2.1).

### 2.2.2 Precipitating Factors

#### 2.2.2.1 Syncope and Postural Orthostatic Hypotension (POH)

Syncope has been defined as a transient, self-limited loss of consciousness, usually leading to a fall.\textsuperscript{148} The multitude of possible aetiologies
and potential recall bias (e.g., retrograde amnesia is common after syncope) make the prevalence of syncope difficult to determine. However, a one year prospective study including 711 older people with a mean age of 87 years, reported an incidence of 6% per year, with a two year prevalence and recurrence rates of 10% and 30% respectively.\textsuperscript{149} Recently, syncope has been identified as a potential risk factor for falls.\textsuperscript{23} The percentage of falls related to syncope has been estimated to range between 0.5\%-3\%, however, the existing overlap between falls and syncope\textsuperscript{150} and the fact that syncope is excluded in most studies of falls, suggest that this percentage might be higher.\textsuperscript{30} There are no studies investigating syncope in COPD, however, both conditions share some common aspects that suggest that the risk of syncope in people with COPD might be significant. The likelihood of syncope is increased with cardiovascular diseases (i.e., coronary heart disease and aortic stenosis) and the use of hypertensive medication.\textsuperscript{151} Due to the multiple effects of smoking and other shared predisposing factors (e.g., systemic inflammation), the risk of cardiovascular disease (OR=2.4; 95\% CI: 1.9 to 3) and hypertension (OR=1.6; 95\% CI: 1.3 to 1.9) in people with COPD is high.\textsuperscript{152} Nevertheless, given that no studies have examined at the association between syncope and COPD, whether there is an increased risk for falls due to a transient loss of consciousness in people with COPD needs to be investigated further (Table 2.2).

Postural orthostatic hypotension (POH) is clinically defined as a fall in blood pressure of at least 20 mmHg systolic or 10 mmHg diastolic when standing
or during head-up tilt testing.\textsuperscript{153} The prevalence of POH in older adults is estimated to lie between the range of 5%-30%.\textsuperscript{153} Age, the use of some medications (e.g., antihypertensives, diuretics, antidepressants) and some clinical conditions (e.g., diabetes, Parkinson’s disease, autonomic disorders) are contributing factors of POH.\textsuperscript{153} Transient dizziness after changing posture, the most commonly reported symptom of POH, is thought to increase the risk for falling, however the association between POH and fall occurrence remains speculative.\textsuperscript{30} From our clinical experience, the prevalence of POH in people with COPD is possibly high. However, there are no formal studies investigating POH in COPD, and as such, its potential implication in fall occurrence among these patients cannot be determined (Table 2.2).

\textit{2.2.2.2 Exacerbations}

An exacerbation is defined as “a sustained worsening of the patient’s condition, from the stable state and beyond normal day-to-day variations, necessitating a change in regular medication in a patient with underlying COPD”\textsuperscript{154}. The exact prevalence of exacerbations in people with COPD is difficult to calculate because it varies substantially depending on the severity of the disease as well as the prior number of exacerbations.\textsuperscript{155} However, recent studies have shown that people with severe and moderate COPD (according to the classification of the Global Initiative for Chronic Obstructive Lung Disease) might experience an average of 3.43 and 2.63 exacerbations per year respectively.\textsuperscript{156}
Since exacerbations usually require hospitalization, prolonged bed rest and aggressive pharmacological interventions (e.g., high doses of oral corticosteroids), muscle atrophy and weakness associated with exacerbations are likely. For example, Spruit et al.,\textsuperscript{157} observed that quadriceps peak torque was reduced in people with COPD (FEV\textsubscript{1}=66 \pm 22 \% predicted) hospitalized due to an exacerbation, compared to a group of clinically stable COPD patients (FEV\textsubscript{1}=86\% \pm 16 predicted). More importantly, this accentuated weakness was still apparent 3 months after discharge from the hospital. Peripheral muscle weakness could contribute to the reduced levels of physical activity observed in people with COPD even one month after exacerbations.\textsuperscript{158} Due to the negative effects of exacerbations on muscle function and physical activity levels, gait and balance deficits after exacerbations cannot be missed. Thus, an increased risk for falls secondary to exacerbations is possible (Table 2.2).

\textit{2.2.2.3 Dyspnea}

Dyspnea is the most common activity-limiting symptom of COPD. Because the level of dyspnea is strongly correlated to the intensity of the activity performed, people with COPD tend to progressively reduce physical activity and ADLs. This further contributes to overall physical deconditioning, which increases the level of inactivity and, in the long term, social isolation.\textsuperscript{159} There are no studies analyzing the potential impact of dyspnea on falls occurrence but it seems unlikely that dyspnea could contribute as a precipitating (acute) factor for falls in people with COPD. Paradoxically, dyspnea leads people with COPD to
adopt a much more sedentary lifestyle that reduces mobility and that could eventually “protect” these patients from falling. However, the long-term consequences of dyspnea and its detrimental impact on physical activity and further deconditioning in COPD are well established. Although dyspnea as a precipitating factor does not appear to increase the risk for falling, the long-term effects of dyspnea have important repercussions on the overall physical status of people with COPD that can increase fall risk (Table 2.2).

2.3 Conclusions

The results of this review suggest that people with COPD may have an increased risk for falling compared to their healthy peers. Most risk factors for falls identified in older people are common in people with COPD. There is evidence that lower limb muscle weakness and impaired activities of daily living are well-established risk factors for falls in people with COPD. Other intrinsic factors such as gait and balance deficits, nutritional depletion, malnutrition, depression, cognitive impairments and medications are possible risk factors that need to be confirmed with further research. Due to the lack of studies, the potential implication of visual deficits on fall occurrence in people with COPD is only theoretical. There is no evidence to suggest that people with COPD may have an increased risk for falls associated with the use of an assistive device. While the role that precipitating factors such as syncope and postural hypotension may have on fall occurrence in COPD is unclear, the long-term effects of dyspnea and exacerbations on limited mobility and progressive physical deterioration might theoretically increase the risk for falls.
In summary, we have used a physiological approach to present a theoretical framework of potential risk factors for falls in COPD (Figure 2.1). Even though our results suggest that fall risk in people with COPD may be high, the lack of epidemiological studies assessing the prevalence of falls and the scarcity of clinical trials analyzing specific risk factors for falls in people with COPD indicates that any conclusions from this review should be cautious. Further research is needed to determine the prevalence of falls and specific risk factors for falls in people living with COPD. In the meantime, we expect that the proposed framework will provide a basis to generate relevant research questions regarding the risk for falls among people with COPD.
Table 2.1 Qualitative analysis of different evidence levels of intrinsic risk factors for falls in people with COPD.

Evidence is categorized into three different levels as established (E), possible (P) and theoretical (T). A rationale to explain the different levels of evidence is provided.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Evidence as risk factor for falls in older people</th>
<th>Rationale</th>
<th>Evidence in people with COPD</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Muscle weakness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strength</td>
<td>E</td>
<td>Deficits in muscle strength are associated with increased fall risk.</td>
<td>E</td>
<td>Deficits in muscle strength and endurance are common in people with COPD.</td>
</tr>
<tr>
<td>Endurance</td>
<td>P</td>
<td>There are no studies reporting on muscle endurance and power and their effect on fall risk. However, strength, endurance and power are highly correlated</td>
<td>E</td>
<td>Muscle power has not been investigated in people with COPD but muscle power is highly correlated with strength</td>
</tr>
<tr>
<td>Power</td>
<td>P</td>
<td></td>
<td>P</td>
<td></td>
</tr>
<tr>
<td><strong>Gait deficits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speed</td>
<td>E</td>
<td>Lower gait speed has been associated with increased fall risk.</td>
<td>P</td>
<td>Only one study has are reported reduced gait speed in people with COPD.</td>
</tr>
<tr>
<td>Distance</td>
<td>P</td>
<td>There are no studies reporting on walking distance and fall risk.</td>
<td>E</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Balance deficits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>Deficits in postural control are associated with increased fall risk</td>
<td>P</td>
<td>Only three studies have reported balance deficits in people with COPD.</td>
</tr>
<tr>
<td><strong>Visual deficits</strong></td>
<td></td>
<td></td>
<td>T</td>
<td>There are no studies reporting on visual deficits in people with COPD but the use of corticosteroids in people with COPD is common and their visual side-effects are well established</td>
</tr>
<tr>
<td>Risk Factor</td>
<td>Evidence as risk factor for falls in older people</td>
<td>Rationale</td>
<td>Evidence in people with COPD</td>
<td>Rationale</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Use of assistive device</td>
<td>E</td>
<td>The use of an assistive device is associated with increased fall risk. However, the underlying mechanisms behind this association are unknown</td>
<td>-</td>
<td>The prevalence of assistive device use among people with COPD compared to healthy peers is unknown</td>
</tr>
<tr>
<td>Impaired ADLs</td>
<td>E</td>
<td>Impaired ADLs are associated with increased fall risk.</td>
<td>E</td>
<td>Impaired ADLs are common in people with COPD and contribute to physical deterioration and reduced mobility</td>
</tr>
<tr>
<td>Depression</td>
<td>E</td>
<td>Depression is associated with increased fall risk. However, the underlying mechanisms behind this association are unknown</td>
<td>P</td>
<td>Depression is common in people with COPD. However, the exact prevalence is equivocal</td>
</tr>
<tr>
<td>Cognitive impairments</td>
<td>E</td>
<td>Cognitive impairments are associated with increased fall risk.</td>
<td>P</td>
<td>Cognitive impairments are common in people with COPD. However, the estimate of prevalence vary</td>
</tr>
<tr>
<td>Medications (type)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotropic</td>
<td>E</td>
<td>Psychotropic and cardiac drugs are associated with increased fall risk.</td>
<td>T</td>
<td>The use of psychotropic and cardiac medications might be high in people with COPD. However, the exact prevalence is unknown. The use of corticosteroids is common in people with COPD.</td>
</tr>
<tr>
<td>Cardiac</td>
<td>E</td>
<td></td>
<td>T</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>P</td>
<td>side-effects of corticosteroid use on muscle weakness and vision are well established</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>-</td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>-</td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Medications (number)</td>
<td></td>
<td>The number of medications is associated with increased fall risk</td>
<td>E</td>
<td>The use of multiple medications is common in people with COPD</td>
</tr>
</tbody>
</table>
Table 2.2 Qualitative analysis of different evidence levels of precipitating risk factors for falls in people with COPD. Evidence is categorized into three different levels as established (E), possible (P) and theoretical (T). A rationale to explain the different levels of evidence is provided.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Evidence as risk factor for falls in older people</th>
<th>Rationale</th>
<th>Evidence in people with COPD</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope</td>
<td>P</td>
<td>Syncope is associated with increased fall risk. However, the prevalence of syncope and its effect on fall risk is unknown</td>
<td>-</td>
<td>There are no studies reporting on the prevalence of syncope in people with COPD</td>
</tr>
<tr>
<td>Postural orthostatic hypotension</td>
<td>T</td>
<td>Postural orthostatic hypotension may produce transient dizziness. The effects of dizziness on fall risk are unknown</td>
<td>T</td>
<td>There are no studies reporting on the prevalence of postural orthostatic hypotension in people with COPD. However, cardiovascular co-morbidities and use of hypertensive medications, both of which are associated with increased fall risk, might be high in people with COPD</td>
</tr>
<tr>
<td>Exacerbations</td>
<td>-</td>
<td>There are no studies reporting on the role of exacerbations on fall risk</td>
<td>E</td>
<td>Exacerbations are common in people with COPD. Exacerbations reduce muscle strength and physical activity levels</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>-</td>
<td>There are no studies reporting on the role of dyspnea on fall risk</td>
<td>E</td>
<td>Dyspnea is the most common symptom in people with COPD. Dyspnea reduces physical activity levels and contributes to physical deconditioning</td>
</tr>
</tbody>
</table>
Figure 2.1 Theoretical framework of the risk factors for falls in people with COPD and potential interactions.

Intrinsic and precipitating factors are depicted by white or shaded rectangles respectively. Since cardiovascular co-morbidities are common in people with COPD, the use of cardiac and hypertensive medications is conceivably high among these individuals. The use of these medications appears to increase the frequency of episodes of postural orthostatic hypotension and syncope, which are precipitating risk factors for falls. Other medications commonly used by people with COPD include corticosteroids and possibly antidepressants. The use of corticosteroids is associated with an increased risk of developing visual problems (e.g., cataracts). In addition, the use of antidepressants is thought to increase reaction time and attention deficits. The number of medications as well as visual deficits and cognitive impairments increase balance deficits and risk for falling. Nutritional depletion, characterized by a reduction of muscle mass (i.e., atrophy), contributes to muscle weakness and, by extension, to balance and mobility deficits (e.g., lower gait speed). Malnutrition, common in people with COPD, may increase balance deficits and impair activities of daily living (ADLs), which lead to progressive deconditioning and a reduction of functional capacity. Deconditioning is further aggravated by dyspnea (i.e., breathlessness), the most common and activity-limiting symptom in people with COPD. Exacerbations of COPD usually require periods of bed rest (e.g., hospitalization) and aggressive pharmaceutical interventions (e.g., systemic corticosteroids) that increase muscle weakness and contribute to a progressive reduction of ADLs.
Muscle weakness
Gait deficits
Balance deficits
Nutritional depletion
Impaired ADLs
Depression and cognitive impairments
Visual deficits
Exacerbations
Dyspnea
Postural orthostatic hypotension
Syncope
Cardiac Hypertensives
Depression
Corticosteroids
Falls
Malnutrition
Antidepressants
Vit D deficiency
Gait deficits
Poor mobility
Poor mobility
Bed rest
Hospitalization
Corticosteroids
Muscle atrophy
Dyspnea
Breathlessness
Corticosteroids
Falls
Nutritional depletion
Muscle weakness
Visual deficits
Medications
Balance deficits
Impaired ADLs
Malnutrition
Vit D deficiency
Corticosteroids
Poor mobility
Bed rest
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Chapter Three: Risk Factors for Falls I: Muscle Strength, Mass and Quality of Knee Extensors: Relationship with Functional Performance in People with COPD

3.1 Introduction

Chronic obstructive pulmonary disease (COPD) is a complex disease with many non-respiratory manifestations, including skeletal muscle dysfunction. Deficits in muscle strength and mass in people with COPD compared with age-matched healthy controls are well reported in the literature. However, little attention has been directed at investigating differences in muscle quality in these individuals. Intramuscular fat (IF), a feature of muscle quality, has only been recently investigated in people with COPD. In a previous study using magnetic resonance imaging (MRI) of the thigh muscles, we found that 20 people with moderate to severe COPD with a percentage predicted force expiratory volume in one second (FEV₁) of 51 ± 17% had, on average, ~35% more IF in the thigh muscles than a group of healthy controls matched for age, gender and body mass index (BMI). Intramuscular fat (IF) has recently been proposed as an important indicator of muscle dysfunction and health status in older adults. For example, increased mid-thigh IF has shown to be independently associated with muscle weakness and self-reported mobility loss in older adults. Furthermore, older people with increased mid-thigh IF are 51% more likely to experience hospitalization. Interestingly, reduced mid-thigh muscle mass does not appear to

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2 A version of this chapter has been submitted for publication. Roig M, Eng JJ, MacIntyre DL, Road JD, Reid WD. Muscle strength, mass and quality of knee extensors: relationship with functional performance in people with COPD.
be related to an increased risk of hospitalization in older adults,\textsuperscript{7} suggesting that muscle quality, assessed by means of IF, might be a more reliable predictor of health status than muscle mass.

Measurements of muscle strength and mass are commonly used in clinical settings as well as research to monitor training adaptations and predict exercise performance in people with COPD. However, recent studies suggest that deficits in muscle mass do not entirely explain the reduction of muscle strength observed in people with COPD.\textsuperscript{8} Thus, it is possible that muscle quality could partially explain deficits in muscle strength in these individuals. More importantly, the relationship between measures of muscle strength, mass and IF with specific measures of functional performance has not yet been investigated in these individuals.

It is generally agreed that mid-thigh muscle strength\textsuperscript{9} and mass\textsuperscript{10} are associated with functional performance in older adults, however, it is unclear if these associations remain valid for people with COPD. Similarly, it is also unknown if an increased IF is associated with deficits in functional performance in these individuals. The main purpose of this study was therefore to compare measures of muscle strength, cross-sectional area (CSA) and IF of the thigh muscles, as well as functional performance in people with COPD and a control group matched for age, gender and BMI. Potential associations between knee extensors muscle strength, mass and IF with functional performance in both
groups were also explored. It was hypothesized that, compared with healthy subjects, people with COPD would show deficits in muscle strength and CSA as well as in functional performance. It was also hypothesized that mid-thigh IF would be increased in people with COPD compared to healthy controls and that knee extensors IF in particular would be associated with functional impairment.

3.2 Methods

3.2.1 Participants

People with COPD and healthy control subjects were recruited on a voluntary basis from the local community from October 2008 to June 2009. Flyers of the study were distributed in waiting rooms of hospitals, pulmonary function laboratories, as well as community and senior centers within greater Vancouver. Inclusion criteria for people with COPD were: moderate to severe disease (stage II or III) based on the Global Initiative for Obstructive Lung Disease (GOLD). Exclusion criteria were: (1) an acute exacerbation within the 3 months prior to the study; (2) regular participation in a formal exercise rehabilitation program during the 1-year period prior to the study; (3) currently smoking; (4) co-morbid cardiovascular or neurological disease and lower extremity musculoskeletal problems that would interfere with or could cause undue risk during the performance study testing; (5) use of portable supplemental oxygen on a continuous basis; (6) \( \alpha \)-1 antitrypsin deficiency without a significant smoking history.
Inclusion criteria for healthy people were: sedentary healthy people. Sedentary was defined as “only performs activities with low metabolic cost, including light activities such as slow walking or cooking”. Exclusion criteria for healthy people were: (1) regular participation in a formal exercise program during the 1-year period prior to the study; (2) currently smoking; (3) respiratory, cardiovascular, neurological disease or lower extremity musculoskeletal problems that interfere with or would cause undue risk during the performance of study testing. The Clinical Research Ethics Board of the University of British Columbia approved the study (Appendix A) and all subjects gave written informed consent prior to participation (Appendix B).

3.2.2 Measurements

3.2.2.1 Initial Screening

Prior to testing, participants were asked to complete a risk-screening questionnaire (Appendix C) to ensure inclusion criteria were met and to minimize any potential risk. Weight and height were measured with shoes off and light clothing on. To confirm the moderate to severe stage of COPD or to rule out pulmonary disease, people with COPD and healthy subjects, respectively, underwent spirometry using a portable spirometer (CPFS/D spirometer, Medi Graphics Corp., MN, USA). Spirometry was performed according to the guidelines of the American Thoracic Society (ATS) and European Respiratory Society (ERS).
3.2.2.2 Physical Activity Level

Level of physical activity was assessed with the Physical Activity Scale for the Elderly (PASE).\textsuperscript{16,17} The PASE has been validated by comparison with physical activity values assessed using portable accelerometers in a sample of healthy elderly people.\textsuperscript{18} This scale is a 12-item self-administered questionnaire that scores physical activity levels based on scores ranging from 0 to 400 (Appendix D).

3.2.2.3 Knee Extensors Muscle Strength

Concentric average peak torque of the knee extensors of the dominant leg (determined by preference for kicking a ball) was assessed on the KinCom\textsuperscript{®} dynamometer version 5.30 (Chattanooga Group Inc., TN, USA). Participants were seated on the KinCom\textsuperscript{®} with the knee joint aligned with the center of rotation of the dynamometer. The resistance pad was positioned distally at 75\% distance from the lateral femoral epicondyle to the lateral malleolus. Stabilizing belts were used to secure the pelvis and the upper body and to minimize extraneous movements. An angular velocity of 30°/s was chosen because it has shown high reproducibility (ICC=0.99) in a previous study of people with COPD.\textsuperscript{19} A testing range of motion (ROM) of 10° to 90° of knee flexion was set to diminish joint discomfort and reduce force variability produced by the action of the hamstrings at the end of knee extension. After a warm-up consisting of 5 sub-maximal contractions, participants were asked to extend their knee as fast and hard as they could. To ensure maximal efforts, participants were vigorously
encouraged. Three maximal trials were recorded interspersed by two-minute rest intervals. The three trials were averaged to obtain the peak torque.

3.2.2.4 Functional Performance

Functional performance was assessed using the following tests: Repetitive Sit-To-Stand (RSTS), Self-Selected Gait Speed (SSGS) and Six-Minute Walk (6MWT) tests. For the RSTS the time required to complete five repeated sit-to-stand and stand-to-sit maneuvers was measured using similar instructions and identical apparatus as described previously. The SSGS was assessed by measuring the self-selected gait speed to complete 5m on an 8m walkway. The 6MWT was performed according to the guidelines of the ATS. Briefly, participants were instructed to walk as far as possible for 6 minutes in a 25-meter hallway and the distance walked was recorded. With the exception of the 6MWT, participants performed two trials for all tests, with two minutes of recovery in between. The same tester (MR) timed all the tests manually and the best of the two trials was saved for further analysis.

3.2.2.5 Thigh Muscles CSA and Intramuscular Fat (IF)

A computerized tomography (CT) scan of the thigh was performed at 50% distance from the tibial plateau to the anterior inferior iliac spine using a Siemens “Sensation 16” Multislice CT scanner (Siemens Medical Solutions, Erlangen, Germany) with the subject in the supine position. Images were acquired using the following technical parameters: 120 kVp and 100-250 mA, 0.5-sec gantry
rotation time (100 mA), 15mm table speed per rotation and 9mm slices
reconstructed using high (“b50s”) spatial frequency reconstruction algorithms.
Analysis of all CT images was quantified by the same tester (MR) in a blinded
1.3.1_03) by manually defining regions of interest (ROI) for: 1) all thigh muscles
first (knee extensors, flexors and hip adductors); 2) knee extensors (rectus
femoris and vastus lateralis, medialis, intermedius); and knee flexors (biceps
femoris, semitendinosus, semimembranosus) individually. Bone CSA was
subtracted from the ROI.

Images were visualized on a 512x512 matrix of pixels using a visual field
of 40cm². The numerical value of each pixel reflects different attenuation
coefficients measured as Hounsfield units (HU) and corresponds to the gray level
of the image. Adipose tissue is represented by “dark” pixels (negative attenuation
values) while muscle tissue and bone are shown lighter (positive attenuation
values). Intramuscular fat (IF) was estimated only for knee extensors and flexors
and calculated from the number of pixels within the range of Hounsfield units for
adipose tissue (-190 to -30). A larger number of pixels within this range
indicates greater fat infiltration. This method to estimate IF has been described
elsewhere and has been shown to be reliable and valid. All measurements
were performed on the dominant leg only.
### 3.2.3 Statistical Analyses

The sample size was based on previous studies that assessed similar outcomes.\(^3,4\) We calculated standardized effect sizes by dividing the difference of the means between the COPD and control groups by the pooled standard deviation.\(^26\) Standardized effect sizes ranged from 0.8 to 1.3. With an overall effect size (\(d\)) of 0.8 and assuming a 80% power rate at an \(\alpha_2\) level of 0.05, we estimated that at least 20 participants per group were needed\(^26\) to detect significant differences in muscle strength, CSA and IF.

Assumptions of normality for all variables were explored through visual analysis of histograms and normality plots.\(^27\) Owing to the lack of normality in the levels of physical activity, differences between groups were compared with non-parametric statistics (Mann-Whitney-U test). Pearson or Spearman (for non-normally distributed data) correlation coefficients were used to explore associations and multicollinearity among dependent variables and potential covariates. Colinear covariates showing weaker associations (\(r<0.5\)) were eliminated. A regression model with age as a covariate was used to determine differences between groups in measures of muscle torque and functional performance. For differences in IF and CSA, the regression model was adjusted for age and BMI. These covariates were chosen because they were associated with the measures of interest. Bivariate correlations were used to explore associations between measures of muscle strength, CSA and IF with functional performance (RSTS, SSGS, 6MWT) for each group. The strength of the
correlations \( (r) \) was categorized as low (0-0.25), moderate (0.25-0.50), strong (0.50-0.75) and very strong (>0.75).\(^{26}\) To explore specific differences between groups in the association of IF and functional performance, homogeneity tests were performed.\(^{28}\) Data are presented as medians with percentiles \((P_{25}, P_{75})\) or means \(\pm\) standard deviation (SD) with 95% confidence intervals (CI). All analyses were performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) using two-tailed probability tests with a level of significance set at \(p<0.05\). The SPSS syntax codes for the main analyses are shown in Appendix E.

### 3.3 Results

#### 3.3.1 Participants

Thirty-eight people with COPD and 26 healthy control subjects were recruited. Twenty-two participants were excluded because they did not meet the inclusion criteria. Reasons for exclusion as well as details of the recruitment process are shown in **Figure 3.1**. After exclusion, 21 non-oxygen dependent, clinically stable people (11 males and 10 females) with moderate to severe COPD and 21 sedentary healthy controls matched for age, sex and BMI were included in the study. Participants’ characteristics are shown in **Table 3.1**. People with COPD had a significantly lower FEV\(_1\), forced vital capacity (FVC) and FEV\(_1\)/FVC compared to the healthy group \(p<0.05\). The group with COPD tended to be older (mean difference = 3.8 years; 95% CI: -1.3 to 9) \(p=0.08\) and showed a lower median score \((P_{25}, P_{75})\) of 103.3 (53.8 to 156.3) in the PASE,
compared to values shown by the healthy controls, with a median score (P_{25}, P_{75})
of 141.4 (78.3 to 204.5) (p=0.087). No significant differences in height, weight
and BMI were observed between groups.

### 3.3.2 Knee Extensors Muscle Strength and Functional Performance

Results for knee extensors muscle strength and functional performance
are shown in Table 3.2. Knee extensors concentric average peak torque was
29% lower in people with COPD as compared to control subjects. Similarly, the
group with COPD showed lower performance in all functional tests. In short,
individuals with COPD required 21% more time to complete the RSTS. Gait
velocity in the SSGS was 20% lower and distance walked in the 6MWT was 28%
lower in the group with COPD compared with healthy control subjects.

### 3.3.3 Thigh Muscles CSA and Intramuscular Fat (IF)

Results for CSA and IF of the thigh muscles are shown in Table 3.3.
People with COPD showed, on average, a 17% smaller CSA of the thigh
muscles. More specifically, the group with COPD had a smaller muscle CSA for
knee extensors (17%) and knee flexors (16%). However, differences between
groups for knee flexors were not significant (p=0.076). Compared with control
subjects, people with COPD showed greater levels of IF in knee extensors
(~89%) and flexors (~113%). Figure 3.2 shows a CT scan of the thigh of a
person with COPD and a healthy participant matched for age, gender and BMI.
3.3.4 Relationship Between Measures of Muscle and Functional Performance

In people with COPD, IF of knee extensors showed non-significant trends suggestive of a moderate association between increased IF and lower performance in the SSGS ($r=-0.41; p=0.07$) and RSTS tests ($r=0.43; p=0.06$), respectively (Figure 3.3). In contrast, the association of IF of knee extensors and functional performance in the healthy group was not apparent (Figure 3.3). The homogeneity tests confirmed that the slopes of the regression lines ($b_1$) describing the association between knee extensors IF and functional performance had significantly different patterns between groups ($p<0.05$) in all functional tests except for the RSTS (Figure 3.3). Neither knee extensors concentric torque nor CSA showed significant associations with the functional tests in any of both groups (Figure 3.4).

3.4 Discussion

The main finding of this study is that, compared with healthy subjects matched for age, gender and BMI, muscle quality of knee extensors and flexors, reflected by the level of IF, is markedly reduced in people with COPD. In addition, people with COPD show notable deficits in all measures of functional performance in comparison with the healthy group. Another important finding of this study is that the group with COPD showed lower levels of knee extensors muscle strength as well as reduced CSA of the thigh muscles. Lastly, IF of knee extensors showed a non-significant trend suggestive of a moderate association
with functional performance in the SSGS and the RSTS in people with COPD. Interestingly, associations between muscle strength and CSA with functional performance were not apparent in either group.

This study confirms that people with COPD have a significant reduction in muscle quality in addition to the deficits in knee extensors and flexors muscle strength and mass already reported in previous studies. The group with COPD showed, on average, ~100% more IF in knee extensors and flexors than the healthy group. This finding is consistent with a previous study, in which we used MRI and found ~35% more IF in the thigh muscles of people with COPD compared with a matched control group. The reason for the greater IF in the present study is possibly due to the fact that we adjusted between groups comparisons for age and BMI. Before adjustment, differences in IF between groups were very similar (45%) to those reported in our previous study. In addition, in this study the group with COPD was slightly older and we used CT rather than MRI. While CT scanning entails the risk of X-ray radiation, it also provides more absolute thresholds to quantify adipose tissue, rather than relative signal intensities provided by MRI.

It could be argued that the greater accumulation of IF in people with COPD was caused by reduced physical activity and accompanying physiological consequences. However, in this study, sedentary controls were purposely recruited to minimize potential confounding arising from differences in physical
activity levels. Since physical activity only tended to be higher in the healthy controls, the greater accumulation of IF in people with COPD cannot be solely explained by differences in physical activity. Moreover, although both groups were matched for age, gender and BMI, covariates associated with IF accumulation (i.e., age and BMI) were factorized into the analysis to further reduce potential confounding variables. The mechanisms for the increase in IF are likely complex and remain largely unknown however it is possible that the reduced oxidative capacity and the predominance of glycolytic metabolism observed in the muscles of people with COPD might compromise the ability to utilize intramuscular triacylglycerols and result in the concomitant increase in IF.

Functional performance tests, including the RSTS, SSGS and 6MWT, reflect different components of mobility such as postural control, muscle strength and coordination required in tasks of daily living in older adults. Only a couple of recent studies have systematically described the functional limitations encountered by people with COPD. In accordance with a preliminary report, our results indicate that people with COPD have marked deficits in functional performance compared with healthy adults. These deficits may have significant implications for mortality or fall risk. For example, on average, people with COPD were unable to walk more than 400m in the 6MWT, a distance that is below the threshold previously reported to increase mortality in people waiting for lung transplant. Similarly, compared with the control group, gait speed in the group
with COPD (1.2 m·s⁻¹) was closer to the threshold associated with an increased fall risk (1 m·s⁻¹) in older adults. More studies are required to establish normative values and specific cut-points of these functional tests that are prognostic of an increased fall risk in people with COPD.

The second hypothesis of this study was that IF of the knee extensors would be associated with functional performance in people with COPD. We only showed non-significant trends for associations between muscle quality of knee extensors, reflected by the degree of IF, and functional performance tests. Although recent studies underline the importance of assessing muscle quality as an important factor associated with self-reported mobility loss in the elderly, this is the first study evaluating direct associations between IF and functional performance. In spite of a moderate tendency towards a relationship between IF and the RSTS and SSGS, associations between reduced muscle quality and functional impairment were not significant. It is important to note, however, that the trend demonstrated between IF and functional impairment was stronger than the association of functional performance with either knee extensors muscle strength or CSA.

For exploratory purposes only, we investigated if there were potential differences between the nature of the associations between IF and functional performance. First, we compared, for each group, the slopes (b₁) of the regression lines of the scatter plots generated to explore associations between
measures of knee extensors IF and functional performance tests (Figure 3.3). We then performed homogeneity tests to confirm if $b_1$ values were significantly different between groups. The visual analysis of the slopes indicated that the association between knee extensors IF and functional performance tended to be more accentuated in the COPD group. In addition, the regression lines of both groups were parallel in some but not all associations, especially for the relationship between IF and the 6MWT (Figure 3.3). The homogeneity tests confirmed that the slopes of the regression lines were significantly different between groups ($p<0.05$) in all the tests except for the RSTS. These results suggest that differences in the relationship between measures of muscle and functional performance between groups might exist. This observation is relevant, because it indicates that either the nature or the magnitude of the association between muscle quality and functional performance might be specific for each population group and for each functional test. Hence, caution should be taken when results from studies with healthy older adults are extrapolated to people with COPD.

Neither muscle strength nor CSA of the knee extensors were associated with functional performance in people with COPD. Interestingly, these associations were not significant in the healthy control group (Figure 3.4), although there is some evidence in the literature that lower-extremity strength and, possibly to a lesser extent, CSA are associated with functional performance in healthy older individuals. One possible explanation for this lack of
association could be the existence of a strength threshold beyond which further increases do not translate into specific functional performance tests.\textsuperscript{41} Indeed, non-linear relationships between knee extensors strength and functional performance (i.e., gait speed) have been described in older populations.\textsuperscript{42} Perhaps the healthy group was already operating at strengths in excess of this threshold thus explaining the lack of association with functional measures.

Another possible explanation for this lack of association could be that knee extensors are not representative of the overall lower-limb muscle action involved in the selected functional tests. However, knee extensors were chosen because they play a major role in walking and other common activities of daily living (e.g., standing from a chair) and because they have been associated with exercise performance in people with COPD.\textsuperscript{43} More importantly, associations between measures of muscle and functional performance using other muscle groups such as the knee flexors (e.g., strength) or the whole thigh (CSA) were not significant either. It therefore seems that the selection of knee extensors as a primary muscle group is unlikely to be the cause of the lack of association between measures of muscle and functional performance.

A more likely explanation for the lack of association concerns the selection of our sample size and how this limited the power of the correlation analysis. Our sample size was estimated to detect differences between groups in measures of muscle and functional performance. Our results suggest that this sample size
was appropriate, however, perhaps this sample size was insufficient to detect associations between measures of muscle and functional performance. To explore this, we calculated the power achieved with the correlation analysis between knee extensors IF and measures of functional performance in the group with COPD. According to Portney and Watkins,\textsuperscript{26} with a sample of 21 people with COPD and a resulting correlation of $r=0.5$ the power we achieved was only 34%, meaning that with this sample size we had a 66% chance of not detecting a true association (type II error). To achieve a power of 80% for detecting potential associations between knee extensors IF and functional performance, at least 46 people with COPD should have been recruited.\textsuperscript{26} Thus, the study was likely underpowered to investigate these associations.

3.5 Conclusions

This study shows that people with moderate to severe COPD have marked deficits in muscle strength, mass, quality and functional performance compared with a healthy control group. We did not, however, find measures of muscle strength, CSA or IF to be associated with performance of functional tasks. The most likely explanation for this result is the lack of power of the correlation analysis. A graphical analysis of these associations revealed that important differences between groups and functional tests might exist. Recent studies point out the clinical relevance of assessing muscle strength and mass as predictors of adverse events such as falls in the elderly.\textsuperscript{44} In addition, other reports have confirmed that thigh muscles strength and CSA are good predictors of mortality\textsuperscript{45,46} and health care services utilization\textsuperscript{47} in people with COPD. In
contrast, our results suggest that other aspects mediate the functional impairment observed in people with COPD. Further studies with larger sample sizes should investigate potential underlying mechanisms for the functional impairment in these individuals and the potential association with IF.
Table 3.1 Characteristics of the participants of the study. Data are presented as means ± SD.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Healthy (n=21)</th>
<th>COPD (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Range</td>
</tr>
<tr>
<td>Age (y)</td>
<td>67.4 ± 8.6</td>
<td>50-85</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.7 ± 0.1</td>
<td>1.4-1.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.8 ± 14.6</td>
<td>47-104</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.3 ± 4</td>
<td>20-36</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>98.1 ± 11.9</td>
<td>76-114</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>108 ± 20.6</td>
<td>67-141</td>
</tr>
<tr>
<td>FEV₁/FVC (% predicted)</td>
<td>69.5 ± 7.7</td>
<td>57-85</td>
</tr>
</tbody>
</table>

BMI: body mass index; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity.

* Indicates significant difference between groups at p<0.05.
Table 3.2 Regression model adjusted for age for assessing differences in knee extensors concentric strength and functional performance between people with COPD (n=21) and healthy subjects (n=21). Data are presented as means + SD and 95% CI for the mean difference.

<table>
<thead>
<tr>
<th>Measures</th>
<th>Healthy</th>
<th>COPD</th>
<th>Mean difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Torque (Nm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee extensors</td>
<td>80.5 ± 31.8</td>
<td>56.8 ± 23.9</td>
<td>23.7 (4.7 to 42.7)</td>
<td>0.016*</td>
</tr>
<tr>
<td><strong>Functional performance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSTS (s)</td>
<td>9.3 ± 1.3</td>
<td>11.8 ± 2.3</td>
<td>-2.5 (-3.6 to -1.4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>SSGS (m/s)</td>
<td>1.5 ± 0.2</td>
<td>1.2 ± 0.2</td>
<td>0.3 (0.2 to 0.4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>6MWT (m)</td>
<td>554.9 ± 65</td>
<td>397.5 ± 63.9</td>
<td>157.3 (114.8 to 199.9)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

RSTS: Repetitive Sit-To-Stand; SSGS: Self-Selected Gait Speed; 6MWT: Six-Minute Walk.

* Indicates significant difference between groups at p<0.05.
Table 3.3 Regression model adjusted for age and body mass index (BMI) for assessing differences in thigh muscles CSA and IF between people with COPD (n=21) and healthy subjects (n=21). Data are presented as means ± SD and 95% CI for the mean difference.

<table>
<thead>
<tr>
<th>Measures</th>
<th>Healthy</th>
<th>COPD</th>
<th>Mean difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSA (cm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thigh</td>
<td>82.3 ± 18.9</td>
<td>67.9 ± 16.6</td>
<td>14.4 (4.2 to 24.6)</td>
<td>0.007*</td>
</tr>
<tr>
<td>Knee extensors</td>
<td>36.6 ± 9.4</td>
<td>30.2 ± 6.9</td>
<td>6.4 (1.7 to 11)</td>
<td>0.008*</td>
</tr>
<tr>
<td>Knee flexors</td>
<td>15.2 ± 5.1</td>
<td>12.7 ± 3.7</td>
<td>2.5 (-0.3 to 5.2)</td>
<td>0.076</td>
</tr>
<tr>
<td>Fat infiltration#</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee extensors</td>
<td>101.5 ± 39</td>
<td>190 ± 120.8</td>
<td>-88.4 (-144.8 to -32.1)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Knee flexors</td>
<td>56 ± 39.1</td>
<td>119.1 ± 116.7</td>
<td>-63 (-106.3 to -19.8)</td>
<td>0.005*</td>
</tr>
</tbody>
</table>

# Number of “dark” pixels within the -190 to -30 Hounsfield units, which is the range of attenuation corresponding to adipose tissue.

* Indicates significant difference between groups at p<0.05.
Figure 3.1 CONSORT diagram showing the recruitment process and the reasons for exclusion.

Total participants screened
n=64

Healthy participants
n=26

Excluded (n=5)
Not sedentary=1
Smoking=1
Lung dysfunction=1
Age not matched with other group=2

Healthy participants included
n=21

People with COPD
n=38

Excluded (n=17)
Co-morbidities=2
Smoking=3
Disease severity=8
Oxygen dependent=3
α1-antitrypsin deficiency=1

People with COPD included
n=21
Figure 3.2 Computerized tomography (CT) scan of the mid-thigh in a healthy participant (a) and a person with COPD (b) matched for sex, age and body mass index (BMI). Note the marked atrophy and the greater low attenuation areas (dark) stippling the cross-sectional area (CSA) within the epimysial borders of the various thigh muscles. This indicates a greater presence of intramuscular fat (IF) infiltration in the person with COPD compared with the healthy participant.
Figure 3.3 Scatter plots showing the relationship between intramuscular fat (IF) of knee extensors and the RSTS (a), SSGS (b) and 6MWT (c) in people with COPD (filled circles) and healthy participants (open circles). The level of IF was estimated from the number of “dark” pixels within the range of attenuation corresponding to adipose tissue (-190 to -30 Hounsfield units). Note the greater number of “dark” pixels in the COPD group. Regression lines for people with COPD (solid) and healthy participants (dashed) with correlation coefficients for people with COPD (C) and healthy participants (H) are provided.

- For the RSTS (a): $r=0.43; p=0.06$ (C) and $r=0.18; p=0.43$ (H).
- For the SSGS (b): $r=-0.41; p=0.07$ (C) and $r=-0.22; p=0.30$ (H).
- For the 6MWT (c): $r=-0.21; p=0.36$ (C) and $r=0.10; p=0.67$ (H).
Figure 3.4 Scatter plots showing the relationship between knee extensors concentric strength and the RSTS (a), SSGS (b) and 6MWT (c) in people with COPD (filled circles) and healthy participants (open circles). Regression lines for people with COPD (solid) and healthy participants (dashed) with correlation coefficients for people with COPD (C) and healthy participants (H) are provided.
References


Chapter Four: Risk Factors for Falls II: The Stair Climb Power Test: Associations with Muscle Strength and Functional Performance in People with COPD

4.1 Introduction

Chronic obstructive pulmonary disease (COPD) is a clinical condition with numerous systemic manifestations\(^1\) that compound the loss of function commonly observed in people with this respiratory disease.\(^2\) Skeletal muscle dysfunction has recently gained recognition as an important systemic effect of COPD that contributes to functional limitation in these individuals (see for review\(^3\)). In COPD, skeletal muscle dysfunction is characterized by deficits in muscle strength and endurance,\(^4\) muscle atrophy (i.e., reductions of muscle mass)\(^5\) as well as alterations in muscle composition (e.g., increased intramuscular fat).\(^6\) The relevance of assessing muscle strength in people with COPD has been emphasized in recent studies. For example, Decramer et al., found that knee extensors muscle weakness is a good measure to discriminate between individuals with COPD in regard to either high or low utilization of health care resources.\(^7\) More recently, knee extensors muscle strength has been identified as a simple and powerful predictor of mortality in people with COPD.\(^8\) Other studies confirm the clinical importance of assessing muscle strength as an important factor associated with exercise capacity in COPD.\(^9\)
Muscle strength in people with COPD has traditionally been assessed either with isokinetic or isotonic dynamometers. However, most of these devices are large, expensive, not accessible to clinicians and often require procedures involving complex and time-consuming protocols. Recently, more sophisticated methods for assessing muscle activation such as femoral magnetic stimulation have been made available.\textsuperscript{10} These techniques are appealing to researchers because they permit potential confounders related to the volitional capacity of the subject to be minimized and thus reduce testing variability. However, these methods also require specialized equipment that can be impractical in clinical settings. Thus, alternative functional means of assessing muscle performance in people with COPD are required.

The Stair Climb Power Test (SCPT) has been recently proposed as a simple and safe measure associated with measures of lower limb muscle strength, power and functional performance in older adults.\textsuperscript{11} Since the SCPT does not require additional equipment it could provide a reasonable alternative to more sophisticated tests for measuring lower limb muscle impairments in people with COPD. We conducted a study whose first aim was to compare the SCPT between people with moderate to severe COPD and a healthy control group matched for age, gender and body mass. The second aim was to determine associations between the SCPT and measures of muscle strength and functional performance. We hypothesized that people with COPD would show lower values in the SCPT compared with the healthy controls and that the SCPT would
correlate with knee extensors muscle torque. We also hypothesized that the SCPT would show moderate correlations with measures of functional performance.

4.2 Methods

4.2.1 Participants

People with COPD and healthy control subjects were recruited on a voluntary basis from the local community from October 2008 to June 2009. Flyers of the study were distributed in waiting rooms of hospitals, pulmonary function laboratories, as well as community and senior centers in the area of Vancouver. Inclusion criteria for people with COPD were: moderate to severe disease (stage II or III) based on the Global Initiative for Obstructive Lung Disease (GOLD). Exclusion criteria were: (1) an acute exacerbation within the 3 months prior the study; (2) regular participation in a formal exercise rehabilitation program during the 1-year period prior to the study; (3) currently smoking; (4) co-morbid cardiovascular or neurological disease and lower extremity musculoskeletal problems that interfere with or could cause undue risk during the performance of study testing; (5) use of portable supplemental oxygen on a continuous basis; (6) α-1 antitrypsin deficiency without a significant smoking history.

Inclusion criteria for healthy people were: sedentary healthy people. Sedentary was defined as “only performs activities with low metabolic cost,
including light activities such as slow walking or cooking". Exclusion criteria for healthy people were: (1) regular participation in a formal exercise program during the 1-year period prior to the study; (2) currently smoking; (3) respiratory, cardiovascular, neurological disease and lower extremity musculoskeletal problems that interfere with or would cause undue risk during the performance of study testing.

To estimate an appropriate sample size, anticipated standardized effect sizes from previous studies assessing strength deficits in COPD were calculated by dividing the difference between mean scores of COPD and control groups by the pooled standard deviation. Standardized effect sizes ranged from 0.8 to 1.2. Assuming a standardized effect size of 0.8 and 80% power and an \( \alpha \) level of 0.05, we estimated that at least 20 participants per group were needed to detect differences in muscle strength. The Clinical Research Ethics Board of the University of British Columbia approved the study (Appendix A) and all subjects gave written informed consent (Appendix B) prior to participation.

### 4.2.2 Initial Screening

Prior to testing, participants were asked to complete a risk-screening questionnaire (Appendix C) to guarantee suitability for participation and minimize any potential risk. To confirm the severity of COPD or to rule out pulmonary disease individuals with COPD and healthy subjects, respectively, underwent spirometry using a portable spirometer (CPFS/D spirometer, Medi Graphics
Corp., MN, USA). Spirometry was performed according to the guidelines of the American Thoracic Society (ATS) and European Respiratory Society (ERS).\textsuperscript{17}

4.2.3 Measurements

4.2.3.1 Stair Climb Power Test (SCPT)

The SCPT was assessed by recording the time required to climb a staircase of 10 stairs as fast and safely as possible. Briefly, participants were instructed to ascend the 10 stairs as fast as they could. If required, they were allowed to use the handrail only to increase their own safety. However, they were specifically instructed not to use the handrail to ascend the stairs faster. A more detailed description of the procedures of the SCPT is available elsewhere.\textsuperscript{11} Briefly, velocity is calculated by dividing the distance, which in this case is the total vertical height of stairs, by the time required to climb the 10 stairs (v=d/t). Force is calculated by multiplying body weight by acceleration (F=m·a), the latter of is the constant for the effect of gravity (9.81N). Thus, power (P=F·v) for the SCPT is determined by the equation:

\[
\text{SCPT} = \left[\frac{\text{total vertical height of stairs}}{\text{time}}\right] \times \left[\text{body weight} \times 9.81\right].\textsuperscript{11}
\]

Participants performed two trials of the SCPT with at least two minutes of recovery in between. The same tester (MR) timed the SCPT manually with a stopwatch and the best of the two trials was saved for further analysis.
4.2.3.2 Knee Extensors and Flexors Muscle Strength

Concentric and eccentric average peak torque of the knee extensors and flexors of the dominant leg (determined by preference for kicking a ball) was assessed on the KinCom® dynamometer version 5.30 (Chattanooga Group Inc., TN, USA). Briefly, participants were seated on the KinCom® with the knee joint aligned with the center of rotation of the dynamometer. The resistance pad was positioned distally at 75% distance from the lateral epicondyle to the lateral malleolus. Stabilizing belts were used to secure the pelvis and the upper body and to minimize extraneous movements. An angular velocity of 30°/s was chosen because it has shown high reproducibility (ICC=0.99) in a previous study of people with COPD.™ The testing range of motion (ROM) was set at 10° to 90° and 20° to 80° of knee flexion for knee extensors and flexors, respectively. This ROM was selected to diminish joint discomfort and force variability produced by the action of the hamstrings at the end of knee extension. After a warm-up consisting of 5 sub-maximal contractions, participants were asked to extend their knee as fast and hard as they could. Knee flexors were tested with the same procedures but by asking participants to bend their knee. The same apparatus was used to assess isometric knee extensors average peak torque at 90° of knee flexion. In this case, participants were asked to extend their knee as fast and hard as they could and maintain force production for three seconds. To ensure maximal effort, participants were vigorously encouraged. Three maximal trials for each muscle contraction and muscle group were recorded interspersed by two-minute rest recovery intervals. The three trials were averaged to obtain the peak torque.
4.2.3.3 Functional Performance

Functional performance was assessed with the Timed Up-and-Go (TUG) and the Six-Minute Walk (6MWT) tests. Briefly, the TUG test was assessed by timing the ability to stand from a chair, walk three meters, cross a line marked on the floor, turn around, walk back and sit down. Participants performed two trials of the TUG with two minutes of recovery in between. The same tester (MR) timed the TUG manually and the best of the two trials was saved for further analysis. The 6MWT was performed according to the guidelines of the ATS. Briefly, participants were instructed to walk as far as they could for 6 minutes in a 25-meter hallway and the distance walked was recorded.

4.2.4 Statistical Analyses

Assumptions of normality of data distribution for all variables were explored through histograms and normality plots. Pearson’s or Spearman’s (for non normally distributed data) correlations were used to explore associations and multicolinearity among dependent variables and potential covariates. Colinear covariates showing weaker association ($r<0.5$) were eliminated. A regression model with age and body weight as covariates was used to determine differences between groups in all measures. The regression model was adjusted for age and body weight because these variables were independently correlated with measures of functional performance and muscle torque, respectively. Pearson’s product-moment correlations were used to explore associations between the SCPT and measures of knee extensors muscle torque and functional
performance. The strength of the correlations ($r$) was categorized as low (0-0.25), moderate (>0.25-0.50), strong (>0.50-0.75) and very strong (>0.75).\textsuperscript{15} Data are presented as means ± standard deviation (SD) and 95% confidence intervals (CI). All analyses were performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago., IL., USA) using two-tailed probability tests with a level of significance set at $p<0.05$. The SPSS syntax codes for the main analyses are shown in Appendix F.

### 4.3 Results

#### 4.3.1 Participants

Thirty-eight people with COPD and 26 healthy control subjects were recruited. Twenty-two participants were excluded because they did not meet the inclusion criteria. The reasons for exclusion and the details of the recruitment process are illustrated in Figure 4.1. After exclusion, 21 non-oxygen dependent, clinically stable individuals (11 males and 10 females) with moderate to severe COPD\textsuperscript{12} and 21 sedentary healthy control subjects matched for age, sex and BMI were included in the study. Participants' characteristics are illustrated in Table 4.1. People with COPD were slightly older (mean difference=3.8 years; 95% CI: -1.3 to 9) ($p=0.08$). In addition, people with COPD showed moderate to severe levels of airflow limitation, which was confirmed by the lower values in spirometric measures (FEV\textsubscript{1}, FVC and FEV\textsubscript{1}/FVC) in comparison with the healthy group ($p<0.05$).
4.3.2 Stair Climb Power Test (SCPT)

A detailed description of the results of the regression model for the SCPT is shown in Table 4.2. All participants were able to perform the SCPT safely and no adverse effects or unexpected events were reported. Compared to healthy subjects, people with COPD developed, on average, 28% lower power during the SCPT. Test-retest reliability for the SCPT within the same session was very high (ICC=0.9).

4.3.3 Knee Extensors and Flexors Muscle Strength and Functional Performance

The results of the regression model for measures of muscle torque and functional performance are shown in Table 4.2. Compared to healthy control subjects, people with COPD showed significantly lower values in all torque measures (~32%), except for eccentric knee flexion, whose difference was not statistically significant. Performance in the TUG in the group with COPD was significantly lower by 23%. Test-retest reliability for the TUG within the same session was very high (ICC=0.95). The distance walked in the 6MWT by the group with COPD was 28% lower compared to the healthy group.

4.3.4 Association Between the SCPT and Measures of Muscle Strength and Functional Performance

A graphical analysis of the data showed that in the healthy group, the SCPT displayed a linear relationship with all measures of muscle torque. The
Pearson’s correlation analysis confirmed that the SCPT was very strongly associated \((r \geq 0.69; p \leq 0.001)\) with measures of knee extensors concentric, eccentric and isometric torque in healthy control subjects. In contrast, associations between the SCPT and measures of strength in the group with COPD tended to be more moderate and only statistically significant for eccentric \((r=0.53; p=0.015)\) and isometric \((r=0.46; p=0.043)\) knee extensors. When the relationships among the SCPT and measures of functional performance were explored (Figure 4.2), the Pearson’s correlation analysis also revealed notable differences between groups. In the group with COPD, the SCPT was strongly associated with the 6MWT \((r=0.68; p=0.001)\) and moderately associated with the TUG \((r=-0.46; p=0.04)\). In contrast, the healthy group only showed a trend of a significant relationship between the SCPT and the 6MWT (Figure 4.2).

### 4.4 Discussion

The main finding of this study is that people with moderate to severe COPD developed significantly lower power during the SCPT compared with healthy control subjects matched for age, gender and BMI. Interestingly, while the SCPT was only moderately related to thigh muscle strength in the group with COPD, this relationship was very strong in the healthy group. In contrast, the SCPT was strongly to moderately related to the 6MWT and the TUG in the group with COPD, however, weaker or non significant relationships were found in healthy participants.
The lower performance observed in the SCPT suggests that, similar to the deficits in strength previously reported in these individuals, muscle power is impaired in people with COPD. Although the preferential atrophy of fast twitch muscle fibers in the lower limb muscles of these individuals is suggestive of a decreased ability to perform activities involving fast and powerful muscle contractions such as those required for the SCPT, the study of muscle power, has received little attention in COPD. Lower limb muscle power maybe particularly important to evaluate clinically because it has been shown to be more closely related to postural control and functional performance than muscle strength. Furthermore, since rapid anticipatory movements are required for the maintenance of postural control, it has been suggested that muscle power might be more important in the prevention of falls than strength.

In this study, we explored the use of the SCPT, which is a simple and functionally relevant test associated with leg muscle power in older adults. Most functional tests previously used in people with COPD tend to focus on measures of aerobic capacity (e.g., walking tests), rather than muscle power. The SCPT, in contrast, emphasizes the capacity to exert rapid muscle contractions with the muscles of the lower limb during stair climbing. While our results suggest that leg muscle power is possibly reduced in people with COPD, we did not explicitly measure muscle power, and therefore we cannot confirm that the SCPT is associated with more mechanistic measures of power in people with COPD. Certainly, the fact that the SCPT showed only a moderate association with
measures of knee extensors muscle torque in the group with COPD suggests that factors others than those related to muscle power can affect the performance of this test.

Since muscle power and strength are usually closely related, we hypothesized that the SCPT could be related to measures of knee extensors muscle torque in these individuals. Of some surprise, knee extensors muscle torque in people with COPD was only moderately correlated with the SCPT in contrast to the strong association in the healthy group. The high correlation of the SCPT with knee extensors muscle torque in the healthy group is consistent with previous reports, which found the SCPT to be associated \((r\geq0.47)\) to leg muscle power in older adults assessed with more mechanistic methods (i.e., isotonic pneumatic machines). In contrast, our results indicate that the SCPT cannot be used as a surrogate for muscle strength in people with COPD.

A potential explanation for the different degree of association between the SCPT and measures of muscle strength between groups could be that factors other than strength come into play during the SCPT in people with COPD. Indeed, our results indicate that during the performance of the SCPT people with COPD were not able to develop powerful muscle contractions in accordance with their strength levels. Stair climbing is a complex functional task that requires a coordinated integration of various body systems (e.g., musculoskeletal, pulmonary, cardiovascular and vestibular systems). It is thus possible that other
aspects such as ventilatory limitation, reduced postural control or even fear of falling\textsuperscript{31} limited the performance of the SCPT in the group with COPD. In contrast, the apparent confidence of healthy participants during the SCPT likely enhanced their capacity to develop powerful muscle contractions, which were more closely dependent on their muscle strength values. These results suggest differences in the relationship between muscle strength and the SCPT between groups and emphasize the importance of evaluating these unique relationships independently.

In addition to the deficits in muscle strength, the group with COPD showed significant deficits in functional performance assessed by the TUG and 6MWT. These results are consistent with the findings of a previous report that used the TUG and the 6MWT to investigate whether these functional tests were sensitive enough to discriminate between fallers and non-fallers in a group of people with COPD.\textsuperscript{32} Compared to the results of our study, however, the scores obtained in the TUG and 6MWT in the fall risk study were approximately 25% lower possibly due to the greater level of impairment of the participants of the latter study, as reflected by their lower FEV\textsubscript{1} (41.5 ± 17% predicted) and the use of supplemental oxygen in 46% of their participants. In spite of these small differences, our results are consistent with recent studies that used similar methods and found deficits in functional performance in people with COPD when compared to healthy subjects.\textsuperscript{33-35}
We also explored similarities and differences between the SCPT and other functional tests, including the 6MWT and the TUG. In view of a recent report that showed no association between the time required to climb 44 stairs and the distance covered in the 6MWT in people with severe COPD (FEV$_1$=33 ± 13% predicted), the strong association between the SCPT and the 6MWT in the group with COPD was not expected. Indeed, while the short and intense muscle contractions elicited during the SCPT indicates that this test requires mainly the activation of anaerobic processes, the 6MWT has been traditionally used as a “gold standard” measure of aerobic capacity. A plausible explanation for the strong association between the SCPT and the 6MWT could be that because of their functional impairment, the 6MWT imposes a high physiological demand on people with COPD. In this regard, Marquis et al. used oxygen consumption analysis and electromyography (EMG) of lower limb muscles to show that people with moderate to severe COPD performed the 6MWT at relatively higher metabolic intensity (i.e., greater percentage of O$_2$ consumption) and muscle work (i.e. faster reduction in EMG median frequency) compared to healthy subjects. Furthermore, recent studies confirm that the same functional test (i.e., 6MWT) provides different physiological information depending on the level and types of impairments of the participants.

Despite a trend suggestive of a moderate relationship between the SCPT and the 6MWT (Figure 4.2), no significant associations between the SCPT and measures of functional performance were found in the healthy group. At face
value, these data may appear to conflict with a previous report that showed a very strong inverse association ($r=-0.83$) between the time required to complete the SCPT and the distance covered in the 6MWT in older adults ($72.7 \pm 4.6$ years). An explanation for this disparity of findings is that power (which considers distance climbed and body weight), not the time to complete the SCPT, was calculated in our study. In fact, when we correlated the time to complete the SCPT with the 6MWT in the healthy group, the association was similar to the one reported in the previous study ($r=-0.7; p<0.001$).

Another potential explanation for the lower associations between the SCPT and the 6MWT and TUG in healthy control subjects is that the high levels of power developed during the SCPT in this group only contribute marginally towards the performance of these functional tests. For example, a recent study indicates that the capacity to produce muscle power at high velocity and lower resistance is more important during the performance of a walking task than simply the magnitude of muscle power or strength. This finding is consistent with the analysis of residuals in our scatter plot (Figure 4.2) that reveals that two healthy participants were able to produce higher levels of power during the SCPT that were not accompanied with greater walked distance in the 6MWT. Thus, the relationship between the SCPT and other measures of functional performance such as the 6MWT may not follow a linear pattern, but rather after a threshold of muscle power is achieved, further improvements in muscle power do not translate to better functional performance.
4.5 Conclusions

In summary, people with moderate to severe COPD show deficits in the SCPT as well as measures of muscle strength and functional performance. The deficits in the SCPT are indicative of reduced leg muscle power in people with COPD, however, more investigations are required to confirm whether the SCPT is associated with more mechanistic measures of muscle power in these individuals. The SCPT is only moderately associated with knee extensors muscle torque in people with COPD and thus it cannot be used as a simple surrogate for muscle strength. However, the SCPT appears to be a less expensive and yet safe and informative alternative to test functional performance in people with COPD. Further studies assessing the nature of the relationship between measures of muscle strength, power and functional performance in people with COPD are required.
Table 4.1 Characteristics of the participants of the study. Data are presented as means + SD.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Healthy (n=21)</th>
<th>COPD (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Range</td>
</tr>
<tr>
<td>Age (y)</td>
<td>67.4 ± 8.6</td>
<td>50-85</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.7 ± 0.1</td>
<td>1.4-1.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.8 ± 14.6</td>
<td>47-104</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.3 ± 4</td>
<td>20-36</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>98.1 ± 11.9</td>
<td>76-114</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>108 ± 20.6</td>
<td>67-141</td>
</tr>
<tr>
<td>FEV₁/FVC (% predicted)</td>
<td>69.5 ± 7.7</td>
<td>57-85</td>
</tr>
</tbody>
</table>

BMI: body mass index; FEV₁: forced expiratory volume in the first second; FVC: forced vital capacity

* Indicates significant difference between groups at p<0.05
Table 4.2 Regression model adjusted for age and body weight for assessing differences between people with COPD (n=21) and healthy subjects (n=21) in the SCPT and measures of muscle torque and functional performance. Data are presented as means ± SD and 95% CI of the mean difference.

<table>
<thead>
<tr>
<th>Measures</th>
<th>Healthy</th>
<th>COPD</th>
<th>Mean difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCPT (W)</strong></td>
<td>378.2 ± 121.3</td>
<td>266.2 ± 80.3</td>
<td>112.1 (74.2 to 150)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Torque (Nm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee ext concentric</td>
<td>80.3 ± 31.8</td>
<td>55.7 ± 23.8</td>
<td>24.6 (10.6 to 38.6)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Knee ext eccentric</td>
<td>144.4 ± 50.9</td>
<td>98.5 ± 29.2</td>
<td>45.9 (25.8 to 66.1)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Knee ext isometric</td>
<td>74.8 ± 21.3</td>
<td>100.2 ± 31.6</td>
<td>25.3 (11 to 39.7)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Knee flex concentric</td>
<td>37.8 ± 15.4</td>
<td>28.4 ± 10.9</td>
<td>9.5 (1.3 to 17.6)</td>
<td>0.024*</td>
</tr>
<tr>
<td>Knee flex eccentric</td>
<td>54.5 ± 19.7</td>
<td>46.5 ± 17.1</td>
<td>8 (-2 to 18)</td>
<td>0.114</td>
</tr>
<tr>
<td><strong>Functional Performance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TUG (s)</td>
<td>7.7 ± 1.1</td>
<td>9.5 ± 2.3</td>
<td>1.8 (0.7 to 2.9)</td>
<td>0.002*</td>
</tr>
<tr>
<td>6MWT (m)</td>
<td>554.9 ± 65</td>
<td>394.6 ± 64.1</td>
<td>160.2 (117.4 to 203)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

SCPT: Stair Climb Power Test; ext: extensors; flex: flexors; TUG: Timed Up and Go; 6MWT: Six-Minute Walk.
* Indicates significant difference between groups at p<0.05
Figure 4.1 CONSORT diagram showing the recruitment process and the reasons for exclusion.

**Total participants screened**

n=64

- **Healthy participants**
  - n=26
  - Excluded (n=5)
    - Not sedentary=1
    - Smoking=1
    - Lung dysfunction=1
    - Age not matched with other group=2
  - Healthy participants included
    - n=21

- **People with COPD**
  - n=38
  - Excluded (n=17)
    - Co-morbidities=2
    - Smoking=3
    - Disease severity=8
    - Oxygen dependent=3
    - α1-antitrypsin deficiency=1
  - People with COPD included
    - n=21
Figure 4.2 Scatter plots showing associations of the SCPT and the 6MWT (a) and TUG (b) tests in people with COPD (filled circles) and healthy controls (open circles). Regression lines for people with COPD (solid) and healthy participants (dashed) with correlation coefficients for people with COPD (C) and healthy participants (H) are provided.

![Figure 4.2 Scatter plots showing associations of the SCPT and the 6MWT (a) and TUG (b) tests in people with COPD (filled circles) and healthy controls (open circles). Regression lines for people with COPD (solid) and healthy participants (dashed) with correlation coefficients for people with COPD (C) and healthy participants (H) are provided.](image-url)
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5.1 Introduction

During strength testing, motivational strategies such as verbal encouragement and visual feedback are commonly used to maximize subject’s effort and to minimize the influence of subject’s volitional limitations, which could compromise the validity of the test results. Despite these strategies, the degree of individuals’ effort during voluntary strength testing and its influence in the level of force developed are difficult to control. To circumvent this limitation, non-volitional methods for assessing muscle strength such as muscle nerve stimulation are performed (see Man et al., for review). In short, these techniques apply an external magnetic or electrical stimulus to depolarize the muscle nerve and thus elicit an involuntary muscle contraction. These methods are appealing to researchers because they permit potential confounders related to the volitional capacity of the subject to be minimized, increasing, theoretically, testing validity and reliability. In addition, the application of these techniques allows for the estimation of the degree of muscle activation during voluntary contractions.

Different strategies can be used to estimate the level of muscle activation using either magnetic or electrical nerve stimulation, including the twitch interpolation technique, originally developed by Merton. This technique has been extensively used to assess muscle activation as well neurological

\[^{4}\text{This chapter is a pilot study.}\]
mechanisms involved in central fatigue. Briefly, the twitch interpolation technique consists of superimposing a supramaximal pulse to the muscle nerve during a maximal voluntary contraction (see Shield et al., for review). If the muscle is fully activated, the superimposed pulse does not increase the force produced voluntarily. In contrast, if the muscle is not fully activated, the superimposed pulse elicits an increase of force, also known as a superimposed twitch (ST). Theoretically, the magnitude of the ST determines the level of potential force that the subject is not able to develop voluntarily (i.e., force reserve). To determine the level of muscle activation, the ratio of the superimposed twitch (ST) and a potentiated twitch (PT), which is delivered at rest after the voluntary muscle contraction, is then calculated.

The main advantage of magnetic over electrical stimulation is that muscle discomfort is minimal, which makes it more suitable, especially for older people with chronic conditions. Recent studies have used magnetic stimulation to assess knee extensors muscle activation in people with chronic obstructive pulmonary disease (COPD). The main findings of these studies are that muscle activation is decreased in people with COPD compared with healthy control subjects and that muscle activation capacity can be increased with appropriate training interventions. Due to the inability of these individuals to perform maximal voluntary contractions, the majority of studies have used superimposed maximal magnetic pulses during sub-maximal muscle contractions at different levels of force to estimate the level of muscle activation. However, several
studies have indicated that the relationship of force and muscle activation does not follow a linear pattern. Since the twitch interpolation technique uses maximal voluntary muscle contractions, it is less affected by the non-linear relationship of force and muscle activation. The main aim of this pilot study was therefore to compare knee extensors muscle activation using femoral magnetic nerve stimulation and twitch interpolation in a group of people with moderate to severe COPD and a healthy control group. It was hypothesized that both non-volitional muscle force and muscle activation would be reduced in people with COPD compared to healthy subjects.

5.2 Methods

5.2.1 Participants

People with COPD and healthy control subjects were recruited on a voluntary basis from the local community. Flyers of the study were distributed in waiting rooms of hospitals, pulmonary function laboratories, as well as community and senior centers in the area of Vancouver. Inclusion criteria for people with COPD were: moderate to severe disease (stage II or III) based on the Global Initiative for Obstructive Lung Disease (GOLD). Exclusion criteria were: (1) an acute exacerbation within the 3 months prior the study; (2) regular participation in a formal exercise rehabilitation program during the 1-year period prior to the study; (3) currently smoking; (4) co-morbid cardiovascular or neurological disease and lower extremity musculoskeletal problems that would interfere with or could cause undue risk during the performance of study testing;
(5) use of portable supplemental oxygen on a continuous basis; (6) \(\alpha-1\) antitrypsin deficiency without a significant smoking history; (7) use of a cardiac pacemaker or other electronically, magnetically or mechanically activated implants; (8) inserted metallic clips or other metallic objects.

Inclusion criteria for healthy people were: sedentary healthy people. Sedentary was defined as “only performs activities with low metabolic cost, including light activities such as slow walking or cooking”. Exclusion criteria for healthy people were: (1) regular participation in a formal exercise program during the 1-year period prior to the study; (2) currently smoking; (3) respiratory, cardiovascular, neurological disease and lower extremity musculoskeletal problems that would interfere with or could cause undue risk during the performance of study testing: (4) use of a cardiac pacemaker or other electronically, magnetically or mechanically activated implants; (5) inserted metallic clips or other metallic objects. The Clinical Research Ethics Board of the University of British Columbia approved the study (Appendix A) and all subjects gave written informed consent prior to participation (Appendix B).

5.2.2 Measurements

5.2.2.1 Muscle Activation

Magnetic pulses were delivered through a double 40-mm figure-eight coil powered by two Magstim 200\(^\circ\) stimulators (Magstim Co., Whitland, Wales, UK) synchronized in bistimulation mode (BiStim). The use of two stimulators working
synchronously allows for an increased maximal power up to 113% compared to one unit working alone, which is considered to be critical to ensure supramaximal nerve stimulation. The power output of the magnetic field was set as a fraction of the maximal power delivered by each stimulator and progressively increased depending on the requirements of the protocol. The KinCom® dynamometer (version 5.30, Chattanooga Group Inc., Hixson, TN, USA) was used to record muscle torque during testing. The following sections describe in detail the sequence of steps followed to measure muscle activation.

### 5.2.2.1.1 Coil Location

The most appropriate coil location for femoral nerve stimulation was determined individually for each patient. Participants were comfortably seated on the KinCom® with the knee joint of the dominant leg aligned with the center of rotation of the dynamometer. The resistance pad was positioned distally at 75% distance from the lateral epicondyle to the lateral malleolus and the joint angle was set at 90° of knee flexion. This position was maintained throughout the entire experimental protocol. Next, the femoral nerve of the dominant leg was located at the base of the femoral triangle. The femoral nerve is lateral to the femoral artery and vein such that it can be located by placement just lateral to the palpation of the femoral pulse. The center of the coil was firmly positioned on the anatomical landmark by pointing the vertex longitudinally. To ensure the best location, 5 to 10 pulses at 50% of maximum power were manually delivered at rest. The best location was determined after minor positional adjustments and based on the
position of the coil that resulted in the highest force output (i.e., highest twitch) observed. The precise coil position was then marked with tape and both the position and angle of the coil remained the same throughout the entire experiment.

5.2.2.1.2 Supramaximality Test

Since the use of supramaximal pulses is necessary to reliably measure muscle activation with the twitch interpolation technique\(^{11}\) an incremental protocol to test for supramaximality was performed. Briefly, with the subject in a resting position (i.e., without contracting the muscle), a single magnetic pulse was delivered manually every 30 seconds at 70, 80, 90, 100 and 100% of maximum power.\(^{12}\) The last pulse at maximum power (100%) was repeated twice to elucidate the potential influence of an accumulated postactivation potentiation effect. The resultant torque data were acquired at a sampling rate of 100Hz and collected with a software application built on Labview® software (National Instruments, Austin, Texas, USA). To determine whether a plateau in the force output was achieved, raw data were then plotted and the force generated in each twitch analyzed with Matlab® (The Mathworks, MA, USA) (Figure 5.1). The plateau is considered to be a sign of supramaximal activation of the femoral nerve (i.e., the femoral nerve is fully activated)\(^{11}\) and it is defined as no further increment of force after the pulse at 90% of maximum power. In other words, to ensure maximal stimulation, the maximum force output had to be reached before the maximal pulses were delivered at 100% of maximum power of the two
5.2.2.1.3 Resting Twitch (RT)

After the incremental protocol to test for supramaximality, participants rested for 20 minutes in a seated position to minimize the influence of muscle post-activation potentiation. Further, participants were asked to remain steady on the KinCom® dynamometer and maintain a relaxed position without contracting the knee extensors. Then, a maximal (100%) magnetic pulse was delivered at rest. The same procedure was repeated three times interspersed with two-minute resting intervals. Torque data were collected at a sampling rate of 1000Hz and the force generated during each resting twitch (RT) was analyzed with Matlab® (Figure 5.2). The average torque of the three RTs was calculated for further analysis. The RT is regarded as the non-volitional contractile capacity of the subject’s muscle.

5.2.2.1.4 Knee Extensors Isometric Muscle Force

Maximal voluntary isometric average force of the knee extensors at 90° of knee flexion was assessed on the KinCom® dynamometer. Stabilizing belts were used to secure the pelvis and the upper body, and to minimize participants’ extraneous movements. After a warm-up consisting of 5 sub-maximal contractions, participants were asked to extend their knee as fast and hard as they could and maintain force production for three seconds. To ensure maximal efforts, participants were vigorously encouraged. Three maximal trials were
recorded interspersed with two-minute rest intervals. Data were collected at a sampling rate of 1000Hz and analyzed with Matlab® to determine the average peak torque, which was calculated from the three trials.

5.2.2.1.5 Twitch Interpolation Technique

A custom-made software application built on Labview® software (National Instruments, Austin, Texas, USA) was designed to acquire and define in quasi-real time the force signal from the KinCom® and to generate magnetic pulses from the Magstim®. This customized software aimed to reduce variability by reliably detecting the plateau of maximal force and triggering the superimposed pulse at a specific user-defined timing. Briefly, participants were instructed to extend their knee as fast and hard as they could and maintain force production for three seconds. To ensure maximal contractions, participants were prompted to maintain constant force levels above the 95% average peak of force threshold determined previously in the isometric force test.³ As a visual target, each participant had a threshold displayed on a computer screen by means of a blue marker zone that had to be reached during each contraction. The importance of using standardized protocols and feedback strategies to ensure maximal contractions during the twitch interpolation technique has been emphasized in previous studies.³
Two seconds after the subject reached the required threshold of torque (95% average peak force), the computer delivered a superimposed maximal pulse, while the participant was maintaining a steady force at the threshold level (i.e., force plateau). The threshold was detected using a force derivative level, which represents the rate of change of force, set at the 95% average peak force determined individually for each participant. In other words, the software application detected the decay of force (i.e., plateau) and triggered the maximal superimposed pulse two seconds afterwards. Immediately after the superimposed pulse was delivered, participants were instructed to stop extending knee extensors and to remain steady. Five seconds after the superimposed pulse was delivered, a second pulse (i.e., potentiated pulse) was automatically delivered at rest.\textsuperscript{16} This protocol was repeated three times interspersed with two-minute resting intervals between trials. The level of muscle activation was calculated from the equation:

\[
(1-\frac{ST}{PT}) \times 100
\]

in which ST is the superimposed twitch generated during the plateau of force and PT is the potentiated twitch generated 5 seconds after the ST.\textsuperscript{3} Since during maximal contractions, the ST appears to be potentiated, the use of PT to calculate the level of muscle activation is preferable.\textsuperscript{17} Post-activation potentiation was calculated from the ratio RT/PT,\textsuperscript{3} RT being the resting twitch and PT the potentiated twitch. Figure 5.3 shows a diagram with the different twitches generated during the twitch interpolation technique protocol.
5.2.3 Statistical Analyses

Assumptions for normality of distribution for all variables were explored through histograms and normal plots. Differences between groups in the supramaximal test were compared with two-way (group and stimulation power level) repeated-measures analysis of variance (ANOVA). Differences in RTs, knee extensors muscle force, PTs, muscle activation and post-activation potentiation were compared with the Student’s t-test. Bivariate correlations were used to explore associations between all these parameters. The strength of the correlations ($r$) was categorized as low (0-0.25), moderate (>0.25-0.50), strong (>0.50-0.75) and very strong (>0.75). Data are presented as means ± SD unless otherwise stated. All analyses were performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) using two-tailed probability tests with a level of significance set at $p<0.05$. The SPSS syntax codes for the main analyses are shown in Appendix G.

5.3 Results

5.3.1 Participants

Twelve (6 males and 6 females) non-oxygen dependent, clinically stable individuals with moderate to severe COPD and 13 (3 males and 10 females) sedentary healthy controls participated in the study. Participants’ characteristics are illustrated in Table 5.1. Both groups had similar anthropometric characteristics. People with COPD were slightly older, but the difference between groups was not significant ($p=0.2$). In addition, people with COPD showed
moderate to severe levels of airflow limitation, which was confirmed by the significantly lower values in spirometric measures in comparison with the healthy group (p<0.05).

5.3.2 Supramaximality Test

The results of the supramaximality test are shown in Figure 5.4. Healthy subjects produced higher twitches than people with COPD at each power level of the incremental test. However, the repeated-measures ANOVA showed no significant differences (p>0.05) between groups at any power level. More importantly, the plateau of force, sign of supramaximal activation, was not achieved by any of the participants.

5.3.3 Resting Twitch (RT) and Knee Extensors Isometric Muscle Force

The values corresponding to the RT and knee extensors isometric torque are shown in Table 5.2. The non-volitional force, assessed as the mean RT, tended to be higher in the healthy group, however, differences between groups were not statistically significant. Similarly, healthy people showed a greater capacity to produce voluntary isometric force that, however, was not significantly different compared with the group with COPD. The RT was not associated with isometric force in the group with COPD. In contrast, a strong (r=0.56;p=0.05) association was observed in the healthy group (Figure 5.5).
5.3.4 Muscle Activation

We were not able to determine differences in the level of activation with the twitch interpolation technique. This was because the magnetic superimposed maximal pulse did not elicit any measurable increment of force in any of the participants and, hence, the ST could not be calculated.

5.3.5 Post-activation Potentiation

The mean PT generated 5 seconds after the superimposed pulse was also higher in the healthy group (Table 5.2). However, differences between groups in this parameter were not significant. The PT was strongly associated with the RT in both groups ($r \geq 0.73; p < 0.005$). However, the association between the PT with isometric force was only significant ($r = 0.58; p = 0.04$) in the healthy group (Figure 5.5). When post-activation potentiation was calculated from the ratio RT/PT, both groups showed similar values (Table 5.2).

5.4 Discussion

The main finding of this pilot study was that the use of the twitch interpolation technique with magnetic stimulation to assess peripheral muscle activation is limited by the inability to maximally activate the femoral nerve. Indeed, the results of the supramaximality test (Figure 5.4) showed that none of the participants in the study were able to reach a plateau of evoked force, a sign of maximality. We speculate that the lack of supramaximality was the main cause for not detecting STs in any of the participants. As a result we were unable to reliably calculate differences in muscle activation between groups with the twitch
interpolation technique. A second main finding of this study is that people with COPD showed non-significant lower levels of voluntary isometric force, non-volitional force (RT) and post-activation potentiation (ST/PT) compared to healthy subjects. The third finding is that the groups showed different relationships between voluntary and evoked muscle force. For example, the lack of association between voluntary force and the RT and PT in the group with COPD contrasted with the strong associations found in the healthy group (Figure 5.5).

The inability to achieve supramaximality observed in our study conflicts with some but not all investigations that used magnetic stimulation in different population groups. For example, Polkey et al., found that supramaximal was achieved at a mean of 83% of the magnetic stimulator’s maximal output in a group of 10 healthy subjects and 10 people with muscle weakness. Further, Vivodtzev et al., used a similar protocol in people with COPD and confirmed that supramaximality was achieved, although specific data were not reported. In sharp contrast, O'Brien et al., recently compared electrical versus magnetic stimulation in 10 healthy males and reported that magnetic stimulation was unable to elicit supramaximal force. These conflicting results are difficult to explain and will require more detailed investigations that are beyond the scope of this pilot study. A possibility is that methodological differences among studies could explain these results. For example, we used a custom-made 40-mm figure-eight coil, which, according to the manufacturer, is specifically designed to assess peripheral muscle activation. Some previous
studies, however, reported using larger coils (70-mm) that appear to deliver greater magnetic fields. It is unclear whether the selection of the coil could have limited the strength field of the magnetic pulse and if this explains the lack of supramaximality in our study. The majority of previous studies have used a strain gauge to measure changes in tension with femoral nerve stimulation. It is possible that, compared to the KinCom® dynamometer, the use of these force transduction mechanisms could be more sensitive to detect changes in force during the twitch interpolation technique. Other methodological differences such as the selection of joint angle, the level of subcutaneous fat and even the time of the day of the testing may affect the results of the twitch interpolation technique.

Consistent with a previous study people with COPD showed lower levels of knee extensors isometric voluntary force. Given the larger number of males in the group with COPD, the fact that differences between groups in muscle force were statistically non-significant should be interpreted with caution. Males tend to produce greater muscle torques compared with females and thus it is possible that the disproportionate number of males in the group with COPD could have attenuated differences between groups. Interestingly, non-volitional torque (RT) and post-activation potentiation (ST/PT) were also lower in people with COPD compared to healthy subjects. These findings are congruent with previous studies that compared non-voluntary muscle torque with magnetic stimulation in people with COPD and healthy subjects. Several factors can explain the lower levels of non-volitional force developed by the group with COPD. For example,
recent studies suggest that apart from muscular alterations (e.g., decreased muscle mass), reduced levels of physical activity contribute substantially to the reduction in non-volitional force. For example, Vivodtzev et al., found that the non-volitional force (RT) increased after 8 weeks of resistance training in a group of 23 healthy sedentary individuals.\textsuperscript{20}

Another interesting finding of this study concerns the differences in the association of measures of voluntary and involuntary muscle force. Strong associations between the RT and the PT and isometric force were observed only in the healthy group (Figure 5.5). The lack of associations between voluntary and non-volitional force in the people with COPD indicates that at the same level of neural drive (i.e., stimulator output), people with COPD tend to produce lower levels of force. This lower neuromuscular efficiency is indicative of alterations in the muscle contractile capacity of these individuals. Due to the multisystemic nature of COPD, the potential underlying mechanisms for these alterations in these individuals are numerous. For example, muscle atrophy and reduced muscle quality are well described among people with COPD.\textsuperscript{23,24} In addition, while non-volitional torque (RT) is relatively independent of central activation factors, whether alterations in the excitation contraction coupling could influence the lower RT observed in people with COPD is currently unknown.
5.5 Conclusions

The use of the twitch interpolation technique with magnetic stimulation to assess peripheral muscle activation is limited by the inability to maximally activate the muscle nerve. Due to this limitation, we were unable to reliably calculate differences in muscle activation between groups with the twitch. Nevertheless, people with COPD showed a tendency toward lower levels of non-volitional force compared with the healthy group. In addition, people with COPD showed a lack of association between measures of voluntary and involuntary force, which is suggestive of a deterioration of the muscle contractile capacity.
**Table 5.1 Characteristics of the participants of the pilot study.** Data are presented as means ± SD.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Healthy (n=13)</th>
<th>COPD (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Range</td>
</tr>
<tr>
<td>Age (y)</td>
<td>66 ± 9.6</td>
<td>50-85</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.6 ± 0.1</td>
<td>1.4-1.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.5 ± 11.6</td>
<td>47-93</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.4 ± 4</td>
<td>20-30.4</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>97.6 ± 13.1</td>
<td>76-114</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>106 ± 21.6</td>
<td>61-133</td>
</tr>
<tr>
<td>FEV₁/FVC (% predicted)</td>
<td>70.5 ± 8.9</td>
<td>57-85</td>
</tr>
</tbody>
</table>

BMI: body mass index; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity

* Indicates significant difference between groups at p<0.05
Table 5.2 Differences between groups in the resting twitch (RT), knee extensors isometric force, potentiated twitch (PT) and post-activation potentiation level. Data are presented as means ± SD.

<table>
<thead>
<tr>
<th>Measures</th>
<th>Healthy (n=13)</th>
<th>COPD (n=12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting twitch (N)</td>
<td>46.6 ± 12.7</td>
<td>40.2 ± 17.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Knee extensors isometric force (N)</td>
<td>87.4 ± 32</td>
<td>76.4 ± 24.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Potentiated twitch (N)</td>
<td>80.4 ± 31.9</td>
<td>61.7 ± 20.8</td>
<td>0.1</td>
</tr>
<tr>
<td>Post-activation potentiation</td>
<td>0.6 ± 0.1</td>
<td>0.6 ± 0.2</td>
<td>1</td>
</tr>
</tbody>
</table>
**Figure 5.1** Example of the incremental protocol to test for supramaximality.

One magnetic pulse was delivered manually at rest every 30 seconds at 70, 80, 90, 100, 100% of maximum power.

**Figure 5.2** Resting twitch (RT) generated at rest.
Figure 5.3 Diagram illustrating the different phases of the twitch interpolation protocol. Note the maximal voluntary contraction (MVC)*, the superimposed twitch (ST) and the potentiated twitch (PT).

* In this case, the participant was asked to perform a knee extension at 50% of MVC.
Figure 5.4 Results of the incremental protocol to test for supramaximality at 70, 80, 90, 100 and 100% of power output. Note the higher level of twitch force developed by the healthy group (dashed line) in comparison with the group with COPD (solid line). Since a plateau of force is not achieved before maximal power is generated, supramaximality cannot be determined. Error bars represent standard error of the mean (SEM).
Figure 5.5 Relationships of the resting twitch (RT) and potentiated twitch (PT) with the voluntary knee extensors isometric muscle force. Regression lines for people with COPD (solid) and healthy participants (dashed) with correlation coefficients for people with COPD (C) and healthy participants (H) are provided.
References


Chapter Six: Risks Factors for Falls IV: Deciphering Deficits in Postural Control in People with COPD^5

6.1 Introduction

Postural control, a term synonymous with postural stability, is critical in preventing older people from falling.^1 Indeed, a recent meta-analysis identifies deficits in postural control as the second most important single individual risk factor for falls following muscle weakness.^2 Data from recent studies indicate that people with chronic obstructive pulmonary disease (COPD) might experience deficits in postural stability^3-6 and an increased risk for falling.^7 For example, postural control, measured by the Berg Balance Scale, has been identified as a valid measure to discriminate between fallers and non-fallers in a group of individuals with COPD.^8 However, most of the studies investigating postural control in COPD, have used functional measures of balance such as the Functional Reach Test^3,4 or the Community Balance and Mobility Scale.^5 While these functional tests have been extensively used in rehabilitation and are useful for assessing overall deficits in postural control, they are not sensitive to elucidate the contribution of the sensory and motor systems to postural control in people with COPD.

It is widely accepted that postural control is mainly regulated by the interaction of the vestibular, somatosensory and visual sensory systems.\(^9\)

^5 A version of this chapter has been submitted for publication. Roig M, Eng JJ, MacIntyre DL, Road JD, Reid WD. Deciphering deficits in postural control in people with COPD.
however, it is unclear whether the impairments of postural stability reported in people with COPD are specifically produced by deficits in one or more of the above sensory systems. We used computerized dynamic posturography to assess postural control with the Sensory Organization Test (SOT). The SOT is a test designed to assess postural sway while exploring the specific contributions of each sensory system to stability when standing.\textsuperscript{10} The primary objective of this study was therefore to investigate differences in postural control between people with moderate to severe COPD and a group of healthy control subjects matched for age, gender and body mass index (BMI). The specific implications of each sensory system in the control of postural stability were also investigated. Further, since muscle weakness is also known to increase postural sway in older adults,\textsuperscript{11} we tested knee extensors muscle strength to explore the potential influence of muscle strength in the control of postural stability in people with COPD. We hypothesized that postural control would be impaired in people with COPD and that muscle weakness would be associated with postural instability.

6.2 Methods

6.2.1 Participants

People with COPD and healthy control subjects were recruited on a voluntary basis from the local community from October 2008 to June 2009. Flyers of the study were distributed in waiting rooms of hospitals, pulmonary function laboratories, as well as community and senior centers in the area of Vancouver. Inclusion criteria for people with COPD were: moderate to severe disease (stage II or III) based on the Global Initiative for Obstructive Lung
Disease (GOLD). Exclusion criteria were: (1) an acute exacerbation within the 3 months prior to the study; (2) regular participation in a formal exercise rehabilitation program during the 1-year period prior to the study; (3) currently smoking; (4) co-morbid cardiovascular or neurological disease and lower extremity musculoskeletal problems that interfere with or could cause undue risk during the performance of study testing; (5) visual or vestibular deficits that could affect postural control; (6) use of portable supplemental oxygen on a continuous basis; (7) α-1 antitrypsin deficiency without a significant smoking history.

Inclusion criteria for healthy people were: sedentary healthy people. Sedentary was defined as “only performs activities with low metabolic cost, including light activities such as slow walking or cooking”. Exclusion criteria for healthy people were: (1) regular participation in a formal exercise program during the 1-year period prior to the study; (2) currently smoking; (3) respiratory, cardiovascular, neurological disease and lower extremity musculoskeletal problems that interfere with or would cause undue risk during the performance of study testing; (4) visual or vestibular problems that could affect postural control. The Clinical Research Ethics Board of the University of British Columbia approved the study (Appendix A) and all subjects gave written informed consent prior to participation (Appendix B).
6.2.2 Initial Screening

Prior to testing, participants were asked to complete a risk-screening questionnaire (Appendix C) to ensure suitability for participation and minimize any potential risk. To confirm the severity of COPD or to rule out pulmonary disease, people with COPD and healthy subjects, respectively, underwent spirometry using a portable spirometer (CPFS/D spirometer, Medi Graphics Corp., MN, USA). Spirometry was performed according to the guidelines of the American Thoracic Society (ATS) and European Respiratory Society (ERS).

6.2.3 Measurements

6.2.3.1 Postural Control

Postural control was assessed with the SOT on an EquiTest® system (NeuroCom International Inc. OR, USA), which is an instrument designed to assess postural sway under increasingly challenging scenarios (Figure 6.1). The SOT, whose reliability and validity are well established, consists of 6 conditions that manipulate visual, somatosensory and vestibular inputs to challenge postural control. A detailed description of each SOT condition is shown in Table 6.1. Depending on which SOT condition is used, the EquiTest® system modifies the support surface (i.e., force plate) or the visual surround (i.e., background) to alter somatosensory and visual inputs, respectively. The vestibular system is specifically challenged in Conditions 5 and 6, when the support surface is altered while visual input is eliminated (i.e., participants’ eyes
are closed) or when both the support surface and visual surround are altered simultaneously (Table 6.1).

The sway gain of the EquiTest® system was set at 1, which causes the support surface or visual surround to follow the individual’s sway exactly. The equilibrium scores (based on an individual’s postural sway) for each SOT condition were calculated by determining the maximum and minimum anterior-posterior (AP) sway angles. The AP sway angle is the angle between a line projecting vertically from the center of foot support and a line from the center of foot support to the center of gravity position on the body (Figure 6.2).19 A composite equilibrium score was then calculated from the 6 conditions of the SOT. A detailed description of the equations used to calculate the composite equilibrium score is available elsewhere.19 A composite equilibrium score of 100 represents no postural sway and lower scores indicate increasingly poor balance or postural instability. Briefly, while standing with shoes on the force plates, participants were given instructions to maintain an upright posture while looking straight ahead with arms at their sides. Prior to testing, participants were allowed to familiarize themselves with the SOT by practicing the 6 conditions in a progressive order of difficulty (1 to 6). During the SOT, three trials of each condition were administered in a random order. Each trial lasted 20 seconds and it was stopped when the participant required a step to regain balance or touched the visual surround for support. If this was the case, the trial received an equilibrium score of zero and it was registered as a “fall”. Depending on the
number of “falls” participants were categorized as “frequent fallers” (2 or more falls) or “fallers” (1 fall). We used this classification, rather than faller (1 or more falls) versus no faller (no fall), to discriminate between occasional fallers and frequent fallers during the SOT.

6.2.3.2 Sensory Analysis

Since each condition of the SOT targets specific sensory systems contributing to postural balance (Table 6.1), sensory analyses were performed to explore potential alterations in somatosensory, visual or vestibular inputs. Briefly, calculating the ratio of Conditions 2:1, the ability of the participant to use the somatosensory system to maintain postural balance was assessed. Similarly, the ratios of Conditions 4:1 and 5:1 were used to assess the ability to use information from the visual and vestibular systems respectively to maintain balance. In addition, to determine the degree to which the subject relied on visual information to maintain balance (i.e., visual preference), the sum of average scores of Conditions 3 and 6 were divided by the sum of the average scores of Conditions 2 and 5. A more detailed description of the above sensory ratios and their functional relevance is provided elsewhere. Sensory ratios provide useful information to explore preferential implications of a specific sensory system in any deficit in postural control.
6.2.3.3 Knee Extensors Muscle Strength

Concentric average peak torque of the knee extensors of the dominant leg (determined by preference for kicking a ball) was assessed on the KinCom® dynamometer version 5.30 (Chattanooga Group Inc., TN, USA). This muscle group was chosen because it is independently associated with postural sway in healthy older adults. Participants were seated on the KinCom® with the knee joint aligned with the center of rotation of the dynamometer. The resistance pad was positioned distally at 75% distance from the lateral epicondyle to the femoral lateral malleolus. Stabilizing belts were used to secure the pelvis and the upper body, and to minimize extraneous movements. An angular velocity of 30°/s was chosen because it has shown high reproducibility (ICC=0.99) in a previous study of people with COPD. A testing range of motion (ROM) of 10° to 90° of knee flexion was set to diminish joint discomfort and force variability produced by the action of the hamstrings at the end of knee extension. After a warm-up consisting of 5 sub-maximal contractions, participants were asked to extend their knee as fast and hard as they could. To ensure maximal efforts, participants were vigorously encouraged. Three maximal trials were recorded interspersed by two-minute rest intervals. The three trials were averaged to obtain the peak torque.

6.2.4 Statistical Analyses

Assumptions for normality of data distribution for all variables were explored through inspection of histograms and normality plots. First, the individual scores of Conditions 2 to 6 were normalized by the scores of
condition 1. Because a preliminary analysis showed significant differences (p=0.008) between groups in **Condition 1**, this normalization procedure was applied to reduce between groups' differences at the baseline.\(^{19}\) Since assumptions of normality were not met, the Mann-Whitney U Test was used to assess differences between groups in **Condition 1**, normalized individual scores of **Conditions 2 to 6**, composite equilibrium scores and sensory ratios. Data of muscle strength were normally distributed, thus differences in knee extensors muscle torque were assessed with the Student's t-test. The Chi-square test was used to determine differences between groups in the ratio of “frequent fallers” (2 or more falls) and “fallers” (1 fall)\(^{20,21}\) during the SOT over the 6 conditions. A “fall” was defined as a zero score in any of the trials during the SOT.\(^{10}\)

Spearman’s correlations were used to explore relationships of muscle strength with each (non-normalized) individual SOT condition, postural control (i.e., composite scores) as well as each sensory system in both groups. The strength of the correlations (r) was categorized as low (0-0.25), moderate (>0.25-0.50), strong (>0.50-0.75) and very strong (>0.75).\(^{24}\) To confirm the influence of muscle strength in specific SOT conditions, we performed an additional analysis of covariance adjusted with knee extensors muscle strength. Prior to this analysis, non-normally distributed data were transformed using logarithm transformation. Data are presented as means ± standard deviation (SD) or medians with percentiles (P\(_{25}, P_{75}\)), unless otherwise stated. All analyses were performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago., IL., USA) using two-tailed probability tests with a level of significance set at p<0.05. The
SPSS syntax codes for the main analyses are shown in Appendix H.

6.3 Results

6.3.1 Participants

Twenty non-oxygen dependent, clinically stable people (10 males and 10 females) with moderate to severe COPD and 20 sedentary healthy controls matched for age, sex and BMI participated in the study. Participants' demographic characteristics are outlined in Table 6.2. People with COPD were slightly older (~4 years older), however, a t-test comparison revealed that this difference was not statistically significant (p=0.08). People with COPD showed moderate to severe levels of airflow limitation, which was confirmed by the lower values in spirometric measures in comparison with the healthy group (p<0.05).

6.3.2 Postural Control

People with COPD showed lower equilibrium scores in (non-normalized) Condition 1 (p=0.008); median (P25,P75) for the healthy group was 92.8 (90.3 to 93.6), and the COPD group was 89.8 (87.7 to 91.8). The analysis of differences between groups in the other normalized SOT Conditions 2 to 6 revealed only a trend towards lower performance in the group with COPD during Conditions 5 (p=0.07) and 6 (p=0.06) (Figure 6.3). People with COPD, on average, demonstrated a 10.8% significantly (p=0.014) lower composite equilibrium score compared with healthy controls (Table 6.3). The chi-square test showed a significant difference in the ratio of “frequent fallers” and “fallers” between groups.
More specifically, there were 10 “frequent fallers” and 4 “fallers” in the group with COPD and 2 “frequent fallers” and 7 “fallers” in the healthy control group. There was a total of 40 “falls” (11.2% of all trials) in the group with COPD, while the healthy control group had 12 “falls” (3.4% of all trials). In the group with COPD, most of the “falls” occurred in Conditions 5 (32.5%) and 6 (62.5%). In the healthy control group, all “falls” were equally distributed between Conditions 5 (50%) and 6 (50%).

6.3.3 Sensory Analysis

Sensory ratios did not reveal significant differences between groups in any specific sensory system (i.e., somatosensory, visual, vestibular) that could entirely explain the deficits in postural control among people with COPD (Table 6.3). However, a modest trend suggestive of a preferential impairment in the vestibular control of balance was found in the group with COPD (p=0.1).

6.3.4 Associations of Knee Extensors Muscle Strength and Postural Control

People with COPD showed, on average, 29.6% lower values in knee extensors concentric strength (p=0.01) compared to the control group. The COPD group had a mean average peak torque of $57.3 \pm 23.9$ Nm, while the healthy control subjects mean average peak torque was $81.4 \pm 31.9$ Nm (Mean difference= 24.1 Nm; 95% CI 42.1 to 6). The Spearman’s correlations showed no significant associations between measures of knee extensors muscle strength
and individual SOT conditions, composite equilibrium scores or specific sensory systems in the group with COPD. Healthy subjects, however, showed a strong association ($r=0.68; p=0.001$) between knee extensors strength and postural control in Condition 4 of the SOT.

6.4 Discussion

The main finding of this study is that, compared with healthy subjects, people with COPD showed marked deficits in postural stability (i.e., composite equilibrium scores). More importantly, deficits in postural stability were accompanied by a greater rate of “falls” during the balance testing in the group with COPD. The odds of having “frequent falls” during the SOT in people with COPD were 8.75 times greater compared with control subjects. The sensory analysis did not reveal significant differences between groups, although a trend ($p=0.1$) suggestive of alterations in the vestibular control of balance was evident in the group with COPD. Further, in spite of the lower levels of strength showed by the group with COPD, knee extensors muscle strength and measures of postural control did not reveal any significant relationship.

The deficits in postural control reported in this study are consistent with previous reports that used functional balance tests to confirm that postural control is impaired in people with COPD. For example, Eisner et al., investigated postural balance in a cohort of people with COPD with a mean predicted FEV$_1$ of 62 ± 23% and found a significantly reduced performance (9%; $p<0.0017$) in the Functional Reach Test when the COPD group (n=1202) was compared with the
control group (n=302). Another study showed significant lower scores in the Community Balance and Mobility Scale in two groups of people with moderate (FEV₁=45.7 ± 3.7% predicted) and severe (FEV₁=29.9 ± 3.7% predicted) COPD compared to a healthy control group. This latter study, however, did not reveal significant differences among groups in postural sway measured through posturography. The fact that we found differences between groups could be attributed to the manipulation of sensory information during the SOT, which compared to conventional posturography, increases the difficulty of the balance task. However, our preliminary analysis showed significant differences (p=0.008) in the median equilibrium scores of Condition 1 between both groups. Thus, alterations in postural control in people with COPD appear to be present even in unchallenged situations of relative postural stability. The use of different balance testing protocols may well explain these conflicting findings.

Perhaps the most striking finding of this study was the high rate of “falls” experienced by the group with COPD during the SOT. This finding is clinically relevant and supports recent studies underlying the potential association between postural instability and fall risk in people with COPD. Despite these results, it is important to take into account that 95% of “falls” in people with COPD in this study occurred during the most challenging conditions of the SOT (i.e., 5 and 6), when sensory information was dramatically altered. These challenging situations are different than what likely occurs during activities of daily living in people with COPD and therefore, the extrapolations of the results
from such experimental conditions to real life situations require further study. More studies are required to investigate the role of postural control deficits as a risk factor for falls in people with COPD.\textsuperscript{7}

Another interesting finding of this study concerns the analysis of sensory ratios. The purpose of this analysis was to explore whether deficits in postural control in people with COPD were catalyzed by specific alterations in either the somatosensory, visual or vestibular domains of postural stability. Sensory ratios did not reveal significant differences between groups, although a trend (p=0.1) suggestive of alterations in the vestibular control of balance was evident in the group with COPD. These deficits in the vestibular domain were consistent with the lower performance in \textbf{Conditions 5 and 6} of the SOT in the group with COPD (\textbf{Figure 6.3}). In addition, when correlated to measures of overall postural balance (i.e., composite equilibrium scores), alterations in the vestibular domain explained more of the deficits in postural control in the COPD group ($R^2=0.62; p<0.001$) than in the control group ($R^2=0.44; p=0.001$). In fact, differences in postural control between groups seemed to originate almost exclusively from deficits specific to the vestibular control of balance in the COPD group (\textbf{Table 6.3}). However, it is unclear why the group with COPD showed this preferential alteration in the vestibular control of balance.

It has been postulated that chronic hypoxemia may alter audio-vestibular function, however, the existing literature pertaining to vestibular impairments in
COPD is inconclusive. For example, El-kady et al., investigated audio-vestibular function in people with COPD suffering from hypoxemia (PO$_2$<75mm Hg) compared to a control group.$^{26}$ Despite poorer general audio-vestibular function in the group with COPD, differences were not significant. Further, in a previous study, Nakano et al.,$^{27}$ used brainstem auditory evoked potentials to investigate the influence of oxygen deficits on audio-vestibular function in people with chronic hypoxemia (PO$_2$=58.2mm Hg). Their results indicated that chronic hypoxemia does not alter audio-vestibular function either. Hence, more studies are required to investigate potential vestibular deficits and their contribution to postural control and fall risk in people with COPD.

Past reports have indicated that postural control in older adults is associated with muscle strength, especially during the most demanding balance tasks.$^{11}$ Thus, a possible explanation for the preferential deficit in the vestibular control of balance in people with COPD could come from the confounding effect of muscle weakness during **Conditions 5 and 6**, when the vestibular system is specifically targeted (**Table 6.1**). In view of this, Marigold and colleagues used the SOT to investigate the contribution of muscle strength to the deficits in postural stability in people with stroke (n=40) and a healthy control group (n=40).$^{19}$ They found that the strength of some muscle groups (i.e., paretic knee extensors) in the individuals with stroke was correlated with postural sway only in the most challenging conditions of the SOT (i.e., 5 and 6),$^{19}$ supporting the notion that strength plays an important role in situations of maximal instability,$^{11}$
particularly when the vestibular system is targeted during the SOT. This, rather
than a specific alteration of the vestibular control of balance, is an explanation
that might be relevant to our results. However, our correlation analysis showed
no significant association between knee extensors muscle strength and the
vestibular component of balance in the COPD group. More importantly, when
knee extensors strength was correlated with the results of each individual SOT
condition in the group with COPD, we did not observe any association with
**Conditions 5 or 6** to support a potential confounding effect of strength in the
preferential vestibular deficits of balance.

To confirm that knee extensors strength was not involved in the deficits in
postural control, we conducted an additional exploratory analysis to determine
differences between groups in **Conditions 5 and 6**, using knee extensors
muscle strength as adjusting factor. Since data were not normally distributed we
first used logarithm transformation to normalize the distribution. Then we used
analysis of covariance with knee extensors concentric strength as a covariate to
determine differences between groups. The introduction of strength as an
adjusting factor had minimal effects on the differences between groups in
**Conditions 5 and 6** of the SOT. Likewise, our findings indicate that the apparent
impairment of the vestibular component of postural balance in people with COPD
is not solely attributable to muscle weakness.
Based on existing literature, we expected somatosensory deficits to explain, in part, the impaired postural control observed in the group with COPD. Indeed, proprioception of the lower limbs appears as a primary somatosensory measure associated with postural sway assessed on a firm surface in older adults. The fact that postural sway was significantly greater in people with COPD during Condition 1 \((p=0.008)\), is therefore suggestive of proprioceptive deficits in this group. Several studies have shown nerve conduction abnormalities\(^{28,29}\) and signs of subclinical peripheral neuropathy (i.e., smaller amplitude potentials, increased latency, decreased conduction velocity), especially in the sensory nerves of people with COPD.\(^{30}\) Peripheral neuropathy, which can be present even in subjects with moderate COPD,\(^{30}\) could have led to somatosensory deficits,\(^{31}\) alterations in postural control and increased fall risk\(^{32}\) in our group with COPD. However, none of the participants with COPD had formally been diagnosed with peripheral neuropathy. More importantly, the sensory analysis did not reveal specific alterations in the somatosensory control of balance (Table 6.3). In spite of these results, the potential implications of proprioceptive deficits in the regulation of postural control in people with COPD cannot be discarded. The strong association of strength with Condition 4 in the healthy control group \((r=0.68; p=0.001)\) in addition to the lack of correlation in the group with COPD, suggest that differences may exist in the integration of sensory information and the motor response to postural instability between healthy people and individuals with COPD.
This study has a number of limitations that need to be considered when results are interpreted. Firstly, the relatively small sample size was sufficient to detect between groups differences in postural control (i.e., composite equilibrium scores) and the proportion of “fallers” and “frequent fallers” during the SOT. However, a larger sample size would be required to establish more reliable correlations between measures of strength and different aspects of postural control. Secondly, based on previous literature we targeted knee extensors as a muscle group potentially associated with postural sway. However, perhaps the assessment of ankle muscles (e.g., gastrocnemius and tibialis) would be more appropriate to detect correlations between muscle weakness and AP postural sway. Thirdly, co-morbidities and medications are important factors contributing to altered postural control and fall risk in older adults. While our exclusion criteria reduced potential confounding from other co-morbidities that could affect postural balance, people with COPD tended to take more medications than the healthy control group. Therefore we cannot rule out the possibility that medications had any impact on postural control in the group with COPD.

6.5 Conclusions

In summary, this study indicated that postural control is impaired in people with moderate to severe COPD compared to healthy control subjects. It is noteworthy that the lower performance in postural control observed in the study resulted in a greater number of “falls” during the SOT as well as greater proportion of “frequent fallers” in the group with COPD. A trend, suggestive of a
potential contribution of the vestibular domain in the deficits of postural control was found in people with COPD. It remains unknown, however, whether potential deficits in vestibular function exist in people with COPD. The deficits of postural control in the group with COPD were not explicitly associated with concentric muscle weakness of knee extensors. Hence, it appears that postural instability in people with COPD is not solely attributable to muscle weakness. Taken together, these findings underscore the importance of targeting deficits in postural control and fall prevention in people with COPD.
Table 6.1 Description of the six conditions of the Sensory Organization Test (SOT).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Sensory systems altered</th>
<th>Sensory systems targeted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Eyes open, fixed surface and visual surround</td>
<td>None</td>
<td>All</td>
</tr>
<tr>
<td>2</td>
<td>Eyes closed, fixed surface</td>
<td>None</td>
<td>Somatosensory &amp; Vestibular</td>
</tr>
<tr>
<td>3</td>
<td>Eyes open, fixed surface, sway referenced visual</td>
<td>Visual</td>
<td>Somatosensory &amp; Vestibular</td>
</tr>
<tr>
<td>4</td>
<td>Eyes open, sway referenced surface, fixed visual</td>
<td>Somatosensory</td>
<td>Visual and Vestibular</td>
</tr>
<tr>
<td>5</td>
<td>Eyes closed, sway referenced</td>
<td>Somatosensory</td>
<td>Vestibular</td>
</tr>
<tr>
<td>6</td>
<td>Eyes open, sway referenced and visual surround</td>
<td>Visual &amp; Somatosensory</td>
<td>Vestibular</td>
</tr>
</tbody>
</table>
Table 6.2 Characteristics of the participants of the study. Data are presented as means ± SD.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Healthy (n=20)</th>
<th>COPD (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Range</td>
</tr>
<tr>
<td>Age (y)</td>
<td>68.2 ± 8.1</td>
<td>53-85</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.7 ± 0.1</td>
<td>1.4-1.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.5 ± 12.6</td>
<td>47-104</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.5 ± 4</td>
<td>20-36</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>98.6 ±12</td>
<td>76-114</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>109.1 ± 20.5</td>
<td>67-141</td>
</tr>
<tr>
<td>FEV₁/FVC (% predicted)</td>
<td>68.9 ± 7.4</td>
<td>57-85</td>
</tr>
</tbody>
</table>

BMI: body mass index; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity

* Indicates significant difference between groups at p<0.05
Table 6.3 Differences in composite equilibrium scores and sensory analysis (ratios) between people with COPD (n=20) and healthy subjects (n=20). Data are presented as medians (P_{25}, P_{75}).

<table>
<thead>
<tr>
<th>Measures</th>
<th>Healthy</th>
<th>COPD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Postural balance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite equilibrium score</td>
<td>72 (66.2 to 75)</td>
<td>62.5 (54.2 to 71)</td>
<td>0.014*</td>
</tr>
<tr>
<td><strong>Sensory ratios</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatosensory</td>
<td>93 (90.1 to 97.3)</td>
<td>93 (89.6 to 95.1)</td>
<td>0.552</td>
</tr>
<tr>
<td>Visual</td>
<td>88.5 (81 to 92)</td>
<td>90 (77.9 to 93.5)</td>
<td>0.978</td>
</tr>
<tr>
<td>Vestibular</td>
<td>59.4 (44.8 to 72.8)</td>
<td>54.6 (26.1 to 67.5)</td>
<td>0.117</td>
</tr>
<tr>
<td>Preference #</td>
<td>96.2 (87.4 to 108.6)</td>
<td>99.9 (78.8 to 113.6)</td>
<td>0.607</td>
</tr>
</tbody>
</table>

* Preference indicates the degree to which participant relies on visual information to maintain balance. See methods section for details on how sensory ratios are calculated.

* Indicates significant difference between groups at p<0.05
Figure 6.1 Participant performing the Sensory Organization Test (SOT) on the EquiTest® system. The different conditions of the SOT test are outlined in Table 6.1.
Figure 6.2 The anterior-posterior (AP) sway angle is the angle between a line projecting vertically from the center of foot support and a line from the center of foot support to the center of gravity (COG) position on the body (55% of person’s height). The equilibrium scores for each SOT condition were calculated by determining the maximum and minimum AP sway angle (Figure modified from Neurocom International Inc.).
Figure 6.3 Differences in equilibrium scores between people with COPD (filled circles) and healthy control subjects (white circles) in conditions 2 to 6 of the Sensory Organization Test (SOT). The equilibrium scores are normalized to the score of condition 1. Data are presented as medians and 95% CI.
References


10. NeuroCom International Inc. Smart equitest system operator’s manual
Clackamas, OR, USA: NeuroCom international; 2001.


Chapter Seven: Incidence of Falls in People with COPD: Implications for Health Related Quality of Life (HRQoL)

7.1 Introduction

Falls, a common problem in older people, have potentially devastating consequences for functional independence, social interaction and life expectancy.\(^1\) Well established risk factors for falls such as lower limb muscle weakness\(^2\) as well as deficits in functional performance\(^3,4\) and postural control\(^5\) are not uncommon among people with chronic obstructive pulmonary disease (COPD) (see Roig et al., for review).\(^6\) Indeed, results from recent studies suggest that the incidence of falls in these individuals is likely higher than previously realized. For example, a large cross-sectional retrospective study (n=4050) investigating the relationship between chronic conditions and fall prevalence reported that 30.8% (95% CI: 27.4 to 34.3) of older women (~69 years) diagnosed with COPD fell at least once in the preceding year.\(^7\) Interestingly, COPD was one of the leading conditions in prevalence of falls, second only to osteoarthritis.\(^7\) In a more recent study that assessed whether deficits in postural control could discriminate between fallers and non-fallers in a group of 39 people with COPD, 46% of participants reported at least one fall in the preceding year.\(^5\) In another cross-sectional retrospective study, Hellstrom and colleagues found

\(^{6}\) A version of this chapter will be submitted for publication. Roig M, Eng JJ, MacIntyre DL, Road JD, FitzGerald JM, Burns J, Reid WD. Prevalence of falls in people with COPD: Implications for health related quality of life (HRQoL).
that 20 out of 80 people (25%) with moderate to severe COPD had fallen in the previous year.⁸

However, these studies⁵,⁷,⁸ collected data with regards to falls retrospectively. Recent international guidelines for the design of fall prevention trials⁹ emphasize the importance of recording fall events prospectively in order to minimize the effect of recall bias that is inherent in most retrospective fall-risk studies¹⁰ and thus likely affects the validity of fall incidence collected in these studies. In addition to the incidence of falls, another important aspect that has not been rigorously investigated is whether falls have any impact on health related quality of life (HRQoL) in people with COPD. It is widely accepted that falls, especially traumatic falls,¹¹ generally have deleterious effects on HRQoL.¹² Furthermore, well established risk factors for falls such as fear of falling,¹³ muscle weakness and deficits in postural control are associated with worse HRQoL in older adults.¹⁴ Since risk factors for falls are present among people with COPD,⁶ it would be anticipated that an increased fall incidence could decrease HRQoL in these individuals. Ascertaining the incidence of falls and potential associations between falls and HRQoL is critical to determine the clinical relevance of preventing falls in people with COPD.

### 7.2 Objectives and Hypotheses

The specific objectives of this study were to: (1) prospectively determine the incidence of falls in people with COPD over a 6-month period; (2) identify
differences in baseline demographic and clinical characteristics between fallers and non-fallers; (3) determine changes in HRQoL between fallers and non-fallers at the end of 6 months and (4) explore associations between fall incidence and risk factors for falls.\textsuperscript{6} We hypothesized that fall incidence among people with COPD would be high and that the domains of HRQoL associated with physical status would decrease more significantly in fallers during the 6 months period of the study.

7.3 Methods

7.3.1 Participants and Recruitment

Between February and June 2009 the contact information of people with COPD was retrieved from databases and caseloads of respirologists based in three hospitals in Vancouver. In addition, flyers about the study were posted in local pulmonary function laboratories and waiting rooms of respiratory clinics. Potential participants were contacted through a letter of invitation. Criteria for participation were: (1) a physician diagnosis of COPD, which was confirmed by spirometry. Exclusion criteria included: (1) very limited mobility that would preclude ability to ambulate using both lower extremities (e.g., hospitalized patients and patients with severe end-stage COPD); (2) comorbid neurological conditions that affect balance or gait (e.g., a prior stroke, Parkinson’s disease); (3) not fluent in English as defined by the ability to provide informed consent and to complete questionnaires related to the study; (4) cognitive impairment that interferes with the ability to provide informed consent or to provide information required in the study’s test measures. The different stages of the recruitment
process are shown in Figure 7.1. The clinical research ethics boards of each of
the hospital sites approved the study (Appendix I) and all participants gave
written informed consent prior to participation (Appendix J).

7.3.2 Study Design

This was a 6-month prospective observational cohort study investigating
fall incidence and its relationship with HRQoL in people with COPD. Independent
associations between fall incidence and the following variables were also
investigated: number and types of medications and chronic conditions, balance
confidence, physical activity level, severity of pulmonary disease (COPD),
oxygen use, number of exacerbations, and use of assistive device (e.g., cane,
walker). Briefly, two weeks before the start of the study, participants received a
mail package with a stamped addressed return envelope containing the
following: instructions for completion (Appendix K), a letter of invitation to the
study (Appendix L), the consent form to participate (Appendix J), a set of fall
diaries formatted to track falls over a six month period (Appendix M), the Medical
Outcomes Study Short Form-36 version 2 (SF-36v2) (Appendix N), the Chronic
Respiratory Questionnaire (CRQ) (Appendix O), the Activities Balance
Confidence (ABC) Scale (Appendix P), the Physical Activity Scale for the Elderly
(PASE) (Appendix D). In addition subjects received a clinical form (Appendix Q)
to record demographic data, current medications, other chronic conditions,
oxygen use, acute exacerbations of COPD, falls during the preceding 6 months
and use of an assistive device.
After receiving the first mailed package, all participants were contacted by telephone to confirm that they wanted to participate in the study and asked if they had any questions related to the forms and questionnaires contained in the package. Participants that agreed to participate were asked to complete all the questionnaires and mail them back. Fall diaries were returned at the end of each month using pre-paid envelopes. Participants who had not returned the fall diaries within the 10 days after the end of each month were contacted by telephone. To ensure compliance with the study and to minimize the number of potential dropouts, follow-up telephone calls were made to participants at the third and fifth month. Five months after the beginning of the study, participants received a second mailed package containing all the above-mentioned questionnaires except the PASE (Appendix D), which was completed only at baseline. All questionnaires of the second package were identical to those of the first package, except for the CRQ and the clinical form. The CRQ provided in the second mail package was a follow-up version of the initial CRQ (Appendix R). In the clinical form of the second package (Appendix S), participants were asked to report any change in medications, newly diagnosed chronic conditions and any exacerbation of COPD since the commencement of the study. Participants were instructed to wait until the end of the sixth month to complete this second set of questionnaires and to mail them back to the investigator.
7.3.3 Outcomes

7.3.3.1 Fall Incidence

Fall incidence was prospectively investigated through monthly fall diaries. Participants were asked to report, on a daily basis, any fall event in a monthly fall diary. More precisely, they were asked: “Have you had any fall including a slip or trip in which you lost your balance and landed on the floor or ground or lower level?” A fall was defined as “an unexpected event in which the participant comes to rest on the ground, floor or lower level.” If any fall was reported in the fall diary, participants were called by telephone to confirm that the recorded fall was consistent with the definition of a fall. In addition, participants were asked, via a standardized questionnaire (Appendix T), about the circumstances of the fall and any resultant injury.

7.3.3.2 Measures of Health Related Quality of Life (HRQoL)

Health related quality of life (HRQoL) was assessed through the self-administered versions of the Health Survey Short Form version 2 (SF-36v2) and the Chronic Respiratory Questionnaire (CRQ). The SF-36, which provides information on HRQoL from eight different health-domain scales, was chosen because it has been shown to be easily administered with good psychometric properties (e.g., sensitivity) to measure generic aspects of HRQoL in people with COPD. Another factor that was taken into account is that the SF-12, a short version of the SF-36, has been shown to be sensitive when correlated to risk factors for falls. The CRQ is a disease-specific HRQoL instrument, which has
proven to be valid, reliable and sensitive to detect changes in health status in people with COPD. The CRQ provides information regarding health status in four different domains: dyspnea, fatigue, emotional function and mastery (i.e., feeling of control over the disease and its effects). The use of both generic (SF-36) and disease specific (CRQ) HRQoL instruments was chosen to capture a broader spectrum of data that can be used to discriminate differences, if any, between people with and without COPD.

7.3.3.3 Balance Confidence

Participants were asked to complete the ABC scale, which assesses balance confidence, and has shown to be a valid and reliable measure to discriminate between levels of functional mobility in the elderly. Balance confidence is an important indicator of functional mobility and independence in older adults. Since postural instability and fear of falling have been commonly identified as risk factors for falls, it is reasonable to surmise that reduced balance confidence measured by the ABC scale might be associated with an increased risk for falling. Briefly, the ABC scale contains 16 items, with each item rated from 0% (no confidence) to 100% (complete confidence). The maximum score is 1600, which is then divided by the number of items (16) to obtain a composite score.
7.3.3.4 Physical Activity Level

Physical activity level was assessed with the Physical Activity Scale for the Elderly (PASE). The PASE has been validated by comparison to values of physical activity using portable accelerometers. Physical activity was assessed because reduced mobility and impaired activities of daily living (ADLs) have been associated with an increased risk for falling. The PASE is a 12-item self-administered questionnaire that measures physical activity levels based on scores ranging from 0 to 400.

7.3.3.5 Medications and Chronic Conditions

The clinical form was used to record the number and types of current medications and chronic conditions (comorbidities). Participants who met the inclusion criteria had retrospective medical record reviews to confirm the names of medications and chronic conditions reported in the clinical form. In cases where any medication or chronic condition in the medical chart was not reported in the clinical form, the participant was contacted and asked to clarify this information. Any prescribed new medication or diagnosed chronic condition during the study (i.e., reported in the clinical form of the second mail-out package) was included in the analysis only if prescribed or diagnosed before the third month of the study. Briefly, medications were categorized according to the Canadian Medical Association as psychotropic (including hypnotics, anxiolytics and antidepressants), analgesics as well as visual, peripheral nervous, cardiovascular (including diuretics), digestive, renal (including urinary tract
medications), endocrine, reproductive (including medications related to sexual dysfunction), immune and respiratory system medications. Information regarding nutritional supplements such as vitamins or minerals was not retrieved. Chronic conditions were categorized as coronary heart disease (e.g., myocardial infarction, angina, ischemic attack), circulatory (e.g., aortic artery disease, peripheral vascular disease), digestive (including gastroesophageal reflux) depression and mood disorders (e.g., anxiety), musculoskeletal (e.g., osteoarthritis, rheumatoid arthritis), endocrine (e.g., osteoporosis, diabetes), peripheral nerve disease (i.e., polyneuropathy), immune (e.g., HIV), renal or eye disease (e.g., cataracts, glaucoma) and cancer. Of note, high blood pressure and hyper-lipidemia were categorized in the group of circulatory diseases. A similar categorization has been used previously to study risk factors for falls.7

7.3.3.6 Severity of COPD, Oxygen Use, Exacerbations, Use of Assistive Device and Previous Fall

To determine the severity of COPD, based on the criteria of the global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (GOLD),30 medical record reviews were performed to retrieve information of the most recent spirometry data recorded prior to the start of the study. The clinical form was used to ask participants whether they were on oxygen and when it was used (e.g., on exertion only, at night only, always), the number of exacerbations in the 6 months preceding the study (first package) and during the study (second package), and the use of an assistive device. An
exacerbation was defined 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”. Specifically, participants were asked if they had a worsening of their COPD that required a change in medications including, for example, prednisone or/and a course of antibiotics. This information and other demographic data such as age, weight and height were confirmed through medical record review. In case of disagreement between the data provided by the participant and the medical record, participants were contacted and asked to clarify this information. In the clinical form, participants were also asked to report the number of falls in the 6 months prior to the commencement of the study.

7.3.4 Statistical Analyses

Departure from normality for all continuous variables was explored through visual analysis of histograms and normality plots. The statistical analyses were limited only to those participants who had returned at least the first monthly fall diary. Fall incidence rate (IR), defined as the number of falls divided by the sum of all months that participants were followed, was calculated with negative binomial regression (NBR). The advantage of NBR over other regression models (e.g., Poisson model) is that it allows the study of recurrent events such as falls that are not independent and that occur at an over dispersed rate (i.e., the variance of falls is greater than the mean number of falls).
addition, NBR analysis adjusts for different follow-up times, and thus accounts for the shortened follow-up of dropouts during the study.\textsuperscript{35}

To determine differences between prospective fallers and non-fallers at baseline, the Pearson’s chi square test for differences in proportions and either the Student’s-t-test or Mann Whitney test for continuous data were used. Differences between fallers and non-fallers in changes in measures of HRQoL (SF-36 and CRQ) as well as balance confidence (ABC) during the 6-month period were assessed by forced entry multivariable regression analyses, with baseline scores and experimental group as independent variables of the model.\textsuperscript{36}

A logistic regression model with faller and non-faller as the dependent dichotomous variable was constructed to explore potential risk factors for falls in people with COPD. First, point biserial correlation analyses were used to explore associations between the dependent variable (faller and non-faller) and the independent variables. Pearson’s or Spearman’s (for skewed data) were used to assess multicollinearity among independent variables. Variables with a $p \leq 0.25$ on bivariate analysis were candidates for the binary regression model.\textsuperscript{37} All candidate variables were entered in the regression model and analyzed using the likelihood ratio method with backward elimination. This method is preferable to forward stepwise regression with the Wald statistic because it reduces the risk of type II error while increasing the reliability of the test statistic.\textsuperscript{38} Data are presented as means and 95% confidence intervals (CI), medians and percentiles.
(P_{25}, P_{75}) and proportions (%). Results for risk factors for falls are presented as odds ratio (OR) with CI. All analyses were performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) using two-tailed probability tests with a level of significance set at \( p \leq 0.05 \). The SPSS syntax codes for the main analyses are shown in Appendix U.

7.4 Results

7.4.1 Recruitment and Follow-up

The first package was mailed out to 316 potential participants with a response rate of 65.5%. Of those participants who responded, 68 declined to enroll in the study with lack of time or poor health being the most common reasons for not participating. Twenty-three participants were excluded at the first stage of the study. Most of these participants did not have a well-established diagnosis of COPD or had diagnoses of neurological comorbidities that were deemed to potentially affect balance or gait (e.g., prior stroke, Parkinson’s). A total of 116 subjects with COPD commenced the study. The number of participants at each stage of the study and the reasons for exclusion and dropouts are shown in Figure 7.1. Data from 101 participants (45 females and 56 males) that filled out one or more fall diaries were included in the analysis. Of these 101 participants, 84 (83.2%) returned 6 fall diaries and 10 (9.9%) returned 5 fall diaries. Eighty-two participants (80.2%) completed all the requirements of the study, including the forms provided in the second mailed package.
7.4.2 Participants

The baseline characteristics of fallers and non-fallers are shown in Tables 7.1 and 7.2. Both groups were similar at baseline, except for the proportion of participants that fell in the 6 months prior to the commencement of the study (p<0.001), the number of medications (p=0.001) and chronic conditions (p=0.007), as well as the proportion of participants who used oxygen on exertion (p=0.02), that were significantly greater in the group of fallers (Table 7.2). In addition, compared to non-fallers, the group of fallers had a disproportionate prevalence of coronary heart disease (p<0.001), a greater proportion of females (p=0.04) and were older compared to non-fallers (p=0.04).

The results of the spirometry tests indicated a notable diversity in the degree of airflow obstruction (i.e., severity of COPD), with participants, based on GOLD criteria,\textsuperscript{30} ranging from very mild to very severe stages of COPD (Table 7.1). However, there were no significant differences in the severity of COPD based on spirometry between fallers and non-fallers. Even though differences between groups were not statistically significant, a greater proportion of people in the group of fallers required oxygen (p=0.07) and the use of an assistive device (p=0.2). In addition, fallers showed a tendency to have more exacerbations during the 6 months preceding the study and lower physical activity scores and balance confidence scores (Table 7.1). The number of exacerbations during the study was significantly greater (p=0.027) in the fallers’ group. Mean balance confidence scores during the study decreased 4 and 6 points in the group of non-
fallers and fallers, respectively. However, differences in the decline of balance confidence between groups were not significant (p=0.3).

### 7.4.3 Fall Incidence

The NBR analysis showed an IR of 0.1 falls per person-month (95% CI: 0.06 to 0.14). Thirty-two participants (31.7%) reported at least one fall during the 6 months of the study. Of these 32 participants, 9 (28.1%) reported 2 or 3 falls and 4 (12.5%) participants reported 4 falls, the largest number of falls per participant. The total number of falls was 57 with an average of 1.8 falls per participant in the group of fallers. Most of the falls occurred during outdoor walking activities. Only one participant had a fall, which led to an injury (right arm fracture). The rest of falls resulted in only minor injuries (e.g., bruises) or no injury.

### 7.4.4 Health Related Quality of Life (HRQoL)

The results for changes in the trajectory of HRQoL measures between fallers and non-fallers at baseline and the 6 months follow-up are shown in Table 7.3. Fallers tended to show lower baseline scores in the physical (physical functioning and role physical) and general health domains of the SF-36. However, there were no relevant between-group differences in the SF-36 at baseline, in spite of significant (p=0.02) increased body pain in the group of non-fallers (Table 7.3). The regression analysis showed no between-group differences in the change scores of the SF-36 at the 6 months follow-up. In
general, the fallers group tended to show non-significant lower scores in the CRQ at baseline except for the dyspnea domain, which was similar between groups (Table 7.3). The regression analysis showed a general trend of a greater decline in the scores of the CRQ after the 6 months in the fallers group. Between groups analysis in the dyspnea domain of CRQ showed a significant decline in the dyspnea domain in the group of fallers (p=0.017).

7.4.5 Risk Factors for Falls

The bivariate correlation analyses showed significant associations between fall incidence and the number of previous falls ($r=0.44;p<0.001$), comorbidities ($r=0.27;p=0.006$), medications ($r=0.32;p=0.001$) as well as age ($r=0.21;p=0.036$) and female gender ($r=0.20;p=0.04$). Coronary heart disease was also associated with fall occurrence ($r=0.39;p<0.001$). Oxygen use ($r=0.19;p=0.053$), balance confidence scores at baseline ($r=-0.17;p=0.1$), and previous exacerbation ($r=0.16;p=0.1$) showed a trend suggestive of association with fall occurrence and thus were included in the initial regression model. Table 7.4 shows the results of the logistic regression analysis with the independent variables included in the final step of the model. The final model accounted for 49% of the variance in predicting a fall ($R^2=0.49$). The number of previous falls was the best predictor of falls (p=0.001). The odds of having a fall in people with COPD who had a previous fall in the 6 months prior to the study entry was 7.36 times greater than those who did not report a previous fall. The second most important predictor was coronary heart disease with an OR of 7.07. Being female
and advanced age (p=0.02) appeared to increase the odds of falling. Oxygen use appeared to be positively associated with an increased fall risk (OR=2.83), although this association was not significant (p=0.08).

7.5 Discussion

This is the first prospective study analyzing the incidence of falls and the impact of falls on HRQoL in people with COPD. The main finding of this study is that people with COPD show a high rate of falls. An annual projection of the IR of falls indicates that individuals with COPD might experience 1.2 falls per person-year, which is a substantially higher rate than what has been previously reported in the elderly (IR=0.24). Fallers tended to show lower baseline scores in the physical domains of the SF-36 and all the domains of the CRQ, except for the dyspnea domain. In addition, the decline of the scores in the dyspnea domain of the CRQ was significantly greater in the group of fallers after 6 months. Of particular interest, fall incidence appears to be relatively independent of the stage of COPD based on spirometry. Of greater prognostic importance, the number of previous falls and diagnosis of coronary heart disease were the most important independent risk factors for falls in people with COPD. Age and female gender also appeared to significantly increase the risk for falls in these individuals.

This study showed that 31.7% of people with COPD sustained at least one fall during the 6-month period of the study, which is a fall prevalence similar to what has been previously reported in older adults. At face value, the
The proportion of frequent fallers (12.9%), defined as people who had 2 falls or more, was within the upper range of prevalence values reported in previous studies with older adults (4%-15%). Compared to fallers, frequent fallers tended to show higher levels of airflow obstruction (i.e., lower FEV₁) and lower physical activity level. In addition, frequent fallers also took more medications and had more comorbidities than fallers. While these results suggest...
a linear association between the level of impairment and the risk for falls, differences between fallers and frequent fallers were not statistically significant. Recurrent falls are important because previous fall history can substantially increase fear of falling (OR=1.75; 95% CI:1.3 to 2.36)$^{23}$ and, more importantly, the odds of experiencing injurious falls (OR=6.7; 95% CI: 2.1 to 21.5).$^{44}$ This might be clinically relevant for people with COPD who show a high prevalence of osteoporosis (68%)$^{45}$ and therefore a potential increased risk for bone fracture. Unfortunately, the majority of previous fall-risk studies did not take into account recurrent falls and fall incidence was simply calculated as if falls were independent events (i.e., number of falls). Therefore, the direct comparison of the results from previous studies with our IR of falls is difficult. Nevertheless, the relatively high rate of frequent falls and the strong association (OR=7.36) between the number of previous falls and fall incidence confirms that falls are recurrent events that are not independent. Hence, to calculate the incidence of falls, appropriate statistical methods taking into account the number of recurrent falls, the over dispersion of fall occurrence and individual differences in the follow-up periods are strongly recommended.$^{34}$

Based on previous research,$^{12}$ we hypothesized that falls could have a deleterious effect on HRQoL. Fallers tended to have lower baseline scores, especially in the physical domains of the SF-36 and in all domains of the CRQ except for the dyspnea domain. It is unclear if the significantly greater number (p=0.027) of exacerbations during the study contributed to the decline in the
dyspnea domain in the group of fallers. However, the minimal changes in HRQoL after 6 months in the group of fallers suggest that the act of falling per se does not have a substantial impact on HRQoL in people with COPD during a 6-month period. Different reasons could explain these results. First, with the exception of one participant that required medical attention, the rest of falls reported during the study caused only minor injuries or no injury at all. A recent report analyzing associations between falls and HRQoL in elderly women found that only falls leading to fracture had a significantly negative impact on HRQoL. It is thus very unlikely that a non-traumatic fall would have a significant impact on HRQoL in people with COPD. Secondly, 14 of the 32 participants who sustained a fall during the study (43.7%) reported at least one fall in the 6 months prior to the study. Therefore, we cannot discard the fact that the relatively lower HRQoL baseline scores in the group of fallers were not already influenced by previous fall events. Third, perhaps a high frequency of falls is required to substantially alter self-perceived HRQoL. However, even though frequent fallers tended to show the lowest scores in the majority of physical domains of HRQoL, differences between fallers and frequent fallers were not significant. Fourth, HRQoL is a multidimensional construct that can be influenced by numerous factors. Fallers tended to have more comorbidities, to take more medications, to be older and, in general, to show a greater overall impairment than non-fallers. An exploratory analysis of the data showed that the number of comorbidities, medications and even balance confidence were significantly associated with most HRQoL measures at baseline. Thus, we cannot completely rule out the
possibility that the relatively lower HRQoL scores in the group of fallers at baseline were not influenced by any of these other factors.

The bivariate analysis of the risk factors for falls showed significant associations between fall occurrence and the number of medications and comorbidities as well as a trend suggestive of associations with balance confidence scores at baseline and at the 6 months follow-up, the number of previous exacerbations and physical activity level. However, in the final regression model, only previous fall history, age, female gender and the presence of coronary heart disease demonstrated a significant capacity to predict falls in people with COPD. Given the results from previous studies, it is unclear why the number of medications was not predictive of falls in our population. It is possible that the specific types of medications taken by participants were not associated with a high risk for falling. The most commonly used medications in this cohort were respiratory, cardiovascular analgesic and endocrine medications. With the exception of cardiovascular medications, which are only moderately associated with increased fall risk (OR=0.9 to 1.6), neither of the other medications appear to independently increase the risk of falling. In addition, the use of central nervous system medications (e.g., psychotrophic), which are powerful predictors of falls in older adults, was relatively low in these participants.
In light of the association between the number of chronic conditions and fall occurrence reported in previous studies,\textsuperscript{7, 50} it is also unclear why the number of comorbidities was not predictive of increased fall risk in people with COPD. A possibility is that not all comorbidities contribute to the same extent in increasing the risk for falls.\textsuperscript{7} For example, in contrast with previous estimates,\textsuperscript{51} the prevalence of depression, a disease strongly associated with increased fall occurrence (OR=2.01; 95% CI: 1.63 to 2.48),\textsuperscript{7} was relatively small (14.8\%) in this cohort of people with COPD. In contrast, due to its high prevalence among people with COPD,\textsuperscript{52} the strong association between fall incidence and coronary heart disease is of clinical importance. A recent cross-sectional study found that coronary heart disease was the third most common chronic condition associated with an increased fall risk (OR=1.82; 95% CI: 1.47 to 2.25) after depression and arthritis.\textsuperscript{7} Thus, it is possible that coronary heart disease could increase the risk for falling among people with COPD. Further studies are required to identify the underlying mechanisms explaining the association between coronary heart disease and increased fall risk.

The independent association between previous fall history and fall incidence found in the present study is consistent with that reported in other studies.\textsuperscript{8} This association is relevant because it emphasizes the importance of avoiding fall events to reduce the risk of further falls or targeting frequent fallers with more aggressive preventive measures. Advanced age\textsuperscript{40} and female gender,\textsuperscript{53} well-established risk factors for falls in older adults, also appeared to
increase the risk of falling in people with COPD. In spite of lower scores in the ABC scale in the group of fallers, balance confidence was not predictive of falls in our group. This finding was surprising given a previous retrospective study that found the ABC scale to be sensitive enough to discriminate fallers and non-fallers in a group with COPD. However, retrospective studies should be interpreted with caution because they are susceptible to reverse causality. For example, a recent study shows that previous falls increase fear of falling and vice versa. Thus, we cannot rule out the possibility that previous fall history reduced balance confidence in the retrospective study. Normative data from older adults establish a threshold at 80 points for the ABC score below which functional impairment starts to decline. Perhaps, the relatively high balance confidence scores reported by the group of fallers (74.4; 95% CI: 66.3 to 82.5) diluted the capacity of the ABC scale to predict falls.

7.6 Limitations

This study has several limitations that need to be considered when results are interpreted. We categorized participants as fallers and non-fallers. This dichotomous classification can be seen as problematic because it does not discriminate between fallers and occasional fallers. Some previous studies suggest that the use of three fall frequency levels such as non-faller, faller and frequent faller (2 or more falls) might be more appropriate. We performed a sensitivity analysis to assess differences between non-fallers, fallers and frequent fallers. While we found that frequent fallers showed, in general, greater levels of impairment compared to non-fallers, the differences between fallers and
frequent fallers were not statistically significant. Further, we explored the appropriateness of a multinomial regression model using these three dependent categories (non-faller, faller and frequent faller) but the multinomial model failed to accommodate all independent variables. Considering the relatively small sample size and the short follow-up period of the study, the use of a binary (non-faller, faller) logistic regression was considered more appropriate.

Other potential limitations include the fact that no control group was recruited. This would provide more reliable data to compare fall incidence in patients with COPD and a healthy control group. In addition, the absence of physiological (functional) data limited the study of potential physical risk factors for falls in these patients.

7.7 Conclusions

People with COPD have a high incidence rate of falls that is associated with a decline in dyspnea related activities associated with HRQoL. In spite of the significant decline in the dyspnea scores of the CRQ in the fallers group, falls do not appear to have a significant impact on other aspects of HRQoL. The minimal influence of falls on HRQoL in people with COPD could be explained by the fact that falls were not traumatic as well as the relatively short follow-up period of the study. The number of falls in the 6 months prior to the study and prior diagnosis of coronary heart disease were identified as the most important predictors of falls in people with COPD. Further larger and longer prospective studies investigating the incidence of falls on HRQoL are needed. In the meantime, fall prevention strategies in people with COPD are strongly recommended.
Table 7.1 Characteristics of participants at baseline. Data are presented as means and 95% CI or proportions (%).

<table>
<thead>
<tr>
<th></th>
<th>Non-fallers (n=69)</th>
<th>Fallers (n=32)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>72.1 (69.6 to 74.5)</td>
<td>75.5 (71.9 to 79.1)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Female (%)</td>
<td>26 (37.7%)</td>
<td>19 (59.4%)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>24.9 (23.3 to 26.5)</td>
<td>27.9 (25 to 30.8)</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Spirometry (% predicted)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean FEV₁</td>
<td>43.4 (36.9 to 49.8)</td>
<td>43.6 (36.4 to 50.8)</td>
<td>0.7</td>
</tr>
<tr>
<td>Mean FVC</td>
<td>71 (64.8 to 77.2)</td>
<td>72.3 (64.3 to 80.4)</td>
<td>1</td>
</tr>
<tr>
<td>Mean FEV₁/FVC</td>
<td>50 (45 to 55.1)</td>
<td>54 (46.6 to 61.3)</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Oxygen use (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>52 (75.4%)</td>
<td>18 (56.3%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Only on exertion</td>
<td>2 (2.9%)</td>
<td>5 (15.6%)</td>
<td>0.02*</td>
</tr>
<tr>
<td>At nights</td>
<td>5 (7.2%)</td>
<td>2 (6.3%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Always</td>
<td>10 (10%)</td>
<td>7 (21.9%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Mean previous exacerbations</td>
<td>0.3 (0.1 to 0.5)</td>
<td>0.4 (0.1 to 0.6)</td>
<td>0.1</td>
</tr>
<tr>
<td>Mean PASE score</td>
<td>108.8 (91.7 to 125.9)</td>
<td>86.2 (66.4 to 105.9)</td>
<td>0.1</td>
</tr>
<tr>
<td>Use of assistive device (%)</td>
<td>16 (23.2%)</td>
<td>11 (34.4%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Fell in previous 6 months (%)</td>
<td>5 (7.2%)</td>
<td>14 (43.8%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mean ABC score</td>
<td>81.5 (76.9 to 86.1)</td>
<td>74.4 (66.3 to 82.5)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

BMI: body mass index; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; PASE: Physical Activity Scale for the Elderly; ABC: Activities Balance Confidence Scale.

* Indicates significant difference between groups at p<0.05.
Table 7.2 Medications and chronic conditions (comorbidities) at baseline.

Data are presented as medians (P25, P75) or proportions (%).

<table>
<thead>
<tr>
<th></th>
<th>Non-fallers (n=69)</th>
<th>Fallers (n=32)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medications (n)</strong></td>
<td>5 (3 to 8)</td>
<td>8 (6 to 10.5)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Medication type (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotropic</td>
<td>14 (20.3%)</td>
<td>9 (28.1%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Peripheral nervous</td>
<td>1 (1.4%)</td>
<td>3 (9.4%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Analgesic</td>
<td>20 (29%)</td>
<td>13 (40.6%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Renal</td>
<td>3 (4.3%)</td>
<td>4 (12.5%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Digestive</td>
<td>14 (20.3%)</td>
<td>5 (15.6%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Immune</td>
<td>8 (11.6%)</td>
<td>3 (9.4%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Reproductive &amp; sexual</td>
<td>1 (1.4%)</td>
<td>0 (0%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Endocrine</td>
<td>21 (30.4%)</td>
<td>14 (43.8%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Respiratory</td>
<td>58 (81.4%)</td>
<td>25 (78.1%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Visual</td>
<td>4 (5.8%)</td>
<td>5 (15.6%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>38 (55.1%)</td>
<td>22 (68.8%)</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Chronic conditions (n)</strong></td>
<td>2 (1 to 4)</td>
<td>4 (2.5 to 5.5)</td>
<td>0.007*</td>
</tr>
<tr>
<td>Chronic condition type (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary</td>
<td>14 (20.3%)</td>
<td>19 (59.4%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Circulatory</td>
<td>34 (49.3%)</td>
<td>19 (59.4%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Digestive</td>
<td>10 (14.5%)</td>
<td>5 (16.1%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Depression &amp; mood</td>
<td>8 (11.6%)</td>
<td>7 (21.9%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Renal</td>
<td>1 (1.4%)</td>
<td>3 (9.4%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Immune</td>
<td>8 (11.6%)</td>
<td>1 (3.1%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>10 (14.5%)</td>
<td>8 (25%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Cancer</td>
<td>9 (13%)</td>
<td>3 (9.4%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Endocrine</td>
<td>27 (39.1%)</td>
<td>16 (50%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Peripheral nerve</td>
<td>2 (2.9%)</td>
<td>2 (6.3%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Eye</td>
<td>5 (7.2%)</td>
<td>5 (15.6%)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

* Indicates significant difference between groups at p<0.05.
Table 7.3. Measures of health-related quality of life (HRQoL) at baseline and at 6 months. Data are presented as means and ± SD.

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-fallers (n=69)</td>
<td>Fallers (n=32)</td>
<td>Non-fallers (n=69)</td>
<td>Fallers (n=32)</td>
</tr>
<tr>
<td><strong>SF-36</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>42.9 ± 25.3</td>
<td>41.6 ± 22.5</td>
<td>42 ± 25.7</td>
<td>34.3 ± 19.9</td>
</tr>
<tr>
<td>Role physical</td>
<td>49.7 ± 30.1</td>
<td>43.5 ± 24.2</td>
<td>50.6 ± 27.6</td>
<td>42.1 ± 26.3</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>23.7 ± 21.4</td>
<td>32.6 ± 22*</td>
<td>25.3 ± 22.4</td>
<td>37.8 ± 22.5</td>
</tr>
<tr>
<td>General health</td>
<td>56 ± 12.1</td>
<td>51.7 ± 14.6</td>
<td>56.4 ± 11.6</td>
<td>54.6 ± 12.8</td>
</tr>
<tr>
<td>Vitality</td>
<td>51.9 ± 11.5</td>
<td>52.7 ± 10.2</td>
<td>53.8 ± 11.7</td>
<td>57.3 ± 8.6</td>
</tr>
<tr>
<td>Social functioning</td>
<td>49.2 ± 13.6</td>
<td>51.6 ± 7.8</td>
<td>50 ± 8.1</td>
<td>54.3 ± 9.7</td>
</tr>
<tr>
<td>Role emotional</td>
<td>72.9 ± 28.7</td>
<td>68.2 ± 29.8</td>
<td>65.8 ± 29.6</td>
<td>66.7 ± 25.7</td>
</tr>
<tr>
<td>Mental Health</td>
<td>63.8 ± 7.5</td>
<td>65.6 ± 11</td>
<td>62.7 ± 11.2</td>
<td>65 ± 7.4</td>
</tr>
<tr>
<td><strong>CRQ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4.9 ± 1.3</td>
<td>4.9 ± 1.3</td>
<td>5 ± 1.2</td>
<td>4.5 ± 1.1**</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4.1 ± 1.4</td>
<td>3.9 ± 1.7</td>
<td>4.2 ± 1.3</td>
<td>3.9 ± 1.2</td>
</tr>
<tr>
<td>Emotional</td>
<td>5.1 ± 1.2</td>
<td>4.8 ± 0.7</td>
<td>4.9 ± 1.3</td>
<td>4.7 ± 1</td>
</tr>
<tr>
<td>Mastery</td>
<td>5.4 ± 1.4</td>
<td>5.2 ± 1.2</td>
<td>5.2 ± 1.5</td>
<td>5 ± 1.2</td>
</tr>
</tbody>
</table>

SF-36: Health Survey Short Form.
CRQ: Chronic Respiratory Questionnaire.
* Indicates significant differences between groups at baseline (p<0.05).
** Indicates significant between-group differences in the trajectory of HRQoL (p<0.05).
Table 7.4. Logistic regression model for assessing risk factor for falls. Data are provided as B values with standard errors (SE) and odds ratio (OR) with 95% CI. The model explained 49% of the variance in fall risk (Nagelkerke $R^2=0.49$).

<table>
<thead>
<tr>
<th>Predictor</th>
<th>B (SE)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous fall</td>
<td>1.99 (0.57)</td>
<td>7.36 (2.39 to 22.69)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Age</td>
<td>0.08 (0.04)</td>
<td>1.09 (1.01 to 1.17)</td>
<td>0.020*</td>
</tr>
<tr>
<td>Gender (F)</td>
<td>1.32 (0.60)</td>
<td>3.73 (1.14 to 12.16)</td>
<td>0.016*</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>1.96 (0.61)</td>
<td>7.07 (2.14 to 23.36)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Oxygen use</td>
<td>1.04 (0.59)</td>
<td>2.83 (0.88 to 9.08)</td>
<td>0.080</td>
</tr>
</tbody>
</table>

* Indicates significant difference between groups at p<0.05.
Figure 7.1 Flow chart showing the different stages of the recruitment process and the study

- **1st Package with letter of invitation sent to**
  - Enrolled in study: n=116
  - Excluded from study: n=23
    - No COPD (6)
    - Limited mobility (4)
    - Neurological condition (12)
    - Not fluent in English (1)

- **2nd Package sent to**
  - Withdrew from the study: n=6
    - Poor health (3)
    - Died (2)
    - Loss of follow up (1)
  - Contact information from flyers of study: n=38
  - Excluded from study: n=26
    - Poor health (6)
    - Died (5)
    - Loss of follow up (15)

- **Contact information from databases and caseloads**
  - n=278
  - Declined to participate: n=68
  - Did not respond to invitation: n=109

- **Completed all study questionnaires**
  - n=82
  - Returned all fall diaries: n=84
  - Withdrew from the study: n=2
    - Poor health (2)
References


Chapter Eight: Summary and Future Directions

8.1 Summary

8.1.1 Risk Factors for Falls Are Increased in People with COPD

We initiated the study of falls in COPD by reviewing the literature in order to identify potential risk factors for falls in people with COPD. We used the literature review (Chapter 2) to create a theoretical framework (pag. 50) that served as a conceptual basis to analyze risk factors for falls in people with COPD. In the cross sectional study (Chapters 3 to 6) we investigated risk factors for falls by comparing measures of muscle and functional performance as well as postural control in 21 people with COPD and 21 healthy subjects matched for age, gender and body mass. As it was hypothesized (Chapter 1), people with COPD showed deficits in measures of muscle strength, cross sectional area (CSA) and functional performance (Chapters 3 and 4) as well as postural control (Chapter 6). Furthermore, these deficits translated into an increased risk of experiencing “falls” in people with COPD during the Sensory Organization Test (Chapter 6). We also found that people with COPD had increased levels of intramuscular fat (IF), indicative of reduced muscle quality (Chapter 3), and developed lower leg muscle power in the stair climbing power test (SCPT) (Chapter 4). Due to technical limitations with the twitch interpolation technique using magnetic stimulation, we could not assess deficits in muscle activation in people with COPD (Chapter 5).
8.1.2 Associations Between Measures of Muscle, Functional Performance and Postural Control Differ Between Groups

In the cross sectional study (Chapters 3 to 6) we also explored associations between measures of muscle and functional performance as well as postural control. Based on previous studies in healthy older adults, we hypothesized that measures of strength and CSA might be associated with functional performance in people with COPD (Chapter 1). We were particularly interested in investigating potential associations between muscle quality assessed as IF and functional performance. Despite trends for significance indicative of a relationship between IF and functional impairment in the group with COPD, we did not find measures of muscle strength, CSA or quality to be significantly associated with measures of functional performance (Chapter 3). In addition, we found that while the SCPT was only moderately related to thigh muscle strength in the group with COPD, this relationship was very strong in the healthy group. In contrast, while the SCPT was strongly to moderately associated with measures of functional performance in the group with COPD, weaker or non significant relationships were found in the healthy participants (Chapter 4). Further, deficits in postural control were not associated with muscle weakness in people with COPD (Chapter 6).
8.1.3 Fall Incidence is High Among People with COPD and Falls Have a Negative Impact on Dyspnea

In the cohort study of this thesis (Chapter 7) we prospectively analyzed fall incidence over a 6-month period and determined whether falls have any impact on HRQoL as well as exploring risk factors for falls in 101 people with COPD. As it was hypothesized (Chapter 1), the incidence of falls in people with COPD was relatively higher compared to previously reported estimates in the elderly. Fallers tended to show greater levels of impairment as reflected by the greater number of comorbidities and medications and lower baseline scores in the physical domains of HRQoL. Interestingly, falls appeared to have a significantly negative impact on the dyspnea domain of the Chronic Respiratory Disease questionnaire (CRQ). The number of previous falls, diagnosis of coronary heart disease and advanced age appeared to be the most important predictors of falls in COPD. In addition, being male appeared to have a protective effect on the risk of falling. Oxygen use was positively associated with an increased fall risk, although this association did not reach statistical significance.

8.2 Strengths and Limitations

Recent studies have shown that lower limb muscle weakness and deficits in functional performance and postural control are common in COPD. In addition, previous work performed in our laboratory showed that IF, a feature of muscle deterioration, was increased in people with COPD compared to
healthy participants.\textsuperscript{5} It should be also noted that previous retrospective studies have reported estimates of fall prevalence in people with COPD\textsuperscript{11-13} This thesis expands this previous work and contributes new information to the study of risk factors, incidence and impact of falls on HRQoL in these individuals. The following paragraphs outline the strengths and limitations of the studies included in this thesis in addition to their novel contributions to the study of falls in COPD.

We investigated intramuscular fat (IF), a feature of muscle deterioration, and how increased IF might be associated with functional impairment (Chapter 3). While IF is not specifically related to increased fall risk, recent studies have shown that it is associated with self-reported functional impairment.\textsuperscript{3} The novelty of this study consisted of exploring potential associations between IF and functional performance. In addition, we wished to determine if IF could act as a better predictor of functional impairment than other muscle measures such as weakness or atrophy. The study of the relationship between IF and functional performance was limited by the relatively small sample and, as shown in the scatter plots presented in Chapter 3, the small variation of IF in the healthy group (i.e., all healthy participants had low levels of IF). We speculated (Chapter 3) that these two factors might explain why only trends for moderate associations between IF and functional performance were found in the group with COPD. Further studies with larger sample sizes are required to determine whether IF can be used as a predictor of functional impairment and fall susceptibility in people with COPD.
We also explored associations between measures of muscle and functional performance in people with COPD and healthy subjects (Chapters 3 and 4). In spite of their potential clinical relevance, there are no studies evaluating associations between measures of muscle and functional performance in people with COPD. The key message derived from our study is that differences might exist in the relationship between measures of muscle and functional performance between groups. We hypothesized that associations between muscle and functional performance may be specific to the functional task performed and the level of impairment of the population tested and, based on previous research, we speculated that these associations might follow a non-linear pattern. These observations indicate that caution should be taken when results from studies with healthy older adults are extrapolated to people with COPD.

We investigated differences in lower limb muscle power developed during the SCPT between people with COPD and healthy participants (Chapter 4). The study of deficits in muscle power in people with COPD has been neglected in the past, making this investigation particularly relevant. Muscle power, defined as the capacity to produce force per velocity of muscle contraction, has recently emerged as an important parameter closely related to functional performance in older adults. The SCPT revealed deficits in leg muscle power in people with COPD. However, the differences in the association between the SCPT and
measures of muscle strength between groups suggest that factors other than leg muscle power influence the performance of this test.

We analyzed differences in postural control between people with COPD and healthy participants and explored potential mechanisms that might help to explain these differences (Chapter 6). The use of dynamic posturography to assess specific sensory alterations offered a novel contribution from this study which allowed us to not only show that deficits in postural control are present in people with COPD but also that these deficits might translate to an increased fall risk for this population. In addition we found that muscle weakness was not related to the deficits in postural control observed in these individuals, underscoring the need for further investigation using more sophisticated methods into the implication of vestibular alterations for postural control impairments in people with COPD.

The novelty of the cohort study (Chapter 7) was the prospective design used to record fall incidence, as well as the study of risk factors for falls and impact of falls on HRQoL in people with COPD. Retrospective studies are confounded by two central methodological limitations: (1) causality between risk factors for falls and fall incidence cannot be established and, (2) recall bias can lead to an underestimate for the incidence of falls. Interestingly, we found that previous fall history and diagnosis of coronary heart disease were the most important predictors of falls in people with COPD. Since previous fall history can
substantially increase the fear of falling\textsuperscript{20} and, more importantly, the risk of experiencing injurious falls\textsuperscript{21} the avoidance of the first fall event appears to be critical to reduce further falls and avoid potential complications in these individuals. Although we found a significant decline in the dyspnea scores of the CRQ in the group of fallers, we were unable to find an overall association between fall incidence and reduced HRQoL. Based on previous studies\textsuperscript{22,23} we speculated that this finding is possibly related to the fact that all participants, except one, experienced non-traumatic falls over the course of this study. We also hypothesized that the relatively short follow-up period of the study could have influenced the low impact of falls on overall HRQoL.

\textit{8.3 Future Directions}

This thesis offered new information regarding incidence, risk factors and impact of falls on HRQoL in people with COPD. There remain, however, several potentially relevant questions yet to be elucidated. The review of the risk factors for falls (\textbf{Chapter 2}) for instance revealed interesting gaps in the literature that warrant further exploration. For example, more studies are required to characterize both deficits and potential associations between measures of muscle and functional performance in people with COPD. There exist, to the best of our knowledge, no studies investigating muscle power in people with COPD in spite of the potential relevance this muscle parameter may have for fall prevention strategies\textsuperscript{24}. Further, little is known about the physiological mechanisms that mediate the deficits in postural control observed in people with
COPD. From a clinical perspective, it would be interesting, for example, to understand whether people with COPD with different levels of impairment show proprioceptive deficits or alterations in postural adjustments or anticipatory strategies in postural control. In addition to this, more studies investigating the prevalence of polyneuropathy in COPD, its causes (i.e., hypoxemia, smoking) and its potential effects on postural control or fall risk are required. From a broader perspective, it would be interesting to obtain normative data for commonly used functional tests (e.g., gait speed) for people with COPD. These normative data might be used to identify people at risk of falling or simply to monitor functional improvements after different training interventions in COPD.

An exciting new area of research concerns the study of cognitive dysfunction in people with COPD. Of special interest is the study of the physiological effects of hypoxemia on cognitive function and the associations between cognitive impairments, deficits in postural control and increased fall risk that may exist. More investigations are required to critically factorize the side effects of medications currently used by these individuals and the potential role of these medications in fall risk. For example, the chronic exposure to corticosteroids and their impact on vision and increased fall risk in people with COPD is unclear. While the deleterious effects of corticosteroids in muscle function is well established, it would be interesting to determine the approximate doses and exposure times necessary to produce these myopathic effects and the potential effects of these medications on fall risk.
Larger and longer prospective studies are required to examine risk factors and the impact of falls on HRQoL in people with COPD. Disease-specific risk factors for falls such as oxygen use, dyspnea and exacerbations should be investigated more thoroughly. The specific mechanisms underlying the strong association between coronary heart disease and fall risk should be investigated further. In addition, it would be interesting to determine the proportion of falls that lead to fracture in these individuals and whether these fractures impact on HRQoL. An economic evaluation of falls and the cost implications of fall injuries in people with COPD are required. In addition, prospective studies assessing fall prevention interventions and the cost-effectiveness of these interventions in people with COPD might prove useful.
References


# Appendix A: Ethics Approval Certificate

## ETHICS CERTIFICATE OF EXPEDITED APPROVAL: RENEWAL

<table>
<thead>
<tr>
<th>PRINCIPAL INVESTIGATOR:</th>
<th>DEPARTMENT:</th>
<th>UBC CREB NUMBER:</th>
</tr>
</thead>
<tbody>
<tr>
<td>W. Darlene Reid</td>
<td>UBC/Medicine, Faculty of Physical Therapy</td>
<td>H07-01716</td>
</tr>
</tbody>
</table>

### INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

<table>
<thead>
<tr>
<th>Institution</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancouver Coastal Health</td>
<td>Vancouver General Hospital</td>
</tr>
<tr>
<td>VCHR/VCHA</td>
<td>GF Strong Rehabilitation Centre</td>
</tr>
<tr>
<td>Providence Health Care</td>
<td>St. Paul’s Hospital</td>
</tr>
<tr>
<td>Other locations where the research will be conducted</td>
<td>N/A</td>
</tr>
</tbody>
</table>

### CO-INVESTIGATOR(S):

- Jeremy D. Road
- Janice Eng

### SPONSORING AGENCIES:

- Canadian Lung Association - "Measures of Thigh Muscle Torque associated with Balance and Functional Tasks in People with Chronic Obstructive"

### PROJECT TITLE:

"Measures of Thigh Muscle Torque and Balance Associated with Functional Tasks in People with COPD"

### EXPIRY DATE OF THIS APPROVAL:

March 16, 2010

### APPROVAL DATE:

March 16, 2009

### CERTIFICATION:

1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.
2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.
3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

The Chair of the UBC Clinical Research Ethics Board has reviewed the documentation for the above named project. The research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved for renewal by the UBC Clinical Research Ethics Board.

Approval of the Clinical Research Ethics Board by:

Page 1 of 1
Appendix B: Informed Consent Forms

Consent Form For People with Lung Disease

Measures of Thigh Muscle Torque and Balance associated with Functional Tasks in People with Chronic Obstructive Pulmonary Disease.

Principal Investigator:
Dr. Darlene Reid, PT, PhD, Department of Physical Therapy, University of British Columbia
604-875-4111 Ext 66056

Co-Investigators:
Dr. Jeremy Road, M.D., Respiratory Medicine, Vancouver Hospital, 604-822-7128
Dr. Janice Eng, PT, PhD, Department of Physical Therapy, UBC, GF Strong Rehabilitation Centre, 604-806-9151
Marc Roig, PhD Student, University of British Columbia, 604-505-8767

Sponsor: The Canadian Lung Association (association research programs): Canadian Respiratory Health Professionals

Invitation to Participate:
You are being invited to participate in this study as someone who has been diagnosed with a lung disease including chronic obstructive pulmonary disease (COPD) or emphysema or bronchitis.

Participation is Voluntary:
You do not have to participate in this research study. It is important that before you make a decision to participate, you read the rest of this form. Please read the following form carefully and ask questions if anything is not clear. The consent form will tell you about the study, why the research is being done, and what will happen during the study and the possible risks, benefits, and discomforts.

Background:
Chronic obstructive pulmonary disease (COPD) is a respiratory disease which affects many Canadians. In addition to affecting the lungs, this condition can lead to poor muscle function, right heart failure, malnutrition, depression, and decreased fitness. This loss of muscular strength contributes to the inability to do daily activities and higher health care costs. Existing guidelines from expert physicians and other health care practitioners provide evidence that exercise and maintaining an active lifestyle have several therapeutic benefits for people with COPD. However, the role that this loss of muscle strength plays in the performance of functional activities in these patients has not yet been investigated.

Purpose:
The purpose of this study is to determine how the loss of strength in the thigh muscles of people with chronic lung disease is related to balance, and the performance of common movements performed during daily activities like climbing up and down stairs, moving from sitting to standing, and the maximal distance walked in 6 minutes.

What does the study involve?
The total time required to participate in the study is about 5 hours. The study will be divided into three different testing sessions that will be performed in two different locations on three different days.

- In the **first session** you will be required to come to our laboratory located at GF Strong Rehabilitation Centre. After a warm-up of gentle leg movements, you will perform three tests similar to movements that you perform during your daily activities. In the first test (sit-to-stand and stand-to-sit) you will be seated on a chair with your arms across your chest and you will be asked to stand up 5 times as quick as possible. In a second test you will be asked to climb stairs at your own pace for 2 minutes. In a third test, you will be required to walk down 2 sets of 12 stairs (for a total of 24 stairs). It is anticipated that this session will take 2 hours to perform the three tests with rest sessions before and after each test.

- In a **second session** at GF Strong Rehabilitation Centre, you will be asked to complete 3 tests:
  - First, you will be asked to maintain an upright standing position in the balance testing device shown in the photograph. Your balance will be tested examining the steadiness of your standing position while the position of the walls or the standing platform is moved.
  - Secondly, you will perform a test to measure the strength of your thigh muscles during contractions while you are straightening your knee, while you are bending your knee and when you are pushing your thigh out against the lever that is not moving, i.e., a static hold. For this type of testing you will perform 5 easy warm-up contractions followed by 3 to 4 maximal voluntary contractions for both the knee straightening and bending movements, and the static holds. Each one of these contractions will last about 3 seconds approximately. During the maximal contraction against the lever when it is not moving, i.e., static hold, we will apply a sub-maximal magnetic impulse for a very brief period of time, i.e., 1 millisecond, which is 1/1000 of a second. By applying a brief magnetic impulse over the thigh, we can determine how well your brain is telling your muscle to contract. The magnetic impulse will be uncomfortable but not painful.
  - In the third test of this session, you will be required to walk for a maximum period of six minutes (if you cannot complete the test you can
stop earlier). For this test, you will be asked to walk around the laboratory room. The distance walked will be recorded for a further analysis.

It is anticipated that the three tests performed in the second session will take 2 hours including the rest periods before and after each test.

- For the third session you will be required to come to the iCAPTURE CT located in the Vancouver Hospital for a Computerized Tomography Scan which will take about 1 hour. A CT scan is a method to examine any part of the body. During the CT scan, a thin beam of x-rays circles completely around the body, collecting a 360-degree view of the area being examined. This information is fed into a computer system that produces a two dimensional picture of this particular view through your body. In this study, a CT scan of the right thigh will be performed to assess girth of the different muscles in your thigh.

Who Can Participate in this Study?
You have been identified because you have been diagnosed with chronic obstructive pulmonary disease and you are over the age of 50. If you agree to take part in the study, a respirologist, Dr. Jeremy Road, will determine if you have any condition that will prevent you from being in the study. In addition, under Dr. Reid’s supervision, the therapeutic risk of you performing exercise will be performed using the exercise screening questionnaire based on the American College of Sports Medicine’s guidelines. Screening should take no more than 15 minutes and will take place when you first visit GF Strong Rehabilitation Centre and before you sign the consent form.

Who Should Not Participate in this Study?
You will be excluded if you currently smoke; or if you are currently taking or have taken systemic corticosteroids within the 6 months prior to study. In addition, if you suspect that you may be pregnant or you are planning to become pregnant during the study, if you require supplemental oxygen, have any injury or disease of the knee or leg which may be aggravated by exercise, any neurological disease (e.g., stroke or Parkinson’s disease), pacemaker, cancer, cardiovascular disease (heart failure, previous heart attack or cardiovascular surgery), respiratory failure or any other condition that excludes you from the type of activity performed during the study, then you will be excluded from the study.

Possible Harm and Side-Effects of Participation:
There are risks associated with the testing that can be minimized when standard procedures are used. The use of the brief magnetic pulse may cause some muscle discomfort when the pulse is applied. Following the functional tests you may experience some mild fatigue and soreness in the thigh muscle immediately afterwards but this should not last longer than 1 to 2 hours. Given the type of exercise performed, it is unlikely that your COPD will be worsened or exacerbated as a result of your participation. To prevent from potential falls, mainly during the functional tests (stair climbing and sit-to-stand and stand-to-sit) a spotter will support you during the tests. CT scans produce doses of radiation that can be reduced with the use of a single slice CT
scan (non-full body). Radiation is calculated in millisieverts (mSv). The average person in the U.S. receives an effective dose of about 3 to 5 mSv per year from naturally occurring radioactive materials. A full body CT scan produces an effective radiation dose of 10 mSv (i.e., equal to two or three years of natural radiation). Due to its reduced time of exposure, the use of single slice CT scan can reduce radiation by 50%-60% compared to a full body scan (i.e., equal to one or one and a half years of natural radiation). In the present study, a single slice CT scan will be used with this purpose.

Benefits to You of Participating in the Study:
There are no direct benefits to you for participating in this study. It is hoped that additional information gained in this research study may be useful in the treatment of other patients with COPD. After completion of the study, you will be given access to the information from your tests and the study results if you request.

Remuneration:
An honorarium (100$) will be paid for your participation in the study to help offset some of the costs related to your participation such as travel and parking expenses.

Alternative Treatments:
You do not have to participate in this study to receive treatment for your condition. Participation is voluntary.

In the Event of an Injury:
In the event you experience a serious side effect during this study you should immediately contact Marc Roig (PhD student) at 604-505-8767, 24 hours a day, seven days a week. Signing this consent form in no way limits your legal rights against the sponsor, investigators, or anyone else. In case of a serious medical event resulting from this study, please report to an emergency room and inform them that you are participating in a research study and Dr. Darlene Reid can be contacted for further information at 604-812-7402.

Confidentiality:
Your confidentiality will be respected. No information that discloses your identity will be released or published without your specific consent to the disclosure. However, research records and medical records identifying you may be inspected in the presence of the Investigator or his or her designate by Health Canada and the UBC Research Ethics Board for the purpose of monitoring the research. However, no records which identify you by name or initials will be allowed to leave the investigators’ offices.
Contact:
If you have any questions or desire further information with respect to this study, or if you experience any adverse effects, you should contact the principal investigator or co-investigators at the numbers listed on page 1 of this consent form.

Subject Rights and Withdrawal from the Study:
If you have any questions about your rights as a research subject, you may call the Research Subject Information Line in the University of British Columbia Office of Research Services at 604-822-8598. Signing this consent form in no way limits your legal rights against the sponsor, investigators, or anyone else.

You have a right to change your mind about participating in this study. If you want to withdraw from the study please inform Dr. Darlene Reid by calling 604-875-4111 Ext 66056. The research team will stop collecting any additional information about you. The research team may use and share information that was gathered before they received your notice of withdrawal.
**Consent**

Dr. Darlene Reid (or her associates) have given you information about this research study. They have explained what will be done and how long it will take. They explained any inconvenience, discomfort or risks that may be experienced during this study.

I ______________________ freely and voluntarily consent to participate in this research study.

print name

I have read and understand the information in this form and have had an opportunity to ask questions and have them answered. **I will be given a signed and dated copy of the consent form to keep for my records.**

______________________________    ____________________
Signature of Subject          Date

______________________________
Print Name of Witness

______________________________    ____________________
Signature of Witness          Date

______________________________
Print Name of Principal Investigator/designated representative

______________________________    ____________________
Signature of Principal Investigator/designated representative          Date
Consent Form For Healthy Control Subjects

Measures of Thigh Muscle Torque and Balance associated with Functional Tasks in People with Chronic Obstructive Pulmonary Disease.

Principal Investigator:
Dr. Darlene Reid, PT, PhD, Department of Physical Therapy, University of British Columbia
604-875-4111 Ext 66056

Co-Investigators:
Dr. Jeremy Road, M.D., Respiratory Medicine, Vancouver Hospital, 604-822-7128
Dr. Janice Eng, PT, PhD, Department of Physical Therapy, UBC, GF Strong Rehabilitation Centre, 604-806-9151
Marc Roig, PhD Student, University of British Columbia, 604-505-8767

Sponsor: The Canadian Lung Association (association research programs): Canadian Respiratory Health Professionals

Invitation to Participate:
You are being invited to participate in this study as a healthy subject with no lung disease for the purpose of comparison to a group of individuals with chronic lung disease.

Participation is Voluntary:
You do not have to participate in this research study. It is important that before you make a decision to participate, you read the rest of this form. Please read the following form carefully and ask questions if anything is not clear. The consent form will tell you about the study, why the research is being done, and what will happen during the study and the possible risks, benefits, and discomforts.

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- In a **second session** at GF Strong Rehabilitation Centre, you will be asked to complete 3 tests.
  
  o First, you will be asked to maintain an upright standing position in the balance testing device shown in the photograph. Your balance will be tested examining the steadiness of your standing position while the position of the walls or the standing platform is moved.
  o Secondly, you will perform a test to measure the strength of your thigh muscles during contractions while you are straightening your knee, while you are bending your knee and when you are pushing your thigh out against the lever that is not moving i.e. a static hold. For this type of testing you will perform 5 easy warm-up contractions followed by 3 to 4 maximal voluntary contractions for both the knee straightening and bending movements, and the static holds. Each one of these contractions will last about 3 seconds approximately. During the maximal contraction against the lever when it is not moving i.e. static hold, we will apply a sub-maximal magnetic impulse for a very brief period of time i.e. 1 millisecond, which is 1/1000 of a second. By applying a brief magnetic impulse over the thigh, we can determine how well your brain is telling your muscle to contract. The magnetic impulse will be uncomfortable but not painful.
In the third test of this session, you will be required to walk for a maximum period of six minutes. (if you cannot complete the test you can stop earlier). For this test, you will be asked to walk around the laboratory room. The distance walked will be recorded for a further analysis.

It is anticipated that the three tests performed in the second session will take 2 hours including the rest periods before and after each test.

For the third session you will be required to come to the iCAPTURE CT located in the Vancouver Hospital for a Computerized Tomography Scan which will take about 1 hour. A CT scan is a popular and effective way of examining any part of the body. During the CT scan, a thin beam of x-rays circles completely around the body, collecting a 360-degree view of the area being examined. This information is fed into a computer system that produces a two dimensional picture of this particular view through your body. In this study, a CT scan of the right thigh will be performed to assess the girth of the different muscles in your thigh.

Who Can Participate in this Study?
You have been identified because you are a healthy adult (free of lung disease) over the age of 50. If you agree to take part in the study, Dr. Darlene Reid, a licensed physiotherapist, will determine if you are eligible to take part in the study. Under Dr. Reid’s supervision, the therapeutic risk of you performing exercise will be performed using the exercise screening questionnaire based on the American College of Sports Medicine’s guidelines. This screening should take no more than 15 minutes and will take place when you first visit the lab and before you sign the consent form.

Who Should Not Participate in this Study?
You will be excluded if you are currently taking or have taken systemic corticosteroids within the 6 months prior to study. In addition, if you suspect that you may be pregnant or you are planning to become pregnant during the study, require supplemental oxygen, have any injury or disease of the knee or leg which may be aggravated by exercise, any neurological disease (i.e. stroke or Parkinson’s disease), cancer, cardiovascular disease (heart failure, previous heart attack or cardiovascular surgery), pacemaker, respiratory failure or any other condition that excludes you from the type of activity performed during the study, then you will be excluded from the study.

Possible Harm and Side-Effects of Participation
There are risks associated with the testing that can be minimized when standard procedures are used. The use of the brief magnetic pulse may cause some muscle discomfort when the electrical pulse is applied. Following the functional tests you may experience some mild fatigue and soreness in the thigh muscle immediately afterwards but this should not last longer than 1 to 2 hours. To prevent from potential falls, mainly during the functional tests (stair climbing and sit-to-stand and stand-to-sit) a spotter will support you during the tests. CT scans produce doses of radiation that can be reduced with the use of a single slice CT scan (non-full body). Radiation is calculated in
millisieverts (mSv). The average person in the U.S. receives an effective dose of about 3 to 5 mSv per year from naturally occurring radioactive materials. A full body CT scan produces an effective radiation dose of 10 mSv (i.e., equal to two or three years of natural radiation). Due to its reduced time of exposure, the use of single slice CT scan can reduce radiation by 50%-60% compared to a full body scan (i.e., equal to one or one and a half years of natural radiation). In the present study, a single slice CT scan will be used with this purpose.

Benefits to You of Participating in the Study:
There are no direct benefits to you for participating in this study. It is hoped that additional information gained in this research study may be useful in the treatment of patients with COPD. After completion of the study, you will be given access to the information from your tests and the study results if you request.

Remuneration:
An honorarium (100$) will be paid for your participation in the study to help offset some of the costs related to your participation such as travel and parking expenses.

Alternative Treatments:
You do not have to participate in this study to receive treatment for your condition. Participation is voluntary.

In the Event of an Injury
In the event you experience a serious side effect during this study you should immediately contact Marc Roig (PhD student) at 604-505-8767, 24 hours a day, seven days a week. Signing this consent form in no way limits your legal rights against the sponsor, investigators, or anyone else. In case of a serious medical event resulting from this study, please report to an emergency room and inform them that you are participating in a research study and that Dr. Darlene Reid can be contacted for further information at 604-812-7402.

Confidentiality:
Your confidentiality will be respected. No information that discloses your identity will be released or published without your specific consent to the disclosure. However, research records and medical records identifying you may be inspected in the presence of the Investigator or his or her designate by Health Canada and the UBC Research Ethics Board for the purpose of monitoring the research. However, no records which identify you by name or initials will be allowed to leave the investigators’ offices.

Contact:
If you have any questions or desire further information with respect to this study, or if you experience any adverse effects, you should contact the principal investigator or co-investigators at the numbers listed on page 1 of this consent form.
Subject Rights and Withdrawal from the Study
If you have any questions about your rights as a research subject, you may call the Research Subject Information Line in the University of British Columbia Office of Research Services at 604-822-8598. Signing this consent form in no way limits your legal rights against the sponsor, investigators, or anyone else.

You have a right to change your mind about participating in this study. If you want to withdraw from the study please inform Dr. Reid by calling 604-875-4111 Ext 66056. The research team will stop collecting any additional information about you. The research team may use and share information that was gathered before they received your notice of withdrawal.
Consent
Dr. Darlene Reid (or her associates) have given you information about this research study.
They have explained what will be done and how long it will take. They explained any inconvenience, discomfort or risks that may be experienced during this study.

I ______________ freely and voluntarily consent to participate in this research study.

print name

I have read and understand the information in this form and have had an opportunity to ask questions and have them answered. **I will be given a signed and dated copy of the consent form to keep for my records.**

____________________________________   _________________
Signature of Subject          Date

____________________________________
Print Name of Witness

____________________________________
Signature of Witness          Date

____________________________________
Print Name of Principal Investigator/designated representative

____________________________________
Signature of Principal Investigator/designated representative          Date
Appendix C: Risk-Screening Questionnaire

Date: 
Name: 
Participant ID: 
Gender: 

I. Risk factors (two or more places individual at moderate risk)

___1. Have any of your brothers or sisters had a heart attack, before the age of 55 (male relatives) or 65 (female relatives)?
___2. Have you smoked cigarettes in the past 6 months?
___3. What is your usual blood pressure (≥ 140/90)? Do you take blood pressure medication?
___4. What is your LDL cholesterol? If you don’t know your LDL, what is your total cholesterol? What is your HDL cholesterol? [Either LDL > 130 (use total cholesterol > 200 if LDL not known) OR HDL < 35 is a risk. Note: HDL > 60 is a “negative” risk factor.]
___5. What is your fasting glucose (≥ 110)?
___6. What is your height and weight (BMI ≥ 30)? Also, what is your waist girth (> 100 cm)?
___7. Do you get at least 30 minutes of moderate physical activity most days of the week (or its equivalent)?

II. Symptoms (one or more places individual at high risk)

___1. Do you ever have pain or discomfort in your chest or surrounding areas? (i.e. ischemia)
___2. Do you ever feel faint or dizzy (other than when sitting up rapidly)?
___3. Do you find it difficult to breathe when you are lying down or sleeping?
___4. Do your ankles ever become swollen (other than after a long period of standing)?
___5. Do you ever have heart palpitations, or an unusual period of rapid heart rate?
___6. Do you ever experience pain in your legs (i.e. intermittent claudication)?
___7. Has a physician ever said you have a heart murmur? (Has he/she said it is OK, and safe for you to exercise?)
___8. Do you feel unusually fatigued or find it difficult to breathe with usual activities?
III. Other

___1. How old are you? (Men > 45, women > 55 are at moderate risk.)

___2. Do you have any of the following diseases: heart disease, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease (emphysema or chronic bronchitis), asthma, interstitial lung disease, cystic fibrosis, diabetes mellitus, thyroid disorder, renal disease, or liver disease? (Yes, to any disease places individual at high risk.)

___3. Do you have any bone or joint problems, such as arthritis or a past injury that might get worse with exercise? (Exercise testing may need to be delayed or modified.)

___4. Do you have a cold or flu, or any other infection? (Exercise testing must be delayed.)

___5. Are you pregnant? (Exercise testing may need to be delayed or modified.)

___6. Do you have any other problem that might make it difficult for you to do strenuous exercise?

Interpretation:

Low risk (young, and no more than 1 risk factor): can do maximal testing or enter a vigorous exercise program.

Moderate risk (older, or 2 or more risk factors): can do submaximal testing or enter a moderate exercise program.

High risk (one or more symptoms, or disease): can do no testing without physician presence; can enter no program without physician referral.

From
Appendix D: Physical Activity Scale for the Elderly (PASE)

Name:____________________                                         Date:_____________________

Leisure time activity

1. Over the past 7 days, how often did you participate in sitting activities such as reading, watching TV or doing handicrafts?

   0. Never (Go to question # 2)
   1. Seldom (1-2 days)
   2. Sometimes (3-4 days)
   3. Often (5-7 days)

1a. What were these activities?
________________________________________________________________________
__________________________________________________________________

1b. On average, how many hours per day did you engage in these sitting activities?

   1. less than 1 hour
   2. 1 but less than 2 hours
   3. 2-4 hours
   4. More than 4 hours

2. Over the past 7 days, how often did you take a walk outside your home or yard for any reason? For example, for fun or exercise, walking to work, walking the dog, etc?

   0. Never (Go to question # 3)
   1. Seldom (1-2 days)
   2. Sometimes (3-4 days)
   3. Often (5-7 days)
2a. On average, how many hours per day did you spend walking?

1. less than 1 hour
2. 1 but less than 2 hours
3. 2-4 hours
4. more than 4 hours

3. Over the past 7 days, how often did you engage in light sport or recreational activities such as bowling golf with a cart, shuffleboard, fishing from a boat or pier or other similar activities?

0. Never (Go to question # 4)
1. Seldom (1-2 days)
2. Sometimes (3-4 days)
3. Often (5-7 days)

3a. What were these activities?
________________________________________________________________________
________________________________________________________________________

3b. On average, how many hours per day did you engage in light sport or recreational activities?

1. less than 1 hour
2. 1 but less than 2 hours
3. 2-4 hours
4. more than 4 hours

4. Over the past 7 days, how often did you engage in moderate sport or recreational activities such as doubles tennis, ballroom dancing, hunting, ice skating, golf without a cart, softball or other similar activities?

0. Never (Go to question # 5)
1. Seldom (1-2 days)
2. Sometimes (3-4 days)
3. Often (5-7 days)

4a. What were these activities?
________________________________________________________________________
________________________________________________________________________
4b. On average, how many hours per day did you engage in light sport or recreational activities?

1. less than 1 hour
2. 1 but less than 2 hours
3. 2-4 hours
4. more than 4 hours

5. Over the past 7 days, how often did you engage in strenuous sport or recreational activities such as jogging, swimming, cycling, single tennis, aerobic dance, skiing (downhill or cross-country) or other similar activities?

0. Never (Go to question # 6)
1. Seldom (1-2 days)
2. Sometimes (3-4 days)
3. Often (5-7 days)

5a. What were these activities?

________________________________________________________________________
________________________________________________________________________

5b. On average, how many hours per day did you engage in light sport or recreational activities?

0. less than 1 hour
1. 1 but less than 2 hours
2. 2-4 hours
3. more than 4 hours

6. Over the past 7 days, how often did you do any exercises specifically to increase muscle strength and endurance, such as lifting weights or pushups, etc?

0. Never (Go to question # 7)
1. Seldom (1-2 days)
2. Sometimes (3-4 days)
3. Often (5-7 days)

Household activities

7. Over the past 7 days, have you done any light housework, such as ducting or washing dishes?

1. No
2. Yes
8. During the past 7 days, have you done any heavy housework or chores, such as vacuuming, scrubbing floors, washing windows, or carrying wood?

   1. Yes
   2. No

9. During the past 7 days, did you engage in any of the following activities? Please answer YES or NO for each item.

   a. Home repairs like painting, wallpapering, electrical work, etc.
   b. Lawn work or yard care, including snow or leaf removal, wood chopping, etc
   c. Outdoor gardening
   d. Caring for another person, such as children, dependent spouse, or another adult

**Work related activity**

10. During the past 10 days, did you work for pay or as a volunteer? ___________

10a. How many hours per week did you work for pay and/or as a volunteer? ______

10b. Which of the following categories best describes the amount of physical activity required on your job and/or volunteer work.

   1. Mainly sitting with light arm movements (examples: office worker, watchmaker, seated assembly line worker, bus driver, etc)
   2. Sitting or standing with some walking (examples: cashier, general office worker, light tool and machinery worker)
   3. Walking with some handling of materials generally weighting less than 50 pounds (examples: mailman, waiter/waitress, construction worker, heavy tool and machinery worker)
   4. Walking with heavy manual work often requiring handing of materials weighing over 50 pounds (examples: lumberjack, stone mason, farm or general laborer)
Appendix E: SPSS Syntax Codes for the Main Analyses of Chapter 3

Regression model adjusted for age for assessing differences between groups in knee extensors concentric strength and functional performance.

DATASET ACTIVATE DataSet1.
GLM GS WD RST EXTCONP BY Group WITH Age
   /METHOD=SSTYPE(3)
   /INTERCEPT=INCLUDE
   /EMMEANS=TABLES(Group) WITH(Age=MEAN) COMPARE ADJ(LSD)
   /PRINT=DESCRIPTIVE HOMOGENEITY
   /CRITERIA=ALPHA(.05)
   /DESIGN=Age Group.

Regression model adjusted for age and BMI for assessing differences between groups in IF and CSA.

GLM CSA CSAEXT CSAFLEX FATPIXELSEXT FATPIXELSFLEX BY Group WITH Age BMI
   /METHOD=SSTYPE(3)
   /INTERCEPT=INCLUDE
   /EMMEANS=TABLES(Group) WITH(Age=MEAN BMI=MEAN) COMPARE ADJ(LSD)
   /PRINT=DESCRIPTIVE HOMOGENEITY
   /CRITERIA=ALPHA(.05)
   /DESIGN=Age BMI Group.
Appendix F: SPSS Syntax Codes for the Main Analyses of

Chapter 4

Regression model adjusted for age and body weight for assessing
differences between groups in the SCPT, muscle torque and functional
performance.

GLM TUG WD NORMPC EXTCOMP EXTECCP ISO FLECONP FLEECCP BY
Group WITH Age Weight
    /METHOD=SSTYPE(3)
    /INTERCEPT=INCLUDE
    /EMMEANS=TABLES(Group) WITH(Age=MEAN Weight=MEAN) COMPARE
    ADJ(LSD)
    /PRINT=DESCRIPTIVE HOMOGENEITY
    /CRITERIA=ALPHA(.05)
    /DESIGN=Age Weight Group.
Appendix G: SPSS Syntax Codes for the Main Analyses of Chapter 5

Student-t Test to assess differences between groups in RTs, knee extensors muscle force, PTs, muscle activation and post-activation potentiation.

DATASET ACTIVATE DataSet1.
T-TEST GROUPS=group(1 2)
  /MISSING=ANALYSIS
  /VARIABLES=MVC RT RTHIGHEST RATIO RPT PT
  /CRITERIA=CI(.95).
Appendix H: SPSS Syntax Codes for the Main Analyses of Chapter 6

Mann-Whitney U Test to assess differences between groups in Condition 1, normalized individual scores of Conditions 2 to 6, composite equilibrium scores and sensory ratios.

NPTESTS
  /INDEPENDENT TEST (COND1 COND2 COND3 COND4 COND5 COND6 NORM2 NORM3 NORM4 NORM5 NORM6 BAL SOM VIS VES PREF) GROUP (Group) MANN_WHITNEY
  /MISSING SCOPE=ANALYSIS USERMISSING=EXCLUDE
  /CRITERIA ALPHA=0.05  CILEVEL=95.

Student-t Test to assess differences between groups in knee extensors muscle torque were assessed with the student-t-test.

T-TEST GROUPS=Group(1 2)
  /MISSING=ANALYSIS
  /VARIABLES=EXTCONP
  /CRITERIA=CI(.95).

Analysis of covariance for assessing differences in conditions of the Sensory Organization Test adjusted for knee extensors muscle strength.

DATASET ACTIVATE DataSet2.
GLM COND1 COND2 COND3 COND4 COND5 COND6 BY Group WITH EXTCONP
  /METHOD=SSTYPE(3)
  /INTERCEPT=INCLUDE
  /EMMEANS=TABLES(Group) WITH(EXTCONP=MEAN) COMPARE ADJ(LSD)
  /PRINT=DESCRIPTIVE ETASQ HOMOGENEITY
  /CRITERIA=ALPHA(.05)
  /DESIGN=EXTCONP Group.
Appendix I: Ethics Approval Certificate

The University of British Columbia
Office of Research Services
Clinical Research Ethics Board – Room 210, 828 West 10th Avenue, Vancouver, BC V5Z 1L8

ETHICS CERTIFICATE OF EXPEDITED APPROVAL:
AMENDMENT

<table>
<thead>
<tr>
<th>PRINCIPAL INVESTIGATOR:</th>
<th>DEPARTMENT:</th>
<th>UBC CREB NUMBER:</th>
</tr>
</thead>
<tbody>
<tr>
<td>W. Darlene Reid</td>
<td>UBC/PhysMed, Faculty of Physical Therapy</td>
<td>H08-02079</td>
</tr>
</tbody>
</table>

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

<table>
<thead>
<tr>
<th>Institution</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancouver Coastal Health (VCHR/VCHA)</td>
<td>Vancouver General Hospital</td>
</tr>
<tr>
<td>Providence Health Care</td>
<td>St. Paul's Hospital</td>
</tr>
</tbody>
</table>

Other locations where the research will be conducted:
Some patients might be initially contacted at these sites. However, the major part of the study will take place at patients’ homes, where patients will fill out the questionnaires at baseline and over a 6-month period.

CC-INVESTIGATOR(S):
Jeremy B. Road
Mark Fitzgerald
A. Jane Burns
Marc Roig

SPONSORING AGENCIES:
N/A

PROJECT TITLE:
Falls in people with chronic obstructive pulmonary disease (COPD)

REMINDER: The current UBC CREB approval for this study expires: March 12, 2010

AMENDMENT(S):

<table>
<thead>
<tr>
<th>Document Name</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
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<td>Consent Forms:</td>
<td></td>
<td></td>
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<tr>
<td>Falls and COPD-consent</td>
<td>3</td>
<td>April 26, 2009</td>
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<td>Advertisements:</td>
<td></td>
<td></td>
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<tr>
<td>Falls and COPD-Letter of initial contact</td>
<td>3</td>
<td>April 26, 2009</td>
</tr>
</tbody>
</table>

AMENDMENT APPROVAL DATE: May 25, 2008

CERTIFICATION:

In respect of clinical trials:
1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.
2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.
3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

The amendment(s) for the above-named project has been reviewed by the Chair of the University of British Columbia.
Appendix J: Informed Consent Form

Falls in people with chronic obstructive pulmonary disease (COPD)

Principal Investigator:
Dr. Darlene Reid, PT, PhD, Department of Physical Therapy, University of British Columbia
604-875-4111 Ext 66056

Co-Investigators:
Dr. Jeremy Road, M.D., Respiratory Medicine, Vancouver Hospital, 604-822-7128
Dr. Mark Fitzgerald, M.D., Respiratory Medicine, Vancouver Hospital, 604-875-4122
Jane Burns, PT, Research Coordinator, Respiratory Medicine, St Paul’s Hospital, 604-806-9151
Marc Roig, PhD Student, University of British Columbia, 604-505-8767

Invitation to Participate:
You are being invited to participate in this study as someone who has been diagnosed with Chronic Obstructive Pulmonary Disease (COPD).

Participation is Voluntary:
You do not have to participate in this research study. It is important that before you make a decision to participate, you read the rest of this form. Please read the following form carefully and ask questions if anything is not clear. The consent form will tell you about the study, why the research is being done, and what will happen during the study and the possible risks, benefits, and discomforts.

Background:
Most risk factors of falls commonly attributed to elderly can also be attributed to people with COPD. Due to the multiple effects of the disease, however, people with COPD might have an increased risk of falling compared to elderly people without the condition. The prevalence of falls and the potential risk involved in falls occurrence in people with COPD have not yet been investigated. Identification of the risk factors of falls is essential to design preventive strategies to reduce falls incidence in these people.

Purpose:
The purpose of this study is to investigate the prevalence of falls in people with COPD and the specific risks factors associated with fall occurrence. The impact of falls on quality of life (QoL) in people with COPD will also be assessed.

What does the study involve?
If you decide to participate in the study, we will mail a package to your home. This package contains a number of questionnaires that you will be asked to fill out. These questionnaires are designed to assess your health status, level of physical activity and
balance confidence as well as the number of medications you take and chronic conditions (diseases) you have been diagnosed with. You can choose not to answer any questions that you are uncomfortable with. In addition, during this six month period, you will be asked to record any falls you may have. The package includes a fall diary for this purpose.

We will contact you by phone two weeks after we put the package in the mail for you to ensure that you have received it and to confirm that you understand what the package contents require. At the one month mark, you will be asked to return your completed questionnaires and the first month of your fall diary using the postage-paid, pre-addressed envelopes that will be included in your package.

Every month onwards you will be asked to return your monthly fall diary again using the postage paid, pre addressed envelopes we will provide you for this purpose. If any of the fall diaries that we receive back from you indicate that you have had a fall, we will contact you by phone to ask you for details about the circumstances of the fall incident. Five months after you have received the package, we will send you a second package with the same questionnaires. At the 6 month mark, you will again be asked to complete the questionnaires (identical to those completed at the one month mark) and return them, along with your last fall diary, by mail.

You will also be asked to provide some information of your clinical history. This information includes the number and types of medications you are taking, whether you have any other clinical condition apart from COPD, and the diagnosis of COPD (i.e., level of impairment). This information will be obtained from your medical charts. The total time required to participate in the study is expected to be about 3 to 4 hours at the most.

**Who Can Participate in this Study?**
Subjects who have been diagnosed with COPD and who are 40 years of age or older.

**Who Should Not Participate in this Study?**
People with COPD with neurological disorders affecting balance or gait (i.e., cerebellar disorders, stroke, Parkinson's); with very low levels of mobility (i.e., wheelchair users).

**Possible Harms and Side-Effects of Participation:**
There are no known harms or side effects associated with participation in this study.

**Benefits to You of Participating in the Study:**
There are no direct benefits to you for participating in this study. It is hoped that additional information gained in this research study may be useful in the prevention of falls in subjects with COPD. After completion of the study, you will be given access to the information of the study results if you request.
Remuneration:
An honorarium ($25) will be paid for your participation in the study. If you decide to withdraw from the study, a pro-rated amount of the honorarium will be paid.

Confidentiality:
Your confidentiality will be respected. No information that discloses your identity will be released or published without your specific consent to the disclosure. However, research records and medical records identifying you may be inspected in the presence of the investigator or his or her designate by Health Canada and the UBC Research Ethics Board for the purpose of monitoring the research. However, no records which identify you by name or initials will be allowed to leave the investigators’ offices.

Contact:
If you have any questions or desire further information with respect to this study, you should contact the principal investigator or co-investigators at the numbers listed on page 1 of this consent form. Marc Roig, the student coordinating this project, is the primary contact for this study.

Subject Rights and Withdrawal from the Study:
If you have any questions about your rights as a research subject, you may call the Research Subject Information Line in the University of British Columbia Office of Research Services at 604-822-8598. Signing this consent form in no way limits your legal rights against the sponsor, investigators, or anyone else.

You have a right to change your mind about participating in this study. If you want to withdraw from the study please inform Dr. Darlene Reid by calling 604-875-4111 Ext 66056. The research team will stop collecting any additional information about you. The research team may use and share information that was gathered before they received your notice of withdrawal.
Consent

Dr. Reid (or her associates) have given you information about this research study. They have explained what will be done and how long it will take. They explained any inconvenience, discomfort or risks that may be experienced during this study.

I ___________________________ freely and voluntarily consent to participate in this research study. I have read and understand the information in this form and have had an opportunity to ask questions and have them answered. I will be given a signed and dated copy of the consent form to keep for my records.

____________________________________   __________________
Signature of Subject          Date

____________________________________
Print Name of Witness

____________________________________   __________________
Signature of Witness         Date

____________________________________
Print Name of Principal Investigator/designated representative

____________________________________   __________________
Signature of Principal Investigator/designated representative Date
Appendix K: Instructions for Completion (First Package)

This package contains the following items:

- A sheet of **instructions and check list** for completion (this sheet)
- A **letter of invitation** to participate in our study
- A **subject consent form** for you to review and complete in order to proceed with participation in the study
- 6 monthly **fall diaries**
- The **Chronic Respiratory Questionnaire** (CRQ-SAS)
- The **Outcomes Study Short Form-36** (SF-36)
- The **Physical Activity Scale for the Elderly** (PASE)
- The **Clinical evaluation form** to record medications and chronic conditions
- The **Activities specific balance confidence** (ABC) scale

**How to Proceed?**

The first thing you have to do is to read the letter of invitation and the consent form. These two documents explain the project and what is required to participate. If you decide to participate in the study, you will sign, date, and write your name on the consent form. Then you have to complete all forms (forms, questionnaires and scales), except for the monthly fall diaries that need to be completed once a month. Take your time to complete the forms, there is no need to rush. Follow the instructions carefully and do not hesitate to give us a call if you need assistance.

Once you have completed the forms, please make sure that all questions have been answered. Place the forms back in the postage-paid pre-addressed envelope provided and wait until the end of the month. At the end of the month, fill out the first fall diary (August) and send it back to us with the consent and questionnaires. Before mailing this out, please complete the checking list provided at the bottom of this sheet to check that you have done everything properly. If you have done things correctly, you will now have only 5 monthly fall diaries left.
The monthly fall diaries are completed on a monthly basis. You will see that each fall diary has a monthly calendar and that we ask you to mark the calendar if you have any fall during that month. Remember to follow the instructions provided in the fall diary carefully. At the end of each month, you will send us back the fall diary (even if you haven’t had any falls). If you have had any fall, we’ll contact you to ask you some questions regarding how the fall occurred. We will ask you to use the fall diaries to report any fall during the 6 months that the study lasts.

Five months after you have received the first package you will receive another package containing the same forms. You will be asked to complete all the forms (forms, questionnaires and scales) included in this second package. You will be asked to do exactly the same as you did when you received the first package. Read the forms and complete them. If you have any question, call us; we will be happy to assist you. Once you have completed all forms, put them in the postage-paid pre-addressed envelope provided and please send them back to us. Remember to include the last fall diary in the package.

**CHECK LIST**

I have read the invitation letter and the consent form

I have written my name, signed, and dated the consent form

I have completed the following forms and questionnaires:

- Chronic Respiratory Questionnaire (CRQ)
- Outcomes Study Short Form-36 (SF-36)
- Physical Activity Scale for the Elderly (PASE)
- Clinical Evaluation Form
- Activities Specific Balance Confidence Scale
- The fall diary for the first month (August)

I have sent all the above documents using the pre paid envelope provided
Appendix L: Letter of Invitation to the Study

Re: Research study entitled: Falls in people with chronic obstructive pulmonary disease

Dear Mr/Mrs:

I am writing this letter to inform you of a University of British Columbia research study for individuals with chronic obstructive pulmonary disease (i.e. emphysema or chronic bronchitis). Persons with chronic obstructive pulmonary disease (COPD) are being invited to take part in a study conducted by the Department of Physical Therapy at the University of British Columbia. This study will examine if people with COPD have an increased risk for falling compared to healthy individuals. In particular, the study investigates whether people with COPD have an increased prevalence of falls over a 6 month period and the impact of these falls on quality of life.

If you agree to participate, you will be asked to record the number of falls you may have over 6 months and to complete 4 questionnaires to evaluate aspects related to fall risk. Even though you have not had any fall in the past, your participation in the study is very important to ascertain the risk of falls in people with COPD. The total time required for the study is about 3-4 hours. An honorarium will be paid for your participation. Please feel free to discuss this study with me if you have any questions or concerns. If you need help to fill out the questionnaires we can help you.

If you would like to learn more about the study or you need some assistance, please contact either:

**Jenny Yin** at: 604 875 4111 ext 62574  
By e-mail: jingyi26@interchange.ubc.ca

**Marc Roig** at: 604-505-8767  
By e-mail: markredj@interchange.ubc.ca

Yours truly,

Dr. Jeremy Road  
604-875-4241  
Co-Investigator  
Department of Medicine  
UBC

Dr. Mark Fitzgerald  
604-875-4122  
Co-Investigator  
Department of Medicine  
UBC

Dr. Darlene Reid  
Principal Investigator  
604-875-4111 ext 66056  
Department of Physical Therapy  
UBC
Appendix M: Fall Diary

Fall Diary

Instructions

- Have you had any fall including a slip or trip in which you lost your balance and landed on the floor or ground or lower level?

- If so, please circle the day of the calendar on which the fall has occurred

- Remember to send us back this fall diary at the end of each month

Please direct all inquiries and concerns to:
Jenny Yin 604-875-4111 ext 62574 jyinak@interchange.ubc.ca
Marc Roig 604-505-8767 markrea@interchange.ubc.ca
Appendix N: Medical Outcomes Study Short Form-36 (SF-36v2)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please mark an ☑ in the one box that best describes your answer.

1. In general, would you say your health is:

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑ 1</td>
<td>☑ 2</td>
<td>☑ 3</td>
<td>☑ 4</td>
<td>☑ 5</td>
</tr>
</tbody>
</table>

2. Compared to one year ago, how would you rate your health in general now?

<table>
<thead>
<tr>
<th>Much better now than one year ago</th>
<th>Somewhat better now than one year ago</th>
<th>About the same as one year ago</th>
<th>Somewhat worse now than one year ago</th>
<th>Much worse now than one year ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑ 1</td>
<td>☑ 2</td>
<td>☑ 3</td>
<td>☑ 4</td>
<td>☑ 5</td>
</tr>
</tbody>
</table>

Thank you for completing this survey!
3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>b</td>
<td>Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf</td>
<td>□ 1 ........... □ 2 ........... □ 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>Lifting or carrying groceries</td>
<td>□ 1 ........... □ 2 ........... □ 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>Climbing several flights of stairs</td>
<td>□ 1 ........... □ 2 ........... □ 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e</td>
<td>Climbing one flight of stairs</td>
<td>□ 1 ........... □ 2 ........... □ 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>f</td>
<td>Bending, kneeling, or stooping</td>
<td>□ 1 ........... □ 2 ........... □ 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>g</td>
<td>Walking more than a kilometre</td>
<td>□ 1 ........... □ 2 ........... □ 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>h</td>
<td>Walking several hundred metres</td>
<td>□ 1 ........... □ 2 ........... □ 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i</td>
<td>Walking one hundred metres</td>
<td>□ 1 ........... □ 2 ........... □ 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>j</td>
<td>Bathing or dressing yourself</td>
<td>□ 1 ........... □ 2 ........... □ 3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

a. Cut down on the **amount of time** you spent on work or other activities..........................☐ 1 ............ ☐ 2 .......... ☐ 3 ............ ☐ 4 ............ ☐ 5

b. Accomplished less than you would like ............................................☐ 1 ............ ☐ 2 .......... ☐ 3 ............ ☐ 4 ............ ☐ 5

c. Were limited in the **kind of work or other activities**............................☐ 1 ............ ☐ 2 .......... ☐ 3 ............ ☐ 4 ............ ☐ 5

d. Had **difficulty** performing the work or other activities (for example, it took extra effort)........☐ 1 ............ ☐ 2 .......... ☐ 3 ............ ☐ 4 ............ ☐ 5
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

- Cut down on the amount of time you spent on work or other activities......................... 1 ............ 2 ............ 3 ............ 4 ............ 5
- Accomplished less than you would like ......................................................... 1 ............ 2 ............ 3 ............ 4 ............ 5
- Did work or other activities less carefully than usual ........................................ 1 ............ 2 ............ 3 ............ 4 ............ 5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>

7. How much bodily pain have you had during the past 4 weeks?

<table>
<thead>
<tr>
<th>None</th>
<th>Very mild</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
</tbody>
</table>
8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
</table>

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
</table>


b. Have you been very nervous?............ ![1] ............... ![2] ............... ![3] ............... ![4] ............... ![5]

c. Have you felt so down in the dumps that nothing could cheer you up?......................... ![1] ............... ![2] ............... ![3] ............... ![4] ............... ![5]


e. Did you have a lot of energy?............ ![1] ............... ![2] ............... ![3] ............... ![4] ............... ![5]


g. Did you feel worn out?.................... ![1] ............... ![2] ............... ![3] ............... ![4] ............... ![5]

h. Have you been happy?..................... ![1] ............... ![2] ............... ![3] ............... ![4] ............... ![5]

10. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?**

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▾</td>
<td>▾</td>
<td>▾</td>
<td>▾</td>
<td>▾</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>

11. **How TRUE or FALSE is each of the following statements for you?**

<table>
<thead>
<tr>
<th></th>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don’t know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>a I seem to get sick a little easier than other people..........................</td>
<td>▾</td>
<td>▾</td>
<td>▾</td>
<td>▾</td>
<td>▾</td>
</tr>
<tr>
<td>b I am as healthy as anybody I know ..................................................</td>
<td>▾</td>
<td>▾</td>
<td>▾</td>
<td>▾</td>
<td>▾</td>
</tr>
<tr>
<td>c I expect my health to get worse ......................................................</td>
<td>▾</td>
<td>▾</td>
<td>▾</td>
<td>▾</td>
<td>▾</td>
</tr>
<tr>
<td>d My health is excellent .................................................................</td>
<td>▾</td>
<td>▾</td>
<td>▾</td>
<td>▾</td>
<td>▾</td>
</tr>
</tbody>
</table>

Thank you for completing these questions!
Appendix O: Chronic Respiratory Questionnaire (CRQ) First Administration

Self-Administered Standardized Format (CRQ-SAS)

First Administration
This questionnaire is designed to find out how you have been feeling during the last 2 weeks. In the first section, you will be asked to answer questions about activities which make some people feel short of breath. In the next section, you will answer questions about your mood and how you have been feeling.

Please read these instructions for completing this questionnaire:

- Please read each question carefully and then place an "x" in the box beside the answer that best describes you.
- If you are unsure about how to answer a question, please give the best answer you can.
- If you would like to change an answer, put a line through the box you want to change. Place an "x" in the box beside the option you would like to choose instead.
- There are no right or wrong answers.
- Your answers to this questionnaire will be kept confidential.

Please continue on the next page.
Below is a list of activities which make some people with lung problems feel short of breath.

For each of the activities below, place an "x" in the box that best describes how much shortness of breath you have had while doing that activity during the **LAST 2 WEEKS**.

The last column has been provided for you to indicate if you have **NOT DONE** an activity during the last two weeks.

(Place an "x" in one box on each line)

<table>
<thead>
<tr>
<th>ACTIVITIES:</th>
<th>Extremely short of breath</th>
<th>Very short of breath</th>
<th>Quite a bit short of breath</th>
<th>Moderate shortness of breath</th>
<th>Some shortness of breath</th>
<th>A little shortness of breath</th>
<th>Not at all short of breath</th>
<th>Not Done</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Feeling emotional such as angry or upset</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>2 Taking care of your basic needs (bathing, showering, eating or dressing)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>3 Walking</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>4 Performing chores (such as housework, shopping groceries)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>5 Participating in social activities</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>
These next questions ask you about your energy in general and how your mood has been during the **LAST 2 WEEKS**. Please put an "x" in a box, from 1 to 7, that best describes how you have felt.

6. In general, how much of the time during the **LAST 2 WEEKS** have you felt frustrated or impatient?
   1. All of the time
   2. Most of the time
   3. A good bit of the time
   4. Some of the time (Place an "x" in one box only)
   5. A little of the time
   6. Hardly any of the time
   7. None of the time

7. How often during the **LAST 2 WEEKS** did you have a feeling of fear or panic when you had difficulty getting your breath?
   1. All of the time
   2. Most of the time
   3. A good bit of the time
   4. Some of the time (Place an "x" in one box only)
   5. A little of the time
   6. Hardly any of the time
   7. None of the time
8. What about fatigue? How tired have you felt over the **LAST 2 WEEKS**?

1. Extremely tired

2. Very tired

3. Quite a bit of tiredness

4. Moderately tired (Place an "x" in one box only)

5. Somewhat tired

6. A little tired

7. Not at all tired

9. How often during the **LAST 2 WEEKS** have you felt embarrassed by your coughing or heavy breathing?

1. All of the time

2. Most of the time

3. A good bit of the time

4. Some of the time (Place an "x" in one box only)

5. A little of the time

6. Hardly any of the time

7. None of the time
10. In the **LAST 2 WEEKS**, how much of the time did you feel very confident and sure that you could deal with your illness?

1. None of the time  
2. A little of the time  
3. Some of the time  
4. A good bit of the time  
5. Most of the time  
6. Almost all of the time  
7. All of the time  

(Place an "x" in one box only)

11. How much energy have you had in the **LAST 2 WEEKS**?

1. No energy at all  
2. A little energy  
3. Some energy  
4. Moderately energetic  
5. Quite a bit of energy  
6. Very energetic  
7. Full of energy  

(Place an "x" in one box only)
12. In general, how much of the time did you feel upset, worried, or depressed during the **LAST 2 WEEKS**?

   1. All of the time  
   2. Most of the time  
   3. A good bit of the time  
   4. Some of the time  (Place an "x" in one box only)  
   5. A little of the time  
   6. Hardly any of the time  
   7. None of the time  

13. How often during the **LAST 2 WEEKS** did you feel you had complete control of your breathing problems?

   1. None of the time  
   2. A little of the time  
   3. Some of the time  
   4. A good bit of the time  (Place an "x" in one box only)  
   5. Most of the time  
   6. Almost all of the time  
   7. All of the time  
14. How much of the time during the **LAST 2 WEEKS** did you feel relaxed and free of tension?

1. None of the time
2. A little of the time
3. Some of the time
4. A good bit of the time (Place an "x" in one box only)
5. Most of the time
6. Almost all of the time
7. All of the time

15. How often during the **LAST 2 WEEKS** have you felt low in energy?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time (Place an "x" in one box only)
5. A little of the time
6. Hardly any of the time
7. None of the time
16. In general, how often during the **LAST 2 WEEKS** have you felt discouraged or down in the dumps?

1. All of the time  
2. Most of the time  
3. A good bit of the time  
4. Some of the time  
5. A little of the time  
6. Hardly any of the time  
7. None of the time  

(Place an "x" in one box only)

17. How often during the **LAST 2 WEEKS** have you felt worn out or sluggish?

1. All of the time  
2. Most of the time  
3. A good bit of the time  
4. Some of the time  
5. A little of the time  
6. Hardly any of the time  
7. None of the time  

(Place an "x" in one box only)
18. How happy, satisfied, or pleased have you been with your personal life during the **LAST 2 WEEKS**?

   1. Very dissatisfied, unhappy most of the time
   2. Generally dissatisfied, unhappy
   3. Somewhat dissatisfied, unhappy
   4. Generally satisfied, pleased
   5. Happy most of the time
   6. Very happy most of the time
   7. Extremely happy, could not be more satisfied or pleased

(Place an "x" in one box only)

19. How often during the **LAST 2 WEEKS** did you feel upset or scared when you had difficulty getting your breath?

   1. All of the time
   2. Most of the time
   3. A good bit of the time
   4. Some of the time
   5. A little of the time
   6. Hardly any of the time
   7. None of the time

(Place an "x" in one box only)
20. In general, how often during the **LAST 2 WEEKS** have you felt restless, tense, or uptight?

1. All of the time

2. Most of the time

3. A good bit of the time

4. Some of the time (Place an "x" in one box only)

5. A little of the time

6. Hardly any of the time

7. None of the time
# Appendix P: Activities Balance Confidence (ABC) Scale

**CODE:** __________________________  **Date:** __________________________

For each of the following activities, please indicate your level of self-confidence by choosing a corresponding number from the following rating scale. Answer all items even if they are activities you would not do or are unsure about.

<table>
<thead>
<tr>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not confident</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Completely confident</td>
</tr>
</tbody>
</table>

*How confident are you that you will not lose your balance or become unsteady when you....*

a) .....walk around the house? _____%
b) .....walk up and down stairs?______%
c) .....pick up a slipper from the floor?_____%
d) .....reach at eye level?______%
e) .....reach while standing on your tiptoes?_____%
f) .....stand on a chair to reach?______%
g) .....sweep the floor?_____%
h) .....walk outside to nearby car?______%
i) .....get in and out of a car?______%
j) .....walk across a parking lot?______%
k) .....walk up and down a ramp?______%
l) .....walk in a crowded mall?______%
m) .....walk in a crowd or get bumped?______%
n) .....ride an escalator holding the rail?______%
o) .....ride an escalator not holding the rail?______%
p) .....walk on icy sidewalks?______%
Appendix Q: Clinical Form First Package

CODE: ______________________   Date: ______________________

1. Age: ______

2. Date of birth: ______

3. Weight: ______

4. Height: ______

5. In the last 6 months, have you had any fall including a slip or trip in which you lost your balance and landed on the floor or ground or lower level?

6. If you did, how many times have you fallen down in the last 6 months?

7. Do you remember the dates of these falls (approximately)?

8. Do you use a walker, crutches a cane or scooter to move around?

9. In the last 6 months, have you had to go to the emergency room of the hospital due to a worsening of your COPD?

10. If you did, how many times?

11. While in Hospital, did they give you corticosteroids (prednisone) and/or antibiotics?

12. Do you take oxygen? Always, only during the day or only at nights?
Please list all the clinical conditions (diseases) that you have been diagnosed with and the approximate date when you were diagnosed. You can start with COPD, which includes emphysema and chronic bronchitis (see example provided).

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>DATE OF DIAGNOSIS</th>
</tr>
</thead>
<tbody>
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<td>COPD</td>
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</tbody>
</table>
Please list all the medications that you are currently taking: if you can, please include the dose, the frequency and the reason why you are taking this medication. Please, include also when you started to use it. See example provided (Aspirin).

<table>
<thead>
<tr>
<th>NAME</th>
<th>DOSE</th>
<th>FREQUENCY</th>
<th>REASON</th>
<th>START DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>0.1g</td>
<td>daily</td>
<td>Prevent cardiac problem</td>
<td>July, 2007</td>
</tr>
</tbody>
</table>
Appendix R: Chronic Respiratory Questionnaire (CRQ) Follow-up Administration

Self-Administered Standardized Format (CRQ-SAS)

Follow-up Administration
You have previously completed a questionnaire containing questions on how you have been feeling and how your lung disease was affecting your life. This is a follow up questionnaire designed to ask you how you have been since that time.

Please read these instructions for completing this questionnaire:

- Please read each question carefully and then place an "x" in the box beside the answer that best describes you.
- If you are unsure about how to answer a question, please give the best answer you can.
- If you would like to change an answer, put a line through the box you want to change. Place an "x" in the box beside the option you would like to choose instead.
- Remember there are no right or wrong answers.
- Your answers to this questionnaire will be kept confidential.

Please continue on the next page.
This questionnaire is designed to find out how you have been getting along since the last time you saw us. You previously completed this questionnaire telling us how short of breath you were while performing the following activities.

For each of the activities below, place an "x" in the box that best describes how much shortness of breath you have had while doing that activity during the **LAST 2 WEEKS**.

The last column has been provided for you to indicate if you have **NOT DONE** an activity during the last two weeks.

(Place an "x" in box on each line)

<table>
<thead>
<tr>
<th>ACTIVITIES:</th>
<th>Extremely short of breath</th>
<th>Very short of breath</th>
<th>Quite a bit short of breath</th>
<th>Moderate shortness of breath</th>
<th>Some shortness of breath</th>
<th>A little shortness of breath</th>
<th>Not at all short of breath</th>
<th>Not Done</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Feeling emotional such as angry or upset</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>2 Taking care of your basic needs (bathing, showering, eating or dressing)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>3 Walking</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>4 Performing chores (such as housework, shopping groceries)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>5 Participating in social activities</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>
These next questions ask you about your energy in general and how your mood has been during the LAST 2 WEEKS. Please put an "x" in a box, from 1 to 7, that best describes how you have felt.

21. In general, how much of the time during the LAST 2 WEEKS have you felt frustrated or impatient?
   8. All of the time
   9. Most of the time
   10. A good bit of the time
   11. Some of the time
   12. A little of the time
   13. Hardly any of the time
   14. None of the time

22. How often during the LAST 2 WEEKS did you have a feeling of fear or panic when you had difficulty getting your breath?
   8. All of the time
   9. Most of the time
   10. A good bit of the time
   11. Some of the time
   12. A little of the time
   13. Hardly any of the time
   14. None of the time

   (Place an "x" in one box only)
23. What about fatigue? How tired have you felt over the **LAST 2 WEEKS**?

8. Extremely tired  
9. Very tired  
10. Quite a bit of tiredness  
11. Moderately tired  
12. Somewhat tired  
13. A little tired  
14. Not at all tired  

(Place an "x" in one box only)

24. How often during the **LAST 2 WEEKS** have you felt embarrassed by your coughing or heavy breathing?

8. All of the time  
9. Most of the time  
10. A good bit of the time  
11. Some of the time  
12. A little of the time  
13. Hardly any of the time  
14. None of the time  

(Place an "x" in one box only)
25. In the **LAST 2 WEEKS**, how much of the time did you feel very confident and sure that you could deal with your illness?

8. None of the time

9. A little of the time

10. Some of the time

11. A good bit of the time

12. Most of the time

13. Almost all of the time

14. All of the time

(Place an "x" in one box only)

26. How much energy have you had in the **LAST 2 WEEKS**?

8. No energy at all

9. A little energy

10. Some energy

11. Moderately energetic

12. Quite a bit of energy

13. Very energetic

14. Full of energy

(Place an "x" in one box only)
27. In general, how much of the time did you feel upset, worried, or depressed during the **LAST 2 WEEKS**?

8. All of the time

9. Most of the time

10. A good bit of the time

11. Some of the time (Place an "x" in one box only)

12. A little of the time

13. Hardly any of the time

14. None of the time

28. How often during the **LAST 2 WEEKS** did you feel you had complete control of your breathing problems?

8. None of the time

9. A little of the time

10. Some of the time

11. A good bit of the time (Place an "x" in one box only)

12. Most of the time

13. Almost all of the time

14. All of the time
29. How much of the time during the LAST 2 WEEKS did you feel relaxed and free of tension?

8. None of the time
9. A little of the time
10. Some of the time
11. A good bit of the time (Place an "x" in one box only)
12. Most of the time
13. Almost all of the time
14. All of the time

30. How often during the LAST 2 WEEKS have you felt low in energy?

8. All of the time
9. Most of the time
10. A good bit of the time
11. Some of the time (Place an "x" in one box only)
12. A little of the time
13. Hardly any of the time
14. None of the time
31. In general, how often during the **LAST 2 WEEKS** have you felt discouraged or down in the dumps?

8. All of the time  
9. Most of the time  
10. A good bit of the time  
11. Some of the time  
12. A little of the time  
13. Hardly any of the time  
14. None of the time  

(Place an "x" in one box only)

32. How often during the **LAST 2 WEEKS** have you felt worn out or sluggish?

8. All of the time  
9. Most of the time  
10. A good bit of the time  
11. Some of the time  
12. A little of the time  
13. Hardly any of the time  
14. None of the time  

(Place an "x" in one box only)
33. How happy, satisfied, or pleased have you been with your personal life during the LAST 2 WEEKS?

8. Very dissatisfied, unhappy most of the time

9. Generally dissatisfied, unhappy

10. Somewhat dissatisfied, unhappy

11. Generally satisfied, pleased

12. Happy most of the time

13. Very happy most of the time

14. Extremely happy, could not be more satisfied or pleased

(Place an "x" in one box only)

34. How often during the LAST 2 WEEKS did you feel upset or scared when you had difficulty getting your breath?

8. All of the time

9. Most of the time

10. A good bit of the time

11. Some of the time

12. A little of the time

13. Hardly any of the time

14. None of the time

(Place an "x" in one box only)
35. In general, how often during the **LAST 2 WEEKS** have you felt restless, tense, or uptight?

   8. All of the time  
   9. Most of the time  
  10. A good bit of the time  
  11. Some of the time  
  12. A little of the time  
  13. Hardly any of the time  
  14. None of the time  

   (Place an "x" in one box only)
Appendix S: Clinical Form Second Package

CODE:_______________ Date:_______________

1. In the last 6 months, have you had any fall including a slip or trip in which you lost your balance and landed on the floor or ground or lower level?

2. If you did, how many times have you fallen down in the last 6 months?

3. Do you remember the dates of these falls (approximately)?

4. In the last 6 months, have you had to go to the emergency room of the hospital due to a worsening of your COPD?

5. If you did, how many times?

6. While in Hospital, were you treated with corticosteroids (prednisone) and/or antibiotics?
Ever since the start of this survey (6 months ago), have you been diagnosed with any **NEW** clinical condition or disease? If so, please name the clinical condition and the approximate date when you were diagnosed using the table provided below. Please, report only **NEW** clinical conditions that have been diagnosed during the last 6 months.

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>DATE OF DIAGNOSIS</th>
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</table>
Please list all the **NEW** medications that you have been prescribed with in the last 6 months. If you can, please include the dose, the frequency and the reason why you are taking this medication. Please, include also when you started to use it. Please, **DO NOT** include **OLD** medications that you were already taking when you joined the survey study (6 months ago).

<table>
<thead>
<tr>
<th>NAME</th>
<th>DOSE</th>
<th>FREQUENCY</th>
<th>REASON</th>
<th>START DATE</th>
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Appendix T: Fall Questionnaire

**Instructions**: For each fall incident, please answer the following nine questions.

<table>
<thead>
<tr>
<th>Date:</th>
<th>Subject Code:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Where did you fall?</td>
<td></td>
</tr>
<tr>
<td>2. When did you fall?</td>
<td></td>
</tr>
<tr>
<td>3. What were you doing when you fell?</td>
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<tr>
<td>4. What caused you to fall?</td>
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<tr>
<td>5. Which assistive device were you using when you fell?</td>
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<td>6. Which direction did you fall?</td>
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<tr>
<td>7. What did you land on?</td>
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</tr>
<tr>
<td>8. Were there any injuries?</td>
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<tr>
<td>9. Did you require medical attention?</td>
<td></td>
</tr>
</tbody>
</table>
Appendix U: SPSS Syntax Codes for the Main Analyses of

Chapter 7

Regression model for measures of health-related quality of life (HRQoL) at baseline and at 6 months.

DATASET ACTIVATE DataSet1.
REGRESSION
/DESCRIPTIVES MEAN STDDEV CORR SIG N
/MISSING LISTWISE
/STATISTICS COEFF OUTS R ANOVA CHANGE ZPP
/CRITERIA=PIN(.05) POUT(.10)
/NOORIGIN
/DEPENDENT CRQDYS2
/METHOD=ENTER CRQDYS1 FALLER.

REGRESSION
/DESCRIPTIVES MEAN STDDEV CORR SIG N
/MISSING LISTWISE
/STATISTICS COEFF OUTS R ANOVA CHANGE ZPP
/CRITERIA=PIN(.05) POUT(.10)
/NOORIGIN
/DEPENDENT CRQFAT2
/METHOD=ENTER CRQFAT1 FALLER.

REGRESSION
/DESCRIPTIVES MEAN STDDEV CORR SIG N
/MISSING LISTWISE
/STATISTICS COEFF OUTS R ANOVA CHANGE ZPP
/CRITERIA=PIN(.05) POUT(.10)
/NOORIGIN
/DEPENDENT CRQEM2
/METHOD=ENTER FALLER CRQEM1.

REGRESSION
/DESCRIPTIVES MEAN STDDEV CORR SIG N
/MISSING LISTWISE
/STATISTICS COEFF OUTS R ANOVA CHANGE ZPP
/CRITERIA=PIN(.05) POUT(.10)
/NOORIGIN
/DEPENDENT CRQMAST2
/METHOD=ENTER FALLER CRQMAST1.

REGRESSION
/DESCRIPTIVES MEAN STDDEV CORR SIG N
Regression model for measures of balance confidence at baseline and at 6 months.
Logistic regression model for assessing risk factor for falls.

LOGISTIC REGRESSION VARIABLES FALLER
  /METHOD=STEP(LR) AGE PREVFALLS OXY COMORB MEDICATIONS GENDER PREVEXC CHDDIS ABC1
  /CONTRAST (OXY)=Indicator
  /CONTRAST (GENDER)=Indicator
  /CLASSPLOT
  /PRINT=GOODFIT CORR ITER(1) CI(95)
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).