Limitations in Physical Performance in People with Chronic Obstructive Pulmonary Disease

by

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Abstract

People with chronic obstructive pulmonary disease (COPD) show deficits in physical performance, including skeletal muscle dysfunction (atrophy, weakness), and activity limitation due to fatigue, dyspnea, and pain. Little is known about the pattern of pain and muscle dysfunction and how they impact physical performance in people with COPD. Based on the components of the International Classification of Functioning, Disability and Health (i.e. body structure, body function, and activity limitation), the purposes of this thesis were to examine patients with COPD to determine: 1) thigh muscle shape and size changes; 2) the severity, interference, and characteristics of pain; 3) how comorbidities relate to pain; 4) the relationships between pain and physical performance (muscle strength, walk distance, and daily physical activity).

Methods and Results: Three sets of cross-sectional experiments were performed. Study 1: Size and shape descriptors derived from magnetic resonance imaging of thighs were compared in COPD patients to healthy people. Muscle atrophy and shape changes were common and non-uniformly distributed among individual thigh muscles compared to healthy people (Chapter 2). Study 2: A survey study demonstrated that pain severity and interference (measured by the McGill Pain Questionnaire and Brief Pain Inventory) were higher in people with COPD compared to age- and gender-matched controls (n=47 per group). The number of comorbidities was an independent correlate of pain severity in COPD (Chapter 3). A second analysis of the survey data was performed on a larger sample of COPD patients who experienced pain (n=54) further explored the pattern of comorbidities and pain. The number of comorbidities was associated with pain severity and interference; musculoskeletal and endocrine conditions contribute to pain severity;
and people with COPD were under-treated for pain (Chapter 4). **Study 3:** This cross-sectional study demonstrated that pain was associated with a lower six-minute walk test, shorter active and standing times, and longer sedentary times (measured by three-dimensional accelerometry), and increased body mass index (Chapter 5). **In summary,** regional muscle atrophy might contribute to deficits in muscle performance in people with COPD. In addition, pain is significant in people with COPD and can be considered as an activity-limiting factor in COPD.
Preface

All research in this thesis is in compliance with the University of British Columbia’s Policy #89- Research involving human participants.

Published Papers

A version of the Chapter 2 has been published.


Contribution: 80% - Bahareh HajGhanbari, Dr. Reid, and Dr. Hamarneh provided study concept and design, study coordination, data analysis and manuscript preparation. Neda Changizi performed the image processing. Dr. Ward provided consultation at all steps of the research process and critically reviewed the manuscript before submission.


Contribution: 80% - Bahareh HajGhanbari and Dr. Reid provided study concept and design as well as manuscript preparation. Drs. Holsti and Road critically reviewed the manuscript before submission (Chapter 3). Ethical approval was obtained from the University of British Columbia Clinical Research Ethics Board, Ethics Certificate Number: H09-01774.
Submitted Papers

A version of Chapter 4 is submitted for publication.

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A version of Chapter 5 is submitted for publication.


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List of Abbreviations

3D: Three-Dimensional
6MWT: Six-minute Walk Test
ADL: Activities of Daily Living
ACSM: American College of Sports Medicine
ANOVA: Analysis of Variance
ATS: American Thoracic Society
BFL: Biceps Femoris, Long head
BFS: Biceps Femoris, Short head
BPI: Brief Pain Inventory
BMI: Body Mass Index
CAT: COPD Assessment Test
CI: Confidence Interval
CHAMPS: Community Health Activities Model Program for Seniors
CNS: Central Nervous System
COPD: Chronic Obstructive Pulmonary Disease
CSA: Cross Sectional Area
CT: Computerized Tomography
DOMS: Delayed Onset Muscle Soreness
EE: Energy Expenditure
ERS: European Respiratory Society
FEV₁: Forced Expiratory Volume in the 1st second
FI: Fatigue Index
FVC: Forced Vital Capacity
GOLD: Global Initiative for Obstructive Lung Disease
HRQoL: Health Related Quality of Life
ICF: International Classification of Functioning, Disability, and Health
IL-1: Interleukin 1
IL-1β: Interleukin-1β
IL-6: Interleukin-6
IL-8: Interleukin 8
LE: Lower Extremity
MCS: Mental Component Score
MDC: Mean of Distances to the Centroid
MET: Metabolic Equivalent of Task
MPQ: McGill Pain Questionnaire
MRI: Magnetic Resonance Imaging
mMRC: modified Medical Research Council Breathlessness Scale
MPQ: McGill Pain Questionnaire
MSK: Musculoskeletal
MVC: Maximal Voluntary Contractions
NHANES III: National Health and Nutrition Examination Survey
NPS: Numeric Descriptor Scale
NO: Nitric Oxide
NSAIDS: Non-Steroidal Anti-Inflammatory Drug
PCC: Pearson Product Moment Correlation Coefficient
PCS: Physical Component Score

PPI: Present Pain Intensity

QoL: Quality of Life

RF: Rectus Femoris

RPE: Rating of Perceived Exertion

ROM: Range of Motion

ROS: Reactive Oxygen Species

SD: Standard Deviation

SDC: Standard Deviation of Distances to the Centroid

SE: Standard Error

SF-36: Health Survey Short Form 36

SM: Semimembranosus

ST: Semitendinosus

SOT: Sensory Organization Test

SPSS: Statistical Package for the Social Sciences

SVM: Support Vector Machine

TSK: Tampa Scale for Kinesiophobia

TNF-α: Tumor Necrosis Factor-Alpha

WHO: World Health Organization

VAS: Visual Analog Scale

VL: Vastus Lateralis

VM: Vastus Medialis

IASP: International Association of the Study of Pain
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Dedication

This thesis is dedicated to my beloved mother and father, who introduced me to the joy of reading from birth, enabling such a study to take place today. You were and will be the greatest love of my life.

Thank you mom for letting me spread my wings and explore the world outside of Iran even though it cuts into shopping and our afternoon tea times. Thank you for sitting with me all those times from pre-school reading me stories every night to high school when I struggled staying up late at night to complete my study tasks. Your patience and enthusiasm are unparalleled, and for that you are my best mentor for life. Your love, positive attitude, and your unwavering faith in me, always made my day better, over and out!

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Chapter One: Introduction

1.1 Introduction

1.1.1 Definition of chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease (COPD) is a disease defined by persistent and progressive airflow limitation associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases (Global Initiative for Chronic Obstructive Lung Disease 2011), and leads to significant morbidity and mortality (Health Canada 2012; O'Donnell et al. 2008). Exacerbations and comorbidities contribute to the overall severity in individual patients. Chronic airflow limitation is characterized by slowing of expiratory airflow that is reflected by a persistently low forced expiratory volume in the first second (FEV₁), and a low ratio of FEV₁ to forced vital capacity (FVC). Much of the airflow limitation in COPD is not reversible with treatment. FEV₁ is commonly used to determine the severity of the COPD disease, and it is expressed as a percentage of a predicted normal value based on a person's age, gender, height and weight (Health Canada 2012). More recent classifications schemes have also included health status scores, dyspnea, and risk of future untoward events (At-A-Glance Outpatient 2011). The severity of COPD, as defined by the GOLD criteria (At-A-Glance Outpatient 2011) is described in Table1.1.

Chronic bronchitis and emphysema are the two sub-types of COPD, and are the two commonly co-existing obstructive diseases of the lung (Barnes 2000). Chronic
bronchitis is defined clinically by the existence of cough and sputum production for at least 3 months of a year, for two consecutive years (Barnes 2000). Inflammation in the central airways and hyper-secretion of mucus results in chronic bronchitis, and contributes to narrowing of the airways. With the progression of the disease, the progressive fibrosis of the airway walls will accentuate the airflow limitation further (Barnes 2000). Emphysema is characterized by the damage to lung parenchyma, inflammation of the air sacs and destruction of their walls. Enlargement of distal air spaces beyond terminal bronchioles that reduces the elasticity of the lung tissue and decreases its tethering action on small airways leads to their premature collapse on expiration, which further contributes to the limitation of airflow (Barnes 2000).

1.1.2 Epidemiology of COPD

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in Canada and projected to be the third cause of death for both males and females by 2020 (The Lung Association 2010). The prevalence of COPD is approximately 5% of the population or 13.5 million people in the USA (Make et al. 1996), or possibly up to 25 million people if undiagnosed cases are included (Make et al. 1996).

In 2007, approximately 210 million people were diagnosed with COPD worldwide (World Health Organization, 2012). More than 3 million people died of COPD in 2005 that includes the 5% of total mortality rate globally (World Health Organization, 2012).
death from COPD is estimated to increase by more than 30% in the next 10 years (World Health Organization, 2012). Although the overall prevalence and associated socio-economic burden of the disease is increasing worldwide, the incidence of COPD varies substantially among different countries (Buist et al. 2005).

1.1.3 Etiology of COPD

Tobacco smoking is considered to be the primary and the most important risk factor for COPD in developed nations. Eighty to 90% of cases of COPD in the United States are due to smoking (Young et al. 2009). The risk of developing COPD increases with age and continued smoke exposure, which is measured by the number of cigarette packages smoked per day multiplied by the number of years of smoking (pack-years). Other risk factors for airflow obstruction include prolonged exposure to occupational dusts, industrial waste gases, and chemicals (Devereux 2006), indoor and urban air pollution (Halbert et al. 2006), genetic factors, such as deficiency of the serine protease α1-antitrypsin (Stoller & Aboussouan 2005), bronchial hyper-responsiveness and repeated lung infections (Wedzicha 2007).

1.1.4 Pathophysiology of COPD and systemic inflammation

Prolonged exposure to noxious particles will incite an inflammatory reaction of the lungs (Burrows et al. 1966). With prolonged exposure, an inflammatory response can be found in the systemic circulation (Barnes et al. 2003; Gan et al. 2004). It is not understood how COPD is caused by the exposure to noxious particles; however, the
main processes leading to lung damage and systemic manifestations of COPD have been described as: 1) oxidative stress due to increased levels of free radicals in tobacco smoke; 2) increased levels of cytokines due to inflammation of the lungs; 3) impaired activity of antiprotease enzymes, such as alpha 1-antitrypsin caused by tobacco smoke or genetic predisposition (Barnes et al. 2008).

1.1.5 Systemic manifestations and comorbidities in COPD

The pathogenesis and clinical manifestations of COPD are not restricted to inflammation and structural pathophysiology of the lungs. Rather, this disease is accompanied by clinically significant systemic consequences. It is proposed that the “spill over” of pro-inflammatory molecules from the lung through blood circulation, the production of pro-inflammatory cytokines by other organs (such as liver, bone marrow and skeletal muscle), and finally the initiation of the systemic inflammation by cigarette smoke can induce the systemic inflammation of COPD (Agusti 2007). Systematic manifestations of COPD include congestive heart failure, muscle wasting (Gosselink et al. 1996), depletion of fat-free mass (Engelen et al. 2000), deconditioning, exercise intolerance (O’Donnell et al. 2008), and all are associated with increased mortality and morbidity (Sin et al. 2006) that progress with aging (Viegi 2007).

In addition to systemic manifestations, people with COPD have a high prevalence of several comorbidities. Comorbidity is defined as a disease coexisting with the primary disease of interest (Yawn & Kaplan 2008). Specific to COPD, comorbidity is defined as:
1) the presence of one or more distinct disorders in addition to COPD, regardless of whether the comorbid conditions are or are not directly related to COPD; and 2) a distinct disorder or disease that is not part of the spectrum of the natural history of COPD (Yawn & Kaplan 2008).

The prevalence of comorbidities is not consistent among different studies. However, many studies agree on the higher incidence of cardiovascular and musculoskeletal comorbid conditions in COPD. The major comorbidities in COPD include angina, ischemic heart diseases, hypertension, cardiac arrest, atrial fibrillation, myocardial infarction, stroke, atherosclerosis, weight loss (cachexia) (Rabe et al. 2007), diabetes (Blacher et al. 2005; Marquis et al. 2005), osteoporosis or osteopnea (Bolton et al. 2004; Sin et al. 2003), obesity and hyperlipidemia, arthritis, cancer, neurological impairments (Agrawal 2007; Ozge et al. 2001), and anxiety/depression (Wagena et al. 2005). Many of these comorbidities contribute to muscle wasting and weakness, and activity limitation (Pitta et al. 2005) due to fatigue and dyspnea. Studies have shown that most COPD patients are reported to die of comorbid, extra-pulmonary diseases such as ischemic heart failure, rather than the respiratory consequences of COPD itself (Yawn & Kaplan 2008). Tobacco smoke and inflammation have been determined to be the underlying factors for multiple comorbid diseases in COPD (Yawn & Kaplan 2008).

1.1.6 Physical performance and activity limitation in COPD

Physical inactivity has been shown to be an important indicator of morbidity and
mortality in the COPD population (Pitta et al. 2006; Pitta et al. 2006). Studies revealed that people with COPD tend to be very inactive (Furlanetto et al. 2010; Pitta et al. 2005; Pitta et al. 2006; Pitta et al. 2006a). Several studies assessing physical activity using three dimensional accelerometry have reported that COPD patients tend to spend less time in walking and standing; with less movement intensity during walking; and higher sitting and lying time compared to healthy age-matched group (Pitta et al. 2005). Furthermore, the worsening of COPD severity is associated with a decline in physical activity, especially after transition from grade II to III of the disease as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (Furlanetto et al. 2010; Pitta et al. 2005). Lack of adequate physical activity predictably leads to deconditioning e.g. an accelerated decline in aerobic performance (Oga et al. 2006). Therefore, activity limitation is a major contributor to the development of systemic consequences, such as skeletal muscle dysfunction (fiber atrophy, type I fiber loss, metabolic changes) (Wuyam, et al. 1992), muscle weakness, and fat-free mass depletion (Engelen et al. 2000; Gosselink et al. 1996), and is likely to influence multiple co-morbid conditions. In addition, muscle weakness and fatigue might contribute to further worsening of the physical condition of the patient, leading to increased dyspnea with exertion. This vicious cycle of increased dyspnea leading to further deconditioning can accentuate disease symptoms of fatigue and exercise intolerance.

1.1.7 Muscle composition, strength, and mass in COPD

Skeletal muscle dysfunction has been documented in many patients with COPD, and
contributes significantly to the reduced exercise capacity and quality of life in COPD (Wuyam et al. 1992). Some proposed mechanisms of skeletal muscle dysfunction in COPD include: 1) systematic chronic inflammation manifested as prolonged secretion of cytokines that can facilitate the degradation of myosin heavy chains and cell death; 2) oxidative stress that incites muscle fatigue and proteolysis; 3) hypoxemia that suppresses protein synthesis in muscle cells, and can lead to the loss of amino acids and reductions in expression of myosin heavy chain isoforms (Sue 2003).

One pathway involved in the systemic inflammation in COPD is the “spill-over” of inflammatory metabolites from lungs to other organs; the second mechanism is hypoxia which progresses with disease severity. Hypoxia can result in increased cytokine production, which by itself can activate the tumor necrosis factor-α (TNF-α) system in COPD. It is also postulated that some extra-pulmonary cells, such as endothelium and fat tissue can produce inflammatory metabolites. Studies have shown that muscle cells are involved in production of pro-inflammatory cytokines, such as TNF-α and IL-6 (Tews & Goebel 1995). TNF-α and IL-6 have been shown to be the major markers of cachexia and selectively target myosin protein content in skeletal muscle. IL-6 induces the release of acute phase proteins from the liver and may be associated with skeletal muscle weakness measured by quadriceps strength and exercise capacity (Yende et al. 2006). An increase in TNF-α is associated with hypoxemia, skeletal muscle atrophy and weakness in COPD (Tracey et al. 1988). These cytokines may cause skeletal muscle weakness without causing muscle wasting by compromising the contractile properties of
the skeletal musculature. TNF-α directly stimulates the degradation of muscle-specific proteins, such as fast-type myosin heavy chain (Li et al. 1998). TNF-α may trigger muscle cell apoptosis and DNA fragmentation in skeletal muscle in prolonged inflammatory conditions (Phillips & Leeuwenburgh 2005).

The exact intracellular mechanisms of skeletal muscle wasting in COPD are not fully understood. However, an imbalance between protein synthesis and protein degradation, and between the loss and gain of muscle fibers nuclei may contribute to skeletal muscle wasting in COPD. Another mechanism might be through decreased protein synthesis after prolonged exposure to TNF-α or IL-1β, which causes reductions in the insulin-like growth factor-1 (Thissen 2007). TNF-α and IL-1β also inhibit muscle differentiation and myoblast fusion (Langen et al. 2001), which adversely affects efficient muscle growth, regrowth, and regeneration after atrophy. This process will compromise the ability of the muscle to recover from atrophy and contribute to muscle wasting in COPD (Hawke & Garry, 2001).

Oxidative stress, which is an imbalance between the formation of and protection against reactive oxygen species (ROS), can contribute to muscle dysfunction in COPD and to the development and progression of the disease (Maltais et al. 1996). The production of ROS in muscle, vascular and airway epithelial cells is activated by inflammation (Domej et al. 2006). The level of injury caused by ROS depends mainly on the antioxidant status of the tissue that may be impaired by disuse and chronic hypoxia (Wüst & Dengens
Hypoxia can also increase oxidative stress, and can lead to muscle fiber atrophy (Wüst & Dengens 2007). Adaptations to hypoxemia leads to fiber type change in skeletal muscles in COPD, i.e. the reduced proportion of type I fibers and an increase in the proportion of type II fibers (especially type Ila fibers) as compared with normal individuals (Engelen et al. 1999), and a reduction in cross-sectional area of type I and type Ila fibers (muscle atrophy). This phenomenon helps to preserve muscle strength, however, it reduces the aerobic capacity of the muscle and makes the exercising muscles more prone to fatigue. This change occurs mainly because of the higher lactic acid production and the inefficiency of anaerobic fibers in synthesizing ATP relative to the aerobic metabolism (Kushmerick et al. 1992).

Other factors contributing to skeletal muscle dysfunction in COPD include: 1) Patients with COPD demonstrate reductions in the number of capillaries in the muscles (Banzett et al. 2000) and increases in blood lactate levels at very low work rates (Maltais et al. 1996), which is due primarily to the reduced oxidative capacity of the muscle and to early activation of anaerobic metabolism; 2) Steroid-induced myopathy after prolonged use of corticosteroids has been shown in COPD with myopathic changes and generalized fiber atrophy (Engelen et al. 1999; Kushmerick et al. 1992), and contributes to muscle weakness in COPD muscle; 3) Nutritional deficits (mainly the protein calorie malnutrition) in COPD can result in loss of muscle mass and fiber atrophy that leads to
decreased muscle strength and endurance (Engelen et al. 1999; Kushmerick et al. 1992; Wüst & Dengens 2007); 4) Inactivity can lead to the loss of muscle mass, a decrease in force production capacity, reduced oxidative capacity and, decreased resistance to fatigue, the number and density of mitochondria, and the number of capillaries (Casaburi 1996). These changes contribute to further deconditioning and more impairment in skeletal muscle function. Loss of muscle strength, especially in lower extremities is documented in COPD (Gosselink et al. 1996; Bernard et al. 1998). The preferential weakness of lower limb muscles has been attributed to the reduced physical activity in these patients; however, the amount of decline in muscle strength shows a considerable variability across studies from normal values to losses of 30-50% (Gosselink et al. 1996).

Loss of muscle volume has been studied as one of the factors that contributes to muscle weakness. Studies have found reductions in single cross-sectional area of the thigh muscles using the variety of techniques such as MRI, ultrasound, and computed tomography scanning (Bernard et al. 1998; Marquis et al. 2002; Roig et al. 2011; Seymour et al. 2009), and some have reported that loss of muscle volume is proportional to the reduction in thigh muscle cross-sectional area (Bernard et al. 1998) and reported lower muscle volumes in lower extremities in patients with COPD compared to healthy controls (Bernard et al. 1998; Mathur et al. 2008; Seymour et al. 2009). However, these studies reported on muscle groups (Bernard et al. 1998; Roig et al. 2011; Mathur et al. 2008) rather than individual muscles, which do not estimate
changes in regional muscle volume and might mask the regional shape and size changes in peripheral muscles. Furthermore, there has been controversy on the number of cross-sections used to estimate the muscle volume in previous studies. Many relied on a single CSA (Bernard et al. 1998; Roig et al. 2011; Seymour et al. 2009), using the 50% of the thigh length or the CSA of a number of cross-sections (Mathur et al. 2008) to estimate thigh muscle volume. Mid-thigh measures represent the largest difference in muscle CSA between healthy and COPD patients, and thus might not demonstrate precisely the volume differences between groups. One study used multiple slices along the thigh and calculated the thigh muscle volume based on the assumption that the muscle is conical in shape (Mathur et al. 2008), which might not be the accurate measure of thigh muscle volume (Roberts et al. 1993). The equivocal data from cross-sectional areas and the study of regional muscle shape and size changes point to other plausible explanations for the loss of force in COPD patients. Deficits in muscle quality rather than volume reductions may have a more adverse impact on muscle performance in people with COPD.

1.1.8 Pain
Fatigue and dyspnea are described as the main factors limiting physical activity in people with COPD (Killian et al. 1992); however, people with this condition are reported to experience pain, which likely contributes to the lack of mobility and decreased exercise tolerance (Lynn et al. 2000; Lohne et al. 2010). The International Association for the Study of Pain (IASP 2011) (available at: www.iasp-pain.org) defines pain as "an
unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Acute pain has been defined as awareness of noxious signaling from recently damaged tissue, complicated by sensitization in the periphery and within the central nervous system (IASP 2011). Acute pain signals tissue trauma, and sensitization inhibits normal behavior in a protective manner to minimize risk and promote tissue healing (IASP 2011). Chronic pain is defined as 'pain that persists beyond the normal time of healing' (IASP 2011). Chronic pain has been described as the pain that persists for 3 months and 6 months since onset (Turk & Okifuji 2001), however; some researchers have placed the transition from acute to chronic pain at 12 months (Main & Spanswick 2001).

The underlying etiology of pain in COPD is not clear, but some of the potential mechanisms for pain in COPD are postulated to be due to systemic inflammation; hyper-expansion of the chest wall; similar central processing centers for dyspnea and pain; and decreased physical activity and increased body mass index. Based on the chronic nature of comorbidities in COPD and their pain-related symptoms, chronic prolonged systemic inflammation in COPD and its associated chronic pathological changes in different body organs and tissues, we believe that pain in COPD is of chronic nature.
1.1.8.1 Potential etiology of pain in COPD

1.1.8.1.1 Systemic inflammation

The inflammatory cell profile in COPD includes macrophages, neutrophils, and T lymphocytes (Jeffery 2000). Macrophages increase in the lungs are part of the nature of the disease (Linden et al. 1993; Abboud et al. 1998) where they coordinate pulmonary inflammation and parenchymal damage (Barns 2003). Macrophages release large amounts of pro-inflammatory cytokines, such as TNF-α, interleukin-1β (IL-1β), IL-6 (Culpitt et al. 2003) and proteases (Russell et al. 2002); secrete neutrophil and macrophage chemotactic factors, such as interleukin 8 (IL-8) (Lohmann-Matthes et al. 1994; Mio et al. 1997); and generate ROS (Fantone & Ward 1982). This process culminates in airway inflammation. The primary role of inflammatory metabolites, such as cytokines and ROS, in the development of pain has been established by previous studies.

TNF-α released from macrophages can activate other cells to release cytokines such as interleukin 1 (IL-1), as well as nitric oxide (NO), and ROS. These metabolites enhance and prolong the inflammatory response and induce further inflammation and tissue injury (Wang et al. 1992). Studies have reported that neurons in the CNS can synthesize TNF-α and IL-1, which may participate in a bi-directional neuronal communication (Breder et al. 1998; Breder et al. 1994). Moreover, cells of the immune system can produce endorphins, acetylcholine and other neurotransmitters (Watkins & Maier 2002). The importance of the interaction between the nervous and immune systems in the
development of pathological pain has been previously demonstrated (Watkins & Maier 2002). It has been proposed that cytokines produced by inflammatory and glial cells can alter neuronal excitability; therefore, they can directly contribute to the development of intractable pain and hyperalgesia (hyper-sensitivity/ hyper-responsiveness to painful stimulus) (Watkins & Maier 2002). Cytokine antagonists have been found to reduce hyperalgesia, suggesting that activation of cytokines has a major role in the development of inflammatory pain (Poole et al. 1999). IL-1β is associated with increased pain and hyperalgesia, especially in neuropathies and chronic inflammatory diseases (Watkins & Maier 1999). Under pathological conditions, IL-1β can be released from different cell types such as mononuclear cells, fibroblasts, synoviocytes, schwann cells, dorsal root ganglia neurons, and endothelial cells (Watkins & Maier 1999). Furthermore, the possible effects of IL-1β on sensory processing of pain at dorsal root ganglion have been proposed. IL-1β might be a major contributor to the generation of mechanical hyperalgesia (Ferreira et al. 1988). It has been reported that the endogenous IL-1 receptor antagonist can prevent inflammatory hyperalgesia, and that neutralizing antibodies to IL-1 receptors can reduce pain-associated behavior (Cunha et al. 2000).

Strong associations between tissue TNF-α levels and pain/hyperalgesia in a number of painful diseases have been reported (Lindenlaub & Sommer 2003; Shubayev & Myers 2000). In animal studies, TNF-α has been shown to increase mechanical allodynia (pain perception with non painful stimuli) and thermal hyperalgesia (Cunha et al. 1992) and
decrease the mechanical activation threshold in C fibers (Junger & Sorkin 2000).

Furthermore, TNF-α has been shown to be involved in the generation and maintenance of neuropathic pain (Wagner & Myers 1996). The production of TNF-α by Schwann cells after injury suggests a possible role for TNF-α in neuropathic pain (Wagner & Myers 1996). Blocking TNF-α has been shown to reduce hyperalgesia in painful neuropathy (Sommer et al. 1998). Therefore, it is likely that the prolonged production of TNF-α contributes to the development of neuropathy in people with COPD. Several studies have reported the incidence of polyneuropathy in people with COPD (Ozge et al. 2001); however, the underlying mechanisms are not fully established.

Marked increases in the cytokine IL-6 is associated with increased pain and hyperalgesia (Callens et al. 2009). Increased IL-6 serum levels have been detected in conditions such as neuropathies, malignant tumors, musculoskeletal disorders, burn injury, autoimmune and chronic inflammatory conditions. Hypersensitivity of the affected tissues and tenderness sensation has been found in all of these conditions.

Pro-inflammatory cytokines can induce or increase inflammatory and neuropathic pain. COPD is associated with marked and prolonged release of cytokines from the lung to different body organs. It is therefore very likely that the inflammatory cells contribute to the generation and accentuation of chronic and neuropathic pain in people with COPD (Ozge et al. 2001). More research is required to explore the molecular mechanisms underlying the cytokine actions in the context of pain in COPD.
1.1.8.2 Changes in chest wall and accessory respiratory muscles

Airflow limitation in COPD, which is worse during expiration, leads to hyper-inflated lungs and a hyper-expanded chest wall. Because lung volumes are much larger at end expiration, all the inspiratory muscles and especially the diaphragm have a shorter resting length. The underlying lung disease also results in trapped air that greatly increases the residual volume and as a consequence, vital capacity is reduced. Hyperinflation is accentuated by exertion similar to daily activities such as the 6 minute walk test (6MWT) (Marin et al. 2001), which could increase residual volume further and diminish the vital capacity. In short, the inspiratory muscles are at a mechanical disadvantage because of their reduced resting length and limited range of motion.

Some studies have reported greater experience of pain in the chest, neck, and shoulder areas in COPD population (Bentsen et al. 2011; Blidermann et al. 2009; Borge et al. 2011; HajGhanbari et al. 2012). This pain might be related to the abnormal breathing patterns at higher lung volumes (that also require higher levels of minute ventilation); people with COPD overuse both the primary and accessory inspiratory muscles. The fatigue of these muscles might induce pain (MacIntyre 2006). Pain from the diaphragm, which is known as the primary muscle of inspiration, typically refers to the shoulder area (Brox 2003). Accessory muscles of inspiration such as sternocleidomastoid, scalenes, pectoralis minor and major are mainly located around neck, upper chest, arm and shoulder areas. Thus, it is likely that the pain from the overload of these muscles would be felt in those areas.
In addition to fatigue, overuse of the inspiratory muscles may induce muscle spasm and overuse injury. The limited range of motion (ROM) due to hyperinflation may result in reactive muscle spasm similar to what occurs in other conditions with limited ROM of joints and reduced operating lengths of muscle, such as osteoarthritis (Hunter 2009). In addition, the mechanical disadvantage of the inspiratory muscles in the hyper-inflated state may make these muscles more prone to overuse injury as evidenced by microscopic muscle injury in COPD patients (Orozco-Levi et al. 2001), and associated delayed onset muscle soreness that has been reported in healthy people (Mathur et al. 2010). In summary, the hyper-expanded thorax may contribute to muscle spasm and muscle soreness, and pain in people with COPD.

Osteoporosis and osteoarthritis are common conditions in people with COPD. Osteoporosis has been reported to occur in 60-70% in people with COPD (Ferguson et al. 2009). It is a major predisposing factor to vertebral compression and rib fractures due to trivial trauma i.e. coughing (Australian Acute Musculoskeletal Pain Guidelines Group 2004). Osteoarthritis is very common in the general population with an increasing prevalence to 40% at the age 75 years (Kopec et al. 2007). Osteoarthritis can lead to spinal pain and back pain that is very common in the general population (Hunter 2009). Common musculoskeletal (MSK) comorbidities in COPD, including osteoporosis and osteoarthritis, could accentuate pain in the cervical spine or thorax. The impact of these conditions on COPD requires further study.
1.1.8.3 Similar central structures are involved in processing dyspnea and pain

Dyspnea or shortness of breath is one of the most common symptoms in people with COPD, usually described by the patient as breathlessness or air hunger (O'Donnell et al. 1997). It is reported that pain and dyspnea share similar sensory and affective-related brain networks that contribute to activation of behaviors involved in experiencing distress and discomfort (Lansing et al. 2009). Both breathlessness and pain are uncomfortable, complex and distressing symptoms, and one could possibly be misinterpreted as the other by the patient and as a result be perceived and reported without precision (Yorke 2008).

Both pain and dyspnea have been mapped to activation of common brain areas including the anterior/mid insula, dorsal anterior cingulate cortex, sensorimotor and somatosensory cortex II, supplementary motor area, amygdala and medial thalamus (Casey 1999; von Leupoldt et al. 2009). Brain mapping studies performed during severe dyspnea report the activation of the mid/anterior insular cortex, predominantly on the right side (Banzett et al. 2000). It has been noted that increased blood CO$_2$ increases signals in the limbic cortex, mainly in the cingulate gyrus and the mid/anterior insular cortex. Intriguingly, human brain mapping studies have reported increased insular activation, mainly in the anterior portion of the right insula during painful stimuli (Casey 1999). The anterior insula might play a key role not only in alerting the individual to potentially distressing stimuli such as dyspnea and elevated blood CO$_2$ but also to the perception of painful stimuli (Reiman 1997).
The medial thalamus is another center in the brain that is involved in processing dyspnea by transmitting the dyspnea signals from medullary respiratory centers to the cortex (Chen et al. 1992). There are also extensive projections from the medial thalamus to the anterior insula (Allen et al. 1991); the medial thalamus is involved in processing pain signals in chronic and acute conditions. Through the internal capsule of thalamus, third-order neurons send axons to the somatosensory cortex, including the post central gyrus, where discrete localization of the noxious stimulus occurs. In addition to somatosensory localization, fibers from the interlaminar and medial nuclei of the thalamus radiate to the anterior cingulate gyrus and become involved in the emotional components of pain (Merchand 2008; Millan 1993; Schaible & Grubb 1993). These facts exemplify how similar central structures are involved in the perception of both dyspnea and pain signals.

Over the prolonged course of the disease, people with COPD experience dyspnea following moderate activities, which can be increased during periods of disease exacerbation. The prolonged activation of brain centers involved in processing dyspnea signals might induce permanent changes that alter the perception of pain. Because of the close proximity of central processing structures, it is possible that the signals related to dyspnea could be interpreted as pain, especially after sensitization from protracted dyspnea stimuli.
1.1.8.4 Decreased physical activity and increased body mass index (BMI)

Fatigue and dyspnea have been found to be major factors limiting physical activity levels in COPD (Killian et al. 1992). Dyspnea contributes to the decrease in physical activity, that in turn will affect the limb muscles, specifically lower limb muscles and related reductions in muscle mass and strength (Polkey & Moxham 2006). Improvements in aerobic enzyme capacity and reductions in lactic acid accumulation lead to significant decreases in leg pain after interval training in patients with COPD (Coppoolse et al. 1999). These positive findings support the use of muscle strengthening programs for pain reduction in COPD. Inactivity and muscle weakness can cause many secondary conditions that will contribute to de-conditioning and increased experience of pain.

Furthermore, there is a well documented rise world wide in the prevalence of overweightness or obesity and currently a large proportion of COPD patients have a body mass index over 25 kg/m² (Guerra et al. 2002). Pain has been strongly correlated with BMI (Borge et al. 2011). Increased musculoskeletal leg pain has been found in obese females (Tsuritani et al. 2002). In the elderly, chronic pain has been found to be strongly associated with increased BMI (McCarthy et al. 2009). In addition to the biomechanical reasons for obesity that contribute to increased pain, further studies are required to investigate other potential underlying factors that cause pain in obesity.
1.2 Overview of the Thesis

The overall purpose of this PhD thesis was to investigate several limitations of physical performance in people with COPD. Figure 1.1 shows the theoretical framework for examining physical performance in people with COPD and how it can result in functional disability. This framework illustrates the relationship between the pathophysiology of COPD and study outcomes of this thesis (Figure 1.1). This thesis investigates factors limiting physical performance in people with COPD that can be classified according to the major components of International Classification of Functioning, Disability, and Health (ICF), i.e. structure, function, and activity limitation (Stucki 2005). The content of this thesis is organized into three major cross-sectional studies with three main objectives. In Chapter 2, we examined muscle volume and shape deficits of thigh muscles in COPD patients versus matched healthy individuals that is associated with the “structure” component of ICF. The study of pain, physical activity and comorbidities in COPD patients compared to matched healthy people (Chapters 3-5) are associated with the “activity limitation” component of ICF, and the study of muscle strength and functional performance in Chapter 5 is related to the “function” component of ICF. The content of this thesis is organized into three major cross-sectional studies with three main objectives and hypotheses that are outlined below.
1.3 Objectives and Hypotheses of the Thesis

1.3.1 Study I: MRI-based 3D shape analysis of thigh muscles in people with COPD versus healthy older adults (Chapter 2)

Objective 1: To investigate the differences in three-dimensional shape and size measurements of individual thigh muscles between patients with COPD and healthy controls.

Hypothesis 1: People with COPD will demonstrate more abnormalities in measures of muscle structure, namely muscle volume, and anatomical shape anomalies across individual thigh muscles, compared to age- and gender-matched healthy people.

1.3.2 Study II: Severity and characteristics of pain in people with COPD (Chapters 3 & 4)

Objective 2: The purpose of this study was to investigate the pain intensity and pain interference in people with COPD compared to healthy age- and gender-matched older adults (Chapter 3). The secondary objective was to determine the characteristics of comorbidities associated with pain in people with COPD (Chapter 4). This second analysis was performed on a larger sample of COPD patients using the survey methodology described in Chapter 3.

Hypothesis 2: People with COPD will experience more severe pain and more interference of pain with daily activities as compared to the age- and gender-matched
healthy people. Comorbidities will be associated with increased pain in COPD.

1.3.3 Study III: Relationships between pain and physical performance in people with COPD (Chapter 5).

Objective 3: To determine the associations between pain and measures of muscle and functional performance (6MWT, muscle strength and physical activity) in people with COPD.

Hypothesis 3: Pain will be negatively correlated to physical activity, 6MWT, and muscle strength, and will be positively correlated to fatiguability of knee extensors.
Table 1.1 GOLD classification of COPD.

<table>
<thead>
<tr>
<th>GOLD Classification Based on FEV&lt;sub&gt;1&lt;/sub&gt;</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>In patients with FEV&lt;sub&gt;1&lt;/sub&gt;/FVC &lt; 0.70</td>
<td></td>
</tr>
<tr>
<td>GOLD 1</td>
<td>Mild</td>
</tr>
<tr>
<td>GOLD 2</td>
<td>Moderate</td>
</tr>
<tr>
<td>GOLD 3</td>
<td>Severe</td>
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<tr>
<td>GOLD 4</td>
<td>Very Severe</td>
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<table>
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<tr>
<th>Combined Assessment of COPD</th>
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<tbody>
<tr>
<td>Patient Level</td>
<td>Characteristic</td>
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<tr>
<td>----------------</td>
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</tr>
<tr>
<td>A</td>
<td>Low Risk Less Symptoms</td>
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<td>B</td>
<td>Low Risk More Symptoms</td>
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<td>C</td>
<td>High Risk Less symptoms</td>
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<tr>
<td>D</td>
<td>High Risk More Symptoms</td>
</tr>
</tbody>
</table>

The combined assessment of COPD is based on the degree of airflow limitation as defined by the FEV<sub>1</sub> and FVC (upper table) in addition to symptoms and risk of untoward events (lower table). Symptomology is based on health status (measured by the COPD Assessment Test [CAT]), and dyspnea score (measured by the modified British Medical Research Council [mMRC] breathlessness scale). The number of exacerbations is a major consideration for assessing future events as well as hospitalizations and mortality. **Abbreviations**: CAT, Chronic Obstructive Pulmonary Disease Assessment Test; FEV<sub>1</sub>, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council Breathlessness Scale.
Figure 1.1 Factors limiting performance in people with COPD.

Chronic Obstructive Pulmonary Disease

Indoor & outdoor pollutants
Occupational exposures
Primary & secondary tobacco smoke
Hyper-reactivity of the airways
Overall lung growth
Genetics

Environmental Factors

Host Factors

Skeletal Muscle Dysfunction

Systemic factors

Structure

Function

Activity Limitation

Muscle Size (Volume)

Shape Deficits

Strength

Endurance

Pain

Physical activity

Comorbidities

All thigh muscles

Shape descriptors of regional atrophy

Concentric torque

Time to task failure

MPQ, BPI

TSK

CHAMPS (Frequency of activities & energy expenditure)

Accelerometry

Activity duration

Abbreviations: MPQ, McGill Pain Questionnaire; BPI, Brief Pain Inventory; TSK: Tampa Scale for Kinesiophobia.
Chapter Two: MRI-based 3D Shape Analysis of Thigh Muscles: People with COPD versus Healthy Older Adults

2.1 Introduction

Skeletal muscle weakness, particularly in the lower extremities, is common in people with chronic obstructive pulmonary disease (COPD) (Bernard et al. 1998; Gosselink et al. 1996; Hamilton et al. 1995; Nici et al. 2006). In fact, lower limb muscles are affected more than respiratory muscles in this patient population, in part because of disuse (Bernard et al. 1998). COPD-related muscle weakness is associated with other systemic comorbidities including abnormal arterial blood gases (hypoxia, hypercapnea), malnutrition, systemic inflammation, oxidative stress and low testosterone levels (Casaburi 2001; Hamilton et al. 1995). Of interest, the magnitude of skeletal muscle weakness in people with COPD ranges widely among patients (Casaburi 2001), likely reflecting individual differences in the contribution of factors involved in poor muscle performance, including the clinical manifestations of COPD and related comorbidities.

It has been suggested that the loss of muscle mass (size) is associated with skeletal muscle weakness in people with COPD (Bernard et al. 1998). However, the contribution of reduced muscle mass relative to other factors, such as changes in the muscle

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contractile apparatus and/or neuromuscular activation, is unknown (Gosselink et al. 1996). Comprehensive measures of muscle size and shape are required to examine more precisely the relative contribution of muscle mass reduction to force loss. Magnetic resonance imaging (MRI) can be used to accurately distinguish muscle from bone, connective tissue, nerves and blood vessels, and can therefore provide accurate measures of muscle cross-sectional area (CSA) (Engstrom et al. 1991).

Achieving an accurate estimate of muscle size and atrophy is an important concern in strength training, aging, metabolic, and immobilization research (Tracy et al. 2003), all of which aim to design effective preventive and therapeutic strategies. MRI can generate multiple image slices from which muscle volume can be estimated. Previous studies have used a single axial CSA as a surrogate measure of muscle size (Akima et al. 2001; Bernard et al. 1998; Marquis et al. 2002; Overend et al. 1992; Seymour et al. 2009; Visser et al. 2005) and a few reports have described the measurement of several, but not all, axial slices along the whole muscle (Tracy et al. 2003, Mathur et al. 2008). However, the measurement of CSA throughout all axial slices is preferable because it allows for a more accurate measure of muscle size (Tracy et al. 2003). Of further concern, previous researchers have reported only on a single measure of thigh muscle CSA or the CSA of groups of thigh muscles (e.g. knee extensors and flexors) rather than exploring individual thigh muscle volumes and size measures to determine whether aging and/or pathology differentially affect individual muscles (Akima et al. 2001; Bernard et al. 1998; Marquis et al. 2002; Mathur et al. 2008; Overend et al. 1992;
Although muscle atrophy, as defined by muscle volume and CSA, has been reported in patients with COPD, other descriptors of surface area and shape abnormalities have not been explored (Bernard et al. 1998; Mathur et al. 2008; Seymour et al. 2009). Three-dimensional shape descriptors can provide regional information about surface area, muscle size and shape, and the distribution of atrophy. However, whether muscle atrophy occurs uniformly or with inter- or intra-muscle heterogeneity in COPD is unknown.

The objective of this study was to determine the differences, between COPD subjects and healthy controls, in 3D shape and size measurements of individual thigh muscles. To meet this objective, we performed 3D segmentations of eight individual thigh muscles from MR images of 20 COPD patients and 20 healthy controls (i.e. a total of 320 individual muscles were segmented). We then computed seven 3D shape and size measures of each segmented muscle, both globally (for each muscle as a whole) and regionally (by separating each muscle into four partitions and computing the measures on each partition).

2.2 Methods

2.2.1 Participants

A convenience sample of twenty people with COPD and twenty healthy older adults (55-
79 years old) participated in the study (Table 2.1). People with COPD were recruited at local hospitals and COPD clinics, and were included if they had moderate to severe (Stage II to III) COPD based on GOLD guidelines (forced expiratory volume in 1 second (FEV$_1$) < 80% of predicted and FEV$_1$/forced vital capacity (FVC) < 70%) (Global Initiative for Obstructive Lung Disease, 2011), and were >50 years old. Exclusion criteria were: acute exacerbations and oral corticosteroids during the six months prior to the study, and participation in a formal exercise rehabilitation program for at least one year prior to the study. Participants in the control group were recruited from the general population and were included if they were >50 years old, free of lung disease, non smokers, and had not been participating in any formal exercise rehabilitation program for at least one year prior to the study. The healthy group was matched for age, gender, and body mass index (BMI) with the COPD group. These individuals were screened for medical history and spirometric outcomes to ensure that no respiratory disease was present. Exclusion criteria for subjects in both groups included: comorbid cardiovascular disease (e.g. heart failure, previous myocardial infarction, or cardiovascular surgery); neurological conditions (e.g. stroke or Parkinson disease); or lower-extremity musculoskeletal problems (e.g. knee or hip injury or arthritis).

Height and weight were measured with shoes off and light clothing. Spirometry was conducted according to the standards described by the American Thoracic Society (1999) to measure FEV$_1$ and FVC for the purposes of confirming the presence and defining the severity of COPD (Table 2.1). All subjects provided written informed
consent prior to participation in the study. Ethical approval was granted by the University Clinical Ethics Research Board at the University of British Columbia.

2.2.2 Measurements

2.2.2.1 Magnetic Resonance Imaging (MRI)

A 1.5 Tesla MRI scanner (1.5T Horizon Echospeed Scanner, General Electric, Milwaukee, WI) was used to determine differences in muscle volume and shape of individual knee extensor and flexor muscles. MRI was chosen as the imaging technique for this study because it allows for the clear distinction between muscle, bone, and adipose tissue and is recognized as a valid and reliable method to analyze and quantify muscle tissue (Beneke et al. 1991; Mitsiopoulos et al. 1998) without the use of ionizing radiation (Engstrom et al. 1991; Lohn et al. 1999). For the purposes of this study, MRI was used to determine differences in muscle volume and shape of individual knee extensor and flexor muscles including the quadriceps femoris (rectus femoris, vastus lateralis, vastus medialis, vastus intermedius) and the hamstring muscles (semimembranosus, semitendinosus, biceps femoris-long head and biceps femoris-short head) in people with COPD compared to a healthy, matched group.

For each subject, T1-weighted MR images (TE = 8 ms, TR = 650 ms) were obtained from the anterior superior iliac spine to the tibial plateau. The images were 5mm thick, contiguous, axial slices obtained in a 40 cm² field of view with a 512 × 384 pixel matrix (in-plane resolution = 0.78 × 0.78 mm). Two sets of images, one for each of the upper
and lower thigh regions, were collected in immediate succession for each subject without change in subject position. A landmark at the mid-thigh (half the distance between the anterior inferior iliac spine and the superior margin of patella) was identified on the MRI scans to guide the merging of the two sets of images into a single set for the entire thigh using an image interpolation technique. The MRI scan yielded two sets of images, one for each of the upper and lower thigh regions, for a total of approximately 100 slices for each participant. Figure 2.1 shows a selection of representative MRI slices taken from a subject’s thigh at different levels.

2.2.2.2 Image pre-processing

Image pre-processing consisted of three main steps: image volume merging, manual delineation (segmentation) of muscles, and segmentation interpolation. The details of these steps are described in the following paragraphs.

Two sets of images were collected in immediate succession for each patient without change in patient position and were merged into a single set of images using the Merge module in the Amira 3.1 software package (Mercury Computer Systems, Inc). Because the patient position was unchanged between scans, the merging procedure required only a very small transformation to achieve visibly accurate alignment. As an additional redundancy check, we ensured that the location of the landmark in both images coincided after merging. The standard interpolation option was selected in this module, which linearly interpolates between the surrounding voxels from both image sets.
The resulting merged image was then loaded into the ITK-SNAP 1.6.0.1 software that was used for the manual slice-by-slice segmentation of individual muscles from the axial MR images. The ITK-SNAP tool's core functionality and the validity of the software for manual segmentation of human tissue have been previously described (Yushkevich et al. 2006). In order to correctly delineate the margins of each muscle, manual segmentation was performed by a physical therapist with expert anatomical knowledge. Furthermore, the Visible Human Server (http://visiblehuman.epfl.ch/), Grant's Atlas of Anatomy (Agur et al. 2009), an MRI Atlas (Marinkovic et al. 2000), the study by Willan et al. (2002), and inspection of human cadavers by the physical therapist were used as referring sources. Non-contractile tissue including fascia, adipose tissue and blood vessels outside the muscle periphery and tendons were excluded. By moving from slice to slice, the segmentations could be viewed in all three orthogonal slice windows of ITK-SNAP at once in order to carefully verify the accuracy of the segmentation (Figure 2.2). After the completion of each slice-by-slice muscle segmentation, the segmented muscles were viewed in three dimensions (3D) using the mesh application of ITK-SNAP (Figure 2.2).

The segmentations were further analyzed using MATLAB™ 7.6 (Mathworks, Natick, MA, USA). Due to the 5 mm slice thickness of the data, the slice-by-slice segmentations were sparse in the out-of-plane direction. To obtain a set of object surface points that were dense along all axes, the contours around the segmented muscles were
interpolated in 3D (Figure 2.3). This interpolation was performed by establishing the correspondence between neighboring points on adjacent contours and adding new surface points at equal (1 mm) distances along the segment lines joining corresponding points. Muscle size was normalized to femur length as a surrogate measure of patient size by scaling the muscle surface point coordinates to the ratio of the patient’s femur length to a reference femur length (mean of all observed femur lengths).

2.2.2.3 Shape descriptor computation

We computed seven 3D shape and size descriptors of each of the muscles, described in the following paragraphs. All shape descriptors were computed globally, for each muscle as a whole. Four of the shape descriptors were computed regionally, whereby each muscle was divided into four quarters (regions) along its length (Figure 2.4), and the measures were calculated for each region.

2.2.2.3.1 Mean (MDC) and standard deviation (SDC) of distances to the centroid

The centroid of a 3D shape is a point in three dimensions that is in the center of the shape. Intuitively, it can be thought of as a point that is not biased toward any region or side of the shape over another. The distances from each point on the shape surface to this centroid can be analyzed to obtain two measures: (1) the overall size of the object (by taking the mean) and (2) the difference between the shape and a perfect sphere (by taking the standard deviation). For a perfectly spherical shape, these distances will all be the same, and their mean of distances to centroid (MDC) will be exactly equal to the
radius of the sphere. As the shape becomes less spherical, these distances become more different from one another; this is reflected in the standard deviation of distances to the centroid (SDC). Figure 2.5 illustrates how the magnitude of the SDC reflects asphericity in the form of surface roughness or irregularity. These measures were computed regionally by averaging the MDC and SDC values computed for each slice within each region.

2.2.2.3.2 3D moment invariants (Three measures)

Three 3D moments, J1, J2, and J3, which are invariant to translation and rotation, were computed for the surface points of each muscle. Intuitively, moments capture characteristics of the spatial distribution of the voxels that make up the muscle surface (Sadjadi & Hall 1980). Informally, these are considered to be higher order extensions of quantities such as the mean and standard deviation. The moment invariants were calculated using the methodology described by Ward et al. (2007). Moment invariants could not be assessed regionally, because the division of the muscle introduces sudden flat caps at the division boundaries, which would result in misleading moment measurements.

2.2.2.3.3 Surface area and volume

To compute the surface area of each muscle, the closest points on the contours of adjacent slices were connected to form a triangular mesh (Figure 2.6). The sum of the triangular areas provided an estimate of muscle surface area (Lorensen & Cline 1987).
The volume of each muscle was computed by counting the number of voxels inside the segmentation of the muscle and multiplying this number by the spatial volume occupied by each voxel. This measure was computed regionally as well.

### 2.2.3 Statistical analyses

Comparisons of muscle shape and size measures were performed using SPSS version 16.0 (SPSS, Inc, Chicago, IL). Each descriptor was tested for normality using the Shapiro-Wilk test, which showed that the data were normally distributed (P>0.05). As such, a two-tailed t test was performed for each descriptor to evaluate the null hypothesis, which stated that the means of the healthy and COPD groups did not differ. For the regional analysis, the t test was repeated for three regional features because of removal of extreme outlier values (outliers were defined as ±2 standard deviations or more). The P values reported by the t tests indicated the statistical significance of the differences in the measurements in the COPD group compared to the healthy control group. Because the outcomes (shape features) were highly correlated (with the pairwise correlation within each of two groups for each shape descriptor lying within the range of 0.8 to 0.9), a Bonferroni correction seemed to be an overly conservative approach (Pocock et al. 1987). Therefore, we applied a modified Bonferroni correction to avoid potential type I error for multiple comparisons (Pocock et al. 1987). The pre-established level of significance of α= 0.01 was selected for the comparison of shape descriptors for global and regional analyses. The null hypothesis was rejected for measurements which resulted in P values < α and therefore were considered to be statistically significant.
2.2.4 Classification accuracy

The shape measures from global analysis were compared to test their clinical significance by evaluating the ability of a trained automated classifier to distinguish the healthy from the COPD groups using the computed measures. We inputted the entire feature vector of each muscle into a soft-margin nonlinear support vector machine (SVM) classifier (Fradkin & Muchnik 2006). The SVM classifier classifies subjects as normal or COPD based on a chosen feature vector. We chose to consider all of the features together rather than each feature individually to improve the discrimination between the two groups. We then measured the classification accuracy as the percentage of correct classifications reported in a leave-one-out cross-validation.

2.3 Results

2.3.1 Analysis of global muscle shape descriptors

The results of the analysis of the global shape descriptors of the knee extensor and the knee flexor muscles are presented in Table 2.2, which shows the six measures of the five muscles for which statistically significant differences were found between the normal and the COPD groups. In general, all of the values for the seven shape descriptors were smaller in the COPD group compared to the healthy controls. Knee extensors showed more shape abnormalities in the COPD group compared to healthy controls ($P<0.01$). Of the knee extensors, the vastus intermedius showed significant
differences in seven shape descriptors in the COPD group compared to healthy subjects. The box plots in Figure 2.7 depict the sampling distribution of global shape descriptors of the vastus intermedius. The vastus medialis and rectus femoris showed significant differences in one (surface area) and two (moments 1 and 2) shape descriptors, respectively, in the COPD group compared to healthy subjects.

Fewer shape abnormalities were found in the knee flexors compared to the knee extensors (Table 2.2). Of the knee flexors, significant shape abnormalities were found in the semimembranosus in MDC, SDC, and moment 1. The short head of the biceps femoris showed significantly lower values in moments 1 and 2 (which reflect differences in the distribution of muscle mass) in patients with COPD. In general, among all of the knee flexor and extensor muscles, shape abnormalities were most apparent in the semimembranosus and vastus intermedius muscles of patients with COPD (Table 2.2). The semitendinosus, the long head of biceps femoris and vastus lateralis did not show any differences in shape descriptors. Although muscle volumes in patients with COPD were lower, no significant differences in volumes of any of the knee extensor and flexors were found between groups.

2.3.2 Analysis of regional shape descriptors

The regional morphology of knee extensor and flexor muscles was investigated more closely by examining each muscle in 4 regions, subdivided into four equal distances along the total length of each muscle from origin to insertion (Figure 2.4).
Results related to the regional analysis of 3D shape descriptors are presented in Table 2.3. Significantly lower surface areas were found in Region III of rectus femoris, vastus lateralis, and vastus intermedius, the middle two regions of vastus medialis, and the second region of semimembranosus in the COPD group as compared to the control group. Likewise, lower SDC was found in regions of rectus femoris (Region III), and vastus medialis (Region II, III, IV). Significantly lower volumes were found for Region II and III of vastus lateralis. In the COPD group, knee extensors showed significantly lower measures in shape descriptors (i.e. more shape abnormalities) in the middle to proximal regions of the muscles, whereas shape abnormalities in knee flexors were found closer to the insertion of the muscles (i.e. distal sections) as compared to the healthy control group.

Among the knee extensors, vastus medialis showed the highest number of regional abnormalities in the COPD group, whereas vastus lateralis, rectus femoris, and vastus intermedius showed lower numbers of regional shape abnormalities. SDC, an indicator of surface roughness, was significantly lower in the COPD group in the Region III of rectus femoris and Region II, III, and IV of vastus medialis. Surface area was significantly lower in the COPD group in the Regions II and III of vastus medialis, and the Region III of vastus lateralis and rectus femoris. Significantly lower volumes were found in Regions II and III of vastus lateralis in the COPD group. Of the knee flexors, regional shape abnormalities were found mainly in the distal regions of semimembranosus (i.e. area and volume of Region II). No significant differences
between groups were found when the short and long heads of biceps femoris and semitendinosus were examined for regional differences.

### 2.3.3 Classification accuracy

The SVM classifier provided 95% to 100% accuracy in differentiating muscles from healthy subjects from those of patients with COPD (Table 2.4). Our implementation requires two parameters: one assigning a penalty C to classification errors and another defining the width g of a radial basis function used within the SVM. A standard logarithmic grid search was used to determine the optimal values for the parameters C and g for each muscle type using leave-one-out cross-validation.

### 2.4 Discussion

#### 2.4.1 Differences in MDC, surface area, and SDC

Higher MDC and surface area values in the healthy group reflect a bigger muscle girth. However, one intuitively expects that measures of size, including MDC, surface area, and volume of the muscle, should all increase as the size of the muscle increases. In this study, we observed increases in MDC and surface area in the normal group, without a concomitant increase in muscle volume. To understand these results, it is important to note that these three measures are different in the way that they describe the muscle size, and the term “muscle size” can imply different meanings. For example, the “size” of a sphere increases as its volume, surface area, or MDC (or radius) increases. However, these three measures relate differently to the radius r of the
sphere; volume is proportional to \( r^3 \), surface area is proportional to \( r^2 \), and MDC is proportional to \( r \), and so they all relate to “size” in different ways. Some size measures are more sensitive to changes in the radius or thickness of the muscle than others. For example, if the radius doubles, the volume will increase by an approximate factor of 8, whereas the surface area only increases by an approximate factor of 4.

The SDC measure reflects the variability in the thickness (or radius) of the entire muscle, or portions thereof, in global and regional analysis respectively. The closer SDC is to zero, the more constant the thickness of the muscle and the more closely the muscle approximates a sphere shape with a fixed radius from the center to any point on the surface. As such, the significant increase in SDC alone indicates that regardless of differences in volume, the thickness differs along the muscle or muscle section. Likewise, the lower SDC in the COPD group indicates fewer indentations on the surface and smoother muscle periphery.

**2.4.2 Physiologic implications of global and regional measurements**

Our results indicated that the semimembranosus and vastus intermedius had smaller or fewer indentations or folds (lower SDC) at their periphery in the COPD group. Three possible reasons might explain this lower surface irregularity in patients with COPD. First, in the elderly, fascicles within the muscle become shorter and less pennate (Kubo et al. 2003; Narici & Capodaglio 1998), mainly because of decreases in the contractile tissue packed along the tendon aponeurosis (Narici & Capodaglio 1998). Second, this
phenomenon becomes even more apparent in cases of disuse (Kawakami et al. 1993). Because knee extensors are primarily pennate muscles (Kendall et al. 2005), it is likely that they are more susceptible to the pennation-reducing effects of disuse in COPD, resulting in a reduction in the indentation of the muscle surface. Third, the selective atrophy of type II fibers in COPD (Gosker et al. 2002), which are more superficially distributed in the quadriceps (Johnson et al. 1973), might contribute to the reduced surface irregularity.

Moreover, lower regional surface area and SDC were detected, while muscle volumes were only non-significantly lower in patients with COPD. This might be related to age-related and disuse-related reductions in pennation angle and atrophy of superficial type II fibers of knee extensors in the COPD group, as discussed above. Other contributing factors to the loss of regional surface irregularity could include regional neuropathic changes with associated motoneuron death and/or muscle cell apoptosis, which would lead to a marked decrease in the number as well as the size of muscle fibers. Previous studies provide evidence in support of polyneuropathy (Faden et al. 1981; Pozza & Marti-Masso 1997) and skeletal muscle myopathy (Faden et al. 1981) due to local increases in cytokines and reactive oxygen species within the muscle as well as corticosteroid use (Agusti et al. 2003) in COPD.

Furthermore, although shape abnormalities were present throughout the middle to proximal regions of the knee extensor, morphologic anomalies were less evident among
knee flexors and were mainly restricted to the distal regions closer to the insertion of the muscles (i.e. region II of the semimembranosus). Significant atrophy of the middle two regions of the vastus lateralis and region II of the semimembranosus was evidenced by the reductions in volume and surface area of these sections in the COPD group. The differential patterns of shape abnormalities between knee extensors and flexors require further study. One possibility is that this variability could be related to how muscles are differentially affected by the increased muscle fat infiltration (Mathur et al. 2005, Mathur et al. 2008), neuropathy, and polyneuropathy (Faden et al. 1981; Pozza & Marti-Masso 1997) that are characteristic of COPD. In line with this, selective pathology of femoral or tibial nerves or branches, or regional loss of motor neurons, might be involved in the regional atrophy of these muscles.

2.4.3 Measurement of muscle volume and comparison to previous studies

We found no significant differences in muscle volumes between the two groups in our global analysis, although values tended to be lower in patients with COPD. Our results are discordant with those of previous studies that described lower muscle volumes in patients with COPD compared to healthy controls (Bernard et al. 1998; Seymour et al. 2009; Mathur et al. 2008). This discrepancy might be due to different methodologies used to estimate muscle size. Previous studies reported on muscle groups (Bernard et al. 1998; Mathur et al. 2008), rather than individual thigh muscles, which may have masked and diminished variances in regional muscle atrophy. A second issue is the small sample sizes and locations of the thigh muscle slices used to estimate volume in
previous studies. A single CSA (Bernard et al. 1998; Seymour et al. 2009) at the mid-thigh or the CSA of a number of slices (Mathur et al. 2008) was used to estimate thigh muscle mass in these studies. Mid-thigh measures may represent the largest differences between healthy subjects and those with COPD, so a single slice at the mid-thigh may exaggerate differences between COPD and healthy subjects. Even when using multiple slices (Mathur et al. 2008), muscle volumes were calculated by summing 17 selected slices plus estimated volumes of intermediate sections on the basis of the truncated cone formula. This technique is based on the tenuous assumption that the muscle is conical in shape, which may not accurately reflect thigh muscle shapes (Tracy et al. 2003; Roberts et al. 1993).

2.4.4 Automated group classification on the basis of shape measures

The trained SVM-based classifier is capable of distinguishing between the COPD and healthy groups with an accuracy of 95% to 100% across the eight thigh muscles examined. Although it was not our objective to immediately develop a computer-aided diagnosis system for individual thigh muscles, the accuracy of these classifications provide support for future work to translate this technique to the clinic.

2.4.5 Conclusions

Our study reveals that among the thigh muscles, morphologic changes appear more in knee extensor muscles than in knee flexors in patients with COPD. Furthermore, shape differences are most apparent in the middle to proximal regions of the knee extensors.
and the lower regions of the knee flexors in patients with COPD. These findings could inform the design of strength training programs as well as targeted prescription of therapeutics, such as neuromuscular electrical stimulation and biofeedback, to the more affected muscles or muscle sections. Our study suggests a need for more attention to the middle to proximal regions of the knee extensors (regions showing more atrophy or shape abnormalities). Furthermore, hypertrophied muscle is reported to have a higher angle of pennation compared with untrained muscle (Kubo et al. 2003). Therefore, it is likely that a more appropriately localized treatment approach could improve the pennation angle in affected muscle regions in COPD.

This study compared the thigh muscle volume and shape changes of in COPD patients versus matched controls that addresses some factors associated with the “structure” component of the ICF. The next study (Chapters 3 and 4) surveyed pain, comorbidities, quality of life, and physical activity in COPD patients compared to matched controls that are factors related to the “activity limitation” component of the ICF.
Table 2.1 Characteristics of subjects with COPD and healthy older adults (mean ± SD).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Healthy older adults (n=20)</th>
<th>People with COPD (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>64.4±8.1</td>
<td>68.2±10.0</td>
</tr>
<tr>
<td>Sex, women/men</td>
<td>11/9</td>
<td>11/9</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.67±0.13</td>
<td>1.66±0.09</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>69.0±14.4</td>
<td>72.1±14.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.3±2.2</td>
<td>26.6±4.7</td>
</tr>
</tbody>
</table>

**Lung Function**

<table>
<thead>
<tr>
<th></th>
<th>Healthy older adults (%)</th>
<th>People with COPD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, L (%)</td>
<td>2.28±0.72 (81±20)</td>
<td>1.34±0.41 (51±17)</td>
</tr>
<tr>
<td>FVC, L (%)</td>
<td>3.05±1.11 (83±20)</td>
<td>2.58±0.47 (78±14)</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>77±9</td>
<td>52±14</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMI=body mass index; FEV₁=forced expiratory volume in 1 second; FVC=forced vital capacity.
Table 2.2 Differences between 3D shape descriptors for global analysis in healthy people minus those with COPD.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>MDC (mm)</th>
<th>SDC (mm)</th>
<th>Moment1 (mm²)</th>
<th>Moment2 (mm²)</th>
<th>Moment3 (mm⁶)</th>
<th>Area (mm⁶)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RF</td>
<td>3.08 (1.33)</td>
<td>1.19 (0.74)</td>
<td>7.68E7 (2.91E7)*</td>
<td>4.78E15 (1.71E15)**</td>
<td>4.18E22 (1.84E22)</td>
<td>2549.10 (1523.03)</td>
</tr>
<tr>
<td></td>
<td>(0.39,5.79)</td>
<td>(0.31,2.70)</td>
<td>(1.78E7, 1.36E8)</td>
<td>(1.32E15, 8.25E15)</td>
<td>(4.58E21, 7.91E22)</td>
<td>(534.11,5632.31)</td>
</tr>
<tr>
<td>VI</td>
<td>5.31 (1.66)**</td>
<td>3.12 (1.00)**</td>
<td>1.58E8 (5.52E7)**</td>
<td>1.83E16 (6.42E15)**</td>
<td>4.87E23 (1.81E23)*</td>
<td>7492.95 (2364.59)**</td>
</tr>
<tr>
<td></td>
<td>(1.95,8.67)</td>
<td>(1.08,5.15)</td>
<td>(4.57E7, 2.69E8)</td>
<td>(5.31E15, 3.13E16)</td>
<td>(1.22E23, 8.52E23)</td>
<td>(2706.08,12279.82)</td>
</tr>
<tr>
<td>VM</td>
<td>2.12 (1.06)</td>
<td>0.74 (0.79)</td>
<td>8.49E7 (4.15E7)</td>
<td>1.11E16 (5.33E15)</td>
<td>2.83E23 (1.46E23)</td>
<td>4667.11 (1770.98)*</td>
</tr>
<tr>
<td></td>
<td>(0.03,4.27)</td>
<td>(0.87,2.35)</td>
<td>(9.07E5, 1.69E8)</td>
<td>(3.14E14, 2.19E16)</td>
<td>(1.14E22, 5.78E23)</td>
<td>(1081.94,8252.27)</td>
</tr>
<tr>
<td>BF-SH</td>
<td>3.78 (1.55)</td>
<td>2.13 (0.855)</td>
<td>3.65E7 (1.39E7)*</td>
<td>7.15E14 (2.71E14)*</td>
<td>2.84 E21 (1.21E21)</td>
<td>2277.42 (1171.59)</td>
</tr>
<tr>
<td></td>
<td>(0.63,6.92)</td>
<td>(0.40,3.87)</td>
<td>(8.39E6, 6.47E7)</td>
<td>(1.68E14, 1.26E15)</td>
<td>(3.96E20, 5.29E21)</td>
<td>(94.35,4649.18)</td>
</tr>
<tr>
<td>SM</td>
<td>5.30 (1.56)**</td>
<td>2.47 (0.88)**</td>
<td>7.49E7 (2.36E7)**</td>
<td>3.25E15 (1.46E15)</td>
<td>3.87E22 (1.97E22)</td>
<td>4516.24 (1732.28)*</td>
</tr>
<tr>
<td></td>
<td>(2.15,8.45)</td>
<td>(0.689,4.24)</td>
<td>(2.71E7, 1.23E8)</td>
<td>(2.99E14, 6.21E15)</td>
<td>(1.21E21, 7.86E22)</td>
<td>(1009.41,8023.07)</td>
</tr>
</tbody>
</table>

Statistical measures are reported as mean difference (SE) and 95% CI of the difference. Mean difference is defined as the average difference of group means for each shape descriptor (independent values).

**Abbreviations:** BF-SH, biceps femoris–short head; CI, confidence interval; COPD, chronic obstructive pulmonary disease; MDC, mean distance to the centroid; RF, rectus femoris; SDC, standard deviation of distances to the centroid; SE, standard error; SM, semimembranosus; VI, vastus intermedius; VM, vastus medialis.

*Significant difference between groups at P<0.01 (light shading); **Significant difference between groups at P<0.005 (dark shading).
Table 2.3 Differences of 3D shape descriptors for regional analysis in healthy people minus those with COPD.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Shape descriptor</th>
<th>Region*</th>
<th>Mean (SE) of difference</th>
<th>P value</th>
<th>95% CI of difference</th>
<th>Lower bound</th>
<th>Upper bound</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RF</td>
<td>SDC (mm)</td>
<td>III</td>
<td>0.91 (0.32)</td>
<td>0.004</td>
<td>0.26</td>
<td>1.54</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Area (mm²)</td>
<td>III</td>
<td>1280.20 (460.65)</td>
<td>0.008</td>
<td>347.66</td>
<td>2212.73</td>
<td></td>
</tr>
<tr>
<td>VL</td>
<td>Volume (mm³)</td>
<td>II</td>
<td>35101.15 (9491.81)</td>
<td>0.001</td>
<td>15850.87</td>
<td>54351.44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Area</td>
<td>III</td>
<td>31114.11 (8840.89)</td>
<td>0.001</td>
<td>13200.76</td>
<td>49027.46</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>III</td>
<td>2373.28 (860.72)</td>
<td>0.009</td>
<td>629.30</td>
<td>4117.26</td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>Area</td>
<td>III</td>
<td>2634.61 (739.64)</td>
<td>0.001</td>
<td>1137.29</td>
<td>4131.94</td>
<td></td>
</tr>
<tr>
<td>VM</td>
<td>SDC</td>
<td>II</td>
<td>1.28 (0.33)</td>
<td>0.000</td>
<td>1.35</td>
<td>1.94</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Area</td>
<td>IV</td>
<td>0.96 (0.29)</td>
<td>0.002</td>
<td>0.37</td>
<td>1.56</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>II</td>
<td>1461.19 (475.00)</td>
<td>0.004</td>
<td>499.60</td>
<td>2422.79</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>III</td>
<td>1160.76 (313.56)</td>
<td>0.001</td>
<td>523.54</td>
<td>1797.99</td>
<td></td>
</tr>
<tr>
<td>SM</td>
<td>Area</td>
<td>II</td>
<td>1441.56 (546.37)</td>
<td>0.005</td>
<td>335.48</td>
<td>2547.64</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Volume</td>
<td>II</td>
<td>16631.14 (5140.63)</td>
<td>0.003</td>
<td>6215.23</td>
<td>27047.05</td>
<td></td>
</tr>
</tbody>
</table>

The shape descriptors and corresponding regions that revealed significant between group differences in regional analysis are presented in columns 2 and 3, respectively. Statistical measures are reported as mean difference (SE) and 95% CI of the difference. Mean difference is defined as the average difference of group means (healthy minus COPD) for each shape descriptor (independent values).

**Abbreviations:** CI, confidence interval; COPD, chronic obstructive pulmonary disease; RF, rectus femoris; SDC, standard deviation of distances to the centroid; SE, standard error; SM, semimembranosus; VI, vastus intermedius; VL, vastus lateralis; VM, vastus medialis.

*Regions are defined in the text and Figure 2.4.
Table 2.4 The Support Vector Machine (SVM) classification rates.

<table>
<thead>
<tr>
<th>Muscle groups</th>
<th>Muscle</th>
<th>Classification rate using all features (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee extensors (Quadriceps)</td>
<td>Rectus femoris</td>
<td>99.9</td>
</tr>
<tr>
<td></td>
<td>Vastus medialis</td>
<td>97.0</td>
</tr>
<tr>
<td></td>
<td>Vastus intermedius</td>
<td>99.9</td>
</tr>
<tr>
<td></td>
<td>Vastus lateralis</td>
<td>97.5</td>
</tr>
<tr>
<td>Knee flexors (Hamstrings)</td>
<td>Biceps femoris- long head</td>
<td>99.9</td>
</tr>
<tr>
<td></td>
<td>Biceps femoris-short head</td>
<td>95.0</td>
</tr>
<tr>
<td></td>
<td>Semimembranosus</td>
<td>97.3</td>
</tr>
<tr>
<td></td>
<td>Semitendinosus</td>
<td>99.8</td>
</tr>
</tbody>
</table>
Figure 2.1 Sample MRI slices of a subject’s thigh from proximal (top) to distal (bottom).
Figure 2.2 Sample segmentation of knee extensor and flexor muscles in ITK-SNAP: axial (top left), sagittal (top right), coronal (bottom right), and 3D mesh view (bottom left). The different knee extensors and flexors are represented by different fill colors.
Figure 2.3 The interpolation technique for knee extensor and flexor muscles.

The parallel white contours depict the segmentation boundaries on the acquired magnetic resonance slices with a 5-mm inter-slice spacing. The colored regions uniting the segmentation boundaries are the product of the interpolation technique.
Figure 2.4 A sample muscle (rectus femoris) divided into four regions (quarters) as defined by four equal lengths along the vertical axis of the muscle.

Region IV is most proximal, whereas region I is the most distal.
Figure 2.5 Description of the standard deviation of distances to centroid (SDC) measure.

Three such distances are illustrated as d1, d2, and d3. Note how a perfect circle or sphere exhibits zero variability in the distances to the centroid (left), whereas the standard deviation of these differences will not be zero for a rough or irregular shape with more variability in d1, d2, and d3 (right).
The surface area of the muscle is estimated as the sum of the area of all triangles that constitute the mesh.
Figure 2.7 Sampling distribution of surface area (top), mean distance to the centroid (MDC; middle), and standard deviation of distances to the centroid (SDC; bottom) for the vastus intermedius.

All three measures differed between groups at p<0.005. The upper and lower margins of each box indicate the 75th and 25th percentiles respectively, and the band near the middle of the box indicates the 50th percentile (the median). The ends of the whiskers indicate the range of scores at each end of the distribution.
Chapter Three: Pain in People with COPD

3.1 Introduction

COPD is a major health burden worldwide and is estimated to be the third leading cause of death by 2020 (Global Strategy for the Diagnosis, Management and prevention of Chronic Obstructive Pulmonary Disease, 2009). The recent guidelines note the multi-systemic effects of COPD including its impact on peripheral muscle dysfunction, right heart failure, malnutrition, depression, and decreased exercise tolerance (O’Donnell et al, 2008). These guidelines and other statements provide solid evidence to support the therapeutic benefit of exercise and maintaining an active lifestyle (Global Strategy for the Diagnosis, Management and prevention of Chronic Obstructive Pulmonary Disease, 2009). However, exercise prescription and lifelong adherence to physical activity for people with COPD is limited (Bourbeau & Bartlett 2008). Reasons for the lack of adherence to physical activity programs require further exploration.

Most commonly, lower extremity (LE) fatigue alone or in combination with dyspnea has been reported to be major limiting symptoms during exercise tests and is considered to limit physical activity of COPD patients (Killian et al. 1992). Recent reports suggest that pain may be of equal or greater concern. Pain was a significant contributor to reduced health related quality of life (HRQoL) as demonstrated by the Health Utility Index and

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2 A version of this chapter has been published. HajGhanbari B, Holsti L, Road J, Reid WD. Pain in people with Chronic Obstructive Pulmonary Disease (COPD). Respiratory Medicine, 2012,106: 998-1005.
Medical Outcomes Study Short Form-36 (SF-36) evaluations of people with severe emphysema who underwent lung volume reduction surgery (Miller et al. 2008). Pain has been reported in stable COPD patients (Lohne et al. 2010; Borge et al. 2011), COPD patients toward the end of life (Lynn et al. 2000; Lohne et al. 2010), and as components of quality of life (Hajiro et al. 1999). However, the characteristics of pain, such as fear of movement due to pain, and its relationship with comorbidities and physical activity have not been examined.

In addition to an increasingly sedentary lifestyle, several factors related to the manifestations of the disease may contribute to pain in people with COPD. Firstly, the activation of cytokines has a major role in the development of inflammatory pain (Watkins & Maier 1999). It is therefore tenable that the systemic inflammatory process contributes to the generation of chronic and neuropathic pain in people with COPD (Ozge et al. 2001). Secondly, the hyper-expanded and relatively rigid chest wall (Laghi & Tobin 2003) could position thoracic articulations in a hyper extended position and decrease their range of motion. Abnormal joint position and limited range of motion contribute to pain in several joint pathologies (Hunter 2009) and similarly, may contribute to thoracic pain experienced by people with COPD. Lastly, inactivity may aggravate common age-related comorbidities, such as osteoarthritis (Kopec et al. 2007), low back pain (Hunter 2009), and osteoporosis (Ferguson et al. 2009).
Reductions across multiple dimensions in HRQoL, including depression, anxiety, and mental health, and activity limitation have been reported in nonmalignant pain patients (Niels et al. 1997). Therefore, it is highly probable that people with COPD who experience substantial pain will demonstrate similar consequences. To date, the severity of pain in people with COPD and its association with physical activity and quality of life have not been studied extensively. The purpose of this study was to determine if pain severity and interference with activities are more common in COPD patients than in healthy people and if pain is related to self-reported physical activity and HRQoL. Another aim was to determine independent correlates of pain in COPD patients.

3.2 Methods

3.2.1 Participants

Sedentary healthy people, and people with moderate to severe COPD (FEV$_1$ < 80% predicted, FEV$_1$/FVC < 0.7) (O’Donnell et al. 2008), over 50 years of age, matched for age and gender participated in a cross-sectional survey study. Exclusion criteria were: (1) comorbidities that interfered with independent ambulation; (2) lack of English fluency or cognitive impairment that interfered with the ability to provide informed consent or to complete the questionnaires. In addition, people with COPD were excluded if they had an acute exacerbation within the last three months. Sedentary healthy people were excluded if they had self-reported respiratory conditions, such as bronchitis, emphysema, moderate to severe asthma or if they met exclusion criteria (1) or (2)
stated above. COPD patients were recruited from the caseload of respirologists and pulmonary rehabilitation programs at local hospitals. Healthy people were recruited from the posters at local community centers and newspaper advertisements. Approval for the study was obtained from the Clinical Research Ethics Board of the University of British Columbia. Informed consent was achieved from the subjects before participation in the study.

3.2.2 Measurements

Participants were initially screened using a standardized questionnaire via telephone. Chart reviews were performed on all COPD participants in order to confirm the diagnosis of COPD. After obtaining informed consent, standard survey methods were employed by mailing a package of forms and questionnaires to participants (Dillman 2000). The package included: instructions, a form to record medications and comorbidities, the Medical Outcomes Study Short Form-36 (SF-36), the short form of the McGill Pain Questionnaire (MPQ), the short form of the Brief Pain Inventory (BPI), the Community Health Activities Model Program for Seniors (CHAMPS), and the modified Tampa Scale for Kinesiophobia (TSK). One week later, all subjects were contacted by telephone to address any questions. Subjects were asked to return packages in a self-addressed stamped envelope by mail.

3.2.2.1 Pain characteristics

The MPQ asks about pain characteristics over the past week and consists of: 1) 11
sensory related items; 2) 4 affective related items; 3) the visual analog scale to provide the intensity pain score. A fourth component, evaluates Present Pain Intensity (PPI) (Melzack 1987).

The BPI measures the intensity of pain (sensory dimension), uses body diagrams to indicate pain location, and evaluates interference of pain in the patient's life (including general activity, mood, sleep, enjoyment of life, and relationship with others) over the last week. It also asks the patient about pain relief, pain quality, and pain medications. Because of these different attributes, the BPI and MPQ were used to provide a more comprehensive description of the pain experienced by individuals (Sawyer et al. 2008). Both the MPQ (Love et al. 1989; Reading et al. 1982) and the BPI (Keller et al. 2004; Tan et al. 2004) have been established as valid and reliable tools for assessing pain severity and interference.

The TSK evaluates the pain-related fear of re-injury due to movement and activities. The TSK consists of 17 questions that identify fear of injury/re-injury due to activities with item scores ranging from 1 (strongly disagree) to 4 (strongly agree), which are tallied to a potential total score ranging from 17 to 68. The modified version of TSK was used (without reversed key items) as it has been found to improve the internal consistency (Roelofs et al. 2004). The potential total scores for the modified version of TSK ranges from 13 to 52.
3.2.2.2 Physical activity

The CHAMPS questionnaire includes 41 questions that ask the participants to rate the length of time spent on a variety of activities in a typical week during the past month. It includes physical and leisure activities that vary in intensity including household chores and several non-physical activities (such as reading, card games, and social participation). This provides a broad selection of activities such that respondents tend to minimize overestimation of physical activities. The CHAMPS questionnaire provides measures for frequencies and estimated energy expenditure for moderate and high intensity activities (Stewart et al. 2001). The CHAMPS questionnaire has been shown to be reliable (Giles et al. 2009; Stewart et al., 2001), valid (Feldman et al. 2009), and sensitive to change in activities in older adults (Stewart et al. 2001).

3.2.2.3 Health related quality of life

The SF-36 contains 36 items distributed across eight domains (physical-functioning, role-physical, bodily pain, general health, vitality, social-functioning, role-emotional, and general health perception), and has two component scales (physical and mental) (Ware & Sherbourne 1992).

The data related to medications and comorbidities were obtained using self-report questionnaires. In addition, patients' medical charts and hospital databases were reviewed to verify the medications and comorbidities. Medications were coded according to the Canadian Medical Association (Canadian Medical Association, 2002).
3.2.3 Statistical analyses

Precise sample size calculation was not possible, as similar studies have not been performed. However, comparing a group of healthy subjects with a patient group, we expected to have a medium effect size (0.5). Therefore, a sample size of 75 in each group would provide a power for a t-test with an $\alpha < 0.05$ to be more than 0.8 (Cohen 1988). However, sampling was stopped after statistically significant differences were achieved.

Normal distribution of the data was confirmed by inspecting the histograms and normality plots. Frequencies were determined for the total number of pain locations, comorbidities and medications in addition to the number of participants that had at least one pain location, one comorbid disease or one medication. MPQ, BPI, and TSK scores were calculated as the percentage of the maximum score that could be obtained on each questionnaire. Two-tailed t-tests were performed to examine for differences in pain severity (MPQ and BPI), pain interference (BPI), physical activity, pain-related fear of movement/re-injury (TSK), number of pain locations, HRQoL, number of comorbidities, and number of medications between healthy people and those with COPD.

The chi-square test was performed to detect between group differences in the number of subjects who reported pain for different body locations, the number of subjects who had at least one comorbid condition, and the number who reported at least one medication. Means and standard errors are reported unless otherwise specified. In
order to avoid type I error for multiple comparisons, a p value of < 0.01 was set to indicate significant differences (Pocock et al. 1987).

Correlations were performed amongst pain measures in order to determine their convergent and discriminant validity. Independent correlates that might be predictive of pain were determined by performing correlation analysis followed by linear regression. Correlations between pain measures (severity–by MPQ and BPI and interference by BPI severity) and potential predictors of pain (TSK, CHAMPS, comorbidities, medications) were examined using two-tailed Pearson product moment correlations. Variables that were moderately to highly correlated to pain severity and interference scores (p<0.01 and r>0.40) were entered into the linear regression model. The model was not controlled for age and gender as the groups were matched for these factors. The outcomes were checked for multicollinearity; if two measures were highly correlated, one was removed (e.g. medications removed because of high correlation with comorbidities).

### 3.3 Results

Forty-seven COPD patients and 47 healthy people completed all questionnaires. The mean ages of the groups were 70 ± 6.7 (SD) and 68.2 ± 8.8 (SD) years, respectively. Both groups had female:male ratio of 20:27 and the COPD group had an FEV$_1$ of 44.7 ± 19.2 (SD) percent predicted. Originally 87 healthy people and 92 people with COPD were invited, and consented to participate in the study. Of these people, sixty-
three healthy (72%) and 65 people (70%) with COPD completed the study. To match
groups for age and gender, people younger than 55 and older than 86 were excluded
from the study, which resulted in 47 (female/male = 20/27) participants in each group.
Considering a medium effect size of 0.5 in order to have a power of more than 0.8 using
a t-test at $\alpha_2<0.05$ (Cohen 1988), we originally aimed for 75 people in each group.
However, we stopped the recruitment when we reached the significance level of
($p=0.000$) for primary outcomes.

Severity of pain (measured by the MPQ and BPI), bodily pain (lower score indicates
more pain for SF-36) and pain interference (measured by BPI) was greater in COPD
patients than in healthy people (Table 3.1; $p<0.001$). The number of COPD patients with
moderate to very severe pain was 7.5 and 2.2 times greater than for healthy people
evaluated by the MPQ and BPI, respectively (Figure 3.1; $p<0.002$). The number of
COPD patients who had moderate to very high pain interference with activities was 5.4
fold greater than for healthy people (Figure 3.1; $p<0.002$). The number of pain locations
was greater in COPD patients compared to healthy people with the most common
occurrence in the neck and trunk region (Figure 3.2; $p<0.005$). COPD patients also had
a greater pain-related fear of movement/re-injury (TSK) (Table 3.1; $p<0.001$) than
healthy people.

Significant correlations amongst pain measures are shown in Table 3.2. Pain severity
and interference measured by the MPQ and BPI showed strong correlations (Cohen
1988) amongst the three measures in each of the participant groups and in both groups combined. These pain measures also showed moderate to strong correlations (Cohen 1988) with analgesic medications and the number of pain locations in the COPD patients and both groups. Pain-related fear of movement/re-injury (TSK) was correlated to a lower degree to MPQ and BPI pain measures in the COPD patients and both groups; only pain interference (BPI) was correlated to pain-related fear of movement (TSK) in COPD patients.

Self-reported physical activity (CHAMPS) was lower in COPD patients compared to healthy people (Table 3.1; p<0.001), and the total energy expenditure estimated from CHAMPS demonstrated a moderate inverse correlation (Cohen 1988) to pain interference (BPI) (r = -0.294, p=0.004) for both groups. Physical and Mental Component Scores of the SF-36 were lower in COPD patients than in healthy people (Table 3.1; p<0.000). Pain severity (measured by the MPQ and BPI) and pain interference showed moderate to strong negative correlations (Cohen 1988) to the Physical Component Score of the SF-36 (−0.45, −0.61, −0.70, respectively; p<0.001).

Regarding the number of comorbidities and medications, COPD patients had a greater frequency of self-reported circulatory (47 versus 22; p=0.002), musculoskeletal (33 versus 14; p=0.005), digestive (15 versus 3; p=0.001), and renal diseases (11 versus 3; p=0.02) compared to healthy people. In accordance, COPD patients had a greater numbers of respiratory (p=0.000), cardiovascular (p=0.030), immune (p=0.008), and
analgesic medications (p=0.030) than the healthy group. From the regression analysis, only the number of comorbidities was a significant independent correlate of pain severity (MPQ and BPI) in people with COPD (Figure 3.3; \( r =0.61 \) and 0.56, respectively; \( p=0.000 \)).

### 3.4 Discussion

Our study demonstrated that people with COPD report almost 2.5 times greater pain compared to healthy adults. In addition, pain interferes with daily activities 3.7 times more often in people with COPD than in healthy people. Furthermore, not only is pain more severe, it is more common in people with COPD. Moderate to severe pain was self-reported 2.2 and 7.5 times more often in COPD patients than matched healthy people as measured by the BPI and MPQ, respectively. Moderate to severe pain affected half of our COPD sample of participants, a rate which falls between the 25–70% found in end-of-life COPD patients reporting pain (Lynn et al. 2000) and a rate much higher than the 20% who reported more than low intensity chronic pain in a large survey (\( n = 3605 \)) of general practice patients (Elliot et al. 1999).

Greater pain in people with COPD might be due to the prolonged induction of painful stimuli or possibly to lower thresholds for pain compared to healthy people. Possible etiologies could be systemic inflammation, central adaptations related to pain and dyspnea, and musculoskeletal disorders including mechanical limitation of chest wall movement due to hyperinflation.
Systemic inflammation in COPD may provide one explanation for increased pain severity in these patients. The macrophage and neutrophilic response central to the etiology of the lung disease (Linden et al. 1993) results in the release of large amounts of proinflammatory cytokines that perpetuate a local inflammatory response and can also impact distant tissues via the circulation (Culprit et al. 2003; Mio et al. 1997). TNF-α has been shown to increase mechanical allodynia and thermal hyperalgesia (Junger & Sorkin 2000) and decrease the mechanical activation threshold in C fibers (Wagner & Myers 1996). It is involved in the generation and the maintenance of neuropathic pain (Sommer et al. 1998). Moreover, IL-1β is considered to be a key cytokine associated with increased pain and hyperalgesia, especially in neuropathies and inflammatory diseases (Lindenlaub & Sommer 2003; Watkins & Maier 1999). Marked increase in cytokine IL-6 is associated with increased pain and hyperalgesia (Banzett et al. 2000). Thus, proinflammatory cytokines can induce or increase inflammatory pain. Given that COPD is associated with marked and prolonged systemic elevation of inflammatory cytokines due to lung pathology, it is tenable that this systemic inflammation may contribute to the generation of pain or lower the threshold to painful stimuli.

COPD patients may have an altered sensation to pain due to protracted central processing of dyspnea and pain. In addition to their common unpleasant, alarming character, dyspnea or pain are prominent and threatening symptoms in several pulmonary diseases, such as asthma (von Leupoldt et al. 2009) and COPD (O’Donnell et al. 2008). Both pain and dyspnea have been mapped to activation of common brain
areas including the anterior/mid insula, dorsal anterior cingulate cortex, sensorimotor and somatosensory cortex II, supplementary motor area, amygdale and medial thalamus (Casey 1999; von Leupoldt et al. 2009). Due to similar sensory and affective-related brain networks, the protracted experience of dyspnea in COPD patients and associated prolonged activation of brain centers may induce permanent changes in the perception of pain, especially after sensitization. Whether or not the reduced sensitivity to discriminate between different noxious and non-noxious stimuli, such as pain and dyspnea at cortical level, is affected by sensitization and is impaired in people with COPD requires further investigation.

The pain severity and interference scores are somewhat similar to those previously reported. The pain severity score of BPI in our study is lower than that of Borge et al. (2011) (28.5/100 versus 3.7/10), whereas the pain interference scores in our study are similar (35.5/100 versus 3.9/10). These results are similar to those of previous studies, which reported marked pain in COPD patients (Borge et al. 2011; Lohn et al. 2010; Lynn et al. 2000; Bentsen et al. 2011). Regarding SF-36 data, Hajiro et al. (1999) found higher scores in the pain domain (indicated better HRQoL) compared to our pain domain scores of the SF-36. However, these authors also suggested that this domain had a small number of items, which may “bring less discriminatory power to the SF-36 when evaluating the HRQoL of patients with stable COPD” (Hajiro et al. 1999, p 1636).
Of interest, pain in the neck and trunk was more common than in other body locations, which is consistent with previous studies (Borge et al. 2011; Bentsen et al. 2011). This finding might be attributable in part, to the location of the primary and accessory muscles of respiration. For example, the diaphragm and intercostal muscles might be overused during the abnormal breathing pattern in COPD (Borge et al. 2011; Bentsen et al. 2011) accentuated by their mechanical disadvantage due to hyperexpansion of the chest wall. Chest wall hyperinflation in COPD consequent to alveolar destruction and airway inflammation results in the resting position of the chest wall being shifted to the left on the pressure–volume curve causing higher volumes with a decreased available range of motion during ventilation, i.e. decreased thoracic excursion. This hyperinflation is accentuated by exertion even during such functional tests as the 6 min walk test (6MWT) (Callens et al. 2009). The limited range of motion due to hyperinflation may result in reactive muscle spasm similar to what occurs in other conditions with limited range of motion of joints and reduced operating lengths of muscle, such as osteoarthritis (Hunter 2009).

In addition to joint pain and muscle spasm, the mechanical disadvantage of the inspiratory muscles in the hyperinflated state, compounded by increased levels of tidal ventilation, may make these muscles more prone to overuse injury and subsequent delayed onset muscle soreness (DOMS) as evidenced by microscopic muscle injury in COPD patients (Orozco-Levi et al. 2001). DOMS of the inspiratory muscles has been reported in healthy people (Mathur et al. 2010). In summary, the mechanical
abnormalities of the thorax due to hyperinflation and increased levels of ventilation may contribute to muscle spasm and delayed onset muscle soreness in people with COPD.

Our data indicate that the frequency and number of COPD patients with self-reported musculoskeletal disease is about double that found in healthy adults; this difference likely contributes to the two- to three-fold greater number of pain locations in the upper and lower extremities compared to healthy people. We did not explore the types of musculoskeletal comorbidities that might contribute to pain in our study samples. However, osteoporosis is commonly reported (60–70%) in COPD (Ferguson et al. 2009) and the age-related prevalence of osteoarthritis ranges from 14 to 58% (Kopec et al. 2007) in the 50–86 year age-range of our study participants. Along with joint specific pathologies, systemic influences of inflammatory cytokines and central processing of altered sensations may increase the pain experienced in the extremities by COPD patients compared to healthy people.

The number of comorbidities was found to be an independent correlate of pain severity in people with COPD, as measured by MPQ and BPI. This result is not surprising given that many comorbidities manifest with pain symptoms (Boersma & Linton 2006). During a week-long general practice survey, 22% of approximately 3,000 patients presented with pain as a primary complaint with the most common underlying cause being musculoskeletal (50%) followed by visceral including cardiovascular (20%), infectious (15%) and headaches (8%). From a mail survey of general practice patients, the
subsample of those who were 55 years or older, attributed pain most often to
musculoskeletal causes (40%) and angina (6.3%) [55–64 years] to 11.1% [≥75 years]
(Elliot et al. 1999). In comparison, just over 50% of COPD patients complained of pain
and self-reported cardiovascular conditions (67%) and musculoskeletal conditions
(51%), which may be primary sources of pain in our survey sample. Further
investigation is required to determine the contributing factors to the etiology of pain in
COPD patients.

The significance of pain in people with COPD was reflected in greater pain-related
interference in activities (BPI) that may explain, in part, the lower Physical Component
Scores in HRQoL (SF-36) and the lower physical activity scores (CHAMPS
questionnaire) in people with COPD compared to healthy adults. Patients with COPD
also experience greater pain-related fear as indicated by the scores on the modified
TSK, a finding which is similar to chronic pain patients compared to healthy people
(Boersma & Linton 2006). People experiencing pain can worry about how increasing
pain may lead to progressive disability and this can be heightened if they perceive
themselves as being beyond help by care givers and health care providers (Boersma &
Linton 2006). Fear and anxiety are associated with pain-exacerbating activities, such as
avoidance of physical activity that can reduce muscle flexibility, strength, and endurance
leading to a downward spiral of increased disability (Boersma & Linton 2006). Indeed,
fear of movement and injury are better predictors of functional limitations than
biomedical parameters or even pain severity and duration (Crombez et al. 1999).
Treating symptoms of fear and anxiety, and also establishing pain coping strategies is essential for optimizing pain management.

To date, pain does not appear to be strongly associated with the severity of airflow limitation. We did not find a significant relationship between FEV$_1$ and pain severity scores of MPQ, similar findings to those of previous studies that examined the severity of pain measures with spirometry (Borge et al. 2011, Boueri et al. 2001; Tsukino et al. 1996). That being said, these results do contrast the moderate correlation that we found between BPI severity and interference scores and FEV$_1$. One plausible explanation might be that in our sample, people with minor disease severity may be more active and expose themselves to more extraneous activities that can induce pain. Given these disparate findings, further research is required to clarify the relationship between pain and disease severity.

3.5 Conclusions

Compared to their healthy counterparts, pain is more common and of a greater magnitude in people with COPD. The relationship between pain interference and daily physical activities requires further exploration to determine whether or not pain is a major contributor to decreased physical activity and HRQoL in COPD patients. The assessment and treatment of pain can be overlooked in the plan of care for COPD patients. A greater appreciation of factors involved in pain perception will be beneficial for designing COPD-specific pain management programs aimed at improving physical,
psychological, and social well-being in people with COPD.

As comorbidities were found to be an independent correlate for pain in this study (Chapter 3), we decided to explore further the pattern of comorbidities (the type and number of comorbid conditions), the type of pain medications and pain treatments in COPD patients who reported pain. Therefore, Chapter 4 describes the more detailed data from the same survey (Chapter 3). However, Chapter 4 includes the data from a larger sample of COPD patients (n=54) rather than that of Chapter 3 (n=47). In Chapter 4, we included the data from several subjects that were previously excluded when the COPD group was age- and gender-matched to the control group. Different attributes of pain and how they related to different comorbidities were examined in Chapter 4.
Table 3.1 Measures of pain, physical activity, health-related quality of life, medication and comorbidities in healthy people and COPD patients.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Healthy mean ± SE</th>
<th>COPD mean ± SE</th>
<th>Mean difference</th>
<th>Fold</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td><strong>Pain measures</strong></td>
<td></td>
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<tr>
<td>Severity – MPQ (/100)</td>
<td>7.5 ± 1.5</td>
<td>20.1 ± 2.8</td>
<td>12.6</td>
<td>2.63</td>
<td>0.000</td>
</tr>
<tr>
<td>Severity – BPI (/100)</td>
<td>12.4 ± 1.9</td>
<td>28.5 ± 3.5</td>
<td>16.1</td>
<td>2.30</td>
<td>0.000</td>
</tr>
<tr>
<td>Bodily pain SF-36</td>
<td>76.7 ± 3.2</td>
<td>49.1 ± 4.2</td>
<td>27.60</td>
<td>0.64</td>
<td>0.000</td>
</tr>
<tr>
<td>Interference – BPI (/100)</td>
<td>9.7 ± 1.8</td>
<td>35.5 ± 4.1</td>
<td>25.8</td>
<td>3.66</td>
<td>0.000</td>
</tr>
<tr>
<td>Fear of movement – TSK (/52)</td>
<td>22.2 ± 0.8</td>
<td>27.0 ± 1.0</td>
<td>4.7</td>
<td>0.21</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of pain locations</td>
<td>1.3 ± 0.2</td>
<td>3.1 ± 0.4</td>
<td>1.8</td>
<td>2.38</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>Physical activity – CHAMPS</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>All activities – EE (calories)</td>
<td>4184 ± 309</td>
<td>1748 ± 221</td>
<td>2435</td>
<td>−0.42</td>
<td>0.000</td>
</tr>
<tr>
<td>Moderate EE (MET ≥ 3.0)</td>
<td>2560 ± 239</td>
<td>710 ± 135</td>
<td>1849</td>
<td>−0.28</td>
<td>0.000</td>
</tr>
<tr>
<td>Number of comorbidities</td>
<td>1.77 ± 0.23</td>
<td>3.85 ± 0.30</td>
<td>2.08</td>
<td>2.18</td>
<td>0.000</td>
</tr>
<tr>
<td>Number of medications</td>
<td>2.21 ± 0.34</td>
<td>6.64 ± 0.54</td>
<td>4.43</td>
<td>3.00</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>Health related quality of life</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Physical component score</td>
<td>52.0 ± 1.3</td>
<td>35.2 ± 1.7</td>
<td>16.9</td>
<td>−0.68</td>
<td>0.000</td>
</tr>
<tr>
<td>Mental component score</td>
<td>54.7 ± 1.30</td>
<td>42.0 ± 1.8</td>
<td>12.8</td>
<td>−0.78</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Data is reported as mean ± SE. **Abbreviations**: MPQ, McGill Pain Questionnaire-short form; BPI, Brief Pain Inventory-short form; TSK, Modified Tampa Scale of Kinesiophobia; CHAMPS, Community Health Activities Model Program for Seniors; SE: standard error of difference; EE, Energy Expenditure; MET, Metabolic Equivalent of Task.
Table 3.2 Significant correlations amongst pain measures in healthy people and COPD patients at p < 0.01. r (p value) are shown.

<table>
<thead>
<tr>
<th></th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt;</th>
<th>Pain severity (MPQ)</th>
<th>Pain severity (BPI)</th>
<th>TSK – (pain-related fear of movement)</th>
<th>Analgesic Medications</th>
<th>Number of pain locations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain severity – MPQ</strong></td>
<td></td>
<td></td>
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<tr>
<td>Healthy</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.39 (0.007)</td>
</tr>
<tr>
<td>COPD</td>
<td>–</td>
<td></td>
<td></td>
<td>0.38 (0.009)</td>
<td>0.68 (0.000)</td>
<td></td>
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<tr>
<td>Both groups</td>
<td>–</td>
<td></td>
<td></td>
<td>0.362 (0.000)</td>
<td>0.42 (0.000)</td>
<td>0.67 (0.000)</td>
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<td><strong>Pain severity – BPI</strong></td>
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<tr>
<td>Healthy</td>
<td>–</td>
<td>0.77 (0.000)</td>
<td></td>
<td></td>
<td>0.36 (0.013)</td>
<td>0.44 (0.002)</td>
</tr>
<tr>
<td>COPD</td>
<td>0.46 (0.003)</td>
<td>0.82 (0.000)</td>
<td></td>
<td></td>
<td>0.54 (0.000)</td>
<td>0.683 (0.000)</td>
</tr>
<tr>
<td>Both groups</td>
<td>–</td>
<td>0.76 (0.000)</td>
<td>0.36 (0.000)</td>
<td>0.54 (0.000)</td>
<td>0.681 (0.000)</td>
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<tr>
<td><strong>Pain interference – BPI</strong></td>
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<tr>
<td>Healthy</td>
<td>–</td>
<td>0.72 (0.000)</td>
<td>0.82, (0.000)</td>
<td></td>
<td>0.38 (0.008)</td>
<td>0.46 (0.001)</td>
</tr>
<tr>
<td>COPD</td>
<td>0.56 (0.000)</td>
<td>0.66 (0.000)</td>
<td>0.74, (0.000)</td>
<td>0.49 (0.001)</td>
<td>0.36 (0.012)</td>
<td>0.58 (0.000)</td>
</tr>
<tr>
<td>Both groups</td>
<td>–</td>
<td>0.73 (0.000)</td>
<td>0.79, (0.000)</td>
<td>0.52 (0.000)</td>
<td>0.42 (0.000)</td>
<td>0.63 (0.000)</td>
</tr>
</tbody>
</table>

MPQ, McGill Pain Questionnaire-short form; BPI, Brief Pain Inventory-short from; TSK, Modified Tampa Scale of Kinesiophobia; FEV<sub>1</sub>, forced expiratory volume in 1 s.
Figure 3.1 Number of healthy people and COPD patients that self-reported moderate, severe or very severe for pain severity (McGill Pain Questionnaire [MPQ] and Brief Pain Inventory [BPI]) and pain interference (BPI).

* indicates significant difference from healthy people at $p < 0.002$. 

![Graph showing the number of healthy people and COPD patients reporting pain severity and interference.]

- Healthy and COPD patients are compared for MPQ severity, BPI severity, and BPI interference.
- The asterisk (*) indicates statistical significance at $p < 0.002$. 

The graph illustrates: 
- Healthy and COPD patients both report pain severity.
- COPD patients report significantly higher pain severity compared to healthy people.
- Pain interference is also higher for COPD patients compared to healthy people, with significant difference.

Number of Participants

- Very severe
- Severe
- Moderate

Healthy

COPD

MPQ Severity

BPI Severity

BPI Interference

15

10

5

0

Healthy

COPD

Healthy

COPD

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Figure 3.2 Number of pain locations in healthy people and COPD patients

** indicates significant difference at p < 0.005.

* indicates a tendency to be different from healthy people at p < 0.04.
Figure 3.3 Scatter plots depicting relationship between McGill and Brief Pain Inventory pain severity scores and the number of comorbidities
Chapter Four: Pain and Comorbidities in People with COPD

4.1 Introduction

Pain is a pervasive medical condition worldwide and most commonly limits activity. It is estimated that 80% of physician visits are prompted complaints of pain (Gatchel & Epker 1999). The prevalence of pain in a recent study was reported to be approximately 26% in the general population (Toblin et al. 2011). The most common comorbidities associated with pain in the general population are of musculoskeletal (MSK) origin (Elliot et al. 1999; Frølund & Frølund 1986; Magni et al. 1990; Toblin et al. 2011), being approximately three-fold more common than other causes (Elliot et al. 1999). Furthermore, pain is most commonly attributed to arthritis, accident/injury, sciatica/slipped disc/spondylosis in the general population (Toblin et al. 2011). The most commonly cited painful locations have been described to be the low back or back (Elliot et al. 1999; Frølund & Frølund 1986; Magni et al. 1990; Gureje et al. 1998) followed by joint pain (Frølund & Frølund 1986; Magni et al. 1990; Gureje et al. 1998).

People with COPD report significant pain and it appears to be more common than the general population (Bentsen et al. 2011; HajGhanbari et al. 2012). Pain has been reported in people with stable COPD (Bentsen et al. 2011, Borge et al. 2011, Lohne et al. 2010), and as components of quality of life (Hajiro et al. 1999). Two reports described pain as the second most common symptom experienced in COPD patients in the last year of life (Lynn et al. 2000; Elkington et al. 2005). Severe dyspnea was a more common symptom (70-98%), and moderate to severe pain was described in 23-34%
of patients in one study (Lynn et al. 2000) and 72% in another (Elkington et al. 2005).

The most common pain locations in COPD patients has been reported to be the trunk (Bentsen et al. 2011), the neck, shoulder, upper arms, and lumbar regions (Borge et al. 2011; Lohne et al. 2010). The lower extremities were described as being the second most common region in one report (see Chapter 3). The underlying mechanisms that contribute to the high prevalence of pain in COPD are not well investigated; however, pain may be due to similar mechanisms that affect the general population as well as disease-specific pathological changes that could provide additional causes or amplify pain (see Chapter 3).

MSK comorbidities that are the most common cause of pain in the general population (Toblin et al. 2011; Elliot et al. 1999; Frølund & Frølund 1986; Magni et al. 1990; Gureje et al. 1998) might be an underlying cause for some of the pain experienced by people with COPD. MSK and endocrine comorbidities are common in people with COPD and could contribute to their experience of pain; the prevalence of osteoporosis in COPD is reported to be 60-70% (Ferguson et al. 2009) and the age-related prevalence of osteoarthritis ranges from 14 to 58% in the 50 to 86 year age-range (Kopec et al. 2007). Whether the presence of MSK or endocrine comorbidities contributes to pain in people with COPD is unknown.

Multiple comorbid conditions are negatively associated with physical activity in COPD and could be a major contributing factor to increased pain these patients. Chronic
Comorbidities independently predict the improvements after pulmonary rehabilitation (Crisafulli et al. 2008; De Fazio et al. 2006), and adversely affect the increase of both exercise tolerance and quality of life after rehabilitation (Crisafulli et al. 2008). Furthermore, impairments in social and emotional functioning in COPD are shown to be associated with comorbidities, and not COPD (van Manen et al. 2003). Comorbidities are related to the reduced ability to perform daily activities, and increased primary care attendance in COPD (Yeo et al. 2006). These findings might be especially evident in the presence of MSK diseases with associated with painful symptoms that in turn contribute to immobility and further deconditioning in COPD.

In order to better understand factors that might contribute to pain in COPD, we explored the pattern of comorbidities (number and type), pain medications and treatments, and how comorbidities relate to the experience of pain in people with COPD. The purpose of this study was to determine if pain and pain interference were associated with comorbidities in people with COPD and secondly, to determine if specific types of comorbidities are associated with more pain and a particular location of pain.

4.2 Methods

4.2.1 Participants

Fifty-four people with moderate to severe COPD (30% $\leq$ FEV$_1$ $<$ 80% predicted, FEV$_1$/FVC $<$ 0.7) (Global Initiative for Chronic obstructive Lung Disease, 2011), from the sample recruited for the survey study (Chapter 3) were included in this study for further analysis. People with COPD were recruited from the caseload of respirologists based at
local hospitals, pulmonary function laboratories, and respiratory clinics. People with COPD were excluded if they had: 1) an acute exacerbation of COPD within the three months prior to the study; 2) were unable to ambulate independently; 3) insufficient English fluency or cognitive impairment that interfered with the ability to provide informed consent or to complete the questionnaires. Ethical approval for this study was obtained from the Clinical Research Ethics Board of the University of British Columbia and informed consent was obtained from the participants.

4.2.2 Experimental protocol

Using a cross-sectional descriptive study design, the severity and characteristics of pain (pain severity, interference, and locations), the number and type of comorbidities and medications were investigated in people with COPD who experienced pain. Subjects were administered a screening questionnaire via a telephone interview to ensure they met the inclusion criteria. After obtaining consent, a package of forms and questionnaires were mailed to the participants that included: a sheet of instructions for completion, a form to record medications and co-morbidities, the McGill Pain Questionnaire (MPQ), and the Brief Pain Inventory (BPI). After receiving the package, all subjects were contacted by telephone to address any questions related to the forms and questionnaires. Participants were asked to mail back the package after completion. In order to confirm the diagnosis of COPD, participants had retrospective chart reviews to examine recent spirometric data. Charts were also reviewed to confirm the medications taken and the presence of comorbidities in order to supplement, as required, self-reported data by the subjects.
4.2.3 Measurements

Both MPQ and BPI were used to assess the intensity of pain, and BPI also provided measures of pain interference and locations of pain. The form that listed comorbidities was based on the Charlson Index as modified by Deyo (1992). In addition common musculoskeletal conditions were listed. Medications were categorized according to the Canadian Medical Association 2002.

4.2.4 Statistical analyses

Data are reported as counts/frequencies and means and standard deviations unless otherwise indicated. Severity and interference of pain were categorized by dividing scores of the MPQ severity, BPI intensity and BPI interference into quartiles corresponding to: minimal or no pain, moderate, severe, and very severe pain. Subjects who reported no pain (n=10) were not included in the subsequent analyses that examined relationships to comorbidities and medications.

Correlations were examined for pain severity (measured by VAS of MPQ) and other variables using two-tailed Pearson or Spearman product moment correlations. The variables included: MPQ-severity, BPI-severity, BPI-interference, number and type of comorbidities (namely MSK, cardiovascular, endocrine), number of medications, number of pain locations). Unpaired t-tests were used to determine if the presence or absence of a particular type of comorbidity showed higher pain scores. A Chi-square test was used to determine the associations between two sets of categorical data, i.e. pain locations and types of comorbidities. The p value of <0.05 was used to report the
statistical significance.

4.3 Results

Eighty-one percent of COPD patients experienced pain. Forty-four patients (female/male=22/22) reported pain and 10 patients (female/male=6/4) reported no pain. COPD patients that experienced pain were of a similar age (72.4±7.8 vs 70.6±5.8 yr), had a similar BMI (26.71±5.7 vs 25.16±4.5 kg/m²), and similar FEV₁ (48.3±18.2 vs 42.9±20.6 % predicted; non-significant) compared to those who did not experience pain. Pain severity and interference scores of the MPQ and BPI and their distributions are reported in Table 4.1.

Regarding the prevalence of comorbidities in our sample of COPD patients who experienced pain, 93% of patients self-reported more than one comorbid conditions (Figure 4.1), 66% had between 1 and 4 comorbidities and 30% had 5 to 8 comorbidities (Figure 4.1). The most common comorbidities were cardiovascular (circulatory and heart [29%]) followed by musculoskeletal (20%) and endocrine conditions (13%) (Figure 4.2). The types of self-reported cardiovascular diseases included: high blood pressure (44%), symptoms of lightheadedness or dizziness by changing position (20%), low blood pressure (16%), peripheral vascular arterial disease (13%) and hyperlipidemia (7%). The self-reported musculoskeletal diseases included: osteoarthritis or related surgical interventions (64%), rheumatoid arthritis (19%), or a history of broken bones (17%).
The number of comorbidities was positively correlated to pain intensity/severity and interference as measured by the MPQ \((r=0.40, p<0.01)\), BPI severity \((r=0.36 \ p<0.01)\), and BPI interference scores \((r=0.50, p<0.001)\). Table 4.2 shows the counts and percentages of patients with different levels of pain and different types and numbers of comorbidities. Notably, the most common comorbidities in people with severe or very severe pain were cardiovascular (100%), musculoskeletal (100%), and endocrine (69%) (Table 4.2). Patients with MSK and endocrine conditions had significantly more pain (BPI severity score) than those without MSK or endocrine comorbidities. Pain scores were \(40.3 \pm 4.1\) versus \(26.3 \pm 3.8\) for those with and without a MSK disorder \((p<0.05)\), and \(42.6 \pm 24.5\) versus \(29.8 \pm 15.5\) for those with and without an endocrine condition \((p<0.05)\). No differences in mean pain scores were found in COPD patients with and without cardiovascular diseases.

The most common location for pain as indicated on the body diagram of the BPI was the trunk, which consisted of the shoulder, low back, chest, neck, buttock, thoracic spine, and abdomen (Figure 4.3). The second most common location was the lower extremities, then the upper extremities (Figure 4.3) and lastly, the head. Not only did this hold true when the data was expressed as total counts of pain locations (Figure 4.3), but also when expressed as the percentage of patients that experienced pain in a particular region (Figure 4.4). In the trunk, more COPD patients reported pain in the low back, neck, chest, and shoulder (Figure 4.4). In lower extremity, more COPD patients reported pain in the knee and calf regions. The chi-square test showed no significant associations between pain in specific locations and comorbidities, although there was a
trend that those with MSK comorbidities had more pain in the trunk and lower extremities ($X^2 = 3.38, p=0.06$).

BPI interference score showed that 73% of COPD patients with pain, experienced moderate to very high pain interference with their daily activities. Examination of the seven items that contributed to the BPI interference subscores (out of 10) indicated that pain interference was highest with normal work ($5.3 \pm 3.0$), and walking ability ($5.2 \pm 3.2$), followed by general activity ($4.5 \pm 2.9$), sleep ($4.4 \pm 3.2$), mood ($3.6 \pm 2.8$), and relationship with others ($3.1 \pm 2.7$). Significant positive correlations were found between pain intensity/severity (measured by the BPI or MPQ) and the BPI interference items of general activity, walking, normal work, relationship with others, sleep and pain (Table 4.3).

The most common self-reported pain treatments were non-prescription, over the counter pain medications; 64% stated that they took acetaminophen or ibuprofen (Figure 4.5). Prescription narcotic medications were taken as well. Other pain treatments included physiotherapy modalities/massage, and acupuncture.

4.4 Discussion
This study demonstrated that the number of comorbidities was associated with pain severity and interference with daily activities. Eighty one percent of people with COPD in this sample experienced pain and 96% self-reported one or more comorbid conditions, with 73% of the patients reporting moderate to very severe pain-related
interference with daily activities. Forty-six percent of the patients on the MPQ and 66% on the BPI reported moderate to very severe pain that interfered with walking ability, sleep, and normal work. COPD patients with musculoskeletal (MSK) or endocrine disorders had higher levels of pain. In contrast to the most common pain medications reported in general population (Toblin et al. 2011), 64% of people with COPD mainly used acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDS), and only 3% used physiotherapy to relieve their pain.

The high prevalence and severity of pain reported in our study is consistent with the findings of a recent study that reported a significantly higher percentage of COPD patients with pain compared to general population (45 versus 34%) (Bentsen et al. 2011). Our study provided a more standardized assessment of pain by using two valid and reliable pain assessment tools whereas the investigation by Bensten et al. (2011) asked the question: “Are you generally bothered by pain?” A second study also reported higher pain intensity in COPD as compared to healthy controls; the severity of pain was rated at the upper end of mild pain score in patients with hip or knee osteoarthritis and pain experienced by cancer patients (Borge et al. 2011). Factors that might explain the increased pain in our cohort of COPD patients include: the increased number and type of comorbidities with associated painful symptoms, prolonged systemic inflammation that might reduce the pain threshold in COPD (see discussion in Chapter 3), and changes in chest wall structure.
4.4.1 Comorbid conditions associated with pain

In our study, the most common comorbid conditions were cardiovascular and MSK diseases i.e. osteoarthritis followed by endocrine diseases, i.e. osteoporosis and diabetes. This finding is similar to the data from several studies (Crisafulli et al. 2008; Mapel et al. 2000; Sidney et al. 2005; Soriano et al. 2005) that had a primary focus of determining the most prevalent comorbidities in COPD. In these studies, the prevalence of arthritis ranged from 28% to 70% in samples of COPD patients (Soriano et al. 2005; van Manen et al. 2001; Walsh et al. 2006). A previous report of COPD patients who experience pain stated that the major comorbid conditions were cardiac conditions, osteoporosis, diabetes, cancer, and asthma (Bentsen et al. 2011). However, a subsequent report from the same group of investigators stated that musculoskeletal comorbidities (such as osteoarthritis, rheumatoid arthritis) and osteoporosis were more common than cardiac conditions in COPD (Bentsen et al. 2012). Thus, our comorbidity data are within the range reported by studies that focused on comorbidities and also to a report by Bentsen et al. (2012) that examined comorbidities in COPD patients that experienced pain. Worthy of note, we found that COPD patients with MSK and endocrine disorders experienced more pain compared to those without these comorbidities, which implicates these conditions as potential contributors to the pain experienced. This supposition requires further investigation that utilizes assessment specific to these particular disorders.

4.4.2 Pain locations

In our study, the most common pain locations were neck, shoulder, chest, and low back
followed by the calves, which are similar to the results of other studies that investigated pain locations in COPD (Bentsen et al. 2011, Borge et al. 2011, Lohne et al. 2010). Our analyses relating the type of comorbidity to pain location did reveal a strong trend that those COPD patients with MSK conditions experienced more pain in the trunk and lower extremities (p=0.06). Further study is required to explore the relationship between the possible etiology of pain and pain locations by using a larger sample size and by asking patients to note their self-perceived or diagnosed cause of pain for each painful region indicated on the body diagram.

The increased pain in chest, neck, and shoulder in COPD patients might be due to the hyperexpanded chest wall, the overload and fatigue of accessory muscles of inspiration that are located in neck, shoulder, and chest, and the protracted processing of pain and dyspnea (Bentsen et al. 2011, Borge et al. 2011, HajGhanbari et al. 2012). Respiratory muscle dysfunction might contribute to the increased prevalence of pain in the low back (O’Sullivan & Beales 2007), shoulder, and neck (Kapreli et al. 2009) in people with COPD. Associations between chronic neck pain and decreased maximal voluntary ventilation and decreased respiratory muscle strength have been documented (Kapreli et al. 2009). Faulty postures, such as increased forward head posture (dysfunction of neck and shoulder muscles) are strongly correlated to decreased respiratory muscle strength in chronic neck pain patients (Kapreli et al. 2009). Moreover, positive associations have been found between the dysfunction of diaphragm and core muscles and altered respiration in chronic low back pain (O’Sullivan & Beales 2007). Whether low back and neck pain are the causes or the result of respiratory dysfunction is not
known but these connections warrant investigation in people with COPD who experience pain.

Approximately one-quarter of COPD patients had calf pain that might be attributed to the manifestations of peripheral vascular disease and/or the side effects of beta2-agonist medications commonly prescribed to alleviate bronchospasm (O’Donnell et al. 2008). COPD patients have a high prevalence of cardiovascular disease that can manifest as intermittent claudication resulting in calf pain during walking. A secondary explanation might be due to beta2-agonist medications that can affect skeletal muscles by causing shakiness and cramping of the hands, legs and feet, which in turn might affect physical activity and walking ability in patients with COPD (O’Donnell et al. 2008). The precise mechanisms that contribute to calf pain in COPD needs further study.

### 4.4.3 Medications and treatments

In our study, acetaminophen, followed by NSAIDS were the most common pain medications, with only 6% of patients using non-drug treatments, such as physiotherapy and massage (3%), or acupuncture (3%). This is in contrast with pain medications commonly used in the general population (Toblin et al. 2011). In a study by Toblin et al. (2011), 45.7% of people with pain used opioids (including 36.7% of those with mild pain), 34.5% used NSAIDS, and only 3.9% used analgesics, whereas our sample showed that 9% used opioids, 12% used NSAIDS (ibuprofen and celecoxib) and 55% used analgesics, such as acetaminophen. Considering the greater prevalence and magnitude of pain in COPD as compared to the general population, these findings
suggest that people with COPD might not be receiving adequate pain medication and thus, are undertreated.

Our findings related to the non-medication pain treatments and the low rates of physiotherapy for pain treatment in COPD are similar to the data reported by Bentsen et al. (2011). This group reported that patients with COPD used acupuncture/transcutaneous electrical nerve stimulation (TENS) more frequently as compared to physiotherapy; whereas, physiotherapy was used more commonly in the general population (Bentsen et al. 2011). The use of non-physiotherapy treatment in COPD might be related to their sedentary life style and reluctance to be involved in physically demanding activities, such as exercise treatments prescribed by physiotherapy or rehabilitation programs. The tendency of COPD patients to seek immediate relief of symptoms by taking over-the-counter painkillers might not provide optimal outcomes, i.e. insufficient pain relief and not addressing the underlying cause of pain.

4.5 Conclusions

Our findings suggest that comorbidities are very common in COPD and might contribute to the increased pain experienced by these patients. Adequate prevention, monitoring and treatment of comorbid conditions, along with proper assessment and individually designed treatment for pain in COPD should be considered in clinical settings. Adequate pain medication, combined with individually tailored rehabilitation programs to address co-existing conditions could potentially improve function, exercise capacity, and quality of life in this patient group. Further research is required to investigate the
etiology of pain in COPD.

The next chapter investigates the associations between pain and measures of physical performance (muscle strength, daily physical activities, functional exercise capacity [6MWT], and health related quality of life) in patients with COPD. The outcomes of this study address the aspects related to the “activity limitation” component of ICF.
Table 4.1 Pain severity, intensity and interference in COPD patients.

The mean scores and the number (percentage) of patients with minimal, moderate, severe and very severe pain severity/intensity and interference are provided based on the quartiles of total scores of McGill Pain Questionnaire (MPQ), and subscores of the Brief Pain Inventory (BPI) (n=44).

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Minimal pain</th>
<th>Moderate pain</th>
<th>Severe pain</th>
<th>Very severe pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MPQ severity /100</strong></td>
<td>24.8 (2.8)</td>
<td>24 (55%)</td>
<td>13 (29%)</td>
<td>5 (11%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td><strong>BPI intensity /100</strong></td>
<td>35.6 (3.1)</td>
<td>15 (34%)</td>
<td>16 (36%)</td>
<td>11 (25%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td><strong>BPI interference /100</strong></td>
<td>44.8 (3.6)</td>
<td>12 (27%)</td>
<td>10 (23%)</td>
<td>20 (45%)</td>
<td>2 (5%)</td>
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Table 4.2 Frequencies of patients with different pain severities compared to types and number of comorbidities.

<table>
<thead>
<tr>
<th>Type of comorbidity</th>
<th>Cardiovascular</th>
<th>MSK</th>
<th>Endocrine</th>
<th>Psychological</th>
<th>Digestive</th>
<th>Immune</th>
<th>Cancer</th>
<th>Neurological</th>
<th>Renal</th>
<th>Eye</th>
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<td><strong>BPI severity score</strong></td>
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<td>Mild (n=15)</td>
<td>10 (67%)</td>
<td>6 (40%)</td>
<td>6 (40%)</td>
<td>3 (20%)</td>
<td>1 (6%)</td>
<td>0 (27%)</td>
<td>0</td>
<td>5 (33%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Moderate (n=16)</td>
<td>16 (100%)</td>
<td>12 (75%)</td>
<td>5 (31%)</td>
<td>5 (31%)</td>
<td>6 (37%)</td>
<td>2 (12%)</td>
<td>4</td>
<td>4 (25%)</td>
<td>4</td>
<td>3 (19%)</td>
</tr>
<tr>
<td>Severe to Very severe (n=13)</td>
<td>13 (100%)</td>
<td>13 (100%)</td>
<td>9 (69%)</td>
<td>5 (38%)</td>
<td>6 (46%)</td>
<td>2 (15%)</td>
<td>1</td>
<td>2 (15%)</td>
<td>3</td>
<td>0 (23%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of comorbidities</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BPI severity score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (n=15)</td>
<td>1 (6%)</td>
<td>3 (20%)</td>
<td>6 (40%)</td>
<td>3 (20%)</td>
<td>1 (6%)</td>
<td>0</td>
<td>0</td>
<td>1 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Moderate (n=16)</td>
<td>1 (6%)</td>
<td>0</td>
<td>1 (6%)</td>
<td>4 (25%)</td>
<td>4 (25%)</td>
<td>3 (19%)</td>
<td>1 (6%)</td>
<td>2 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Severe to Very severe (n=13)</td>
<td>0</td>
<td>0</td>
<td>2 (18%)</td>
<td>3 (27%)</td>
<td>2 (18%)</td>
<td>3 (27%)</td>
<td>2 (18%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Upper panel shows the distribution of pain severity and its association with the type of comorbidities; lower panel shows the distribution pain intensity and its association with the number of comorbid conditions. **Abbreviations:** MSK: musculoskeletal; BPI: Brief Pain Inventory.
Table 4.3 Correlations among pain intensity/severity and interference with daily activities in people with COPD who have pain.

<table>
<thead>
<tr>
<th>BPI interference scores</th>
<th>MPQ severity</th>
<th>BPI intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Activity</td>
<td>0.34*</td>
<td>0.27</td>
</tr>
<tr>
<td>Mood</td>
<td>0.23</td>
<td>0.12</td>
</tr>
<tr>
<td>Walking</td>
<td>0.50**</td>
<td>0.29*</td>
</tr>
<tr>
<td>Normal Work</td>
<td>0.40**</td>
<td>0.35*</td>
</tr>
<tr>
<td>Relationship with others</td>
<td>0.32*</td>
<td>0.25</td>
</tr>
<tr>
<td>Sleep</td>
<td>0.37**</td>
<td>0.35*</td>
</tr>
<tr>
<td>Enjoyment of Life</td>
<td>0.29</td>
<td>0.30</td>
</tr>
</tbody>
</table>

The severity scores of the MPQ and the BPI were correlated with each of the seven items that contribute to BPI interference scores. **Abbreviations:** BPI= Brief Pain Inventory; MPQ= McGill Pain Questionnaire

* p<0.05; ** p<0.01; Ψ p<0.001
Figure 4.1 The number of comorbidities in COPD patients who experience pain.

The numbers in white font indicate the number of comorbidities and the numbers in black font indicate the percentage of 44 COPD patients that experienced pain.
Figure 4.2 The percentage of different types of comorbidities in COPD patients who experience pain.

- Heart: 9%
- Circulatory: 20%
- Musculo-skeletal: 20%
- Endocrine: 13%
- Digestive: 8%
- Neuro: 4%
- Mood: 8%
- Immune: 2%
- Cancer: 6%
- Renal: 8%
- Eye: 2%
- Renal: 8%
- Cancer: 6%
- Circulatory: 20%
- Musculo-skeletal: 20%
- Endocrine: 13%
- Digestive: 8%
- Neuro: 4%
- Mood: 8%
- Immune: 2%
- Eye: 2%
Figure 4.3 The pain locations (reported as the number of counts for each region) as identified on the body diagram of the Brief Pain Inventory (n=44).

Abbreviations: L/E= lower extremity; U/E= upper extremity.
Figure 4.4 The pain locations (reported as the percentage of the total number of patients) as identified on the body diagram of the Brief Pain Inventory (n=44).
Figure 4.5 The percentage of different pain treatments used by COPD patient who experience pain.
Chapter Five: Pain and Physical Performance in People with COPD

5.1 Introduction

People with stable COPD experience significant pain compared to age- and gender-matched healthy people and pain interferes with daily activities (Bentsen et al. 2011; Borge et al. 2011; HajGhanbari et al. 2012). COPD patients demonstrated 2.6 times more pain and pain interfered with daily activities 3.7 times more than age- and gender-matched healthy group (HajGhanbari et al. 2012, see Chapter 3). This greater prevalence in COPD patients is similar to the recent report by Bensten et al. (2011) who found that a significantly higher percentage of patients with COPD (45%) reported pain than the control group (34%; P = 0.02). In addition, a study by Borge et al. (2011) stated that 72% percent of the patients with COPD reported pain as assessed by using a body diagram. These investigations unequivocally indicate that pain in COPD is more common and severe compared to healthy people. Further investigation is required to better understand the impact of pain on physical activities.

Fatigue, dyspnea (Killian et al. 1992; O'Donnell et al. 1997), and muscle weakness (Engelen et al. 2000; Gosselink 1996) can adversely affect functional mobility and physical capacity in COPD patients. Pain has been associated with limitations in physical activity in people with chronic arthritis (van Dijk et al. 2008), and reductions in health related quality of life (HRQoL) in patients with nonmalignant pain (Niels et al. 1997). Given that pain limits physical activity and reduces quality of life in people with other chronic conditions, those with COPD may be affected in a similar fashion. In spite
of the apparent frequent occurrence of this symptom, the effects of pain on muscle
performance and whether it interferes with physical performance in people with COPD
have not been described. A better understanding of the pain in COPD needs to be
considered in order to design the most effective prescriptions for exercise, activity
participation, and maintaining mobility.

To expand our understanding about the experience of pain in COPD and whether pain
can be considered as an additional activity-limiting factor in COPD (besides fatigue and
dyspnea), we determined the relationships between pain and three physical
performance measures: a) muscle performance (concentric torque of knee extensors),
and b) physical activity levels (as measured by 3D accelerometry) and c) six minute
walk test (6MWT).

5.2 Methods
5.2.1 Participants
A convenience sample of 26 people with moderate to severe COPD (based on their
percent predicted forced expiratory volume in one second [FEV$_1$] of 30% ≤ FEV$_1$ < 80%
predicted, FEV$_1$/FVC <0.7) (Global Initiative for Chronic Obstructive Lung Disease,
2011) were recruited from rehabilitation programs at local hospitals and from the local
respirologists. People with COPD were included if they: 1) had moderate to severe
disease according to the criteria described above; and 2) were over 50 years of age.
Participants were excluded if they: 1) had experienced an acute exacerbation of COPD
during the last 3 months; 2) had unstable cardiovascular, neurological, musculoskeletal
or other condition(s) that interfere with independent ambulation or safe performance of the testing; 3) had taken oral corticosteroids within the last three months; 4) had cognitive impairment; and 5) were not fluent in English. The clinical ethics board at the University of British Columbia approved the study and all subjects gave informed written consent before participation in the study.

5.2.2 Measurements

Retrospective chart reviews were conducted to confirm the diagnosis of COPD as demonstrated by spirometric data. In addition, the medication history and information about comorbidities were extracted. Participants were asked to refrain from physical exercise, caffeine and alcohol on test days. Participants made two visits to the laboratory. During the first laboratory visit, spirometry was performed to determine disease severity and patients were asked to fill out questionnaires including: a form to record medications and co-morbidities, the Medical Outcomes Study Short Form-36 (SF-36), short form of McGill Pain Questionnaire (MPQ), the short form on Brief Pain Inventory (BPI), and a form for screening the risks of exercise based on American College of Sports Medicine (ACSM) guidelines. Height and weight were measured, and each subject performed the 6MWT. Subjects were familiarized with the accelerometer (DynaPort Activity Monitor; McRoberts BV), and received instructions on how to wear and use the device supplemented with a manual containing written instructions and figures. Subjects were asked to wear the device for two full days. The DynaPort has been tested for validity and reliability in patients with COPD (Pitta et al. 2004 & 2005). It measures precisely the time spent in walking, cycling, standing, sitting, or lying, as well
as movement intensity during walking, and is as accurate as video recordings. Two
days was chosen as this time was shown to be sufficient to achieve an acceptable
intraclass reliability coefficient (0.70 < intraclass reliability coefficient < 0.88) with a five-
day activity monitoring with the device (Pitta et al. 2005). During the second laboratory
visit (at least 3 days after the first visit), subjects were tested for maximal voluntary
concentric torque, followed by repetitive fatiguing maximal concentric contractions,
using an isokinetic Biodex dynamometer.

5.2.2.1 Assessment of disease severity
Spirometry was performed to determine COPD severity from FEV₁ and FVC values. To
calculate percent-predicted pulmonary function values, we used predictive equations
derived from the third National Health and Nutrition Examination Survey (NHANES III)
(Hankinson et al. 1999).

5.2.2.2 Pain severity and interference
Assessment of pain severity was assessed using the MPQ, and BPI. The MPQ consists
of: 1) eleven items to assess sensory components; 2) four items to assess affective
aspects of pain over one week; 3) a visual analogue scale to provide the intensity score
of the pain over one week; and 4) a Present Pain Intensity (PPI) scale. This form is
reported to be reliable (Love et al. 1989), valid (Reading et al. 1985), and has been
found to be appropriate for use with geriatric patients who experience pain (Gagliese &
Melzack 1997).
The BPI was used to identify pain locations on a body diagram and to assess two dimensions of pain: severity and interference with daily life over the last week. The BPI measures the interference of pain in the general aspects of patient's life including: general activity, mood, sleep, enjoyment of life, and relationship with others. The BPI has been shown to have predictive validity in a number of patient populations with chronic conditions (Mendoza et al. 2004 & 2006; Tan et al. 2004). Because of these different attributes, both the BPI and MPQ were used to provide a more comprehensive description of the pain experienced by individuals (Sawyer et al. 2008). The MPQ has been shown to be an excellent tool to evaluate the quality of pain while the BPI is preferred in the assessment of physical function and functional impact of pain (Lynch et al. 2011).

5.2.2.3 Functional exercise capacity and quality of life

Assessment of functional exercise capacity was performed with the 6MWT (Brooks et al. 2003). Briefly, participants were instructed to walk as far as they could in 6 minutes in a 30-meter hallway, and the total distance walked was recorded in meters. Percent predicted values for 6MWT were calculated based on the method described by Enright & Sherrill (1998). Assessment of HRQoL was performed using SF-36 (Ware & Sherbourne 1992).

5.2.2.4 Physical activity

Assessment of physical activity level in daily life (activity monitoring) was performed with a DynaPort MiniMod MoveMonitor (McRoberts, The Hague, The Netherlands). The
device has been validated and used in people with COPD. It measures step counts, and the time spent in different postures, such as standing, sitting or lying, walking and locomotion. Data were processed through online software to estimate physical activity for 2 days (Watz et al. 2009; Pitta et al. 2005). Subjects were asked to wear the accelerometer for 2 full days between the two laboratory visits. The data were assessed from 9 am to 9 pm on each day for the purpose of the analysis (Pitta et al. 2005). Participants were asked to perform their usual daily activities and not to change their routine while wearing the device (Watz et al. 2009). For the purpose of data analysis, total number of step counts over 2 days, and the activity durations (in minutes) for different types of activity (lying, sitting, walking, and standing) were recorded.

5.2.2.4 Muscle strength and fatigue

Assessment of maximal voluntary concentric torque of the dominant leg (the leg that a person uses to kick a ball) was performed with the isokinetic dynamometer (Biodex System 4; Biodex, Shirley, NY). The shin pad was placed at 75% of the distance from the head of the fibula to the distal edge of the lateral malleolus. The knee was aligned with the rotating lever. Subjects were familiarized with producing maximal concentric contractions of the knee extensors. Concentric torque of the knee extensor muscles was tested by having the subject performing 3 to 5 sub-maximal warm-up contractions followed by 5 maximal voluntary contractions (MVC) through a range of motion from 80° to 10° of knee flexion at an angular velocity of 90° per second (Janaudis-Ferreira et al. 2006). Participants received vigorous verbal encouragement. MVCs were performed until the maximum force recorded during two contractions differed by 5% or less.
The highest MVC peak torque was used to represent the subject’s maximal concentric contraction (Kannus 1994).

For the fatigue protocol, subjects performed repetitive maximal concentric knee extension contractions of the knee extensors while the counter movement was performed passively by the device. The contracting and passive return time ratio was 2:1 with about 1 sec rest during the counter movement. Subjects were asked to perform as many contractions as they could up to a maximum of 100 contractions (Janaudis-Ferreira et al. 2006). Visual and verbal feedback was provided during each contraction to ensure that the maximum amount of force was produced. The first 34 contractions were chosen for measuring fatigue index (FI) because it was the maximum number of contractions that all patients were able to perform. The FI was calculated by the following formula to yield a percentage decrease in peak isokinetic torque:  
\[ FI = 100 - \left( \frac{\text{Peak MVC of 34}^{\text{th}} \text{ contraction}}{\text{Peak MVC of 1}^{\text{st}} \text{ contraction}} \times 100 \right) \]  (Fujita et al. 2007).

5.2.3 Statistical analyses

Frequencies were determined for the total number of pain locations, comorbidities and medications. MPQ, and BPI scores were calculated as the percentage of the maximum score that could be obtained on each component of the questionnaire: severity for MPQ and BPI, and interference for BPI. Descriptive statistics were performed to describe subject characteristics and frequency distributions of the outcomes.
The distribution of data was tested for normality using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Levene’s test was used to test for the homogeneity of the variances. Pain severity, as measured by MPQ and BPI, was tested for correlations with the physical activity data (step counts, activity duration), peak torque, fatigue index, and HRQoL (SF-36). The Pearson product moment correlation coefficient (PCC) was used for normally distributed data and the Spearman’s correlation coefficient was used for non-normally distributed data. Correlations (r) were categorized as low (0<r<0.25), moderate (0.25<r<0.50), strong (0.50<r<0.75), and very strong (0.75<r) (Cohen 1988).

Furthermore, the subjects were divided into two groups: those with severe pain and those with mild to moderate or no pain, and two-tailed t-tests were performed to investigate between group differences in pain severity and interference, functional exercise capacity, physical activity, muscle performance, and HRQoL.

The cut points of 30, 40, and 40 were selected for MPQ intensity, BPI severity and BPI interference scores, respectively, based on visual inspection of the distribution plots. Two-tailed t-tests were performed for 6MWT, physical activity, torque, and quality of life measures to compare between groups with severe pain versus those with mild to moderate pain. The ratio of the number of patients with mild to moderate pain for MPQ, BPI severity, and BPI interference scores were (21/5), (20/6), and (21/5), respectively. Statistical analyses were performed using the SPSS software package (version 16.0, Chicago, IL). The significance level of (p<0.05) was selected.
5.3 Results

Twenty-six patients with moderate to severe COPD completed the study. Subjects had a mean age of 70.4 ± 9.3 years (14 males), and a mean BMI within the normal range (Table 5.1). Mean pain scores on the MPQ intensity were slightly lower than BPI severity and BPI interference. Means and standard errors for pain levels, 6MWT, quality of life scores; physical activity and torque measures are reported in Table 5.2. MPQ pain severity was negatively correlated with the 6MWT (Table 5.3, Figure 5.1). The t-test for the 6MWT showed that those subjects with severe pain walked a shorter total distance (-115 ± 57 based on the MPQ and -42 ± 51 m based on BPI severity scores). Subjects with more pain had shorter predicted distance on the 6MWT as compared to those with less amounts of pain (Table 5.4) (p<0.01). Females walked 350 ± 121 m (70% predicted) while males walked 402 ± 119 m (88% predicted). Those with more pain had 41% less active time (p<0.01), had 49% less standing time (p<0.01), and had 16% more sedentary time (p<0.05) (Table 5.4). No significant correlations were found between maximal concentric torque, and pain severity or pain interference.

MPQ pain severity, BPI pain severity, and BPI interference scores were negatively correlated with Physical Component Score (PCS) of SF-36 (p<0.05) (Table 5.3). Between group comparisons showed that those subjects with more pain severity (p<0.01) and interference (p<0.001) scored lower on PCS of the SF-36 (Table 5.4). Significant negative correlations were found between Mental Component Score (MCS), and pain severity (p<0.05) and pain interference (p<0.001) of the BPI (Table 5.3).
Between group comparisons also showed that those with more severe pain (BPI) and greater pain interference (on the BPI) had lower MCS of the SF-36 (p<0.05).

MPQ severity (p<0.001, Figure 5.1) and BPI interference scores (p<0.05) were positively correlated with BMI (Table 5.3). As compared to those with minimal or no pain, subjects with severe pain reported more pain interference with daily activities (p<0.05) and had on average 2-3 more comorbidities (Table 5.4). The number of comorbidities was positively correlated with MPQ severity (p<0.001) (Table 5.3, Figure 5.1), BPI severity, and interference scores (p<0.05) (Table 5.3). The most common comorbid condition was cardiovascular (54%), followed by endocrine which included osteoporosis (50%), and musculoskeletal disease (46%). Of the 26 patients, eight had diagnosed osteoporosis, 11 had diagnosed osteoarthritis, and 9 reported calf pain during the 6MWT.

Subjects with more pain had a higher number of pain locations and medications (Table 5.4). Consistent with the fact that all subjects had a diagnosis of COPD and the most prevalent comorbidity was cardiovascular disease (n=14), and respiratory and cardiac medications were the most common (n=70).

5.4 Discussion

Our study demonstrated that pain severity (assessed by the MPQ) was inversely related to 6MWT. People with more severe pain walked 25.6% less than those with moderate to no pain on the 6MWT. Those with severe pain also had significantly lower standing and
activity times, and a higher sedentary time as compared to those with less pain. In addition, BMI and comorbidities appear to influence pain. BMI and the number of comorbidities were related to pain severity and those with severe pain had 2 to 3 more comorbidities compared to those with lower levels of pain.

During the 6MWT, those with more pain walked 114 m less than those with less or no pain. Based on the normative values described by Bohannon (2007), our male participants walked 53 m, and females walked 149 m less than their age and gender predicted distances. These differences are considerably higher than the minimal important difference of 25 m for the 6MWT in people with COPD (Holland et al. 2010). Limitations of 6MWT in people with COPD have been attributed to COPD-related symptoms and comorbidities (Waatevik et al. 2012). Our results support the postulate that painful arthritis of the hips or knees might be another underlying cause of limited walk distance in addition to symptoms of fatigue and dyspnea. Osteoarthritis (OA), a degenerative joint disease is increasingly more common with aging. The prevalence of OA increases from 14% at the age of 50 to 58% at the age of 86 years (Kopec et al. 2007) and most commonly affects the hips, knees and hands (Felson et al. 2000). Pain, muscle weakness, and loss of function are primary clinical manifestations of OA. Degenerative arthritis may in part, contribute to pain and limited walk distance in people with COPD. Another potential cause of pain during activity might be the intermittent claudication of the calf muscles associated with the high prevalence of cardiovascular diseases in COPD.
Lower levels of physical activity were demonstrated in COPD patients who experience pain, as shown by shorter standing and active time, and sedentary time being approximately twice the active time. Similar mean differences in sitting, standing and active times have been reported when COPD patients were compared to healthy age- and gender-matched controls (Janaudis-Ferreira et al. 2006). Lower physical activity levels could be, in part, due to degenerative arthritis and osteoporosis that were reported by the significant proportion of our patients (31% and 42% respectively). Osteoporosis and its clinical sequale, including spinal compression fractures could provide another plausible explanation. Osteoporotic-related compression fractures of the spine can induce significant pain in standing and have been shown in people with COPD (Ferguson et al. 2009). Osteoporosis is more common in COPD than the general population with a prevalence ranging from 32% to 70% in people with COPD (Bolton et al. 2004; Ferguson et al. 2009) compared to 15% in the general population (Srivastava & Deal 2002). Osteoporosis-related vertebral deformity (spinal fractures) is more prevalent in COPD patients compared to controls (31% vs 18%) (Kjensli et al. 2009). Pain due to osteoporosis-related vertebral fractures is significant as shown by ratings of 6-7 out of 10 cm on a visual analogue scale (Blasco et al. 2012; Fahrleitner-Pammer 2011). Similar to COPD, physical inactivity is highly prevalent in people with OA (Dunlop et al. 2011; Farr et al. 2008). People with OA were reported to have an average of 608 min of no to very low activity and 21 min of moderate to vigorous activity by Dunlop et al. (2011), and 24 min/day of mild to moderate activity and 0.95 min/day of vigorous activity by another study (Farr et al. 2008). Furthermore, lower physical activity has been shown to be associated with severe pain in people with OA (Lee et al. 2013).
Thus, it is likely that OA of lower extremities and back and painful compression fractures of the spine may have contributed to decreased standing and active time in COPD patients with severe pain.

Of interest, although patients with more severe pain demonstrated significantly higher sedentary times, no significant between group differences were found for sitting and lying times. Our data indicates a mix of lying and sitting for sedentary time rather than longer lying times. The somewhat unexpected finding for some COPD patients could be explained by the dyspnea experienced by some COPD patients in lying. Some people with COPD might experience orthopnea when lying flat and as a consequence will find sitting to be a more comfortable position to relieve dyspnea while this might not be the case for others. Thus, the optimal rest position in people with COPD likely reflects their ability to relieve a composite of symptoms that might be unlike that reflected by people without chronic respiratory disease who might only have pain as a primary symptom.

Other pain-inducing activity limiting factors in COPD patients might be related to the specific medications and symptoms of deconditioning i.e. calf pain that was reported in 35% of our patients. It has been documented that some COPD specific medications, such as beta-2 agonists cause cramps in the calf muscles (O'Donnell et al. 2008) that might interfere with walking ability and activity duration in COPD patients. Furthermore, decreased physical activity and its related deconditioning effects in COPD (Wagner 2006) might contribute to the increased pain in COPD over time. According to the Vlaeyen's fear-avoidance model (Vlaeyen & Linton 2000), the vicious cycle of
deconditioning begins with an attempt to avoid pain by reducing daily physical activities. While avoiding activity may result in less pain over the short term, the reduction in activity may lead to more deconditioning, which then can lead to increased pain. The increase in pain then leads to more avoidance of activity.

We found a significant positive correlation between BMI and MPQ pain severity and BPI interference in COPD patients. This is consistent with data from a recent study that found a significantly higher mean BMI in people with COPD who experienced more pain as compared to those with no pain (Borge et al. 2011). Chronic pain is reported to be strongly associated with obesity in the elderly (McCarthy et al. 2009). Obesity (as measured by BMI) is known to be an important health issue in patients with COPD with a reported prevalence that ranges from 28% (Monteiro et al. 2012) to 54% (Eisner et al. 2007). Obesity is postulated to increase the prevalence of pain by increasing proinflammatory cytokines, and increasing the risk of osteoarthritis and low back pain (McCarthy et al. 2009). In a vicious cycle, pain might also increase the risk of obesity by reductions in physical activity or hormonal changes (McCarthy et al. 2009).

There was evidence of muscle weakness and fatigability in our subjects with an average of 90.5 N.m for the whole group versus the concentric torques in healthy subjects reported by Janaudis-Ferreira et al. (2005), i.e. 203 N.m for males and 179 N.m for women. Furthermore, the fact that the average torque reduction was 50% with only 34 repetitions, which is considerably greater than healthy controls, and consistent with other reports of COPD patients (Janaudis-Ferreira et al. 2005). Despite this clear
deterioration in muscle performance, we did not find significant correlations between maximal concentric torque and pain severity in patients with COPD. This is similar to the findings of Steultjens et al. (2001) who found no clear relationship between pain and muscle strength in 123 patients with hip and knee OA and that muscle strength only accounted for about 5% of the variance in pain levels. As muscle weakness has been well documented in COPD, one explanation might be related to the fact that rather than inhibition due to pain, other factors such as the systemic effects of the disease account for the major loss of muscle strength in COPD. These systemic effects include the prolonged inflammation, and changes in muscle metabolism and structure (fiber atrophy, fiber loss). Another reason might be related to the small sample size and variability amongst subjects in muscle strength, and fatiguability may have resulted in type II error. Furthermore, the fact that the fatigue index was not related to pain severity suggests that the distance travelled in the 6MWT might be influenced more by pain, pulmonary and cardiovascular factors than the muscle fatigue of the knee extensors.

**5.5 Conclusions**

Pain in people with COPD is associated with decreased exercise capacity and physical activity, and with obesity. This study suggests that evaluation of pain in addition to physical, social, psychological domains of health status should be considered in the evaluation and treatment plan of people with COPD.
Table 5.1 Subject characteristics (mean ± SD).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Subjects</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male (n=14)</td>
<td>Female (n=12)</td>
<td>All</td>
</tr>
<tr>
<td>Age (years)</td>
<td>72.6±10.6</td>
<td>67.8±6.9</td>
<td>70.4±9.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.5±4.4</td>
<td>26.8±6.3</td>
<td>26.4±5.3</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>48.4±15.4</td>
<td>47.7±17.0</td>
<td>48.9±15.8</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>0.61±0.16</td>
<td>0.59±0.17</td>
<td>0.60±0.16</td>
</tr>
</tbody>
</table>
Table 5.2 Pain, functional exercise capacity, physical activity health-related quality of life and muscle performance measures (mean ± SE).

<table>
<thead>
<tr>
<th>Category</th>
<th>Variable</th>
<th>Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain severity</td>
<td>MPQ</td>
<td>16.8 ± 3.1</td>
</tr>
<tr>
<td></td>
<td>BPI-S</td>
<td>27.3 ± 5.0</td>
</tr>
<tr>
<td>Interference</td>
<td>BPI-I</td>
<td>25.0 ± 4.9</td>
</tr>
<tr>
<td>Functional Exercise Capacity</td>
<td>6MWT % Predicted</td>
<td>82.7 ± 4.8</td>
</tr>
<tr>
<td>HRQoL</td>
<td>SF-36 PCS</td>
<td>35.7 ± 1.9</td>
</tr>
<tr>
<td></td>
<td>SF-36 MCS</td>
<td>48.3 ± 3.0</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>Step count</td>
<td>4588 ± 548</td>
</tr>
<tr>
<td></td>
<td>Standing time (min)</td>
<td>146.4 ± 12.9</td>
</tr>
<tr>
<td></td>
<td>Sedentary time (min)</td>
<td>486.7 ± 15.9</td>
</tr>
<tr>
<td></td>
<td>Active time (min)</td>
<td>219.9 ± 16.8</td>
</tr>
<tr>
<td>Muscle Performance</td>
<td>Fatigue Index</td>
<td>52.1 ± 2.7</td>
</tr>
<tr>
<td></td>
<td>CON $T_{max}$ (N.m)</td>
<td>90.5 ± 7.0</td>
</tr>
</tbody>
</table>

**Abbreviations:** MPQ: McGill Pain Questionnaire; BPI-S: BPI severity score; BPI-I: BPI interference score; 6MWT %P: Six minute walk distance test (percent predicted); PCS: SF-36 Physical Component Score; MCS: SF-36 Mental Component Score; CON $T_{max}$: Max concentric torque.
Table 5.3 Significant correlations between pain measures and 6MWT, quality of life measures, number of comorbidities, and BMI (p<0.05).

<table>
<thead>
<tr>
<th>Variable</th>
<th>MPQ</th>
<th>BPI-S</th>
<th>BPI-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWT % Predicted</td>
<td>-0.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>-0.43</td>
<td>-0.39</td>
<td>-0.40</td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td></td>
<td>-0.40</td>
<td>-0.59*</td>
</tr>
<tr>
<td>Number of comorbidities</td>
<td>0.70*</td>
<td>0.42</td>
<td>0.47</td>
</tr>
<tr>
<td>BMI</td>
<td>0.47*</td>
<td></td>
<td>0.50*</td>
</tr>
</tbody>
</table>

The table shows the r value for Spearman or Pearson correlations; all comparisons are significant at p<0.05 except for the values with asterisks that are significant at p<0.001.

**Abbreviations:** MPQ: McGill Pain Questionnaire; BPI-S: BPI severity score, BPI-I: BPI interference score; 6MWT: Six minute walk distance test (percent predicted); PSC: SF-36 Physical Component Score; MCS: SF-36 Mental Component Score; BMI: body mass index.
Table 5.4 Significant between group differences for 6MWT, physical activity measures, BMI, number of comorbidities, pain locations and medications, and quality of life measures.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>MPQ</th>
<th>BPI Severity</th>
<th>BPI Interference</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWT (% Predicted)</td>
<td>-25.6 ±11.3**</td>
<td>-10.9 ± 11.4</td>
<td>-19.1 ± 11.8</td>
</tr>
<tr>
<td>Sedentary time (min)</td>
<td>56.4 ± 40.9*</td>
<td>89.9 ± 36.7*</td>
<td>39.3 ± 41.2</td>
</tr>
<tr>
<td>Standing time (min)</td>
<td>-4.4 ± 33.5</td>
<td>-78.3 ±19.2**</td>
<td>-7.9 ± 33.5</td>
</tr>
<tr>
<td>Active time (min)</td>
<td>-4.8 ± 40.5</td>
<td>-99.1 ± 35.3**</td>
<td>-19.3 ± 43.3</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>3.1 ± 2.6</td>
<td>4.3 ± 2.4</td>
<td>5.7 ± 2.4*</td>
</tr>
<tr>
<td>Number of comorbidities</td>
<td>3.0 ± 0.6†</td>
<td>2.0 ± 1.5**</td>
<td>2.2 ± 0.7†</td>
</tr>
<tr>
<td>Number of pain locations</td>
<td>6.0 ± 1.3†</td>
<td>3.6 ± 1.5**</td>
<td>3.5 ± 1.6*</td>
</tr>
<tr>
<td>Number of medications</td>
<td>3.3 ± 1.9*</td>
<td>2.1 ± 1.8</td>
<td>4.1 ± 1.8*</td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>-11.9 ± 4.3**</td>
<td>-4.7 ± 4.6</td>
<td>-13.2 ± 4.2†</td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>-6.8 ± 7.7</td>
<td>-14.7 ± 6.6*</td>
<td>-20.4 ± 6.6†</td>
</tr>
</tbody>
</table>

Groups were defined as those with severe pain vs those with minimal to moderate pain based on the maximum scores achieved on MPQ and BPI severity, and BPI interference measures. Data are reported as: mean ± SE. * significance level of p<0.05, ** significance level of p< 0.01, † significance level of p< 0.001.

Abbreviations: MPQ: McGill Pain Questionnaire; BPI: Brief Pain Inventory; BMI: body mass index; 6MWT: Six minute walk distance test (percent predicted); PSC: SF-36 Physical Component Score; MCS: SF-36 Mental Component Score.
Figure 5.1 Significant correlations between MPQ and 6MWT ($r = -0.41$, $p< 0.005$), BMI ($r = 0.70$, $p< 0.001$), and number of comorbidities ($r = 0.47$, $p<0.001$).
Chapter Six: Summary and Future Directions

6.1 Summary

Many factors have been identified as possible contributors to reductions in physical performance in patients with COPD. Figure 1.1 summarizes both the environmental and host factors that may limit physical performance in people with COPD.

Lower extremity fatigue alone or in combination with dyspnea have been reported to be major limiting symptoms during exercise tests in 74% of COPD patients, and both are considered to limit physical activity of COPD patients (ATS/ERS Statement on pulmonary rehabilitation 2006; O’Donnell et al. 1997). Because of dyspnea, people with COPD often reduce their level of physical activity and adopt sedentary lifestyles, resulting in deconditioning of the cardiovascular system and skeletal muscle dysfunction. In addition, COPD, as a chronic inflammatory disease, involves several multi-systemic effects that result in various conditions, such as peripheral muscle dysfunction, decreased exercise tolerance, right heart failure and other comorbidities (Global Initiative for Chronic Obstructive Lung Disease 2011; O’Donnell et al. 2008). Recent reports suggest that people with COPD also experience significant pain that can contribute to the reduced activity participation and reduced health related quality of life in this patient group (Hajiro et al. 1999; Lohne et al. 2010; Lynn et al. 2000; Miller et al. 2008). A better understanding of the factors limiting physical performance in COPD will help in designing the most effective prescriptions for exercise and activity participation.
Based on the components of the International Classification of Functioning, Disability, and Health (ICF), i.e. body structure, function, and activity limitation (Stucki 2005, Figure 1.1), this thesis addressed some of the gaps in the literature that affect physical performance in people with COPD. First, it provided a detailed examination of the thigh muscles mass that was associated with the body structure component of ICF (Chapter 2). Second, it examined the severity of pain and its interference with daily activities (Chapter 3) that is related to the activity limitation component of ICF. Third, it described the comorbidities, pain medications and pain treatments in COPD that were associated with the activity limitation component of ICF (Chapter 4). Fourth, it examined the associations of pain with muscle function and physical activity in people with COPD (Chapter 5) that are associated with the function and activity limitation component of ICF respectively. The sample of people with COPD consisted of patients with moderate to severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, and the sample of healthy controls were selected from the general population with no respiratory, cardiovascular, neurological or musculoskeletal conditions that interfere with independent ambulation. Muscle mass was examined through the estimation of muscle atrophy, and shape and size changes in people with COPD as compared to healthy controls (Chapter 2). Muscle function was examined through the measurement of concentric torque, and fatigue index during fatiguing concentric contractions of knee extensors (Chapter 5). Physical activity was measured using 3D accelerometry and self-reported physical activity questionnaire (CHAMPS Physical activity Questionnaire) (Chapters 3 & 5). Pain was assessed using the McGill Pain Questionnaire and Brief Pain Inventory (Chapters 3-5). Functional performance
was tested using a six-minute walk distance test (6MWT) (Chapter 5).

The following sections highlight the main conclusions from each study that comprised the thesis, and discuss the strengths and limitations of each studies and directions for future research.

6.1.1 MRI-based 3D shape analysis of thigh muscles: people with COPD versus healthy older adults (Chapter Two)

MRI is a non-ionizing, non-invasive tool that provides high-resolution images, and has been used extensively in the study of muscle structure because it facilitates the distinction between muscle, fat and connective tissues (Ross 2003). In addition, MRI is used in the study of individual muscles so that shape and size of specific muscles can be investigated.

To address aspects related to the “body structure” component of ICF (Figure 1.1), we used a new method to provide a more precise estimate of muscle volume and shape. We studied more detailed size measures by comparing global and regional three-dimensional (3D) shape and size measurements of individual thigh muscles between COPD subjects and healthy controls. Participants underwent MRI by taking 80 to 100 images along the length of the thigh. Individual knee flexor and extensors muscles (n=8) were outlined manually in the dominant limb by drawing contours along the muscle boundaries in all images. Using Matlab and ITK-SNAP softwares, these contours were stacked to provide a 3D image of the muscle shape. Several mathematical algorithms
were applied to thigh muscle shapes to determine differences in size and shape between healthy people and people with COPD (Ward et al. 2007). Shape descriptors provided information regarding the center and spatial distribution of mass, circular versus oval versus stellate shapes, surface area and volume of the muscle. Our study revealed that among eight thigh muscles, rectus femoris, semimembranosus, vastus lateralis and vastus medialis showed the most shape discrepancies in people with COPD, supporting the fact that the disease might affect some muscles and regions within a muscle more than other thigh muscles.

This study suggests that CSA and muscle volume might not adequately demonstrate the distribution of atrophy among thigh muscles in people with chronic disorders such as COPD. More comprehensive measures, such as shape descriptors, are required for a more complete description of how the underlying pathologies affect the loss of muscle mass in these conditions.

6.1.1.1 Strengths and limitations

This study reported a more comprehensive non-invasive estimate of muscle size and shape of the thigh muscles in people with COPD using an advanced analysis of the imaging method, magnetic resonance imaging (MRI). As described earlier in the chapter, MRI is a non-invasive, non-radiating imaging technique that allows for the differentiation of tissues based on brightness or signal intensity. MRI can provide multiple slices along the length of the muscle that represent a more precise estimate of muscle size, rather than a single cross-sectional area (CSA). We included all CSAs of
thigh muscles and individual muscles separately (rather than muscle groups) for the estimation of muscle volume while previous studies used a single CSA (Bernard et al. 1998; Seymour et al. 2009) at the mid-thigh or the CSA of a number of slices (Mathur et al. 2008) to estimate thigh muscle mass, which may not accurately reflect thigh muscle mass. Furthermore, previous studies reported on muscle groups (Bernard et al. 1998; Mathur et al. 2008) rather than individual thigh muscles that will not reveal the regional muscle atrophy and shape changes.

Although the small sample size is a limitation of this study, using our novel strategy, the results of this study provide further impetus to investigate the etiology of regional muscle atrophy and shape abnormalities in COPD. Although we excluded the intermuscular fat by separate delineation of individual thigh muscles, we were unable to remove the volume of intramuscular fat within the epimysium from the total cross sectional area of the muscle. Therefore, volumes of the knee flexor and extensor muscles included intramuscular fat, although this was likely a small proportion of the total muscle volume. Further studies may employ more advanced techniques to estimate the fat-free muscle volume and size because muscle quality in addition to muscle quantity can influence force production.

6.1.1.2 Future directions

Future work, using a larger sample size and parallel measurements of shape descriptors, regional muscle biopsy, angle of pennation, strength, and muscle fat infiltration, will be necessary to elucidate the mechanisms that govern not only the
muscle atrophy characteristic of COPD but also the increased susceptibility of the muscles of the anterior thigh to atrophy-related anatomic anomalies.

Future work is also directed by the results given by the 3D moment invariant measures, which showed significant differences between the healthy and COPD groups. These measures could potentially be useful to the eventual computer-aided diagnosis of muscle abnormalities consequent to COPD or to other disorders that affect muscle.

6.1.2 Pain in people with COPD (Chapters 3 & 4)

The findings presented in Chapters 3 and 4 provide support for the early assessment of pain and comorbid conditions with associated pain symptoms in patients with COPD. Using a cross-sectional study design, and based on the “activity limitation” component of ICF, we investigated the severity of pain, pain interference with daily life, physical activity, and health related quality of life (HRQoL) in people with COPD as compared to age- and gender-matched controls (Chapter 3). Healthy and COPD groups, matched for age and gender, completed a package of questionnaires that included: a sheet with instructions for completion, a form to record medications and chronic conditions, the Medical Outcomes Trust – Short Form 36 (SF-36), the short form of the McGill Pain Questionnaire (MPQ), the short form of the Brief Pain Inventory (BPI), the CHAMPS Physical Activity Scale for the Elderly, and the Tampa Scale for Kinesiophobia (TSK). The results showed that more than 50% of participants with COPD experience moderate to severe pain. The severity of pain in people with COPD was about 2.5 times greater than healthy adults, and pain interfered with daily activities 3.7 times more in
COPD patients than in healthy people. The number of comorbidities was an independent predictor of pain severity in COPD.

In order to describe the comorbidities and how they relate to pain, we explored the number and type of comorbidities, pain locations, and pain medications and treatments in COPD patients who experienced pain (Chapter 4). Chapter 4 reports on a second analysis of the survey data (Chapter 3) that included a larger sample of COPD patients with pain. The larger sample for this study was obtained by including the patients that were primarily excluded from the survey (Chapter 3) when groups were matched for age and gender. The results revealed that pain was prevalent in 81% of COPD patients, with 96% of patients having one or more comorbid conditions, and 73% reporting moderate to very severe pain interference with daily activities. Pain interfered more so with general activity, walking ability, sleep, and normal work than mood, enjoyment of life, relations with others. We found that the number of comorbidities, were associated with pain severity and interference; the most common comorbidities were cardiovascular followed by musculoskeletal disease, and the most common locations for pain were shoulders, neck and trunk areas followed by the lower extremities. We also found that among COPD patients who had pain, those with musculoskeletal and endocrine diseases had greater pain compared to those without musculoskeletal disease.

The findings of this study suggest that the pain experienced in people with COPD is of chronic nature. Firstly, we found that the number of comorbidities can predict pain severity in COPD and many comorbidities have been shown to manifest with chronic
pain symptoms (Boersma & Linton 2006). Secondly, patients with COPD also showed greater pain-related fear that has been similarly shown in chronic pain patients as compared to healthy people (Boersma & Linton 2006). Fear and anxiety can also lead to the avoidance of physical activity that can contribute to chronic pain and increased disability and (Crombez et al. 1999; Vlaeyen & Linton 2000). Furthermore, we found that COPD patients with pain are under-treated pharmacologically and that only a very small percentage of the patients receive non-medication treatments, such as physiotherapy, to relieve their pain.

6.1.2.1 Strengths and limitations

We used two pain-specific measurement tools i.e. the Brief Pain Inventory and McGill Pain Questionnaire to examine pain in our sample of COPD patients. No previous study has used both of these valid and reliable pain measurement tools in people with COPD, although these questionnaires have been used in people with other chronic conditions and older adults (Briggs 1996; Burchiel et al. 1996; Eija et al. 1996; Gagliese & Melzack 1997; Katz & Melzack 1999; Tesfaye et al. 1996).

The primary limitation of these studies (Chapters 3 and 4) is the use of self-report questionnaires. Although self-report is a valid method to evaluate pain and the participant’s perception is essential to evaluate pain, other constructs, such as activities, comorbidities and medications can be underestimated or overestimated using this method of inquiry (Dillman 2000). In addition, the study sample also came from a small geographical location. The experience and underlying causes of pain may vary in
different cultures because of associated variations in the prevalence of disorders causing pain and pain perceptions. Furthermore, this study did not examine the effects of dyspnea, a major symptom of people with COPD nor did it ask about the patients regarding the underlying cause of pain.

6.1.2.2 Future directions

Future studies need to investigate the relationship between dyspnea and pain (commonalities and differences), as the perception of dyspnea shares many characteristics with the perception of pain. Associations between smoking and pain in COPD need to be explored. Pain has been shown to be associated with smoking in the general population (Goldberg et al. 2000; Leboeuf-Yde C 1999; Shiri et al. 2010), with the former smokers at a lower prevalence of low back pain compared to the current smokers (Shiri et al. 2010). The etiology is unknown, yet cigarette smoking has been shown to be a cause of low back pain, only if it precedes low back pain onset (Shiri et al. 2010). As low back pain is a common symptom in COPD, future studies need to explore if COPD patients who are currently smoking experience more pain than former smokers. Future studies also need to investigate the underlying physiological and/or pathological mechanisms that contribute to the increased pain and comorbid conditions in COPD. Based on the biopsychosocial model, qualitative studies are required to focus on psychological, social, and economic factors that interact with the physical pathology to modulate a patient’s experience of pain and quality of life. Such a multifaceted approach will provide much needed understanding of pain as perceived by people with COPD.
6.1.3 Pain and physical performance in people with COPD (Chapter 5)

Using a cross-sectional correlational study design and based on the “function” and “activity limitation” components of ICF, this study examined the relationships between pain and measures of physical activity levels assessed by accelerometry, walking distance (6MWT), and muscle performance (concentric torque, fatigue index) in people with COPD. Pain was assessed using the McGill Pain Questionnaire and Brief Pain Inventory. Daily activities were monitored by a 3D accelerometer for 2 days (Pitta et al. 2005). Maximal concentric torque of the knee extensors was tested using an isokinetic dynamometer. Fatiguability of knee extensors from repetitive maximal concentric contractions was defined as a percent decrease in peak isokinetic torque as described by Fujita et al. (2007). Functional exercise capacity was examined by the 6MWT.

The novel findings of this study included: 1) an inverse relationship was found between pain severity and exercise functional capacity (as measured by 6MWT), and people with more severe pain walked 25% less than those with moderate to no pain during the 6MWT; 2) compared with those with minor or no pain, COPD patients with more pain also had significantly lower physical activity levels during a 2-day evaluation using acceleometry as shown by lower standing and activity times, and had a higher sedentary time; 3) the BMI and number of comorbidities had strong positive relationships with pain severity, and patients with severe pain reported 2 to 3 more comorbidities compared to those with minor or no pain.
We did not find significant correlations between pain severity and maximum concentric torque and the fatigue index of the knee extensors. These findings were inconsistent with our primary hypotheses that people with more pain would demonstrate lower concentric torque and more fatigability of quadriceps muscles. Further research is required to investigate the relationships between pain and muscle strength and fatigue using a bigger sample size.

### 6.1.3.1 Strengths and limitations

The major limitation of this study was the relatively small sample size, especially when the group was divided in two groups. Our sample was also recruited from a small geographical location, which might limit the generalizability of our findings. The study did not consider the social and psychological aspects of pain as a multidimensional experience that might affect how each patient responds to various items in the questionnaires. Finally, muscle testing was limited to the knee extensors.

### 6.1.3.2 Future directions

Future research needs to investigate the relationship between pain and muscle imbalance by testing several muscle groups around the joints in common painful areas, such as shoulder, neck, trunk, and respiratory muscles. Further study is also required to investigate the potential causes for pain, the pattern of change in pain during time, and effects of different types of training (aerobic, strength and endurance) on pain intensity and interference in patients with COPD.
6.2 Contributions to the Field of Study

Based on the components of the International Classification of Functioning, Disability and Health (i.e. body structure, body function, and activity limitation), this thesis addressed several factors that might lead to limitations in physical performance and deconditioning in people with COPD (Figure 1.1). The novel findings of this thesis include: 1) Skeletal muscle atrophy might be non-uniformly distributed in chronic conditions such as COPD and atrophy might target specific individual muscles and specific regions of a muscle. These findings report on the gaps in the literature related to the “structure” component of the ICF (Figure 1.1); 2) Pain is significant in COPD and it interferes with physical activities and quality of life. These findings report on aspects related to the “activity limitation” component of the ICF (Figure 1.1); 3) Comorbid conditions contribute to pain severity in patients with COPD. COPD patients experiencing pain are likely under-treated for pain relief through the use of medications and physiotherapy treatment. These findings report on the factors associated with the “activity limitation” component of the ICF (Figure 1.1); 4) In addition to fatigue and dyspnea, pain can be considered as an activity limiting factor in COPD. This finding addresses aspects related to the “activity limitation” and “function” components of the ICF (Figure 1.1).

6.4 Conclusions

In summary, this thesis addressed some of the factors that affect physical performance in people with COPD. Firstly, it provided evidence that a more precise evaluation of muscle mass is required to better understand how much loss of muscle mass or
changes in muscle structure contribute to muscle weakness in patients with COPD. Secondly, it provided evidence that pain is significant in people with COPD and is likely a major limiting factor for physical activities in this patient group. The findings of this thesis may have implications for the early evaluation and treatment of pain and comorbidities with associated pain symptoms in people with COPD aimed at improving physical, and psychological, and social health status in people with COPD.
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Appendices

Appendix A: Subject Screening Forms

A-1 Telephone screening form for people with COPD (Chapters 2-4)

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you been taking corticosteroids over the last 6 months regularly?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you had any acute exacerbations over the last 6 months?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you ever had any heart problems?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you have or have you ever had any neurological problems (Parkinson’s, Stroke)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you have a pacemaker?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you have any conditions that interfere with independent ambulation?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you been regularly involved in a supervised exercise program over the last 6 months?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you taking any pain medication?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you require supplemental oxygen?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Name: ____________ Date: ____________

Telephone number: ____________

E-mail: ____________

Age: ____________

Height: ____________ Weight: ____________
A-2 Telephone screening form for healthy subjects (Chapters 2-5)

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you have heart or lung disease?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you ever had any heart problems?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you have a pacemaker?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you have or have you ever had any neurological problems (Parkinson’s, Stroke)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you have any conditions that interfere with your independent ambulation?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you taking any pain medications?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you been involved in a supervised exercise program over the last 6 months?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is there anything else that restricts your capacity for exercise?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Name:                                                                                     |     |
| Date:                                                                                      |     |
| Telephone number:                                                                          |     |
| E-mail:                                                                                    |     |
| Age:                                                                                       |     |
| Height:  Weight:                                                                          |     |
A-3 AHA/ACSM screening questionnaire (Chapter 5)

Assess your health status by marking all TRUE statements

**History**
You have had:
___ a heart attack
___ heart surgery
___ cardiac catheterization
___ coronary angioplasty (PTCA)
___ pacemaker/implantable cardiac defibrillator/rhythm disturbance
___ heart valve disease
___ heart failure
___ heart transplantation
___ congenital heart disease

**Symptoms**
___ You experience chest discomfort with exertion
___ You experience unreasonable breathlessness
___ You experience dizziness, fainting, or blackouts
___ You take heart medications

**Other health issues**
___ You have diabetes
___ You have asthma or other lung disease
___ You have burning or cramping sensation in your lower legs when walking short distances
___ You have musculoskeletal problems that limit your physical activity
___ You have concerns about the safety of exercise
___ You take prescription medication(s)
___ You are pregnant

**Cardiovascular risk factors**
___ You are a man older than 45 years
___ You are a woman older than 55 years, have had a hysterectomy, or are postmenopausal
___ You smoke, or quit smoking within the previous 6 months
___ Your blood pressure is >140/90 mm Hg
___ You do not know your blood pressure
___ You take blood pressure medication
___ Your blood cholesterol level is > 200 mg/dL
___ You do not know your cholesterol level
___ You have a close blood relative who had a heart attack or heart surgery before age 55 (father or brother) or age 65 (mother or sister)
___ You are physically inactive (i.e., you get <30 minutes of physical activity on at least 3 days per week)
___ You are > 20 pounds overweight

___ None of the above
Physical Signs Suggestive of Cardiovascular, Respiratory or Metabolic Disease

Shortness of breath at rest, with mild exertion, while lying flat or at night

Ankle edema - bilaterally or unilaterally. May be indicative of heart failure, venous insufficiency, lymphatic blockage or thrombosis

Palpitation or tachycardia
Intermittent claudication – pain that occurs with exertion
Unusual fatigue or shortness of breath – with usual activities

Interpretation

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

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

High risk (one or more symptoms of respiratory, cardiovascular, metabolic disease or known to have one of these conditions): can do no testing without physician presence; can enter no program without physician referral.
Appendix B: Instructions and checklist (Chapters 3 and 4)

Dear .............

This package contains the following items:

- A sheet of instructions and a checklist for completion (this sheet)
- A subject consent form for you to review and complete in order to proceed with participation in the study
- The Outcomes Study Short Form-36 (SF-36)
- The Clinical evaluation form to record medications and chronic conditions
- The CHAMPS physical activity questionnaire (CHAMPS)
- The Modified TSK
- The SF-MPQ
- The Brief Pain Inventory- Short form (BPI-SF)

*Please be sure to complete the questionnaires in the order listed above beginning with the Outcomes Study Short Form-36 (SF-36).

How to Proceed?

First, please read the consent form. If you decide to participate in the study, sign, date, and write your name on the consent form, place it back in smallest pre-paid, pre-addressed envelope and mail it back to us. Then, complete all of the forms (forms, questionnaires and scales) in the order
Appendix B: Instructions and checklist ( Chapters 3 and 4)-continued

specified in the list above. Please note that the forms are double sided, so please ensure that you complete both sides. It is important to know that these must be returned to us in the bigger white envelope, separate from the consent form that is to be returned to us in the smallest envelope.

Take your time when completing the forms; there is no need to rush. We do appreciate if you can mail the package back within two weeks after you receive it. Follow the instructions carefully and do not hesitate to give us a call at any time if you have any concerns, questions or uncertainties, we will be happy to help you.

Your response is very important to us. Please make sure that ALL of the questions have been answered. However, it is ok for you to choose not to answer any questions that you feel uncomfortable about. Please write clearly; this helps us understand your responses better. Please ensure that for multiple choice questions, you only make one selection. Then complete the check list provided at the bottom of this sheet to confirm that you have done everything properly. Place the forms back in the postage-paid, pre-addressed envelope provided and mail them back to us. THANK YOU for taking the time to participate in this study.
Appendix B: Instructions and checklist (Chapters 3 and 4)-continued

CHECK LIST

I have read the consent form and taken the time to have all my questions answered.  

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

I have completed the following forms and questionnaires:

The Outcomes Study Short Form-36 (SF-36)

The Clinical evaluation form to record medications and chronic conditions

The CHAMPS physical activity questionnaire

The Modified TSK

The SF-MPQ

The Brief Pain Inventory- Short form (BPI-SF)

I have returned all the above documents using the pre paid envelopes provided.
Appendix C: Forms and questionnaires

C-1 Outcomes Study Short Form-36 (Chapters 3-5)

CODE: __________
Date: __________

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:

   Excellent ▼
   □ 1
   Very good ▼
   □ 2
   Good ▼
   □ 3
   Fair ▼
   □ 4
   Poor ▼
   □ 5

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

   Much better now than one year ago ▼
   □ 1
   Somewhat better now than one year ago ▼
   □ 2
   About the same as one year ago ▼
   □ 3
   Somewhat worse now than one year ago ▼
   □ 4
   Much worse now than one year ago ▼
   □ 5
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>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
</table>

a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports ▼ ▼ ▼

b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf ▼ ▼ ▼

c. Lifting or carrying groceries ▼ ▼ ▼

d. Climbing **several** flights of stairs ▼ ▼ ▼

e. Climbing **one** flight of stairs ▼ ▼ ▼

f. Bending, kneeling, or stooping ▼ ▼ ▼

g. Walking **more than a kilometre** ▼ ▼ ▼

h. Walking **several hundred metres** ▼ ▼ ▼

i. Walking **one hundred metres** ▼ ▼ ▼

j. Bathing or dressing yourself ▼ ▼ ▼
### 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>

- 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. **Did work or other activities less carefully than usual**: 1 □ 2 □ 3 □ 4 □ 5 □
C-1 Outcomes Study Short Form-36 (Chapters 3-5)-continued

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>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>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>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</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>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</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


C-1 Outcomes Study Short Form-36 (Chapters 3-5)-continued

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>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>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

a. I seem to get sick a little easier than other people ............. □ 1 .......... □ 2 .......... □ 3 .......... □ 4 .......... □ 5

b. I am as healthy as anybody I know ................................ □ 1 .......... □ 2 .......... □ 3 .......... □ 4 .......... □ 5

c. I expect my health to get worse ........................................ □ 1 .......... □ 2 .......... □ 3 .......... □ 4 .......... □ 5

d. My health is excellent .................................................. □ 1 .......... □ 2 .......... □ 3 .......... □ 4 .......... □ 5

Thank you for completing these questions!
C-2 Record of medication and comorbidities (Chapters 3-5)

Date of birth (yyyy/mm/day): .................................. Subject’s code: __________

Height: ........... Weight: ........... Age: ............

Please check √ all medical conditions that you have been diagnosed with and the approximate date of diagnosis.

<table>
<thead>
<tr>
<th>Medical Condition of diagnosis</th>
<th>Date of diagnosis</th>
<th>Medical Condition</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Myocardial infarction</td>
<td></td>
<td>☐ Diabetes</td>
<td></td>
</tr>
<tr>
<td>☐ Angina (pain in chest or heart)</td>
<td></td>
<td>☐ Thyroid disease</td>
<td></td>
</tr>
<tr>
<td>☐ Ischemic attack</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Congestive heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Circulatory disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Hyperlipidemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Peripheral artery disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Peripheral vascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Faintness, lightheadedness, or dizziness by changing position</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ High blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Low blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal disease</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>☐ Osteoarthritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Rheumatoid arthritis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>☐ Broken bones (please specify):________</td>
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<tr>
<td><strong>Endocrine disease</strong></td>
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<tr>
<td>☐ Osteoporosis</td>
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<tr>
<td><strong>Neurological disease</strong></td>
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<tr>
<td>☐ Polyneuropathy ______________</td>
<td></td>
<td>☐ Parkinson ______________</td>
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<tr>
<td></td>
<td></td>
<td>☐ Stroke ______________</td>
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<tr>
<td><strong>Mood</strong></td>
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<tr>
<td>☐ Depression ______________</td>
<td></td>
<td>☐ Anxiety ______________</td>
<td></td>
</tr>
<tr>
<td><strong>Digestive disease</strong></td>
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<tr>
<td>☐ Gastroesophageal reflux ______</td>
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<tr>
<td><strong>Immune disease</strong></td>
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<tr>
<td>☐ HIV ______________________</td>
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<td></td>
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<tr>
<td><strong>Cancer</strong> – Name Type</td>
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<tr>
<td><strong>Eye disease</strong></td>
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<tr>
<td>☐ Glaucoma ______________</td>
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<td></td>
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<tr>
<td><strong>Renal disease</strong></td>
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<td></td>
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<tr>
<td>☐ Unintentional urine leakage_______</td>
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</tbody>
</table>

Do you have asthma, emphysema, chronic bronchitis, shortness of breath? If yes, please list conditions:

If you have any other major health problems not listed above, please describe and name the conditions:

__________________________________________________________________________
C-2 Record of medication and comorbidities (Chapters 3-5)-continued

Please list all the medications that you are currently taking: including the dose, the frequency and why you are taking this medication. Please include also when you started to use it. See example provided. You may also attach a copy of your pharmacy or Shoppers list of medications. See example provided in gray.

<table>
<thead>
<tr>
<th>NAME</th>
<th>DOSE</th>
<th>FREQUENCY</th>
<th>START DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>20 mg</td>
<td>Twice a day</td>
<td>July, 2007</td>
</tr>
</tbody>
</table>
C-3 CHAMPS activities questionnaire for older adults (Chapter 3)

Subject’s code: ........

This questionnaire is about activities that you may have done in the past 2 weeks. The questions on the following pages are similar to the example shown below.

INSTRUCTIONS

If you DID the activity in the past 2 weeks:

Step #1 Check the YES box.
Step #2 Think about how many TIMES a week you usually did it, and write your response in the space provided.
Step #3 Circle how many TOTAL HOURS in a typical week you did the activity.

Here is an example of how Mrs. Jones would answer question #1: Mrs. Jones usually visits her friends Maria and Olga twice a week. She usually spends one hour on Monday with Maria and two hours on Wednesday with Olga. Therefore, the total hours a week that she visits with friends is 3 hours a week.

<table>
<thead>
<tr>
<th>In a typical week during the past 2 weeks, did you…</th>
<th>How many TOTAL hours a week did you usually do it?</th>
<th>Less than 1 hour</th>
<th>1-2½ hours</th>
<th>3-4½ hours</th>
<th>5-6½ hours</th>
<th>7-8½ hours</th>
<th>9 or more hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Visit with friends or family (other than those you live with)?</td>
<td>How many TIMES a week?</td>
<td>YES</td>
<td>2</td>
<td>LESS THAN 1 HOUR</td>
<td>1-2½ HOURS</td>
<td>3-4½ HOURS</td>
<td>5-6½ HOURS</td>
</tr>
<tr>
<td>NO</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

If you DID NOT do the activity:

- Check the NO box and move to the next question
<table>
<thead>
<tr>
<th>In a typical week during the past 2 weeks, did you</th>
<th>C-3 CHAMPS activities questionnaire for older adults (Chapter 3)-continued</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Visit with friends or family (other than those you live with)? □ YES How many TIMES a week? → □ NO</td>
<td>How many TOTAL hours a week did you usually do it?</td>
</tr>
<tr>
<td>2. Go to the senior center? □ YES How many TIMES a week? → □ NO</td>
<td>How many TOTAL hours a week did you usually do it?</td>
</tr>
<tr>
<td>3. Do volunteer work? □ YES How many TIMES a week? → □ NO</td>
<td>How many TOTAL hours a week did you usually do it?</td>
</tr>
<tr>
<td>4. Attend church or take part in church activities? □ YES How many TIMES a week? → □ NO</td>
<td>How many TOTAL hours a week did you usually do it?</td>
</tr>
<tr>
<td>5. Attend other club or group meetings? □ YES How many TIMES a week? → □ NO</td>
<td>How many TOTAL hours a week did you usually do it?</td>
</tr>
<tr>
<td>6. Use a computer? □ YES How many TIMES a week? → □ NO</td>
<td>How many TOTAL hours a week did you usually do it?</td>
</tr>
<tr>
<td>7. Dance (such as square, folk, line, ballroom) (do not count aerobic dance here)? □ YES How many TIMES a week? → □ NO</td>
<td>How many TOTAL hours a week did you usually do it?</td>
</tr>
<tr>
<td>8. Do woodworking, needlework, drawing, or other arts or crafts? □ YES How many TIMES a week? → □ NO</td>
<td>How many TOTAL hours a week did you usually do it?</td>
</tr>
<tr>
<td>9. Play golf, carrying or pulling your equipment (count walking time only)? □ YES How many TIMES a week? → □ NO</td>
<td>How many TOTAL hours a week did you usually do it?</td>
</tr>
<tr>
<td>Question</td>
<td>Yes/No Options</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>10. Play golf, riding a cart (count walking time only)?</td>
<td>☐ YES How many TIMES a week? → □ NO</td>
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<td>11. Attend a concert, movie, lecture, or sport event?</td>
<td>☐ YES How many TIMES a week? → □ NO</td>
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<tr>
<td>12. Play cards, bingo, or board games with other people?</td>
<td>☐ YES How many TIMES a week? → □ NO</td>
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<td>13. Shoot pool or billiards?</td>
<td>☐ YES How many TIMES a week? → □ NO</td>
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<tr>
<td>14. Play singles tennis (do not count doubles)?</td>
<td>☐ YES How many TIMES a week? → □ NO</td>
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<tr>
<td>15. Play doubles tennis (do not count singles)?</td>
<td>☐ YES How many TIMES a week? → □ NO</td>
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<tr>
<td>16. Skate (ice, roller, in-line)?</td>
<td>☐ YES How many TIMES a week? → □ NO</td>
</tr>
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<tr>
<td>17. Play a musical instrument?</td>
<td>☐ YES How many TIMES a week? → □ NO</td>
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<tr>
<td>18. Read?</td>
<td>☐ YES How many TIMES a week? → □ NO</td>
</tr>
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</tr>
<tr>
<td>19. Do heavy work around the house (such as washing windows, cleaning gutters)?</td>
<td>☐ YES How many TIMES a week? → □ NO</td>
</tr>
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</tr>
<tr>
<td>In a typical week during the past 2 weeks, did you</td>
<td>C-3 CHAMPS activities questionnaire for older adults (Chapter 3)-continued</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>-----------------------------------------------------------------------</td>
</tr>
<tr>
<td>20. Do light work around the house (such as sweeping or vacuuming)?</td>
<td>How many TOTAL hours a week did you usually do it? Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours</td>
</tr>
<tr>
<td>□ YES How many TIMES a week? ➔</td>
<td>□ NO</td>
</tr>
<tr>
<td>21. Do heavy gardening (such as spading, raking)?</td>
<td>How many TOTAL hours a week did you usually do it? Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours</td>
</tr>
<tr>
<td>□ YES How many TIMES a week? ➔</td>
<td>□ NO</td>
</tr>
<tr>
<td>22. Do light gardening (such as watering plants)?</td>
<td>How many TOTAL hours a week did you usually do it? Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours</td>
</tr>
<tr>
<td>□ YES How many TIMES a week? ➔</td>
<td>□ NO</td>
</tr>
<tr>
<td>23. Work on your car, truck, lawn mower, or other machinery?</td>
<td>How many TOTAL hours a week did you usually do it? Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours</td>
</tr>
<tr>
<td>□ YES How many TIMES a week? ➔</td>
<td>□ NO</td>
</tr>
</tbody>
</table>

**Please note: For the following questions about running and walking, include use of a treadmill.**

| 24. Jog or run? | How many TOTAL hours a week did you usually do it? Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours |
| □ YES How many TIMES a week? ➔ | □ NO |
| 25. Walk uphill or hike uphill (count only uphill part)? | How many TOTAL hours a week did you usually do it? Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours |
| □ YES How many TIMES a week? ➔ | □ NO |
| 26. Walk fast or briskly for exercise (do not count walking leisurely or uphill)? | How many TOTAL hours a week did you usually do it? Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours |
| □ YES How many TIMES a week? ➔ | □ NO |
| 27. Walk to do errands (such as to/from a store or to take children to school {count walk time only})? | How many TOTAL hours a week did you usually do it? Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours |
| □ YES How many TIMES a week? ➔ | □ NO |
### C-3 CHAMPS activities questionnaire for older adults (Chapter 3)-continued

<table>
<thead>
<tr>
<th>In a typical week during the past 2 weeks, did you</th>
<th>C-3 CHAMPS activities questionnaire for older adults (Chapter 3)-continued</th>
</tr>
</thead>
<tbody>
<tr>
<td>28. Walk leisurely for exercise or pleasure?</td>
<td>□ YES  How many TIMES a week?  ➔  How many TOTAL hours a week did you usually do it?  ➔  Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours</td>
</tr>
<tr>
<td>□ NO</td>
<td></td>
</tr>
<tr>
<td>29. Ride a bicycle or stationary cycle?</td>
<td>□ YES  How many TIMES a week?  ➔  How many TOTAL hours a week did you usually do it?  ➔  Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours</td>
</tr>
<tr>
<td>□ NO</td>
<td></td>
</tr>
<tr>
<td>30. Do other aerobic machines such as rowing, or step machines (do not count treadmill or stationary cycle)?</td>
<td>□ YES  How many TIMES a week?  ➔  How many TOTAL hours a week did you usually do it?  ➔  Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours</td>
</tr>
<tr>
<td>□ NO</td>
<td></td>
</tr>
<tr>
<td>31. Do water exercises (do not count other swimming)?</td>
<td>□ YES  How many TIMES a week?  ➔  How many TOTAL hours a week did you usually do it?  ➔  Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours</td>
</tr>
<tr>
<td>□ NO</td>
<td></td>
</tr>
<tr>
<td>32. Swim moderately or fast?</td>
<td>□ YES  How many TIMES a week?  ➔  How many TOTAL hours a week did you usually do it?  ➔  Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours</td>
</tr>
<tr>
<td>□ NO</td>
<td></td>
</tr>
<tr>
<td>33. Swim gently?</td>
<td>□ YES  How many TIMES a week?  ➔  How many TOTAL hours a week did you usually do it?  ➔  Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours</td>
</tr>
<tr>
<td>□ NO</td>
<td></td>
</tr>
<tr>
<td>34. Do stretching or flexibility exercises (do not count yoga or Tai-chi)?</td>
<td>□ YES  How many TIMES a week?  ➔  How many TOTAL hours a week did you usually do it?  ➔  Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours</td>
</tr>
<tr>
<td>□ NO</td>
<td></td>
</tr>
<tr>
<td>35. Do yoga or Tai-chi?</td>
<td>□ YES  How many TIMES a week?  ➔  How many TOTAL hours a week did you usually do it?  ➔  Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours</td>
</tr>
<tr>
<td>□ NO</td>
<td></td>
</tr>
<tr>
<td>36. Do aerobics or aerobic dancing?</td>
<td>□ YES  How many TIMES a week?  ➔  How many TOTAL hours a week did you usually do it?  ➔  Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours</td>
</tr>
<tr>
<td>□ NO</td>
<td></td>
</tr>
<tr>
<td>37. Do moderate to heavy strength training (such as hand-held weights of more than 5 lbs., weight machines, or push-ups)?</td>
<td>□ YES  How many TIMES a week?  ➔  How many TOTAL hours a week did you usually do it?  ➔  Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours</td>
</tr>
<tr>
<td>□ NO</td>
<td></td>
</tr>
<tr>
<td>In a typical week during the past 2 weeks, did you</td>
<td>C-3 CHAMPS activities questionnaire for older adults (Chapter 3)-continued</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>□ NO</td>
<td>□ NO</td>
</tr>
<tr>
<td>38. Do light strength training (such as hand-held weights of 5 lbs. or less or elastic bands)?</td>
<td>How many TOTAL hours a week did you usually do it?</td>
</tr>
<tr>
<td>□ YES How many TIMES a week? ➔</td>
<td>Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours</td>
</tr>
<tr>
<td>□ NO</td>
<td>How many TOTAL hours a week did you usually do it?</td>
</tr>
<tr>
<td>39. Do general conditioning exercises, such as light calisthenics or chair exercises (do not count strength training)?</td>
<td>Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours</td>
</tr>
<tr>
<td>□ YES How many TIMES a week? ➔</td>
<td>How many TOTAL hours a week did you usually do it?</td>
</tr>
<tr>
<td>□ NO</td>
<td>How many TOTAL hours a week did you usually do it?</td>
</tr>
<tr>
<td>40. Play basketball, soccer, or racquetball (do not count time on sidelines)?</td>
<td>How many TOTAL hours a week did you usually do it?</td>
</tr>
<tr>
<td>□ YES How many TIMES a week? ➔</td>
<td>Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours</td>
</tr>
<tr>
<td>□ NO</td>
<td>How many TOTAL hours a week did you usually do it?</td>
</tr>
<tr>
<td>41. Do other types of physical activity not previously mentioned (please specify)?</td>
<td>How many TOTAL hours a week did you usually do it?</td>
</tr>
<tr>
<td>□ YES How many TIMES a week? ➔</td>
<td>Less than 1 hour 1-2½ hours 3-4½ hours 5-6½ hours 7-8½ hours 9 or more hours</td>
</tr>
<tr>
<td>□ NO</td>
<td>How many TOTAL hours a week did you usually do it?</td>
</tr>
</tbody>
</table>
## C-4 Modified Tampa Scale of Kinesiophobia (TSK) (Chapter 3)

(Miller, Kori and Todd 1991)

1 = strongly disagree  
2 = disagree  
3 = agree  
4 = strongly agree

<table>
<thead>
<tr>
<th>Question</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I’m afraid that I might injury myself if I exercise</td>
<td></td>
<td></td>
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<tr>
<td>2. If I were to try to overcome it, my pain would increase</td>
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<tr>
<td>3. My body is telling me I have something dangerously wrong</td>
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<td></td>
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<tr>
<td>4. People aren’t taking my medical condition seriously enough</td>
<td></td>
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<tr>
<td>5. My accident has put my body at risk for the rest of my life</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6. Pain always means I have injured my body</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>7. I am afraid that I might injure myself accidentally</td>
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<tr>
<td>8. Simply being careful that I do not make any unnecessary movements is the safest thing I can do to prevent my pain from worsening</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>9. I wouldn’t have this much pain if there weren’t something potentially dangerous going on in my body</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>10. Pain lets me know when to stop exercising so that I don’t injure myself</td>
<td></td>
<td></td>
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<tr>
<td>11. It’s really not safe for a person with a condition like mine to be physically active</td>
<td></td>
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<tr>
<td>12. I can’t do all the things normal people do because it’s too easy for me to get injured</td>
<td></td>
<td></td>
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<tr>
<td>13. No one should have to exercise when he/she is in pain</td>
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</tbody>
</table>

C-5 McGill Pain Questionnaire (MPQ)-short form (Chapters 3-5)

Subject's code: …………

A. PLEASE DESCRIBE YOUR PAIN DURING THE LAST WEEK. (✓ one box on each line.)

<table>
<thead>
<tr>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Throbbing</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2. Shooting</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3. Stabbing</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4. Sharp</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5. Cramping</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>6. Gnawing</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>7. Hot-burning</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>8. Aching</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>9. Heavy</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>10. Tender</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>11. Splitting</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>12. Tiring-exhausting</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>13. Sickening</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>14. Fearful</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>15. Punishing-cruel</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

B. RATE YOUR PAIN DURING THE PAST WEEK
The following line represents pain of increasing intensity from “no pain” to “worst possible pain”. Place a slash (|) across the line in the position that best describes your pain during the past week.

No Pain | Worst possible pain | Score in mm (Investigator’s use only)

C. PRESENT PAIN INTENSITY
0  No pain  1  Mild  2  Discomforting  
3  Distressing  4  Horrible  5  Excruciating
C-6 Brief Pain Inventory (BPI)-short form (Chapters 3-5)

Date: ___________________________
Subject’s code: ___________________

1. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts most.

2. Please rate your pain by circling the one number that best describes your pain at its worst in the last week.

   0  1  2  3  4  5  6  7  8  9  10
   No pain  Pain as bad as you can imagine

3. Please rate your pain by circling the one number that best describes your pain at its least in the last week.

   0  1  2  3  4  5  6  7  8  9  10
   No pain  Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain on average.

   0  1  2  3  4  5  6  7  8  9  10
   No pain  Pain as bad as you can imagine

5. Please rate your pain by circling the one number that tells how much pain you have right now.

   0  1  2  3  4  5  6  7  8  9  10
   No pain  Pain as bad as you can imagine
6. What treatments or medications are you receiving for your pain?

[Extended text]

7. In the last week, how much relief have pain treatments or medications provided? Please circle the one percentage that best shows how much relief you have received.

[Table]

<table>
<thead>
<tr>
<th>Percentage</th>
<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>Relief</td>
<td>No relief</td>
<td>10% relief</td>
<td>20% relief</td>
<td>30% relief</td>
<td>40% relief</td>
<td>50% relief</td>
<td>60% relief</td>
<td>70% relief</td>
<td>80% relief</td>
<td>90% relief</td>
<td>Complete relief</td>
</tr>
</tbody>
</table>

8. Circle the one number that describes how, during the past week, pain has interfered with your:

a. General activity

<table>
<thead>
<tr>
<th>Interference Level</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doesn’t interfere</td>
<td>Doesn’t interfere</td>
<td>Slightly interferes</td>
<td>Moderately interferes</td>
<td>Much interferes</td>
<td>Completely interferes</td>
<td></td>
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</table>

b. Mood

<table>
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<tr>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<td>Moderately interferes</td>
<td>Much interferes</td>
<td>Completely interferes</td>
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</table>

c. Walking ability

<table>
<thead>
<tr>
<th>Interference Level</th>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<th>9</th>
<th>10</th>
</tr>
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<tbody>
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<td>Doesn’t interfere</td>
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<td>Much interferes</td>
<td>Completely interferes</td>
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</tbody>
</table>

d. Normal work (includes both outside the home and housework)

<table>
<thead>
<tr>
<th>Interference Level</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<th>10</th>
</tr>
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<tbody>
<tr>
<td>Doesn’t interfere</td>
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<td>Slightly interferes</td>
<td>Moderately interferes</td>
<td>Much interferes</td>
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</table>

e. Relations with other people

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<tr>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doesn’t interfere</td>
<td>Doesn’t interfere</td>
<td>Slightly interferes</td>
<td>Moderately interferes</td>
<td>Much interferes</td>
<td>Completely interferes</td>
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</table>

f. Sleep

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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<td>Slightly interferes</td>
<td>Moderately interferes</td>
<td>Much interferes</td>
<td>Completely interferes</td>
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</table>

g. Enjoyment of life

<table>
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<tr>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doesn’t interfere</td>
<td>Doesn’t interfere</td>
<td>Slightly interferes</td>
<td>Moderately interferes</td>
<td>Much interferes</td>
<td>Completely interferes</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
C-7 Activity log for physical activity monitoring (Chapter 5)

Subject’s code: …………… Date:…………

Activities to include in the table include: **sitting, standing, walking, locomotion** (when in the car, bus, elevator), **sleeping**.

<table>
<thead>
<tr>
<th>Time</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 - 6:30 am</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6:30 - 7 am</td>
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<td></td>
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<tr>
<td>7 - 7:30 am</td>
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<tr>
<td>7:30 - 8 am</td>
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<tr>
<td>8 – 8:30 am</td>
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<tr>
<td>8:30 - 9 am</td>
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<tr>
<td>9 - 9:30 am</td>
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<tr>
<td>9:30 - 10 am</td>
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<td></td>
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<tr>
<td>10 - 10:30 am</td>
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<td></td>
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<tr>
<td>10:30 – 11 am</td>
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<tr>
<td>11 - 11:30 am</td>
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<tr>
<td>11:30 – 1 noon</td>
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<td></td>
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<tr>
<td>12 - 12:30 pm</td>
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<td></td>
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<tr>
<td>12:30 - 1 pm</td>
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<td></td>
<td></td>
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<tr>
<td>1 - 1:30 pm</td>
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<td></td>
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<tr>
<td>1:30 - 2 pm</td>
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<tr>
<td>2 - 2:30 pm</td>
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<td>2:30 - 3 pm</td>
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<tr>
<td>3-3:30 pm</td>
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<td>3:30 - 4 pm</td>
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<tr>
<td>4 - 4:30 pm</td>
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<td></td>
<td></td>
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<tr>
<td>4:30 - 5 pm</td>
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<tr>
<td>Time</td>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 3</td>
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<tr>
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<tr>
<td>5 - 5:30 pm</td>
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<td>5:30 - 6 pm</td>
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<td>6 - 6:30 pm</td>
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<td>11 - 11:30 pm</td>
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<td>12 - 12:30 am</td>
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<td>12:30 - 1am</td>
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<td>1 - 1:30 am</td>
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<td>2 - 3 am</td>
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<td>3 - 4 am</td>
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<td></td>
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<td>4 - 5 am</td>
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<td></td>
<td></td>
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<tr>
<td>5 - 6 am</td>
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<td></td>
</tr>
</tbody>
</table>
### C-7 Activity log for physical activity monitoring (Chapter 5)-continued

Please answer the following questions for each day:

<table>
<thead>
<tr>
<th>Day Date</th>
<th>Pain</th>
<th>Breathlessness</th>
<th>Fatigue</th>
<th>General Daily Wellness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pain Score (0 lowest-10 highest)</td>
<td>What time</td>
<td>Breathlessness Score (0 lowest-10 highest)</td>
<td>What time</td>
</tr>
<tr>
<td>Example: Monday Oct 6</td>
<td>2-4 pm</td>
<td>7</td>
<td>6-6:30 pm</td>
<td>5</td>
</tr>
<tr>
<td>Day1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
C-7 Activity log for physical activity monitoring (Chapter 5)-continued

Instructions:
● Please do not change your daily activities while you are wearing this device. The aim of the study is to look at your activities during a typical, normal day.
● Please make sure the waist belt is positioned on your lower trunk i.e. the upper edge of the waist belt is over or just below your belly button and the lower edge of the waist belt is on your hip bones. The centre of the DynaPort device (the clear plastic window) should be positioned in line with the spine (over the middle of your back). Avoid wearing the waist belt too loose or too tight.
● It is most comfortable to wear the DynaPort device underneath the uppermost layer of clothing. Please avoid positioning the device directly on your skin for sanitary reasons.
● Please keep the device on all the time during day and night, except before going to the shower or swimming. Because the DynaPort device is not waterproof, you should remove the waist belt before taking a shower or going swimming.
● Wearing the DynaPort device during the night is recommended, so please keep the device on during your sleeping hours at night unless it makes you uncomfortable during your sleep. If you have to take off the device at night, please leave it somewhere handy to make sure you put the device back on first thing in the morning.
● When replacing the device after a swim or a shower, please make sure the belt is not attached inside out or upside down. The green label is upright and on the outside of the belt. To assure that reliable data is collected, it is important to attach the waist belt correctly. The green light and the white printing of “DynaPort” should be observable through the plastic window.
● Please avoid removing the Dynaport device from the waist belt for any other reason, except for charging, showering or swimming.
● Before you sleep on the second night, remove the small gray Dynaport device from the waist belt and insert it into the charger overnight. In order to do so, align the five pin receptacle of the device to the five-in plug of the charger.
● If at any time the green light stopped blinking, or for any emergency inquiry, please contact Bahareh Ghanbari on her cell phone at:
   Tel: 604 771 2273
We do appreciate your help and your collaboration with our research study.